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XXIX CONGRESSO BRASILEIRO
GENÉTICA MÉDICA 2017

III CONGRESSO BRASILEIRO DE ENFERMAGEM EM GENÉTICA E GENÔMICA

Bento Gonçalves | 20 a 23 de junho

DA PESQUISA À PRÁTICA CLÍNICA

CITOGENÉTICA

Código #12652

Título: Um raro cariótipo apresentando monossomia Xp e trissomia 17q em um paciente com MAC/DI.

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Muitas translocações cromossômicas envolvem microdeleções e/ou microduplicações acarretando em anomalias cromossômicas associado com múltiplas anomalias congênitas e deficiência intelectual (MCA/DI).

Caso clínico: AA, sexo masculino filho único de casal jovem, não-consangüíneo e saudável, Russos, nasceu no sexto mês de gestação por cesariana e gestação sem intercorrências, apresentando ao parto circular de cordão, icterícia (tratamento de fototerapia) permanecendo na maternidade por 6 meses em oxigenação. Encaminhado ao SAG por apresentar MAC/DI. Na avaliação genético-clínica aos 3 anos e 11 meses, antecedentes de pneumonias recorrentes, cianose ao nascimento e até o presente, CIV, hipospadia, criptorquidia, atraso psicomotor grave, na fala e no desenvolvimento físico. Comprimento de 86cm (percentil <2,5%), peso de 9.700kg (percentil <2,5%), PC de 40cm (percentil <2,0%), 73cm de envergadura . Apresentava microcefalia, microstomia, retrognatismo, e orelhas com baixa implantação.

Estudos citogenéticos e moleculares: A analise citogenética por GTG e GTG-AR revelou cariótipo 46, XY, t(X;17)(p22.3;q21.2)/46, XY, t(x;17)(Xqter->Xp22.3::17q21.2->17qter,17pter->17q21.2). O exame de FISH (Coatasome 17 ONCOR® e XCP-MetaSYstems®) confirmou a translocação X/17. As análises citogenéticas dos pais revelaram-se normais. Foi realizado a-CGH (Affimetrix) que revelou trissomia parcial 17q e monossomia parcial Xp. A microduplicação de 17q era de 6,5Mb (31004189 até 37527127), e a monossomia de Xp era de 0,9Mb (168551 até 1102585). Este exame também revelou uma microdeleção em 17q de 1,2Mb (37532969 até 38780383).

Discussão: Não foi localizado na literatura desbalancamento cromossômico compatível com o presente caso. Foram localizados Com aproximadamente 40 casos na literatura, de duplicação 17q, microdeleção 17q e monossomia Xp. A correlação fenótipo-genótipo constatou-se dentre os genes que se localizam nas regiões não-balanceadas, os que se apresentam suas funções prejudicadas são : microduplicação 17q12-q21.2 - *SPACA3, LIG3, RAD51D, GAS2L2, MMP28, LHX1, PCGF2, RPL19*; envolvidos com processos de transcrição, duplicação e reparação de DNA, desenvolvimento embrionário, remodelação e homeostase de tecidos, desenvolvimento dos sistemas renal e urogenital e sistema muscular esquelético. Microdeleção 17q12-q21.2 são*: MED1, NEUROD2, PPP1R1B, TCAP, PGAP3, CSF3, MED24, NR1D1, MSL1, CDC6, GJD3, TOP2A*. Envolvidos com transcrição de DNA, diferenciação de células neuronais, funcionamento neurológico, regulação de sistemas

muscular esquelético e cardíaco, sistema imune, funções metabólicas e cardiovasculares e divisão celular. Microdeleção Xp22.33 são: *PPP2R3B, SHOX*. Envolvidos com processos celulares e crescimento do indivíduo.

Conclusão: O estudo contribui para corroborar a relação da presença de trissomia parcial do braço longo do cromossomo 17 associada a presença de um quadro de MAC/DI para posteriores estudos de genes específicos envolvidos.

Código #12626

Title: **CHROMOSOMAL ABERRATIONS IN COUPLES WITH RECURRENT MISCARRIAGES**

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Objective: Taking into account the importance of determining the karyotypes of couples with a reproductive history characterized by the occurrence of two or more spontaneous abortions, as well as the risks for future generations, the present study aimed to investigate the occurrence of chromosomal aberrations in couples which had spontaneous recurrent abortions.

Method: For this purpose, we evaluated 62 couples reported to the Genetic Counseling Ambulatory by the infertility service of a Teaching Hospital in the interior of São Paulo in the period between 2006 to 2016. Karyotypes were obtained from short-lived cultures of peripheral blood lymphocytes and determined after analysis of 20 metaphases in G banding.

Results: The results showed an average of 3 miscarriages / couples, mainly occurring between 4-8 weeks of gestation, mean maternal and paternal ages at the time of karyotype was 28 ± 3.8 years and 36 ± 4.3 years, respectively. The karyotype analyzes showed the occurrence of chromosomal aberrations in 12 couples (19.35%): 45,XX,t(14;15); 46,XX,t(11;14); 46,XX,del(3q); 45,XX,t(2;13); 46,XX,inv(9); 46,XX,inv(10); 46,XY,t(4;5); 46,XY,t(3;8); 46,XYt(18;13), 46,XY,der(13;15); 46,XY/46,XY,t(1q;8q). The results were reported during the counseling appointment.

Conclusion: The chromosomal alterations diagnosed in the present study occurred in a larger number in the female spouse, and more frequently than in the literature (5 - 10%), and may be involved in the etiology of spontaneous abortions in the population evaluated. In addition, they emphasize the need to perform the karyotype examination in couples with a history of recurrent miscarriages of unknown cause, as well as the balanced aberrations in the parents being involved with a high rate of recurrence of fetal losses also represent an increased risk of birth of children with Unbalanced chromosomal rearrangements with congenital malformations and / or mental deficiency.

Keywords: Recurrent Abortion; Chromosome aberrations; Karyotype.

Código #13285

Title: Cytogenomic fine map of 4p16.3 chromosome rearrangements

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Objectives: Deletions in the 4p16.3 region cause Wolf-Hirschhorn syndrome (WHS), a contiguous gene deletion syndrome involving variable size deletions. This study aimed to stablish the cytogenomic profile of the chromosome rearrangements involving the 4p16.3 region and to perform a gene interaction network analysis within the WHS critical region.

Methods: 16 samples from individuals with a clinical indication of WHS were retrospectively analyzed of which 11 had a cytogenetic visible deletion and 5 a submicroscopic deletion not previously identified. Using FISH, chromosomal microarray analysis, WGS and WES, we localized the breakpoints of the 4p critical region. A gene interaction network analysis was performed using the GeneMANIA Cytoscape (http://apps.cytoscape.org).

Results and discussion: In addition to 11 classical terminal deletions, we mapped 1 interstitial deletion, 3 ring chromosomes and 1 typical translocation 4;8. The deletions sizes ranged between 3.7 and 11 Mb. We present the genotype-phenotype correlation in each patient and fully characterize the location and size of the deletions in 8 samples. Previous genotype-phenotype correlations of the 4p16.3 region have been hampered by the presence of other imbalances leading to duplication in part of the WHS critical region, which was a confounding factor in some of these correlations. In this study, only patients with 4p deletion due to different types of chromosome rearrangements were included, which enabled us to further refine the 4p critical region map and to explore new insights on mechanisms associated with CNVs within the 4p16.3 region. The individuals in our study whose deletions encompass the terminal 875 kb 4p16.3 region were reported as having microcephaly and seizures, typical of WHS. So far, two separate intervals have been identified in association with seizures; the distal seizure candidate region is a 197 kb segment starting from 368 kb of the terminus of 4p, while the proximal seizure candidate region maps from 0.76 to 1.3 Mb from the end of 4p terminus, and includes three candidate genes (*CPLX1, FGFRL1, and CTBP1*).

Conclusions: 4p16.3 chromosomal rearrangements have different mechanisms of origin, which leads to a heterogeneous spectrum of phenotype features in affected patients, from very subtle or mild, to a wide range of severe abnormalities. This study explored the genes causing seizures and microcephaly in the context of WHS, and refined the critical chromosomal susceptibility region in the chromosome rearrangements within 4p16.3.

Código #12693

Title: GENOTYPE/PHENOTYPE CORRELATION WITH PARTIAL DUPLICATIONS OF 6P AND 6Q

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Partial trisomies 6p and 6q are rare and clinical features include craniofacial changes, mental retardation and developmental delay. The present study aims to correlate the genotype/ phenotype of a 6p and 6q duplication carrier.

Case report: MVSN (SAG 8016), female, single daughter of nonconsanguineous and healthy young couple. The father has a 13-year-old son from a previous relationship. Delivered by C-section, gestation of 37 weeks. The clinical analysis revealed: microcephaly, brachycephaly, syndromic facies, prominent forehead, hyperarousalism, strabismus, short nose, anteverted nares, smooth philtrum, thin lip, upper lip tented, micrognathism, dental anomalies, low-set ears, slender fingers, nails malformation, digitiform thumb, bilateral flat foot, hypotonia and neuropsychomotor developmental delay (NPMD). In the physical examination performed at 2 years of age, weight was 7,570 Kg (<3,58%), length was 74 cm (<3,95%) and cephalic perimeter was 43 cm (<2%).

Cytogenetics, molecular analysis and cytogenomic: Classic cytogenetic techniques were performed (GTG banding and high resolution GTG), molecular cytogenetic (FISH) and cytogenetic (aCGH). The karyotype showed a mosaicism 47, XX, + mar [9]/46, XX[11]. The parental karyotype was normal. The chromosomal changes found by aCGH indicate a genetic gain at chromosomal regions 6p11.2→q12 and 6q14.1→q14.3 with a size of 10.335 Mb and 10. 765 Mb, respectively. The patient presented mosaicism of a marker chromosome (sSMC) identified by the technique of FISH as coming from chromosome 6.

Results: In the chromosomal region 6p11.2→q12 the genes present are: *PRIM2, GUSBP4, MTRNR2L9, KHDRBS2, LGSN, PTP4A1, PHF3, EYS* and *MCART3P*. Heart defects and kidney problems were cited in the literature as being characteristic of trisomy 6p. However, our patient did not present any of these phenotypic changes. Therefore, it is relevant to question that the breaking point 6p11.2→q12 is present in a centromeric region of chromosome 6 and that possibly because it is a region of heterochromatin generally few genes are transcribed, not significantly influencing the phenotype. The chromosomal region 6q14.1→q14.3 contains more than 20 genes. The clinical signs found in our patient such as: developmental delay, mental retardation, forehead prominent, short nose and thin lips has been described in other studies in the literature as characteristic of 6q trisomy. The presence of mosaicism excludes the possibility of sSMC as the sole responsible for the patient's phenotype, since normal gene dosage balancing occurs.

Conclusion: Our study correlates the phenotypic characteristics presented by the patient with partial trisomy 6q collaborating for family genetic counseling.

Código #13330

Título: PACIENTE COM CROMOSSOMO MARCADOR NÃO IDENTIFICADO NO CGH ARRAY E DELEÇÃO 22q11.21

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Objetivos: Reportar um paciente do sexo masculino de 5 anos e 3 meses que iniciou investigação para atraso no desenvolvimento e dismorfias por cariótipo com resultado de cromossomo marcador não identificado ao CGH *array* e com deleção característica da Síndrome VeloCardiofacial.

Metodologia: O paciente foi avaliado por cariótipo com banda G, RON (região organizadora de nucléolo) e banda C (heterocromatina constitutiva) de sangue periférico, CGH *array* e FISH com sonda centromérica para o cromossomo 15 e 22. Também foram realizados os cariótipos com banda G de sangue periférico de ambos os pais.

Resultados: O cariótipo com Banda G de sangue periférico do paciente teve resultado 47,XY,+mar. O bandamento RON mostrou tratar-se de um cromossomo bissatelitado, enquanto que o bandamento C evidenciou a presença de dois centrômeros. O teste de CGH *array* identificou uma deleção intersticial no braço longo do cromossomo 22, afetando a banda 22q11.21 e com tamanho de 2,9 Mb. Neste teste não foram identificadas regiões de ganho que explicassem a origem do cromossomo marcador. O teste de FISH com a sonda centromérica do cromossomo 22 mostrou sinal de hibridização apenas no par de cromossomos 22. Por outro lado, FISH com a sonda centromérica do cromossomo 15 evidenciou 4 sinais de hibridação, dois no par de cromossomo 15, conforme esperado, e dois sinais adjacentes no cromossomo marcador confirmando a sua origem. O resultado do cariótipo do pai do paciente foi 46,XY, e da mãe : 47,XXX[3]/45,X[2]/46,XX[70].

Conclusão: Marcadores são cromossomos extranumerários de origem indeterminada que ocorrem numa frequência de 0,05% na população, e já foram descritos em todos os cromossomos. A Síndrome de deleção 22q11.21 caracteriza-se clinicamente por um espectro fenotípico bastante amplo, com mais de 180 achados já descritos, contudo, nenhum deles é patognomônico ou mesmo obrigatório, o que acaba por dificultar o diagnóstico. A presença de um cromossomo marcador pode interferir na segregação normal dos cromossomos homólogos, ou na troca dos mesmos, resultando numa inviabilidade celular ou malformação na prole. A permanência de um marcador na célula também depende da sua estabilidade no processo de divisão celular, que é possibilitado pela presença do centrômero ou neocentrômero. No caso o marcador é um cromossomo com dois centrômeros e bissatelitado, portanto apenas a região de heterocromatina está presente e por este motivo não foi identificado pelo teste de CGH array uma vez que não existem sondas para estas regiões. Contudo foi identificada a deleção 22q11.21 responsável pelo fenótipo apresentado pelo paciente.

O cariótipo da mãe apresenta um mosaicismo cromossômico de três linhagens germinativas distintas por provável erro de disjunção, contudo os dados não sugerem uma relação direta na formação das duas alterações cromossômicas detectadas: microdeleção 22q11.21 e marcador do cromossomo 15.

Código #13376

Title: Ring of Chromosome 13 with Noonan Syndrome Phenotyp.

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Goals: To describe a patient with ring chromosome 13 with Noonan Syndrome phenotype.
Methods: Clinical examination, informed consent, patient chart review and genomic microarray research with Multiplex Ligation-Dependent Probe Amplification (MLPA).

Results: Patient referred with 8 years for mild intellectual disability, perceived with 4 years. Third child of non-consanguineous, with gestation without intercurrences and born to term. He evolved without delay of the psychomotor frames but presented difficulty in articulating the words. Presented early pubarca with 7 years. No family history of pathologies. On physical examination, short stature within the familiar canal, microcephaly, implantation of hair in trident, blepharophimosis, bilateral epicanthus, telecanthus, unilateral ptosis, short and winged neck, apparent brachydactyly, pectus carinatum and excavatum, inverted nipples and hypogenitalism with micropenis. Ressonance of brain, spine radiography and audiometry were normal. Echocardiogram with left atrium at the upper limit of normality and ultrasonography of the abdomen with pelvic dilatation. Karyotype 45, XY, -13 [2] / 46, XY, R (13) [98]. MLPA showed deletion 13q34. Karyotype of the father was performed 46, XY, 9QH +, and the mother 46, XX, both with normal clinic examination.

Conclusion: Ring chromosomes are rare but have been detected for every human chromosome. This event can produce terminal arm rearragements, includying deletions; however, the phenotype-genotype correlation has not been identified clearly. The patient described has a phenotype of Noonan Syndrome, that is an autosomal dominant disorder characterized mutations in several genes, including PTPN11, SOS1, RAF1 and KRAS. Affected individuals have normal chromosome studies and any of these genes are located at chromosome 13, what suggests a candidate region for futher studies of genes related to Noonan Syndrome.

Código #13238

Título: SYSTEMATIC REVIEW AND METANALYSIS OF DIAGNOSTIC YIELD OF CHROMOSOMAL MICROARRAY FOR OROFACIAL CLEFT

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Objetivos: The orofacial clefts (OC) are the most common craniofacial defect in humans. However, a diagnostic tool of first-line choice for OC has not been reported. The aim of this study was to carry out a systematic review of studies that performed chromosomal microarray (CMA) for etiologic diagnosis of OC and calculated the diagnostic yield.

Metodologia: We search for primary studies, that verified the diagnostic contribution of CMA for genetic etiology of OC, in MEDLINE, EMBASE, Web of Science, Scopus, Lilacs and The Cochrane Library databases, up to July 2015. No language or other search restrictions were imposed and reference lists of primary studies were checked for additional references. All studies were selected by two independently reviewers.

Resultados:
A total of 434 citations were retrieved from the databases, we selected six references for full text assessment, from which three studies met our inclusion criteria, additionally one article was included by manual search. The meta-analyzed diagnostic yield of CMA was 10.18% for patients with typical orofacial cleft, 15 % for syndromic patients and 7% for non-syndromic patients. For cleft palate patients it was 18% and for cleft lip/cleft lip-palate patients was 10%.

Conclusão:
The diagnostic yield described for patients with OC is compatible with the diagnostic yield of CMA for patients with birth defects in general, intellectual disability and correlate disorders, the main motivations for diagnostic use of this genetic testing. According to GRADE approach the quality of evidence derived from the primary studies is very low, which demonstrate the lack of studies about this subject and the methodological limitations of the analyzed studies.

DIAGNÓSTICO PRÉ-NATAL E MEDICINA REPRODUTIVA

Código #13211

Title: ANGIOGENESIS AND OXIDATIVE STRESS-RELATED GENE VARIANTS IN RECURRENT PREGNANCY LOSS

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Objective: Recurrent pregnancy loss (RPL) affects 5% of the couples attempting to conceive and in around 50% of cases the aetiology remains unknown. Prostaglandin-endoperoxide synthase 2 (PTGS2), vascular endothelial growth factor (VEGFA) and nitric oxide (NO) system play important roles in reproductive physiology, participating in several steps including implantation and apoptosis of trophoblast cells. The objective of this study was to evaluate genetic polymorphisms in *NOS2*, *PTGS2* and *VEGFA* genes as susceptibility factors for (RPL).

Methods: We performed a case-control study including 149 women with idiopathic RPL and 208 fertile women with a history of at least one uncomplicated, live term birth, no pregnancy losses and no major medical problems. In total, eight polymorphisms were analysed; rs2297518 and rs2779249 in *NOS2*; rs689465 and rs689466 in *PTGS2*; and rs699947, rs1570360, rs2010963 and rs3025039 of *VEGFA*. Chi-square test and binary logistic regression were used to analyse the distribution of the variants between the groups.

Results: All polymorphisms were in Hardy-Weinberg equilibrium with exception of rs699947of *VEGFA* (p = 0.002). Haplotype analysis indicates four haplotypes in *NOS2*, three in *PTGS2* and seven in *VEGFA*. The allelic and genotypic frequencies of polymorphisms and the distribution of haplotypes did not differ between RPL and controls. However, the T allele for both rs2779249 and rs2297518 SNPs showed higher frequency in RPL group.Considering that the frequencies of T allele of both *NOS2* polymorphisms were slightly higher in RPL patients, we then analyzed whether an allele was related to a higher risk to RPL. Using a binomial logistic regression we compared the frequencies of T allele between both groups. We observed that the genotypes TT and GT of rs2779249 are associated to RPL risk when compared with the GG genotype (OR = 1.58, CI 95% = 1.03-2.44; p = 0.037). The increased risk remained significant when adjusted for number of pregnancies, alcohol consumption and ethnicity (OR = 1.92, CI 95% = 1.18-3.11; p= 0.008).

Conclusion: In conclusion, we have shown that the functional polymorphism rs2779249 in the *NOS2* promoter is a potential risk factor for recurrent pregnancy loss.To the best of our knowledge, this is the first study to investigate a possible role of *NOS2* variants in RPL.
These results help to expand the hypothesis and knowledge on developmental oxidative stress and inflammatory events during embryo implantation and pregnancy, pointing to a potential role of *NOS2* polymorphisms as risk factors for RPL.However, further studies are necessary in order to evaluate the actual risk of these polymorphisms in RPL and to predict if there is a clinical relevance of our findings.

Key words: repeated miscarriage, *NOS2*, *PTGS2* and *VEGFA*, angiogenesis, oxidative stress.

Financial Support: CNPq, INaGeMP, FIPE/HCPA.

Código #12658

Title: CHARACTERISTICS OF PREGNANT WOMEN WHO UNDERWENT FETAL KARYOTYPING IN A REFERENCE FETAL MEDICINE SERVICE FROM SOUTHERN BRAZIL

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Objectives: To outline the profile of pregnant women attending a Fetal Medicine reference service in Southern Brazil who underwent fetal karyotyping.

Methods: Data were collected from medical records of pregnant women attending the Fetal Medicine Service of Hospital Materno Infantil Presidente Vargas (HMIPV), Rio Grande do Sul, Brazil, during 8 years.

Results: Our sample consisted of 155 pregnant women. Her ages ranged from 13 to 45 year-old (mean 28.5 year-old). Forty-one patients (26.5%) were 35 year-old or more. The main indication for fetal karyotyping was the presence of a fetal malformation (73.5%). Chromosomal abnormalities were identified in 38 cases (24.5%). Only 78 patients (50.3%) had undergone first trimester ultrasound screening and 44 (56.4%) were considered altered. Echocardiography, as well as magnetic resonance imaging (MRI), were important complementary exams, showing that the second trimester ultrasound accuracy for the detection of congenital heart defects was low (22.6%). We found that at time of procedure, fetuses with karyotypic abnormalities have been more often classified with multiple than isolated defects, when compared to normal fetuses (P=0.007348). Fetuses with multiple defects were 1.5625 times more likely to have a karyotypic abnormality. The presence of multiple defects was considered a satisfactory approach for invasive karyotyping (area under ROC curve 0.624). Higher frequencies of chromosomal abnormalities were seen in fetuses presenting commitment of the following systems: hygroma/hydrops (P=0.0219), cardiovascular system (P=0.0003) and face and neck (P=0.0039). There was a tendency to have a negative association between chromosomal abnormalities and anomalies of the urinary tract (P=0.0927).

Conclusion: Fetal echocardiography and MRI could be useful in order to classify in multiple or isolated defects, thus better indicating the invasive procedure. Pregnancy planning allied to a greater access to health care and a better qualification of the ultrasound performing physicians would also help to increase this prenatal detection of malformations and hence chromosomal abnormalities.

Código #13216

Título: DESENHO DE ARRAY-CGH ORIENTADO PARA O DIAGNÓSTICO PRÉ-NATAL IDENTIFICA 10% DE CASOS PATOLÓGICOS, LIMITANDO A 0.6% OS CASOS COM VARIANTES DE SIGNIFICADO INCERTO: EXPERIÊNCIA EM >1.000 CASOS

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Instituição dos Autores: NIMGenetics

Objetivos: O array-CGH é uma tecnologia cuja implementação para o diagnóstico genético pré-natal (DP) é limitada pela sua resolução e informação inconclusiva. Para superar essas limitações, utilizamos um array-CGH com desenho orientado ao DP para a análise de >1000 amostras pré-natais.

Metodologia: Foram incluídas um total de 1053 amostras pré-natais, como líquido amniótico, fragmentos de vilosidade coriônica ou cultivo proveniente da citogenética pré-natal. Os DNAs foram extraídos das amostras e analisados utilizando o array-CGH com desenho orientado para o DP, apresentando maior resolução em regiões associadas com no mínimo 124 síndromes genéticas com prognóstico conhecido. Adicionalmente, esse desenho permite a detecção de regiões não polimórficas com tamanho superior a 2 megabases.

Resultados: Das 1053 amostras incluídas no estudo, 1043 (99%) foram analisadas por array-CGH optimizado para o DP. Em 110 casos (10.44%) foram identificadas variantes genômicas patogênicas já descritas, que poderiam explicar os achados ecográficos informados ou estavam associadas a um fenótipo sindrômico evidente.
Foram identificadas em seis amostras, variantes desconhecidas com tamanho superior a 2 megabases (0.6%): 2/6 amostras foram classificadas como possivelmente patogênicas, considerando o tamanho, relação com as características observadas e revisão bibliográfica; 4/6 amostras foram investigadas nos progenitores, devido ao caráter potencialmente patogênico, sendo as quatro classificadas como variantes de novo.

Conclusão: A utilização de um array-CGH orientado para patologias presentes no pré-natal permite uma ótima detecção (10%) de variantes patogênicas relacionadas com um fenótipo sindrômico ou malformativo e reduz quase que totalmente (0.6%) os casos com variantes de significado incerto que podem gerar incertezas no diagnóstico pré-natal.

Código #12668

Title: EXPERIENCE OF A FETAL MEDICINE SERVICE OF REFERENCE FROM SOUTHERN BRAZIL WITH PATIENTS REFERRED FOR EVALUATION DUE TO SUSPECTED GASTROSCHISIS

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Objectives: Our aim was to report the experience of a Fetal Medicine Service of reference from southern Brazil with patients referred for evaluation due to suspected gastroschisis.

Methods: A retrospective study in which the sample was composed of patients referred due to suspected gastroschisis for the Fetal Medicine Service of Hospital Materno Infantil Presidente Vargas (HMIPV), Porto Alegre, Brazil, from January 2005 to November 2014. It was conducted a collection of clinical and radiological data.

Results: Thirty four patients were identified with suspected gastroschisis. From these, 2 were excluded due to another diagnosis. Regarding the age of pregnant women, 71% were aged less than or equal to 20 years. Twenty-one were primiparous (65.6%). The diagnosis of gastroschisis was performed on average at 19.4 weeks of gestation (ranged from 10 to 34 weeks). Two cases (6.3%) had the diagnosis made in the first trimester, 23 (71.9%) in the second trimester and 7 (21.8%) in the third. Almost all cases (90.6%) consisted of gastroschisis classified as isolated. There were no cases of intrauterine death. Almost all children were born by cesarean section (92.6%) due to prenatal diagnosis of gastroschisis. Half of them (50%) was premature.

Conclusion: Gastroschisis is considered the most common type of abdominal wall defect. Prenatal and early diagnosis of gastroschisis is possible, and the period of performance of the first trimester ultrasonographic screening seems to be a good time for it. This detection is especially important in our midst for the birth planning. The mode of delivery remains controversial, but the choice of cesarean section has been carried out to try to plan the child's birth for the prompt and adequate surgical evaluation.

Código #12687

Title: Potential for transmission of chromosomal abnormalities resulting from apparently balanced translocations and Robertsonian translocations

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Keywords: balanced translocations, Robertsonian translocations, preimplantation genetic diagnosis, preimplantation genetic screening, microarray and karyotype.

Objective: To identify the types of embryonic genetic alterations inherited from parents that present apparently balanced translocations and Robertsonian translocations. To relate whether these alterations involve or not the chromosomes present in the altered karyotype of the parents.

Methods: A survey of cases was made of embryos that entered for PGD (Pre Implantations Genetic Diagnosis) in the Chromosome laboratory from 2014 to 2016, originated from parents who presented a karyotype with balanced or Robertsonian chromosome translocations. At first, the couple sought an assisted human reproduction laboratory to undergo *in vitro* fertilization. A pool of cells from embryos were collected and sent for analysis at Chromosome laboratory where they were analyzed through the Microarray (SNP array) technique that simultaneously investigate thousands of genomic sequences to detect chromosomal segment gains (duplications) and losses (deletions) on the 24 chromosomes in the GeneChip® Scanner 3000 (Affymetrix, California, USA) device. All results were collected and placed on a table so that the data were analyzed and compared with the chromosomal abnormality of the parents.

Results: A total of 106 embryos were analyzed from 37 patients. A normal result was observed in 22 embryos (20.75%). Some type of chromosomal alteration was observed in 81 embryos (76.42%), of which 45 (42.45%) presented chromosomal alterations unrelated to their parents alterations, and 36 (33.96%) presented chromosomal alterations related to their parents alterations. It was not possible to obtain a result for 3 embryos (2.83%) due to amplification failure.

Conclusion: Most genetic alterations present in embryos originated from parents with chromosomal translocations involved chromosomes that were not related to the maternal or paternal karyotype.

Código #12688

Title: Retrospective cohort study of embryos originated from couples with indication for monogenic hereditary diseases analyzed by Chromosome Medicina Genômica laboratory from 2014 to 2016

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Keywords: Hereditary diseases, monogenic, pre-implantantation genetic diagnosis, embryos, sickle cell anaemia, thalassemia.

Objective: To indicate the most recurrent monogenic hereditary diseases studied in analysis of embryos for pre-implantation genetic diagnosis (PGD) from couples with a positive familiar history for a given genetic disease during 2014 to 2016 at Chromosome *Medicina Genômica* laboratory. In addition, the proportions of normal, carrier and affected embryos were calculated.

Methods: A sample of blood or buccal swab from couples that underwent genetic counseling was collected for genetic linkage study and haplotype determination using polymerase chain reaction and capillary electrophoresis of fluorescent microsatellite markers located near the gene. Samples of other relatives were optionally collected. After this initial step, the couple sought an assisted human reproduction laboratory to undergo *in vitro* fertilization. A single cell or a pool of cells from embryos were collected and sent for analysis at Chromosome laboratory where each embryo was genotyped. The comparison between genotypes allowed the classification of each embryo as normal, carrier or affected, depending of the inheritance pattern of the genetic disease.

Results: A total of 48 monogenic hereditary diseases were analyzed. Each one of 111 couples was genotyped for the genetic linkage study and haplotype determination and 70 of these couples (~58%) sent embryos for PGD analysis. Considering all cases, PGD was performed for a total of 41 monogenic hereditary diseases. The most recurrent five diseases counted for 35.72% of cases, in which *12.86% were tested for sickle-cell anaemia*, *7.14% for Thalassemia, 7.14% for spinal muscular atrophy Type 1, 4.29% for Lynch Syndrome,* 4.29% for Spinocerebellar Ataxia type 3, the other disease represent 2.86% for *Cystic fibrosis, Marfan Syndrome,* Arthrogryposis, *Methylmalonic acidemia, Leber congenital amaurosis, Amyloidosis, Severe Combined Immuno deficiency, Nonketotic hyperglycinemia, Neurofibromatosis Type 1, Autosomal dominant polycystic kidney* disease, *Fragile X syndrome and 1.43% for Adrenoleukodystrophy,* Charcot Marie Tooth, Cleidocranial dysostosis, *Myotonic dystrophy* type 1, Becker's Muscular Dystrophy, Duchenne Muscular Dystrophy, Huntington Disease, *Epidermolysis bullosa, Tuberous sclerosis type 2, Hereditary multiple exostoses, Hemophilia x-linked, Retinitis Pigmentosa, Retinoblastoma,* Joubert syndrome, *Li–Fraumeni syndrome, Meckel-Gruber syndrome,* Smith-Lemli-*Opitz syndrome, von Hippel-Lindau syndrome, Trichorhinophalangeal syndrome type I, Rh System and Tyrosinemia Type*
I. A total of 554 embryos were analyzed, 142 (26.10%) were classified as normal, 129 (23.71%) as carriers (for non-dominant disorders) and 208 (38.24%) as affected. It was not possible to obtain a result for 33 (6.07%) embryos due to amplification failure.

Conclusion: The most recurrent monogenic hereditary diseases analyzed by *Chromosome Medicina Genômica* laboratory were *Sickle-cell Anaemia, Thalassemia, Spinal Muscular Atrophy Type 1, Lynch Syndrome and* Spinocerebellar Ataxia type 3*. PGD proved to be efficient for the selection of normal embryos for a broad spectrum of genetic diseases.*

Código #13192

Título: Risk of Spontaneous abortion (SAB) and correlation with environmental factors in São Luís, Maranhão (BRAZIL)

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Objetivos: Spontaneous abortion (SAB) is considered the most common complication in early pregnancy, occurring 20 weeks or earlier into gestation, with an incidence of about 17–22 % of all pregnancies. This study aimed to examine the association between spontaneous abortion and seasonal variation of air pollutants and environmental variables in São Luís, Maranhão, Brazil.

Metodologia: A retrospective review of the medical records of SAB (all hospital admissions between 01 January 2002 and 31 December 2014) was conducted. Annual average PM10 (μg/m^3), Air temperature (°C) and Relative humidity (%) levels were measured at São Luís Air Quality Monitoring stations. SAB were counted and correlated with mean monthly levels of air pollutants (PM_{10}) and environmental factors by means of regression analysis and Spearman's rank correlation coefficient. *p-value* <0.05 were considered statistically significant. The total number of SABs, the birth rate (the number of live births per 1000 residents), the SAB ratio (number of SAB/number of live births) and the SAB rate (the number of SAB per 1000 fertile women) were determined. The monthly number of live births, residents, fertile women and SABs at regional level were derived from Department of Information Technology of SUS (DATASUS).

Resultados: Globally were recorded 244 cases of SAB. The median ratio SAB was 0.78 (range 0.64-1.64) and median rate SAB was 0.04 (range 0.03-0.06). The annual median temperature and humidity were, respectively, 27.3°C (range 26.3–28.3) and 77.0 % (range 70.0–83.0). Median air levels of PM_{10} (22.2 μg/m^3, range 18.2-26.9μg/m3), value below the limits set by the National Council for the Environment, Brazil. SAB rate and ratio correlated poorly with environmental PM_{10} concentrations.

Conclusão: The results presented corroborate the hypothesis of the correlation between environmental pollutants and the occurrence of spontaneous abortion. In addition, the findings reinforce the establishment of public policies aimed at controlling the emission of pollutants, fires and industrial activity to reduce the risk of abortion in urban areas. Studies at the individual level are suggested to establish the causal relationship between spontaneous abortions and environmental factors.

Código #13234

Title: TWINNING RATES BRAZIL: TEMPORAL AND SPATIAL TRENDS OF TWIN BIRTHS IN FOURTEEN YEARS.

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Institutions: [1]Universidade Federal do Rio Grande do Sul; [2]Hospital de Clinicas de Porto Alegre; [3]Universidade do Vale do Rio dos Sinos; [4]Instituto Nacional de Genética Médica Populacional.

Keywords: twinning rate; temporal trends; spatial trends; maternal age; HDI.

Objectives: Considering that only one study described an average rate of twin births in Brazil as a whole using data of 11,099 births collected in 1996, our main goal is to describe temporal trends of the twin pregnancies in Brazil from 2001 to 2014. Taking into account the diversity of the country, we also aim to characterize the twinning rate (TR) according to its politic divisions as well as demographic factors such as Human Development Index (HDI) and biological factors as maternal age.

Methodology: Data was obtained from the public database Live Births Information System (SINASC) from all five regions, 27 states, and 5,565 municipalities. TRs per 1,000 (‰) were obtained through: [(individual twin births/2)/ total of pregnancies) x 1,000]. Brazil's 2010 Census was used to collect the information about HDI. Statistical analysis and graphic models were performed in SPSS v20.0 software and Time Series Trends was analyzed with R v3.2.3 software. Spatial trends were analyzed in ArcGIS v10.3 software using clusters analysis tool.

Results: We analyzed 41,013,511 pregnancies between 2001 and 2014, where 385,477 were of twins (0.94%) and 9,502 of multiple (0.02%). The national TR mean was 9.41‰ with an increment of 17.34% from 2001 to 2014, however it was not uniformly distributed among the geographic regions: Southeast region presented the highest rate and variation (10.39‰ and 23.16%, respectively) and North region presented the lowest rate and second lowest variation (7.32‰ and 8.88%). We found a positive correlation between 2001 and 2014 and TR in Brazil as a whole (Spearman's $\rho = 0.9780$, $p < 0.001$) and a similar result was observed in all the five geographic regions of the country. Besides, the data spatialization by states and municipalities revealed that there is a trend of high rates from Sergipe (9.08‰) to Rio Grande do Sul (10.51‰) following the coastline's direction. The highest TR was found in São Paulo's state (10.69‰) and the lowest in Roraima (6.88‰). In a time series trends analysis considering maternal age groups, in only four states (Roraima, Amapá , Maranhão and Piauí) was not detected a statistically significant increasing trend in TR corrected for maternal age. The clusters spatial analysis at the municipality's level corroborated the scenario observed for the states. Furthermore, we also detected a strong correlation (Spearman's $\rho = 0.6170$, $p < 0.001$) between the states TR mean and the HDI based on 2010 Census data.

Conclusion: The knowledge about epidemiology of twins is important because, compared to singleton pregnancies, they have higher maternal-neonatal morbidity and mortality. The increase in TR observed in Brazil seems to follow what happened some years ago in high income countries. This assumption is consistent with the fact here observed, where a positive correlation between urbanized areas with higher HDI have higher TRs.

DISMORFOLOGIA

Código #13233

Title: 22q11.2 DELETION SYNDROME (22q11.2 DS): CLINICAL FEATURES IN 77 CASES FROM BRAZIL´S CRANIOFACIAL PROJECT

Authors: Ana de Miranda Henriques Moura[1], Elaine Lustosa Mendes[1,2], Josiane de Souza[2], Ana Carolina Xavier[3], Agnes Cristina Fett-Conte[4], Ilária Cristina Sgardioli[1], Roberta Mazzariol Volpe Aquino[1], Vera Lúcia Gil-da-Silva-Lopes[1], Társis Paiva Vieira[1], and Brazil´s CranioFacial Project´s Contributors[5].

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Objectives: To conduct a retrospective analysis of the main clinical signs of patients with 22q11.2 DS registered in the Brazilian Database on Craniofacial Anomalies/22q11.2 Deletion Syndrome (BDCA/SDEL22q). Methods: Data from 77 patients, with a previous molecular diagnosis of a proximal 3 Mb (73) or 1,5 Mb (4) 22q11.2 deletion, were extracted from the BDCA/SDEL22q and analyzed using the Excel (Microsoft®). All patients were evaluated by a clinical geneticist, through a standardized clinical protocol, previously published by this research group. The percentage of each clinical sign was described. Some patients did not have all data available. In these cases, frequency of abnormalities was calculated in patients with recorded data. Results: This sample was composed by 45% of males and 55%female, with age varying from 0 to 32 years old. In view of the prevalence, the five main clinical features should be highlighted: palatal abnormalities, developmental delay, congenital heart diseases, behavioral/psychiatric diseases, and immunological diseases. Regarding palatal abnormalities, of 67 patients with recorded data, 80,6% had palatal abnormalities: 67% presented symptoms that suggested palatal abnormalities, which were: nasal voice (89%), nasal reflux (16%) and dysphagia (13%); and anatomical/ functional defects were: velopharyngeal insufficiency (50%), cleft palate (31,5%) and submucous cleft palate (29,6%). Of 64 patients with developmental skills data, 82,8% presented developmental delay, and 92,5% of 40 patients, older than 10 years old, presented learning disabilities. Of 70 patients with recorded data, 64,3% had congenital heart diseases; the most frequent types were: ventricular septal defect (47%), atrial septal defect (29%) and tetralogy of Fallot (16%). Behavioral and psychiatric diseases were found in 49,2%, of 61 patients with recorded data, the most common were attention deficit hyperactivity disorder

(56,7%), impulsivity (20%) and perseveration (10%).

Symptoms that suggested immunological or hematological diseases were described in 70,6% of the patients. In addition, 10% of the patients had central nervous system structural anomalies; 50% (of 20) had endocrinological diseases; 44,6% (of 56) had hearing loss; 43% (of 49) had ophthalmologic abnormalities; 17% (of 47) had genitourinary abnormalities; 49% (of 55 patients) had gastrointestinal abnormalities; 36,4% (of 77) have skeletal abnormalities. Regarding facial dysmorphisms, the most common were: elongated face (55%) alar hipoplasia (47%) dysmorphic ear (40%) and bulbous nose (35%). Conclusions: To the best of our knowledge, to date this is the largest sample of Brazilian patients with 22q11.2 DS described. This data show similar frequencies of the major anomalies presented by patients reported by previous international studies. Despite the significant phenotypic variability, these data support the main clinical signs previously reported. Grants: PIBIC-CNPq, FAPESP.

Código #12756

Title: 22q11.2 Deletion Syndrome: unusual clinical report associated with an atypical deletion detected by array-CGH

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Abstract: The 22q11.2 Deletion Syndrome (22q11.2DS), also known as Velocardiofacial or Di George Syndrome, is an autosomal dominant genetic disorder which has a prevalence of 1:2000-7000 individuals, caused by a microdeletion in chromosomic region 22q.11.2, covering 1,5 or 3Mb. It is characterized by cardiac abnormalities, cleft palate, facial dysmorphisms, thymic hypoplasia, learning disabilities and behavior disorders. However, the clinical presentation is highly variable. The clinical diagnosis of 22q11.2 isn't always easy and genetic tests are usually recommended in the presence of at least two positive clinical criteria, *e.g.* cleft palate and congenital cardiopathy. The severity of this contiguous genes syndrome is not directly associated with the extension of the deletion, although many studies pointed to *TBX1* as the most important deleted gene for the phenotypic etiology. Herein we describe the etiologic investigation of a female patient presenting failure to thrive, microcephaly, elongated face, narrowed palpebral fissures, high palate, down-turned corners of mouth, mental retardation, learning disabilities and emotional lability. She developed frequent episodes of infection and seizures, arthritis and significant weight loss. There weren't typical clinical criteria for 22q11.2DS, but the array-CGH (HumanCytoSNP-12 BeadChip /Illumina Technologies®) detected an atypical 3.233.125 pb deletion in 22q11.21q11.23 (20,737,903-23,971,028) that does not affect *TBX1.* According to *OMIM Genes,* this region comprises about 30 genes, 6 of which are considered pathological. One of them, *SNAP29,* stands out by its association with cerebral dysgenesis, neuropathy, microcephaly, neuro-developmental delay, growth retardation and facial dysmorphisms. The present report demonstrates the variability of the clinical presentation of 22q11.2DS and the importance of applying molecular techniques in the etiological definition, especially in atypical deletions situations.

Código #12673

Tittle: AUDIOLOGY EVALUATION IN PATIENTS WITH 22Q11.2 DELETION SYNDROME

Authors: Bibiana Fuzer da Silva; Rafael Fabiano Machado Rosa; Pricila Sleifer; Paulo Ricardo Gazzola Zen.

Institute of the authors: Universidade Federal de Ciências da Saúde de Porto Alegre (UFSCPA); Universidade Federal do Rio Grande do Sul (UFRGS).

Objectives: describing and analyzing the peripheral and central auditory findings in patients with 22q11.2 deletion syndrome (SD22q11.2).

Methodology: three patients between 04 and 18 years of age medically diagnosed with SD22q11.2, confirmed by the fluorescence in situ hybridization technique (FISH). All the patients participated in hearing evaluations, that include peripheral and a central auditory evaluation. The peripheral auditory evaluations consisted of pure tone audiometry, by air and bone, in the frequencies of, 250, 500, 1000, 2000, 3000, 4000, 6000 e 8000 Hz, and vocal audiometry, first through the speech recognition threshold (SRT), and then through the percentage of speech recognition index (SRI). The central auditory evaluation, conducted with electrophysiological procedures, was performed using the long-latency auditory evoked potentials (PEALL) exogenous (P1, N1, P2, N2) and endogenous (*mismatch negativity*).

Results: It was observed that two of the three patients presented alterations in at least one of the evaluations. One patient (33,3%) presented an alteration in the peripheral auditory evaluation and two in the PEALL evaluation. One of the patients, due to behavioral alterations, could not perform the electrophysiological exams, making the result inconclusive.

Conclusion: Our findings suggest that auditory alterations, both peripheral as central, can be present in individuals with SD22q11.2, being that central alterations could be correlated with cognitive alterations associated to the syndrome.

Código #13300

Título: Avaliação da Qualidade de Vida de Adultos com Osteogênese Imperfeita

Autores: Ana Paula Vanz, Bruna Pinheiro, Marina Zambrano, Evelise Brizola, Liliane Todeschini de Souza, Neusa Sica da Rocha, Têmis Maria Félix

Instituição dos Autores: Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Objetivos: A Osteogênese Imperfeita (OI) afeta a biossíntese do colágeno, caracterizada por fragilidade óssea, fraturas de repetição, deformidades ósseas e baixa estatura. O quadro clínico leva a uma variável limitação funcional, dependendo da gravidade da OI. O objetivo do trabalho é avaliar a qualidade de vida (QV) de adultos com OI.

Metodologia: estudo transversal, com amostragem por conveniência. A QV foi mensurada pelo instrumento SF-36. Os pacientes foram classificados em tipos de OI de acordo com avaliação clínica e radiológica. As variáveis dor e número de fraturas foram coletadas de forma autorreferida.

Resultados: Foram incluídos 31 adultos com diagnóstico de OI, com média de idade de 32,84 anos (± 12,11), destes 24 (77,4%) do sexo feminino. Em relação ao tipo de OI, 24 (77,4%) OI tipo I, 2 (6,4 %) OI tipo III, 2 (6,4%) OI tipo IV, 3 (9,8%) OI tipo V. Com relação à QV, o escore que apresentou menor média foi de *capacidade funcional* (41,9±12,3) e o que apresentou melhor média foi a *vitalidade* (53,3±9,3). Quando comparados pela condição física, forma moderada/grave (tipo III, IV e V) *versus* forma leve (tipo I), o domínio de capacidade funcional continuou com a menor média (30,91), não sendo observada diferença significativa entre os grupos. A variável dor mostrou correlação negativa nos escores *capacidade funcional* (p=0,04 r=-0,3), *aspectos sociais* (p=0,02 r=-0,4) e *aspectos emocionais* (p=0,02 r=-0.4). Foram testadas as correlações das variáveis classe econômica e número de fraturas em relação aos escores de QV estudados, não sendo encontrada significância estatística. Neste trabalho, os domínios apresentam menores médias se comparados a outros estudos na mesma população, com diferença significativa.

Conclusão: Observou-se que em adultos, mesmo aqueles com forma leve, (OI tipo I) mostram-nos o impacto da doença em diversos aspectos, principalmente na capacidade funcional, reforçando a importância do acompanhamento clínico destes pacientes.

Código #13224

Título: Avaliação genética em berçário de alta complexidade – experiência de 33 meses

Autores: José Ricardo Magliocco Ceroni[1], Rachel Sayuri Honjo[1], Guilherme Lopes Yamamoto[1], Vera Lúcia Jornada Krebs[2], Maria Esther Jurfest Rivero Ceccon[2], Regina Schultz[3], Débora Romeo Bertola[1], Chong Ae Kim[1]

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Objetivos: Descrição da casuística, taxa de diagnóstico dos casos avaliados por serviço de Genética em dois berçários de alta complexidade.

Metodologia: Levantamento retrospectivo dos atendimentos de recém-nascidos avaliados pela equipe da Unidade de Genética nos dois berçários de alta complexidade do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) no período de 05/2014 a 01/2017. Foram analisadas as fichas de avaliação clínica genética, prontuário, exames complementares e laudos de necropsia quando disponíveis. A avaliação clínica foi feita por anamnese, exame físico geral com registro fotográfico e heredograma. A avaliação laboratorial foi feita por exames complementares laboratoriais e de imagem; a investigação etiológica foi feita por citogenética, biologia molecular e ensaios enzimáticos quando necessário.

Resultados: No período de 33 meses foram realizadas 224 avaliações. Após a investigação inicial, os pacientes com uma malformação maior foram 55/224 (24,6%) e com múltiplas malformações foram 169/224 (75,4%). Em 198/224 (88,4%) foi possível fazer suspeita diagnóstica específica. Destes, 48/198 (24,2%), o diagnóstico citogenético e/ou molecular foi possível e foram: trissomia 21 (13), trissomia 18 (11), trissomia 13 (3), síndrome de Turner (5), hiperplasia adrenal congênita (2), esclerose tuberosa (2), displasia esquelética diastrófica (2), Síndrome de Pfeiffer (1), doença do Xarope do Bordo (1), Mucopolissacaridose tipo VI (1), Beckwith-Wiedemann (1), Cat-eye (1), Wolf-Hirschhorn (1), Emanuel (1), Deleção 18q (1), cromossomo marcador (1), embriopatia por Zika Vírus (1). Todos os casos foram encaminhados para reavaliação e seguimento ambulatorial. Quando o desfecho foi óbito durante a internação, necropsia foi realizada em 39 casos. Destes, 23 (74,4%) não tiveram amostra de sangue para extração de DNA coletada, apesar de solicitada.

Conclusão: A importância da avaliação de recém-nascidos com malformações congênitas no período neonatal por médicos geneticistas é ressaltada pela existência de doenças genéticas graves, com altos índices de mortalidade. Os dois berçários estudados são de alta complexidade e isso se reflete na alta prevalência de pacientes com múltiplas malformações e doenças genéticas mais raras. A disponibilidade de apenas cariótipo para investigação genética no SUS é insuficiente para a maioria dos casos avaliados. Há necessidade de introdução de técnicas mais atuais, como MLPA, *Array,* painéis e sequenciamento de nova geração para atingir definição etiológica e oferecer o aconselhamento genético adequado. A coleta de amostra de sangue para extração de DNA é de extrema importância,

principalmente em recém-nascidos graves que podem ter sua investigação diagnóstica concluída mesmo após o óbito.

Código #13244

Título: BOOK SYNDROME: FAMILIAL CASE REPORT OF A RARE ECTODERMAL DYSPLASIA WITH LEARNING DISORDERS

Autores: Thereza Taylanne Souza Loureiro Cavalcanti[1]; Rayana Elias Maia[1]; Carolina Paes Torres[2]; Jair Huber[1]; Ester da Silveira Ramos[1]

Instituição dos Autores: Thereza Taylanne Souza Loureiro Cavalcanti[1]; Rayana Elias Maia[1]; Carolina Paes Torres[2]; Jair Huber[1]; Ester da Silveira Ramos[1]

Agência de fomento: FAEPA

Objectives: To report a case of a familial case of increased sweating, premature greying of hair, oligodontia and facial features which are compatible to Book syndrome.

Methods: Clinical history assessment with odontological and dysmorphologic evaluation of the proband and relatives apart of charts reviews.

Results: An 8 years female patient was referred by an university dentistry service due to oligodontia and learning disorders with similar familial history. She was the second child of a young and non-consanguineous couple after an uneventful pregnancy. Although early developmental milestones was reported as normal, learning disorders were observed since the beginning of her studies. The parents report delayed teeth eruption, missing permanent teeth, cutaneous xerosis and hyperhidrosis in hands. At physical examination, it was observed a long face with sparse and down turned elbrows, thin superior lip, midface hypoplasia, prognatism, mildly prominent ears, thin and fragile nails and bilaterally increased distance between the first two toes. Hair looked healthy. Dental examination: agenesis of the upper and lower seconds premolars and, upper and lower first and second molars; upper conoid lateral incisors; class III malocclusion. Common audiometry found mild to moderate hearing loss with inconsistent responses, but Brainstem Evoked Response Audiometry resulted normal. Normal ophthalmologic and fonoaudiologic evaluation, with no velopharyngeal incompetence. Patient has stated psicopedagogic support with good learning outcomes. Patient's father had learning disorder which was solved and he has also the criteria for Book syndrome: partial anodontia with persistence of some deciduous dental elements, with abnormalities of number and shape of the teeth and early canycie. A father's brother has premature greying of hair and hyperidrosis, another has only oligodontia, his mother has premature greying of hair and oligodontia. This variability occurs also for her sibs and it has been inherited from her father. Other relatives are unknown.

Conclusion: Book syndrome is an autossomal dominant ectodermal dysplasia characterized by hypersidrosis, premature grey hair and premolar aplasia. Twenty five cases were reported from a four-generation Swedish family with these features was described by J. A. Böök, in 1950. This four-generation Brazilian family corroborates the idea of a variable expressivity with complete penetrance. The first report of an isolated case was published in 2001 with additional features as narrow palate, hypoplastic nails, eyebrow anomalies, unilateral simian crease, and poorly formed

dermatoglyphics. Some of these features were observed in the proband though no one of the previous cases has learning disorders reported. The diagnosis is established by clinical criteria since there is no genes related to this condition described. This report may help to identify the molecular basis of this pathology on the future.

Key-words: Ectodermal Dysplasia; Inheritance Patterns; Medical Genetics

Código #12986

Título: Características Clínicas e citogenética molecular dos pacientes com Sequência de Pierre Robin (SPR) atendidos no Hospital de Clínicas de Porto Alegre

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Instituição dos Autores: Hospital Escola da Universidade Federal de Pelotas / Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Objetivos: Realizar uma caracterização clínica dos pacientes com diagnóstico de SPR atendidos no Hospital de Clínicas de Porto Alegre (HCPA).

Metodologia: Estudo retrospectivo de casos com diagnóstico de SPR definido como micrognatia, glossoptose e disfunção respiratória com ou sem fenda palatina. Dados clínicos foram coletados com ênfase em dados perinatais, exame físico e exames complementares, incluindo cariótipo de array CGH. Análise descritiva foi realizada.

Resultados e discussão: Dentre os 80 pacientes incluídos, foram identificados 54 casos sindrômicos (67,5%). História familiar de fenda labial e/ou palatina ou de SPR foi relatada em 21,9%. Dentre os casos sindrômicos, 13% tinham diferentes alterações citogenéticas, citadas a seguir: trissomia do 18, síndrome com associação com SPR já estabelecida; deleção 18q22.1-q23 (associação desta região cromossômica com SPR sugerida por GOMEZ-OSPINA e BERNSTEIN, 2015); duplicação 7q11.23-q22 (micrognatia e FP foi descrita na literatura, porém sem menção de SPR); deleção 7q33-q36, apresentava fenda labiopalatina (FLP) bilateral, epilepsia e Tetralogia de Fallot. FLP e cardiopatias complexas estão associadas a deleções 7q, porém não há descrição SPR associada; deleção 2q31.1 em uma paciente com FP e assimetria facial (o envolvimento deste lócus com FP/FLP foi descrito por Jakobsen em 2006). Por fim, dois pacientes polimalformados foram diagnosticados com as seguintes alterações cromossômicas: 46,XY,der(4)t(4;14)(p14;q11) e 46,XY,der(4)t(1;4)(q41;q35); ambos tinham uma translocação de origem materna. Quanto as síndromes clinicamente reconhecíveis, a Síndrome de Stickler e de Treacher-Collins foram as mais prevalentes, com 5 pacientes cada uma (9,2%), seguidas pela Síndrome de Richieri-Costa-Pereira (5,5%), Síndrome de Melnick-Needles (3,7%) e Microssomia Craniofacial (3,7%). Foram identificados 21 casos (38,8%) de SPR com anomalias cardíacas associadas, sem diagnóstico genético específico, dentre os pacientes considerados sindrômicos. Foi observada uma alta taxa de necessidade de ventilação mecânica (46,3%) e de traqueostomia (32,5%). A necessidade de traqueostomia em PRS na literatura varia de 2 a 34%. Um total de 53 (66,3%) pacientes foram submetidos à distração osteogênica de mandíbula, tratamento cirúrgico com maior experiência no HCPA.

Conclusão: As características dos pacientes com SPR atendidos no HCPA foi semelhante à de estudos prévios em outros centros com uma tendência a maior gravidade clínica. Devido à alta prevalência de cardiopatia congênita na amostra sugerimos a inclusão do ecocardiograma como parte da avaliação de pacientes com SPR. Do mesmo modo a inclusão da avaliação oftalmológica (principalmente para identificação precoce de Síndrome de Stickler) e CGH array (devido porcentagem elevada de alterações citogenéticas) devem ser consideradas.

Código #13336

Title: CARDIOLOGIC FINDINGS IN 101 PATIENTS WITH WILLIAMS SYNDROME

Authors: Pedro Henrique Santana Castro[1], José Ricardo Magliocco Ceroni[1], Rachel Sayuri Honjo[1] , Erika Arai Furusawa[2], Gabriela Nunes Leal[3], Jaqueline Wagenführ[4], Evelin Aline Zanardo[5], Leslie Domenici Kulikowski[5], Débora Romeo Bertola[1], Chong Ae Kim[1]

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Objective: To identify and describe the cardiologic findings of 101 patients with Williams Syndrome (WS) confirmed by molecular studies.

Methods: Retrospective and observational study of the cardiologic findings in 101 patients with molecularly confirmed WS, evaluated from 2008 through 2016 diagnosed by echocardiography or electrocardiography.

Results: The total cohort consisted of 101 patients, 62.4% males and 37.6% females. A total of 77 (76.2%) WS children were found to have a congenital structural heart defect. Overall 44 (57.1%) of the 77 WS patients with heart anomalies had a single defect, while the remaining 33 (42.9%) had two or more concomitant heart defects. The most common abnormality was supravalvular aortic stenosis (48%), found in 37 patients, of whom 15 (40.5%) had another heart defect. Other defects included: Aortic stenosis (7.8%), pulmonary stenosis (26%), stenosis of the branch pulmonary arteries (14.3%), mitral valve prolapse (19.5%), mitral insufficiency (11.7%), aortic coarctation (7.8%), aortic insufficiency (3.9%), ventricular septal defect (3.9%), atrial septal defect (3.9%), bicuspid aortic valve (2.6%). Dilated aortic root, tricuspid insufficiency and hypertrophic *cardiomyopathy* were all found each in one patient (1.3%). Electrocardiographic (ECG) studies were performed in 80 patients (80%) of the cohort. A total of 28 patients (35%) had a completely normal ECG, while left ventricle overload, the most common ECG abnormality, was found in 5 patients (6.3%). Other findings included: abnormal ventricular depolarization (2.5%), right atrial overload (1.2%), conduction delay (1.25%) and ectopic atrial rhythm (1.2%). High blood pressure was diagnosed in 42 of 101 (41.6%) patients. Heart transplantation was carried out in a 19-year-old female patient who presented supravalvular aortic stenosis and refractory congestive heart failure. This patient had been previously submitted to aortic stenosis correction twice. Unfortunately, the patient died due to CMV infection on the 47th day after transplant.

Conclusions: A high incidence of potentially hazardous congenital heart diseases has been reported in patients with WS. There are few descriptions of heart transplantation procedures in patients with

genetic syndromes and, up to date, only one in a WS patient. Cardiovascular diseases are responsible for the greatest morbidity and mortality in WS, but are preventable and treatable with the appropriate care. It is recommended that all patients have periodic cardiology and nephrology follow-up, in order to prevent, manage, and treat possible complications and improve both quality of life and survival rates.

Código #13265

TITLE: Case Report: Recurrence of achondroplasia in half-sisters, daughters of normal height parents.

AUTHORS: Marcos José Burle de Aguiar; Leticia Lima Leão; Bruna Gláucia Farah; Laura de Mello Andrade;

AUTHORS' AFFILIATION: Hospital das Clinicas da Universidade Federal de Minas Gerais (UFMG).

OBJECTIVES: Propose a discussion about education and genetic counseling in cases of achondroplasia, through the report of a probable germline mosaicism case.

METHODS: We report a case attended in our hospital: Two half-sisters, daughters of parents of normal stature, with diagnosis of achondroplasia due to probable germline mosaicism.

RESULTS: Achondroplasia is the most common form of disproportionate short stature, leading to rhizomelic shortening of the limbs and with an estimated worldwide incidence of 1: 15,000 to 1: 30,000 live births. It has an autosomal dominant inheritance pattern with complete penetrance. Despite this, only 20% of achondroplasia cases are inherited from one parent. The recurrence of achondroplasia in children of normal parents is rare, and this may result from germline mosaicism, and not just because of spontaneous mutations. To date, we have found two reports of germline mosaicism as the cause of recurrence of achondroplasia in offspring with molecular confirmation. In the report where germline mosaicism was proven by the detection of the mutation in spermatozoa, the exact recurrence risk couldn't be established, since the exact percentage of mutated spermatozoa cannot be defined. According to the conducted studies, the estimated recurrence risk for achondroplasia, with unaffected parents, is 0.02%, much lower than expected for the other autosomal dominant conditions, which remains around 1 to 7%

CONCLUSIONS: Germline mosaicism in achondroplasia is a rare occurrence. The estimated recurrence risk for achondroplasia for normal height parents is much lower than expected for other autosomal dominant conditions. In such cases, it is necessary to emphasize proper education and genetic counseling to reassure and guide the parents.

Código #12648

Title: CAUDAL REGRESSION SYNDROME: REPORT OF A FETUS PRESENTING FINDINGS THAT OVERLAP WITH SIRENOMELIA AND VACTERL ASSOCIATION

Authors: Maiara Anschau Floriani, Stephan Philip Leonhardt Altmayer, Bruna Brasil Dal Pupo, Gabriel Ricardo Loesch Siebiger, Caroline Suemi Nunes Pereira, Rosilene da Silveira Betat, Jamile Dutra Correia, Ernani Bohrer da Rosa, Paulo Ricardo Gazzola Zen, Rafael Fabiano Machado Rosa.

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Objectives: Our aim was to describe the findings of a fetus with diagnosis of caudal regression syndrome presenting findings that overlap with sirenomelia and VACTERL association.

Methods: We performed the description of the case, along with a review of the literature.

Results: A 22-year-old woman was referred to a reference fetal medicine hospital as result of a diagnosis of gestational syphilis and evidence of severe oligohydramnios by an ultrasound (US) evaluation at 17 weeks. It was her first gestation; the husband was 21 years old, healthy and non-consanguineous. There was no history of malformations or genetic disorders in the family. A 22-week US revealed a cystic image at the lumbosacral region measuring 1.3 x 0.9 cm (suggestive of myelomeningocele), dextrocardia with pericardial effusion, left-sided aortic arch and undifferentiated genitalia. The stomach, kidneys and bladder were not visualized. Fetal karyotype was normal (46, XY). More recent US at 27 weeks confirmed the previous findings and was indicative of bilateral renal agenesis. Fetal development was in the 25th percentile for gestational age. Fetal magnetic resonance imaging (MRI) performed at 29 weeks confirmed the severe oligohydramnios and showed severe pulmonary hypoplasia, dextrocardia, pericardial effusion and bilateral renal agenesis. Genitalia could not be identified. The MRI findings were suggestive of myelomeningocele measuring 2 cm in its biggest axis associated with an elongated 3.5 cm x 0.8 cm cystic collection. The vertebral column was tortuous, though not properly visualized below the level of the midline lesion. Additional findings were suggestive of bilateral lower limb hypoplasia. The couple decided to terminate the pregnancy. The fetus was stillborn at 33 weeks of gestation, weighing 1,475 g. Postnatal evaluation revealed a flattened face (Potter's facies); flat nasal bridge; marked infraorbital rim; micrognathia; small, low-set and posteriorly-rotated ears with marked overlapping of the superior helixes; cloacal exstrophy; ambiguous genitalia; absence of the anus and deformities of lower limbs, including club foot. The previously suspected myelomeningocele was in fact a terminal myelocystocele. Radiographic evaluation revealed several axial skeleton abnormalities, including hemivertebrae, butterfly vertebrae, fused ribs, bifid ribs and total sacral agenesis.

Conclusion:

We believe that caudal regression syndrome, sirenomelia and VACTERL association could have a common etiology. Our case present findings of each condition, what add evidences that they may integrate the same spectrum.

Código #13450

Title: CONGENITAL ADRENAL HYPERPLASIA: NOT ALWAYS WHAT IT SEEMS TO BE

Authors: Ana Paula Kurz de Boer**;** Bibiana Mello de Oliveira**;** Felipe de Siqueira Toledo Koerich Kahl; Moacir Wajner; Julio Cesar Loguercio Leite.

Authors Institution: Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Objectives: To describe the diagnostic process of a male 6 year old patient with Xq21 deletion, multisystemic features and additional phenotype not yet described: Dandy-Walker malformation.

Methods: Case report and literature review.

Results: A 6 year old adopted male patient was referred to genetic evaluation due to a suspicion of congenital adrenal hyperplasia, muscular dystrophy, megacolon and Dandy-Walker malformation. He was born by cesarean delivery at 38 weeks, with Apgar score 6/7 and normal neonatal screening. At 60th day of life he was diagnosed with congenital adrenal hyperplasia, when gluco- and mineralocorticoids were initiated. Adoptive parents also told he was submitted to two normal liver biopsies due to increase of transaminases. He had growth retardation and severe developmental milestones delay. His mother and maternal uncles had learning disability. In his first genetic evaluation at 6 year old, weight and length were under 5th percentile, he had microcephalus, palpebral ptosis, downturned eyelid fissures, facial weakness, scoliosis, global hypotonia, hyporeflexia, calf pseudohypertrophy and poor speaking. MRI findings were suggestive of Dandy-Walker spectrum. He had normal karyotype, echocardiogram showed interatrial communication and creatine-kinase was high (534U/L). Considering multisystem involvement, including muscular dystrophy and possibility of a microdeletion syndrome, it was ordered Comparative Genomic Hybridization array (aCGH). The analysis showed a 9.2Mb deletion of region Xp21.3-p21.1 involving IL1RAPL1, NR0B1, GK and DMD, among other genes. This genotype has been previously related to boys with Duchenne muscular dystrophy associated with glycerol kinase deficiency, intellectual disability and congenital adrenal hypoplasia (and not adrenal hyperplasia, the previous diagnosis of the patient). Cases of heterozygous females with intellectual disability have been described. Additional evaluation was performed after aCGH, with novel creatine-kinase 6502 U/l, organic acids analysis with significant increase of glycerol, normal electrolytes, cortisol levels and glycemia. Androstenedione and ACTH were under normal values and renin level was high, under gluco- and mineralocorticoid treatment. After this evaluation, the patient was referred to a multidisciplinary team with endocrinology attention and to neuromuscular evaluation. The investigation of biological relatives will occur as adoptive relatives contact at risk family members.

Conclusion: The recognition of multisystem affections that did not suggest a common origin and subsequent etiological investigation through cytogenetic-molecular tools were fundamental in the conduct of this case. Through the molecular findings the endocrine diagnosis of the patient was

modified and this allowed an adequate treatment, even in case of acute life-threatening complications. We also note that the finding of Dandy Walker's malformation have not been previously described in patients with this genotype.

Código #13056

Title: DANDY-WALKER MALFORMATION IN A CHILD PRESENTING AN OCCIPITAL MENINGOCELE

Authors: Matheus Henrique Paschoaloni de Freitas, Fabiana Tabegna Pires, Jônio Vieira Ferreira**,** Gabriel Drumond Ferreira, Filipe Rodrigues Silveira, André Ricardo Jakimiu, Lucas Augusto Camillo de Souza, Luciano Vieira Targa, Paulo Ricardo Gazzola Zen, Rafael Fabiano Machado Rosa.

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Objectives: To describe a child presenting an occipital meningocele associated with Dandy-Walker malformation, discussing the possible association between both.

Methods: This is a descriptive study, based on a case report with literature review.

Results: The patient was a 26-year-old woman in her first pregnancy. She was referred to the service due to fetal ultrasound with description of cyst in the posterior cervical region. On the first second trimester examination, at 30 weeks of gestation, it was verified the presence of a skull defect with occipital meningocele measuring 5.1 cm x 4.3 cm x 3 cm and apparent cyst of posterior fossa measuring 1.9 cm X 1.2 cm. It had not been identified dilation of the posterior horns of the lateral ventricles. Fetal karyotype performed through amniocentesis revealed a normal female chromosome constitution (46,XX). Fetal magnetic resonance imaging (MRI) performed soon after showed an abnormality of the cerebellar vermis, with wide communication between the fourth ventricle and subarachnoid space, compatible with Dandy-Walker malformation. Furthermore, it was observed occipital meningocele measuring 5 cm x 4 cm, and moderate supratentorial hydrocephalus. Sonographic evaluation at 37 weeks of pregnancy was consistent with the findings of the fetal MRI. The child was born by cesarean section at 38 weeks of gestation, measuring 46 cm, with a head circumference of 35 cm and Apgar scores of 9 in the first and fifth minutes. The surgery of occipital meningocele correction was carried out at 6 days of life. At 2 months of age, it was placed a ventriculoperitoneal shunting.

Conclusion: Meningocele or, in this case, cephalocele is defined as a herniation of the meninges through a defect in the skull bone. In most cases, the lesion arises from the midline of the occiput, and less often in the parietal and frontal bones. Despite the small number of reports in the literature, it is known that occipital meningocele may be associated with Dandy-Walker malformation, as observed in our case. In addition, MRI was essential for the proper recognition of these abnormalities. Thus, these aspects should always be considered in the evaluation of fetuses with occipital meningocele.

Código #13236

Title: DELIVERY AND PERINATAL FINDINGS OF PATIENTS WITH CONGENITAL HEART DISEASE FROM SOUTHERN BRAZIL

Authors: Jamile Dutra Correia, Daniélle Bernandi Silveira, Ernani Bohrer da Rosa, Patrícia Trevisan, Céres Andréia Oliveira, Carolina Geitens Grapiglia, Maurício Rouvel Nunes, Marilu Fiegenbaum, Paulo Ricardo Gazzola Zen, Rafael Fabiano Machado Rosa.

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Objectives: Our aim was to verify the delivery and perinatal characteristics of patients with congenital heart disease (CHD) hospitalized in a reference cardiac and pediatric intensive care unit (ICU) from Southern Brazil.

Methods: Cross-sectional study with controls. The cases consisted of patients with CHD during their first hospitalization. Controls were composed of patients with no clinical evidence of CHD who were hospitalized soon after cases. The cases underwent high-resolution GTG-Banding karyotype and fluorescence in situ hybridization (FISH) for 22q11 microdeletion. We analyzed delivery and perinatal characteristics of patients and compared them with those from general population.

Results: Our sample was composed of 198 cases and 198 controls. No statistically significant differences were observed between weight, length, head circumference and Apgar scores at birth between cases and controls. However, patients with syndromic aspect and chromosomal abnormalities had more birth weight <10th percentile. None CHD was associated with abnormal weight, length and head circumference values at birth. In comparison to general population, individuals with CHD presented more often weight <2,500 g and Apgar scores ≤7.

Conclusion: There are few international and especially national studies assessing the delivery and perinatal characteristics of patients with CHD. These individuals more often have low birth weight than general population, especially in cases with associated chromosomal abnormalities and syndromic aspect. This also applies to Apgar scores, especially at first minute. These delivery and perinatal characteristics have been associated with higher rates of mortality and a worse prognosis, which may have important implications, especially in our country where seems to have a scarce prenatal diagnosis associated to a limited number of ICUs and reference centers that could make an appropriate cardiac assessment and treatment (including the surgical one).

Código #13257

DYSMORPHIC CHARACTERIZATION IN PATIENTS DIAGNOSED WITH AUTISM SPECTRUM DISORDER (ASD)

Authors: Juliana Birelli Kasteckas; Gabriela Dias Nunes; Rodrigo Ambrosio Fock; Marinilza Barbosa da Silva; Daniella Vieira Moura; Mirlene Cecília Soares Pinho Cernach

Institution of Authors: UNIMES – Universidade Metropolitana de Santos- Santos, SP, Brazil.

Objectives: This study intends to determine in three institutions in Santos: 1. the frequency of children with positive screening for ASD according to the Autism Checklist Behavior (ABC) scale; 2. The percentage of patients with dysmorphic characteristics; 3. The recurrent phenotypic characteristics in patients with ASD.

Methodology: Following the consent of the parents, the children accompanied by the APAE-Santos), Association of Parents, Friends and Educators of Autistics (APAEA-Santos), and at the School of Special Education July 30 (CEB - July 30) and previously screened for the diagnosis of ASD through the ABC scale, were photographed, evaluated by the Autism Dismorphology Measure (ADM) scale (Miles et. Al, 2008) and subjected to anthropometric exam. The measurements were classified using tables and graphs appropriate for age and sex. All the results, value obtained in the ABC scale and dysmorphic characteristics were coded and organized in spreadsheet for analysis.

Results: 118 patients were evaluated with aged between 3 and 17 years old, being 17 APAE, 68 APAEA and 33 CEB. 79.66% (94) were males and 20.33% (24) were females. The patients with a previous diagnosis of genetic syndrome and those with incomplete data were excluded. The final sample had 79 children, of whom 60 were positive screening by ABC (76%) for TEA and 19 (24%) with negative screening. Regarding the classification by the ADM, 48.2% of the patients with positive screening were considered dysmorphic, compared to 68.4% of the children with negative screening. The most frequent dysmorphic features among children with ASD are ocular hyperthelorism and ear anomalies.

Conclusion: 1. In the evaluated institutions, 76% of the children have positive screening for ASD.
2. When patients are evaluated according to dysmorphic characteristics, a greater number of patients with dysmorphic characteristics are concentrated among those with negative screening, although the difference is not significant.
3. The most recurrent dysmorphic characteristics among patients with positive and negative screening for ASD are ocular hyperthelorism and ear anomalies

Código #13258

Title: Evaluation of the central auditory system in children with Down syndrome: preliminary results.

Authors: Letícia Gregory; Rafael Fabiano Machado Rosa; Paulo Ricardo Gazzola Zen; Pricila Sleifer

Affiliations: Universidade Federal de Ciências da Saúde de Porto Alegre e Universidade Federal do Rio Grande do Sul

Objective: To describe and analyze the answers obtained through the central auditory evaluation in children with Down syndrome, verifying if there is association between audiological findings, gender, age and difference between ears.

Methods: A cross - sectional, prospective, contemporary and comparative study was carried out in which 9 children with Down syndrome were compared to the control group, composed of 9 children without genetic and hearing alterations, matched by sex and age. The evaluations were composed by tonal audiometry, vocal audiometry, acoustic immitance measures, long latency auditory evoked potential and cognitive potential.

Results: Increased latency of P1, N1, P2, N2 and P3 waves was observed in patients with Down syndrome when compared to the control group. There was no significant difference with respect to amplitude. Just as no relation was found between sex, age and difference between ears.

Conclusion: Children with Down syndrome present alterations in the long latency auditory evoked potential and cognitive potential, suggesting alteration of processing, discrimination and attention of sound stimuli. These changes do not vary by age or gender.

Código #13345

Title: GAPO syndrome associated with congenital bilateral glaucoma

Authors: Renata Barreto Tenório; Felipe Siqueira Kahl; Têmis Maria Félix
Authors' academic institution : Hospital de Clínicas de Porto Alegre.

Objectives: to report a case of GAPO syndrome associated with congenital glaucoma.

Methodology: observational; case report.

Results: L.V.L is a 2-year old afro-descendant female, third daughter of non-consanguineous parents and sister of 2 healthy girls. She was born at 36 weeks, after an uneventful pregnancy by cesarean section. The neonate presented respiratory distress and congenital pneumonia which responded to positive pressure ventilation and antibiotics. At birth dysmorphic features as cardiac systolic murmur and bilateral corneal clouding was noticed. At her 3rd day of life she was transferred to Hospital de Clínicas de Porto Alegre. The child presented height and weight persistently below 3rd centile; cephalic perimeter below 2 standard deviation; wide anterior fontanel; frontal bossing; full lips; depressed nasal bridge; umbilical hernia and bilateral corneal clouding. Ophthalmologic evaluation showed congenital glaucoma. At 8 months old she was submitted to surgery for glaucoma and progressive optic atrophy was diagnosed. She evolved with normal psychomotor development. Scalp hair was present at birth but was lost by age 1 and never regrew. At 1 year and 8 months old we observed no erupted teeth. Investigations including beta oxidation enzyme deficiency , body x-ray, abdominal and cerebral ultrasound, karyotype and echocardiogram were normal. A cranial radiograph showed impacted upper and lower teeth. Based on clinical findings of growth retardation, alopecia, pseudoanodontia and progressive optic atrophy the diagnosis of GAPO syndrome (OMIM 230740) was made.

Conclusion: GAPO is the acronymous for Growth retardation, Alopecia, Pseudoanodontia and Optic atrophy. It was first described in 1947; around 40 cases have been published describing subjects of various ethnic origins and less than 5 had congenital glaucoma. Most affected individuals had consanguineous parents and recurrence in siblings was common, which suggested autosomal recessive inheritance pattern. In 2013, Stranecky et al. identified homozygous pathogenic variants in gene *ANTXR1* of chromosome 2q13.3 in 4 individuals with GAPO syndrome; one year later, Bayram et al. identified 5 patients with mutations at the same gene. Antrax toxin receptor 1 (*ANTXR1*) contains 18 exons and encodes a protein involved in cell attachment and migration. There is strong evidence suggesting that ANTXR1 defects causes progressive extracellular matrix build-up, a possible explanation for GAPO syndrome pathophysiology. GAPO syndrome is a very rare disease that can be usually recognized at an early age due to striking features. Congenital glaucoma has been reported in 4 cases and the prevalence of congenital glaucoma in GAPO syndrome is likely around 10%.

Código #13368

Title: Genitopatellar Syndrome – Case Report

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Hospital of Ribeirão Preto Medical School - University of São Paulo

Goals: Describe a rare condition characterized by anogenital abnormalities, missing or underdeveloped kneecaps (patellae), renal anomalies, agenesis of the corpus callosum, joint contractures, and others features.

Methods: Clinical examination, karyotype, informed consent, patient folder review, and complementary exams.

Results: During the prenatal period, fetal US evidenced cerebral ventriculomegaly, cardiomegaly, renal pelvic dilatation, indefinite genitalia and pelvic presentation. Due to the several alterations, the hypothesis of trisomy 18 was given. Patient was born with 39 weeks, cesarean birth, with 50cm, 3485g and cephalic perimeter of 35.5cm, APGAR 4/9, showing severe hypotonia, and pediatrcic ICU it was taken requiring ventilatory support. A multidisciplinary clinical investigation and complementary examinations were performed. Physical examination showed coarse facies, bitemporal narrowing, broad nose, bulbous nasal tip, prominent cheeks, microretrognathia, imperforate anus, single transverse palmar crease, bilateral hip dysplasia with flexion deformities of knees and hips, arthrogryposis, ambiguous genitalia with bilateral cryptorchidism and hypoplasia of labioscrotal eminence. Additional tests showed: karyotype 46,XY[11], pulmonary hypoplasia, agenesis of patella, bilateral ureteropelvic dilatation, corpus callosum agenesis with colpocephaly, mild pulmonary artery stenosis and right ventricular hypertrophy, otoacoustic emissions (EOAT) absent in both ears. From the described findings, the patient received from the medical genetics team the clinical diagnosis of Genitopatellar Syndrome (**OMIM 606170)**. It is important to point out that the parents are non-consanguineous, the mother is 24 years old and the father is 52 years old. Currently at 8 months patient is tracheostomized and gastrostomized, showing a severe psychomotor retardation. He is in clinical follow-up with several specialties.

Conclusion: Genitopatellar syndrome is caused by mutations in the *KAT6B* gene. This gene codifies a type of enzyme called histone acetyltransferase. These enzymes modify histones. Little is known about the function of the histone acetyltransferase produced from the *KAT6B* gene. It appears to regulate genes that are important for early development, including development of the skeleton and nervous system. The Say-Barber-Biesecker-Young-Simpson syndrome (SBBYS) (OMIM 603736) variant of Ohdo syndrome is an allelic disorder with overlapping features. KAT6B-related disorders are inherited in an autosomal dominant manner. To date, most individuals with a KAT6B-related disorder have had a de novo pathogenic variant.

Area: Dysmorphology

Key-words: Genitopatellar Syndrome, Genital anomalies, Patellae, Corpus callosum, Renal anomalies

Support: HCFMRP-USP, FAEPA

Código #13199

Título: IMPORTÂNCIA DO SEQUENCIAMENTO DO EXOMA EM RESOLVER FENÓTIPOS COMPLEXOS: RELATO DE CASO

Autores: Renata M. Minillo1, Murilo C. Cervato1, Marcel Caraciolo2, Nair Hideko Muto1, João Renato R. Pinho1, Cristóvão Luis P. Mangueira1, João Bosco O. Filho2,Roberta Sitnik1

Instituição dos Autores:1. Departamento de Genética Molecular, Hospital Israelita Albert Einstein
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Objetivos: Ressaltar a importância da indicação do sequenciamento completo do exoma (SCE) para investigar casos com fenótipos mistos/complexos, geralmente não descritos na literatura.

Metodologia: Paciente do sexo masculino com 11 meses de idade apresentava doença renal policística, doença fibropoliscística hepatobiliar da infância, miocardiopatia concêntrica e imaturidade imunológica. Era primeiro filho de casal não-consaguíneo sem história familiar. Dada a complexidade do fenótipo clínico, indicou-se o SCE (captura com kit Agilent SureSelect All Exon V4 e sequenciamento em plataforma Illumina).

Resultados: o SCE identificou heterozigose composta no gene PKHD1, que está associado a doença renal policística autossômica recessiva (duas variantes provavelmente patogênicas, c.10637delT e c.3367G>A; mãe era portadora da primeira variante e o pai, portador da segunda) e heterozigose para variante provavelmente patogênica de novo no gene MYH7 (c.2063delT), que está associado a cardiomiopatias de herança autossômica dominante (também confirmada por Sanger, ausente nos genitores).

Conclusão: A utilidade do SCE na identificação de genes conhecidos e novos em famílias segregando com doenças mendelianas é bem estabelecida e, para pacientes que exibem fenótipos complexos, através do SCE (que identifica aproximadamente 4% a 7% desses casos1,2) é possível identificar variantes em genes conhecidos, já que o fenótipo pode ser separado nas suas partes constitutivas e variantes causais podem ser identificadas e explicar as características fenotípicas específicas. Isso, por sua vez, pode permitir o tratamento individualizado com impacto positivo no cuidado ao paciente e melhor compreensão holística da doença.

Código #13274

Title: **LEOPARD Syndrome: Case Report and Genotype - Phenotype Correlation.**

Authors: Luiza Virmond[1]; Eduardo Perrone[1]; Kelin Chen[1]; Manuella Galvão[1]; Ana Beatriz Alvarez Perez[1]; Vera de Freitas Ayres Meloni[1].

Author´s Institution: 1. Universidade Federal de São Paulo.

Purpose: To report a case of LEOPARD syndrome (LS) with a T468M mutation in the *PTPN11* gene, and to compare this case with previous published cases in order to establish a genotype-phenotype correlation.

Methods: Clinical and morphological evaluation of a patient with LS who was referred to our medical genetics clinic. For the review, we performed a search with the key words “LEOPARD” and “syndrome” on the PubMed database. We excluded publications without case reports and those which were not written in English or Portuguese. We subsequently reviewed the morphological and molecular findings of LS and divided the patients into two groups. Group 1 had a *PTPN11* gene T468M mutation (such as our patient) and Group 2 had other mutations.

Results: Our patient was a six year-old girl, the only child of non-consanguineous parents. Morphological examination revealed multiples lentigines (mainly affecting the face), cafe-au-lait spots (especially in the abdomen and left leg), and ocular hypertelorism. Echocardiogram revealed a non-obstructive asymmetric septal hypertrophy and the audiologic evaluation was normal. Sequencing of *PTPN11* gene showed a heterozygous pathogenic T468M variant (exon 13). We found 156 previously reported cases with LS. In our statistical analysis, we included our patient (N=157) (36.9% female, mean age of diagnosis: 16 years and median: 12 years). Lentigines were reported in 85.9% of the cases, hearing loss in 33.7%, hypertelorism in 66.8%, hypertrophic cardiomyopathy in 46.1%, abnormal ECG in 46.1%, pulmonic stenosis in 22.9%, intellectual disability in 19.1%, growth retardation in 57.3%, family history in 38.8% and cryptorchidism in 20.2% (males). Variants at *PTPN11* gene were present in 68.1% of 157 patients (107/157). The variant T468M was present in 38.6% (41/106) of the patients with *PTPN11* variant (Group 1). Group 2 presented with a significantly higher frequency of hearing loss compared to Group 1 (55.8%x11.8%;
p<0.001), hypertrophic cardiomyopathy (64.8%x43.2%; p=0.042), growth retardation (67.9%x35.1%; p=0.02) and intellectual disability (52.9%x15%; p=0,014). Familial cases showed a significantly higher frequency in Group 1 than in Group 2 (67.6%x43.8%; p=0.033). Comparing the clinical features frequency between the excluded group (without the molecular diagnosis) and all patients with *PTPN11* molecular diagnosis, we found that only hearing loss (p=0.2), hypertrophic cardiomyopathy (p=0.528) and familial history
(p=0.725) showed a similar distribution. Our patient showed lentigines and ocular hypertelorism but did not show hearing loss, pulmonic stenosis, ECG abnormalities or hypertrophic cardiomyopathy, corroborating with our review’s findings.

Conclusions: We reviewed the clinical and morphological findings of 157 LEOPARD syndrome patients. Some clinical features are more frequently found in LS cases with mutations other than the T468M variant. Our patient illustrates the variable expressivity of LEOPARD syndrome.

Código #14345

Título: Microduplication on exon 4 of *GRHL3* gene in nonsyndromic cleft lip/palate individuals

Autores: Jalsi Tacon Arruda; Betânia Severino da Silva Maranhão; Camila Cristina de Oliveira Alves; Nádia Aparecida Bergamo; Lucilene Arilho Ribeiro Bicudo

Instituição: Universidade Federal de Goiás, Instituto de Ciências Biológicas, Goiânia, GO, Brasil; Faculdade Araguaia, Goiânia, GO, Brasil; Universidade Estadual Paulista Júlio de Mesquita Filho, Instituto de Biociências de Botucatu, SP, Brasil.

Objetivos: The aim of this study was to analyzed individuals with nonsyndromic cleft lip with or without cleft palate (NSCL/P) from the Central Western and Northern Brazil, by Multiplex Ligation-dependent Probe Amplification (MLPA) in Interferon Regulatory Factor 6 (*IRF6*) and Grainyhead-like transcription factor 3 (*GRHL3*) genes.

Metodologia: We analyzed a set of 80 cases NSCL/P of patients of Associação de Combate as Deformidades Faciais. These individuals come from the states of Goiás and Pará – Brazil, where the institution operates. This group is composed by 44 male and 36 female, and of this, 45 are cleft lip and palate, 32 are cleft lip and 3 are cleft palate. A peripheral blood sample was collected from each individual participant and his or her families when available. Epidemiological and clinical data about the period of pregnancy and familial history were obtained. The extraction of genomic DNA was performed with FlexiGene Genomic Purification Kit (Qiagen). MLPA SALSA kit probemix P304-B1-IRF6 GRHL3 (Lot B1-0116), following the manufacturer's instructions (MRC-Holland).

Resultados: This study finds six individuals with a microduplication of a genomic region on exon 4 of *GRHL3* gene. All these six individuals presented with cleft lip and palate. DNA samples from parents of the three individuals who presented the microduplication were available for study, and did not show any variation. DNA samples of the parents from the other three individuals were not available for study. A new MLPA assay was performed for these six patients and the results were confirmed.

Conclusão: Previous studies have demonstrated mutations in both *IRF6* and *GRHL3* cause almost the same clefting phenotypes and causes the autosomal dominant Van der Woude syndrome, which is the most common syndromic form of cleft lip and palate. *GRHL3* may be associated with the risk of NSCL/P and recent studies by genome-wide association studies (GWAS) and sequencing approaches have indicated a missense variant (rs41268753) in *GRHL3* increases risk for NSCL/P. Although the primary focus of this study is to investigate specific genes involved in the occurrence of NSCL/P it is recognized environmental factors are also important. Population differences may affect the results of genetic association study in complex diseases. We observe this group trying to link them to ethnic and socio-economic factors in the region. However, miscegenation was shown to be very high, and very heterogeneous socioeconomic factors, which did not allow us at this time, detect a positive association between these factors and the NSCL/P.

Keywords: Cleft lip, cleft palate, polymorphism, embryology, malformation.
Financiamento: CAPES

Código #12838

Title: Multicentric Carpotarsal Osteolysis Syndrome: clinical and radiological findings in mother and daughter.

Kelin Chen[1], Maria de Fatima de Faria Soares[2], Vera Ayres Meloni[1].

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OBJECTIVE: report on two cases of Multicentric Carpotarsal Osteolysis Syndrome (MCTO) misdiagnosed as Juvenile Rheumatoid Arthritis (JRA).

METHODS: describe clinical and radiological findings of a family evaluated in the Center of Medical Genetics – UNIFESP and compare to the literature.

RESULTS: MCTO (OMIM #166300) is a rare skeletal disorder presenting in early childhood mimicking JRA, characterized by articular pain, progressive osteolysis, predominantly of the carpal and tarsal bones, minor facial anomalies, and oftentimes nephropathy and chronic renal failure, with autosomal dominant inheritance. Mutations in *MAFB* gene were described in 35 patients with MCTO (Zankl et al, 2012; Dworschak et al, 2013; Mehawej et al, 2013; Mumm et al, 2014; Sun et al, 2016). The 13-year-old female patient with skeletal deformities was referred for further investigation as the mother has JRA diagnosis and similar deformities. The patient is the first offspring of unrelated parents and has a nine-year-old brother and a seven-year-old maternal half-sister, both without similar symptoms. She presented unremarkable antenatal and postnatal histories, and normal growth and psychomotor development. At the age of 12, she developed pain in the upper limbs and feet, progressive joint restriction, and finger swelling. The first genetic evaluation at the age of 13, she presented mild facial dysmorphic features, flexion contracture of the right elbow, radial deviation of hands, swollen fingers and *pes cavus*. The proband's skeleton X-rays showed osteopenia, carpal and tarsal bones dissolution, proximal and distal metacarpal and metatarsal erosions. The mother's radiological findings indicated progressive bone resorption as the carpal and tarsal bones were completely destroyed. The clinical and radiographic features, and also the natural history of disease were suggestive of MCTO in both patients.

CONCLUSION: The clinical history and findings and the radiological abnormalities are consistent with MCTO. Likewise other cases of MCTO, this one was misdiagnosed and followed up as JRA. For a precise assessment, complementary tests for renal function monitoring were requested. The siblings

must be evaluated and monitored since they present 50% risk for the disease.

The correct and early diagnosis allows the appropriate follow-up and specific therapeutics for changing the natural history of the disease. Studies indicate that drugs targeting *Mafb* signaling such as anti-*RANKL* may perform better than bisphosphonates in the treatment of the bone disease of MCTO, thus presenting as an alternative therapeutics.

Código #13205
Title: MULTIPLE PTERYGIUM SYNDROME ESCOBAR TYPE: CASE REPORT IN RIO GRANDE DO NORTE

Authors: Kaio Luis de Souza Mendonça; Hugo Macedo de Moura; Maria Antonia Ferreira Gomes; Lana Lira Cantidio de Medeiros; Francielly Tertulino Cunha; Luciana Emerenciano Silveira; Inayara Jade Nunes Silva; Luiz Guilherme dos Santos Pinheiro; Zêmia Maria Câmara Costa Ferreira; João Ivanildo da Costa Ferreira Neri.

Authors' Institution: Centro de Reabilitação e Habilitação do Rio Grande do Norte (CERH-SESAP-RN) and Universidade Potiguar (UnP), Natal-RN, Brazil.

Case Summary:
Objectives: To report a case of a patient presenting Multiple Pterygium Syndrome, Escobar type.

Methods: Case report**.**

Case: B.G.C.S., 14 years old, female, was evaluated at the outpatient clinic for syndromic features. She is the youngest daughter of two from non-consanguineous parents and her case is the only one in her family. The family reported no intercurrences during pregnancy and a normal childbirth followed by 3 days in an incubator. She started physiotherapy at the age of two, walking at the age of three. No psycho-cognitive changes were observed in the patient, speaking fluently since the first year of life. At clinical examination, the patient presented weight and stature deficit, plagiocephaly, middle face hypoplasia, low-set and posteriorly rotated ears, slightly winged neck, pectus excavatum, camptodactyly of all fingers, valgus deformity and skin folds (pterygium) in armpits, elbows, pubes and knees. As part of the complementary investigation, radiographs of spine, basin, knees, hands and feet revealed several abnormalities and abdominal ultrasonography showed a normal result.

Discussion: Multiple Pterygium Syndrome is an extremely rare autosomal recessive disorder, with no accurate epidemiological data and no exact prevalence established by the literature. The postnatal diagnosis, as occurred with this patient, happens in the majority of cases and it can be clinical, from the evaluation of typical signs and symptoms of the disease, or molecular, which is also used for diagnostic confirmation. Regarding the treatment, the syndrome is not curable, so therapeutic approach seeks to manage signs and symptoms and requires a multi-professional involvement, such as from orthopaedist and physiotherapist, as in the case above.

Conclusion: The diagnosis of Multiple Pterygium Syndrome, Escobar type, was made. As the patient parents are no longer in a relationship, genetic counseling about recurrence was not performed, whereas guidance on requesting future counseling was also made for the patient or for any of her relatives at reproductive age. The multidisciplinary follow-up with orthopedic and physiotherapy activities were advised in order to minimize the impact of her abnormalities. Psychological and social service monitoring was suggested, so that problems as bullying can be prevented and overcome.

Código #13448

Title: NEU-LAXOVA SYNDROME (MIM 256520): CLINICAL REPORT

Authors: Thiago Rodrigues Cavole[1], Felipe Soares Castelliano Lucena de Castro[1], Saulo Bernardo Lança[1], Eduardo Perrone[1], Ana Beatriz Alvarez Perez[1], Marcia Marcelino de Souza Ishigai[1], Mirlene Cecilia Soares Pinho Cernach[1]

Authors Institution: 1. Universidade Federal de São Paulo (UNIFESP)

Objectives: Report a case of a clinical genetics and pathological evaluation of a stillbirth with Neu-Laxova Syndrome.

Methods: The patient was evaluated by clinical genetics and pathology shortly after death. Our findings have been compared to the ones found in the literature.

Results: We report a stillborn with 36 gestational weeks, first son of a consanguineous, referred to necropsy for clinical investigation. The stillborn had the previous diagnosis of Pena-Shokeir syndrome by fetal ultrasound analysis, wich after the medical genetics evaluation has been excluded and the NLS has been brought to discussion induced by the classical gestalt phenotype. The ultrasound revealed arthrogryposis, subcutaneous edema, thoracic hypoplasia, choroid plexus cysts and intrauterine growth restriction. Based on these points, it's been suggested the diagnosis of Pena-Shokeir syndrome. At 36 gestational weeks, the stillborn was referred to the autopsy, on the exam fetal weight was below the 10th percentile, with a cephalic perimeter of 20 cm (less than 2 Standard Deviations for gestational age). Fetal malformations were featured by skin disorders just like transparent edematous skin with ichthyosis, predominantly, in face associated with craniofacial deformities characterized by microcephaly, sloping forehead, hipertelorism, proptotic eyes with absent lids, flattened nose, thick everted lips with gengival hyperplasia. Brain tissue presented with lissencephaly, corpus callosum agenesis, assimetric enlargement of lateral ventricules and choroid plexus hematoma. Thymus and liver tissues samples have been taken and DNA has been extracted from them to perform Exome sequencing aiming to find the molecular cause of NLS in this stillborn, in present we are waiting for the results.

Conclusion: NLS – #256520 - is a lethal genetic multiple congenital anomaly syndrome of unknown prevalence more commonly seen among inbred populations characterized by prenatal growth deficiency with microcephaly, central nervous system malformations (lissencephaly, corpus callosum agenesis and hipoplastic cerebellum and pons), limb defects (short limbs, syndactyly with puffiness of hands and feet with contractures and pterygia); thin transparent edematous skin with ichthyosis and distinctive facial features (sloping forehead, hypertelorism, proptotic eyes with absent lids or ectropion, flattened nose, thick everted lips, micrognathia, large ears and short neck. It has been recently shown that NLS is caused by the deficiency of serine metabolism representing the severe end of the serine biosynthesis defects re sulting from the deficiency of any of the 3 enzymes involved in serine biosynthesis, namely PGDH (*PHGDH* gene), PSAT (*PSAT1* gene) and PSP (*PSAT*

gene). Up to date, around 60 cases of NLS have been reported. We reported a case of Neu-Laxova syndrome with clinical diagnosis based on clinical genetics and pathological evaluation presenting the classical phenotype syndrome.

Código #13281
Título: Oculocerebrocutaneous Syndrome: Report of a suspicious case in a Male Child.

Autores: Lucas Cadete Caldeira Costa, Dione Fernandes Tavares, Joanna Goes Castro Meira.

Instituição dos Autores: Escola Bahiana de Medicina e Saúde Pública, Complexo Hospitalar Professor Edgar Santos - Universidade Federal Da Bahia.

Objetivos: Oculocerebrocutaneous Syndrome (OCCS, MIM164180) is a rare congenital disorder characterized by eye, brain and skin defects. The eye defects consist in cysts with micropthalmia/anophthalmia, while the skin's includes appendages and focal hypoplasia/aplasia. Brain anomalies are ventricular enlargement and agenesis/dysgenesis of corpus callosum, which may lead to intellectual deficiency, motor skills delay and seizures. OCCS affects more males than females, however it's prevalence is still unknown due to few number (35) of reported cases in medical literature. OCCS etiology are still unknown but some studies suggests that it may be due to an autosomal dominant lethal mutation and survival is related to mosaicism. Report a case of suspicious diagnosis of OCCS.

Metodologia: Case Report and review of literature.

Resultados: Male, 3 years, born by normal delivery, birth weight 2775g, measuring 47cm, with a cephalic perimeter of 33cm and APGAR 9/10. There was no prenatal complications or exposure to teratogenics. He is a son of a non-consanguineous couple with no similar cases in the family. At birth it was detected an appendiculiform verrucous lesion on the right occipital region; ulcerated lesions with cicatricial aspect located on the frontal region, right nostril and upper lip; preauricular appendix. Refered to the geneticist, the physical exam evidenced scalp aplastic and atrophic lesions ; streaky hypochromic skin lesions on right hemiface with verrucous appearance; unilateral microphthalmia, nystagmus, strabismus, supernumerary hypoplastic nipples, flat thumbs and distal narrowing of fingers. The patient evolved with no motor skills delay but he had a light delay on language skills. The complementary exams detected microphthalmia on right eye, persistence of myelin fibers around the optic disc.Karyotype was normal. Brain RMI showed discreet right ventricular enlargement, an image suggestive of optic nerve thickening at right, dysgenesis of corpus callosum and focal superficial lesion at soft parts of the right occipital region. Due to clinical findings, the suspicion of syndrome OCCS was suggested. The diferencial diagnosis was microphthalmia with linear skin defects(MIM309801) due to the presence of linear skin defects and hypoplastic area around the face associated to microphthalmia.

Conclusão: OCCS must be considered as a possible diagnosis in patients with microphtalmia, agenesis of corpus callosum and cutaneous lesions. Besides the OCCS etiology is still unknown, it is very important to recognize it to better define the prognosis of the patients. Due to the few numbers of reported cases in literature it is also necessary to recognize and describe new cases of the syndrome, to allow the development of a more systematic clinical description for greater recognition among the numerous differential diagnoses. In this way, it will be possible to carry out adequate genetic counseling for the families.

Código #13275
Título: Oculocerebrocutaneous Syndrome: Report of a suspicious case in a Male Child.

Autor: Lucas Cadete Caldeira Costa, Dione Fernandes Tavares, Joanna Goes Castro Meira.

Instituição dos Autores: Escola Bahiana de Medicina e Saúde Pública, Complexo Hospitalar Professor Edgar Santos - Universidade Federal Da Bahia.

Introdução: Oculocerebrocutaneous Syndrome (OCCS, MIM164180) is a rare congenital disorder characterized by eye, brain and skin defects. The eye defects consist in cysts with micropthalmia/anophthalmia, while the skin's includes appendages and focal hypoplasia/aplasia. Brain anomalies are ventricular enlargement and agenesis/dysgenesis of corpus callosum, which may lead to intellectual deficiency, motor skills delay and seizures. OCCS affects more males than females, however it's prevalence is still unknown due to few number (35) of reported cases in medical literature. OCCS etiology are still unknown but some studies suggests that it may be due to an autosomal dominant lethal mutation and survival is related to mosaicism.

Objetivos: Report a case of suspicious diagnosis of OCCS.

Metodologia: Case Report and review of literature.

Resultados: Male, 3 years, born by normal delivery, birth weight 2775g, measuring 47cm, with a cephalic perimeter of 33cm and APGAR 9/10. There was no prenatal complications or exposure to teratogenics. He is a son of a non-consanguineous couple with no similar cases in the family. At birth it was detected an appendiculiform verrucous lesion on the right occipital region; ulcerated lesions with cicatricial aspect located on the frontal region, right nostril and upper lip; preauricular appendix. Refered to the geneticist, the physical exam evidenced scalp aplastic and atrophic lesions ; streaky hypochromic skin lesions on right hemiface with verrucous appearance; unilateral microphthalmia, nystagmus, strabismus, supernumerary hypoplastic nipples, flat thumbs and distal narrowing of fingers. The patient evolved with no motor skills delay but he had a light delay on language skills. The complementary exams detected microphthalmia on right eye, persistence of myelin fibers around the optic disc.Karyotype was normal. Brain RMI showed discreet right ventricular enlargement, an image suggestive of optic nerve thickening at right, dysgenesis of corpus callosum and focal superficial lesion at soft parts of the right occipital region. Due to clinical findings, the suspicion of syndrome OCCS was suggested. The diferencial diagnosis was microphthalmia with linear skin defects(MIM309801) due to the presence of linear skin defects and hypoplastic area around the face associated to microphthalmia.

Conclusão: OCCS must be considered as a possible diagnosis in patients with microphtalmia, agenesis of corpus callosum and cutaneous lesions. Besides the OCCS etiology is still unknown, it is very important to recognize it to better define the prognosis of the patients. Due to the few numbers of reported cases in literature it is also necessary to recognize and describe new cases of the syndrome, to allow the development of a more systematic clinical description for greater recognition among the numerous differential diagnoses. In this way, it will be possible to carry out adequate genetic counseling for the families.

Código #12650

Title: POSTAXIAL POLYDACTYLY AND URINARY TRACT ABNORMALITY IN A PATIENT WITH PFEIFFER SYNDROME

Authors: Rafael Fabiano Machado Rosa, Juliana Rosa Chinelato, Vanessa Petersen, Rodrigo Watanabe, André Campos da Cunha**,** Maria Rita Passos-Bueno, Katia Maria da Rocha, Rosilene da Silveira Betat, Ernani Bohrer da Rosa, Paulo Ricardo Gazzola Zen.

Authors institutions: Programa de Pós-Graduação em Patologia, Disciplina de Genética Clínica e Curso de Medicina, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Brasil; Medicina Fetal, Hospital Materno Infantil Presidente Vargas (HMIPV), Brasil, e Centro de Estudos do Genoma Humano, Brasil.

Objectives: Our aim was to report a patient with Pfeiffer syndrome presenting unusual findings.

Methods: It was made the description of the fetus/child together with a review of the literature.

Results: The pregnant woman initially came to the assessment at 25 weeks gestation. She had 20 years and was in her third pregnancy. There was no history in the family of individuals with genetic diseases. Two-dimensional ultrasound showed deformity of the skull with a prominent forehead and mild pyelocalyceal dilation at left. The morphological study conducted soon after, using two and tridimensional ultrasound, also identified decreased bitemporal diameter, and ocular hypertelorism, low nasal root and sharp decline in frontonasal angle. The fetus evolved with dilatation of renal pelvis (especially at the left), left ureter and bladder. Fetal magnetic resonance imaging showed findings similar to those of ultrasound. The child was delivered by caesarian section at 39 weeks gestation, weighing 3,515 g, measuring 49 cm, with head circumference of 37 cm and Apgar scores of 9 both in the first as in the fifth minute. It was observed at physical examination similar findings to the prenatal plus low-set ears, broad and deflected laterally thumbs, bilateral postaxial polydactyly, syndactyly between the third and fourth fingers, and broad hallux. Radiographies and brain CT scan confirmed the diagnosis of craniosynostosis (of coronal and sagittal sutures). Abdominal ultrasound and cystourethrography showed vesicoureteral reflux at left and hydronephrosis at right. Karyotype through GTG-Banding was normal. The diagnosis of Pfeiffer syndrome was confirmed through molecular analysis.

Conclusion: Pfeiffer syndrome is a rare autosomal dominant condition characterized by craniosynostosis and limb abnormalities. It is clinically divided into three subtypes, and, due mainly to lower severity and the absence of cloverleaf skull and ocular proptosis, our case falls within the subtype I. The postaxial polydactyly of the hands and the urinary tract abnormalities are considered unusual findings.

Código #13260

Title: Preliminary results on introduction of a Congenital Anomalies Surveillance Program in a University Hospital in South Brazil – ECLAMC-PUCRS.

Authors: Georgea Malfatti[1], Fernanda Thays Konat Bruzzo[1], Júlia Raquel Figueiró Coelho[1], Giulia Soska Baldissera[1], Maria Elisa Peinado Miller[1], Isadora Chiaradia Mattiello[1], Luísa Nakashima Pereira[1], Karine Inês Scheidt[1], Mariana Horn Scherer[1], Maria Teresa Vieira Sanseverino[1;2]

Instituição dos Autores: [1]Escola de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS); [2]Serviço de Genética Médica do Hospital de Clinicas de Porto Alegre (SGM-HCPA).

Objectives: This paper aims to present the initial results of a surveillance of congenital anomalies program implementation in the São Lucas da PUCRS Hospital (HSL), which is linked to the Latin American Collaborative Study of Congenital Malformations (ECLAMC). ECLAMC is a program of clinical and epidemiological surveillance of congenital anomalies which has registered hospital births in Latin American countries since 1967, and it is internationally recognized. The program monitors trends in the prevalence of different types of congenital anomalies and detects outbreaks of malformations, besides providing epidemiological data to identify risk factors and potential preventive measures, under case-control methodology. The operation of ECLAMC program in São Lucas da PUCRS Hospital (HSL) has begun in August 2016, enabling the creation of an excellent and regularly actualized database. Besides data collection, ECLAMC-PUCRS gives to the medical students the opportunity of learning about the importance of congenital defects.

Methodology: Review of ECLAMC-PUCRS records during the period of August 2016 to January 2017.

Results: A total of 1389 births were registered at HSL-PUCRS in the analyzed period, an average of 231,5 births/month. The sex ratio was of 49,676% (n=690) for males and of 50,324% (n=699) for females. There were 14 perinatal deaths, an average of 2,3 deaths/month. Among the births during this period, sixty newborns (n=60; 4,32%) presented congenital defects, an average of 10 malformed babies/month. Among those, forty six presented isolated defects and ten (n=10; 16,66%) presented an association of more than one congenital anomaly. There were three cases of trisomy (n=3; 5%) and one case of holoprosencephaly sequence. Among the main malformations registered, the more frequent were dermatological abnormalities (n=13), ear anomalies (n=16), polydactyly (n=8) and congenital clubfoot (n=4).

Conclusion: The etiology of most congenital defects results from a complex interaction between genetics and environmental factors, but in a significant number of cases remains unknown. So the main objective and strategy of ECLAMC is “prevention by research”. Additionally, the implementation of this program in a School Hospital becomes an important didactic tool to introduce concepts on dysmorphology and congenital defects for medical students.

Código #13231

Title: PRENATAL AND POSTNATAL FINDINGS OF A CHILD WITH HYDROLETHALUS SYNDROME

Authors: Luiza Emy Dorfman, Camilla Machado do Valle Pereira**,** Marina Cornelli Girotto, Pedro Menna Barreto, Jorge Alberto Bianchi Telles, Rosilene da Silveira Betat, Jamile Dutra Correia, Robert Pogue, Paulo Ricardo Gazzola Zen, Rafael Fabiano Machado Rosa.

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Objectives: To report a fetus with findings consistent with Hydrolethalus syndrome, which were confirmed in the postnatal period.

Methods: It was made the description of the fetus/child together with a review of the literature.

Results: The child was the first daughter of young, healthy and nonconsanguineous parents. Ultrasound evaluation, at second trimester, identified Dandy-Walker malformation, agenesis of the corpus callosum, microphthalmia, reduced thoracic diameter and length of limbs, cystic retrovesical lesion and polyhydramnios. Fetal echocardiography was normal. After confirmation of these findings through fetal magnetic resonance imaging (MRI), Hydrolethalus syndrome was suspected. The child was born by cesarean section at 35 weeks gestation, weighing 2,649 g, measuring 46 cm, with head circumference of 33 cm and Apgar score at first minute of 3 and 5 at fifth minute. She needed mechanical ventilation. Physical examination identified a median cleft lip and palate, micrognathia, hypoplastic and malformed tongue, dysplastic and low-set ears, short neck with redundant skin, narrow chest, postaxial polydactyly of hands, contracture of wrists and fingers, labia majora hypoplasia, anterior placed anus and broad/bifid hallux. The evaluation through GTG-Banding karyotype was normal (46,XX). Brain ultrasound confirmed the prenatal findings and identified dilation of cerebral ventricles. Abdominal/pelvic ultrasound showed pielocalicinal dilatation and didelphic uterus with hydrometrocolpos. Radiographies of whole body showed narrow thorax with short ribs, underdeveloped vertebrae and shortening of the humeri. The child died of acute respiratory failure at 25 days of life.

Conclusion: The clinical findings presented by the patient were consistent with the diagnosis of Hydrolethalus syndrome, a rare and lethal autosomal recessive genetic disease. We did not find cases in Brazilian literature, and most were reported in Finland, where the incidence is 1:20,000 births. Our findings also stand out the importance of the multidisciplinary team in the evaluation of the mother during the prenatal period. This, by itself, was able to provide important information for proper genetic counseling and obstetric, postpartum and pediatric care of the patient and her family.

Código #13240

Título: PROFILE OF A SAMPLE OF CHILDREN AND ADOLESCENTS WITH DOWN SYNDROME IN THE CITY OF SANTOS (SP): CLINICAL CONDITIONS, ACCESS TO HEALTH SERVICES AND FAMILY IMPACT.

Autores: Gabriela Dias Nunes; Juliana Birelli Kasteckas; Rodrigo Fock e Mirlene Cecília Soares Pinho Cernach

Instituição dos Autores: Universidade Metropolitana de Santos, Santos, SP, Brazil

Objetivos: To characterize the profile of children and adolescents with Down Syndrome (SD) at APAE-Santos and 30 de Julho Scholl regarding the quality of clinical follow-up, besides characterizing the sociodemographic profile of their families and the impact of the child with DS on the family relationship.

Metodologia: Twenty-two families of 22 children and adolescents diagnosed with DS were accompanied at APAE-Santos and 30 de Julho School. They were interviewed with specific records according to the age of the individual, elaborated by the rules from the National Guidelines for Attention to Child with DS. Questions on sociodemographic evaluation and family impact were added to the forms. The data were complemented in research of the patients' charts, coded and tabulated in Excel spreadsheet (Microsoft Corporation, United States).

Resultados: Of the 22 children evaluated, 15 were male and 7 females. Regarding age, it ranged from 10 to 227 months, with an average of 102.7 months and an average of 56.5 months. Of the 22 patients analyzed, 16 patients performed a karyotype and none of them went through genetic counseling (GA). Several families showed interest in AG and were afraid of having another child because they did not understand the mechanism of SD in their child. Regarding clinical follow-up, only 7 (31.82%) individuals presented complete follow-up, 11 (50%) had partial follow-up and 4 (18.18%) had no specific follow-up. Those with incomplete follow-up more frequently performed thyroid function research. The average age of the individuals with incomplete follow-up was higher than those with partial or complete follow-up, demonstrating an improvement of assistance in the last years. As for the family structure, 15 (68.18%) individuals live with mother and father, 5 (22.72%) with the mother, 1 (4.54%) with grandparents and 1 (4.54%) did not respond. The average family income is 4274.28 reais (R$) with a variation of R$880.00 to R$10.550,00. Eleven families who receive between 2 and 3 minimum wages (SM), spent at least 1 SM with the child's health, including health insurance and medications.

Conclusão: The quality of clinical follow-up is poor. The greatest impact of the child with SD in the family is the financial impact. Some families gave up continuing their offspring due to the absence of GA.

Código #13190

Title: PTEN pathogenic variant in a patient with Autism Spectrum disorder (ASD) and macrocephaly: case report.

Authors: Eduardo Perrone[1]; Rodrigo Ambrosio Fock[1]; Thais Arbocese Zanolla[1]; Ana Beatriz Alvarez Perez[1]; Viviane Nakano[2,3]; Ariane Falconi[2]; Maria Fernanda Milanezi[2]; Décio Brunoni[4].

Authors Institutions: 1.Universidade Federal de São Paulo; 2.Departamento de Patologia Molecular do Laboratório Salomão Zoppi; 3.Universidade de São Paulo; 4.Universidade Presbiteriana Mackenzie

Purpose: To report a PTEN pathogenic variant gene in a patient with autism spectrum disorder (ASD) and macrocephaly, reinforcing the importance of investigating PTEN variants in patients with this phenotype.

Methods: Clinical, morphological and molecular evaluation of ASD patient, following ACMG (American College of Medical Genetics and Genomics) standards and guidelines.

Results: The patient was referred due to ASD. The patient was a 3 year-old male with macrocephaly (OCF = 58.5 cm, above 97th percentile), who previously underwent the following testing: karyotype, Fragile X molecular DNA and SNP-array research (all results were normal). Following ACMG guidelines, the PTEN gene was sequenced using next generation sequence technology. A heterozygous, probably pathogenic variant (c.71A>G; p.D24G) was detected, which was previously described in relationship to PTEN hamartoma tumor syndrome. This variant, however, has not yet been described with ASD and macrocephaly. This finding reinforces previous clinical reports which show that the same variant, segregating in the same family, can exhibit different phenotypes (ASD and macrocephaly, Cowden Syndrome, Bannayan – Riley –Ruvalcaba syndrome). Defining the etiology of our patient allowed proper clinical management, as there is an increased risk of certain neoplasias (thyroid neoplasias) in these patients.

Conclusions: PTEN sequencing can be an important tool in elucidating the etiology of patients with ASD and macrocephaly.

Title: Pulmonary function in Osteogenesis Imperfecta

Authors: Bruna de Souza Pinheiro, Simone Chaves Fagondes, Têmis Maria Félix

Institution: Universidade Federal do Rio Grande do Sul (UFRGS); Serviço de Genética Médica (SGM) and Serviço de Pneumologia do Hospital de Clínicas de Porto Alegre (HCPA), Brazil.

Objectives: To describe the respiratory pattern of patients with Osteogenesis Imperfecta at a Reference Center for the treatment of the disease in Southern Brazil.

Methods: Transversal study was conducted. The inclusion criteria were diagnosis of OI and age 5 years old or older. Clinical characteristics and pulmonary function as forced vital capacity (FVC), forced expiratory volume in one second (FEV1), maximum midexpiratory flow (MMEF) were measured by spirometry. Respiratory muscle strength (maximal inspiratory pressure [MIP] and maximal expiratory pressure [MEP]) were also evaluated by manovacuometry.

Results: We evaluated 36 patients (61.1% female), median age 13.9 years (25-75 percentiles 9.5-22.9 years). Most cases presented OI type I (50%), followed by type IV (30.6%) and type III (19.4%). 72.2% patients were able to walk independently, 19.4 % were restricted to wheelchair, 5.6% were able to walk short distances with or without assistance and 2.8% were able to walk at home with or without assistance. Of the 36 patients evaluated, 29 performed spirometry. FVC: 2.27 ± 1.01L (0.78 – 4.19); FEV1: 2.02 ± 0.95L (0.0 – 3.71) and MMEF: 2.73 ± 1.2 (0.66 – 5.37). There was no significant association between OI type and FVC, FEV1 and MMEF. Only one adult patient had a significant bronchodilator response. Seventeen patients between 5 and 18 years presented MIP 103.0cmH_2O (25-75 percentiles 70 – 150) and MEP 96.0cmH_2O (25-75 percentiles 81 – 122) and 9 patients over 18 years of age showed MIP 99.0cmH_2O (25-75 percentiles 76.5 – 151.0) and MEP 103.0cmH_20 (25-75 percentiles 78.0 – 158.0).

Conclusion: The preliminary results reported here were not statistically significant regarding OI severity, probably due to a small sample size. We reinforce the importance of respiratory evaluation in OI patients to trace strategies that help management throughout life.
This study is supported by FIPE / HCPA.

Código #13356

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Authors: Bruna de Souza Pinheiro, Simone Chaves Fagondes, Têmis Maria Félix

Institution: Universidade Federal do Rio Grande do Sul (UFRGS); Serviço de Genética Médica (SGM) and Serviço de Pneumologia do Hospital de Clínicas de Porto Alegre (HCPA), Brazil.

Objectives: To describe the respiratory pattern of patients with Osteogenesis Imperfecta at a Reference Center for the treatment of the disease in Southern Brazil.

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Results: We evaluated 36 patients (61.1% female), median age 13.9 years (25-75 percentiles 9.5-22.9 years). Most cases presented OI type I (50%), followed by type IV (30.6%) and type III (19.4%). 72.2% patients were able to walk independently, 19.4 % were restricted to wheelchair, 5.6% were able to walk short distances with or without assistance and 2.8% were able to walk at home with or without assistance. Of the 36 patients evaluated, 29 performed spirometry. FVC: 2.27 ± 1.01L (0.78 – 4.19); FEV1: 2.02 ± 0.95L (0.0 – 3.71) and MMEF: 2.73 ± 1.2 (0.66 – 5.37). There was no significant association between OI type and FVC, FEV1 and MMEF. Only one adult patient had a significant bronchodilator response. Seventeen patients between 5 and 18 years presented MIP 103.0cmH_2O (25-75 percentiles 70 – 150) and MEP 96.0cmH_2O (25-75 percentiles 81 – 122) and 9 patients over 18 years of age showed MIP 99.0cmH_2O (25-75 percentiles 76.5 – 151.0) and MEP 103.0cmH_20 (25-75 percentiles 78.0 – 158.0).

Conclusion: The preliminary results reported here were not statistically significant regarding OI severity, probably due to a small sample size. We reinforce the importance of respiratory evaluation in OI patients to trace strategies that help management throughout life.
This study is supported by FIPE / HCPA.

Código #12794

Title: Revisiting prune belly sequence – new insights about an old phenotype

Authors: Carolina Araujo Moreno[1], Nara Sobreira[2], Denise Pontes Cavalcanti[1]

Affiliation: [1]Perinatal Genetic Program, Department of Medical Genetics, State University of Campinas, Campinas, Brazil; [2]McKusick-Nathans Institute of Genetic Medicine, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, USA.

Objectives: The prune-belly sequence (PBS) is characterized by a typical appearance of the abdominal wall (loosed and wrinkled) due to abdominal musculature hypoplasia, associated with urinary tract anomalies and cryptorchidism in males. In general, it results from a lower urinary obstruction caused by mechanical or functional mechanism. Most cases of PBS are sporadic, however, monogenic disorder or chromosomal anomaly can be associated with. The purpose of this investigation was to evaluate the genetic-clinic diversity of PBS in a series of 24 infants investigated in the local Perinatal Genetic Program (PGP) over the last 23 years.

Subjects and Methods: Clinical and molecular data of patients with PBS were rescued from the PGP database archives, including medical records, clinical photos, and X-rays. The molecular investigation was performed in some cases according the phenotype and included the Sanger sequencing of *ACTG2*, *ACTA2*, and *CHRM3*, and the whole exome sequencing (WES).

Results: We classified the 24 infants with PBS as I) isolated (14), and II) multiple congenital anomalies (MCA)/syndromic (10). Among the group II infants, a clinical or etiologic diagnosis was established in six children: del(9q) [1]; urorectal septum malformation sequence [1], diabetic embryopathy [1] and megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) [3]. The pathogenic mechanism related to the PBS could be defined in 87.5% of the infants. It was mechanical in majority of children (75%), and functional in three infants with MMIHS (12.5%). Recurrence in sibs and parental consanguinity were observed in one family with MMIHS. The male gender was predominantly affected (83.3%), and ambiguous genitalia was observed in three cases. The only female had PBS due to a functional mechanism. The mortality rate was 58.3%. Associated extra-urinary anomalies in 16 individuals were the following: skeletal (8), gastrointestinal (7), genital (4), heart (4), functional - hypomotility dysfunction (3), central nervous system (2), spleen (2) and ocular (1). Molecular investigation was performed in six individuals. Sanger sequencing of the *CHRM3* was performed in four individuals with isolated PBS. *ACTG2* and *ACTA2* sequencing was performed in two individuals with MMIHS. One infant with MMIHS was studied by WES. A heterozygous variant c.532C>T (de novo) in *ACTG2* was identified in one patient with MMIHS and a candidate novel gene (autosomal recessive) related to MMIHS was identified in one patient (final analysis in a process). None pathogenic variant was identified in *CHRM3*, neither in *ACTA2*.

Conclusions: The results reinforce the genetic heterogeneity related to PBS and emphasize the importance of phenotypic characterization to determine the etiology. Since the occurrence of PBS in

females is rare, the possibility of non-obstructive mechanism should be considered in this situation.

Although *CHRM3* is related to PB, it seems to be uncommonly altered.

Grant sponsors: NHGRI (1U54HG006542); CNPq (590148/2011-7); FAEPEX (0348/16).

EDUCAÇÃO GENÉTICA

Código #13373

Título: Alelos de baixa atividade da enzima CYP2C9:um estudo da população Ribeirão Pretana

Autores:
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Fernanda Viana Fígaro[1]
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Instituição dos autores: [1]Escola de Enfermagem de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto – SP, Brasil.
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Resumo:

Objetivo: o objetivo geral do estudo foi verificar a incidência de indivíduos portadores de alelos associados ao metabolismo reduzido e que utilizaram fármacos metabolizados pela enzima CYP2C9.

Método: trata – de um estudo quantitativo, do tipo transversal, de caráter observacional descritivo, cuja amostra final foi de 67 indivíduos. Os participantes do estudo acusaram uso, além de efeitos adversos percebidos, de fármacos comumente utilizados e metabolizados pela CYP2C9, listados em cartilha de farmacogenética oferecida. Além disso, tiveram 4mL de sangue venoso coletados, para posterior extração de DNA por método *salting out* e genotipagem dos polimorfismos CYP2C9*2 e CYP2C9*3 através de PCR em tempo real utilizando ensaios Taqman.

Resultados: A amostra desse estudo foi composta por brasileiros (100%), mulheres (62,7%), com idade entre 40 a 49 anos (43,3%), de cor branca (76,1%) e com o ensino médio completo (43,3%). Mais de 75% dos sujeitos já utilizaram entre 2 ou 4 das medicações listadas na cartilha. A respeito dos eventos adversos, os participantes do estudo reportaram 19 ocorrências sintomáticas percebidas. A frequência alélica do polimorfismo *2 e *3 na população do estudo foi de 11,1% e 7,5%, respectivamente.

Conclusão: Esse estudo demonstrou que a genotipagem dos alelos *2 e *3 é relevante na estrutura genética da população brasileira.

Descritores em português: Citocromo P-450 CYP2C9; Farmacogenética; Efeitos Colaterais; Reações Adversas Relacionados a Medicamentos.
Descritores em espanhol: Citocromo P-450 CYP2C9; Farmacogenética; Efectos Colaterales; Reacciones Adversas Relacionados con Medicamentos.
Descritores em inglês: Cytochrome P-450 CYP2C9; Pharmacogenetics; Drug-Related Side Effects; Adverse Reactions.

Código #13317

Título: An inclusive experience in Medical Genetics learning: how the Liga de Genética Médica da Universidade Federal do Rio Grande do Sul (LiGeM) works

Autores: Marco Antônio Baptista Kalil 1; Mariana Sbaraini da Silva 1; Daniela Burguêz 1; Louise Piva Penteado 1; André Anjos da Silva 3; Lavinia Schüler Faccini 2,3; Ida Vanessa Doederlein Schwartz 2,3

Instituição dos Autores: 1 FAMED - Faculdade de Medicina da Universidade Federal do Rio Grande do Sul. 2 SGM/HCPA - Serviço de Genética Médica Hospital Clínicas Porto Alegre. 3 UFRGS - Departamento de Genética da Universidade Federal do Rio Grande do Sul.

Objetivos: To show how LiGeM is holding its schedule so as to attract graduate students in Medicine into the issues of Medical Genetics, as well as research and medical-caring activities.

Metodologia: Description of the LiGeM activities since its establishment.

Resultados: LiGeM was established in October 2015, initially following the tutoring activities of the discipline *Human Genetics* for medical students. In March 2016, after an opening symposium with great attendance from the academic community, enrollment was made possible for students. From this moment on, the LiGeM activities became independent, following its own schedule of weekly classes, which were taught by physicians of the Medical Genetics Service at Hospital de Clínicas de Porto Alegre (SGM/HCPA), and of Genetics Deparment of Universidade Federal do Rio Grande do Sul (UFRGS) professors, post-graduate students, and its own members. The aim of these lessons were to guide students through the main areas of medical Genetics. LiGeM also aspired beyond its internal limits, taking part in events such as *Interligas de Genética* in São Paulo, 2016, in which five papers were submitted, and two were awarded prizes. In 2015, at the same event, a work presented by one of the members of LiGeM had already won 1st place. Along with other leagues of the university, there have been partnerships, resulting in the symposium *Simpósio das Ligas de Genética e de Oncologia da UFRGS*, an open event in order to explore concepts of the oncogenetics area. In concern of medical-caring activities, the highlights were the internal capacitation in Fetal Alcohol Syndrome with the objective of later teaching local pregnant women about the risks of alcohol consumption and the *I Short Course on Dysmorphology,* in the Medical Academic Week at UFRGS.

Conclusão: Even though LiGeM is still blooming, it has great ambition to present knowledge in Genetics to graduate students. All its activities are set to give the students as much space within this medical specialty as they wish. Not only do we focus on stimulating students to follow this area, but also to provide support for anyone that aspires to have broader knowledge. In addition, LiGeM also offers to the students the possibility for research, since many members have the opportunity to present works in events, as well as rising interest in this area, which is responsible for the fact that some of the members are seeking their first research experience through LiGeM. The LiGeM mission within the community is just as important, as it has the target to promote open access events, from

symposiums for the academic community, to the whole society, since one of the objectives is to hold public meetings with the lay population in order to inform people about genetics and its relation with public health.

Código #12830

Title: ANALYSIS OF PREVIOUS KNOWLEDGE IN GENETICS OF MEDICINE STUDENTS

Authors: Raddib Eduardo Noleto da Nobrega Oliveira; Daniela Estephany Delgado Guevara; Ricardo Tanao Sanches Yoshikawa

Institution of Authors: Faculdade de Ciências Biomédicas de Cacoal - FACIMED

Introduction / Objectives: The teaching of Medical Genetics is often underestimated in undergraduate courses in Medicine in Brazil, which makes medical education deficient and produces professionals who deal with genetic disorders based on knowledge obtained from unsafe sources, Without scientific evidence, for lack of a more solid foundation, which the faculty should provide. The objective of this work was to analyze the knowledge in Medical Genetics of a group of students who are new entrants in the first semester of Medicine of the Faculty of Biomedical Sciences of Cacoal, to investigate their previous concepts on some simple subjects related to the area.

Methodology: A questionnaire was applied, on March 10, 2017, to 54 students from the first semester of the Faculty of Biomedical Sciences of Cacoal. The students Answered questions about the specialization in Medical Genetics, what types of doctors can do genetic counseling, the concept of congenital disease, which means karyotype examination, and, finally, what importance they would attribute to the teaching of Medical Genetics at undergraduate.

Results: Only 47.6% of the students were sure of the existence of specialization in Medical Genetics; 45.4% think that only postgraduates in Genetics can do genetic counseling; 51.5% of those analyzed do not know the correct meaning of the word "congenital"; However, 100% of the participants are familiar with the basic concept of karyotype examination. The results also show that 72.7% of the students consider the teaching of Medical Genetics essential for their training.

Conclusion: Correction of erroneous concepts perpetuated by popular knowledge and the development of medical professionals increasingly prepared to diagnose and treat genetic disorders, regardless of their specialty, depends on a more solid graduation course, with a more significant presence of Medical Genetics during the course.

Código #13404

Cognitive control: outcome of the genetic counseling process in a referral service in clinical genetics.

Autores: Flória-Santos, M.; Luiz, A. A.; Santos, J. T.; Bacalá, B. T.; Segundo-Ribeiro, M; Teodoro, M. L.; Tomazela, M. ; Pina-Neto, JM.

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Empowerment is a multidimensional construct, and it is an important patient outcome, valued by families and geneticists during the genetic counselling process. Cognitive control is one of its dimensions. In this context, we aimed to evaluate the cognitive control of patients at a referral service in clinical genetics at the Brazilian Unified Health System, using a PROM, the Genetic Counselling Outcomes Scale (GCOS-24). After IRB approval, during 2015/2016, 278 patients or their family members, who were affected or at risk for genetic diseases, answered GCOS-24. Data were analysed by means of descriptive statistics, simple frequency analysis, Fisher's exact test, Kruskal-Wallis test, and Dunn's post-test; with significance level of 5%. The mean age of participants was 38 years; the majority were females (77%); with low income (56%); 27% with less than nine years of education. The respondents presented a satisfactory level of cognitive control, with an association statistically significant with schooling, and numbers of genetic counselling consults (questions 01 (<0.01), 12 (0.02), 16 (0.02) and 17 (0.03)). GCOS-24 is an instrument with potential to evaluate clinical genetics services, also to measure counselees' cognitive control. The scale can provide important information for clinicians who would like to develop new interventions to benefit patients and their family members.

Código #13302

Título: DOWN SYNDROME OUTPATIENT CLINIC: INTERDISCIPLINARY CARE FOR HEALTH MANAGEMENT.

Authors: Raquel Boy[1], Isabela Tamiozzo[1], Gabriela Yang[1], Ana Clara Reis[1], Renata Zlot[2], Gustavo Guida Goudinho[2], Anna Paula Baumblat [2], Simone Augusta Ribas[2],Edneusa Oliveira Flor[2], Julio Cesar Jacob Jr[2].

Institution: 1- Faculdade de Ciências Médicas; 2-Hospital Universitário Pedro Ernesto - Universidade do Estado do Rio de Janeiro, Brasil.

Aims:To present epidemiological and clinical data of an interdisciplinary project carried out by Medical Course students and fellows of Nutrition and Speech Therapy. The target population is the Down Syndrome children in their first three years of life. This project aims to promote early contact of the students with patients presenting the most common chromosomal syndrome in the general population associated with intellectual disability and their clinical comorbidities and medical, nutritional, physiotherapeutic and speech-language demands.

Methodology: Retrospective, cross-sectional study. The data were obtained from the survey of standardized questionnaires used by an interdisciplinary team composed by pediatrician, clinical geneticist, nutritionist, physiotherapist and speech therapist.

Results: A total of 19 patients and their families were followed up from February 2016 to January 2017, approximately 60 visits (mean of 3.1 visits per patient), with a mean age of 7 months old at their first visit. The karyotype was obtained in 13 of the 19 patients, most of them presented with free trisomy of chromosome 21, and just one of them showed 21q; 21q translocation. The main congenital malformations were: heart disease (52%); duodenal atresia, pre-axial polydactyly, and congenital clubfoot (5.2%). When evaluating the nutritional status between admission and the third follow-up visit (median), among 18/19 patients, there was a decline in the percentage of patients with low weight and short stature (16.7% to 13%) and 33% of the patients were overweight. The introduction of complementary food was late, with erroneous eating habits (inadequate fractionation, early introduction of cow's milk, excess of flour and supply of large meals in liquidized form) favoring the picture of eating disorders. Among the physiotherapeutic diagnosis, 100% of the patients presented delayed psychomotor development (60% with moderate global hypotonia, 30% mild and 10% with severe hypotonia). Delayed speech development was found in 100% of children and oropharyngeal dysphagia in 47.4% of children.

Conclusion: The project offered the integration of knowledge in pediatrics, dysmorphology, cytogenetics and genetic counseling areas as well provided physiotherapeutic, nutritional and speech therapy diagnosis and specific treatment. It was an opportunity to students to learn about preventive practices for the detection of comorbidities and early interventions for children with Down Syndrome, with optimization of family and professional time. Interdisciplinarity has helped in the

empowerment of the family as a center for early intervention, strengthening the mother-baby bond and adherence to the necessary and oriented treatments.

Código #13301

Título: EDUCATION IN GENETICS: EXPERIENCE OF THE GENETICS OUTPATIENT CLINIC FOR UNDERGRADUATE STUDENTS FROM UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

Autores: Giovanna Resmini Ramalho[1], Gabriela Wünsch Lopes[1], Luiz Felipe da Silva Portela[1], Ida Vanessa Doederlein Schwartz[2,3], Lavínia Schuler-Faccini[2,3], Patrícia Ashton-Prolla[2,3], Roberto Giugliani[2,3], André Anjos da Silva[2]

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Objective: To describe the characteristics of medical consultations held at the Genetics Clinic of the Medicine Human Genetics and Clinical Genetics disciplines, offered by Universidade Federal do Rio Grande do Sul (UFRGS) / Hospital de Clínicas de Porto Alegre (HCPA).

Methods: Retrospective study, based on analysis of computerized medical records of patients who attended the UFRGS-HCPA Genetics Clinic in the period between March 2015 and February 2017. Supervision of the Clinic's activities is provided by professors, postdoctoral students and doctoral students in didactic internship, all of them being medical geneticists. The patients are evaluated by the discipline's monitors, who take part in the UFRGS-HCPA Genetics League, or by HCPA Genetics residents. Most of the consultations are accompanied by undergraduate students from one of the two disciplines in this area. The cases directed for care in the referred clinic usually involve patients recently diagnosed with pathologies within the various areas of Genetics.

Results: During the analyzed period, 112 medical attendances were performed, in which 40 patients have been evaluated. The consultations were categorized into three areas of Genetics: Dysmorphology (67,5%), with preponderance of Down Syndrome diagnosis; Inborn Errors of Metabolism (27,5%), with most of the attendances due to Mucopolysaccharidosis type IV-A and Autist Spectrum Disorder; and Oncogenetics (5%), that aimed to genetic counseling for cancer predisposition syndromes.

Conclusion: The reported experience of the Genetics Clinic carried out at UFRGS teaching hospital is a successful example of learning environment diversification. It can be performed by other institutions and medical teaching areas, seeking for the improvement of professional qualification.

Código #12627

Título: Genetic Consultations in a Teaching Hospital in the South of Rio Grande do Sul

Autores: Simone de Menezes Karam; Eduarda Cecilia Pinguello; Henri Luiz Morgan.

Instituição dos Autores: Universidade Federal do Rio Grande – FURG.

Objective: To describe the pattern in consultations requests by the non-genetic professionals from the Hospital Universitário - Universidade Federal do Rio Grande (HU-FURG) and the main diagnoses established subsequently.

Methods: A retrospective study was lead, based on Medical Genetics consultation records accomplished in the HU-FURG in two periods: January 2006 to December 2010 and January 2014 to December 2016. A standard form was developed for the data collection with the following variables: age, gender, applicant unit, reason to request, diagnosis and laboratorial exams requested. The data collection, processing and analysis were elaborated by two medical students and their teacher in the period of November to December 2016, using Excel software.

Results: In the studied population, 64% (n=32) of the people were male and 57% (n=26) were from 0 to 7 days of life in the moment of the consultation. In terms of the applicant units, 90% (n=45) were pediatrics departments: Neonatal ICU (44%; n=22), Pediatric Ward (22%; n=11), semi-intensive care unit (20%; n=10) and Maternity Ward (4%; n=2). The main reasons to requesting were: dysmorphisms (42%; n=21), musculoskeletal disturbs (14%; n=7), syndromic face (14%; n=7) and suspect of Inborn Errors of Metabolism - IEM - (6%; n=3). During the patients investigation the principal exams requested were GTG Karyotype (48%; n=24), image exams (34%; n=17) like echocardiography (16%; n=8) and screening to IEM (14%; n=7). In 28% of the cases (n=14) it was not necessary to request complementary exams. After the consultation, 78% (n=39) of the cases were diagnosed, and 8 of them continued in outpatient clinic follow-up. Non-genetic disease diagnosis occurred in 26% (n=13) of the cases. With respect to the genetic diseases, the most frequent were chromosomal (20%, n=10), followed by Mendelian (18%; n=9) and multifactorial (10%; n=5).

Conclusion: The majority of the cases evaluated received a diagnosis, and about inconclusive cases (n=11), 8 of them maintained the bound with the service, remaining in investigation. In 28% of the cases it was not necessary requesting complementary exams to corroborate the diagnosis, strengthen the attitude of choosing appropriate tools and when to use these properly. Therefore, genetic consultations have been shown to be a very important device to health professionals, increasing the accuracy in diagnosis and speeding the process from the admission to the therapeutics, primarily to pediatricians, for whom the call for this procedure seems to be part of the routine. All patients assessed and/or their relatives were submitted to genetic counseling and the ones whose diagnosis were a genetic disease held on outpatient clinic or were forwarded to references centers.
Key-words: genetic consultation; medical genetics; genetic counseling.

Código #13407

Título: MEDICAL GENETICS ACADEMIC LEAGUE OF THE FEDERAL UNIVERSITY OF MARANHÃO: THREE YEARS OF ACTION IN CONTINUED EDUCATION IN MEDICAL GENETICS

Autores: Antônio Augusto Lima Teixeira Júnior; Elis Vanessa de Lima e Silva; Fabrício Maciel Soares; Linajanne Borges Muniz; Thiago de Almeida Bezerra; Emilly de Jesus García Ataíde; Jéssica Cavalcante dos Santos de Paiva; Jenilson Mota da Silva; Raissa Lacerda Ponte; Silma Regina Ferreira Pereira;

Instituição dos Autores: Federal University of Maranhão.

Objetivos:
To survey the activities carried out by the Medical Genetics Academic League (LAGeM) of the Federal University of Maranhão, from March 2014 to March 2017, and its contributions to the advances of medical genetics in the academic and social spheres.

Metodologia:
We carried out a survey of all LAGeM's activities, such as seminars, campaigns, participation and organization of events, published papers, didactic materials developed, participation in courses and internships, as well as other projects developed during LAGeM's 3 years of existence.

Resultados:
In the period evaluated, three cycles of seminars were presented, with an approach of 34 genetic diseases; three projects, one of which corresponds to a research project an two to extension projects, were developed; six scientific-educational events were organized by LAGeM which also participated in 15 national and regional genetics scientific events, including four congresses, six genetics update courses, two internships and two regional symposia; 25 papers were presented at the events in which LAGeM participated, of which 17 were published in proceedings. Moreover, an informative booklet on genetic diseases was written, in which 12 topics in medical genetics were discussed.

Conclusão:
The work of the Medical Genetics Academic League (LAGeM) of the Federal University of Maranhão, besides supporting the formation of the academic community in genetics, also enables the integration of scientific knowledge into the community, through operating in partnership with associations and groups of families and carriers of genetic diseases in the State of Maranhão. In the academic field, during these three years it was possible to observe an increase on the demand for information, updates and trainings in the area by students, health and relates areas professionals. Thus, LAGeM's performance reflects the importance of medical genetics academic leagues in the process of medical genetics continuing education.

Código #13177

Título: PERCEPTION OF UNDERGRADUATE MEDICAL STUDENTS ABOUT THE MEDICAL GENETICS DISCIPLINE AND ITS IMPACT IN THE SOCIETY AND ON THE TRAINING OF MEDICAL PROFESSIONALS.

Autores: Karina A. R. Ribeiro

Instituição dos Autores: Faculdade de Medicina São Leopoldo Mandic, SLM - Unidade Campinas, São Paulo, Brasil.

Objectives: To evaluate the perception of undergraduate medical students about the Medical Genetics discipline, its applications and its impact on the training of medical professionals.

Methodology: Participated in the study 62 first year students of the Medicine course of a Private School in the interior of São Paulo state. Voluntarily, they responded to an unidentified questionnaire available on the Google Drive Forms platform and sent via email between March 2 to March 15 of 2017. The database allowed for the completion of a single questionnaire by activating the e- Mail, thus preventing duplication of responses by the same person. The questions available on the form addressed quantitatively and/or qualitatively, variable for each of the questions, the students level of knowledge on a number of relevant topics in medical genetics, the future therapeutic and scientifical possibilities of genetics and the relevance of genetics Within the medical and/or social area. After the deadline for participation in the survey, data were evaluated and processed.

Results: 59.7% were female, compared to 40.3% male. The age group was distributed between 16-18 years (37.1%); 19-21 (29%); 21-25 (19.4%) and over 25 years (14.5%). When questioned about how they classified their level of knowledge in genetics when entering the College, only 50% responded to be GOOD, 4.8% excellent and all the rest (45.2%) said to be reasonable or bad. When questioned about the impact of Genetics in Diagnostic Medicine, (53) 85.5% of students said to be very significant, whereas, 2 individuals (3.6%) said they did not know. Regarding the contribution of the discipline to vocational training, 50 (80.6%) said that the discipline will contribute a lot to medical training and 60 students (96.8%) agree with the idea that Medical Genetics will greatly influence in the future, not only of Medicine but especially of society as a whole. When assigning a degree of importance to the discipline, together with the others that occur in the same semester, such as Anatomy, Physiology and Cell Biology, 98.3% of the students consider it necessary and stimulating, and finally, understanding the molecular basis of genetic diseases and/or hereditary factors and the factors associated with the occurrence of gene mutations and their correlation with the development of diseases, were the subjects that the students considered of more pertinence to the graduation of the medical professional.

Conclusion: The results allowed to conclude that the discipline of Medical Genetics seen as necessary and stimulating to first year students of Medicine, and that they are already able to understand the fundamental role of Medical Genetics in the formation of a critical sense of a professional Medical, generalist or specialist, since its applications in diagnostic and therapeutic medicine permeate all

areas and medical specialties.

Keywords: medical genetics discipline; perception of undergraduate medical students; genetics applications.

Código #13347

Título: Radiografia do Ensino de Genética Médica nas Universidades Federais do Brasil

Autores: Dione Fernandes Tavares[1]; Victor Evangelista de Faria Ferraz[2]; Thiago Rhangel Gomes Teixeira[1]; Laércio Moreira Cardoso-Júnior[1]; Angelina Xavier Acosta[1]

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Palavras Chave: Genética Médica; Educação Médica; Diretrizes Curriculares

Introdução: a genética médica é uma das áreas de maior avanço em medicina, exigindo que os médicos possuam conhecimentos básicos sobre os princípios da genética, e sua aplicação numa ampla variedade de problemas clínicos. As doenças genéticas tem apresentado um papel crescente no perfil de morbi-mortalidade da nossa população. Entretanto, o Brasil possui atualmente apenas 241 especialistas em genética médica cadastrados no conselho de classe, concentrados na sua grande maioria nas regiões Sul e Sudeste, portanto há uma expressiva necessidade de formação de médicos especialistas nessa área. Portanto, os conhecimentos em genética médica devem ser indispensáveis às práticas do médico generalista pelas justificativas já demonstradas. Diante desse contexto, o Ministério da Educação (MEC) publicou em 2014 as novas Diretrizes Curriculares Nacionais do Curso de Graduação em Medicina (DCN), havendo dentre as competências na subseção da atenção às necessidades individuais de saúde, conhecimento sobre as indicações de realização de aconselhamento genético.

Objetivos: verificar o estado da arte em relação ao ensino de genética médica nas Universidades Federais do Brasil a luz das DCN do curso de Medicina.

Metodologia: a partir da lista de Universidades Federais disponibilizadas pelo MEC, utilizou-se o e-MEC, sistema de tramitação eletrônica dos processos de regulação das Instituições de Ensino Superior. Nesse sistema foram consultados os cursos de graduação em funcionamento e suas respectivas instituições; quantidade de vagas; existência de mais de um campus com oferta do curso e suas avaliações, mantendo apenas as universidades que ofertavam a graduação em medicina. Utilizou-se como referencial o Projeto Pedagógico dos cursos para avaliação da existência de disciplinas obrigatórias, optativas, eletivas ou a presença de conteúdo de genética médica presente em módulos.

Resultados e conclusões: o levantamento de dados incluiu todas as 63 Universidades Federais do país, dentre elas 53 oferecem a graduação em Medicina, totalizando 76 cursos, tendo em vista a oferta em mais de um campus. Contatou-se, ao avaliar as variáveis acima mencionadas, uma grande heterogeneidade quando a oferta de disciplinas de genética médica. Ressalta-se a necessidade de se garantir competências mínimas em genética na formação dos médicos generalistas, por demanda da própria DCN.

Código #13086

Title: TEACHING HUMAN AND MEDICAL GENETICS IN THE MEDICAL GRADUATION COURSE

Authors: Natália Lima Moraes[1]; Vanessa de Aquino Gomes[1]; Cristina Wide Pissetti[1]

Institution of the Authors: 1. Centro de Ciências Médicas, Universidade Federal da Paraíba, João Pessoa - PB, Brazil.

Objectives: To identify, by means of a self-reported questionnaire, how the students of the Course of Medicine of the Universidade Federal da Paraíba, Campus I, João Pessoa evaluate the teaching of the content of Human and Medical Genetics for the medical practice. To compare the responses given by the students of the initial periods of the course with those of the intern students.

Methodology: Descriptive, transversal, quantitative study, carried out in the Center of Medical Sciences of the Universidade Federal da Paraíba, Campus I, João Pessoa. Study participants were students of the first, eighth, tenth and twelfth periods of the Course of Medicine. The periods were selected due to being the periods in which the modules are taught that contain some Genetics content. The semi-structured questionnaire applied was developed by the researchers, based on an instrument used in a similar study for the evaluation of basic concepts in Genetics, prevention of congenital defects and genetic counseling (VIEIRA, 2012). The questionnaire contains closed questions referring to the knowledge on Basic Genetics, Medical Genetics and the importance of the knowledge of Genetics for the formation of the general physician. At the end of the interviews the data obtained were organized in a Microsoft Excel® spread sheet and analyzed by means of the Chi-squared Test.

Results: It was observed that, when questioned regarding Oncogenetics, the intern students considered their knowledge “good”, whereas the evaluation of the students of the initial periods was negative regarding this subject (X^2; p=0.005). Evaluating the knowledge on Genetics and common illnesses of the adult, the intern students also considered their knowledge “good”, unlike the students of the initial periods (X^2; p=0.004). In relation to the treatment of genetic illnesses, it was observed that the intern students considered their knowledge “poor”, unlike the students of the initial periods (X^2; p=0,028). **Conclusion**: Generally, for all the subjects investigated, no statistically significant differences were observed between the self-reports of the Intern students and the students of the initial periods. However, regarding the subjects Oncogenetics and Genetics and common illnesses of the adult, the intern students considered their knowledge “good” unlike the other students. In relation to the knowledge related to the treatment of genetic illnesses, the opposite was observed, possibly explained by the fact that the intern students had direct contact with the patient and, therefore, had tested their knowledge in the practice. The students of the initial periods dealt only with theoretical knowledge and not in practice, therefore had not yet had direct

contact with the patient.

Bibliographic reference: VIEIRA, T. A. Genética Comunitária: A inserção da Genética Médica na atenção primária à saúde em Porto Alegre, 2012. Tese (Doutorado) – Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, 2012.

Código #14177

Title: The teaching of genetics in Neurology: a new perspective in Postgraduate Degree at UNIRIO.

Authors: Soniza Vieira Alves-Leon[1,2]; Fabrícia Lima Fontes-Dantas[1]; Ingrid Mendes Paschoal[1] ; Claudia Cristina Ferreira Vasconcelos[1]; Glenda Correa Borges de Lacerda[1]; Fernando Ferry [1]; Regina Papais Alvarenga [1], Jorge Paes Barreto Marcondes de Souza[1, 2],Cleonice Alves de Melo Bento [1]

Authors institutions: 1-Programa de Pós Graduação em Neurologia da Universidade Federal do Estado do Rio de Janeiro (UNIRIO) and Hospital Universitário Gafrée e Guinle. 2- Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro.

Objectives: The emergence of genomic represents a shift in traditional medical genetics with its focus on rare genetic diseases toward more personalization and prevention of common diseases. The Postgraduate Degree in Neurology (PPGNEURO) at UNIRIO has been publishing since its inception papers on the field of genetics and molecular biology. There's huge number of biological samples coming from multiple researches from PPGNEURO, despite the unavailability of an own laboratory. These numbers are made possible due to the accompanying of and are distributed to different laboratories in Rio de Janeiro and around the world. We seek to better integrate students in the routine of experiments giving them a more in depth academic development that in turn will lead to greater impact in scientific studies. The main goal is to present the experience of creating the Center of Neuroscience at University Hospital Gafrée e Guingle (HUGG).

Methodology: Through the joint effort of professors from PPGNEURO, the HUGG provided 600m² where the Center of Neuroscience will be constructed. The Translational Neuroscience Laboratory along with a series of other resources and laboratories will also be created in the same place. These will make the advance of assistance, education and research possible in HUGG. Several approved projects have been acquiring resources for infrastructure, material and scholarship grants from the development agencies like FAPERJ, CNPq, CAPES and FINEP allowing academic and independent research in neuroscience.

Results: In addition to structuring the Laboratory with the professors the three post-doctoral students currently in Translational Neuroscience Lab also contribute to PPGNEURO with their respective knowledges in the fields of genetics and molecular biology. The laboratory has so far been able to acquire the following equipment: a Thermo Fischer -86ºC ultra-low temperatures freezer, an Eppendorf refrigerated ultra-centrifuge, an Thermo Fischer Ion S5 and Ion Chef next generation sequencing system, a Thermo Fischer QuantStudio 3 real time PCR, Applied Biosystems Veriti Thermal Cycler, a Thermo Fischer Qubit Fluorometric Quantitation and a Life Technologies Atune NXT flow cytometer. The next step is to standardize the methodologies and to start the related projects.

Conclusion: The Center of Neuroscience will pioneer the integration of professional qualification and an educational center in a public university hospital. It will contribute not just for scientific research but for diagnosis of complex and mendelian inheritance diseases and therapeutic monitoring of

different response to different treatments through molecular investigation. The convergence of public health and genetics holds the possibility of improved understanding of the etiology, prevention, and management of diseases. This will put HUGG in the new era of medicine, associating clinical assistance with the direct benefits of these advances may bring to the patients.

Código #13399

Título: USING BIOINFORMATICS TOOLS FOR TEACHING PHARMACOGENETICS.

Autores: Samara Y S Rios; Vanessa R Paixão-Côrtes

Instituição dos Autores: Programa de Pós Graduação em Genética e Biodiversidade, Universidade Federal da Bahia, Brasil.

Objective: Enabling the Pharmacy students to identify know polymorphisms involved in response variation to drugs, associated it to the adverse or null effects caused by the ingestion of standard dose, using bioinformatics tools.

Methodology: We developed this work in the discipline Genetic Health (BIOA79) in the Universidade Federal da Bahia, in 2 under graduation classes, offered in the 1st semester of the Pharmacy class (19 students), an in a class that included students from several courses of different semesters (BI - technology, BI- Health, Nursing and others; 14 students). After a theory lesson of pharmacogenetics, where we question the importance of genetics for health and if there was some association with genetic and drugs, we play this activity in 1 hour class, with the use of drugs guidelines (brought by students), computers and internet access. The practice followed a predetermined script, in which the student should search and identify genes and polymorphisms mentioned in the drugs guidelines in the suggest databases (NCBI- https://www.ncbi.nlm.nih.gov/pubmed e Pharmagkb - https://www.pharmgkb.org/) genetic changes related to drug response.

Results: Before performing the activity, 77% of the students answered that genetics was important to assist health professionals in the diagnosis and treatment of diseases. When asked if they knew any medication that the response could be different depending on the gene variation, only three students said they do. Thirty-three students have participated of the activity and brought drugs guidelines, which only two mentioned genes or polymorphisms. Forward, the search was directed to the bank PharmaGKb using the name of the drug. As a result, twenty-five students identified a relationship among drug, genes, polymorphisms, functionality and the adverse effects of each drug. Therefore, this activity made it possible to have a first contact and to develop basic database manipulation skills, which can help medical investigations. In addition, it is possible to develop critical sense because most of the drug guidelines they brought had no pharmacogenetics information even though they could show adverse effects in some patients. Further, it was possible to understand the importance of genetics for health not only associated to disease, but also in relation to different responses to the drug prescribed in a standard dose. Finally, it was possible to consolidate learning related to mutations, genetic code and pharmacogenetics.

Conclusion: We reached our goal through this practice since it was possible for the students to realize the importance of genetics to the daily life of health-related careers. The applied knowledge of the genetic factors that have a determinant role in the drug response variability reinforced the importance of the concepts taught in the course for the future action of health professionals. However, the

students presented some limitations regarding the use of the databases caused by the difficulty to understand the English language.

Código #13196

Título: ***Validation of a Human Molecular Genetics Class Project and Development of an Accompanying Research Guideline***

Autores: Viktoria Weihermann; Angelo Bannack; Rodrigo Coutinho de Almeida; Angelica Beate Winter Boldt

Instituição dos Autores: Laboratório de Genética Molecular Humana, Universidade Federal do Paraná, Curitiba, Brazil

Abstract

Objective: In order to train medical students in the challenging task of sorting out relevant information among twenty public free genome databases and web sites available online, teachers of the Genetics and Evolution discipline (BG037) of the Federal University of Paraná introduced in 2013, a project in which small groups of 6-7 first year medical students, each one supervised by monitors, have to conduct a research about a clinically relevant gene. In this project, they write a paperwork describing the gene's location, structure, phylogenetic origin, expression and polymorphisms, also discussing recent publications on these topics. The aim of the present study is to develop a guideline for medical students and doctors to facilitate this research, and to validate the project as a teaching tool in Human Molecular Genetics.

Methods: For the guideline's development, we conducted a survey of twenty genetic databases and tools, available online, and selected those most frequently updated, with both accurate and easily obtained information, to underpin each topic of the project. We also compared student's project and exam grades and presence in class from 2013 to 2016, using nonparametric Mann-Whitney or Kruskal-Wallis and Spearman correlation tests, conducting all these analysis with Graphpad Prism software.

Results: In four years, 138 genes have been analyzed by about 700 students. Most of the investigated genes played a role in the immunological response, cell cycle regulation, metabolism, regulation of gene expression and neurological mechanisms. To construct the guideline, we organized available search tools and databases according to their proposal, supporting institution and year of creation, and ranked them according to update rate and ease of use. For gene structure, transcripts, protein isoforms and gene phylogeny, we recommended Ensembl. For mRNA and protein expression, we suggested GTEX, Genecards and Protein Atlas. For polymorphism analysis (number of catalogued polymorphisms, population frequency and functional consequences), Ensembl, OMIM and GWAS Catalog were the main options. Next, we validated the project that inspired this guideline as a teaching tool, comparing student's test and project grades. Independently of the semester, project grades were consistently higher than test grades (e.g. class of second semester of 2016 (2016.2), $p<0.0001$). Students with higher project grades also had higher test grades in all semesters (e.g. in 2016.2, $r=0.294$, $p=0.0035$). Presence in class was important: students who missed classes had lower

test grades (e.g. in 2016.2, $r=-0.379$, $p=0.0001$) and lower project grades (e.g. in 2016.2, $r=-0.333$, $p=0.0009$).

Summary: We validated this project as an effective tool to help medical students to consolidate fundamental concepts of Human Molecular Genetics. The guideline will hopefully improve research skills in this area, which is an utmost required expertise in Modern Medicine.

ERROS INATOS DO METABOLISMO

Código #13262

Título: AÇÕES REALIZADAS NO CEARÁ PARA REDUÇÃO DAS FALTAS À TERAPIA DE REPOSIÇÃO ENZIMÁTICA PARA MPS II

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Objetivos: Descrever as ações que objetivaram a redução à falta na terapia de reposição enzimática (TER) para MPS II bem como o impacto de cada uma delas.

Metodologia: Estudo quantitativo, descritivo, longitudinal sobre falta às TER para MPS II no Ceará de 2006-2017.

Resultado: As ações realizadas pela equipe de saúde foram: (1) distribuição de cestas básicas para quem não faltassem as infusões mensalmente, (2) fornecimento de transporte do domicílio ao centro de infusão, (3) contato semanal com as famílias para educar sobre a necessidade de adesão a terapia e avaliar os motivos de falta a TER, (4) descentralização da TER do centro de referência para os municípios de origem do paciente, (5) controle mensal do número de frascos da farmácia, (6) comunicação periódica com órgãos governamentais sobre a necessidade de manter a TER, (7) mudança da data da TER nos dias de feriado, (8) prescrição atualizada de acordo com o peso do paciente trimestralmente para órgãos governamentais. Todas as ações foram realizadas por profissionais do serviço público, privado e terceiro setor. A ação 1 ocorreu de 2006-2010, a 2 de 2008-2010, 3 de 2010-2015, 4 de 2015-2017, 5 e 6 de 2014-2017, 7 de 2006-1017, 8 iniciou em 2017. Os motivos de falta a infusão foram (a) processos infecciosos/febre, (b) falta de transporte, (c) falta de fornecimento da enzima, (d) motivos fúteis. Cada ação teve entre 3-12 casos. Essa variação ocorreu por causa da ocorrência de óbito, diagnósticos novos, condições de elegibilidade dos pacientes. O número de casos devido (a) foi reduzido ao passo que o paciente aumentou o número de infusões realizadas, (c) foi reduzida pelas ações 5 e 6. A ação 2 não foi efetiva, pois as famílias dispensavam o transporte por motivos fúteis, como demora para acordar, necessidade da mãe comparecer a outros compromissos e falta de acompanhante. A ação 3 não foi bem aceita pelas famílias, sendo considerada invasão de privacidade. A descentralização da TER foi a ação mais efetiva para aumentar a adesão a terapia, reduzindo os motivos fúteis. Essa ação também tem a adesão dos profissionais da região em que mora o paciente, colaborando com as ações educacionais para aumentar a adesão as consultas e realização dos exames de controle, além da atenção especial pela equipe de saúde, devido ao menor número de casos. O controle do número de frascos e a comunicação periódica aos órgãos governamentais responsáveis pela TER foram responsáveis pela redução da falta de fornecimento da enzima. Não foi possível observar o impacto da ação 8, pois iniciou há menos de 1 ano.

Conclusão: A redução das faltas à TER no Ceará é resultado de várias ações, sendo a descentralização da TER a ação que tem sido considerada como sucesso pois trouxe maior humanização à terapia, reduzindo os motivos fúteis de faltas. A falta do fornecimento da enzima foi resultado do controle do número de frascos e a comunicação periódica aos órgãos governamentais.

Código #13353

ADESÃO AO TRATAMENTO DE PACIENTES COM GLICOGENOSE HEPÁTICA ACOMPANHADOS EM UM SERVIÇO DE REFERÊNCIA EM ERROS INATOS DO METABOLISMO

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Instituição dos autores: [1] Universidade Federal do Rio Grande do Sul, [2] Hospital de Clínicas de Porto Alegre

Objetivo: Caracterizar a adesão ao tratamento de pacientes com diagnóstico de glicogenose hepática (GSD) acompanhados em um serviço de referência para Erros Inatos do Metabolismo. **Métodos:** Estudo transversal, descritivo, com amostragem por conveniência. Os dados foram coletados através de revisão de prontuário e entrevistas com pacientes ou familiares que responderam questionários semi-estruturados. Para a classificação da adesão foram considerados somente os pacientes que realizaram pelo menos três coletas de sangue no período de 18 meses anteriores à inclusão no estudo. Os marcadores analisados foram: nível sérico de glicose, lactato e triglicerídeos com 4hs de jejum pós uso de amido cru. Foi considerado aderente o paciente que teve, em pelo menos 80% das coletas, valores normais de pelo menos dois dos três marcadores. Os demais foram considerados como não aderentes.

Resultados: Dezenove pacientes foram incluídos. Destes, dez (52,63%) têm GSD tipo 1a, quatro (21,05%) GSD tipo 1b, três (15,78%)GSD tipo III e dois (10,52%) tipo IX. A mediana de idade foi de 12 anos e a mediana de idade do diagnóstico foi de nove meses (variando de 3 meses - 6 anos). A maioria dos pacientes enquadrou-se na classificação econômica B1. Dez pacientes (52,63%) foram considerados aderentes. A mediana de idade destes foi de 11 anos e dos não aderentes, de 17 anos. A média da distância entre o Serviço de Referência e a residência do paciente aderente foi de 1.300,39 km e do paciente não aderente foi de 1.027,77km. Não foi verificada diferença entre os dois grupos quanto à religiosidade, classificação econômica e idade do diagnóstico. A mãe é a principal cuidadora de 80% dos pacientes aderentes e de 44% dos não aderentes. Sobre as dificuldades encontradas, as mais citadas foram: não poder comer alimentos saborosos, o Serviço de referência ficar longe de casa e a dieta especial ser cara.

Conclusão: O estudo até o momento evidenciou uma adesão insatisfatória em aproximadamente 50% dos pacientes. A distância entre o serviço de referência e a residência do paciente, bem como a classificação econômica não mostraram ser relevantes para a adesão. O tratamento da GSD é complexo e exige constante e permanente atenção quanto aos horários de ingestão do amido cru, bem como o cuidado com os alimentos que são permitidos e proibidos na dieta. A adesão é um tema complexo que deve sempre ser avaliado nas doenças metabólicas hereditárias em que o tratamento é basicamente dietético e nutricional. As dificuldades associadas ao tratamento devem ser trabalhadas em conjunto a fim de serem encontradas as intervenções mais efetivas para cada caso.

Código #13352

Title: ADHERENCE TO TREAMENT IN GAUCHER DISEASE PATIENTS ON ENZYME REPLACEMENT THERAPY

Authors: Alícia Dorneles Dornelles; Amanda Quevedo; Livia Paskulin; Bárbara Krug; Vitoria Zizemer; Ana Paula Vanz; Filippo Vairo; Paulo Picon; Ida Vanessa Doederlein Schwartz

Institution: Centro de Referência Estadual em Doença de Gaucher, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Objective: To evaluate the adherence to treatment of Gaucher disease (GD) patients on enzyme replacement therapy seen at the Reference Center for GD from Rio Grande do Sul (RCGD-RS) on a 5yr period (January 2010-January 2015).
Methodology: A retrospective study based on the review of the patients' medical records. Adherence was measured as recommended by the GD Brazilian guidelines – patient was considered adherent if received more than 50% of the scheduled infusions per year.
Results: Thirty-seven patients were included in the study (aged between 14 and 66 years), of which 68% (n=25) lived in the countryside of RS and 32% (n=12) in the capital or metropolitan region. Eighteen patients were female and three patients have GD type 3. The mean number of non-adherent patients/yr was 3 (8%). Patients receiving home infusion therapy (n= 3) appear to be more adherent. Comparison between the adherent and non-adherent (NA) patients showed the last ones have higher chitotriosidase activity. There was no difference in QOL, or in any other hematological and biochemical parameter evaluated, between adherent and NA patients.
Conclusions: Patients seen at the RCGD-RS show good adherence to treatment, a finding that may reflect the interdisciplinary approach of the Center. The lack of statistical significance found for almost all comparisons performed between NA and A patients is probably due to the low number of NA patients, and to the relatively short period of evaluation.

Código #13412

Title: CHARCOT-MARIE-TOOTH DISEASE TYPE VIB AS A DIFFERENTIAL DIAGNOSIS TO HYPOXIC-ISCHEMIC ENCEPHALOPATHY: DO NOT MISS THE CLUES.

título: ... INSULTO HIPÓXICO-ISQUÊMICO ....

Authorsores: Bibiana Mello de Oliveira; Helena Fussiger; Ana Paula Kurz de Boer; Felipe de Siqueira Toledo Koerich Kahl; Manuela Schubert Baldo; Fabiano Poswar; Filippo Pinto e Vairo; Carolina Fischinger Moura de Souza; Jonas Alex Morales Saute
Authors Institutions:Instituição dos Autores: Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Porto AlegreUniversidade Federal do Rio Grande do Sul, Brasil.

Objectiveos:
To describe the diagnostic process of an infant with history and neuroimaging findings compatible with early life hypoxemia that was later diagnosed with a rare disease related to SLC25A46 gene.
We intend to discuss the clinical investigation of a male patient with perinatal insult history, evaluated at 1 year and 3 months of age, with respiratory failure, hypotonia, severe neuropsychomotor developmental delay, optic atrophy and neuroimaging suggestive ofng perinatal hypoxemia. Despite the peripartum insult history, etiological investigation was continued. After extensive investigation, complete exome sequencing was performed with identification of a homozygous variant not yet described in SLC25A46 gene, which encodes for an internal mitochondrial membrane solute carrier, previously associated with neuropathy, optic atrophy, and neuroimaging similar to those presented by the patient. We intend to analyze the diagnostic process against neonatal insult data and to describe the clinical picture associated to a newly identified variant

Methodsodologia:
Case report.
Resultsados:
A mMale patient with 1 year and 3 months of age, born to nonconsanguineous parents, was referred for genetic consultation , with previousgress history of perinatal hypoxic-ischemic encephalopathyperinatal insult was evaluated at 1 year and 3 months of age in order due toto investigatefor neurodevelopmental delay. He was born by cesarean delivery due to acute fetal suffering at gestational aof36 weeks, with Apgar 2/8 and need of positive pressure ventilation was needed. AAt 8 months of ageinvestigation for developmental delay was started developmental delay was, attributed to neonatal hypoxemia with neuroimaging described as suggestive ofperiventricular leukomalacia and hypoxic-ischemic encephalopathy (HIE). At 1 year and 2 months, he presented respiratory insufficiency with mechanical ventilation (MV) need and was was admitted to the hospital due to respiratory insufficiency with need of mechanical ventilation, then transferred to our tertiarya tertiary referral hospital. On this evaluationPresented global hypotonia, reduced strength, areflexia and optic atrophy were present. Investigation for congenital infections, muscular enzymes, gasometry, serum lactate, ammonia and metabolites were normal. Analysis of alpha-glucosidase activity, Prader-Willi methylation, GTG karyotype and SMN1 deletion had no alterations.
Nerve conduction studies were not performed Electroneuromyography was suggested, but could not be performed due to MV. A novel brain MRI with spectroscopy showed lactate peak, possible lactate

peak, encephalic volume reduction, thin corpus callosum and periventricular and cerebellar white matter T2-hyperintensityof hyperintensit. Since optic atrophy is unusual in HIE, another inherited early-onset condition could not be convincingly excluded. Therefore based on In order to advance the investigation, exome sequencing was orderedrecommended. The Ppatient progressed with difficulty in ventilatory weaning, hyporesponsiveness and marked hypotonia. He pPresented 4 cardiac arrests and progressed to death at 1 year and 10 months. EThrough the exome sequencing revealed a novel, a still undescribed variant in in homozygosity in SLC25A46 (c.779C>Tt) in homozygosis, classified as likely considered possiblypathogenic, was identified. Variants in SLC25A46Variants in this gene are associated to Charcot-Marie-Tooth disease type VIB (CMTVIB), a complex autosomal recessive inheritance condition that presents with optical atrophy, motor and sensory axonal peripheral neuropathy, hypotonia, developmentalneuropsychomotor delay and regression. starting Neuroimaging pattern of CMT-VIB usually showsmay signal a very similar pattern to our patient and may resemble hypoxic-ischemic encephalopathy.
with images similar to those presented by the patient.

Conclusionão:
Hypoxic-ischemic encephalopathy diagnosis requires clear clinical history with suggestive physical and neuroimaging, excluded other conditions. In most cases this diagnosis will be the final one, but the presence of additional findings may give clues to an alternative diagnosis. Differential diagnosis with inherited conditions is important to provide genetic counseling and treatment when possible. Exome sequencing revealed a diagnosis of CMT-VIB related to SLC25A46, previously associated with clinical findings similar to those presented by the patient. This case stresses the importance of a careful differential diagnosis when evaluating patients with HIE suspicion and exemplifies the revolution provided by next-generation sequencing technologies that are directly impacting on families care.

Código #12655

Título: CHEMICAL AND SENSORIAL EVALUATION OF LOW PROTEIN BREADS FOR PATIENTS WITH PHENYLKETONURIA

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Phenylketonuria (PKU) is a metabolism inborn error and it has as treatment a phenylalanine (Phe) restricted diet. Nowadays, patients with PKU have difficulties to find specific products for their diet which impairs their adhesion to the treatment.

Objective: This study aimed to prepare breads with low Phe content as well as to perform sensory and chemical analysis on those.

Methods: Raw material with low Phe content was used in the bread preparations. A common base containing corn starch, sweet manioc starch, manioc flour, oil, sugar and salt was stablished and it was added: a) manioc (*Manihotesculenta*); b) baroa potato (*Arracaciaxanthorrhiza*); c) sweet potato (*Ipomea batatas*), d) English potato (*Solanumtuberosum*); and e) yacon (*Smallanthussonchifolius*) in order to make the breads. Acceptance teste was used for the sensorial evaluation with a hedonic scale of 9 points that assessed the following attributes: appearance, color, taste, texture, overall samples impression and purchasing intention analysis. 47 non-PKU judges of both genders were invited to participate on the evaluation. From the results obtained from the affective test, means and standard deviation were calculated and a Variance Analysis (ANOVA) and a Turkey Test ($p \leq 0,05$) were performed. Subsequently, each preparation was chemically analyzed for: moisture, ash by muffle incineration, proteins by the Kjeldahl method and lipids. This project was approved by CEP/UFRGS.

Results: In the sensorial evaluation all preparations had a satisfactory evaluation. English potato bread was the best preparation ($p<0,05$) in all attributes. In regards to texture, English potato bread preparation did not significantly differ from sweet potato bread. Flavor did not differ from sweet potato and yacon preparations, and purchase intention was similar between sweet potato and English potato. The results obtained in the chemical analysis showed that there was no significant difference in protein (1.42% manioc; 1.41% baroa potato; 1.40% sweet potato; 1.43% English potato; 1.41% yacon) and lipids content among the preparations, however moisture and ash presented significant difference.

Conclusion: The diet of patients with PKU directly influences their decisions mainly in regards to eating habits. Therefore, this study concludes that preparation of breads with low Phe content is viable and they can present the sensorial desirable qualities to consumption. Additional studies are being conducted in order to quantify the Phe amino acid content and may contribute to further information on the formulations nutritional quality.

Acknowledgements: FAPERGS/PROPESQ/UFRGS.

Código #13165

Título: CLINICAL PRESENTATION OF PATIENTS WITH CLASSICAL HOMOCYSTINURIA AT DIAGNOSIS: A RETROSPECTIVE STUDY.

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Instituição dos Autores: Serviço de Genética Médica Hospital Clínicas Porto Alegre (SGM/HCPA) e Departamento de Genética da Universidade Federal do Rio Grande do Sul.

Aims: To evaluate the clinical features presented by Brazilian Classical Homocystinuria patients at diagnosis.

Methodology: A retrospective study based on the review of clinical and biochemical data available for 29,084 patients who have been investigated, from 2000 to 2010, for exclusion of any Inborn Metabolic Errors (IEM) at the Reference IEM laboratory from SGM-HCPA. For the biochemical investigation to be performed, it was necessary that the physician completed a specific form describing the clinical features of the patient, among others. These forms were reviewed for all patients.

Results: Twenty-one patients with confirmed diagnosis of Classical Homocystinuria were identified (male = 12). Patients came from the South (23,8%), Southeast (42,8%), North (9,5%) and Northeast (23,8%) Brazil. The mean age at diagnosis was 13,09 years (SD 9,79). Five patients (23,8%) had a history of consanguinity in the family, and two of them were related (brother and sister). The most prevalent clinical manifestation was involvement of the ocular system (n = 16 patients, 76,1%), including lens luxation and subluxation (n=13), myopia (n=4), strabismus (n=1), retinal detachment (n=1), amaurosis (n=1) and cataract (n=1). The second most common clinical feature was delayed psychomotor development (n=11, 52,3%), followed by seizures and marfanoid phenotype (n=7, 33,3%). Dysmorphias were described in 6 patients (28.5%) and thromboembolic events in 2 patients (9.5%).

Conclusions: Identification of the main features associated with Classical Homocystinuria, such as ocular abnormalities and delayed psychomotor development, is extremely important towards an early diagnosis, in order to alter the natural course of this disease and to reduce the morbidity and mortality.

Código #13286

Título: Coma, developmental regression and refusal to feed: How these symptoms can alert us to the diagnosis of inborn errors of metabolism (IEM)?

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Objetivos: Information Service of inborn errors of metabolism (SIEM) is a pioneering initiative led by a specialized team of geneticists, dietitians, nurses and biologists trained to provide advices in cases of suspected Inborn errors of metabolism (IEM). The tool was created by the Medical Genetics Service of the Hospital de Clínicas de Porto Alegre to disseminate knowledge about IEM and help health care providers in the recognition and interpretation of clinical and laboratory findings. The main objective of this study was to development a simple risk score to correlate signs and symptoms with metabolic disease based on 3000 consultancies data analysis.

Metodologia: Health care providers can access SIEM by phone or e-mail, through the 0800 510 2858 that receives free consultations from all places in Brazil or through the website (http://www.siem.ufrgs.br). This study included a database (EpiData) and the review of 3000 consultancies registered at SIEM from October 1st, 2001 to March 2nd, 2016. The analysis was performed using the program Statistical Package for Social Sciences, version 22.0 to study of frequency and correlation data.

Resultados: SIEM contributed to the definitive diagnosis in 1022/3000 consultancies (34%) and the diagnosis of IEM was confirmed in 10.7% cases. The overall risk of a diagnosis of metabolic disease was 11.9%. We selected 17 signs and symptoms of IEM that were crossed with the occurrence of metabolic disease the significance was determined by the Chi-squared test, estimates of strength of association between the factors and the outcome were obtained through the odds ratio with 95% confidence interval. Through a logistic regression model with anterograde selection of variables we obtained the factors significantly associated to the outcome: coma, developmental regression and food refusal. It was possible to design a simple risk score based on the addition of these significant factors. It was observed that cases presenting with none, one, two or three of the selected symptoms (coma, developmental regression and food refusal) presented a risk of 9.3%, 14.4%, 24.9% and 27.6% respectively, for the outcome of the metabolic disease.

Conclusão: The lack of knowledge and limited number of specialized centers in the diagnosis and treatment of metabolic diseases contributes to the delayed diagnosis and inadequate management. For the IEM, treatable group early diagnosis should determine a chance of cure and can influence morbidity and mortality. The final diagnosis allows the appropriate clinical management, genetic counseling and avoids unnecessary interventions. The analysis and interpretation of data generated by SIEM allowed us to create a simple risk score correlating symptoms as coma, developmental regression and food refusal to a higher risk of outcome as a metabolic disease. This score risk may be useful to generate new diagnosis strategies and proposes the discussion of new approaches and actions to earlier diagnoses.

Código #13395

Título: CYTOKINES IN GLYCOGEN STORAGE DISEASE TYPE 1 PATIENTS: A CONTROLLED CROSS-SECTIONAL STUDY.

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Aim: To determine the cytokine profile in a sample of Glycogen Storage Disease (GSD) type 1 patients in comparison to healthy controls.

Methods: Observational, cross-sectional, controlled study, with convenience sampling. Eighteen GSD type 1 patients (GSD type Ia= 13; type Ib= 5; female= 11; median age 14 years, IQR=12) and 18 healthy controls, sex- age-matched were included. Patients recruited from the outpatient clinics of the Medical Genetics Service at Hospital de Clínicas de Porto Alegre (HCPA), Brazil. The inclusion criteria for patients were: a) having a biochemical and/or genetic diagnostic for GSD type 1; and b) being aged 3 years or older. The healthy controls (HC) were recruited by invitation among the population of RS. Patients and HC had 5 mL of blood collected in heparinized tube. The quantification assay was realized through EMD Millipore's MILLIPEX® MAP Human Cytokine kit, accordingly manufacturer's instruction. All samples were measured in duplicates for 5 cytokines (G-CSF, INFy, GRO, MDC/CCL22 and IL17A). Measurements with divergence ≥ 30% between duplicates would be excluded from data analysis, as well as data of their respective pair (control/patient). The results were compared using non-parametric test for independent samples, U-Mann-Whitney. Statistical analyses ($p \leq 0.05$) were performed with IBM SPSS Statistics for Windows software, version 22 (IBM corp., NY).

Results: All patients were on cornstarch therapy. Patients with GSD type 1b were also receiving G-CSF. Patients and controls did not differ regarding sex or age. None of the samples presented divergence≥ 30% for duplicates. Patient and control groups were statistically different only for MDC/CCL22 (Median for patients= 427.61 pg/ml; for controls= 674.04 pg/ml; p=0.003). MDC/CCL22 levels did not differ between GSD type 1a and 1b patients. Comparison between GSD type Ia and Ib patients showed G-CSF is higher in the later ones (median for Ia=29.26 pg/ml; for 1b= 178.89 pg/ml; p= 0.001).
Conclusion: Our findings do not suggest the presence of an inflammatory status in GSD type 1 patients. However, the low levels of MDC/CCL22 may suggest they are prone to infections and should be better evaluated. G-CSF was higher in GSD 1b patients probably because they were receiving G-CSF.

Código #12660

Título: Disorder of Intracellular Cobalamin Metabolism Type C – A Case Report

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Objective: To describe the clinical presentation, diagnostic and treatment, highlighting the suspicion for diagnosis of one patient diagnosed with disorder of intracellular cobalamin metabolism (Cbl) type C.**Method:**Retrospective study of medical records (Ethics Committee Approval CEP-UNIFESP #2007/11).

Case Report: Female, 1st appointment at our center at 1y3mo of age. First child of an unrelated couple, presented intrauterine growth restriction (IUGR). Microcephaly, hypotonia and poor feeding noticed at first day of life. At 25 days of life she presented spasms, at 35 days of life she presented respiratory distress and was hospitalized. She had anemia, her myelogram revealed severe hypocellularity of red cells, some enlarged erythroblasts (some multinucleated) and funduscopy presented bilateral hypopigmentation of papila and macula. Metabolic workup presented high homocysteine levels, methylmalonic acid elevated in plasma and urine, acylcarnitines profile with increased levels of C3 and decreased level of C0, aminoacids profile showed reduced levels of methionine. At 2 months of age she presented intracranial hemorrhage, the diagnosis of methylmalonic acidemia (MMA) was established and she began specific diet therapy and hydroxocobalamin (vB12) 5000 mcg 3X/week. The hospitalization lasted 10 months and she had a lot of intercurrent infections and an acute renal failure at 8 months of age that needed hemodialysis and peritoneal dialysis for 4 days. She had undergone gastrostomy, tracheostomy and ventriculoperitoneal shunting due to hydrocephalus. When she came to the 1st appointment at our center, she had been under treatment for MMA for the last 11 months, her neurological examination revealed microcephaly, nistagmus, hemiparesis, hypotonia, normal deep tendon reflex and did not role. Based on her clinical presentation and laboratorial findings we established the diagnostic suspicion of Disorders of Intracellular Cbl Metabolism - probably type C. We advised the family to quit the diet therapy and keep only the vB12. The molecular analysis of *MMACHC* gene revealed the mutation c.271dupA in homozigous state in exon 2, this mutation has been previously described related to the early-onset form of the disease. At 1y11m, as patient was clinically stable, we reduced the vB12 dose to 1000 mcg/week and she worsened her hypotonia; thus, the vB12 dose was increased to 5000 mcg/day and after 10 days she had neurological improvement. At 2y11m began to present seizures, without neurological regression. Currently she is 3y6m, can stand up with assistance and had a remarkable improvement of dysphagia and attention.

Conclusion: MMA does not present IUGR, or microcephaly at birth. Whenever physicians face a newborn with increased methylmalonic acid, if there is a pre-natal compromise or severe neurological manifestation such as microcephaly at birth, the suspicious of disorder of Cbl metabolism should be raised and specific treatment initiated.

Código #13180

Título: DRIED BLOOD SPOT B-GLUCURONIDASE REFERENCE RANGE IN HEALTHY INDIVIDUALS

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Objetivos: The mucopolysacharidosis VII called Sly syndrome is caused by deficiency of the β-glucuronidase enzyme (GUSB), which difficult the degradation of the glucuronic acid residues contained in the glycosaminoglycans dermatan sulfate, heparan sulfate and chondroitin sulfate. The diagnosis is performed by measure of enzymatic activity in plasma, dried blood spot (DBS) and leukocyte samples. The aim of this work is to determine the efficiency of the measurement of GUSB activity in 1.2 mm DBS comparing it with the original techniques, through the reference interval.

Metodologia: The reference interval of β-glucuronidase activity was established in 27 blood samples impregnated on filter paper from healthy subjects. The analyzes were performed using the miniaturized technique, with a 1.2mm spot and 4h hours of incubation.

Resultados: The mean activity was 446.2 nmol/h/mL with a standard deviation of 120.08 nmol/h/mL and a minimum value of 174.4 nmol/h/mL and a maximum of 649.0 nmol/h/mL.

Conclusão: The normal range for GUSB obtained in this work is close to that found in plasma (30 to 300 nmol/h /mL), leukocytes (23 to 151 nmol/h/mg of protein) and 3mm DBS (4.02 to 21.93 nmol/h/mL). As previously described for other lysosomal enzymes, plasma activity was close to that in DBS, like plasma chitotriosidase and alpha-iduronidase. Observing this perspective, our results are in agreement with that obtained in the literature for other lysosomal hydrolases and in 3mm DBS. This shows that this technique can be used in diagnostic laboratories, being a good alternative for the original technique, since it has low costs. Supported by CNPq.

Código #13390

Title: Enzyme Replacement Therapy with taliglucerase alfa and breastfeeding in Gaucher disease.

Authors: Tatiéle Nalin, Livia D'Avila Paskulin, Alícia Dorneles Dornelles, Kristiane Michelin Tirelli, Ida Vanessa Doederlein Schwartz

Institution of Authors: Universidade Federal do Rio Grande do Sul and Medical Genetic Service and Hospital de Clínicas de Porto Alegre

Objective: To determinate the β-glucocerebrosidase levels in the breast milk of a patient with GD in ERT with taliglucerase alfa.

Methodology: Blood samples (immediately before and after infusion) and breast milk samples (before, immediately after, and 30 minutes after infusion) were collected from a Brazilian patient with GD type I, genotype p.N370S/L444P, 21.8 years. She has been treated with ERT for a year and, currently, she is on ERT with taliglucerase alfa (30 U/kg, every 15 days). Also, a control milk sample from a healthy mother was included in the study. All samples were tested for β-glucocerebrosidase activity.

Results: β-glucocerebrosidase activity in breast milk were 3.9 nmol/h/mL before infusion, 7.1 nmol/h/mL immediately after and 7.2 nmol/h/mL 30 minutes after infusion, while the level in leukocytes was 1.3 nmol/h/mg prot before infusion and 3.5 nmol/h/mg prot after infusion. β-glucocerebrosidase activity measured in the control milk sample was 42 nmol/h/mL. The newborn do not present intercurrences and is having adequate development.

Conclusions: Levels of β-glucocerebrosidase were found to be much lower in breast milk from the GD patient in use of taliglucerase alfa comparing with the control sample. Thus, the use of taliglucerase alfa during breastfeeding seems to be safe for the newborn.

Código #13367

Palavras-chave: mucopolissacaridose, terapia de reposição enzimática, adesão ao tratamento

Resumo:

Objetivos: Relatar o processo da terapia de reposição enzimática (TRE) e estratégias para manutenção da mesma em ambiente hospitalar universitário. Métodos: Estudo descritivo do tipo relato de experiência. Resultados: A TRE teve início em nosso hospital em 2005. Nossa primeira experiência ocorreu através do estudo clínico TKT 024 – TKT024-EXT, com a participação de dois pacientes que realizavam as infusões em uma enfermaria da Unidade de Pacientes Internos designada para a condução do estudo. Após aprovação e uso comercial da Elaprase®, o número de pacientes aumentou gradativamente, até chegarmos ao número máximo de nove pacientes (atualmente seis falecidos). As infusões passaram a ocorrer na sala de medicação da Unidade de Pacientes Externos, uma pequena sala que foi adaptada para tal finalidade. Desde o início da TRE houve comprometimento e participação das equipes médica e de enfermagem. Em 2011 foi inaugurado o Hospital-Dia (HD), setor que contava com maior espaço, individualização de leitos e melhores condições técnicas e operacionais. Alguns projetos de extensão do nosso hospital passaram a integrar a vivência do HD, como o “Contadores de História” e o “TO brincando”. O projeto “Contadores de História” é composto por alunos de graduação da universidade provenientes de todas as áreas e o projeto “TO brincando” conta com atuação de terapeutas ocupacionais. A equipe de enfermagem organiza comemorações em datas festivas, onde todos participam: pacientes, familiares e a equipe de saúde. Há também a colaboração da “Anjos da Guarda Associação de Apoiadores aos Portadores de Mucopolissacaridose e de Doenças Raras” que ajuda os pacientes e familiares dentro das respectivas necessidades, além a atuação do Serviço Social sediado no hospital. Ao longo do tempo, percebemos que as faltas ao tratamento com a TRE diminuíram e atualmente acontecem por motivo de consulta em outro hospital marcada no mesmo dia da infusão, doença do paciente ou de familiar e problemas com o transporte e/ou trânsito. Conclusão: Ações regulares lúdicas, educativas, de cunho social e direcionadas para a saúde da unidade familiar fortalecem o vínculo da família com a equipe hospitalar e contribuem substancialmente para a melhor adesão ao tratamento.

Código #13331

Título: Estudo das mutações IVS10nt11G>A, V388M, R261Q, R261X, R252W e R408W no gene da fenilalanina-hidroxilase em pacientes com fenilcetonúria do Estado de Mato Grosso.

Autores: Roseli Divino Costa e Marcial Francis Galera

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Palavras chaves: Triagem neonatal, fenilcetonúria, genótipo, fenótipo, Mato Grosso.

RESUMO: A fenilcetonúria é uma doença autossômica recessiva que na sua forma clássica é causada pela deficiência da enzima fenilalanina hidroxilase da (PAH), cuja função é catalisar a reação de hidroxilação da fenilalanina em tirosina. A fenilcetonuria está entre os erros inatos de metabolismo mais bem estudados, por fazer parte do programa de triagem neonatal em todo o mundo. No Brasil essa confirmação ocorre pelo Programa Nacional de Triagem Neonatal, através dos Serviços de Referência em Triagem Neontal e todos os Estados brasileiros estão habilitados. Investigamos as mutações IVS10nt11G>A, V388M, R261Q, R261X, R252W, e R408W no gene da fenilalanina-hidroxilase, descritas como as mais frequentes no Brasil, conforme a literatura.

OBJETIVO: O presente trabalho teve como objetivo identificar as alterações moleculares responsáveis pela hiperfenilalaninemia (HPA) em indivíduos em acompanhamento no Serviço de Referência em Triagem Neonatal do Estado de Mato Grosso.

MÉTODOS: O presente estudo é do tipo transversal descritivo. A população foi composta de 19 pacientes entre adultos e crianças. A extração de DNA foi realizada pela metodologia *Salting out* e quantificados pelo Nanodrop®. Foram analisadas as mutações IVS10nt11G>A, V388M, R261Q, R261X, R252W, I65T E R408W, através da técnica de PCR e digestão com enzima de restrição específica.

RESULTADOS e CONCLUSÕES: Entre os 19 pacientes que participaram da pesquisa, 4 (21,0%) tiveram seus dois alelos genotipados através da metodologia empregada. Em 4 (21,0%) dos pacientes apenas um alelo foi identificado, e 11 (57,9%) dos pacientes ambos os alelos permaneceram sem mutações identificadas. Através da pesquisa das 6 mutações descritas, foi possível identificar 12/38 alelos, correspondendo a 31,6% dos alelos de PKU da amostra. A mutação com maior prevalência foi V388M (13,2% dos alelos), seguida por R261Q (10,1%), seguida por IVS10ntG>A (7,9%), as mutações R261X, R252W e R408W, não foram encontradas com a metodologia empregada. As mutações mais encontradas foram as do tipo troca de sentido, em 8 pacientes (18,42%), e a emenda foi encontrada em 04 pacientes (10,52%). A incidência da fenilcetonúria do período de 2003 a 2015, ficou em 1:33.342 nascidos vivos na população estudada. A média de cobertura do programa no Estado de Mato Grosso no período de 2003 a 2015 ficou em 75,8%. No mesmo intervalo de tempo recebemos 05 pacientes transferidos de outros Estados.

Código #13414

Title: Experience with the use of tetrahydrobiopterin in the Medical Genetics Service of the Hospital de Clínicas de Porto Alegre

Authors: Ida Vanessa Doederlein Schwartz; Tássia Tonon; Luciana Giugliani; Tatiéle Nalin

Institution of Authors: Universidade Federal do Rio Grande do Sul and Medical Genetics Service/Hospital de Clínicas de Porto Alegre

Objective: To report the experience of using the tetrahydrobiopterin cofactor (BH_4) in patients with Phenylketonuria (PKU) and BH_4 deficiency followed in the Medical Genetics Service of the Hospital de Clínicas de Porto Alegre.

Methodology: The data comes from the Metabolic Disorders Outpatient Clinic, which currently follows 85 patients with PKU, due to phenylalanine hydroxylase deficiency, who are undergoing dietary treatment. Four patients with BH_4 Deficiency are also followed in this service and the treatment consists of administration of BH_4 along with adjuvant drugs and none of these patients follow diet therapy. For PKU patients, two different protocols were used to assess BH_4 responsiveness: one based on BH_4 loading test and the other based on the combined L-Phe + BH_4 loading test (Giugliani *et al*., 2011; Nalin *et al*., 2011).

Results: Thirty-four PKU patients performed, at least, one of the BH_4 responsiveness protocols and twelve of them are classified as responsive to the medication, by reducing in, at least, 30% the phenylalanine plasma values. None of these patients are currently using BH_4, but one is awaiting judicial decision to start treatment. On the other hand, all patients with BH_4 Deficiency use the cofactor in their treatment, keeping Phe levels within normal range.

Conclusions: Our findings are in agreement with the literature and indicate that a relevant number of Brazilian patients with PKU are responsive to BH_4. It was observed that, for patients with BH_4 deficiency, the treatment with BH_4 has been used, possibly because there is no other therapeutic option. Currently in Brazil, access to this medication is only through a judicial process. We reinforce the importance of conducting BH_4 responsiveness tests in the Brazilian patients in order to know the population that can benefit from it, as it can be an adjuvant in the treatment of the patients and improve their quality of life.

Código #13370

Title: FIRST BRAZILIAN PATIENT WITH GAUCHER DISEASE TREATED WITH TALIGLUCERASE-ALPHA DURING PREGNANCY.

Authors: Livia D'Avila Paskulin; Alicia Dorneles Dornelles; Amanda Quevedo; Tatiele Nalin; Joshua Werner Bicalho da Rocha; Filippo Pinto e Vairo; Ida Vanessa Doederlein Schwartz

Authors Institutions: Gaucher Disease Reference Center of Rio Grande do Sul, Medical Genetics Service, Hospital de Clínicas de Porto Alegre; Post-Graduation Program in Genetics and Molecular Biology, Universidade Federal do Rio Grande do Sul.

Objective:
This study aims at reporting the first Brazilian Gaucher disease (GD) patient treated with taliglucerase-alpha (tali) during pregnancy.
Methods:
Case report.
Results:
A 20-years-old female was diagnosed with GD after a liver biopsy to investigate hepatosplenomegaly. *GBA1* genotype N370S/L444P, chitotriosidase=27,878nmol/h/mL, platelets=88,000/mm³, Hb=10.6g/dL, AST=127U/L, and ALT=96U/L; hepatic and spleen size by percussion, 8 cm and 13 cm, respectively; abdominal ultrasonography showed massive splenomegaly; SSI was 4 and DS3 severity score was 1.33. Following the Brazilian Ministry of Health recommendations, treatment was initiated with tali 15IU/kg/inf, every 15 days. Before the 8th infusion, during consultation, she revealed being 6 weeks pregnant. A meeting was held between the patient and the medical and allied staff of the GD Reference Center of Rio Grande do Sul (GDRC-RS), in which all the risks and benefits of maintaining or interrupting therapy were disclosed. Patient decided to maintain treatment, and she was referred for prenatal care in the same hospital of the GDRC-RS. She followed all recommendations regarding diet and iron and vitamins supplementation, and didn't experience any complication during the first trimester of pregnancy. After 13 infusions of tali (22 weeks of pregnancy), platelet levels decreased from 88,000 to 72,000/mm³ and Hb from 10.6 to 10.1g/dL, and chitotriosidase from 27,878 to 8,180nmol/h/mL. At that time, the dosage of tali was adjusted to her current gestational body weight. After 36 weeks pregnancy, patient remained with thrombocytopenia (77,000/mm³) and, thus, tali dosage was increased to 20UI/kg/inf. She gave birth through vaginal delivery to a healthy baby boy at 39 weeks and 5 days of pregnancy. Blood tests prior to delivery showed platelets=95,000/mm³, hemoglobin=13.4g/dL, and chitotriosidase=7,919 nmol/h/mL. During labor, she developed petechiae in her face and trunk, which resolved spontaneously after 1 week. There was no significant blood loss described during delivery, although control blood tests showed hemoglobin=8.4g/dL. One day after delivery patient received ERT (20UI/kg/inf), and after two days, both patient and her son, were discharged from the hospital. After 15 days of delivery, patient return to regular ERT infusions.
Conclusion:
The managing of GD patients who start ERT during the pregnancy is challenging. Tali appears to be effective and safe during pregnancy.

Código #13396

Title: *GBA2, SCARB2,* AND *PSAP* AS MODIFIER GENES OF GAUCHER DISEASE TYPE 1.

Authors: Rodrigo Tzovenos Starosta, Suelen Basgalupp, Marina Siebert, Ida Vanessa Doederlein Schwartz.

Authors' institution: Post-Graduation Programs in Genetics and Molecular Biology (PPGBM) and in Medical Sciences (PPGCM), Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil; Hospital de Clínicas de Porto Alegre (HCPA).

Objectives: Explore the possibility that *GBA2, SCARB2* and *PSAP* act as a modifier genes in Gaucher disease (GD). All those three genes encode proteins that interact directly with glucocerebrosidase.

Methods: Nineteen GD type 1 patients were included in the study. DNA samples obtained from those patients were analyzed by Next-Generation Sequencing (NGS) in the IonTorrent PGM platform (Life Technologies). *GBA2, SCARB2* and *PSAP* genes were included in the panel. NGS analyses were performed in Enlis Software. Phenotypes were taken from the patients' medical registry.

Results: Six patients were found to have heterozygote variants of either *GBA2, SCARB2,* or *PSAP*. Patient 1 is a 60 years-old female with a p.I149S variant in *GBA2*, predicted by Polyphen2 (PP2) to be "benign" and by SIFT to be "deleterious with low confidence" and whose ExAC frequency was of 0.4%. Patient 2 is a 40 years-old female with a p.T11T variant in *GBA2* whose ExAC frequency was of 0.4%. Patient 3 is the 47 years-old sister of patient 2 with the same variant as its sibling's. Patient 4 is a 22 years-old male with a p.V149M variant in *SCARB2* predicted by PP2 to be "probably benign" and SIFT to be "tolerated" and whose ExAC and ClinVar frequencies was of 0.2% (1.4% in people from Italian ancestry). Patient 5 is a 50 years-old male with a *SCARB2* p.P128S variant, respectively "possibly damaging" and "deleterious" by PP2 and SIFT, and whose ExAC frequency was 0.009%. Patient 6 (sibling of patient 5) is a 40 years-old male with two *PSAP* variants, p.L118L and p.Y113D, the latter being predicted by PolyPhen to be "probably damaging" and by SIFT to be "deleterious", and whose ExAC frequencies are both 0.001%. Patients 5 and 6 did not refer regarding their clinical phenotype. Patients with and without variants in *GBA2, SCARB2* and *PSAP* also were not found to differ regarding their clinical phenotype.

Conclusion: Our data do not support that *GBA2 SCARB2,* and *PSAP* are modifiers of GD type 1.

Código #13383

Title: GENETIC PROFILE OF BRAZILIAN PATIENTS WITH INBORN ERRORS OF FRUCTOSE METABOLISM.

Authors: Franciele Cabral Pinheiro, Fernanda Sperb-Ludwig, Carolina F. Moura de Souza, Filippo Vairo, Erlane M. Ribeiro, Ida Vanessa Doederlein Schwartz

Authors' Institution: Universidade Federal do Rio Grande do Sul (UFRGS); Hospital de Clínicas de Porto Alegre (HCPA), Faculdade Estácio do Ceará (Estácio FIC), Brazil.

Objectives: To characterize the genetic profile of Brazilian patients who have hereditary fructose intolerance (HFI; aldolase B deficiency) or fructose-1,6-bisphosphatase deficiency (FBD), which are rare inborn errors of metabolism associated with the occurrence of episodes of hypoglycemia. The analysis of aldolase B activity is not available in Brazil whereas the analysis of the fructose-1,6-biphosphatase activity should be done in the liver tissue, making these diagnosis more difficult to achieve based only on biochemical tests.

Methodology: We analyzed DNA samples from unrelated individuals with clinical suspicion (n= 2) or previous genetic diagnosis (n= 2; Sanger sequencing) of HFI, and with clinical suspicion (n= 3), confirmed biochemical (n= 2) or previous genetic and biochemical diagnosis of FBD (n= 1; Sanger sequencing), using the IonTorrent PGM platform (Life Technologies). A multigene panel was customized and both *ALDOB* and *FBP1* were included. All the exonic regions and the intron-exon boundaries had high quality reads and deeply covered base pairs. The variants found will be confirmed using the Sanger sequencing method. For novel missense variants, the impact on protein was predicted by three different *in silico* algorithms.

Results: Our multigene panel approach confirmed the diagnosis of HIF in three individuals (including both individuals with previous genetic diagnosis), and the diagnosis of FBD in two individuals with biochemical diagnosis and in one with high clinical suspicion. However, only one mutation in the patient with previous genetic diagnosis performed by Sanger was found. Two novel mutations were found in the *FBP1* gene: c.986T>C (p.L329P) and c.958G>A (p.G320R). The *in silico* prediction algorithms have conflicting results for the first variant whilst they agree that the second variant is pathogenic.

Conclusions: Our data suggest the multigene panel developed by our group is an useful approach to be used as a first-tier test for the diagnosis of individuals with HFI and FBD.

Código #13405

Tittle: Impact of enzyme replacement therapy (ERT) on bone turnover markers in MPS IVA patients

Authors: Catia Eufrazino; Paula Frassinetti Vasconcelos de Medeiros; Gabriela Oliveira Chaves e Francisco Bandeira

Institution: Genética Médica - Hospital Universitário Alcides Carneiro, Universidade Federal de Campina Grande, Brasil e Serviço de Endocrinologia do Hospital Agamenon Magalhães, SUS – Pernambuco.

Objective: This study aimed to analyze basal and six months ERT impact on bone turnover markers in MPSIV-A patients

Metodology: An observational cross-sectional study to evaluate the impact of ERT on bone metabolic profile after six months TRE in patients with MPSIV-A. Clinical information: age, genre, height, weight, body mass index (BMI), ambulatory capacity, calcium intake, bone fracture. Biomarkers of bone turnover were assessed: alkaline phosphatase, Collagen Type I C-Telopeptide (CTX), 25OH D vitamin, Parathyroid hormone (PTH) and 24h urine calcium. Serum CTX (electrochemiluminometric assay) was the parameter used to evaluate bone resorption, alkaline phosphatase, calcium and 24 hours calciuria were evaluated by the colorimetric method and dosage of 25-Hydroxy Vitamin D and PTH were quantified from the plasma by the Chemiluminescence method. The evaluation of bone mineral density (BMD) and bone mineral content (BMC) was assessed through whole body (WB) and 33% radius bone densitometry (evaluation of cortical bone) . Evaluation of cortical bone BMD of the WB and 33% radius were acquired by dual-energy Xray absorptiometry (DXA). Interpretation of Z-score values for the age group: Z-score equal to or less than -2 standard deviations is defined as "below the range expected for age" and a Z-score above -2 standard deviations is classified as "within the expected limits for age".

Results: 21 patients (9 males and 12 females) with a mean age of 29.95 ± 8.47 years (16 to 46 years). The bone mineral density (BMD) of the whole body (WB) was normal in 20/20 patients. The cortical bone (33% radius) assessed in 15/20 patients showed bone mass below that expected for age in 15/15 patients. Among the patients able to walk, the mean of z-score 33% radius was -3,4 (range -1,6 to -5) while in non-ambulatory patients, it was -4,0 (range -3,7 to -4.2). The z-score of 33% radius was indirectly proportional to the height and age of the patients. Two factors impaired the assessment of BMD of 33% radius in all patients: bone deformation or lack of reference of the z-score for those younger than 20 years old. Alkaline phosphatase, as a marker of bone formation, was normal in all patients. The CTX, a bone reabsorption marker, was over the upper limit of normality in 7/21 patients (0.490 ± 0.280 ng/mL). In 21/21 patients, the calcium intake was lower than the one recommended, but the 25OH D vitamin and PTH were normal.
The high 24h urine calcium could not be valued because it was associated with a low diuresis in all patients whose etiology has not been determined. No patient reported bone fracture. Twelve patients were assessed after six months ERT: the CTX mean value was 0,540 ng/mL + 0,190

ng/mL; In 5/12 patients CTX values was above the upper limit of normal; in 1/12 patient CTX was normal (previously elevated). Alkaline phosphatase, 25OH D vitamin and PTH remained in normal range in 12/12 patients

Conclusão:

Low bone mass for age associated with high levels of CTX, an important marker of bone resorption, were found in MPSIVA patients. After 6 months TRE, the CTX mean value was lower.

Código #13402

Titulo: Impact of enzyme replacement therapy on quality of life of a 34 year-old Mucopolyssacharidosis IVA patient

Autores: Marco Antonio Curiati[1]; Rosângela Maria da Silva[1]; Ana Maria Martins[1]

Instituição dos Autores: [1]Reference Center for Inborn Errors of Metabolism, Universidade Federal de São Paulo

Objetivos: The mucopolyssacharidosis type IVA (MPS IVA), due to the important skeletal dysplasia it develops, can present with severe chronic pain and joint range of motion limitation, causing a severe deficit in patients quality of life. The objective of this study was to evaluate the impact of enzyme replacement therapy (ERT) in the quality of life of a MPS IVA adult patient.

Metodologia: Retrospective study of clinical and laboratorial data from patients files (Ethics committee approval CEP-UNIFESP 2007/11).

Resultados: Female patient, currently 34 years old, referred to our service with 20 years old due to skeletal dysplasia. Had a background of progressive gait impairment, and became wheelchair-dependent with 11 years old. Since 20 years presented daily chronic pain, and refers that it was worsening in frequency and intensity until starting the treatment.
Began ERT in November 2014, aging 32 years 10 months. Patient refers recurring upper airway infections (UAI) previous to ERT, on a monthly basis, needing treatment with antibiotics. Also refers worsening of the hearing impairment during the infections, due to obstruction. After ERT refers improvement of UAI, presenting 1-2 episodes/year, with less compromise of hearing. Patient refers low quality of sleep, with increase of sleep latency due to pain, in every lying position. After ERT, refers that has no trouble sleeping anymore, with less latency. Regarding to snoring, patients mother refers reduced intensity after ERT. Regarding chronic pain, previous to ERT patient presented daily episodes of pain, in lumbar spine, hips and thighs, with severe intensity, referring to cry in some episodes due to intense pain. Refers daily use of common analgesics with partial improvement. After ERT refers much less intense pain, 1-2x/week, mild to moderate intensity, generally presenting pain after several hours seated using the computer. Refers full recovery with usage of ordinary analgesics. Regarding hearing impairment, refers that prior to ERT refers that stopped using hearing aid on right ear, due to complete absence of hearing perception. After ERT re-started using the aid, since noticed residual hearing on that ear. Refers important improvement of fatigue, previous to ERT had daily episodes, after ERT, once a week presents mild fatigue. Regarding reduced joint range of motion, after ERT refers improvement of movement, specially to climb the wheelchair, to change clothes and to stand up with support. On a general basis refers important improvement of humor and wellbeing.

Conclusão: The patient presented improvement in every evaluated aspect, specially regarding chronic pain episodes, showing the significant impact of ERT in improvement of quality of life, even when the treatment begins on adult life.

Código #13150

Título: IMPROVEMENT OF DIAGNOSTIC TECHNIQUE OF MPS VII IN DRIED BLOOD SPOTS

Autores: Jaqueline Cé, Melissa Torres Rodrigues, Janice Carneiro Coelho

Instituição dos Autores: Laboratório de Erros Inatos do Metabolismo - Doenças Lisossômicas de Depósito, Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Brasil.

Objetivos: The mucopolysacharidosis VII called Sly syndrome is caused by deficiency of the β-glucuronidase enzyme (GUSB), which difficult the degradation of the glucuronic acid residues contained in the glycosaminoglycans dermatan sulfate, heparan sulfate and chondroitin sulfate. The diagnosis is performed by measure of enzymatic activity in plasma, dried blood spot (DBS) and leukocyte samples. The aim of this work is to miniaturize, correlate and validate the method for measuring the activity of GUSB in 1.2 mm dried blood spots (DBS).

Metodologia: The fluorimetric technique for the measurement of GUSB activity described by Civallero et al. (2006) was adapted to 1.2 mm DBS. Correlation tests with 14 health individuals were performed. This miniaturized method used reagents reduced 2.5-fold and 4-fold. After the correlation results, the 4-fold reduced technique was used for the validation tests: Interassay, Interpersonal and Intraassay.

Resultados: Comparing the 3.0 x 1.2 mm DBS, in the method with the reagents reduced 2.5-fold the Pearson's coefficient was r = 0.4289, without correlation. On the other hand, the method with 4-fold reduction had a significant correlation (Pearson's r = 0.7908). This last method was validated and the following results were obtained for the coefficients of variation: Intraassay 9.3%, Interassay 11.9%, and Interpersonal 9.4%.

Conclusão: These results show that it is possible to measure the activity of GUSB with a smaller DBS diameter and a 4-fold reduction in the volume of the reagents, as has been done with other lysosomal hydrolases (chitotriosidase, alpha-iduronidase and beta-glicosidase), obtaining the same results. The miniaturization of the MPS VII diagnostic method allows sample saving, which can then be used to screen for other inborn errors of metabolism, and reagents, reducing the cost of the analysis. The results obtained in the validation of the miniaturized method indicate that the three coefficients of variation are within the acceptable value. This demonstrates the accuracy and reproducibility of the method used. Supported by CNPq.

Código #13343

Título: IMPROVEMENT OF THE QUALITY OF LIFE WITH USE OF ENZYMATIC REPLACEMENT IN A WHEELCHAIR PATIENT WITH MORQUIO SYNDROME.

Autores: Helena Pimentel; Melissa Calvão Dumas; Ana Alzira Alves

Instituição dos Autores:HCRS - Hospital Central Roberto Santos, Salvador/BA, Brasil.

Objetivos: Introduce objective improvement (need for emergency attendance and adapted 6 minute walking test – 6MWT) and subjective (patient perception about quality of life) after 1 year of the use of enzymatic infusion in a patient with Mucopolysaccharidosis (MPS) Type IVA.

Metodologia: Clinical follow-up and patient interview. The patient started the infusions on 03/30/2015, and before start infusions we performed the adapted 6MWT (crawling test), we performed the test after 6 months and after 1 year of enzyme replacement therapy (ERT). In addition we performed patient interviews, clinical follow-up and evaluation of medical consultations in an emergency room.

Resultados: After 1 year of ERT, the patient presented a increase in the modified 6MWT (crawling test) - Initially 20 meter and 40 meters after 1 year - and, mainly, according to the patient's own report, an important improvement in the quality of life. As a marker of improvement, we found that after initiation of the infusions the patient did not need emergency services anymore, due to the symptoms of dyspnea, dizziness and arthralgia founded prior to ERT.

Conclusão: The impairment of the patient's mobility, associated with the difficulty of mobilization to a larger medical center, turned impossible to perform complementary exams at baseline and during treatment. However, we consider that the adapted 6MWT, the evaluation of morbidity reduction and the subjective improvement attested by patient interview, made it clear that the ERT performed a concrete benefit for the patient with late diagnosis and handicapped.

Código #13454

Título: Interface entre assistência e pesquisa: o Serviço de Genética e o HOS

Autores: Márcia Gonçalves Ribeiro, Gustavo Guida Godinho da Fonseca, Claudio Baptista Schmidt, Ana Carolina Esposito, Raquel Germer Toja Couto, Raquel Tavares Boy

Instituição dos Autores: Instituto de Pediatria Martagão Gesteira - UFRJ

Palavras-chave: mucopolissacaridose tipo II, síndrome de Hunter, HOS, história natural, acompanhamento

Agências de fomento: Shire Brasil

Resumo:

Objetivos: Descrever o perfil dos pacientes que participam do estudo *Hunter Outcome Survey* (HOS) - "Estudo Observacional, Multicêntrico, Internacional e Prospectivo de Pacientes com Síndrome de Hunter (Mucopolissacaridose II)" e as atividades realizadas para o funcionamento do estudo.

Métodos: Estudo descritivo e transversal. Amostra de conveniência. As variáveis estudadas foram idade atual dos pacientes, idade do óbito dos que já faleceram, gravidade da doença, Terapia de Reposição Enzimática (TRE), tempo de permanência no estudo, motivo de perdas, atividades realizadas pela equipe. Análise descritiva.

Resultados: O projeto foi aprovado pelo Comitê de Ética em Pesquisa (CEP) da nossa instituição em novembro de 2009 e o início das atividades ocorreu em 2010. Foram incluídos até o momento oito pacientes com mucopolissacaridose tipo II, três vivos e cinco falecidos. A mediana da idade dos pacientes ativos é de nove anos (limite inferior = 4; limite superior = 20 anos). A mediana da idade do óbito foi de 20 anos (limite inferior = 12 anos e superior = 33 anos anos). Dos oito pacientes, somente dois apresentavam a forma mais leve da doença. Do total, seis pacientes fazem ou fizeram TRE. O tempo de permanência no estudo em nosso site variou de três a seis anos, sendo que dois pacientes foram incluídos após o óbito, com a autorização do responsável e um paciente retirou consentimento no mesmo dia em que consentiu com sua participação. As visitas de monitoria ocorrem duas vezes ao ano e o contato telefônico para atualização é mensal. São enviados relatórios ao CEP semestralmente e aplicados questionários de qualidade de vida uma vez ao ano. A programação dos exames complementares de rotina é estabelecida pelo Serviço de Genética Médica e os pacientes são pesados de três em três meses aproximadamente. Conclusão: A participação em um estudo desta monta onde é sistemática a entrada de dados auxilia na rotina assistencial do serviço e possibilita o conhecimento deste grupo de pacientes individualmente e em conjunto.

Código #13290

Title: LOSARTAN IMPROVES HEART AND AORTIC DISEASE IN MUCOPOLYSACCHARIDOSIS I.

Authors: Eduardo Cheuiche Antonio[1], Esteban Alberto Gonzalez[1,2]; Edina Polleto[1,2]; Angela Maria Vicente Tavarez[1,3]; Roberto Giugliani[4]; Ursula Matte[1,2]; Guilherme Baldo[1,2]

Institutions: [1]Gene Therapy Center, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [2]Posgraduation Program in Genetics and Molecular Biology, Porto Alegre, Brazil;[3]Posgraduation Program in Physiology, Porto Alegre, Brazil; [4]Medical Genetics Service, Porto Alegre, Brazil.

Aims: Verify the effects of blocking the TGF-β pathway with losartan on cardiovascular disease in a murine model of mucopolysaccharidosis I (MPS I).

Methods: MPS I mice started on treatment at 2 months of age with losartan (0.6g/L in drinking water; n=11) or propranolol hydrocloride (0.5g/L in drinking water; n=5). Untreated wild-type (WT) and MPS I mice (n=12) were used as controls groups. All animals underwent a single ultrasound examination at 6 months of age and subsequently were euthanized. Echocardiography analyses were performed to determine the left ventricular (LV) dimensions and cardiac function. The assessment of LV systolic function was performed using LV shortening fraction (LVSF). Aortic root diameter was determined using echo data was measured at end-diastole from M-mode. Additionally, the measurement of the diameter from ascending aortas was performed in situ using a digital caliper (with a 0.01 mm precision) under magnifying glass immediately after euthanasia.

Results: At 6 months, aortic root diameter was increased 67% in MPS I mice compared to WT (1.07 mm ± 0.13 vs 1.79 mm ± 0.25; p≤0.01). Losartan showed a decrease of 25% in aortic dilatation compared to MPS I (1.34 mm ± 0.15; p<0.01). Echocardiographic analysis showed that losartan also improves the LVSF. MPS I mice presented reduced contractility (36.7% ± 5.1 in WT vs 27.6% ± 3.6, p<0.05) while the heart function in treated mice with losartan was similar to WT (34.8% ± 5.7). Losartan also prevented enlargement of LV chamber dimensions. Heart diameter was enlarged in MPS I mice (p≤0.01) and normalized with losartan. As a comparison, we also treated mice with propranolol, which was also improved cardiac function and LV dimensions but not able to reduce aortic dilatation.

Conclusion: We suggest that losartan becomes a potential therapeutic approach for cardiovascular disease in MPS I, improving heart disease, reducing aortic dimentions and normalizing cardiac function. Propranolol also improved cardiac function, which suggests that heart dysfunction may be independent from TGF-β signaling. We believe that losartan targets the underlying pathophysiology in MPS possibly by antagonism of TGF-β or other pathways which will be investigated.

Código #13334

Title: LOW SERUM ALKALINE PHOSPHATASE – AN IMPORTANT CLUE TO THE DIAGNOSIS OF HYPOPHOSPHATASIA, A TREATABLE DISORDER

Authors: Ricardo Henrique Almeida Barbosa[1], Kelin Chen[1], Cecilia Micheletti[2]; Sônia Maria Mendes Santos[3], Mirela Alves Castro[3], Maret Holanda Rand[4], Carmen Silvia Curiati Mendes[4], Rosangela Maria da Silva[4] , Sandra Obikawa Kyosen[4], Ana Maria Martins[4].

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Objectives: HPP is an autosomal recessive IEM characterized by defect of bone mineralization due to deficiency of the alkaline phosphatase (ALP). The objective of this case report is to emphasize the importance of early clinical suspicion and diagnosis of hypophosphatasia (HPP).

Methods: Retrospective study of medical records (Ethics Committee Approval CEP-UNIFESP #2007/11).

Results: Male, second child of related parents, unremarkable antenatal history except for pregnancy induced hypertension and gestational diabetes and normal obstetric ultrasonographies. He has a 4-year-old brother with nephrolithiasis. At the time of birth, the patient presented respiratory distress requiring ventilatory support and was required 30 days of hospitalization in neonatal intensive care unit, during which he was diagnosed with bilateral hearing loss, cryptorchidism, bilateral congenital dislocation of the hips and congenital clubfeet. He presented several hospitalizations due to dehydration and recurrent infections, failure to thrive and no history of seizures. At the age of 13 months, he was hospitalized due to severe dehydration and respiratory failure after vomiting and diarrhea, requiring mechanical ventilation. On hisphysical examination, he presented microbrachycephaly, large anterior fontanel, flat face, prominent forehead, mild ocular proptosis, blue sclera, epicantal folds, hypertelorism, anteverted nostrils, anodontia, short neck, thorax asymmetry, skin cubital dimple, global hypotonia and developmental delay. His serum tests to investigate inborn error of metabolism (IEM) showed reduction in theALP concentration in three distinct samples, with no other significant changes. Study of the skeletal X-rays showed osteopenia, retarded bone age, widened-appearing sutures, alveolar bone loss, flared metaphyses and focal bony defects of the metaphyses resembling radiolucent "tongues" abnormalities. ALP dosages results performed in both parents and sibling were normal.

Conclusion:
The ALP dosage is a test performed routinely, presenting low cost yet high availability and is part of the essential basic laboratory tests for IEM work-up in our service. It should be part of routine investigation, especially in patients presenting skeletal anomalies, early loss of deciduous teeth and short stature. The diagnosis of HPP should be suspected in patients with severe skeletal defects

resembling vitamin D-resistant rickets with low ALP. This case emphasizes the importance of the assistant physician being aware to low ALP, since most of healthcare professionals are used to solely pay attention to elevations on ALP levels. Establishing the definite diagnosis is paramount in this pathology to enable the early specific treatment with enzyme replacement therapy that can change the natural history of disease.

Código #13398

Metabolic decompensation after related donor hepatic transplantation in a Maple Syrup Urine Disease patient.

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4- Gastropediatrics Service - Hospital de Clínicas de Porto Alegre – RS – Brazil.

Objective: to report the outcome of a hepatic transplantation with a heterozygous donor in a patient with Maple Syrup Urine Disease (MSUD). Methods: case-report. Results: a male patient, 4 yr, born at term, son of a consanguineous couple. Newborn screening performed at SUS: normal (no excludes MSUD). First evaluation at 7 days of life with irritability and vomit after breastfeed, fever, hypotonia, sepsis, ventilatory support, cardiorespiratory arrest, opisthotonus, coma and sweet odor in urine. At 29 days of life, blood amino acid HPLC showed leucine 2130.6 µM/L (48-160), isoleucine 701.1 µM/L (31-86) and valine 863 µM/L (64-294), suggesting the diagnosis of MSUD.He presented normalization of leucine and improved the neurological patternafter starting treatment for MSUD. Despite good adherence to dietary treatment, he required multiple hospitalizations due to metabolic decompensation. He evolved with delayed neuropsychomotor development, hyperreflexia and spasticity. Liver transplantation was so indicated indicated, and the father was the donor. Procedure was performed without intercurrences at 1yr 8 mo. Alloisoleucine decreased immediately after liver transplant (pre transplant values ranging from103 to 490, and zero one month after). He remained in multidisciplinary follow-up, free diet, and leucine, isoleucine and valine levels within the normal range values. When he was 3 yo 5mo, he presented one episode of tonic clonic seizures. EEG showed bilateral focal paroxysmal changes of severe intensity, and brain MRI and blood amino acid HPLC was normal. At 3.5 yo, after a gastrointestinal infection, he presented high levels of leucine, isoleucine and valine (521.2 µM/L, 352.6 µM/L and 678.8 µM/L, respectively). Patient started with free vegetable protein and restricted animal protein diet and Metabolic Formula for MSUD 4 to 5 times / day with normalization of leucine, isoleucine and valine. Conclusions: recent literature describes the occurrence of hyperleucinosis during/just after a gastroenteritis episode and dehydration in MSUD patients previously submitted to hepatic donor-related transplantation, like the present case. The main hypothesis is that visceral ischemia and dehydration compromises hepatic blood flow and BCAA clearance in the graft.

Código #13378

Title: MUCOPOLYSACCHARIDOSES AND AORTIC ROOT DILATATION: A RETROSPECTIVE ANALYSIS

Authors: Fabiano de Oliveira Poswar, Giselle Renata Martins, Roberto Giugliani, Guilherme Baldo

Institution: Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil

Goals: To investigate the occurrence of aortic root dilatation (ARD) in patients with mucopolysaccharidoses (MPS).

Methods: We performed chart review from patients with MPS that had performed echocardiograms from January 2000 until June 2016. Aortic root diameter Z scores were calculated using the formulas from Roman et al. Z scores higher than 2.0 were considered as indicative of ARD. Statistical procedures were performed in SPSS version 18.0. A p value less than 0.05 was considered statistically significant.

Results: A total of 74 patients with MPS were included (27 with MPS I, 23 with MPS II, 14 with MPS IVA and 8 with MPS VI). ARD was identified in all types of MPS with an overall prevalence of 41% and it was especially frequent in MPS IVA (54%) and MPS VI (66%). There was a positive correlation between age and Z scores in patients with MPS IVA (correlation coefficient = 0.181; p = 0.222) and MPS VI (correlation coefficient = 0.419; p < 0.050), although that correlation was not statistically significant in the former group. On the other hand, a negative correlation between age and Z scores was found for MPS I (correlation coefficient = -0.664; p < 0.001) and MPS II (correlation coefficient = -0.358; p = 0.007). We then evaluated the correlation of the time on treatment with ERT on the Z scores of patients with different types of MPS. There was no statistically significant correlation for any group, although a tendency to a significant slight improvement was noticed for patients with MPS I (b1 = -0.013; R^2 0.091; p = 0.066).

Conclusion: Our results are in accordance to previous studies that suggested a high prevalence of ARD in patients with MPS, especially in those with MPS IVA. Moreover, we also identified ARD in patients with MPS VI, which it also correlated with age. In MPS I and MPS II, an inverse correlation between aortic root Z scores and age was noticed, but it is likely that this may be due to the presence of attenuated phenotypes in the older patients. In part of these patients, in whom data before and after ERT were available, it was not observed that ERT clearly promotes resolution of ARD. Considering the potential complications associated to ARD, these results endorse the need of treatments targeting the aortic root in MPS patients.

Código #14107

Title: NEWBORN SCREENING OF BIOTINIDASE DEFICIENCY – RESULTS OF A PRIVATE PROJECT IN BRAZIL

Authors: Eduardo Vieira Neto; Armando A. Fonseca; Marta Aragão Rocha Faria; Michaela de Jesus Nunes de Lima.

Institution: Laboratório "Diagnósticos Laboratoriais Especializados", Rio de Janeiro, RJ, Brasil.

Objective: Biotinidase deficiency is a disorder of the metabolism of biotin inherited in an autosomal recessive manner. It has variable phenotypic expression. Individuals affected by profound enzyme deficiency, when left untreated, develop neurological disorders, which may include seizures, hypotonia, ataxia, developmental delay, vision problems and hearing loss, and skin manifestations (alopecia, dermatitis and susceptibility to infections)[1]. Neonates with biotinidase deficiency identified by newborn screening and submitted to continuous oral replacement of biotin remain asymptomatic. It was included in the Brazilian National Newborn Screening Program in 2012. We report the recall rate, positive predictive value and incidence of (partial or profound) biotinidase deficiency in newborns whose samples were analyzed by a private laboratory.

Methodology: Dried blood spot – DBS specimens were collected from newborns by heel-prick after 24 hours of life. Biotinidase activity was determined by a semi-quantitative fluorometric assay – PerkinElmer Neonatal Biotinidase Kit (Wallac Oy, Finland). Newborns with biotinidase activity < 70 U were recalled for testing in a second DBS sample.

Results: Samples from 172,520 neonates from several Brazilian states were screened between 2014 and 2016. A total of 204 (0.12%) newborns were recalled for confirmatory samples. There was a 74.5% positive response to recall. Eleven children (1 in 15,684) presented low biotinidase activity in the recall sample. No attempt was made to further characterize these children as having partial or profound biotinidase deficiency. The positive predictive value was 5.4%, considering that all neonates that had persistently low biotinidase activity had some degree of biotinidase deficiency.

Conclusion: The incidence of biotinidase deficiency found in this study was similar to the values found in previous studies conducted in Minas Gerais[2] and Rio Grande do Sul[3]. Our recall rate was comparable to that of Pinto *et al.*[4], employing a colorimetric method. Our results clearly support the adequacy of the inclusion of biotinidase deficiency screening in the Brazilian National Newborn Screening Program.

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Código #3341

Título: PERCEPTION OF DISEASE AND COPING STRATEGIES IN ADOLESCENTS AND YOUNG PHENYLKETONURIA PATIENTS

Autores: Flavia Romariz Ferreira; Regina Margis; Ida Vanessa D. Schwartz

Instituição dos Autores: Universidade Federal do Rio Grande do Sul, Departamento de Psiquiatria- Hospital de Clinicas de Porto Alegre, Serviço de Genética Médica- Hospital de Clínicas de Porto Alegre, Brasil

Aims: To evaluate the perception of knowledge about the disease and the coping strategies of adolescents and young Phenylketonuria (PKU) patients at the Medical Genetic Service of Hospital de Clínicas de Porto Alegre (SGM-HCPA).

Methodology: Cross-sectional, observational study with convenience sampling. The Folkman and Lazarus Coping Strategies Inventory (IECFL) and the Brief Illness Perception (IPQ) Questionnaire were applied to 19 Phenylketonuria patients (aged between 15 to 24 years old; female= 19), always by the same interviewer. IPQ comprises a scale from 0 (more positive perception) to 88 (less positive perception) points.

Results: All included patients had an early diagnosis of PKU and have been on treatment since then. The mean of points found on IPQ was 33 (SD=6.52). Five patients (26%) refer do not know what caused their disease. The most commonly used strategies for coping were: self-control, seeking social support, problem-solving, and positive reappraisal.

Conclusions: The rate of knowledge about the cause of the disease can be considered low, and emphasizes the need of a continuous education process for patients with genetic diseases which have been diagnosed at an early age. The adolescents and young PKU patients use functional strategies to deal with health stress situations like your own disease. Those strategies show how adolescents face the situation in a positive way, a finding which is in accordance with the mean of points found on IPQ.

Código #13187

Título: RESULTADOS DE 15 ANOS DE UM SERVIÇO GRATUITO PARA INFORMAÇÕES E SUPORTE EM ERROS INATOS DO METABOLISMO.

Autores: Alessandra Rohenkol de Souza Cardoso; Amanda Teixeira Rosa; Ana Paula Gravina Azevedo; Cláudio Magalhães Dacier Lobato; Luísa Di Santo D'Andréa; Lilia Farret Refosco; Roberto Giugliani; Karyn Koladicz; Carolina Fischinger Moura de Souza.

Instituição dos Autores: SIEM – Serviço de Informações Sobre Erros Inatos do Metabolismo, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Objetivos: Este trabalho tem por objetivo divulgar os resultados obtidos pelo Serviço de Informações Sobre Erros Inatos do Metabolismo no período de outubro de 2001 a dezembro de 2016.

Metodologia: Estudo transversal com levantamento de dados EpiData.

Resultados: De outubro de 2001 até dezembro de 2016, foram 3282 registros (casos e informações), 62,8% foram provenientes das regiões sul e sudeste do Brasil e 25,1% da região nordeste, o restante dos registros (12,1%) tem origem nas regiões norte e centro-oeste do país. Em relação aos profissionais consulentes que procuraram o serviço, 86% buscavam apoio para diagnóstico e conduta inicial e 5% buscavam por informações e bibliografia sobre EIM. Em 34,9% dos casos o contato foi realizado por pediatras e neonatologistas, seguidos por geneticistas (18,8%) e neuropediatras (18,2%). Em relação aos pacientes**,** 67,9% apresentaram sintomas até um ano de vida. Do total de casos registrados no SIEM 51,8% tiveram investigação concluída. Excluindo-se os registros destinados a solicitação de informações, 15,4% foram diagnosticados como sendo uma Doença Metabólica Hereditária (EIM), 36,6% como patologias de origens não metabólicas, 24,7% apresentaram investigação completa sem diagnóstico estabelecido e em 23,3% dos casos houve perda de contato entre o consulente e o paciente. Dos 261 casos com diagnóstico de EIM, 18,8% são aminoacidopatias, 16,7% doenças do metabolismo lisossomal, 12,5% doenças do metabolismo energético, 8,8% doença do metabolismo dos ácidos graxos, 8,1% doenças do metabolismo dos carboidratos, 5,3% doença do metabolismo peroxissomal e 47,5% de outras categorias.

Conclusão: Os erros inatos do metabolismo (EIM) são patologias graves, frequentes e de difícil reconhecimento, seus sintomas iniciais geralmente se manifestam em neonatos e crianças, sendo imprescindível o estabelecimento de um diagnóstico precoce para um adequado manejo do quadro clínico desses pacientes. O SIEM é um serviço gratuito que auxilia profissionais da área da saúde envolvidos no atendimento de pacientes com suspeita ou diagnóstico de EIM. Apesar do conhecimento sobre EIM estar aumentando progressivamente, os profissionais da área da saúde ainda encontram grande dificuldade para identificação precoce dos casos e estabelecimento do tratamento adequado em tempo hábil. A divulgação de informações sobre EIM é de extrema importância para melhor orientação dos profissionais envolvidos no cuidado de pacientes com doenças genéticas. O SIEM vem auxiliando estes profissionais a estabelecer um diagnóstico precoce e um manejo adequado destas patologias, além de contribuir para a divulgação de informações sobre os EIM.

Código #13320

Sensitivity, Clinical Utility and Limitations of a Targeted Next-Generation Sequencing Panel for Diagnosis of Selected Lysosomal Diseases

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Purpose: We developed and validated a TNGS panel of genes related to a subgroup of LDs to be offered as a diagnostic option by a reference service of rare diseases in the state of Rio Grande do Sul, Brazil.

Methods: Genes associated with LDs with overlapping clinical manifestations as well as related deficiencies were included in our panel: *NPC1* (Niemann-Pick type C1), *NPC2* (Niemann-Pick type C2), *GBA1* (Gaucher disease), *LIPA* (Lysosomal Acid Lipase deficiency), *SMPD1* (Niemann-Pick type A/B), *PSAP* (Prosaposin deficiency) and *CHIT1* (Chitotriosidase deficiency). NGS was performed using the Ion Torrent Personal Genome Machine™ (PGM™) System. For the validation phase, we tested 33 blinded-positives probands who underwent previously biochemical test and Sanger sequencing, including 32 different type of variations (SNPs and small insertion/deletion). Run metrics and coverage analyses were performed to identify systematic deficiencies. Intra and inter-run repeatability was also evaluated. This study was approved by the institutional ethics committee.

Results: Validation revealed sensitivity and specificity of 93.75% (30/32; 95% CI = 0.8091-0.9837) and 99.96% (5/15054; 95% CI = 0.9992-0.999), respectively. Uniformity was 98% and a mean depth of coverage of 490X. Intra and inter-run repeatability was also analyzed. Although the breadth of coverage for *SMPD1* gene was expected to be 100%, the actual coverage was just 97.22%. Unfortunately, the low covered region is the location of c.573delT (p.Ser192fs) mutation. Another limitation observed was related to *GBAP1*, a *GBA1* pseudogene with 96% of homology, which makes it difficult the detection of RecN*ci*I allele.

Conclusion: We present here data related to sensitivity, specificity as well as limitations of our TNGS panel for the diagnosis of selected LDs. Our results indicated that the panel is a robust and sensitive tool, faster to run when compared to other methods, and relatively low cost, being a suitable

alternative for genotyping LDs.

Key Words: next-generation sequencing, lysosomal disorders, molecular diagnosis, target gene enrichment.

Financial resources: INaGeMP, FIPE-HCPA, Innovate Peru.

Código #13189

Título: Urinary Organic Acid Analysis for the investigation of mitochondrial disorders

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Instituição dos Autores: 1Centro de Referência em Erros Inatos do Metabolismo, Universidade Federal de São Paulo; 2Laboratório DLE

Objetivos: The urinary organic acid analysis (uOA) is already recognized in literature as an important tool to investigate patients with mitochondrial disorders (MD) hypothesis, being part of the protocol for clinical investigation of patients with this diagnostic hypothesis, in our service. Since this exam is not performed in public health system, our service uses a partnership with a private laboratory to perform the test. The objective of this study was to characterize the clinical features of our patients with MD suspiction and to identify important biomarkers.

Metodologia: Retrospective study of clinical and laboratorial data, and also laboratory's data bank (CEP-UNIFESP 2007/11).

Resultados: from the total of 141 patients with DM suspiction (66M/75F, median age 14,5 years, ranging between 0,7 to 65,8 years), 59 (41,8%) performed uOA. Regarding the clinical manifestations, 56/59 (94,2%) presented neurodevelopment delay; 18/58 (31%) patients had records regarding neurodevelopment regression, 35/59 (59%) had epilepsy, 10/38 (26,3%) had retinal exam abnormalities, 7/22 (31,8%) presented hearing impairment diagnosed via audiometry or otoacustic emissions; 50/59 patients underwent cardiologic assessment and 8 (16%) presented myocardiopathy or arrhythmia. Regarding laboratorial assessment all patients had performed plasma lactate dosage, and 17 (79,6%) presented hyperlactatemia; Only 16 patients were able to perform CSF lactate, which was elevated in 5 (31,2%); 12/59 (20,3%) presented abnormalities in Brain MRI; 5/17 (29,4%) presented abnormalities in muscular biopsy suggesting MD. Only 2 patients (3,4%) presented hepatic impairment and 5 (8,5%) presented renal tubular acidosis. From the total of 59 patients who performed uOA analysis, 41 (69,5%) presented abnormalities suggesting MD, 4 (6,8%) suggesting organic acidaemias, 1 (1,7%) suggesting ketolysis disorder, 7 (11,9%) had abnormalities non-characteristic of MD but insufficient do discard MD hypothesis, 2 (3,4%) had abnormalities but excluded MD hypothesis and 4 (6,8%) presented no abnormalities.

Conclusão: The diagnostic criteria for MD used was the presence of clinical history and/or neurologic exam and/or hiperlactatemia 20% above the upper threshold and/or brain MRI abnormalities and/or muscular biopsy abnormalities and/or uOA compatible with MD. The presence of 3 or more of these criteria confirms the diagnosis, patient starts cofactor-based treatment and clinical response is observed. The uOA as a tool for investigation of MD presented 69,5% of positivity in our patients. This study, like other retrospective studies, has the limitation of lack of control in data collection, which reflects in some missing clinical information. Our study allows to conclude that lactate and uOA are

two fundamental tools for investigation of MD, since molecular analysis is not performed in our public health system.

XXIX CONGRESSO BRASILEIRO
GENÉTICA MÉDICA 2017
Bento Gonçalves | 20 a 23 de junho
Da Pesquisa à Prática Clínica

Fellinievents

Código #14409

Título: WORLDWIDE DISTRIBUTION OF *A-L-IDURONIDASE* MUTATIONS AMONG MUCOPOLYSACCHARIDOSIS TYPE I PATIENTS

Autores: Édina Poletto, Gabriela Pasqualim, Ursula Matte e Guilherme Baldo

Instituição dos Autores: Centro de Terapia Gênica, Centro de Pesquisa Experimental, Hospital de Clínicas de Porto Alegre e Programa de Pós-Graduação em Genética e Biologia Molecular (PPGBM/UFRGS)

Objectives: Analyse the frequencies of common mutations in the *α-L-IDURONIDASE (IDUA)* gene among patients with mucopolysaccharidosis type I (MPS I) worldwide, in order to identify the differences between populations.

Methodology:
Literature search was performed using Pubmed and through references cited in related papers. Inclusion criteria used were: information about the country of origin of patients and the absolute number of alleles in the study. Thirty-five papers were selected and used in the analysis. Patients were grouped according to their country of origin and, for the countries with more than 10 alleles described in total, the combined frequencies of each mutation were calculated. The most common mutation from each country was searched in Genome Aggregation Database (gnomAD) to evaluate its allelic frequency in the general population.

Results: p.Trp402* is by far the most common mutation among MPS I patients, being the major allele in North America, Colombia, Brazil, United Kingdom, Netherlands, Germany, Czech Republic and Slovakia, Spain and Australia, ranging from 63% to 29%. It is followed by p.Gln70*, present mainly in North Europe, as Norway (50%) and Russia (33%), but also in Poland and Austria. Italy has the most variable profile observed: although results showed p.Gln70* as the most frequent mutation, it corresponds to only 14% of alleles, closely followed by p.Pro496Arg (13%), p.Gly51Asp (12%) p.Trp402*(11%) and p.Pro533Arg (10%). North African countries Morocco, Algeria and Tunisia have p.Pro533Arg as the most frequent mutation, corresponding to 92%, 81% and 54% of alleles, respectively. This missense mutation is also present in other Mediterranean countries, such as Turkey, Spain and Italy – mainly in the Sicily region (42%) – and Latin America (Mexico and Brazil), though it is very rare in North Europe, North America and Australia. Mutations frequently observed in East Asians were not found in Western populations, as c.1190-1G>A, p.Ala79Val, p.Leu346Arg and c.613_617dupTGCTC. Conversely, the mutations p.Trp402* and p.Pro533Arg were not found in patients from East Asia. In gnomAD, allelic frequency among individuals without the disease mirrors the data found in patients. For example, the p.Trp402* allele was observed in Europeans (0.0014) and Latinos (0.0004), but it was not present in Asians or Africans.

Conclusion: Most common *IDUA* mutations in MPS I patients are p.Trp402*, p.Gln70* and p.Pro533Arg, but each country has its own mutational profile. The knowledge of the genetic background of MPS I for each population is essential for developing new therapies that depend on the genotype, as well as provide fast diagnosis and improve the management of patients.

GENÉTICA COMUNITÁRIA

Código #13169

Title: A TEN-YEAR RETROSPECTIVE ANALYSIS OF THE FEDERAL UNIVERSITY OF SÃO CARLOS' MEDICAL GENETICS CLINIC

Authors: Débora Gusmão Melo; Thamires Rosa dos Santos; Érica Leticia Angelo Liberato; Tatiane de Abreu; Heloisa Pastana Marsiglio; Lucimar Retto da Silva de Avó; Carla Maria Ramos Germano.

Institution of Authors: Department of Medicine, Federal University of São Carlos (UFSCar), São Paulo, Brazil.

Aims: In 2006, the Medical Genetics Clinic of the Federal University of São Carlos (Universidade Federal de São Carlos, UFSCar) was structured in partnership with São Carlos Municipal Health Secretariat (in São Paulo State). It is an outpatient general genetics clinic incorporated into the Unified National Health System (Sistema Único de Saúde, SUS), which scope covers a population of approximately 350,000 people. The purpose of this analysis was to carry out a systematic survey of UFSCar's Medical Genetics Clinic consultations between August 2006 and December 2016, aiming at characterizing the Clinic's epidemiologic profile.

Methodology:
It is a descriptive and retrospective study, carried out through the systematic review of the "Daily Medical Consultation Data", which are documents a priori used by the São Carlos Municipal Health Secretariat in its institutional information system. Information was collected regarding: number of patients per year, gender and patients' age, the reason of the referral for genetic evaluation and the outcome of the medical assistance. The collected data were analyzed using descriptive statistics.

Results: During the studied period, 681 distinct patients were attended, with an average of 61.9 new patients per year (SD±23.7). The age of the patients varied from 5 days old to 79 years old (average of 14.3 years old, SD±14.6), with predominance of age range between 5 and 10 years old, followed by the one between 20 and 30 years old. The patients' gender ratio was 1:1 and 38 patients (5.6%) were relatives. The main reasons for referring patients to the genetics clinic were: isolated intellectual disability or in association with mild dysmorphic facial features (N=174 patients, 25.55%) and multiple birth defects (major and minor) with or without intellectual disability (N=123 patients, 18.06%). With regard to the outcome of the assistance, in 6 cases (0.88%) the individuals did not have any disease and they have searched the Clinic for primary prevention orientation; 63 patients (9.25%) were diagnosed with pathogenic chromosomal abnormalities; 141 patients (20.7%) were diagnosed with non-chromosomal genetic/congenital disorders (monogenic disorders, microdeletion syndromes, associations or sequences); and 47 patients (6.9%) had isolated major birth defects. Genetic diseases were excluded in 126 patients (18.5%) and clinical diagnoses were not defined in 298 cases (43.76%).

Conclusions: In order to improve the Clinic's diagnosis rate, our main suggestion is the access to the chromosomal microarray analysis to patients with multiple birth defects (major and/or minor), with or without intellectual disability, with no syndromic diagnosis established. By and large, our results

emphasize the need to establish a comprehensive health care for patients with genetic diseases and birth defects in the city of São Carlos and its region, in accordance with the SUS guidelines.

Support:
Pro-Rectory of Extension of the UFSCar (ProEx-UFSCar).

Código #12683

Título: ANÁLISE RETROSPECTIVA DA INCIDÊNCIA DE ANOMALIAS CONGÊNITAS NO MUNICÍPIO DE CHAPECÓ (SC), NO PERÍODO ENTRE 2006 A 2016.

Autores: Nyasmin Mendes Anéli, Kássia Kramer, Mônica Dayane Lammers, Heloisa Malakovski, Sarah Franco Vieira de Oliveira Maciel, Leonardo Leiria

Instituição dos Autores: Universidade Federal da Fronteira Sul - Campus Chapecó, Curso de Graduação em Medicina

Resumo:

Objetivos: As anomalias congênitas são causadas, entre outros fatores, por alterações no DNA que comprometem as funções anatômicas e fisiológicas do feto. Chapecó é uma cidade no estado de Santa Catarina (SC) que possui duas escolas médicas, sendo relevante o entendimento das principais anomalias congênitas na região, a fim de qualificar a formação em saúde e assistência básica. O objetivo principal do estudo foi realizar um levantamento sobre a ocorrência de anomalias congênitas em Chapecó, durante o período de 2006 a 2016.

Métodos: A coleta de dados foi realizada em concordância da Secretaria de Saúde de Chapecó - Vigilância Epidemiológica, por meio da notificação individual e utilização dos programas SinanNet e DATASUS. A demanda por este estudo se deu durante os encontros e atividades do projeto PET-SAÚDE/GRADUASUS 2016/2017, onde foi verificada a necessidade de se trabalhar com a comunidade acadêmica local, a incidência de anomalias congênitas na região.

Resultados: Os dados coletados no DATASUS referentes à 2006 a 2014, mostram a incidência de anomalias congênitas no Brasil, em SC e no município de Chapecó de 72, 87 e 130 casos a cada 10.000 nascidos-vivos, respectivamente. Observa-se que a incidência de anomalias congênitas no município, apesar de constante, acompanhando o crescimento populacional, apresenta taxas maiores do que a estadual e nacional. No mesmo período, a incidência de nascidos-vivos com anomalias congênitas aumentou com a idade materna acima dos 40 anos. Também observou-se uma incidência 47% maior de anomalias congênitas em nascidos vivos do sexo masculino em relação ao feminino (22 e 15 casos a cada 10.000 nascidos vivos, respectivamente). Em relação aos grupos étnicos no município, a população indígena apresentou a maior incidência de anomalias congênitas (280 casos a cada 10.000 nascidos vivos), e a população negra a menor incidência (60 casos a cada 10.000 nascidos vivos). Os dados coletados no SinanNet referentes ao período entre 2015 e 2016, mostram que os principais tipos de anomalias congênitas em nascidos vivos foram pé torto calcaneovalgo, hipospádia não especificada, gastrosquise, hidrocefalia congênita não especificada e Síndrome de Down. Em relação aos óbitos por anomalias congênitas em Chapecó entre 2006 e 2016, foi constatado um total de 212 óbitos, sendo 33 fetais e 179 não fetais. As principais causas em ambos os grupos foram malformação congênita não especificada, malformações congênitas não especificadas do coração, hidrocefalia, Síndrome de Down e gastrosquise. Essas anomalias promovem uma sobrevida variável, de horas a anos, com exceção da gastrosquise, com sobrevida máxima no município de 1 mês.

Conclusão: Nota-se a necessidade e importância da notificação dos casos de anomalias congênitas, bem como a realização adequada do diagnóstico. Mesmo sendo de difícil diagnóstico e baixa incidência, o estudo demonstrou um número significativo de acometidos por anomalias congênitas na população de Chapecó.

Palavras-chave: anomalias congênitas, epidemiologia, nascidos-vivos, óbitos, Chapecó.

Código #13245

Can we avoid the confusion between Osteogenesis Imperfecta and physical child abuse pathological fractures?

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Since the publication of the battered child syndrome in 1962, a physical injury perpetrated by parents or caretakers upon a child was introduced as an important differential diagnosis among disorders associated to pathological fractures such as Osteogenesis Imperfecta (OI). Defined as a genetic disorder of connective tissue, OI comprises bone fragility, susceptibility to deformities and the occurrence of several pathological fractures with minimal trauma. On the other hand, child abuse represents a major cause of morbidity and mortality in children. There are approximately 700,000 to 1.25 million children abused or neglected annually in the United States and nearly 18% of the cases related to physical abuse. Furthermore, in many instances OI children have been misdiagnosed as child abuse and their parents unfortunately subject to great embarrassment and referred to regional Tutelary Council. Therefore, the evaluating clinician, especially at emergency wards, has a challenging responsibility on the differentiation between pathological fractures associated to one constitutional disorder compared to child abuse fractures. The recognition or suspicion of child abuse not only is necessary, but also provides all the resources necessary to prevent subsequent violence and to offer a real protection to the child. We present 03 clinical cases, and discuss and compare clinical and radiological aspects that would guide clinicians to suspect and differentiate pathological fractures associated to a constitutional disorder from child abuse trauma. All cases presented with pathological fractures at birth. Case I, clinical signs of fetal immobility was present characterized by deep dimples in all great joints associated to a “spiral” appearance of the fracture in both femurs of the patient. The long bones were normal with normal cortical; and, no signs of osteoporosis was present. Case II considered as OI, ribs and clavicle fractures with lower limb deformation was suspected already in the prenatal period. Typical radiological features of OI associated to blue sclera was present. Case III, radiographic examination revealed normal configuration of the skull with no evidence of osteopenia or wormian bones; presence of left horizontal parietal hyperlucent line was suggestive of cranium fracture; numerous bilateral fractures in the posterior ribs in various stages of healing were evident. Classical metaphyseal lesions were also present. The evaluation of suspected cases of child abuse/OI should be assessed by clinical history, physical examination, family history, radiologic findings, and, in some cases, complementary investigations such as bone densitometry, biochemical tests or DNA-based sequencing. The early involvement of a multidisciplinary team should be attempted to establish

a timely and accurate diagnosis. The recognition of this disorder demands training and experience of the professionals, and all cases of child abuse must be notified by the physicians.

Código #13289

Título: PERFIL DOS PACIENTES COM A SÍNDROME DE CRI-DU-CHAT: LEVANTAMENTO DE 70 QUESTIONÁRIOS

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Objetivos: Relatar os dados de uma coorte brasileira com síndrome de Cri-du-Chat.

Metodologia: Um questionário com enfoque multidisciplinar foi elaborado e enviado a 700 famílias de pacientes cadastrados na Associação Brasileira da síndrome de Cri du Chat (Núcleo de Aconselhamento e Pesquisa Cri du Chat).

Resultados: 70 questionários foram respondidos. Um paciente era adotado e foi excluído da análise. Houve predominância de pacientes do sexo feminino (42M:27H), com idade atual entre 1 e 41 anos (média: 14 anos). A maioria dos pais observou alterações fenotípicas logo após o nascimento, especialmente o típico choro parecido com miado de gato (93%). O diagnóstico foi feito entre o nascimento e os 14 anos (média: 12,3 meses). Em 65% dos casos, os pais relatam terem realizado estudo citogenético (parental). Em 49% dos casos relatam não terem sido informados sobre o risco de recorrência da síndrome. Os principais problemas de saúde relatados foram: problemas de deglutição (75%) e alimentação (75%), cardiopatias congênitas (32%), alterações de coluna (28%) e sintomas neurológicos (22%). As alterações de comportamento relatadas foram: agressividade, comportamento estereotipado, sinais de ansiedade, fobias e manipulação genital / masturbação. Atraso neuropsicomotor foi relatado na maioria dos casos (96%), apesar de alguns questionários não terem sido respondidos quanto às idades dos marcos de desenvolvimento. Marcha independente foi reportada em 60% dos pacientes; cerca de 40% nunca desenvolveram linguagem expressiva e a grande maioria é dependente nas atividades de vida diária.

Conclusão: Essa foi uma iniciativa pioneira nessa associação de pacientes brasileiros e tem o potencial de melhorar a assistência e cuidado da saúde a esses pacientes, pois tem foco nas demandas de acordo com a perspectiva parental. Além disso, quase metade dos casos afirma não terem recebido informações quanto ao risco de recorrência, dado que sugere a necessidade de ampliação da oferta de serviços de Genética no Brasil.

APOIO: Núcleo de Aconselhamento e Pesquisa Cri du Chat

Código #13384

Título: DIAGNOSTIC AND EPIDEMIOLOGICAL PROFILE OF PATIENTS WITH SKELETAL DYSPLASIAS FROM BETTINA FERRO DE SOUZA UNIVERSITARY HOSPITAL, BELÉM – PA, BRAZIL.

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Objectives: Skeletal dysplasias are a heterogeneous group of diseases wich has a change at shape, size and constitution of bones and/or cartilage, associated with a high morbidity and mortality rate. It is estimated that skeletal dysplasias occur in 2/10,000 live births. Currently, the Hospital Bettina Universitário Bettina Ferro de Souza in Belém-PA do the follow-up of these patients in the genetics clinic, in the “Caminhar" service. The objective of this study is to evaluate the clinical and epidemiological profile of the patients treated in this service, comparing age, sex, procedure and diagnosis of diseases.

Methodology: A survey of cases of dysplasia was performed such as a retrospective study in the medical records of the patients presenting skeletal dysplasias of Hospital Universitário Bettina Ferro de Souza from 2014 to 2016.

Results: In the genetics outpatient clinic, 33 patients with skeletal dysplasia were attended, among them there were 5 patients (15.15%) presenting clinical criteria for achondroplasia, 10 patients (30.3%) for osteogenesis imperfecta, 2 (6%) for Schwartz-Jampel syndrome, 4 (12.12%) for cleidocranial dysplasia, 2 (6%) for multiple exostoses, 1 (3.03%) for Hadju-Cheney syndrome, 1 (3.03%) for mucopolysaccharidosis type 1, 2 (6%) with metaphyseal dysplasia and 6 (18.18%) with indefinite diagnosis. None of the patients had confirmatory molecular analysis for the presented pathology. Among these patients, 21 (63.63%) were male and 12 (36.3%) were female, 14 (42.4%) were between 0 and 5 years old, 10 (30.3%) between 5 and 10 years, 6 (18.18%) between 10 and 20 years, and 3 (9%) above 20. Regarding the origin, 14 patients (42.4%) live in the capital Belém and 19 (57.57 %) of the interior of the state (Breves, Ananindeua, Cametá Abaetetuba, Moaná, Gurupá, Igarapé-açú, Pacajá, Ourém, Santa Izabel and Bragança).

Conclusion: In this way, the clinic presents a great variety of cases of skeletal dysplasias, with predominance of osteogenesis imperfecta and achondroplasia. The majority of patients are at pediatric age group. There are some patients from the capital, but most of them are from the interior of the state. Therefore, a specific outpatient clinic for skeleptal dysplasia would contribute the clinical evaluation, the perform of molecular tests and the genetic counseling benefiting the patients and their relatives. So, considering it’s benefits, it is important an investment project and partnerships to maintain quality and improve the health care for patients with skeletal dysplasias in the state of Pará.

Código #13349

Título: ESTUDO DESCRITIVO: FREQUÊNCIA DE MALFORMAÇÃO CONGÊNITA EM PACIENTES ATENDIDOS NO AMBULATÓRIO DE GENÉTICA MÉDICA DA *ASSOCIAÇÃO DE PAIS E AMIGOS DOS EXCEPCIONAISDE* MANAUS (APAE/MANAUS)

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Objectives: To perform a descriptive and transversal study based on the analysis of 316 patients (probands) attended at the Medical Genetics service of the APAE / Manaus. Methodology: retrospective study of patients seen in the period 2005-2016, through a medical records review. The following data were recorded: gender, origin of referral and etiologic diagnosis, retrospective study of patients seen in the period 2005-2016, through medical records review. The following data were recorded: gender, origin of referral and etiological diagnosis. Results: A total of 362 patients were attended in 615 visits, with an average of 1.7 visits per year per patient. The male sex corresponded to 219 cases (60.7%), the female cases to 143 cases (39.3%) and there were no cases of intersex. The etiological diagnosis was elucidated in 262 patients (72.4%), and 254 (70.1% of the total) had genetic etiology (monogenic syndromes, chromosomal aberrations and multifactorial inheritance) and 8 (2.2%) caused non-genetic. Of the genetic etiologies, 136 (37.6%) were chromosomal aberrations, 72 (19.9%) were multifactorial and 46 (12.7%) were monogenic syndromes. The reports of chromosome etiology constituted the majority of diagnoses with genetic etiology, with Down syndrome being the most frequent (P <0.005). The multifactorial etiology was responsible for 19.9% of the cases, with the overall developmental delay being the most frequent. Followed by inborn errors of metabolism. Only 8 patients attended (2.2%) had other non-genetic causes for malformation. The most common reason for malformations in this group was the use by the pregnant woman of the drug misoprostol (3 cases), and cerebral palsy (2 cases). The main malformation due to misoprostol was the Moëbius sequence. The dominant autosomal diseases prevailed in relation to recessive diseases. Among the dominant and monogenic diseases, the most frequent were Achondroplasias and Skeletal dysplasia. With regard to diseases of autosomal recessive etiology, it was observed that some of the affected were not children of consanguineous couples, except in nine cases. Still in relation to consanguinity, it must first be remembered that, being distant and not between first cousins, the risk for genetic pathologies becomes smaller. The sex of the patient had a statistically significant relation with the presence or not of SD In the analyzed patients (X2 = 4,437, DF = 1, P-Value = 0.035), being more present in men than in women. The estimated sex ratio (males: females) was 1.6. There was no evidence of a sex relation with the age at which the disease occurs in the patients (X2 = 3.930, DF = 6, P-Value = 0.666), nor with the type of inheritance (autosomal dominant, autosomal recessive or otherwise) Of the diseases registered in the patients (X2 = 0.440, DF = 2, P-Value = 0.802). Conclusion: The survey carried out at the APAE / Manaus genetics clinic allowed us to trace the profile of the patients attended. It was verified that the majority of the patients are male, and the diagnosis for chromosomal abnormalities is the most frequent.

Código #13406

Título: HEALTH CARE IN ONCOGENETICS AT THE HOSPITAL UNIVERSITÁRIO BETTINA FERRO DE SOUZA: ANALYSIS OF THE FIRST FAMILIES.

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Introduction/Objectives: The practice of oncogenetics consists of extensive preventive work to identify families with hereditary predisposition to câncer and analyze the gene mutations directly associated with the disease. Cancer has become a worldwide problem with more than 32 million people living with the disease worldwide and responsible for about 8.2 million deaths a year. Besides, about 10% of the total cases are due to hereditary mutations. The service in Medical Genetics of Hospital Universitário Bettina Ferro de Souza, despite being a pediatric service with no oncological profile, has recently started the care of this group of patients and this is still a service in experimentation. This study aims to evaluate the service in implementation of oncogenetics at the Hospital Universitário Bettina Ferro de Souza.

Methods: The methodology were based on a survey of the cases attended in the pilot project of oncogenetic care, from October 2016 to February 2017 at the medical genetics service of the Hospital Universitário Bettina Ferro de Souza.

Results: In the short period of service, 11 families were attended, 2 of them presented clinical criterial for familial adenomatous polyposis (FAP), 1 for cowden's syndrome, 3 for hereditary breast and ovary carcinoma (HBOC), 1 for retinoblastoma, 3 for neurofibromatosis type 1 and 1 patient with multiple primary tumors at young age without criteria for specific syndromes. Only 3 families have performed molecular tests: one patient with molecular confirmation for FAP and another for HBOC with identification of pathogenic variant. The third case corresponds to a patient with Cowden's syndrome with a variant of uncertain significance after PTEN analysis. The remaining cases are waiting the results of exams in progress in the partner laboratories, Laboratório de Genética Humana e Médica (LGHM) and Núcleo de Pesquisa em Oncologia (NPO).

Conclusion: It was possible to clinically evaluate, route molecular testing and provide genetic counseling for this initial group of families that will unfold in benefits to their clinical follow-ups and also to their family members. Even representing initial service in a non-cancer hospital, it was demonstrated that the establishment of a specific outpatient clinic can contribute to better care and better health care for patients in Pará.

Código #13416

Title: MENNONITES IN BRAZIL: ISOLATED COMMUNITIES AS A MODEL FOR INVESTIGATING GENETIC SUSCEPTIBILITY TO COMPLEX DISEASES

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Objective: Mennonites are a Christian Anabaptist group originated in Europe during the XVI century, which passed through at least three recent bottlenecks, living in closed communities since at least 20 generations. In this work, we aimed to characterize familial aggregation of complex diseases in the Brazilian Mennonite population, which arrived 1930 in South Brazil, in order to lay the foundations for further investigations of genetic susceptibility, using next-generation sequencing.

Methodology: Using a slightly modified version of the questionnaire of the National Health Plan of 2013, our group interviewed more than 200 Mennonites from the Colônia Nova (RS) and Witmarsum (PR) settlements. Each interview lasted one hour and included questions about parental origin, place of birth of grandparents and migratory route, eating and health habits, language, family atmosphere, exposure to mutagens, chronic diseases and familial disease aggregation. Of this questionnaire, we extracted information about cancer and gastrointestinal diseases for 71 individuals of Colônia Nova, as a pilot study.

Results: Twenty percent of the 71 interviewed individuals (14) had cancer, of which eight had basal carcinoma, four reported breast or ovarian cancer and two, colorectal cancer. Of the 14 individuals, 13 belonged to different families and reported at least two other cases in the family (among first- and second-degree relatives). Seven individuals, also belonging to different families, reported first- and second-degree relatives with celiac disease, but never investigated this disease, themselves. This becomes particularly important, if considering that three of them also had related complaints.

Conclusion: In this pilot investigation, we found familial aggregation of cancer, especially basal cell carcinoma, and of celiac disease, arguing in favor of a founder effect of polymorphisms increasing the susceptibility of the Mennonite population for these diseases. Accurate prevalence frequencies, as well as the identification of specific susceptibility alleles, shall help to define the risk of this population, encouraging future strategies of Preventive Medicine.

Código #13389

Título: CLINICAL AND EPIDEMIOLOGICAL FINDINGS IN OSTEOGENESIS IMPERFECTA PATIENTS FROM HOSPITAL UNIVERSITÁRIO BETTINA FERRO DE SOUZA, BELÉM – PA, BRAZIL.

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Introduction/Objectives:
Osteogenesis imperfecta (OI) is a heritable connective tissue disorder caused by mutations resulting in an abnormal type I collagen bone matrix. The principal clinical feature of OI is bone fragility, leading to frequent fracture after minimal trauma. This study aims to evaluate the profile of patients with Osteogenesis Imperfecta (OI) treated at the Hospital Universitário Bettina Ferro de Souza in Belém - PA, to evaluate the epidemiological data, compare the age and origin of the patients, compare the clinical manifestations, classify the degree of the disease of according to clinical presentation and evaluate the patient's access to treatment.

Methods: A retrospective analysis of the medical records was performed. The patients are followed at Hospital Bettina Ferro de Souza in Belém from 2014 to 2016.

Results: Out of 10 patients who follow up in the service, 7 are aged from 0 to 10 years old, 2 are aged from 20 to 30 years old and 1 is over 50 years old. There is 7 males and 3 females. They are from the state of Pará, 6 of them from the capital Belém and 4 from the interior of the state (Breves, Cametá and Ananindeua). Regarding the clinical parameters of the disease, there is 1 (11.1%) patient with type 1 of the disease, 5 patients (50%) with type 3 and 3 patients (33.3%) with type 4 of OI. One of the patients does not have a defined type yet. There are 9 patients with bone deformity, 7 with dentinogenesis imperfecta and 3 with blue sclera. About the mobility, 4 patients spontaneously wander, 2 move with wheelchairs and 1 still have not developed ambulation. In addition, 5 patients have already performed surgeries. Currently the treatment with biphosphonates is indicated for 7 patients, of these 6 have indication of pamidronate and 1 of alendronate. Some cases also uses supplementation of Calcium and vitamin D. Of the total, 4 patients are waiting for the procedures of the local health department. The Reference Centers for treatment and management of Osteogenesis Imperfecta that the pacients are followed up are distributed as follows: 3 patients are treated at the Instituto Fernandes Figueira in Rio de Janeiro, 1 at Brasília's Hospital das Clínicas, 1 at the Universidade Federal de São Paulo (UNIFESP) and 1 patient at the Hospital Albert Sabin in Fortaleza.

Conclusion: It was observed a predominance of male patients, in the pediatric age group and with severe forms of the disease. There is no curative treatment for osteogenesis imperfecta, however, treatment with bisphosphonates, when indicated, is extremely important to improve the quality of life of the patients. The northern region of Brazil does not have a reference center for the treatment

of OI yet, for that reason, there are a considerable number of patients in treatment outside the hometown who could have a better quality of life if there were a Reference Center for the treatment of OI in the state of Pará, with support to supply the northern region's demand.

GENÉTICA MOLECULAR

Código #12782

Title: A CASE SERIES IN INCONTINENTIA PIGMENTI: GENETIC, CLINICAL AND PEDIGREE FINDINGS

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Objectives: Incontinentia Pigmenti (IP) is a rare X-linked dominant genodermatosis, characterized by skin, teeth, hair, nail, eye and central nervous system abnormalities, and lethal for males during embryogenesis. The only known cause for IP are mutations in *IKBKG* gene, fundamental for cell development, survival and function, and around 70-80% of IP patients present a recurrent deletion of *IKBKG* exons 4-10 (*IKBKG*del). Our objective was to explore genetic and clinical data from a case series in Incontinentia Pigmenti, studying *IKBKG* mutations from IP patients and addressing the clinical variability within IP families. We also investigated the family pedigrees testing deviations from the expected Mendelian inheritance.

Methodology: Twenty-three IP individuals (12 index-cases and 11 affected family members) were investigated for *IKBKG* mutation. Additionally, 13 non-affected family members were included for pedigree analysis. Patients were subjected to a specific examination by a dermatologist, an ophthalmologist, and a dentist. DNA samples were extracted from peripheral whole-blood samples through Pure Link Genomic DNA (Invitrogen) kit. In order to identify *IKBKG*del, we performed Multiplex Polymerase Chain Reaction (PCR) and long-range PCR. Additionally, all coding regions (exons 1-10) and intron-exon boundaries of *IKBKG* were amplified through PCR and sequenced through Sanger sequencing. The observed and expected proportions by Mendelian inheritance were compared using Chi-squared test.

Results:
1) The *IKBKG*del prevalence in our case-series was 75% (9/12 index-cases), indicating that, irrespectively of ethnical origin, this is the major mutation in *IKBKG*. 2) We described a novel *IKBKG* mutation in one patient; this mutation produces a protein with an extra amino acid stretch leading to protein instability. 3) We realized remarkable intrafamilial clinical variability, having found range from mild skin alterations to serious CNS abnormalities in members of a same family. The high clinical variability in IP is suggested to occur due to X-inactivation mosaicism in IP patients and *IKBKG* pleiotropic role. 4) We demonstrated a possible deviation in the proportions predicted by Mendelian inheritance in IP. The affected:non-affected ratio in females should be 1:1 following Mendelian segregation with male lethality, however, we found a 16:5 (p=0.0164) transmission ratio. We suggest that the mutated version of *IKBKG* appears to be preferentially transmitted in IP families. However we still don't have a clear explanation for this.

Conclusion: Our study points out important new insights in genetic basis of IP and collaborates to the understanding of the biological background involved. This is the first IP genetic investigation in Brazil.

Código #13350

Título: A HIGH RESOLUTION MOLECULAR SCREENING METHOD FOR DETECTION OF FRAGILE X SYNDROME IN A GROUP OF PATIENTS WITH AUTISTIC SPECTRUM DISORDERS

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Objetivos: Autism Spectrum Disorder (ASD) is a serious neuropsychiatric disorder. A significant percentage of patients with ASD can be explained by the presence of Fragile X Syndrome (FXS). The FXS is caused by a change in expression of the FMR1 gene, located on the X chromosome, resulting from the abnormal expansion of the number of CGG repeats in the promoter region. This study aims at the molecular characterization of the FMR1 gene in patients with ASD. In that the specific objectivity lies in defining the number of replicates of the triplet type in the promoter region of the FMR1 gene.

Metodologia: The clinical screening of 27 patients with ASD (21 girls and 6 boys) was done by geneticists and neuropediatricians of the "Caminhar" Service of the University Hospital Bettina Ferro de Souza (Belém-Pará) with the assistance of DSM-IV. Was collected 5.0 mL of blood in tubes containing EDTA for further DNA extraction. Initially, the samples of the male patients were submitted to a first screening method (low resolution) based on the PCR. The samples of the male individuals that indicated some alteration by this method and those of all the girls, were later submitted to the technique of amplification of fragments by PCR and electrophoresis in automatic sequencer according to the protocol described in the commercial Kit Amplidex® FMR1 (Asuragen®).

Resultados: Out of six male patients who presented alterations in the low resolution molecular screening method for FXS, one patient was confirmed by the complete mutation capillary electrophoresis method for the FMR1 gene. Also identified by this method were two girls who presented complete mutation for the FMR1 gene, out of the twenty one analyzed

Conclusão: The SXF presents a high prevalence among patients with intellectual disability. However, his diagnosis is still deficient, especially in the northern region of Brazil. It is imperative to apply confirmatory molecular diagnostic techniques, such as capillary electrophoresis. Molecular approaches based on screening and confirmatory methods for abnormal CGG expansions in the FMR1 gene are crucial for the early diagnosis of FXS and genetic counseling of families at risk for FXS.

Código #12631

A USER-FRIENDLY PLATFORM FOR THE ANNOTATION, FILTRATION, AND INTERPRETATION OF SEQUENCE VARIANTS OF CLINICAL SIGNIFICANCE

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Objectives: With the introduction of next-generation sequencing (NGS) in the medical practice, it became feasible to identify millions of variants. But it is still a challenge to correctly annotate them for downstream analysis in order to prioritize, classify and filter variants with biological or clinical significance. Here we describe the implementation of an open source intelligible web-platform for the annotation, filtration, and interpretation of sequence variants for clinical application.
Methodology: We are currently in the process of implementation of general filters commonly used and available on many platforms, such as: general filters, which include location features (chromosomal positions), variant calling quality, depth of coverage and zygosity patterns; biological meaning filters, which comprises those previously known candidate genes, those already related to a certain group of conditions and also those conditions already linked to a group of genes [1]; consequences, such the variants' location context (exonic, intronic, intergenic, etc.) and effects (silent, missense, nonsense, stop-loss, etc.); Functional *in-silico* predictions (SIFT, Pholyphen, etc.) and finally variant frequency parameters, such as global minor allele frequency, presence or absence in the dbSNP and Beacon databases. As a starting point, we aim to work with Varapp, which is an application to filter genetic variants, with a reactive graphical user interface [2]. Although it can be used as a desktop app, it is currently being developed to be used as a web service. Its use can be motivated by its security, fast, non-trivial filtering, reproducibility, reactive user interface and easy sharing of the results. As an enhancement to this open-source software, we aim to implement the Global Alliance for Genomics and Health's Variants API. The Variants data model, although based on the VCF format, allows adaptable interaction with the data. Instead of sending whole files, the server can send information on specific variants or genomic regions instead of getting the whole genotype. Finally, we understand that an important step is prioritization and classification of variants by using a statistical model or a consensus result from effect prediction algorithms, as they tend to diverge in response. These models could also benefit from a classification algorithm based on the ACMG recommendations for the interpretation of sequence variants [3].
Results: As a pilot to this initiative, we have launched the foundations of a solid free user-friendly platform with the potential to enhance genomic variants interpretation.

Conclusion: This user-friendly platform has the potential to unleash the diagnostic potential of NGS applied to genetic disorders, making it possible for the trained medical professionals to analyze and interpret their own data in a more independent way. This product will be available through the Brazilian Initiative on Precision Medicine (BIPMed, www.bipmed.org).

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This project was supported by CAPES and FAPESP (2013/07559-3).

Código #13340

Título: Ambulatory outcome measures after the initial 48-week period of a long-term, open-label treatment with ataluren in patients previously enrolled in ataluren clinical trials for nonsense mutation Duchenne muscular dystrophy (nmDMD)

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Objetivos: In this ongoing, long-term open-label access trial in Europe, Israel, Australia, and Canada, physical function was assessed in patients with nmDMD receiving ataluren (NCT01557400).

Metodologia: Males with nmDMD who had received ataluren in previous trials were enrolled; the gap between last prior exposure and entry to this trial ranged from 801–1334 days. Patients are to receive ataluren 40 mg/kg/day for up to 240 weeks. Results from the first 48 weeks for ambulant patients (able to run/walk 10 m in ≤30 s upon study entry) are reported. Study assessments were performed at baseline and every 12 weeks during treatment. Change from baseline in 6-minute walk distance (6MWD), timed function tests, and North Star Ambulatory Assessment (NSAA) total score were summarized.

Resultados: Overall, 94 patients were enrolled, 50 (53.2%) of whom were ambulant at study entry. Of those, 49 completed the week 48 observation. At baseline, mean (standard deviation [SD]) age was 12.1 (2.08) years, body mass index was 22.8(4.63) kg/m^2, and 6MWD was 341.6 (108.11) meters. Corticosteroids were used by 47 (94.0%) ambulant patients. Mean (SD) change from baseline in 6MWD, time to stand from supine, time to run/walk 10 m and NSAA score are shown in Table 1. One patient lost ambulation during these 48 weeks of treatment.

Conclusão: The results for this relatively older and potentially more severely-affected ambulant DMD males, suggest a slowing of disease progression in patients receiving ataluren for the first 48 weeks of treatment, compared to the current understanding of natural history.

Código #13266

ANÁLISE DA FREQUÊNCIA DE ALTERAÇÕES SUBMICROSCÓPICAS EM PACIENTES COM ATRASO NO DESENVOLVIMENTO NEUROPSICOMOTOR OU DEFICIÊNCIA INTELECTUAL IDIOPÁTICA AVALIADOS ATRAVÉS DA HIBRIDAÇÃO GENÔMICA EM ARRAY (a-GH).

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Objetivos: O Atraso no Desenvolvimento Neuropsicomotor (ADNPM) e a Deficiência Intelectual (DI) são disfunções heterogêneas do sistema nervoso central que exibem etiologias complexas. A DI tem uma prevalência estimada de 1-3% na população geral, sendo que fatores genéticos estão envolvidos em cerca de 30% destes casos. No Brasil, a citogenética convencional ainda é a principal ferramenta de diagnóstico para detectar anormalidades cromossômicas. Entretanto, com o advento das técnicas de avaliação genômica, tornou-se possível a detecção de rearranjos cromossômicos submicroscópicos. O presente estudo tem como objetivo central avaliar a frequência de variações no número de cópias (CNVs) em pacientes com ADNPM ou DI Idiopática utilizando a técnica da hibridação genômica em array (a-GH).

Métodos: Revisão de prontuários de pacientes em seguimento no Ambulatório de Genética Médica do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto – USP, no período de agosto de 2015 a fevereiro de 2017. Foram selecionados os pacientes com diagnóstico de ADNPM e/ou DI Idiopática, eventualmente associada à dismorfias e/ou malformações congênitas, que realizaram exame de a-GH, pela plataforma CytoScan HD (Affymetrix®) e, que tinham exame de citogenética clássica sem alterações. As CNVs foram analisadas pelo software ChAS (Affymetrix®) e comparadas com informações dos bancos de dados Database of Genomic Variants (DGV) e o Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources (DECIPHER).

Resultados: Foram avaliados 17 pacientes com ADNPM ou DI, dos quais 10 (58,8%) foram identificados como portadores de CNVs, sendo 3 pacientes (17,6%) foram classificados como portadores de CNVs patogênicas, 2 pacientes (11,7%) que apresentaram variantes genômicas de significado clínico incerto (VUS), 1 paciente (5,8%) com CNV não patogênica e VUS concomitante e 4 pacientes (23,5%) com CNVs não patogênicas.

Conclusão: A análise citogenômica, utilizando a plataforma CytoScan HD (Affymetrix®), revelou que 30% dos pacientes avaliados apresentavam alteração no número de cópias em regiões cromossômicas associadas com o fenótipo patogênico. A caracterização do perfil genético por a-GH nos pacientes com Atraso no Desenvolvimento Neuropiscomotor ou Deficiência Intelectual Idiopática possibilita o diagnóstico etiológico preciso, contribuindo para o Aconselhamento Genético adequado das famílias.

Código #13284

Title: ANALYSIS OF *SOX2* EXPRESSION AND ITS RELATIONSHIP TO THE TERMINAL DIFFERENTIATION AND HORMONE PRODUCTION IN THE POST-NATAL DEVELOPMENT IN ANIMAL MODELS OF CONGENITAL HYPOPITUITARISM.

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Aim: To characterize the expression of *Sox2* during the post-natal development of congenital models of hypopituitarism, and the proliferation marker *Ki67*, differentiation marker *S100β*, and genes encoding pituitary hormones in the Ames mice puberty.

Methods: RT-qPCR was performed in pools of pituitary glands from three animal models of congenital hypopituitarism in four periods of post-natal development (P0: at birth, P7: end of the first wave of pituitary development, 4W: puberty, and 8W: adult mice) to analyze the expression of *Sox2* by TaqMan™ (Applied Biosystems, Foster City, CA) and the genes codyfing the hormones GH, TSH, LH/ FSH, CGA, and PRL, as well as *Ki67* and *S100β*, were analyzed in the pubertal period (4 weeks) of the Ames mice by by SYBR® Green (QIAGEN, Valencia, CA). They were normalized by endogenous genes and the assays were performed in triplicate. The target genes relative quantification was performed using the mutant related to its age paired wild type as a calibrator and the results were expressed in fold change.

Results: *Sox2* expression was similar in the normal and mutante mice of the apha-GSU (P0: 0,81; P7: 0,84; 4W: 0,83; 8W: 0,94), while for the Snell mice there was an accumulation of *Sox2* that increases along post-natal development (P0: 1,13x; P7: 1,58x; 4W: 3,12x; 8W: 4,05x). The Ames mice also presented an accumulation of *Sox2* at P0, P7, and 8W ((P0: 1,75x; P7: 2,87x; 8W: 3,97x), showing a reduced expression at 4W (0,22x). The expression of *Ki67* at 4W was also decreased (0,06x), while *S100β* was increased (2,34x). The genes codyfing the pituitary hormones LH, GH, and PRL presented decreased expression (0,06x, 0,26x, and 0,53x respectively), as expected, while the genes encoding FSH, TSH, and CGA presented expression. Leves similar to the wild type mice (0,89x, 1,09x, and 0,77x, respectively).

Conclusion: The reduced expression of *Sox2* and the normal expression of FSH, TSH, and CGA during puberty suggest the activation of cellular differentiation process, despite the absence of *Prop1*, which is confirmed by the reduced expression of proliferation and increased expression of differentiation markers. The possible recovery of some pituitary cell types in mutant animals suggests the involvement of another factor in cell differentiation pathway that could compensate the lack of *Prop1*.

Código #13355

ASSOCIAÇÃO DOS POLIMORFISMOS *GSTT1 nulo* E *GSTM1 nulo* COM A SUSCETIBILIDADE AO DIABETES MELLITUS TIPO II

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Objetivos: Determinar, por meio de estudo caso-controle, a associação de dois polimorfismos nos genes das glutationas-s-transferases (*GSTM1 nulo* e *GSTT1 nulo*), em portadores diagnosticados com o Diabetes *Mellitus* Tipo 2 (DM2), atendidos nas Unidades Básicas de Saúde do município de Parnaíba-PI.

Metodologia: Foram estudadas 662 amostras de DNA, sendo 380 de pacientes com DM2 e 282 de indivíduos sem DM2, ambos os grupos, pertencentes ao banco de amostras do GEHMED, UFPI. Todas as amostras foram genotipadas quanto a detecção da ausência ou presença das duas variantes polimórficas, utilizando a técnica de PCR multiplex; e o gene *CYP1A1* foi utilizado como controle interno de todas as reações. A genotipagem foi visualizada em gel de agarose a 2%. Além do IMC (índice de massa corpórea), foram também registradas as dosagens da glicose em jejum, Hb1Ac, triglicerídeo e colesterol VLDL. Para avaliar a associação dos polimorfismos com DM2 foi realizado o teste do Qui-quadrado (X^2), e para para avaliar a suscetibilidade ao DM2, o cálculo do Odds Ratio, com intervalo de confiança de 95%. O Teste T ou teste de Wilxocon (Mann-Whitney) foi empregado para comparar os registros laboratoriais entre os grupos analisados. Todos os testes adotaram o nível de significância de 5%.

Resultados: De todos os indivíduos analisados, 71% pertenciam ao sexo feminino, sendo 63,61 (± 13,86) anos a média de idade do total de pacientes. Nos pacientes com DM2, foram observados valores mais elevados do IMC, da glicose em jejum, Hb1Ac, triglicerídeos e colesterol VLDL, quando comparados aos registros dos indivíduos sem DM2 ($p<0,05$). Os resultados da distribuição dos genótipos entre os grupos (casos e controles) mostraram que a frequência de *GSTT1 nulo* foi de 19,85% nos casos e 20,76 % nos controles. Já a frequência de *GSTM1 nulo* foi 30,96% nos caso e 33,05% nos controle. Não houve diferença significativa na distribuição de genótipos e na análise de risco associado aos polimorfismos nulos. Foi observado que não houve associação significativa entre os genótipos com o risco de DM2, *GSTT1 nulo* (X^2= 0,077, p= 0,78; OR= 0,94; IC= 0,63-1,41; p=0,86) e *GSTM1 nulo* (X^2= 0,29, p= 0,64; OR= 0,90; IC= 0,64-1,28; p=0,65). A combinação dos dois genótipos de risco, *GSTT1 nulo* ou *GSTM1 nulo,* foi pouco frequente em ambas os grupos (12,43% e 12,29%) e não foram associados com um risco aumentado em relação aos dois genótipos presentes (OR = 0,96; IC = 058-1,60; p = 1,00). No entanto, a combinação genótipo duplo presente foi mais predominante em ambos os grupos (61,65% e 58,09%), com maior proporção no grupo caso ($p<0,004$).

Conclusão: Apesar de polimorfismos nos genes das glutationas-s-transferases promoverem defeitos na defesa antioxidante, e assim, desempenharem um papel importante na etiologia e complicações diabéticas, este estudo mostrou que, na população estudada, os polimosrfismos *GSTT1 nulo* e *GSTM1 nulo* não tiveram relevância na suscetibilidade ao DM2.

Código #12672

Title: ASSOCIATION ANALYSIS OF COMPLEMENT SYSTEM WITH PEMPHIGUS FOLIACEUS

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Objective: Pemphigus foliaceous (PF) is an autoimmune disease endemic in Brazil, also known as "Fogo Selvagem" due to burning sensation. PF is characterized by the presence of autoantibodies specific against epitopes of the desmoglein 1. A process called acantholysis, which is the loss of epidermal cell adhesion, accompanies this, leading to painful skin blisters. The recognition of exposed desmosomal neoantigens results in activation of the complement system (CS), a proteolytic cascade that is one of the main innate mechanisms against infection and also an effector of antibody-mediated immunity. Several CS components occur in PF lesions, causing further tissue damage. Polymorphisms of CS genes alter the efficiency of complement activation and regulation. Therefore, we are investigating if they also influence PF susceptibility.

Methodology: We genotyped 551,839 SNPs (single nucleotide polymorphisms) in 235 patients and 194 controls, through microarray hybridization with the Infinium® CoreExome-24 v1.1 BeadChip (Illumina). We evaluated 999 SNPs located in all 44 genes of the CS. After excluding SNPs with minor allele frequency less than 1%, out of Hardy-Weinberg equilibrium in control samples, and with high linkage disequilibrium ($r^2 \geq 0.8$), 206 SNPs remained. We used the PLINK program to perform Principal Component Analysis (PCA) and for genetic association by independence tests between variables using the binary logistic regression analysis with 2 PCA as covariants.

Results: We found eight SNPs associated with PF. These SNPs occur in six different CS genes. Two encode products that are part of the membrane attack complex (MAC), found deposited on PF lesions: *C9* (rs187875 [*A/G*], p=0.028, OR=1.42 and rs700218 [*A/C*], p=0.042, OR=0.114) and *C7* (rs2271708 [*G/A*], p=0.049, OR=0.305). Both genes are located on 5p13.1, and the *ACA* haplotype was associated with disease susceptibility (p=0.0162, OR=1.7). Two encode complement regulators, one able to block MAC formation - *CD59* (rs1047581 [*A/G*], p=0.022, OR=0.697) and the other able to block the classic and lectin complement pathways - *SERPING1* or C1inh (rs1005511 [*G/A*], p=0.048, OR=0.749), located on 11p13 and 11q12.1, respectively. The *GA* haplotype was associated with PF susceptibility (p=0.0417 OR=0.529). Three other genes encode receptors for complement components, whose recognition stimulate the inflammatory response and phagocytosis of apoptotic bodies. The product of the *ITGAX* gene recognize iC3b (rs11574637, p=0.005, OR=0.628), whereas the *C5AR1* product binds C5a (rs10404456, p=0.016, OR=1.419), and the *CD93* product, C1q (rs6076019. p=0.026, OR=1.373).

Conclusion: The associated variants lead us to suggest an important role for complement regulation, MAC deposition and complement-driven removal of apoptotic bodies in the etiology of PF. Functional validation of these variants will provide a better understanding of the disease and hopefully contribute to the development of new treatment strategies.

Código #12638

Título: ASSOCIATION BETWEEN CANCER AND CHANGED PATTERN OF METHYLATION: A LITERATURE REVIEW.

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Objetivos: The objective is to review of literature on cancer and its association with the changed pattern of methylation, correlating epigenetic changes and predisposition to neoplasms and identifying environmental factors that contribute to these changes.

Metodologia: The articles published between 2010 and 2015 were shortlisted by the databases PubMed and SciELO, using the descriptor: epigenetics. It was analyzed the full texts, potentially relevant for the review. Initially it was identified 136 studies. After the tittles and abstracts review, consideration of inclusion and exclusion test, 23 were sure enough analyzed, but only 4 articles were included in the review, because to be epigenetics related to the topic in its descriptors and/or in the abstracts.

Resultados: Trough a review of the literature performed was observed that epigenetic changes, especially methylation, cause to changes in gene expression that are associated whit a predisposition to neoplasms. The methylation pattern can be changed by obtaining methyl radical by the diet and environmental factors, for example the cigarette, by oxidative stress.

Conclusão: Trough analysis we conclude that chemical agents present as much in the diet as well as external factors, such as cigarette influence the pattern of methylation. So the study of epigenetics is very important in understanding the process that predisposes the development of neoplasms.

Código #13225

Title: Association of *PGC1-α*, *UCP1* and *FNDC5* with severe obesity susceptibility

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Objectives: The aim of the study was to investigate the association between genetic variants in *PGC1-α*, *UCP1* and *FNDC5* genes and severe obesity, anthropometric and pressoric parameters. Those genes encode proteins important to stimulate browning of white adipocytes, increasing energy expenditure.

Methodology: A total of 391 adults subjects were selected, in which 189 were normal weight subjects (Body mass index, BMI: 22.8 [21.1; 23.9]) and 202 were severe obese individuals (BMI: 45.3 [39.7; 51.8]). Genotyping of *PGC1-α* (rs8192678, rs3736265, rs2970847 and rs3755863) and *UCP1* genes (rs6536991 and rs12502572) were performed by real time PCR method. Screening of exons 3, 4 and 5 (including their exon-intron junction) of *FNDC5* gene was carried out by automatic sequencing. These exons were selected in order to screen the region which encodes the irisin hormone and has a key role in the browning pathway.

Results: The genotype and allele frequencies for all variants were obtained. Our results demonstrate a strong association between *PGC1-α* rs2979847 and severe obesity susceptibility (χ^2=7.71; *p*=0.021). Allelic analysis showed that rs2979847 (C) allele was more frequently in obese group when compared to the control group. Furthermore, individuals carrying the rs2979847 (C) allele had a 1.91-fold increased risk of severe obesity when compared to subjects which did not have this allele (OR: 1.91 [1,2-3,03]; *P* = 0.003). The influence of *PGC1-α* and *UCP1* polymorphisms on anthropometric and pressoric levels in the sample was analyzed by linear regression and the potential variables confounders (gender and age) were used to adjust. *PGC1-α* rs2979847 was associated with body weight (*P* = 0.039) and BMI (*P* = 0.030). Additionally, *UCP1* rs12502572 was associated with body weight (*P* = 0.049). The additive effect on variables was observed for both polymorphisms, in which subjects carrying two risk alleles had higher median values. Furthermore, five rare mutations were identified in *FNDC5* gene (Minor allele frequency, MAF>0.05), which one is a novel missense mutation. We did not identify patients carrying two risk alleles. The frequency of rs113173936 (AG) and rs72882318 (AG) were higher in severe obese group; however no statistic difference was found (*P* = 0.372 and *P* = 0.317, respectively).

Conclusion: This study demonstrates that *PGC1-α* rs2979847 influence on severe obesity susceptibility and also body weight and BMI in our sample. Moreover, *UCP1* rs12502572 was associated with body weight and five rare variations of *FNDC5* gene were identified, in which one is novel.

Código #13271

Título: ASSOCIATION OF SEROTONERGIC GENES WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: GENE-BASED AND GENE-SET ANALYSES.

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Objetivos: Attention-deficit/hyperactivity disorder (ADHD) is highly heritable and has been associated with multiple variants within serotonergic genes. Therefore, the aim of this study was to investigate associations between serotonergic pathway genes and ADHD, through both gene-based and gene-set approaches.

Metodologia: The sample comprised 417 subjects with ADHD and 463 controls (negatively screened for ADHD). Individuals were diagnosed according to the DSM-IV criteria at the adult division of the ADHD Outpatient Clinic from Hospital de Clínicas de Porto Alegre (ProDAH-A HCPA). All subjects were unrelated Brazilian adults of European descent. Genome-wide genotypes were assessed using the Illumina *Infinium PsychArray* or imputed based on SNPs linkage disequilibrium. Quality control procedures removed SNPs with minor allele frequency lower than 1% or not in Hardy-Weinberg Equilibrium. The final data retained 7,304,149 SNPs across the genome spanning 18,457 genes in autosomes. Serotonergic gene-set was selected based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) serotonin pathway and literature review. The gene-set comprised 9,048 SNPs of serotonin transporter, receptors and other related genes (*TPH1, TPH2, SLC18A1, SLC18A2, SLC6A4, HTR1A, HTR1B, HTR1D, HTR1E, HTR1F, HTR2A, HTR2B, HTR3A, HTR3B, HTR3C, HTR3D, HTR3E, HTR4, HTR5A, HTR6, HTR7*). Analyses were performed for the SNPs within the genes plus a 100 kilobase pair (kb) upstream and 80 kb downstream flanking region, using Multi-marker Analysis of GenoMic Annotation (MAGMA), from Genome-Wide Association Study (GWAS) summary statistics. Gene-based analysis determines whether any isolated gene is associated with the disorder, while the competitive gene-set analysis evaluates if the set of genes is more strongly associated with the ADHD outcome than the other genes in the genome. This procedure accounts for gene density and size. After correction for multiple comparisons, P-value was considered significant when < 0.0024 for genes.

Resultados: The gene-based analysis revealed nominal associations with *HTR1B* (P = 0.030) and *HTR1E* (P = 0.046) genes. Notwithstanding, the gene-set competitive analysis did not indicate any association with ADHD (P = 0.664).

Conclusão: This study revealed nominal associations of two serotonergic receptor genes with ADHD, indicating that variants along them may play an important role in the pathophysiology of the disorder. Nevertheless, it is likely that the present study lacked power to detect associations due to the limited sample size. Though the gene-set was not associated with the disorder itself, it may be rather associated with other ADHD-related phenotypes, as well as endophenotypes, or yet the serotonergic system could be associated with the disorder through other interacting genes. In this sense, further studies are needed in order to explore such perspective.

Código #13319

Título: AVALIAÇÃO *IN SILICO* DE POLIMORFISMOS DOS GENES *RB1*, *MDM4*, *CDKN1A* EM PACIENTES COM RETINOBLASTOMA

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Objectives: The retinoblastoma (RB), retinal tumor associated primarily with mutations in the tumor supressor gene *RB1*, accounts for 3% of all childhood malignancies, affecting children between 0-5 years old. Both hereditary and sporadic forms of this malignancy are associated with loss-of-function of both *RB1* alleles. In the hereditary form, one *RB1* mutation is constitutional and the other is somatic; carriers of constitutional mutations show variable penetrance and expressivity, a reason why the identification of potential genetic modifiers of the RB phenotype is relevant. Polymorphisms and mutations in *MDM4* have been frequently studied because of their impact on the regulation of *TP53* and *RB1* and its association with some types of cancer (Reis et al., 2012).
The *CDKN1A* gene, which encodes the p21 protein, is related to tumorigenesis and advances in the clinical stages of various types of cancer. Polymorphisms identified in this gene have been associated with reduced transcriptional rate and lower levels of the protein (Lu et al., 2015; Carvalho et al., 2013).
In this way, a variety of algorithms have been used to determine the effects of these variations on proteins and on the levels of their transcripts, in addition, they can estimate the deleterious effects that a variant can cause in the protein (Sayitoğlu, 2016). The identification of polymorphisms in the genes mentioned above, we will use protein modeling tools to verify the commitment that such polymorphisms can cause.

Methodology: DNA samples were obtained from patients with RB; the 27 exons of the *RB1* gene and other genes were amplified by polymerase chain reaction (PCR) and subsequently the amplicons were purified and sequenced. With the observation of polymorphisms in the sequences, in silico analyzes involving the modeling of the coding proteins of each gene will be evaluated.

Results: Carvalho et al. (2013) showed that the presence of the rs1801270CA and rs1059234CT genotype of the *CDNK1A* gene was associated with an increased risk of developing RB (OR = 2.5, 95% CI = 1.38-4.53), while the presence of wild genotype for the two polymorphisms was associated with a lower risk (OR = 0.43, 95% CI = 0.25-0.74), concluding that minority alleles for rs1801270 and rs1059234 may act as risk factors for the development of retinoblastoma (Carvalho et al., 2013). However, little is known about the influence of these polymorphisms on p21 protein function.
An *in silico* analysis was then performed for the two polymorphisms whose results are found below:

With the use of some softwares (PhD-SNP, Polyphen-2, SNPs&GO, TANGO Aggregation Tendency, WALTZ Amyloid Propensity and LIMBO Chaperone Binding Tendency), we evaluated the effects of polymorphisms: rs1801270 C> A is located at codon 31, resulting in a serine exchange for arginine in a highly conserved zinc finger region. Thus, the in silico analyzes showed that this exchange appears to have a neutral or benign effect on the protein, not altering the tendency to aggregation, amyloid propensity and attachment to chaperones. The rs1059234 located in the 3'UTR region seems to positively influence transcript stability since the C> U exchange leads to loss of interaction with the microRNAs -509, -1288, -3169 (predictions made by the program MiRNA SNP).
The rs116197192 *MDM4* also showed to have a neutral or benign effect on the protein; in the *RB1* gene we have some polymorphisms that cause ESE site creation (5) and ESS rupture (3).

Conclusion: With the use of computational modeling techniques, we aimed to find the possible relations of the polymorphisms identified in patients with RB and to understand how these alterations can affect the structure and functioning of the protein, being possible to relate to other factors found in the literature and associated with the phenotype of the individual. Although the results have indicated benign SNPs, it is important to highlight the use of these *in silico* analyses to evaluate the effects that the polymorphisms can cause in the protein and in our study, SNPs located in intronic regions may affect splicing activation and repression sites resulting in modifications to the splicing pattern in the nearest exons.

Código #13312

Título: Can different distribution of normal variation impact molecular testing in the clinical context? A study in the Brazilian population

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Objectives: Medical treatment is set on the average patient, but some treatments are non-effective to a part of the population. Precision Medicine (PM) has emerged recently as a concept in which scientific knowledge and technology will come together to provide the basis for the 21st century medicine. To implement PM, it is important to determine the genetic profile of a population because the distribution of rare and common variants may have different downstream implications in different populations. In addition, due to the historic and demographic constitution of the Brazilian population, it is reasonable to assume that one will find a significant source of genomic diversity which is important for studies aiming to disclose the true genomic viability of the human genome, both in normal and disease states. Therefore, we aim to determine the genomic profile of Brazilian individuals and compared it with data available from other population.

Methodology: We performed Whole Exome Sequencing (WES) in 106 subjects and Affymetrix 6.0 SNP-array in 264 individuals. These are normal/reference individuals from the region of Campinas, SP, BRAZIL. Genomic data produced was deposited in two public databases (www.bipmed.org) which are part of the Brazilian Initiative on Precision Medicine. We used the Leiden Open Variation Database (LOVD) for data storage and visualization. Alternative allele frequencies (AAF) were calculated for each variant in both datasets. In the SNP-array study we compared the frequency from 4 populations (CEU - Northern Europeans from Utah; CHB - Han Chinese in Beijing; JPT - Japanese in Tokyo; YRI - Yoruba in Ibadan), provided by the manufacturer. We compared population allele frequencies using PCA.

Results: In the WES study, we found 624,137 different variants (SNVs and INDELs) from 19,069 genes, among them 68,149 (10.9%) were not detected in any other studies. Furthermore, 45.51% of the variants detected have AAF of less than 1%, 22.44% of the variants have AAF between 1% and 5%, 7.5% have AAF bigger than 50% and 0.3% have AAF equal to 100%. In the SNP array study, the correlation analysis and the PCA showed that our dataset is closer to the CEU population, distant from CHB and JPT. These data also suggest less similarity with YRI. We also found 9 SNPs with reversal of the allele frequency, meaning the more frequent allele identified in the 4 populations used for comparison is actually the less frequent allele in the Brazilian population or vice versa.

Conclusion: Our results clearly indicate that there are differences in the genomic distribution of both rare and common variants in Brazilian individuals as compared to other populations, and demonstrate the importance of constructing a larger and geographically diverse panel of reference genomic

datasets for both rare and common variants in the Brazilian population. This initiative should be the first step in order to provide the basis for the implementation of Precision Medicine in Brazil.

Código #13325

Title: Characterization of microRNAs in circulating extracellular vesicles in the autoimmune diseases pemphigus foliaceus and pemphigus vulgaris.

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Objective: to quantify microRNAs (miRNAs) of extracellular vesicles (EVs) in two blistering autoimmune skin diseases characterized by a Th2-dependent production of pathogenic IgG autoantibodies: endemic pemphigus foliaceus (EPF) and pemphigus vulgaris (PV).

Methodology: Our candidate miRNAs were miR-145, miR-146a, miR-150, miR-155, miR-214 and miR-223 previously described as deregulated in certain tissues of patients with autoimmune diseases. EVs enriched in exosomes were isolated with Total Exosome Isolation Reagent solution (Invitrogen, Carlsbad, CA) from the serum of 16 PF patients, 13 PV patients, and 11 healthy controls. We confirmed the size and amount of EVs by nanoparticle tracking analysis. Protein expression analyses were performed for standard exosome surface markers (CD9 and CD63) by flow cytometry. We isolated total RNA from EVs and performed RT-qPCR for target miRNAs. The significance of differences between patients and controls was evaluated through Mann-Whitney test ($p \leq 0.05$).

Results: The average EV size was 144.35 nm and approximately 50% of particles detected were positive for CD9 and/or CD63 markers, indicating an exosomal enrichment (30-100nm, CD9+, and CD63+). All candidate miRNA were found in serum EVs: miR-223-3p was the most abundant (Cq=29.89); and miR-214 presented the lowest average quantity (Cq=35.67), not being detected in all the individuals. No difference was found when PF patients with active disease were compared to controls. MiR-145 and miR-155 were enriched in patients with inactive EPF ($p=0.0219$, fold 3.68 and $p=0.0604$, fold 4.02, respectively), suggesting a possible role in disease progression that deserves investigation. In PV, only mir-145 e miR-146a were analyzed. We did not observe any difference in miR-146a levels between patients and controls. Although, we found differences in miR-145 levels between patients undergoing treatment and controls ($p=0,0205$, fold 9.19) and a trend of difference between patients without treatment and controls ($p=0,0848$, fold 4.92).

Conclusion: This initial study revealed interesting data on miRNAs of extracellular vesicles in two autoimmune diseases, contributing to identification of potential novel biomarkers of bullous skin diseases. These results should be further explored in larger samples and with functional studies.

Keywords: Extracellular vesicles, exosomes, pemphigus vulgaris, endemic pemphigus foliaceus, microRNA

Financial support: CAPES, CNPq, PRONEX and Fundação Araucária.

Código #13217

Título: *CHRNA5* SNPs and crack/cocaine addiction

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Objectives: Cocaine is a highly addictive drug, associated with behavior, cognitive and physiological impairments. Approximately 18.2 million people worldwide use crack/cocaine, and Brazil is among the countries with higher prevalence. There are several factors involved in crack/cocaine addiction and heritability estimates highlighted the influence of genetic variants on addiction susceptibility. The dopaminergic pathway has an important role in addiction of different substances due to its effects in the reward system, and also interacts with other mechanisms, such as the cholinergic pathway. Nicotinic receptors, members of the cholinergic system, have been associated with nicotine, alcohol and cocaine dependencies. The CHRNA5 gene that encodes the alpha-5 subunit of the nicotinic acetylcholine receptor has been studied on different addiction substances, with some SNPs related to mRNA expression. Our aim was to evaluate the influence of three polymorphisms (rs514743, rs588765, rs16969968) in CHRNA5 on crack/cocaine addiction.

Methods: This study enrolled crack/cocaine addicted patients (n=300) and controls (n=633), both European descendants. Diagnosis and clinical assessments were performed according to DSM-IV criteria and the Addiction Severity Index – 6 (ASI-6) was applied to evaluate crack/cocaine addiction severity. Logistic regression analysis was used to evaluate the influence of SNPs in crack/cocaine addiction; and linear regression to evaluate severity of addiction. All analyses were adjusted for age and sex. Multiple testing correction was performed using Bonferroni correction.

Results: AA-rs16969968 and TT-rs588765 genotypes were associated (OR=0.532 p=0.009/pcor=0.027) and nominally associated (OR 0.581 p=0.037/pcor=0.111) with crack/cocaine addiction. SNPs were not associated with severity of dependence.

Conclusion: We replicated previous findings including the effect of the rs16969968 on protection against crack/cocaine addiction. Previous studies have demonstrated that this SNP apparently presents opposite effects in nicotine and crack/cocaine addictions. *CHRNA5* seems to be a promising candidate gene for common as well as specific effects for addiction to different substances. Our perspectives

include increasing sample size and investigating the influence of *CHRNA5* in other addiction substances including alcohol.

Código #13366

Title: Chromosomal Microarray Analysis (CMA) in Patients with Rokitansky Syndrome

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Rokitansky Syndrome is a rare disease characterized by the malformation or absence of uterus and the upper part of the vagina. Women diagnosed with this syndrome may present abnormalities in the kidneys, heart, bones or hearing. Diagnosis is usually made late because of the absence of menstrual periods or difficulties in sexual intercourse. Among the cases of Rokitansky Syndrome there are five regions that contain changes (deletion / duplication) described as recurrent in the literature: 1q21.1, 16p11.2, 17q12, 22q11.21 and Xp22. Objective: The present work aims to identify genomic regions and / or genes that contribute to the etiology of Rokitansky Syndrome. Methods: The patients were subjected to detailed gynecological exams as an initial evaluation. The first stage was a karyotype exam, with the objective of differential diagnosis with Morris Syndrome, followed by chromosomal microarray analysis. Results: The aforementioned tests were conducted for four patients affected by Rokitansky Syndrome. We did not identify any chromosomal alterations that correlate with the patients' clinical condition. Conclusion: The results obtained in this study reinforce the notion that the genetic heterogeneity of the syndrome is not only due to copy number variations (CNVs), but also to monogenic causes and possibly environmental causes in its etiology.

Código #13232

CLINICAL AND MOLECULAR CHARACTERIZATION OF NEUROFIBROMATOSIS IN SOUTHERN BRAZIL: DETECTION OF POINT MUTATIONS BY NEXT GENERATION SEQUENCING.

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Aim: The clinical diagnosis of the neurofibromatoses type 1 and 2 (NF1 and NF2) can be complicated in sporadic cases and when clinical criteria are not fulfilled. Therefore, molecular diagnosis is an important tool for these diseases. The aim of the present study is to characterize the spectrum of *NF1* and *NF2* mutations in neurofibromatosis patients from South Brazil and correlate these findings with clinical signs, as well as evaluate the probable impact of different mutations on their respective proteins.

Methodology: We recruited 98 patients from 93 unrelated families who were clinically diagnosed or suspected of NF1 and seven unrelated patients suspected of NF2 at the Oncogenetics service from Hospital de Clinicas de Porto Alegre, Rio Grande do Sul, Brazil, and established a molecular method to characterize point mutations in these patients using customized next generation sequencing panels. All variants identified were confirmed by Sanger sequencing.

Results: Overall, 69 distinct heterozygous *NF1* variants were identified in 73 (79%) of the 93 patients and 2 distinct heterozygous *NF2* variants were identified in two (29%) of the seven patients. Of the variants identified, 14 were pathogenic, 34 were likely pathogenic, two were likely benign, 21 were variants of uncertain significance and 33 were novel. A complete and detailed large rearrangement screening (Multiplex Ligation-dependent Probe Amplification and SNP array) was performed in the same NF1 and NF2 patient series and was previously published by our group. Severity and visibility of NF1 patients evaluated according to the type and location of *NF1* mutations did not show novel genotype-phenotype correlations in our population. However, a well-documented and previously established variant (3-bp in-frame deletion c.2970_2972delAAT), which is associated with an absence of neurofibromas, was found in two unrelated familial probands in our study, both with café-au-lait macules, axillary and inguinal freckling and absence of neurofibromas.

Conclusion: Identification of *NF1* mutations is challenging because the *NF1* gene is large and complex. Diagnosis if further complicated by the presence of pseudogenes. Also, both *NF1* and *NF2* genes lack mutational hotspots. Numerous studies have performed complete molecular analysis in many populations worldwide, but none in Brazil. Thus, this is the first report to characterize the complete known genetic background of NF1 and NF2 in Brazil. The molecular diagnosis strategy showed a point mutation detection rate of 79% in *NF1* and 29% in *NF2,* which is similar to other studies worldwide. The data obtained should provide a strategy for early diagnosis and genetic counseling in this country.

Further studies with larger scales are required to identify potential genotype-phenotype correlations in Brazilian patients.

Código #12765

TITLE: CLINICAL DECISION-MAKING AND GENETIC COUNSELLING IN FAMILIES AT RISK FOR X-LINKED DISEASES BASED ON THE X-CHROMOSOME INACTIVATION PROFILE BY THE HUMARA TEST.

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Introduction: The X chromosome carries different types of mutations associated to a clinical phenotype. Monogenic mutations are the most frequent ones and the gene generally identified by the usual sequencing techniques. However, although the presentation of a phenotype may suggest X-linked inheritance, the gene may often has not been identified and/or the variant lacks a definition of its clinical significance. These are variants identified by exome sequencing or in the case of chromosomal abnormalities through CGH-array.

Methods: Genomic DNA was analysed in a series of cases using standard X-chromosome inactivation technique by HUMARA method (Molecular Cytogenetics 2;20,2009). Two obligate Fabry's disease carriers (c.470delA and p.Trp349Ser genotypes, respectively), two families with a X-linked inheritance for intellectual disability (ID), one family with affected brothers with Haemophilia A with two apparently obligate carriers; and, an ASD boy with dupXp22.33 inherited from mother identified by CGH-array were selected. An informative family with Lesch-Nyhan syndrome served as a positive control. With a very pragmatic approach, and taking into account the exceptions reported for skewed inactivation in normal women (newborn, elderly and changes in the imprinting centre-Am J Hum Genet 79:493,2006), our conclusions and clinical implications were critically considered.

Results: The asymptomatic girls with Fabry (normal creatinine clearance), X-chromosome inactivation occurred randomly. As a result, we delayed renal biopsy; and, prescription for enzyme replacement therapy postponed. In both families with ID X-linked inheritance, X-chromosome inactivation occurred in an extreme skewed fashion in both mothers of both propositus. A random inactivation in their sisters (or nieces) was observed, indicating: (1) presence of a pathogenic variant (gene) associated with the phenotype; and, (2) low recurrence risk for the sisters (nieces) due to a random inactivation. The Haemophilia A family, in spite of medical reports that father and uncle were affected, the gene sequencing, including MLPA, did not identify mutations in either gene (Factor VIII and Factor IX). The inactivation study in the proposita revealed a random pattern, in contrary as expected, as an obligate carrier; and, maternal UPD was excluded. Finally, dupXp22.33 in the ASD suggested pathogenic since the mother showed an extreme skewed deviation.

Conclusion: With reasonable doubt and no functional studies performed with the variants, we tested a simple and reliable method discriminating pathogenic from non-pathogenic variants in the genome based in the assumption that a “healthy biological status” versus “disease biological status” could be differentiate. Genetic counselling were concluded.

Código #13401

Title: COMPLEMENT POLYMORPHISMS INFLUENCE SUSCEPTIBILITY TO HIV, AIDS AND HEPATITIS COINFECTION

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Objective: To evaluate the association between functional polymorphisms of genes encoding the major proteins involved in the activation of the lectin pathway of the complement system (*FCN2, FCN3, MASP1* and *MASP2*) and serum concentrations of the ficolins (FCN-2 and FCN-3) and serine proteases associated with the mannose-binding lectin (MASP-2 and MASP-3), with the susceptibility and progression of HIV infection.

Methodology: A retrospective analytical study was conducted in 94 controls and 126 Euro-Brazilian HIV+ patients, of which 57 were positive for past HBV infection, 13 were HBV/HCV coinfected and 4 HCV-coinfected, 71 with AIDS (CDC criteria). We genotyped 22 polymorphisms, using multiplex sequence-specific PCR, and analyzed them by logistic regression, correcting the results, if necessary, by gender and age using STATA (version 9.1) and R (version 3.3.3). The variables that presented $p < 0.20$ were selected for the multiple analysis and the final reduced model was obtained using the level of significance of $p < 0.05$.

Results: Higher MASP-2 levels were associated with resistance against HIV infection (summing all patients: OR=0.02, P=0.001), independently of higher MASP-3 levels. This protein is an inhibitor of the lectin pathway and activator of the alternative pathway, and was associated with susceptibility (OR=12.6, P=0.014). In contrast, *MASP2* genotypes containing low-expression alleles were associated with protection against AIDS (OR=0.19, P=0.028), which may be explained by its pro inflammatory role. Haplotypes *MASP2*CDV* (*g.1961795C*, *p.371D* and *p.377V*) and *FCN3*CInsA* (*g.27373182C, g.27371297-27371298insTATTTGGCC* and *g.27370346C*) were associated with susceptibility to HIV alone (OR=5.1, P=0.013 and OR=2.7, P=0.016, respectively). Higher FCN-2 levels predisposed HIV-infected individuals to HBV coinfection (OR=9.8, P=0.048), in contrast to the *FCN2*AGA* (*g.680489A*, *g.680873G* and *g.681471A*) haplotype, which protected against coinfection (OR=0.11, P=0.018). Finally, *MASP1*58267T* (*rs1109452*), located in the untranslated region of exon 12 and associated with decreased serum MASP-3 levels, was found as a protective factor against any coinfection, HBV or HCV (OR=0.17, P=0.001).

Conclusion: The results lead us to suggest an important role of the lectin pathway of complement in the susceptibility not only of HIV per se, but also of HBV/HCV coinfection and AIDS. Although activation of the lectin pathway seems to be important in getting rid of HIV/HBV/HCV infection, exacerbated inflammation may predispose infected individuals to AIDS.

Codigo #12778

Title: CONTRIBUTION OF CONCOMITANT SUBTELOMERIC DELETIONS/DUPLICATIONS TO RARE DISORDERS: STUDY OF 731 PATIENTS WITH CONGENITAL MALFORMATIONS AND INTELLECTUAL DISABILITY.

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Objective: To study the genotype – phenotype correlations of cases with concomitant subtelomeric deletions and duplications in patients presenting congenital malformations (CM) and intellectual disability (ID).

Methods: We investigated 731 patients with CM and ID using multiplex ligation-dependent probe amplification (MLPA) technique using two specific subtelomeric kits (P036 and P070).

Results: Our analysis revealed 20 cases of concomitant deletions and duplications in assorted genomic locations: sixteen cases presented deletions/duplications in different chromosomes and four cases the alterations occurred in the same chromosome. Among the studied cases, two cases of apparent reciprocal translocations were, in fact, unbalanced translocations with one deletion and one duplication at the specific breakpoints.

Conclusion: The subtelomeric rearrangements are being recognized as the responsible for several rare syndromes but usually the patients do not have concomitant deletions/duplicatons, as it was seen in our analysis. Some of these alterations were already reported as a cause of syndromic phenotypes. Thus, we can conclude that MLPA has a high efficiency to identify pathogenic deletions and duplications unseen by the conventional karyotype and also are essential to a better understanding of the complexity of subtelomeric regions and its relation with clinical features.

Código #13278

Título: ESTUDO DE NOVOS GENES ASSOCIADOS ÀS RASOPATIAS PELO SEQUENCIAMENTO DE NOVA GERAÇÃO.

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Introdução: O avanço das técnicas de biologia molecular na última década, em especial o sequenciamento de nova geração (SNG) através do sequenciamento do exoma, vem permitindo encontrar variantes patogênicas em novos genes responsáveis por diversas doenças mendelianas, incluindo aqui a síndrome de Noonan (SN) e síndromes correlatas, conhecidas, em conjunto, como RASopatias. Desta forma, desde 2013, nove genes novos foram associados à SN (a que apresenta a maior heterogeneidade genética entre as RAsopatias): *RIT1, RRAS, RASA2, A2ML1, MAP3K8, SPRY1* (2013)*, SOS2, LZTR1* (2015)*, PPP1CB* (2016), sendo os genes *SOS2 e LZTR1* identificados pelo nosso grupo.

Objetivos: Descrever os aspectos clínicos e moleculares de pacientes com RASopatias avaliados no ambulatório de Genética do ICr do HC/FMUSP.

Metodologia: Setenta pacientes previamente avaliados em nosso serviço com RASopatia e estudo molecular negativo para os genes previamente conhecidos foram selecionados para a realização de SNG (exoma), priorizando os casos familiais. O estudo genético foi realizado a partir de uma amostra de DNA a partir do sangue periférico. O preparo da biblioteca utilizou kit de captura da Illumina e a corrida foi realizada no aparelho HiSeq. Ferramentas de informática foram utilizadas para alinhamento e processamento dos dados (BWA, GATK6 e ANNOVAR7) e a tabela de variantes foi analisada a partir de bancos de dados públicos: 1000 Genomes, ExAC , ABraOM), sendo as mesmas filtradas para uma frequência menor que 1% nessas populações controle.

Resultados: O estudo mostrou que seis pacientes da nossa casuística com quadro clínico compatível com a SN apresentavam mutações *missense* no gene *RIT1*. O fenótipo incluía com frequência um peso elevado ao nascimento, macrocefalia relativa, miocardiopatia hipertrófica e achados ectodérmicos. Dois genes novos, *SOS2* e *LZTR1* foram encontrados em dois (um familial) e quatro (dois familiais) pacientes, respectivamente. O gene *SOS2*, semelhante ao gene *SOS1*, estava associado a um fenótipo Noonan com comprometimento ectodérmico evidente. O fenótipo dos indivíduos com mutação no gene *LZTR1* era semelhante aos observados naqueles com mutação no gene principal da SN, o *PTPN11*. Recentemente, uma reanálise dos exomas permitiu encontrar um paciente com mutação no gene *PPP1CB*, o mais recente a ser descrito. O fenótipo caracteriza-se por apresentar cabelos esparsos, finos, de crescimento lento, semelhante ao observado em pacientes com mutação no gene *SHOC2*.

Conclusão: A técnica do SNG permitiu a descoberta de novos genes associados à SN, levando a um maior conhecimento dos mecanismos moleculares/vias de sinalização responsáveis por esta doença. Dezesseis genes estão associados à SN, incluindo os dois genes descobertos pelo nosso grupo, mas este número ainda não corresponde a 100% dos casos clínicos. Portanto, pesquisas ainda são necessárias para desvendar todas as bases moleculares que causam esta síndrome, com o objetivo final de um melhor manejo dos afetados. FAPESP 2011/17299-3; CNPq 304130/2016-8

Código #13277

Título: ESTUDO MOLECULAR DE PACIENTES COM ANOMALIAS DE SEGMENTAÇÃO VERTEBRAL

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Introdução: Os defeitos de segmentação vertebral (DSV) podem fazer parte de diversas síndromes, incluindo uma condição radiologicamente definida por múltiplos DSV em associação a anomalias de arcos costais, em geral, mantendo uma conformação simétrica da caixa torácica, a disostose espôndilo-costal (DEC). Há heterogeneidade genética com dois padrões de herança, autossômica recessiva (cujos genes são *DLL3*, *MESP2*, *LFNG* e *HES7)*, e autossômica dominante (*TBX6*).

Objetivos: Descrever os achados clínicos e moleculares em indivíduos com DSV, incluindo pacientes com quadro clínico típico de DEC avaliados no ambulatório de Genética do ICr-HC/FMUSP.

Metodologia: Foram selecionados 11 probandos com diagnóstico de DSV, seis com DEC. O estudo molecular foi realizado através de duas técnicas de sequenciamento: Sanger para o gene *TBX6* e o sequenciamento de nova geração através de um painel customizado que incluía os genes *DLL3*, *MESP2*, *LFNG, HES7 e GDF6* (responsável por alguns casos da sequência de Klippel-Feil).

Resultados: Os achados radiológicos mostravam: escoliose de início precoce (100%, 11/11), segmentação anômala de vértebras (81,8%, 9/11), malformações vertebrais (81,8%, 9/11), fusão de arcos costais (90,9%, 10/11) e hipoplasia de arcos costais (18,2%, 2/11). Foram encontradas mutações em 6 indivíduos, 5 deles com quadro clínico típico de DEC: 4 mutações em *DLL3* (2 em homozigose e 2 em heterozigose composta) , 1 mutação *stop-loss* em *TBX6* (caso familial com transmissão pai para filha) e apenas 1 mutação no gene *LFNG*. Como em casos com escoliose congênita os indivíduos podem apresentar um modelo composto nos quais os afetados apresentam um mutação rara em um alelo do gene *TBX6* e um haplótipo de risco no outro alelo, analisamos também este haplótipo na família aqui estudada, mostrando que dois dos três SNPs estavam presentes nos afetados.

Conclusão: Os achados corroboram os dados da literatura que mostram o gene *DLL3* como responsável por um quadro com um grande envolvimento vertebral, sendo a causa mais frequente da DEC. Um indivíduo, filho de pais consanguíneos e quadro típico de DEC, não apresentou mutações em nenhum dos genes analisados, sugerindo que um novo gene pode ser responsável pela DEC.
Em um dos casos, apenas uma mutação foi encontrada no gene *LFNG*, que requer o envolvimento dos dois alelos, não confirmando que esta alteração é responsável por seu quadro clínico. O encontro do haplótipo de risco na família com mutação em *TBX6* confirma que o modelo composto proposto para a

escoliose congênita, também é importante na patogênese da DEC. Os resultados obtidos apontam para a ampla heterogeneidade genética relacionada a esse grupo de condições e reforçam a importância da continuidade de estudos com o objetivo de caracterizar novos defeitos genéticos relacionados, possibilitando um melhor conhecimento acerca da patogênese da doença e um adequado aconselhamento genético. FAPESP 2011/17299-3; 2015/21783-9; CNPq 304130/2016-8

Código #13085

Title: EXOME SEQUENCING ANALYSIS IDENTIFIES CAUSAL MUTATIONS IN A BRAZILIAN FAMILY WITH STARGARDT DISEASE.

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Objective: To identify possible causal mutations in a Brazilian family with four sisters affected with Stargardt disease (STGD) by performing whole exome sequencing (WES), integrated with deep phenotype (complete ophthalmologic examinations).

Methodology: We performed WES of two affected sisters with more severe STGD symptoms, using Ampliseq technology for library preparation, sequencing with the IonProton platform, alignment and mapping with TMAP software. Based on variant annotations of the ANNOVAR and IonReporter programs, we evaluated mutations in all candidate genes and applied standard filtering steps (no variant in regulatory regions, no intergenic, synonymous variants, and with allele frequency higher than 1%). We also filtered the variants according the results from algorithms that predict the effect of nucleotide change as PolyPhen-2, SIFT, Mutation Taster, FATHMM and Mutation Assessor, and verified pathogenicity of candidate variants in the Clinvar database. To prioritize candidate genes and variants, we also used The Exomiser algorithm, including variants in possible modulatory genes potentially responsible for variable disease expression. We searched for filtered mutations with high-quality reads (evaluated on IGV software) in 14 family members by Sanger sequencing, for further validation.

Results: We identified around 55,330 variants in both patients. After data filtering and analysis, we prioritized nine candidate variants, three of which were present in the *ABCA4* gene, the major STGD candidate gene. Although none of the variants occur in other candidate STGD-associated genes (*CNGB3*, *ELOVL4*, *PROM1*, *PRPH2* and *BEST1*), there were six heterozygous mutations present in genes associated with retinal dystrophies (listed in RetNet), three of them in both sisters. Among them, only the variant in the *TLR4* gene was not previously described in dbSNP (MAF<0.0001 - South Asian population/ExAC Browser). We successfully verified all candidate variants identified by WES using Sanger sequencing in the affected sisters, including one additional affected second-degree relative. All four sisters were heterozygotes for two *ABCA4* missense mutations (MAF 0.00002 and MAF 0.0306 ExAc Browser), as well as for one *RDH11* missense mutation (MAF 0.0163 ExAc Browser). Interestingly, only the *RDH11* and the rare *ABCA4* mutations were predicted to be pathogenic. A first-degree cousin of their mother was homozygote for the rarer *ABCA4* variant and presented late onset of the disease. He had one deceased affected brother with the same phenotype.

Conclusion: The rarer *ABCA4* variant in a homozygous state potentially causes a late onset of STGD. We hypothesize an epistatic interaction among *ABCA4* and *RDH11* genes and possibly a digenic inheritance of STGD1 in this family. Once there is no medication for STGD, we expect that the recognition of pathogenic variants will indicate new targets for possible gene therapy in the future.

Financial support: CAPES, CNPq, Young Talent Fellowship Awards, Science without Borders Program. Clínica de Olhos Vitreo e Consultoria de Curitiba.

Código #13280

Title: EXOME SEQUENCING BY NIMBLEGEN KIT IS NOT SUITABLE FOR SOX2 AND SOX3 MOLECULAR SCREENING DUE TO BALD SPOT

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Aim: The aim of this study is to determine the relation of the coverage of *SOX2* and *SOX3* genes on whole exome sequencing performed by NimbleGen kit with variant discovery in a cohort of patients with idiopathic hypopituitarism.

Patients and Methods: Twenty-six individuals (15 males/11 females) with idiopathic hypopituitarism were selected for this study. Genomic DNA was isolated from blood leukocytes by standard techniques. The only exon of *SOX2* and *SOX3* genes coding regions were amplified by polymerase chain reaction (PCR) using in-house designed primers. Amplicons were sequenced using the ABI Prism BigDye Terminator Cycle Sequencing Ready Reaction Kit according to the recommended protocol and placed on the ABI PRISM 3100 sequencer (Life Technologies Corporation, USA). Genomic DNA samples were used to produce exome captured sequencing library by NimbleGen SeqCap EZ v3.0 kit, following manufacturer's protocol. Paired-end exome-sequencing was done using an Illumina HiSeq2000 System. Raw reads were aligned to the 1000 Genomes Phase 1 reference and mapped to GRCh37 using BWA v0.5.9. Single nucleotide variants, insertions and deletions were called using GATK Haplotype Caller v3.3. Variants were annotated using ANNOVAR. The coverage of exomic regions corresponding to *SOX2* and *SOX3* genes was explored using the software Integrative Genomics Viewer (IGV).

Resultados: Any variants was identified by WES in *SOX2* and *SOX3*. It was observed poor coverage of *SOX3* poly alanine tracts in three patients and more than 50% of the gene coding region, with less than twenty reads per base. *SOX2* gene was also poorly covered in about half of the samples. *SOX3* analysis by Sanger sequencing revealed the polymorphism p.P103T (c.307G>T, rs201101913) in heterozygous state in three patients. In silico analysis and variant population frequency was performed using the prediction sites Mutation Assessor, Mutation Taster, Polyphen2, Human Splicing Finder 3.0, ExAC, and 1000g and the variant was classified according to the American College of Genetics and Genomics (ACMG) as benign.

Conclusão: Exome sequencing by NibleGen capture system shows a poor coverage of genes with high GC contents, as *SOX2* and *SOX3*. Despite the rarity of *SOX2* and *SOX3* mutations, defects in these genes are generally associated to hypopituitarism. Thus, the screening of these genes in patients with congenital hypopituitarism should be by Sanger sequencing.

Código #13239

Title: GENE-SET ANALYSIS OF THE SNARE COMPLEX IN ADULTHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Authors: Cibele Edom Bandeira[1,2], Renata Basso Cupertino[1,2], Bruna Santos da Silva[1,2], Alana Castro Panzenhagen[1,2], Diana Müller[1,2], Stefania Pigatto Teche[2,3], Djenifer B. Kappel[1,2], Nina Roth Mota[4], Eugenio Horacio Grevet[2,3], Claiton Henrique Dotto Bau[1,2]

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Objectives: SNARE complex (Soluble NSF-Attachment Protein Receptors) has been investigated in the context of psychiatry disorders due to its important role on neurotransmitter release. In this sense, evidence from animal models and candidate gene studies suggest an involvement of the SNARE complex in the pathophysiology of Attention-Deficit/Hyperactivity Disorder (ADHD). Therefore, the aim of this study was to evaluate the influence of SNARE complex-related genes on ADHD susceptibility through a gene-based and gene-set approach.

Methods: Our sample comprised 417 adults with ADHD (diagnosed according to DSM-IV criteria) and 463 controls (with negative screening for ADHD). Genotyping was performed through the *Illumina Infinium PsychArray* or imputed based on SNPs linkage disequilibrium. In the gene-based analysis, the mean SNP chi-squared model was used to calculate a gene-wide P-value. Subsequently, we tested whether the selected gene-set was more strongly associated with ADHD than all other genes in the genome (competitive analysis). The genes included in the set were defined through manual curation based on their relevance to the biological context. The set consisted of twelve SNARE complex-related genes: *SNAP25, STX1A, SYT1, SYT2, SYT4, VAMP1, VAMP2, MUNC13, STXBP1 (MUNC18-1), CPLX1, CPLX3, NSF*. Both gene-based and gene-set analyses were conducted using the *Multi-marker Analysis of GenoMic Annotation* (MAGMA) software (v1.06). For each gene, we considered a flanking region of 100 kb upstream and 80 kb downstream.

Results: The SNARE complex gene-set was not significantly associated with ADHD in the competitive analysis ($p = 0.390$). In the gene-based analysis, although none of the selected genes were significantly associated with ADHD, Synaptotagmin 1 (*SYT1*) showed the most promising result to be further investigated ($p = 0.065$, uncorrected).

Conclusion: Despite the non-significant results in the gene-based and gene-set analysis, the growing evidence suggesting a role of the SNARE complex on ADHD etiology should not be disregarded. The lack of association in the present study may be due to the limited statistical power, and further investigations should explore genes/pathways related to the SNARE complex in larger samples.

Código #12637

Title: GENETIC BACKGROUND OF THE MAIN PARKINSON'S DISEASE CLINICAL SIGNS

Authors: Edgar Paulo da Silva Neto; Fernando de Oliveira; Rebeca Menezes de Souza; Nadja Maria Jorge Asano; Manuela Barbosa Rodrigues de Souza.

Institution of authors: CCBS - Center of Biological Sciences and Health, Catholic University of Pernambuco, Brazil.

Objectives: General - analyze the SNCA gene in Parkinson's disease. Specific: (1) To analyze the mutations in the SNCA gene and the onset of Parkinson's disease; (2) To identify the network of gene interaction of the SNCA gene; (3) to correlate changes in the functions of the SNCA gene and the principal clinical signs in Parkinson's disease.

Methods: The first stage of this research used the database PDGene (http://www.pdgene.org) which was confirmed the association of SNCA in the pathophysiology of Parkinson's disease (PD), In addition, a search was made for the mutations described in this gene that were deposited in PDGene (LILL et al., 2012; NALLS et al., 2014). In the second stage we used GeneMANIA software (http://www.genemania.org), a hypothesis generation tool that uses large sets of biological data available in public databases to find correlated genes. The goal of the GeneMANIA algorithm is to extend a list of certain genes, input data by the user, to find new genes that are related to each other. From the SNCA, a predictive association network was generated, comprising protein-protein, protein-DNA interaction, metabolic pathways, co-expression, co-localization, preserved protein domain, orthology and disease information. The construction of this network was based on a set of data collected from 10 public databases (GEO, BioGRID, InterPro, SMART, Pfam, PathwayCommons, BioCyc, Reactome, I2D and Ensembl). In the measure of genetic correlation a weight was indicated that measures each association found, giving safety and precision in the networks predicted by Genemania (MOSTAFAVI et al., 2008; WARDE-FARLEY et al., 2010).

Results: Among the genes that determine Parkinson's disease (PD) the SNCA, also known as park 1, has been shown to be one of the most determinant of the disease, besides being the gene that most relates to the others, according to the databases Used PDGene and Genemania. The Park 1 determines the formation of a protein called alpha-synuclein, whose alteration caused by mutation in the gene, allows the accumulation of proteins that act to neurotoxic form, impeding the function of dopaminergic cells (Perfeito and Rego, 2012). The Park 1 is related to park 2, which determines 50% of cases of PD at early age. Mutations in the park 5 alter the ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) enzyme, allowing abnormal accumulation of proteins, and contributing to the manifestation of the disease. In addition, the mutation in the park 7 gene causes alteration in the dopamine transporter, compromising neurohormonal modulation (Ribeiro et al., 2004).

Conclusion: The databases used provided access to safe and up-to-date information about the SNCA profile. It was also concluded that the relations between the SNCA and the other genes involved in the determination of the disease are highly complex, which makes it difficult to describe the results of their alterations and the clinical signs determined by them. Therefore, PDGene and Genemania helped us to elucidate which gene is most closely linked to the onset of major clinical signs of Parkinson's disease.

Código #12744

Title: GENETIC CHARACTERIZATION OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY FROM A TERTIARY HOSPITAL

Authors: Glauber Monteiro Dias[1], Julianny Freitas Rafael[1], Ana Luiza Sales[1], Fabiana Bergamin Muccillo[1], Thaís Torres Lima[1], Iris Santana[1], Mariana Ramires[1], Eduardo Back Sternick[2], Jorge Albuquerque Coutinho[1], Fernando Eugênio dos Santos Cruz Filho[1]

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Objectives: Hypertrophic cardiomyopathy (HCM) is characterized by unexplained and asymmetric ventricular hypertrophy (VH) in the absence of other cardiac or systemic disease and is the major cause of sudden cardiac death in young people. HCM is an autosomal dominant inherited disease caused by pathogenic mutations in cardiac sarcomere protein genes. HCM phenocopies may be associated with non sarcomeric genes mutations, like PRKAG2, responsible for a cardiac syndrome associated with glycogen storage which includes VH, a familial form of ventricular preexcitation (WPW), atrioventricular conduction disturbances and atrial tachyarrhythmias. Our work presents a genetic overview of the VH patients referred to the Instituto Nacional de Cardiologia.

Methods: Patients were follow up at the cardiomyopathy outpatient clinic, and all had echocardiography and electrocardiography criteria for HCM and VH-WPW. All subjects were screened for the 3 major HCM-genes (MYH7, MYBPC3 and TNNT2), and for those who presented WPW, the PRKAG2 gene was also analyzed. Coding regions of genes were amplified by the polymerase chain reaction (PCR) and sequenced by Sanger method using BigDye Terminator v3.1 and the 3500xl genetic analyzer (Thermo Fisher Scientific).

Results: Twenty-five probands were genotyped, with 60% of positivity, in which were identified at least one variant potentially pathogenic. In the others, only benign variants could be detected. We have detected 28 variants in eighteen subjects: 39% were pathogenic, 29% benign, 21% were variants of uncertain significance (VUS) and 11% were novel. Among the pathogenic variants, six were found in MYH7 gene, three in MYBPC3, one in TNNT2 and one in PRKAG2. Disease-causing variants in MYH7 and MYBPC3 are the most common, accounting for over half of all cases of HCM (1). Moreover, nine pathogenic variants were missense, and two nonsense, while VUS and benign variants were all missense. Two patients have died due to complications of HCM, coincidentally both were carrier of the mutation p.Arg453Cys in MYH7, reported in literature as a malignant variant (2). We had identified three rare novel variants, not deposited in dbsnp, and with no clinical significance report. These variants, p.Glu903Gln (MYH7), p.Lys353fs (MYBPC3) and p.His401Gln (PRKAG2), were not segregated with any pathogenic variant in the subjects and genes analyzed; therefore, they are likely responsible for the clinical phenotype. Four patients with VH-WPW were analyzed, and just the half was positive for PRKAG2 variants.

Conclusion: Positive genetic yield of 60% in patients with unexplained VH is consistent with findings from other populations screened. Precise gene mutation identification had prognostic and therapeutic implications as well as a more effective genetic counseling.

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Código #13348

Title: Genetic polymorphisms of the complement system influence susceptibility to pemphigus foliaceous

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Objective: Pemphigus foliaceus (PF) is a bullous autoimmune disease characterized by autoantibodies against desmosomal antigens, acantholysis and formation of painful epidermal blisters. Autoantigen recognition activates the complement system (CS), whose deregulation collaborates with the acantholytic process and tissue injury. Failure in complement regulation is associated with several autoimmune diseases. In previous case-control studies of our group, polymorphisms of CS genes have been associated to PF susceptibility. The aim of this study was to evaluate possible allelic interactions between CS single nucleotide polymorphisms (SNPs) previously associated by our group, with the susceptibility to PF.

Methodology: We selected 16 SNPs, previously found as associated in studies with the *CD59*, *CR1*, *MASP2* and *FCN3* genes. We analysed them together in 238 PF patients and 268 controls, adjusted for sex and age and genotyped at least for two of these genes, by logistic regression with ethnicity as covariant, using STATA (v.9.2). In this setting, we also evaluated possible associations with sCR1 and MASP-2 serologic levels. Further, allelic interactions were evaluated with PLINK v1.07.

Results: Polymorphisms of complement regulators, as the *CD59* haplotype *GC* (*CD59* alleles: rs861256**G* and rs831625**C*) [OR=2.62, p=0.009] and the *CR1* allele rs3737002**T* [OR=0.647, p=0.027] were independently associated with PF. Isolated association, corrected for ethnic group, was found with molecules of the lectin pathway: *MASP2* genotypes *CV/TV* and *TV+* (*MASP2* alleles: rs17409276 and rs2273346) [respectively: OR=2.002, p=0.031; OR=1.944, p=0.032] and *FCN3* genotypes *InsC+* and *DelC/InsC* (*FCN3* alleles: rs28362807*indel and rs4494157**C*) [respectively: OR=0.273, p=0.033; OR=0.193, p=0.042]. The other SNPs presented not significant trends in the expected direction. *MASP-2* serum levels higher than 400ng/μL were associated with *MASP-2* haplotypes *CVTV* and *TV+* (respectively: OR=3.78, p=0.013; OR=4.42, p=0.006), and levels between 200 to 400ng//μL of this same protein with *CD59* haplotype *GG* (rs861256**G* and rs831625**G*) (OR=2.64, p=0.021). Interestingly, 8 analysed SNPs interacted with at least one other SNP: *CD59*rs861256* with *CD59*rs831629* (p=0.009), *CD59*rs704701* (p=0.013), and with *FCN3*rs28362807* (p=0.012); *FCN3*rs28362807* with *CD59* SNPs *rs1047581* (p=0.004), *rs831625* (p= 0.019) and *rs704697* (p=0.026); and finally, *FCN3*rs4494157* with *CR1*rs2274567* (p=0.027).

Conclusion: These results corroborate strong associations previously found by our group and indicate biological interactions between variants of CS genes. Possible interactions will be further evaluated in functional settings, in order to understand the pathogenesis of PF and other autoimmune diseases.

Key-words: Pemphigus foliaceus; complement system; genetic polymorphisms.

Financial support: CAPES, CNPq, PRONEX and Fundação Araucária.

Código #12681

Title: GENOMIC BASIS OF CONGENITAL HEART DEFECTS: A PROSPECTIVE STUDY IN 44 CASES *post-mortem*.

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Objectives: Congenital heart defects (CHD) are the most common birth defect, affecting approximately 8 per 1,000 newborns. Errors in septation, valve formation and proper patterning of the great vessels are leading causes of pediatric death around the world. Advances in genomics became possible to understand how alterations in the genoma (including aneuploidies, copy number variation and gene mutation) can directly influence the heart development. Thus, the aim of this study was analyze the genome alterations in *post-mortem* samples of syndromic CHD carriers and associate this abnormality with the development of heart malformation.

Methods: We investigated the contribution of genomic abnormalities in the pathogenesis of CHD using molecular methods in 44 cases of stillbirth and new-born from Serviço de Verificação de Óbitos, HC-FMUSP. DNA samples from skin and heart tissues were evaluated using AmpFℓSTR® MiniFiler™ PCR Amplification Kit (Life Technologies™, California, USA) and Multiplex Ligation-dependent Probe Amplification (MLPA) with different kits (MCR-Holland, Amsterdam, the Netherlands).

Results and Discussion: The results showed relevant alterations in 16 cases. One case of mosaic of monosomy X and several different cases of trisomy 21 were associated with coarctation of the aorta (CoA). Also, cases of aneuploidies 13, 16, 18, 21 and one case of *IGSF9B* gene duplication showed strong association with atrial and ventricular septal defects. One case of *ARSA* and *SHANK3* deletion concomitant with *ZNF74* duplication was associated with dilatation of the right chamber. Our results are consistent with the literature, but this is the first time that CHD is directly linked with cases of trisomy 16, duplication of *IGSF9B*, deletion of *ARSA* and *SHANK3* genes concomitant with ZNF74 duplication.

Conclusion: The genomic analysis showed efficiency for identifying the genomic basis in post-mortem samples of CHD carrier and also help to provide the adequate genetic counseling to families.

Finnancial Support: FAPESP: 09/53105-9 and MCTI/FINEP-CT-INFRA 01/2011-SP08

Código #13291

Title: High success in molecular diagnosis of skeletal dysplasias using a customized NGS panel and the identification of a gene related to Beemer-Langer syndrome

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Objectives: Skeletal dysplasias (SD) are rare diseases whose diagnosis is usually a challenge because of the phenotypic heterogeneity of most conditions. The molecular investigation is fundamental for both, to get the final diagnosis and to providing a precise genetic counseling. Although next-generation sequencing (NGS) techniques have been used to promote large-scale sequencing of several individuals in an easier and less expensive way, most of the reported results so far have shown a detection rate of mutation around or less than 50%. Here we present the results of a cohort of 36 patients with SD analyzed by NGS.
Methods: The sequencing was performed on MiSeq sequencer using a customized NGS panel (TruSeq Custom Amplicon - Illumina) with 39 genes related to SD. Sanger sequencing confirmed all pathogenic variants.

Results: All patients, except one, had a previous precise clinical-radiological diagnosis. Pathogenic mutations were found in 25 (69,4%) of the patients, however, for ten patients regions of bad coverage of the respective genes are still being investigated. Regarding the severity of the conditions, for 14 lethal and 23 non-lethal SD, the detection rates of mutations were 78.6% and 63,6%, respectively. For the whole group, we identified 32 different pathogenic variants, being 25 novel mutations and one recurrent mutation (*DYNC2H1*- p.Met2671Thr) in 3 patients. One mutation (*PCYT1A* gene) was found only by Sanger sequencing during the investigation of a region insufficiently covered of the gene. Another interesting and novel result was the identification of a cilia-related gene associated with Beemer-Langer syndrome.

Conclusion: Our results confirm the advantage of NGS in the diagnosis of the SD, showing a high detection rate (69.4%) of mutations. We also identified for the first time a cilia-related gene associated

with the Beemer-Langer syndrome. Finally, we put in evidence the importance to analyze by Sanger sequencing the regions with insufficient coverage by NGS.

Grants: FAPESP (98/16006-6;2015/22145-6); CNPq (590148/2011-7)

XXIX CONGRESSO BRASILEIRO
GENÉTICA MÉDICA 2017
Bento Gonçalves | 20 a 23 de junho
Da Pesquisa à Prática Clínica

Fellinievents

Código #13323

Título: IDENTIFICATION OF CROHN'S DISEASE ESCHERICHIA COLI PATHOTYPE BY GENETIC TOOL

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Objetivos: Crohn's disease (CD) is one the most frequent forms of inflammatory bowel diseases (IBD) in human species. What triggers the inflammation and perpetuates it is still not totally elucidated but it is known that immunological and microbiological aspects are involved in the pathogenesis. In general, the diagnosis of IBD is difficult, requiring clinical, pathological, histological, radiological and endoscopic analysis of the patient and, even so, it may be inconclusive, delaying the treatment or leading to an inappropriate initial therapy. Considering the microbiological aspect of the disease, adherent invasive *Escherichia coli* (AIEC) have been isolated from the tissues and are strongly linked to the disorder. Here we compared by genetics and bioinformatics tools the sequences of the type 1 fimbriae of AIEC and different pathotypes of *E. coli*. Fimbriae are appendages that extend from bacterial surface and mediate the interaction with host tissues and thus are keys in the first steps of pathogenesis. Type 1 fimbriae are the major fimbriae related to the adherence and invasiveness of ExPEC (Extraintestinal Pathogenic *Escherichia coli*) to host cells. Type 1 fimbriae are encoded by chromosomal *fimAICDFGH* operon, which is highly conserved and widely found in commensal and pathogenic *E. coli*. *fimH* gene is responsible for the expression of the adhesin tip that interacts with mannose receptors in host tissues. The aim of this work was to analyze the genetic diversity of *fimH* of AIEC isolated from CD in relation to others *E. coli* pathotypes.

Metodologia: As methodology thirty-three *fimH* sequences were collected from the National Center for Biotechnology Information Database (GenBank) plus one sequenced (with adherent and invasive phenotype) and their phylogenetic relationship were established by Neighbor-Joining tree based on Kimura-2 parameters. The was built by MEGA 5 Program.

Resultados: The phylogenetic analysis revealed two big groups, one with ExPEC and intestinal pathogenic *E. coli* (A group) and other only with ExPEC members (B group) including the AIEC. All the three sequences of AIEC strains used for this study, linked to Crohn's Disease, clustered together and only with the ExPEC group (B), no one with intestinal pathogenic *E. coli*, which is in agreement with the virulence traits they share in common with ExPEC.

Conclusão: This methodology allowed identifying the *E. coli* pathotype related to Crohn's Disease, that does not has specific genes profile, by sequencing and phylogenetic analysis of *fimH*. In addition, makes it possible the diagnosis of Crohn's Disease indirectly by isolating this pathotype from patients suspected to have the disorder.
Supported by: CAPES PNPD Institucional 2011 nº 23038007126201144.

Código #13209

Título: IN SILICO IDENTIFICATION OF NEW GENETIC VARIATIONS AS POTENTIAL RISK FACTORS FOR ALZHEIMER'S DISEASE IN A GENOME-WIDE ASSOCIATION DATABASE

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Objetivos: objective of the study was the use of bioinformatics in the search of the new risk genetics factors for Alzheimer's Disease.

Metodologia: Data used in the preparation of this article were obtained from the Alzheimer 's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations, as a $60million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years." For up-to-date information, see www.adni-info.org. There are three subsets of participants: 380 individuals for Aβ-42 in cerebrospinal fluid biomarkers, 654 individuals for Aβ-42 and Aβ-40 in plasma biomarkers for baseline and 538 observed individuals for plasma biomarkers collected one year late (M12). We analyzed the main effects of quantitative traits of single nucleotide polymorphisms (SNPs) in Aβ-40 and Aβ-42 biomarkers. Both Association Test and a linear regression method were used to investigate the main effects of SNPs for MCI and AD. The p-values results were adjusted for multiple comparisons by the Bonferroni method and we focused on corrected p-values

($p < 0.001$).

Resultados: The subsets show different SNPs association in diagnostic groups. We identified seven SNPs as potential candidates, in the regions of the *TOMM40*, *PAMR1*, *TRIM9* and *CCDC112* genes and three SNPs in the non-coding region reached association significance. In addition to known candidate, gene *TOMM40*, the genes *TRIM9* and *PAMR1* are associated with dementias. We identified one novel gene candidate *CCDC112* and a novel SNP (rs5904473) on the chromosome X were associated with Plasma biomarkers related to AD.

Conclusão: Our analysis of the ADNI GWAS identified several putative loci that are in genetic association with A*β*-42 levels in CSF and A*β*-40 levels in CSF and Plasma. The most significant associations were identified using AD subjects probably because the variances of the CSF biomarker levels are smaller in MCI and normal subjects. Thus, our analysis demonstrates that quantitative trait linkage of biomarkers A*β*-40 and A*β*-42 via genome-wide screening can reveal additional insights into the mechanism that connects these biomarkers with potentially new candidate genes for AD and MCI.

Código #13276

Title: Investigation of IL-06 and IL-10 polymorphisms and serum levels in Down Syndrome

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Objective: The interleukin 6 (IL-06) and 10 (IL-10) regulate the immune and inflammatory responses, and several single nucleotide polymorphisms (SNPs) in these genes could lead to functional alterations of these cytokines and susceptibility to infections and autoimmune diseases. Down syndrome (DS) individuals present many immunological changes and increased frequency of infections and autoimmune diseases. Then, this study evaluated serum levels of IL6 e IL-10 in DS (case group) and without DS individuals (control group), the polymorphisms frequency in IL-6 (rs15800795), IL-6 (rs15800796), IL-6 (rs15800797), IL-10 (rs1800872), IL-10 (rs1800871), IL-10 (rs1800896) in gene promoter region, and the association these genotypes with the serum levels of these cytokines, aiming to explain the immunological changes in DS.

Materials and methods: Genotyping was performed by allelic discrimination technique through real time PCR using TaqMan SNP Genotyping Assays (Applied Biosystems®) or Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR-RFLP) in 200 DS and 200 without DS individuals. The IL-06 and IL-10 concentrations were measured by ELISA. The Multiple Logistic Regression was used to evaluate the polymorphism frequency by SNPSTATS software. Haplotype and linkage disequilibrium analysis was performed by Haploview program. The GraphPad Prism 6 software was used to evaluate the IL-6 e IL-10 concentrations between case and control group and the association of the polymorphisms with interleukins levels.

Results: There was no difference in the genotypic distribution and Haplotype frequency between the groups (P> 0.05). The Haplotype analysis showed that IL-06 and IL-10 polymorphisms are in strong linkage disequilibrium in both groups. The analysis of IL-06 serum levels did not show difference between case and control groups and these levels were not associated to the haplotypes, genotypes and genotypic combination. The IL-10 serum levels were increased in case group in relation to the control group (P=0.0019), however was not observed association of this polymorphisms with IL-10 serum levels.

Conclusion: The IL-6 e IL-10 serum levels are not associated with the polymorphisms evaluated. However, the increased frequency of infections in DS individuals can be partly explain by IL-10 high levels, which play a role in the inhibition of the immune response, reducing the production of inflammatory protein, recruitment and proliferation of proinflammatory cells.

Grant: FAPESP, CNPq, CAPES, FAMERP/FUNFARME, FAPERP.

Código #13360

Title: Large deletion of chromosome 11p in a patient with a complex phenotype including aniridia.

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Abstract
WAGR syndrome is clinically characterized by the presence of Wilms' tumor, aniridia, genitourinary alterations and intellectual disability (ID). The molecular diagnosis for the syndrome is the deletion of the *WT1* and *PAX6* genes, which have essential function in the urogenital system and ocular development, respectively. In addition, both genes also play a role in the development of the central nervous system. Objective: The objective of this study was to describe a patient with delay neuropsychomotor development associated to aniridia and other malformations. Methods: We performed blood collection for karyotype and Chromosome Analysis by Microarray. Results: In this study, we describe a three year old female patient referred to the genetics clinic because of a delay in neuropsychomotor development associated with malformations. The karyotype analysis was normal (46, XX) and the Chromosomal Analysis by Microarray identified a 10 Mb deletion in the short arm of chromosome 11, spanning the critical region for the WARG syndrome. The total deletion of two contiguous genes, namely *WT1* and *PAX6* confirms the diagnosis of WAGR syndrome. Conclusion: The patient presents classic symptoms such as aniridia and intellectual deficiency, in addition to other symptoms, such as short stature and pulmonary stenosis. The presence of other signs can be explained by the large segment deleted on chromosome 11.

Código #13249

Title: LETHAL SKELETAL DYSPLASIAS: MOLECULAR INVESTIGATION IN 57 BIRTHS, INCLUDING TWO FETUSES WITH A NOVEL PHENOTYPE

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Objectives: Around 50 skeletal dysplasias (SD) diagnosed in the perinatal period are lethal or semi-lethal. The precise diagnosis for this group of SD is necessary for the correct genetic counseling and consequently for reproductive decisions, for instances, the preimplantation genetic diagnosis (PGD). While the radiological diagnosis is sufficient for the most frequent lethal SD (LSD) [ex: thanatophoric d. (TD) and osteogenesis imperfecta type II (OI-II)], regarding the rarest types, the molecular investigation is usually necessary to the differential diagnosis. Over a period of 26 years, more than 500 patients with SD have been evaluated at our service, of which almost 30% were fetuses with LSD. Among these fetuses, about a half had a molecular investigation. The goal of this work is to present the preliminary results of this group of LSD with molecular investigation.

Methods: The revision of the local series of 136 LSD, allowed us to rescue 57 fetuses with molecular investigation, being 40 cases analyzed by classical Sanger sequencing, and 17 by next generation sequencing (NGS) technology. For NGS we used a custom panel (TruSeq Custom Amplicon - Illumina) including 39 genes. All mutations found by NGS were confirmed by Sanger sequencing. We also used whole exome sequencing (WES) for studying two fetuses with a novel phenotype.

Results: The molecular investigation confirmed the clinical-radiological diagnosis in 49 fetuses (89,1%). Both fetuses with the novel phenotype are still under the WES analysis, and for all remaining cases, except one, the regions with bad coverage by the NGS are still under evaluation by Sanger sequencing. The main diagnoses were distributed in the following five groups: FGFR3 (26), collagenopathies type-2 (7), ciliopathies (7), Campomelic dysplasia (3) and OI type II (3). The other 11 fetuses received the following radiological diagnosis (7 positives for a mutation in their respective gene): Fibrochondrogenesis (1), Atelosteogenesis type 2 (1), Achondrogenesis type 1A (1), Opsismodysplasia (1), Desbuquois d. types I and II (2 and 1), Blomstrand d. (2) and the novel phenotype (2). The few cases of OI-II is the consequence of a late inclusion of the collagen 1 genes in our panel. Regarding the inheritance pattern of these LSDs, while the majority in this series of cases is autosomal dominant, 16 fetuses had an autosomal recessive condition, 13 confirmed by the molecular study.

Conclusions: The high mutation rate detection found (89,1%) seems to be a consequence of previous radiological diagnosis. The analysis of the WES in the two novel LSD may reveal another gene

associated with the SD.

Grants: FAPESP (98/16006-6; 2015/22145-6); CNPq (590148/2011-7).

Código #13380

Objective: The main objective of this study was to analyze the deletion of the survivor motor neuron (*SMN)* and the neuronal apoptosis inhibitory protein (*NAIP)* genes in a sample of children with clinical symptoms of Spinal Muscular Atrophy (SMA).

Method: Polymerase chain reaction (PCR) combined with restriction fragment length polymorphism (RFLP) were used to analyze the deletion of SMN and NAIP genes in twenty five patients, ages varying between 3 months to 8 years, with clinical characteristics for SMA, according to the criteria of the International SMA Consortium.

Result: We found exons 7 and/or 8 of the SMN gene deletion in 67% of patients with SMA-II and in 62% of SMA-III. We detected homozygous deletion for both exons in SMN and NAIP genes in 100% of SMA-I patients, 33% SMA-II and 15% SMA-III. Moreover, we found no deletion of SMN and NAIP genes in 11 parents, 2 unaffected sibs and 40 normal controls evaluated.

Conclusion: The findings of homozygous deletion of exons 7 and 8 of SMN gene confirmed the diagnosis of SMA, suggesting that the deletion of SMN exon 7 is a major cause of SMA in the sample, and NAIP gene may be a modifying factor for SMA severity. According with our results, we proposed that molecular diagnosis system based on PCR-RFLP analysis could conveniently be apply in the clinical testing, genetic counseling and prenatal diagnosis of SMA.

Key words*:* Spinal muscular atrophy, PCR, RFLP, deletion, exons.

Código #13221

Title: Molecular analysis with a panel of genes in a cohort of 18 patients with Skeletal Dysplasia associated with multiple joint dislocations

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Objective: Currently skeletal dysplasia associated with multiple joint dislocations (SDMJD) encompasses at least the following conditions with their respective genes: Desbuquois D. (CANT1 and XYLT1 genes), Spondyloepimetaphyseal D. Leptodactylic-type and Beighton-type (respectively *KIF22* and *B3GALT6*), SED CHST3 type (CHST3), Diastrophic D. (SLC26A2/DTDST), Larsen syndrome (FLNB) and a new phenotype related to IMPAD1 gene. All these genes, except FLNB and KIF22, are involved in the proteoglycans synthesis , an important constituent of joints. Due to the overlapping features among some of these SD, the diagnosis could be a challenge. Therefore, the purpose of this study was to investigate a cohort of patients with a radiological diagnosis of SDMJD utilizing a panel with related genes.

Methods: Eighteen patients selected by their clinical-radiological phenotype were investigated with a panel of the following genes FLNB, CANT1, XYLT1, KIF22, B3GALT6, CHST3, SLC26A2/DTDST, and IMPAD1. The molecular analyses were performed with automated Sanger bidirectional sequencing. In two patients, for whom the radiological diagnosis was Larsen S. (FLNB), the investigation was performed through the Ion Torrent Personal Genome Machine PGM™.

Results: The initial clinical evaluation allowed classifying 14 patients with typical phenotype and four with a suggestive phenotype. For the whole group of patients, the rate of a positive result was 61.1% (11/18). The mutations were observed only in patients with typical phenotype (11/14 – 78.5%). Mutations were observed in the following genes: FLNB (1 case), XYLT1 (1 case), KIF22 (3 cases), B3GALT6 (1 case), CHST3 (1 case) and SLC26A2/DTDST (4 cases). The most mutations were missense and six were novel. No pathogenic variants were identified in 7/18 (38.8%) patients with typical (3) and suggestive (4) phenotypes.

Conclusion: In conclusion, the high rate of positivity in the current cohort reinforces the importance of the previous clinical-radiological classification of the patients before the molecular investigation. The negative results in seven patients indicate genetic heterogeneity of these phenotypes, for whom the investigation will going on with next-generation sequencing.

Grants: CNPq 402008/2010-3, 590148/2011-7 - CAPES 33003017023p6

Código #13377

Molecular characterization of a family with hereditary multiple exostoses

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Objective: The current project is focused on a molecular characterization of a family with hereditary multiple exostoses (MHE)

Methods: Initial sequencing of DNA from the proband was carried out using the Illumina TruSeq Cancer panel on the MiSeq platform. Subsequent confirmation of the mutation in further family members was carried out using Sanger sequencing.
Results: This analysis showed a novel mutation in the *EXT1* gene. This was a heterozygous variation, c.289A>T; p.K97STOP, in all affected individuals but not in an unaffected family member. The substitution results is a nonsense mutation that leads to premature termination of translation and a predicted truncated protein or transcript destruction by nonsense-mediated decay.

Conclusion: MHE or osteochondromatosis is an autosomal dominant genetic skeletal disease characterized by multiple projections of bone capped by cartilage, exostoses or osteochondromas. These are most numerous in the juxta-epiphyseal region of long bones, but also occur on flat bones, vertebrae, and ribs. Deformity of the legs, forearms and hands is frequent. Approximately 2-5% of patients will have their exostoses progress to malignancy. It is one of the most common inherited musculoskeletal disorders, with an incidence of 1 in 50,000, however de novo mutations can also occur. In the most patients, the disease is caused by alterations in the *EXT1* or *EXT2* genes, but additional multiple exostoses loci have been described. These genes encode Golgi-associated glycosyltransferases responsible for heparan sulfate (HS) biosynthesis. HS chains are key constituents of cell surface and extracellular matrix-associated proteoglycans, which are known regulators of skeletal development. Our result describes a new mutation in *EXT1*, and this finding may be helpful for early diagnosis, prenatal genetic screening and preimplantation genetic diagnosis.

Keywords: Multiple Hereditary Exostoses. *EXT1* gene. Preimplantation genetic diagnosis

Código #13303

Título: MOLECULAR GENETIC TESTING OF BRAZILIAN PATIENTS WITH MONOGENIC DIABETES

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Objetivos: In this study, we aimed to identify pathogenic mutations in *GCK* gene in a cohort of patients with a phenotype consistent with monogenic diabetes. Until now, there have been very few studies of Maturity Onset Diabetes of the Young (MODY) in Brazil and the prevalence and characteristics of monogenic diabetes are still unclear. Despite this, the diagnosis of GCK-MODY is extremely important since they may be assumed to be Type 1 or Type 2 and receive treatment that is unnecessary and ineffective. Besides, the identification of these patients should be encouraged since women with *GCK* mutations have 50% chance of carrying a baby without this alteration. This could lead to macrosomia and insulin may be required.

Metodologia: The study included seven Brazilian probands (3 males and 4 females) with a phenotype consistent with GCK-MODY having autosomal dominant inheritance with at least two affected generations on the same side of the family, an early onset <25 years (mean age at onset 16.28 ± 7.76), a primary defect in pancreatic β-cell function, negative autoantibodies and IMC <30 Kg/m^2. Genomic DNA was isolated from peripheral blood lymphocytes for all subjects using Wizard Genomic DNA purification kit following standard protocols. The screening of the entire coding region was performed by Sanger Sequencing.

Resultados: We identified five variants, four *missense* mutations p.Tyr61Asp (c.181T>G), p.Thr228Met (c.683C>T), p.Arg191Trp (c.571C>T), p.Ala384Val (c.1151C>T) and one deletion p.Fen150del (c.449_451delTCT). The p.Thr228Met, p.Arg191Trp and p.Ala384Val mutations had previously been described as causes of GCK-MODY. The p.Tyr61Asp and p.Fen150del are new variants.

Conclusão: We found pathogenic variants in 5 of 7 patients (71%), this results show the importance of *GCK* screening in diabetes patients with familial recurrence and phenotypes suggestive of MODY and have important clinical implications.

Financial Support: CNPq, FAPERJ, FIOCRUZ.

Código #13203

Title: MOLECULAR INVESTIGATION IN RASOPATHIES BY WHOLE EXOME SEQUENCING

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Objective: RASopathies are a class of developmental disorders caused by germline mutations in genes that encode for components or regulators of RAS/MAPK pathway. These syndromes have many overlapping characteristics, including craniofacial dysmorphology, cardiovascular abnormalities, musculoskeletal abnormalities, cutaneous lesions, neurocognitive impairment and increased risk of tumor. Clinical heterogeneity, added to the large number of genes involved (mostly without hotspots), argues in favor of innovative molecular diagnostics. Due to these factors, the present work was a pilot study based on Whole Exome Sequencing (WES) of six patients with typical clinical features of RASopathies: 02 Noonan (S1,S2), 02 Costello (S3,S4) and 2 NF1 (S5,S6) patients, that will aid in the diagnosis of these diseases.

Metodology: Genomic DNA was isolated from peripheral blood using PureLink Genomic DNA Mini Kit (Invitrogen). Samples were sequenced at the *Idengene Medicina Diagnóstica (São Paulo, SP)*. Library preparation was performed using *Nextera Rapid Capture Exome* (Illumina), and sequencing using *NextSeq500 v2 MIDOUTPUT* 300 cycles (Illumina) in the NextSeq 500 (Illumina) platform. *Bowtie2* was used for mapping exome reads to human genome reference (GRCh38), followed by *SNP calling* with GATK software, based on ≥10x coverage cutoff. Subsequently, the variations found in each sample were annotated by means of *SNPEFF* and *ANNOVAR*.

Results: On average, coverage was of 30 million high quality reads (Q≥30) and 19 Gb for each sample. Initial analysis focused on 22 genes previously described in RASopathies, where 65 variants were identified per patient. Variants filtering were performed according to the following criteria: presence in the coding regions, non-synonymous or frame-shift (in/dels) type of variants and an expected population frequency below 1%. The results are as follows: Patiente S1: *BRAF:* c.770A>G:p.Q257R previously described associated to Cardiofaciocutaneous Syndrome; patient S2: *PTPN11*: c.1381G>A:p.A461T previously described associated to Noonan Syndrome with Multiple Lentigines (NSML); patient S3: *PTPN11*: c.854T>C:p.F285S, previously described associated to Noonan Syndrome; patient S4: a typical Costello patient where no mutation was found, including those related to HRAS gene; and, finally, patients S5/S6: where no mutations were found, including *NF1* gene. In patients S3 and S6 *A2ML1*: c.1444_1445del: p.S482fs, and c.2096C>T:p.A699V SNP's was respectively found inherited from one of the parents. All mutations ocurred *de novo* and were

confirmed using Sanger sequencing.

Conclusão: Based on these results, three of the six sequenced patients still remained without a molecular diagnosis and need to be further investigated in order to search for new variants in other genes that might be interacting with the RAS/MAPK pathway and consequently associated with RASopathies. These preliminary results support WES as the sequencing method compared to the traditional Sanger method besides of its complexities.

Financial suport: Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro(FAPERJ), Fundação CAPES and Fiocruz (Fundação Oswaldo Cruz)

Código #13394

Título: MOLECULAR SCREENING OF PATIENTS WITH INTELLECTUAL DISABILITY AND AUTISTIC SPECTRUM DISORDER: A FOCUS ON X-FRAGILE SYNDROME.

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Objetivos: The present study aimed do the molecular screening to FXS for patients with Intellectual Disability (ID) and Autism Spectrum Disorder (ASD) at the University Hospital Bettina Ferro de Souza (HUBFS).

Metodologia: Clinical selection of 144 ASD (n = 92) and ID (n = 52) patients was done in the HUBFS using DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) as criteria.
Molecular screening method was PCR-based used to amplified trinucleotide expansions in the promoter region of FMR1. PCR products were visualized on a 6% polyacrylamide gel stained with silver nitrate.

Resultados: A total of 2 ID and 5 ASD patientes shown complete mutation for promoter region of FMR1, representing 4.9% of the total of patients attended and one ID patient presented a pre-mutation. The other 136 male patients presented PCR fragments compatible with the normal phenotype (10 to 40 CGG repetitions), indicating that the etiology of ID may be different.

Conclusão: Molecular screening of FXS for TEA and ID patients is a fundamental step in the clinical diagnosis process besides ensuring proper genetic and reproductive counseling. Those results could bring greater epidemiological knowledge of FXS in the North of Brazil, helping the improvement of genetic services and genetic diseases prevention programs.

Código #13167

Title: MUTATIONS SCREENING OF *RMRP* GENE AND RNA ANALYSIS IN PATIENTS WITH CARTILAGE-HAIR HYPOPLASIA

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Key words: Cartilage-Hair Hypoplasia; *RMRP* gene; pathogenic mutations; RNA analysis; skeletal dysplasia.

Goals: The goal of this study was to identify mutations in the *RMRP* gene and evaluate the *RMRP* gene transcription in patients with clinical and radiographic suspicion of Cartilage Hair Hypoplasia (CHH).

Methods: This study was approved by ethical comitee of IFF, UNICAMP and HCPA. For mutations screening, genomic DNA was extracted from peripheral blood by salting-out method. Promoter and transcribed regions of *RMRP* gene were PCR amplified, cloned and sequenced by Sanger method. In order to investigate the transcript expression, a pilot study was performed with five patients. Total RNA was extracted from mononuclear cells by trizol, cDNA synthetized using superscript II and used as template in RT-qPCR in order to analyze the relative quantification of RMRP.

Results: We identified twenty-two distinct alterations in *RMRP* gene in a group of 20 different patients. All genotypes occurred in compound heterozygosity. Different types of mutation were observed: duplication, triplication, insertion and/or point mutations, among which 11 are new putative mutations. We also reported seven types of polymorphisms already described in the literature concomitant to pathogenic mutations. Most of patients in our cohort presented the g.196C>T mutation. This frequency was not found previously in other countries. Interesting, the worldwide frequent described mutation in CHH patients, g.71A>G, was not found in our group of patients. Furthermore, all patients presented a reduction of RMRP transcripts in comparison of controls, in accordance with literature.

Conclusion: Clinical diagnosis were molecular confirmed in twenty patients with CHH suspicion, allowing genetic counseling of the families. The correct diagnosis is also important to anticipating clinical interventions in patients, avoiding serious clinical complications, such as varicella. Together, this data can contribute to better understanding the mechanisms underlying the pathology and for future epidemiological studies in Brazil.

Financial Support: CAPES and FICORUZ

Código #13365

Title: Next-generation sequencing approach in skeletal dysplasias: 4-year experience of a tertiary center in Brazil

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Objectives: Evaluation of the yield of Next-Generation Sequencing testing by whole exome and focused panel in skeletal dysplasia´s (SD) patients in a tertiary center in Brazil (HCFMUSP).

Methods: Since 2012, DNA samples from 144 individuals were tested for a Next Generation Sequencing (NGS) panel of 80 genes associated with SD (125) or whole-exome sequencing (WES) (19): 136 patients were evaluated at the Clinical Genetics outpatient clinic in Instituto da Criança (ICr) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo/CEGH, while eight patients were evaluated in other Genetic Centers in Brazil and DNA samples were sent to our Center for genetic analysis after clinical discussion. If the clinical and radiological findings allowed a specific diagnosis and the gene was included in the panel, the DNA sample was sent for this specific molecular test. Otherwise, WES was performed. The cohort included patients from different groups of the Nosology. Patients presenting the most common skeletal dysplasias in which the cinical and radiological features are straightfoward, such as achondroplasia, were not included routinely in this study. Patients with osteogenesis imperfecta (OI) were only included if presenting a severe phenotype or consanguinity. The NGS library preparation was performed with Nextera Custom Enrichment – Illumina, with a set of more than 80 genes associated with SD (panel) or Agilent SureSelect whole exome V6. Sequencing was performed in MiSeq (panel) or Hi-Seq (WES) from Illumina. Bioinformatics pipelines with BWA-MEM aligner, GATK, picard, and ANNOVAR were applied in NGS analysis.

Results: Pathogenic variants identified: Panel: 75/125 (60%); WES: 10/19 (53%). In 2 patients, one from panel and the other one from WES, only one variant was identified in disorders that present an autosomal recessive mode of inheritance. The most frequent disorders tested and confirmed by the panel include the groups 2 (COL2A1), 4 (sulfation disorders) and 25 (osteogenesis imperfecta). In the latter, only one out of 10 showed a homozygous variant in P3H1, the others presented variants in COL1A2.

Conclusions: NGS sequencing in cohorts with well defined Mendelian disorders provides high diagnostic yields as already described in the literature in different settings. When the phenotype is suggestive of a specific Mendelian disorder, panel sequencing can provide very high yields at lower costs. As NGS sequencing costs diminishes the availability of these tests will increase and better genetic counseling will be possible for the families. There are still some disorders with unidentified genes in which WES of the families or cohort of patients may identify new genes which can lead us to a better understanding of human physiology and possible drug targets.

Código #13215

Título: O sequenciamento do exoma em trios é uma ferramenta de elevada rentabilidade diagnóstica para as doenças genéticas

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Objetivos: Avaliação da rentabilidade diagnóstica na análise do exoma em trios (pai, mãe e probando), considerando que, o sequenciamento completo do exoma tem sido implementado na prática clínica, como uma ferramenta que permite uma maior eficácia no diagnóstico molecular das doenças de origem genética.

Metodologia: O sequenciamento do exoma foi realizado com a tecnologia Ion AmpliSeqTM Exome RDY, utilizando as plataformas Ion ProtonTM e Ion S5-XLTM. A leitura das sequências e a identificação das variantes foram realizadas no Torrent Suite, Ion Reporter e utilizando um pipeline bioinformático próprio.

Resultados: Analisamos 260 casos de trios, incluindo 57% de casos neuropediátricos com deficiência intelectual sindrômica. A etiologia genética foi potencialmente estabelecida em 94 probandos, portadores de 56 variantes identificadas como causais e 38 variantes provavelmente causais, o que resultou em uma rentabilidade diagnóstica de 36%. Das 94 variantes identificadas, 57 eram de novo, 7 estavam em hemizigose, 7 em heterozigose composta in trans, 18 em homozigose e 5 eram herdadas. Os pacientes com deficiência intelectual sindrômica e com alterações neurológicas específicas mostraram uma rentabilidade diagnóstica de 42% (62 de 149 casos) e 39% (13 de 33 casos), respectivamente. Uma rentabilidade menor foi observada em pacientes com deficiência intelectual não sindrômica, 21% (11 de 51casos).

Conclusão:
Neste estudo, a análise do exoma em trios demonstrou uma rentabilidade diagnóstica de 36%, nos pacientes com resultado não informativo pelo diagnóstico genético tradicional. A análise em trios é, também, uma estratégia efetiva para a identificação das variantes potencialmente causais: de novo,

hemizigotas, homozigotas e heterozigotas compostas. A implementação do sequenciamento completo do exoma revelou uma elevada rentabilidade diagnóstica, especialmente em pacientes com deficiência intelectual sindrômica.

Código #12777

Title: OSTEOGENESIS IMPERFECTA: HAPLOINSUFFICIENCY AND HELICAL GLYCINE MUTATIONS IN COLLAGEN TYPE I GENES.

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Objective: The aim of this study was to associate the Osteogenesis Imperfecta (OI) type I, III and IV with the two main classes of mutations in *COL1A1* and *COL1A2* might result in protein defect: Haploinsufficiency (quantitative protein defect) and Helical glycine mutations (qualitative protein defect).

Methods: The study comprised individuals with a clinical diagnosis of OI type I, III or IV and *COL1A1* or *COL1A2* mutations. DNA sequence analysis was performed with OI panel that covers 100% of the coding region of *COL1A1* and *COL1A2* by the Ion Torrent Personal Genome Machine platform. Data were processed using Torrent Suite software (version 5.0) and called variants were annotated using Ion Reporter (version 5.0). Statistical analyses were performed by SPSS (version 18). The study was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre (CAAE: 14619713.4.0000.5327).

Results: In total 48 individuals were included, 32 cases with mutations in *COL1A1* and 16 cases in *COL1A2*. Quantitative defect was found in 19 individuals, 17 (89.5%) in *COL1A1* and 2 (10.5%) in *COL1A2*. Of these cases, 15 (78.9%) was in triple helix domain (13 in *COL1A1* and 2 in *COL1A2*), 2 (10.5%) into N-terminal telopeptide domain in *COL1A1*, 1 (5.2%) into N-terminal propeptide domain in *COL1A1* and 1 (5.2%) into C-terminal telopeptide in *COL1A1*. The cases identified with haploinsufficiency, 15 were diagnosed with OI type I and 4 with OI type IV. Mutations that lead to qualitative protein defects were identified in 22 cases (11 in *COL1A1* and 11 in *COL1A2*) all into triple helix domain. All 7 cases with clinical diagnosis of OI type III were identified with qualitative mutations into triple helix domain of the protein (4 in *COL1A1* and 3 in *COL1A2*). Comparison of the protein defects with OI type, quantitative defects were associated with type I whereas qualitative defects with type IV (p=0.003).

Conclusion: OI is a heritable bone fragility disorder caused mainly by mutations in collagen type I genes, characterized by a wide clinical spectrum since lethality in early life to mild early onset osteoporosis. OI type III was identified with the helical glycine mutations that cause the qualitative protein defects and, in general, it is associated with severe form. The majority of type IV cases also were identified with qualitative defect, since it is a moderate form of OI. Quantitative protein defect was associated with OI type I that is associated with a mild form. These findings are in accordance to

the literature. Understanding of the molecular mechanisms of OI is important for genetic counseling, prognosis and correlation to treatment options.

Financial Support:
Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) e Fundo de Incentivo à Pesquisa e Eventos do Hospital de clínicas de Porto Alegre (FIPE).

Código #13295

Título: Polimorfismos p.H63D, p.S65C e p.C282Y no gene *HFE* na região nordeste do Rio Grande do Sul, Brasil.

Autores: Edinéia Zimmermann, Letícia Guerra, Roxane Miranda Susin, Jovana Mandelli.

Instituição dos Autores: Grupo Diagnose, Caxias do Sul, Rio Grande do Sul, Brasil.

Objetivos: Verificar a presença de polimorfismos no gene *HFE* em pacientes com sobrecarga de ferro. Comparar as mesmas com frequências conhecidas.

Metodologia: Os testes de hemocromatose hereditária (HH) foram realizados em pacientes (entre os anos 2009 e 2016) nos quais as causas secundárias de sobrecarga de ferro tiveram sido excluídas e com persistência de índice de saturação de transferrina maior que 45%, em pelo menos duas dosagens. O DNA genômico foi obtido de sangue periférico ou *swab* bucal, utilizando-se o kit de extração *Wizard® Genomic DNA Purification* (Promega®, Wisconsin, EUA). A detecção dos polimorfismos no gene *HFE* (p.C282Y, p.H63D e p.S65C) foi realizada através do método da PCR-RFLP (*Restriction Fragment Length Polymorfism-Polimerase Chain Reaction*) até o ano de 2013. Após, as avaliações foram realizadas com o equipamento 7500 Fast Real-Time PCR System utilizando TaqMan® Genotyping Master Mix, *primers* e sondas TaqMan®, todos da *Applied Biosystems (Foster City, CA)*, seguindo as recomendações do fabricante.

Resultados: A análise de 2566 exames apresentou 1182 (46%) de casos com presença de polimorfismo no gene *HFE*. Destes, 60.1% são heterozigotos para p.H63D e 16.4% são heterozigotos para p.C282Y. A frequência alélica encontrada para p.C282Y, p.H63D e p.S65C foi de 6.5%, 20% e 1%, respectivamente.

Conclusão: No presente estudo, foi possível detectar alta frequência do polimorfismo p.H63D em homozigose e heterozigose, divergindo de outros resultados que indicam a mutação p.C282Y como a mais frequente. O efeito fundador poderia explicar esse fenômeno, visto que a população avaliada faz parte de uma região inicialmente colonizada por imigrantes italianos, que podem ter trazido essa característica genética para seus descendentes. Alem disso, se faz necessário ampliar estudos, como por exemplo, a verificação de outros polimorfismos envolvidos nos altos níveis de ferro no sangue.

Title: Refining the critical region for deletion 22q11.2 syndrome like

Authors: Évelin Aline Zanardo[1]; Marília Moreira Montenegro[1]; Diogo Cordeiro Queiroz Soares[2]; Marcília Sierro Grassi[2]; Gil Monteiro Novo-Filho[1]; Fabrícia Andréia Rosa Madia[1]; Rachel Sayuri Honjo[2]; Magda Maria Carneiro-Sampaio[2]; Chong Ae Kim[2]; Leslie Domenici Kulikowski[1,2].

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Objective: Cytogenomics has become a fast-moving field, with potential to improve the characterization of clinical distinguishable phenotypes associated with a common genomic region, however, for some cases the establishment of their correct diagnostic is challenging.

Methods: We studied six patients with initial clinical suspicion of the 22q11.2 deletion syndrome using MLPA (multiplex ligation-dependent probe amplification) technique with P064 kit for multiple microdeletion syndromes and P250 kit specific for the DiGeorge syndrome and others control regions (MRC-Holland). These patients were later evaluated by the array technique to better characterization of changes using the Infinium CytoSNP-850K BeadChip (Illumina).

Results: Unexpected the molecular analysis by MLPA technique revealed the presence of the 8p23.1 deletion in five patients and 8p23.1 duplication in one patient, involving in all cases the genes *PPP1R3B*, *MSRA* and *GATA4*. The analysis of the arrays confirmed these alterations in all patients and determined the correct breakpoint that was similar for all alterations: approximately 6,945,876-12,559,475 in the deletions and 8,093,065-19,173,427 in the duplication. No other pathogenic copy number variations were observed in the patients.

Discussion: The 22q11.2 and 8p23.1 deletions show similar clinical signs as cardiac malformations, facial dysmorphisms and behavioral changes. However the patients with 8p23.1 deletion may present congenital diaphragmatic hernia, convulsions, ophthalmic problems, aggressive behavior with abrupt changes that usually appear in childhood, and eczemas. The *GATA4* gene is associated to cardiac abnormalities and the deletion or duplication in this gene can generate several different cardiac defects with variable penetrance and expressivity. The MLPA screening was efficient to accomplish the differential diagnosis, since it discarded the initial suspicion and also detected the genomic alteration associated with phenotype. Also the array analysis provides accurate genomic coordinates to help improve the critical region for deletion 22q11.2 syndrome like.

Conclusion: Thus these results can contributes directly to the elucidation of new syndromes and the appropriate clinical management of the patients and allowing the adequate genetic counseling.

Grants: MCTI/FINEP-CT-INFRA 01/2011-SP08.

Código #13269
Title: RNA-seq in Bloom's syndrome: beyond DNA repair

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Objectives: Bloom Syndrome (BS) is a rare chromosome instability syndrome, with recessive autosomal inheritance. The main clinical manifestations are pre and postnatal growth deficiency, microcephaly, malar hypoplasia, telangiectasic facial erythema and compromised immune system, among others. Patients with BS present increased risk to the development of neoplasias at an early age, which is the main cause of death. Cytogenetic test is used as a diagnostic marker for BS since the patient's cells present increase in spontaneous chromosomal breaks and sister chromatid exchange (SCE). In addition, the literature reveals that most patients also present mutations in the BLM gene, which are related to defects in the DNA repair mechanism; however, it is still not completely understood. In this sense, we studied the transcriptome of two patients with Bloom's syndrome and three controls using the RNA-seq methodology (Illumina, Inc., San Diego, CA).

Methodology: We performed a deep-sequencing RNA-Seq profiling using high throughput sequencing (Illumina HiSeq 2500 platform) of samples derived from two patients with BS and three unaffected controls. The raw data analysis was generated using specialized softwares (CASAVA 1.8.2, Bowtie2, EdgeR, Rsubread and DESeq2).

Results: Differential expression analysis revealed 216 differentially expressed genes related to immunological pathways such as: negative replication of the regulation of the viral genome replication, positive regulation of B cells proliferation, gama-interferon mediated signalization pathway, B cells activation, virus response, adaptive immune response and immune effector process, and absence of difference of DNA repair genes expression. At the same time, we observed the hyperexpression of the BLM gene for both patients contributing for the destabilization of genes involved in immunological pathways, a phenomenon also observed in some tumors.

Conclusions: Thus, we suggest that the combination of lymphoid proliferation defects and cell signaling defects added to others such as cell loss and altered expression of the BLM gene may contribute directly to the main characteristics observed in Bloom's syndrome, such as growth failure and high risk of cancer. In the future, the study of the transcriptome applied to other BS carriers and other instability syndromes, will allow a more accurate analysis of the relevant gene interactions to the destabilization of the genome.
Financial support: Cappesp, MCTI/FINEP-CT-INFRA 01/2011-SP08

Código #13264

Título: Screening of mutations in the *GBA* and *ATP13A2* genes associated with Parkinson's disease in the Brazilian population: establishment of genotype-phenotype correlations.

Autores: Danielle Dutra Voigt[1]; Camilla Pereira da Silva[2]; Caroline Macedo Nascimento[2]; Ritiele Bastos de Souza[1]; Andressa Pereira Gonçalves[2]; Jussara Mendonça dos Santos[2]; Veluma Calassara[2]; Vivianne Galante Ramos[1]; João Santos Pereira[2]; Luiz Felipe R Vasconcellos[4]; Ana Lucia Rosso[4]; Pedro Hernan Cabello[1;3]; Márcia Mattos Gonçalves Pimentel[3].

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Objetivos: The present study aims to investigate whether the changes in the *GBA* and *ATP13A2* genes constitute a risk factor and predisposition for the development of this disorder, in order to contribute to the design of subtypes of Parkinson Disease (PD) in the Brazilian population. To that end, we selected a group of 350 unrelated patients of both sexes, screened at the main movement disorder clinics of the Rio de Janeiro (HUPE, HUCFF, HUAP, HFSE, INDC and Santa Casa de Misericordia).
Metodologia: The DNA was extracted from peripheral blood or saliva and molecular analyzes are being performed using Real Time PCR techniques and automatic sequencing. For the *GBA* gene, we are performing the complete screening of the exons as well as the regions of the introns-exons boundaries. As for the *ATP13A2* gene, the screening will be performed for exons 2, 3, 12, 13, 14, 15, 16, 26 and 27.

Resultados: Up to the present time, for the GBA gene, we have observed seven changes (K27R, IVS2+1G>A, N370S, L444P, T369M, A456P and E326K). These changes have been described previously by other studies in different populations. In addition, several intronic alterations were identified.

Conclusão: After screening the genes, we will perform a genotype-phenotype correlation analysis. Our results are preliminary and considering the scarcity of studies of this nature in the Brazilian population, we believe that conducting this research, with clinically well-documented samples, will provide relevant data about the contribution of the genetic factors investigated to the endophenotypes of Parkinson's disease.

Código #13219

Título: SCREENING OF POLYMORPHISMS IN GENES ASSOCIATED WITH OBESITY IN BAIXADA FLUMINENSE POPULATION.

Autores: Raisa da Silva Martins; Carolina Aquino Lima Gomes; Vivianne Galante Ramos; Danielle Dutra Voigt; Pedro Hernan Cabello.

Instituição dos Autores: Unigranrio – Universidade do Grande Rio.

Objetivos: This work aims to track polymorphisms in the candidate genes or associated to obesity in Baixada Fluminense population. In this way, we can define a genomic profile that may characterize the existence or not of a genetic predisposition, allowing then, the clinical application of personalized treatments.

Metodologia: The project estimates a sample number of 600 individuals, but still is in the catchment phase and currently has 342 samples. The selected attendees from the inclusion and exclusion criteria are evaluated clinically and in relation to the anthropometric measures. The used methodology comprises the extraction of genomic DNA from peripheral leukocytes, the genotyping through real-time PCR with TaqMan probes of 17 polymorphisms present in the *FTO, ADRB1, MC4R, LEPR, LEP, UCP1, AGTR1* and *RENBP* genes and statistical analysis of results.

Resultados: Until the moment, 8 polymorphisms have already been genotyped and their allelic frequencies have shown to be similar to the world frequencies when compared to the data of 1000 genomes project. Conclusão: We expect at the end of the study to contribute to the understanding of the interactions between different genes and their possible relation with obesity and related phenotypes.

Código #13251

Título: The challenge of whole exome sequencing as a molecular diagnosis for Autism Spectrum Disorder

Autores: Tatiana Ferreira de Almeida; Maria Rita dos Santos Passos-Bueno

Instituição dos Autores: Laboratório DLE; Universidade de São Paulo, Departamento de Genética e Biologia Evolutiva - IBUSP

Objetivos: The present work has the objective of comparing the efficacy of the whole exome sequencing (WES) for the molecular diagnosis of autism spectrum disorders (ASD) between two different approaches. The first approach considers the traditional analysis method of searching and categorizing individual variants and a new approach based on multivariate logistic regression model for a larger set of chosen variants.

Metodologia: Fifty four individuals with ASD and 115 controls, with other clinical diagnosis than ASD, had WES. The sequencing was made with Illumina's platform following internal protocols from library preparation to variant annotation. Low quality variants were removed from the analysis. For the first approach variants were filtered for 243 genes present in SFARI database and each subject had their variants accounted and prioritized, loss-of-function (LoF) variants (frameshift, stopgain/loss and splicing site) were divided into two groups, one considering all the variants in the SFARI genes, and other considering the ExAC LoF intolerance genes, creating a subset of 151 genes from SFARI. Missense variants were prioritized using SPRING software. False positive and false negative rates were calculated for each type of variants and ROC curves were plotted. The second approach was constructed based on the counting of variants present in 8789 genes and separated by type and population frequency. A logistic regression model was applied to the set of variants and a ROC curve was constructed based on the regression predictions.

Resultados: For the first approach, there was no difference in the mean number of LoF and missense variants between the groups. The false positive rates and false negative rates for all the groups were above 50%. The area under de ROC curve were very close to 0,5 in all occasions. The regression approach obtained a sensitivity and specificity of 75%, with an AUC near 75%.

Conclusão: The regression model approach was far superior in identifying the cases and controls from a cohort, thus indicating that the analysis of WES for ASD should not be performed as mendelian diseases are commonly done, but with an approach that takes into consideration all aspects of genetic variantion in ASD candidate genes.

Código #13381

Título: The impact of depth to genotype attribution in next generation sequencing panel.

Autores: Armando Fonseca, Tatiana Ferreira de Almeida, Renato David Puga

Instituição dos Autores: Laboratório DLE

Objetivos: This work has the purpose of testing which is the best percentage of depth in a 10 genes panel for correct genotyping in next generation sequencing.

Metodologia: We separated 58 different individuals with at least 98% of bases covered at 20x in a 10 genes panel for limb-girdle muscular dystrophies, and separated the pathogenic variants described at the final report. For all the individuals, we did a resampling from 90% to 0,1%, with decreases of 10%, of the reads in the bam file, and recalculated the panel percentage of depth for 10x and 20x for each one. For the same percentages, we did 1000 random resamples of the pathogenic variant to obtain the proportion of false negatives for each depth scenario.

Resultados: The results showed that for the 10x depth the chance of false negatives, above the threshold of 0,001 is around 30% with coverages above 99% 10x for the whole panel. For the 20x depth this chance drops for less than 5% with coverages above 98% 20x for the whole panel.

Conclusão: This results strengths the previous conception that depth coverages above 98% 20x for next generation sequencing panels is preferable over 99% 10x, with a chance of false negative 25% inferior for the second scenario.

Código #13388

Título: Pharmacogenetic Study of Response to Erythema Nodosum Leprosum Treatment

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Goals: Erythema Nodosum Leprosum (ENL) is an acute and systemic inflammatory reaction that affects about 20-30% of patients with borderline lepromatous leprosy (BL) or lepromatous leprosy (LL), types of leprosy. ENL is characterized by involvement of several organs being a very important cause of disability. The treatment of ENL is based on decreased levels of TNF-alpha and the drugs used in Brazil are mainly thalidomide and prednisone. Both are effective on ENL control, but due to long treatment, the use of these drugs may put significant health risks, such as corticosteroid tolerance and dependence, and thalidomide-related teratogenicity and neurotoxicity. Pharmacogenetics studies with these drugs have been conducted in other pathologies to identify genetics profiles more susceptible to adverse effects and differences in response to treatment. The targets of prednisone studies are the *NR3C1* and *ABCB1* genes, whereas *TNF-alpha* and *CYP2C19* genes have been studied with thalidomide treatment. This study aims verify the existence of genetic variants that might be associated with the response to ENL treatment.

Methodology: Single nucleotide polymorphisms (SNPs) in the *TNF-α* (rs361525, rs1800629, rs1799724, rs1800630, rs1799964), *CYP2C19-CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893) and *CYP2C19*4* (rs28399504), *ABCB1* (rs1045642), and *NR3C1* (rs6189, rs6190, rs6195, rs41423247, rs6198) genes were analyzed in 112 ENL patients from different regions of Brazil with the inference of haplotypes. The participants were using thalidomide and/or prednisone and different genotypes of each polymorphism were compared to each other in relation to the doses of the drugs and adverse effects.

Results: A total of 112 patients were evaluated, being 92% (81.2%) males and 79 (70.5%) with lepromatous leprosy (LL). All patients (112) used thalidomide and the majority (82%) used thalidomide and prednisone at some period of the treatment. The maximum dose was 400mg for Thalidomide and the mean dose was 112mg/day. In relation to Prednisone, the maximum dose was 80mg and mean was 22mg/day. The most common adverse effects were neurological (26.8%), followed by gastrointestinal (19.6%) and immunological (17%) effects. There was no association between dose reduction or adverse effects when compared to haplotypes. Analyzes of the influence of the polymorphisms individually on the dose of prednisone and thalidomide were evaluated and no

polymorphism was found to influence the change in the dose of the drug during the analyzed period. For the *NR3C1* gene, haplotype 2 (*GR9*βT / *BclI*G) was the most frequent (56.5%), followed by haplotype 1 (*GR9*βT / *BclIC*) (27.8%).

Conclusions: There was no association between polymorphisms and haplotypes studied on the change in drug doses over time or the manifestation of adverse effects. However, further studies are needed to identify dose-related genetic profiles and adverse effects that may improve the response to treatment of ENL.

Código #13392

Título: WAGRO ASSOCIADO A ALTERAÇÃO DE ERRO INATO DE METABOLISMO: RELATO DE CASO

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INTRODUÇÃO: WAGR (W – tumor de Wilms; A – aniridia; G – anomalias genitais; R – retardo mental) é uma síndrome genética com frequência de 1:500.000 a 1:1000.000 de indivíduos. Na maioria dos casos está relacionada a deleção *de novo* da região cromossômica 11p14–11p12 e, raramente, por herança familial decorrente de translocação, envolvendo o braço curto do cromossomo 11. O fenótipo está relacionado a haploinsuficiência de alguns genes, a saber: PAX6 – relacionado ao desenvolvimento dos olhos; WT1 – relacionado ao tumor de Wilms; BRAIN-DERIVED NEUROTROPHIC FACTOR (BNDF) – relacionado à sobrevivência de células nervosas e à homeostase energética, localizado na região 11p14.1, portanto, associado à obesidade (WAGRO). Por esta razão, é conhecida como síndrome de genes contíguos.

OBJETIVO: Apresentar o caso de paciente com WAGRO e triagem para Erros Inatos de Metabolismo (EIM) alterada para tirosina e metabólitos.

RELATO: Paciente feminina, terceira filha de pais jovens, não consanguíneos. Nascida de parto pélvico cesáreo aos 8 meses, com catarata congênita bilateral; submetida à cirurgia onde foi confirmada aniridia. Evoluiu com atraso psicomotor (APM), deficiência mental e distúrbio de comportamento. Aos 4 anos e 9 meses pesava 24 kg (p90), 102 cm (p10) de altura, perímetro cefálico (PC) de 48,5 cm (p50), genitália própria para sexo e idade, associada à compulsão alimentar. Aos 8 anos foi constatado glaucoma. Desenvolvimento puberal normal, com padrão hormonal de síndrome de ovários policísticos. Ultrassom revelou rim único, esteatose hepática e litíase biliar. Raio X de coluna detectou deficiência da soldadura L5/S1 com redução do tamanho de corpo vertebral de T12-L1. Cariótipo 46, XX; pesquisa de EIM com alteração da tirosina e seus metabólitos no sangue e urina. A técnica de Multiplex Ligation Probe Amplification (MLPA) detectou deleção em heterozigose dos genes FSHB (exon 3) presente no segmento 11p14.1, e os genes DCDC1 (exon 4) e PAX6 (exon3) localizados na região 11p13.

DISCUSSÃO: O caso traz relevância por se tratar de síndrome rara, associada a distúrbio metabólico no grupo da tirosina talvez por interação entre BDNF e o gene TIROSINA HIDROXILASE (TH). Acredita-se que o BDNF atue na ativação do promotor do gene TH cuja disfunção leva à acentuada deficiência mental. O BDNF desempenha papel fundamental na homeostase energética causando obesidade.

Resistência insulínica e obesidade estão associados ao ovário policístico, além disso, a obesidade justifica a alteração esquelética encontrada. Não há indícios de desenvolvimento de Tumor de Wilms, no entanto, a presença do rim único mediano pode ser explicada por deleção do gene WT1 que tem papel importante durante a nefrogênese e desenvolvimento genital. O EIM foi pesquisado devido à catarata congênita por associação à oligossacaridoses.

CONCLUSÃO: É importante ressaltar que o fenótipo auxilia na determinação do ponto de quebra da região cromossômica envolvida 11p14–11p12.

Código #12669

Title: Whole Exome Sequencing (WES) identifies *CDH2* as a possible candidate gene for congenital Combined or Isolated Growth Hormone (GH) deficiency

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Objective: Pituitary hormone deficiency is a genetically heterogeneous condition, and many cases with isolated GH deficiency progress to multiple hormone deficiencies. Therefore, WES is a promising approach for molecular diagnosis of patients with congenital pituitary hormone deficiency. To use WES to identify the genetic basis for pituitary hormone deficiency in a sporadic case.

Metodology: We performed WES in a female patient, born to consanguineous parents, harboring GH, TSH, ACTH and LH/FSH deficiencies and ectopic posterior pituitary visualized by magnetic resonance imaging. The variants were filtered assuming autosomal recessive inheritance, considered rare in population databases (ExAC, 1000 genomes and ABraOM), predicted as deleterious through in silico analysis, and that expressed in appropriate tissues (pituitary and/or hypothalamus). The best candidate was a p.Val289Ile in CDH2 gene. In an effort to identify additional patients with rare, deleterious variants in CDH2, we used a large-scale sequencing (LSS) panel to sequence CDH2 in 50 patients with GH isolated and combined deficiency. Since CDH2 interacts with β catenin (CTNNB1), to evaluate functional impact of p.Val289Ile, we obtained a CDH2 cDNA WT plasmid and produced the mutant (MUT) one through mutagenesis, and conducted a transient transfection and dual luciferase reporter assay. Expression vectors for the WT and MUT CDH2 were cotransfected with CTNNB1 cDNA and TOPflash plasmids, in two different mammalian cell lines (HEK293FT and CACO-2).

Results: The index case harbored 4 rare variants predicted as deleterious in homozygous state, and only c.865G>A (p.Val289Ile) in CDH2 affected a gene expressed in the developing pituitary gland. Furthermore, an essential step in pituitary development involves regulation of CDH2 expression and alteration in cell-to-cell adhesion. Sanger sequencing was used to confirm WES results and check segregation in the family. The father, mother and unaffected sister were heterozygous, and the proband was confirmed as homozygous. The luciferase assay showed decreased activation of TOPflash by CTNNB1 in the presence 150 ng MUTCDH2 compared to WT in both cell lines. CDH2 sequencing of additional patients by the LSS panel identified rare, likely deleterious heterozygous variant, c.1202C>A (p.Ala401Asp), in a female patient with isolated GH deficiency, mental retardation and ataxia. This variant is absent from ExAC, 1000 genomes and ABraOM, and it is predicted to be deleterious by in

silico analysis. Sanger sequencing confirmed the variant in the proband, and ruled out that mother and half-unaffected sister were carriers. The Father is not available for testing.

Conclusion: We describe two patients carrying CDH2 mutations, suggesting that CDH2 may be a new candidate gene for congenital GH deficiency. Molecular screening in a larger cohort and in vivo functional studies are important to elucidate the role of CDH2 in pituitary development.

Código #13346

Título: Whole ROR2 gene deletion uncovering a pathogenic mutation in a patient with autosomal recessive Robinow syndrome.

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Objetivos: Robinow Syndrome is a genetically heterogeneous disorder characterized by a triad of facial dysmorphisms, including hypertelorism, short stature and genital hypoplasia with extreme clinical variability. More severe bone involvement and marked short stature are observed in the autosomal recessive form of the syndrome (RRS) caused by biallelic mutations in *ROR2* (receptor tyrosine kinase-like orphan receptor 2), whereas heterozygous mutations in *WNT5A, DVL1* and *DVL3* have been identified in a subset of patients with autosomal dominant Robinow syndrome. These genes encode for components of the Wnt signaling complex which play a key role in the regulation of cell differentiation and patterning. Here we report a patient with recessive Robinow syndrome caused by a whole *ROR2* deletion and a hemizygous mutation in the other allele.

Metodologia: Patient is a 3-month old boy born to non-consanguineous parents with typical recessive Robinow syndrome phenotype, referred to our genetic service for molecular confirmation of the diagnosis. Mutation screening was performed by using next generation sequencing (NGS) using ION PGM™ Inherited Disease Panel as described by the manufacturer. Investigation of deletions and duplications on *ROR2* was performed by MLPA using kit P179. Chromosome Microarray analysis was performed for delimitation of the deleted segment using the Affymetrix 750K platform.

Resultados: NGS revealed a single pathogenic mutation in *ROR2* (c.1970G>A, p.Arg657His), allegedly in homozygosity. Patient was homozygous for other polymorphic variants in *ROR2*. Considering that the parents were not consanguineous we performed MLPA that revealed a deletion of all probes for *ROR2*. Chromosome microarray analysis delimited the deletion to a 470 Kb on 9q22 (arr[hg19] 9q22.31(94,381,136-94,851,388)x1). The deletion includes *ROR2* and *SPTLC1* genes.

Conclusão: The patient here described presents a chromosomal microdeletion including *ROR2* gene uncovering a pathogenic mutation on the other allele of *ROR2*. These findings corroborate the diagnostic of RRS and sheds light to the importance of a criterious evaluation of NGS data for differentiation of hemizygous and homozygous mutations.

NEUROGENÉTICA

Código #13263

Título: 6Q26 AND 16P12.2 HETEROZYGOUS DELETIONS SUPPORT OLIGOGENIC MODEL FOR AUTISM SPECTRUM DISORDER

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Introduction: We reported a 10-year-old autistic female with developmental and speech delay, seizures, difficulty with coordination and literacy, repetitive thoughts and movements and tendency to social isolation. The *PARK2* gene, located in 6q26, encodes the protein parkin that has important roles in mitochondrial homeostasis and degradation of damaged proteins and has been associated with development of ASD as well as other neurodegenerative diseases. The region 16p12.2 encompassing *OTOA*, *METTL9* and *IGSF6* genes, microdeletions in this region has been previously reported in individuals with autistic features, and was proposed to contribute to the development of ASD when other factors are present.

Aims: Search for genotypic characteristics of a patient with ASD associated with phenotypic characteristics.

Methods: Microarray-based comparative genomic hybridization (aCGH) was performed with DNA extracted from peripheral blood using a 135K-feature whole-genome microarray (SignatureChip Oligo Solution TM, Version 3.0 based on UCSC 2006 hg18 assembly, custom-designed by Signature Genomic Laboratories, made by Roche NimbleGen, Madison, WI), according to previously described methods. FISH analysis of interphase nuclei was performed using the BAC clones RP11-150P20 from 6q26 and RP11-120F20 from 16p12.2, according to standard methods.

Results: In the proband aCGH identified a 130 kb loss at 6q26 (chr6:162,607,391-162,737,394, hg18) within *PARK2* and a 176 kb loss at 16p12.2 (chr16:21,482,830-21,659,267, hg18) encompassing *OTOA*, *METTL9* and *IGSF6*. Maximum deletion coordinates within *PARK2* were chr6:162,563,347-162,765,304. No additional copy number changes at recognized microdeletion and microduplication syndrome loci or at other clinically significant loci were identified. FISH analysis of interphase nuclei confirmed a heterozygous deletion of both regions. FISH analysis could not rule out a rearrangement of either of these regions. Parental samples were not available for testing.

Conclusion: Although the deletion described here in *PARK2* is possibly limited to an intron, it might have a role in disease development by influencing the mechanism of splicing and thus the formation of the protein. These two deletions may be collaborating synergistically on the phenotype presented

by this patient. Further research into the genetics of ASD is needed for more complete understanding of any possible association between ASD and or 16p12.2 region. Taking into account the fact that the genetics of ASD is still poorly understood and, in cases such as this one, possibly oligogenic, genome-wide testing using tools such as aCGH and/or whole exome/whole genome sequencing will likely continue to prove useful in elucidating genes contributing to the development of ASD.

Código #12699

Title: A FAMILY REPORT OF SPG5: A POTENTIALLY TREATABLE SUBTYPE OF HEREDITARY SPASTIC PARAPLEGIA

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Objectives: To report the case of a family with Hereditary Spastic Paraplegia (HSP) type 5 (SPG5), a rare and potentially treatable subtype of HSP.

Methods: Case report

Results: We describe clinical and molecular findings of a family from Rio Grande do Sul, Brazil, in which 4 siblings are affected by SPG5. They were born to non-consanguineous, asymptomatic parents and referred 8 additional asymptomatic siblings. Three of them had a pure HSP phenotype, while one presented with phenotype complicated by ataxia, dysphagia, and parkinsonism. Mean (SD) age at onset of spasticity was 34 (4.9) years (range: 30-40 years), disease duration was 15.7 (5.5) years and Spastic Paraplegia Rating Scale was 28 (8) points (range: 0-52, higher scores indicating greater severity). Use of canes/walkers was required by 3 out of 4 patients; none was wheelchair restricted. Two patients presented dyslipidemia and were using simvastatin for 2 years; both report stable disease symptoms in the period. Next-generation sequencing panel of 12 common HSP-related genes was performed. Two missense variants in *CYP7B1* were detected, the well-established pathogenic variant c.889A>G and the novel variant c.961G>A, and confirmed by Sanger sequencing. Segregation analysis showed that variants segregated with disease phenotype and were in *trans*. 27-hydroxycholesterol levels (a disease marker of SPG5) were markedly elevated in plasma and cerebrospinal fluid of patients providing functional evidence for the diagnosis. According to ACMG guidelines (2015), variant c.961G>A was classified as pathogenic, and a diagnosis of SPG5 was made.

Conclusion: SPG5 is a rare autosomal recessive (AR) subtype of HSP, presenting pure or complicated phenotypes. This disease is characterized by lower limbs spasticity, degeneration of spinal sensory tracts and white matter abnormalities on neuroimaging, which is clinically indistinguishable from other HSP subtypes. The *CYP7B1* gene codes for the enzyme oxysterol-7α-hydroxylase that is involved in cholesterol degradation into primary bile acids, leading to accumulation of 27-

hidroxycholesterol (27OHC), a neurotoxic oxysterol, both in plasma and cerebrospinal fluid. As the origin of 27OHC is extra cerebral, drugs that reduce cholesterol levels, such as statins, were proposed, aiming to prevent neurologic impairment. Since this is a potentially treatable condition, geneticists and neurologist must be aware that SPG5 should be one of the first diagnosis to be confirmed/excluded by molecular analysis when assisting a patient with HSP and possible AR inheritance.

Funding: MCTI/CNPQ/Universal 14/2014 (460941/2014-3) and FIPE-HCPA (GPPG-HCPA 14-0695).

XXIX CONGRESSO BRASILEIRO
GENÉTICA MÉDICA 2017
Bento Gonçalves | 20 a 23 de junho
Da Pesquisa à Prática Clínica

Fellinievents

Código #13397

A relação perímetro cefálico/perímetro torácico pode ser um preditor de microcefalia tardia em pacientes com Síndrome da Zika Congênita e perímetro cefálico normal ao nascimento?

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Objetivos: Síndrome da Zika Congênita (SZC) é uma nova doença com poucas informações sobre a sua história natural. Sabe-se que a infecção pré-natal pelo Zika vírus é caracterizada por uma disrupção do desenvolvimento neuronal levando às alterações neurológicas e dismorfológicas típicas. O presente estudo tem como objetivo analisar vinte pacientes com diagnóstico de Síndrome da Zika Congênita sem microcefalia e com alteração da relação perímetro cefálico/perímetro torácico ao nascimento e o aparecimento de microcefalia tardia.

Métodos: Trata-se de um estudo descritivo e retrospectivo de uma série de casos de pacientes acompanhados no Ambulatório de Síndrome da Zika Congênita do Hospital Infantil Albert Sabin, referência pela Secretaria de Saúde do Estado do Ceará para o atendimento de crianças com Síndrome da Zika Congênita (SZC). Os dados primários foram provenientes deste ambulatório e coletados entre o período de outubro de 2015 e janeiro de 2017.

Resultados: Dos vinte pacientes com SZC e perímetro cefálico normal ao nascimento, nove possuíam a relação perímetro cefálico/perímetro torácico alterada com valores ≤ 1, os demais não possuíam o registro do perímetro torácico ao nascimento. Todos os nove apresentaram microcefalia tardia e piora do quadro neurológico.

Conclusão: O estudo revela que a alteração da relação perímetro cefálico/perímetro torácico em pacientes com perímetro cefálico ao nascimento normal pode estar relacionado à microcefalia tardia e piora do quadro neuropsicomotor. Sugerimos uma maior atenção à relação perímetro cefálico/perímetro torácico ao nascimento e novos estudos para confirmar essa hipótese e elucidar o mecanismo fisiopatológico.

Código #13261

Título:ANALYSIS OF THE *SLC6A3* 3'-UTR VNTR (RS28363170) AND *SLC6A3* INTRON 8 VNTR (RS3836790) POLYMORPHISMS IN THE TIME ESTIMATION PERFORMANCE AND DORSOLATERAL PREFRONTAL CORTEX ASYMMETRY

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Objetivos: To investigate if the *SLC6A3* 3'-UTR VNTR (rs28363170) and *SLC6A3* intron 8 VNTR (rs3836790) polymorphisms influence the performance in time estimation task and the asymmetry in the *dorsolateral prefrontal cortex.*

Metodologia: Were chosen 107 male right-handed individuals (middle age= 22±1.5 years, age range= 18-32 years) for captation in the quantitative electroencephalography (qEEG) at the moment of execution of time estimation task. The alpha band asymmetry in F3-F4 was analyzed by qEEG. The absolute error of the time estimation task (TET) for the time intervals of 1s, 4s, 7s and 9s was verified. The estatistical analyses were performed by two-way ANOVA test, in order to analyze the performance in TET; by binary logistic regression, in the prediction of *SLC6A3* rs28363170 and rs3836790 polymorphisms as a function of TET and by one way ANOVA in order to evaluate the influence of the genotypes in asymmetric data (F3-F4) in the qEEG alpha band oscillations. We considered $p<0.05$ as significant and a confidence interval (CI) of 95%. The study was approved by Federal University of Piauí Human Research Ethics Committee.

Resultados: For rs28363170, the allelic frequencies of 10R and 9R were 0.75 and 0.25, respectively; and for rs3836790, the allele frequencies of 6R and 5R were 0.72 and 0.28, respectively. All polymorphisms were in Hardy–Weinberg equilibrium ($p>0.05$). Two-way ANOVA did not reveal differences between the studied variants ($p>0.05$). The regression analysis indicated that rs28363170 polymorphism did not have a significant effect on TET ($p>0.05$). However, the regression analysis for rs3836790 indicated significant effects for time intervals of 1s(R^2=0.76, B=0.87, p=0.001) and 9s (R^2=0.81, B=0.21, p=0.002). One-way ANOVA showed no significant associations between rs28363170 genotypes and F3-F4 asymmetry ($p>0.05$). Nevertheless, we found a significant association for rs3836790 genotypes with the F3-F4 asymmetry (greater activation in the left dorsolateral prefrontal cortex)[F(2,102)=10,767, p=0.001 η^2p=0.45, power=0.87].The post hoc test revealed a greater cortical activation of 6R/5R genotype at 0.248% compared to the 6R/6R genotype (95% CI=-0.028 to 0.085, $p<0.001$).

Conclusão: We suggest that rs3836790 polymorphism acts on the time intervals encoding of 1s and 9s and that this variation is associated with the modulation of dopamine uptake in the dorsolateral prefrontal cortex, both mechanisms advantageous in cognitive processes embedded in time perception, such as memory and attention.

Código #13033

Title: CAG repeat numbers seem to influence genetic fitness and meiotic drive of ATXN2 alleles

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Funding: FIPE-HCPA number GPPG 16-0320

Background: Spinocerebellar ataxia type 2 (SCA2) is caused by an expansion of a CAG repeat tract (CAGexp) at *ATXN2.* CAGexp explains 50 % of the variability in age at onset (AO) and is related to anticipation. Very disabling, SCA2 would be prone to selective forces. In spite of that, SCA2 frequency seems to be stable in populations.

Aims: to estimate fitness and segregation distortion in SCA2.

Methods: Adult, symptomatic carriers were invited to participate from July, 2016 to January, 2017. Informants provided data about all his/her relatives, about their date-of-birth, parents, order of birth, symptomatic status, and number of children. Complete pedigrees were built up. Number of children of affected individuals was compared to their unaffected sibs in order to estimate fitness. Progenies were studied when affected parent was older than 52 years of age, and if reproductive history of the individual and his/her affected parent were entirely known.

Results: Twenty out of 31 SCA2 families diagnosed in our institution were included, including 1,017 individuals (164 affected), born from 1840 to 2012. Mean (± SD) AO was 36.6±14.9 years. One hundred sixty four subjects fitted the inclusion criteria for fitness analysis: 97 were asymptomatic – therefore assumed to be non-carriers - and 67, symptomatic individuals – assumed to be carriers. Average numbers of children of the non-carriers and carriers were 2.39 and 3.10, respectively ($p<0.025$, Mann-Whitney U test). Fitness of carriers was of 1.29. The number of symptomatic individuals (carriers) was smaller than the number of asymptomatic subjects (non-carriers) in all age groups. In order to study segregation distortion, we included individuals older than 52 years of age with complete sibships, children of affected parents. A total of 230 subjects fitted the inclusion criteria: 137 were non-

symptomatic or non-carriers (59.6%) and 93 were carriers (40.4%) (chi-square= 4.2476, p=0.04).

Discussion: We raised evidence in favor of increased fitness related to the carrier state at *ATXN2*. This finding is in agreement with the increased fitness observed in similar diseases such as SCA3 and Huntington disease. In contrast, results suggested a segregation distortion favoring the normal allele with 22 repeats, which can explain presence of this allele in more than 90% of human chromosomes.

XXIX CONGRESSO BRASILEIRO
GENÉTICA MÉDICA 2017
Bento Gonçalves | 20 a 23 de junho
Da Pesquisa à Prática Clínica

Fellinievents

Código #12916

Title: Causal factors behind early- and late-onset Machado-Joseph disease patients do not interfere with the rate of neurological deterioration

Authors: Camila Maria de Oliveira[1,2], Estela Rosa Reckziegel[1,2], Marina Coutinho Augustin[1,2], Anastácia Guimarães Rocha[1,2], Gabriela Bolzan[1,2], José Augusto dos Santos[1,2], Gabriel Vasata Furtado[1,3,4], Eduardo Preusser Mattos[1,3,4], Maria Luiza Saraiva-Pereira[1,3], Harm H. Kampinga[5], Jonas Alex Morales Saute[1,3,6], Laura Bannach Jardim[1,3,4,6].

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Introduction: Spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD) is an autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion (CAG_{exp}) at *ATXN3*. CAG_{exp} strongly correlates with age of onset (AO) and protein aggregation propensity. Furthermore, extreme phenotype sampling is a powerful approach to discover additional factors that modulate phenotype.

Objective: The aim of the present study was to analyse the disease progression in patients with extremely early and late AO.

Methods: Extreme outliers for AO-CAG_{exp} were identified within the Rio Grande do Sul SCA3/MJD cohort. Distribution of AO and CAGexp were obtained for the overall cohort (n=431) and patients with AO more than one standard deviation (SD) above (AO_{late}) or below (AO_{early}) their expected AO according to CAG_{exp} were recruited. AO_{late} (n=15) and AO_{early} (n=15) groups were examined at baseline and 15±4.7 months later with Neurologic Examination Score for Spinocerebellar Ataxia (NESSCA) and with Scale of Assessment and Rating of Ataxia (SARA). Parametric tests were used in all comparisons.

Results: Mean AO were 23.1±9.9 years for AO_{early} and 47.9±9.2 years for AO_{late}, which was respectively -1,67±0.55 and +1,60±0.42 SD different from the expected AO of the overall cohort ($p<0.0001$). Correlation between CAG_{exp} and AO was $r=-0.79$ ($p<0.0001$). NESSCA and SARA correlated well with disease duration at baseline ($r=0.66$ and 0.69, $p<0.0001$). However, differences in NESSCA and SARA scores at baseline and at follow-up were similar between early- and late-onset groups.

Conclusion: Early- and late-onset SCA3/MJD patients showed the same progression rates of disease, as measured with both NESSCA and SARA. This implies that causal factors behind early/late-onset cases, albeit still unknown, are different from those that modulate the speed of neurological deterioration. This finding has large implications for experimental studies on aggregation prevention and disease-onset delay toward clinical utilizations, in terms of preventive or therapeutics applications.

Funding: CNPq (project 402968/2012-3), CAPES (project CAPES/NUFFIC 061/15), FIPE 13-303. CMO and GB were supported by FAPERGS; ERR, MCA, GVF, EPM, MLSP and LBJ were supported by CNPq.

Código #13241

Title: Clinical and molecular characterization of patients with Hereditary Spastic Paraplegia type 11 (SPG11) from Rio Grande do Sul

Authors: Daniela Burguez[1,2]; Laís Alves Jacinto Scudeiro[1,6]; Márcia Polese Bonatto[2,4]; MSc; Ursula da Silveira Matte[3,9], PhD; Laura Bannach Jardim[1,2,7], MD, PhD; Maria Luiza Saraiva-Pereira[1,2,4,8], PhD; Marina Siebert[3,5], PhD; Jonas Alex Morales Saute[1,2,6*], MD, PhD.

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Objectives: To characterize the clinical and molecular findings of the most frequent form of autosomal recessive (AR) hereditary spastic paraplegia (HSP) in Rio Grande do Sul, SPG11.

Methods: A case series of patients consecutively recruited at neurogenetics unit of Hospital de Clínicas de Porto Alegre with HSP suspicion is presented. Molecular diagnosis of SPG11 was performed with next generation sequencing (NGS) panel of 12 HSP-related genes and confirmed by Sanger sequencing of *SPG11*. Variants were classified according to ACMG guidelines (2015).

Results: Variants in *SPG11* were responsible for 5 families (6 patients, 4 females), representing 26.3% of families with AR-HSP in our region. We found 6 different mutations in *SPG11*. All mutations were private, 2 were novel (c.432_433insC and c.6776_6784delTATTAAAGT), and 2 occurred in exon 39. Interestingly, we found 3 *SPG11* mutations reported as pathogenic in a single patient and we were able to discharge pathogenicity of variant c.6526T>C. All patients presented a complicated-HSP phenotype; except for a single patient that was homozygous for the likely pathogenic in-frame deletion c.6776_6784delTATTAAAGT who presented a pure-HSP phenotype. Most frequent complicating features in SPG11 were intellectual disability, 5/6 (83.3%); motor neuron involvement, 4/6 (66.7%); dysarthria, 3/6 (50%); keratoconus, 2/6 (33.3%); and parkinsonism and ataxia, 1/6 (16.7%) patients each. Brain MRI was performed in 4/6 patients, 2/4 (50%) presented thin corpus callosum. Mean (SD) age at onset was 22 (11.5) years (range: 14-45 years), disease duration was 15 (6.7) years and Spastic Paraplegia Rating Scale was 35 (8) points (range: 0-52, higher scores indicating greater severity). Five out of six (83.3%) patients required a wheel chair, only the patient with pure-HSP was still able to walk independently.

Conclusion: SPG11 was considered the most common form of AR-HSP worldwide until recent studies that found higher prevalence of SPG7 in large cohorts of patients from Germany and Australia. In a recent study, we found that SPG11 was the most common form of AR-HSP in Rio Grande do Sul and similarly to studies from other populations, SPG11 patients presented more severe phenotypes than other forms of AD-HSP and AR-HSP, with 83.3% of patients being wheel-chair dependent.

Interestingly, 2/6 SPG11 patients (2 families) presented bilateral keratoconus, an extra-neurological feature that has not been previously associated with SPG11 and therefore our report broadens this complex disease phenotype. Recent studies depicted that spatacsin, the protein coded by *SPG11*, is pivotal for autophagic lysosome reformation, a pathway that generates new lysosomes and suggested that dysfunction of the autophagy/lysosomal biogenesis machinery would lead to neurodegeneration. Further studies on the physiopathology and natural history of SPG11 are necessary for a better understanding of this rare, neglect and currently untreatable disease.

Funding:
MCTI/CNPQ/Universal 14/2014 (460941/2014-3) and FIPE-HCPA (GPPG-HCPA 14-0695).

Código #13229

Title: CLINICAL AND MOLECULAR CHARACTERIZATION OF PATIENTS WITH HEREDITARY SPASTIC PARAPLEGIA TYPE 4 (SPG4) FROM RIO GRANDE DO SUL

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Objectives: To characterize the clinical and molecular findings of the most frequent form of autosomal dominant (AD) hereditary spastic paraplegia (HSP) in Rio Grande do Sul, SPG4.

Methods: A case series of patients consecutively recruited at neurogenetics unit of Hospital de Clínicas de Porto Alegre with HSP suspicion is presented. Molecular diagnosis of SPG4 was performed with next generation sequencing (NGS) panel of 12 HSP-related genes and confirmed by Sanger sequencing of *SPAST*. Variants were classified according to ACMG guidelines (2015).

Results: Variants in *SPAST* were responsible for 6 families (15 patients, 10 females), representing 60% of families with AD-HSP in our region. We found 6 different pathogenic variants in *SPAST* (4 missense, 1 nonsense and 1 small deletion). All mutations were private and one them was novel (c.1273G>C, which occurred *de novo* in the index case). All SPG4 cases presented a clear autosomal dominant heritance and were classified as pure forms of HSP. Age at onset was highly variable varying from 1 to 73 years-old. Two variants with missense effect were associated with earlier age at onset; for variant c.1273G>C all affected individuals started in the first year of life with pyramidal involvement; and for variant c.1412_1413delinsAC (p.Gly471Asp) ages at onset were 4 and 7 years-old. None of identified SPG4 index cases carried the p.Ser44Leu disease modifying polymorphism in *SPAST*. Mean (SD) disease duration of SPG4 cases was 9.6 (8.5) years and Spastic Paraplegia Rating Scale (SPRS) was 17.8 (8.6) points (range: 0-52, higher scores indicating greater severity). Use of canes/walkers were required by 6/15 patients and only a single patient required a wheel chair (this patient has 20 years of disease duration and SPRS score of 37). Mean age at onset, disease duration and SPRS for patients requiring canes/walkers was 23.4 (19.6) years, 11 (8.8) years and 21 (8.3) points, respectively; compared to 30.2 (29) years, 7.6 (8.3) years and 13.9 (6.3) points for independent walking patients.

Conclusion: SPG4 is by far the most common cause of AD-HSP in Rio Grande do Su, Brazil (60% of families), consistent with European studies with similar eligibility criteria. In our series, 2/6 index patients with SPG4 started symptoms with ≤10 years-old and no patient with mutations in *ATL1* (SPG3A, previously considered the main cause of childhood-onset AD-HSP) was found. Use of

canes/walkers were required by 40% of SPG4 patients and only a single patient required a wheel chair. These numbers are similar to large European cohorts and confirms the very slow disease progression of SPG4. Further studies to detail the natural history of SPG4 in different standardized instruments are necessary for planning both disease modifying and symptomatic therapeutic trials for this rare and currently untreatable disease.

Funding: MCTI/CNPQ/Universal 14/2014 (460941/2014-3) and FIPE-HCPA (GPPG-HCPA 14-0695).

Código #12701

Título: DNA METHYLATION PROFILES IN ADHD: DIFFERENCES BETWEEN BOYS AND GIRLS

Autores: Thais Virginia Moura Machado Costa[1]; Fabio Albuquerque Marchi[2]; Jullian Gabriel Damasceno[1]; Evelin Aline Zanardo[1]; Fabricia Andreia Rosa Madia[1,3]; Gil Monteiro Novo-Filho[1]; Amom Mendes Nascimento[1,3]; Viviane Schuch[4]; Mauro Muszkat[4]; Leslie Domenici Kulikowski[1,3].

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Objetivos: Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorder diagnosed in childhood. ADHD is etiologically heterogeneous. On the other hand, it has a high heritability (around 80%) and it is diagnosed twice more often in boys than in girls. The genetic architecture of ADHD is still unknown and molecular markers for diagnosis have not been identified yet. DNA methylation is an important epigenetic mechanism associated with silencing of genes. Thus, the investigation of methylation profile in patients with ADHD is very important and could reveal different and interesting aspects of the disorder.

Metodologia: DNA methylation profiles were performed using DNA extracted from blood lymphocytes of 13 carrying ADHD (9 boys and 4 girls, ages 06-14) by Illumina Infinium HumanMethylation450 BeadChip. Children were referred for neuropsychological assessment from the Interdisciplinary Child Neuropsychological Care Group (Núcleo de Atendimento Neuropsicológico Infantil Interdisciplinar - NANI) in Sao Paulo, Brazil. The diagnosis was established according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). We processed the array data using specific packages within the environment R and used the BRB-ArrayTools to make the cluster. We performed two analyzes: a comparison between boys and girls and a differential analysis of all the samples. In the first analysis, we considered delta-beta ($\Delta\beta$ = Male - Female) < -0.20 and > +0.20. In the second, the probes were selected according to SD > 0.1 and we classified the methylation status of probes with $\beta \leq 0.2$ as unmethylated and with $\beta \geq 0.8$ as methylated. The probes were annotated according to the data provided by Illumina using the genome hg19 reference.

Resultados: In the comparison between boys and girls we obtained 249 probes with $\Delta\beta < -0.20$ and the range for these vallues was from -0.43 to -0.20. We also obtained 242 probes with $\Delta\beta > +0.20$. In these probes, the $\Delta\beta$ was between +0.20 and +0.34. In the differential analysis of all the samples we selected a total of 3,348 probes using SD > 0.1 as selection criteria. Among them, 375 probes – 138 unmethylated and 237 methylated – were selected considering the cutoff $\beta \leq 0.2$ as unmethylated and $\beta \geq 0.8$ as methylated. We used the β vallues of the 3,348 selected probes to make the samples cluster.

Conclusão: The cluster indicates that there is a clear hierarchical separation of 13 ADHD children. Two groups were clearly formed. The first group, consisting of the first four children, all girls (from left to right). And the second group, which covers the others individuals, all boys. It is tempting to speculate about the formation of these two groups in the clustering of the samples of this study. Therefore, differences in DNA methylation profiles of boys and girls may be showing that there is indeed real differences in DNA methylation by gender.

Financial Support: FAPESP: 2014/02565-8, 2015/05350-5; MCTI/FINEP-CT-INFRA 01/2011-SP08 and CAPES.

Código #13255

Title: GENETIC PROFILE OF PATIENTS WITH DYSTROPHINOPATHIES FROM RIO GRANDE DO SUL

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Objectives: We aimed 1) to determine the genetic profile of patients with dystrophinopathies from Rio Grande do Sul; 2) to assess genotype-phenotype correlation according to the reading-frame rule and; 3) to estimate the proportion of patients with Duchenne muscular dystrophy (DMD) amenable to novel mutation-specific disease modifying therapies.

Methods: We selected all index patients with clinical and/or molecular diagnosis of either DMD or Becker muscular dystrophy (BMD) that were regularly followed at neurogenetics unit of Hospital de Clínicas de Porto Alegre from September 2014 to March 2017. DMD, BMD and intermediate form (IMD) (grouped with DMD) were classified according to age of ambulation loss (DMD/IMD<16 years and BMD ≥16 years). Rearrangements and small-scale mutations in *DMD* gene were assessed by Multiplex Ligation-dependent Probe Amplification (MLPA) and next generation sequencing (NGS, *Ion Torrent PGM)*, respectively. Variants were classified according to the 2015 ACMG guidelines.

Results: A total of 47 index cases were diagnosed either with DMD/IMD (n=33, 70%) or BMD (n=13, 27.6%); 1 patient phenotype was not classified. Mean (SD) age at onset of DMD/IMD and BMD index cases was 3.3 (1.7) and 8.5 (7.9) years, respectively. Large deletions were found in 29 families (61.7%), large duplications in 5 families (10.6%), small-scale mutations in 12 families (25.5%) and a single index case with typical BMD phenotype with massive CK increase and X-linked inheritance had normal results on MLPA and NGS of *DMD* (2%). In 5/31 (16%) families, mutations occurred *de novo* or due to germline mosaicism. Among DMD/IMD cases, 23 (70%) presented large deletions, 17/19 (90%) compatible with the predicted phenotype, and 1 (3%) amenable to exon 51 skipping approach; 3 (9%) presented large duplications, 2/2 (100%) compatible with the predicted phenotype; and 7 (21%) presented small-scale mutations, including 2 (6%) nonsense mutations and 2 novel pathogenic frameshift variants (c.5831dupC and c.10210dupG). Among BMD index cases, 5 (38%) presented large deletions, 2/4 (50%) compatible with the predicted phenotype, and 1 (7%) amenable to exon 51 skipping approach; 2 presented large duplications, none of them compatible with the predicted phenotype; and 5 (38%) presented small-scale mutations.

Conclusion: Little is known about genetic profile of dystrophinopathies in Latin America. Most of data from Rio Grande do Sul is similar to previously reported European and USA cohorts, except for a

lower proportion of DMD cases amenable both to read-through (6%) and exon 51 skipping (3%) therapies. Further comprehensive studies with a population-based approach are necessary for a better knowledge of genetic profile of dystrophinopathies in Brazil. Such data may drive important insights for public health planning considering the rising availability of novel mutation-specific disease modifying drugs for this devastating disorder.

Funding:
Research grant from PTC Therapeutics. PTC Therapeutics had no role on research planning or analysis.

Código #12753

Title: LONG CONTIGUOUS STRETCHES OF HOMOZYGOSITY DETECTED BY MICROARRAY IN A COHORT OF 350 INDIVIDUALS WITH NEURODEVELOPMENTAL DISORDERS.

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Objective: The aim of this work was to assess the frequency and the implication of long continuous stretches of homozygosity (LCSH), detected by array CGH in patients with neurodevelopmental disorders in the state of Santa Catarina.

Methodology: The LCSH were analyzed in results of array CGH (Affymetrix CytoScan® HD or 750k) from 350 cases with intellectual disability, autism, epilepsy and/or congenital anomalies. The exams were requested by medical geneticists and neurologists from the Children and the University Hospitals and private clinics of Florianópolis, from 2013 to 2016, through the Laboratório Neurogene (Florianópolis). LCSH were considered only when ≥ than 3Mbp on the autosomal chromosomes. When present on a single chromosome with a sum of ≥ 10Mbp, a possible uniparental disomy (UPD) was considered. For LCSH ≥ 5Mbp on various chromosomes, possible consanguinity was investigated according to Kearney, Kearney and Conlin (Clinics in Laboratory Medicine, v. 31, no. 4, pp. 595-613, 2011). Written informed consent was obtained from at least one of the patients' guardians.

Results: Of the 350 cases, 5% did not present any LCSH > 3Mbp; 47% had more than one LCSH 3 ≤ 5Mbp distributed on the autosomal chromosomes (considered ancestral markers of an outbred population); 24% of the exams contained only one LCSH 3 ≤ 5Mbp restricted to a single chromosome [63% where on chromosome 16p11.2p11.1 (~31,451,698-35,220,544) with an average size of 3.5Mbp]. Other 22.8% indicated various degrees of consanguinity, of which: 14.6% present an consanguinity coefficient which suggest a kinship of seventh degree among the parents (e.g. third cousins); 3.7%, fifth degree (e.g., second cousins); 1.7%, fourth degree (first cousins once removed); 2%, third degree (first cousins/half uncle with niece), and 0.85% a second degree kinship of the parents (half-siblings, uncle-niece, double first cousins). In five patients, the LCSHs suggested an UPD: 2q24.3-q31.1 > 30Mbp; 6q25.1-q26 > 13Mbp; 10q25.2-q26.13 ~12Mbp; 14q13.2-23.2 ~28Mbp, and on chromosome 22q12.1-q13.1 ~14Mbp.

Conclusions: In our analysis, we found consanguinity in about 22.8% of the cases. However, most of those suggest distant descent (seventh degree), which may be due to regional characteristics of

immigration and marriages within the same ethnic group of immigrants. About 8.25% of the cases suggested second to fifth grade descent, which are more likely to have a clinical impact. These calculations are estimates and may not correspond exactly to the degree of consanguinity attributed. Of the UPD findings none is related to the classical imprinting syndromes, namely Angelman, Beckwith-Wiedemann, Prader-Willi and Silver-Russell syndromes. The UPD on chromosome 6q25.1-q26 encompasses an imprinted region, where IGF2R is to be mentioned, very relevant in mice, however with polymorphic imprinting and not reported to be related to neurodevelopmental disorders in humans. No imprinting disease is known to be related to the other suspected UPD regions we found.

Código #13267

Título: LUNG FUNCTION IN ATALUREN-TREATED, NON-AMBULATORY PATIENTS WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY FROM A LONG-TERM EXTENSION TRIAL VERSUS UNTREATED PATIENTS FROM A NATURAL HISTORY STUDY.

Autores: Craig M. McDonald[1]; Mar Tulinius[2]; Kathryn Selby[3]; Andressa Federhen[4]; Joseph McIntosh[4]; Panayiota Trifillis[4]; Tuyen Ong[4]; Robert Spiegel[4]; Stuart W. Peltz[4]; Francesco Muntoni[5]

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Objetivos: Nonsense mutation Duchenne muscular dystrophy (nmDMD) is a rare, debilitating X-linked genetic disorder, caused by a nonsense mutation in the dystrophin gene, which leads to muscle function decline and eventually to loss of pulmonary function. Forced vital capacity (FVC) is a clinically useful measure in DMD. The effects of ataluren on lung function in non-ambulatory boys with nmDMD were assessed as part of an open-label, long-term follow-up and safety trial (NCT01557400, study 019).

Metodologia: Data from patients in study 019, who were receiving ataluren 40 mg/kg/day, were compared with data from patients not receiving ataluren ("untreated") from a long-term DMD natural history study (NCT00468832; Cooperative International Neuromuscular Research Group [CINRG]). Patient populations were matched using the following criteria: non-ambulatory (requiring wheelchair use), ≤ 25 years old, with ≥ 24 months of corticosteroid use. To reflect the standard of care available during study 019, only CINRG data from 2012 onward were included. Data were analyzed using piecewise linear regression. Absolute FVC was assessed.

Resultados: Overall, 114 patients from the CINRG study and 53 patients from study 019 were included (mean age: 15.9 years, 14.1 years; mean baseline absolute FVC: 1.74 L, 2.03 L [CINRG, 019, respectively]). As expected, absolute FVC increased with age in untreated patients until 12.5 years; after this breakpoint, absolute FVC tended to decrease with increasing age. In comparison, the breakpoint in ataluren-treated patients was 16.5 years. Using the geometric mean log FVC, adjusted for within-patient correlation using a repeated-measures analysis of variance, a difference of 13.8% in predicted absolute FVC was seen in favor of ataluren-treated patients compared with untreated patients ($p = 0.005$).

Conclusão: In summary, this historically-controlled, matched analysis shows preservation of lung function in ataluren-treated versus untreated patients with nmDMD.

Código #13391

Título: NEUROLOGICAL AND OPHTHALMOLOGICAL CHARACTERISTICS OF A CASE SERIES OF CARRIERS OF SPINOCEREBELLAR ATAXIA TYPE 7.

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Objetivos: to describe the neurological and ophthalmological findings in a case series of symptomatic (Scarriers) and asymptomatic carriers (Acarriers) of spinocerebellar ataxia type 7 (SCA 7) - quite rare SCA that stands out from other SCA by the appearance of a retinal dystrophy with progressive loss of central vision.

Metodologia: after consent, Scarriers and their at 50% risk relatives were evaluated by ataxia (SARA, CCFS, PATA and 8-MW) and neurological scores (NESSCA and INAS); a visual functioning questionnaire (NEI-FVQ 25); evaluation of visual acuity (ETDRS), average loss of vision in campimetry (ALVC; Humphrey Field Analyzer 745, Carl Zeiss) and macular thickness in swept source optical coherence tomography (SS-OCT; Triton Topcon Medical Systems, Inc.). SARA and visual acuity (ETDRS) were chosen as the gold-standard variables of disease severity. Molecular analysis of the ATXN7 was done blindly; at risk individuals interested in receive their results were sent to pre-symptomatic testing program. Non-carriers were not included in this report.

Resultados: six carriers were studied up to now: two were Acarriers. Ages (range) and CAGexp (range) of S and Acarriers were 29-58 and 24-27 years of age (yo), and 39-44 and 39 repeats. Mean (range) of age at onset of gait ataxia (AO) and disease duration (DD), among Scarriers, were 34.25 (19-42) yo and 12.5 (10-16) years. Clinical characteristics of S and Acarriers were compared. Completely separated profiles were obtained for SARA, CCFS, PATA, INAS, NESSCA, visual acuity (ETDRS), and ALVC distributions between S and Acarriers were completely separated. Mean (range) of ALVC obtained in S and Acarriers were -13.35dB (-28.17 to -5.97) and -1.99dB (-2.84 and -1.16). Since ALVC up to -2,00dB is considered normal, one Acarrier (27yo) already presented losses in visual fields. The same Acarrier also presented a borderline macular thickness in SS-OCT. After that, we looked for correlations ($p < 0.05$, Spearman) between the gold-standard variables of disease severity (SARA and ETDRS) and the other clinical variables, in order to explore which will be probably

validated in a study with power. SARA correlated (rho) with NESSCA (0.94), CCFS (0.88), PATA (0.92), 8-MW (0.98), and ALVC (0.89). Visual acuity (ETDRS) correlated with INAS (0.85), ALVC (0.81) and NEI-FVQ 25 (0.89). INAS also correlated with ALVC (0.88).

Conclusão: Loss of visual fields (ALVC) stood out as the best candidate for a biomarker of disease progression in SCA7, since it was the first clinical alteration detected in still an asymptomatic carrier. Macular thickness in SS-OCT seems to be another good candidate. Moreover, ALVC correlated well with both gold-standards of disease progression ETDRS (visual acuity) and SARA (ataxia). This study is underway and we hope that with a larger sample, these conclusions can be better demonstrated.

Código #13411

Título: Origem ancestral de alelos mutantes de pacientes com doença de Machado-Joseph de diferentes regiões do Brasil.

Autores: Gabriel Vasata Furtado[1,2]; Ana Carolina Mello[1]; Tailise Conte Gheno[1]; Jonas Alex Saute[3]; Laura Bannach Jardim[1,3,4]; Maria Luiza Saraiva-Pereira[1,2,3,5] on behalf of Rede Neurogenética.

Instituição dos Autores: [1]Laboratório de Identificação Genética – HCPA; [2]PPG em Genética e Biologia Molecular – UFRGS; [3]Serviço de Genética Médica – HCPA; [4]Departamento de Medicina Interna – UFRGS; [5]Depto. de Bioquímica – UFRGS, Porto Alegre, RS.

Objetivos: A doença de Machado-Joseph ou a ataxia espinocerebelar tipo 3 (MJD/SCA3) é uma doença autossômica dominante de início tardio caracterizada principalmente por ataxia cerebelar progressiva e sinais piramidais . A MJD/SCA3 é causada pela expansão do trinucleotídeo CAG no éxon 10 do gene *ATXN3*. No Brasil, alelos mutantes para essa expansão são bastante prevalentes e análises haplotípica em pacientes brasileiros com MJD/SCA3 são relevantes para definir a origem dos alelos na nossa população. O objetivo deste estudo foi determinar haplótipos associados a alelos mutantes no gene *ATXN3*.

Metodologia: O estudo incluiu 300 pacientes brasileiros com MJD/SCA3 (220 pacientes do Rio Grande do Sul e 80 pacientes de outros estados) e amostras de 50 indivíduos saudáveis. Foram utilizados três polimorfismos intragênicos de um nucleotídeo único (*single nucleotide polymorphism* - SNP) para determinar a linhagem MJD/SCA3, e quatro repetições curtas em tandem curtas (*short tandem repeats* - STR) flanqueadoras para determinar a origem da população. A reconstrução do haplótipo foi estabelecida através do software da Phase v.2.1 e as análises estatísticas foram realizadas usando SPSS v.18.

Resultados: O haplótipo mínimo ACA foi o mais prevalente em ambas subpopulações de pacientes com a doença, sendo fortemente representada em alelos mutantes de pacientes do estado do Rio Grande do Sul (RS). O haplótipo GGC foi encontrado em 19 famílias no grupo de pacientes de outros estados e em apenas uma família do estado RS. A distribuição dos haplótipos mínimos também foram estabelecidas nos alelos normais de pacientes com MJD/SCA3 e nas amostras de indivíduos saudáveis, e a distribuição dos haplótipos foi semelhante em ambos os grupos. O haplótipo ampliado, combinando os SNPs com os STRs, mostraram que a grande maioria dos alelos mutantes, independentemente da origem dos pacientes, compartilham a mesma linhagem.

Conclusão: Os dados obtidos nesse estudo e relatados nesse trabalho confirmam a linhagem ACA como a mais frequente em alelos mutantes de pacientes com MJD/SCA3 no Brasil. Esse é o mesmo haplótipo encontrado em Portugal e em outras populações europeias. A análise de um maior número de amostras de outros estados do Brasil seriam importantes para melhor definir a origem ancestral dos alelos mutantes *ATXN3* na população brasileira.

Apoio financeiro: CNPq, FAPERGS, FIPE-HCPA

Código #13242

Título: STUDY OF CANDIDATE POLYMORPHISMS IN KAINATE RECEPTOR 6 SUBUNIT GENE (GLUR6) IN A SAMPLE OF PATIENTS WITH AUTISM SPECTRUM DISORDER

Autores: Carlos Eduardo de Melo Amaral[1,2], Marcella Montenegro[1]; Amira Figueiras[3], Isabel Cristina Neves de Souza[3], Maria Suley Bezerra Fernandes[3], Luiz Carlos Santana da Silva[1].

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Autism Spectrum Disorders (ASDs) are severe developmental neuropsychiatric diseases. The diagnosis criteria recently published at Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. (DSM-5) includes two main classifications: deficit of social communication and fixated or repetitive behavior. It is known that ASDs has a significant association with genetic inheritance even though the exact transmission is not completely clear. Previous studies suggest that ASDs are complex neurologic disorders that outcome from the interaction between multiple genetic and environmental factors. The gene which codifies the subunit 6 from glutamate kainate receptor (GluR6 ou GRIK2) is localized on 6q21 region. It has been suggested that this gene can be related to ASDs' etiology based on the association of the protein receptor with cognitive functions, such as learning and memory.

Objective: The main goal of this study was to determine the frequencies and to verify the possibility of association of the following SNPs: rs3213607, rs2227281, rs2227283, rs2235076, rs4839797, rs2518261 on GluR6 gene and ASDs.

Methods: From 279 individuals analyzed, 49 were trios (non-affected father and mother and affected offspring), 57 duos (non-affected father or mother and affected offspring) and 18 affected patients without matching samples from their parents. The diagnosis of ASD was realized by a well-trained clinical staff, according to DSM-IV criteria. The hypothesis of association was assessed by a family based method, through PLINK and FBAT programs.

Results and Conclusion: We found preferential transmissions of allele C on SNP: rs4839797 (χ 2 = 5, p = 0,02535) and allele G on SNP: rs2227283 (χ 2 = 8,333, p = 0,003892), showing that these polymorphisms are related to ASD in samples of Brazilian patients. Moreover, we demonstrated that the allele A of SNP: rs3213607(C/A) may be associated to a lower risk in developing comorbidities as seizure and panic attack (p=0,040 e p=0,041, respectively).

Acknowledgements: INAGEMP/INCT/CNPq; FAPESPA.

Código #13243

Título: STUDY OF *GRIK2* GENE POLYMORPHISMS IN PATIENTS WITH PARKINSON'S DISEASE

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Parkinson's Disease (PD) is a complex neurodegenerative disorder resulting from the multiple combination of genetic and environmental factors. One of the factors that may contribute to PD development is the excitotoxicity, a pathophysiological process caused by intense stimulation of glutamatergic receptors. This neurotoxic phenomenon is associated with the excessive influx of ions in the cell (Na +, Cl- and especially Ca 2+), resulting in neuronal death. It was evidenced that the GluK2 subunit of the kainate type glutamate receptor interacts with parkin, accentuating the excitotoxic process. The *GRIK2* gene encodes this subunit, expressed in regions of the brain involved in motor activity, and may undergo alternative splicing or RNA editing, introducing new isoforms that may alter the ion conductance at the receptor. There are no studies in the literature on the association of polymorphisms in the GRIK2 gene with PD.

Objective: This study aimed to determine the genotypic and allelic frequencies, as well as to verify a possible influence of the SNPs rs3213607, rs2227281, rs2227283, rs2235076, rs4839797, rs2518261 from *GRIK2* gene in a group of patients with PD.

Methods: A case-control study was performed, with analysis of DNA samples from 129 individuals from the control group and 61 patients from the PD group.

Results and Conclusion: It was found that for the SNP rs2518261 (C/T), allele T appeared to have a risk effect in the DP group (x2= 19.085; p-value <0.0001; OR = 2.75; CI = 1.75-4 , 27). In this polymorphism it was also observed that TT genotype may represent a factor associated with the tremor presence in the PD group (p-value = 0.02). These pioneer results of this study, suggest that further research is needed to investigate the contribution of *GRIK2* gene to PD.

Acknowledgements: INAGEMP/INCT/CNPq; FAPESPA.

Código #13322

Título: The Impact of Congenital Heart Disease on the Neuropsychomotor Development of Down Syndrome Patients: a Case-Control Study.

Autores: Maria Denise Fernandes Carvalho [12345]; Juliana Guerreiro Mota [3]; Filipe Lins Linhares de Sousa[3]; Ítalo da Silva Barbosa[3]; Ellaine Doris Fernandes Carvalho[1234].

Instituição dos Autores: 1 Genpharma, 2 APAE-Fortaleza, 3 Centro Universitário Christus, 4 UECE - Universidade Estadual do Ceará, 5 UFC - Universidade Federal do Ceará

Objetivos:
To analyze and compare the neuropsychomotor development of patients with Down Syndrome (DS) with and without Congenital Heart Disease (CC), by means of medical records, assessing the following aspects: cephalic support, unsupported sitting, initial language development, based on the developmental milestones of the Denver Development Test.

Metodologia:
This is a case-control, retrospective, quantitative and analytical study with the medical records of patients with Down Syndrome. The research was carried out in the Association of Parents and Friends of the Exceptional (APAE), in Fortaleza, Ceará. The study was carried out from August 2016 to February 2017. Patients with or without congenital heart disease who were included in the APAE were included in the study. The instrument used was the Denver Development Test. The exposure groups between those with congenital cardiopathy and those who did not presented were compared. Epiinfo v 3.5.2 software was used, using qui quadrado to statistical analisis. This study is in accordance with the ethical principles of research involving human beings in Resolution 196/96 of the National Health Council.

Resultados:
The medical records of 205 patients were analyzed. Among these, 52,70% (108) had CC, 34,14% (70) did not present and 13,16% (27) did not have this information. In 33,65% (69) patients there was delay in the development of cephalic sustenance; of these 42,03% (29) had CC; 37,68% (26) did not have it and 20,29% (14) had no information on cardiac pathology. In addition, 31,70% (65) subjects presented delay in the ability to sit without support, of which 46,15% (30) had CC, 33,85% (22) didn't and 20,00% (13) had no cardiac information. Of the patients analyzed, 41,46% (85) had retarded ability to walk without support, 35,29% (30) had CC, 43,53% (37) did not have it and 21,18% (18) had no information regarding the presence of cardiac pathology. Finally, 70 patients presented delay in the initial development of speech, 24 of which had CC, 24 did not have it and 17 had no cardiac information.

Conclusão:
There is not signification difference when compare the neuropsychomotor development of patients with Down Syndrome (DS) with and without Congenital Heart Disease (CC).

Código #13338

Título: WHOLE EXOME SEQUENCING FOR THE DIAGNOSIS OF PATIENTS WITH VARIOUS NEUROGENETIC DISORDERS

Autores: Joana Rosa Marques Prota, Ingrid Faber de Vasconcelos, Murilo Guimarães Borges, Marcondes Cavalcante França Junior, Benilton de Sá Carvalho, Marcio Balthazar, Antonia Paula Marques de Faria, Iscia Lopes Cendes.

Instituição dos Autores: University of Campinas – UNICAMP

Objectives: To determine how effective is whole exome sequencing (WES) to achieve molecular diagnosis in patients with various neurogenetic disorders.

Methods: We ascertained 19 patients regularly followed at the neurogenetics outpatient clinic of the UNICAMP university hospital. Clinical diagnosis were spastic paraplegia, spinocerebellar ataxia, familial dementia, and undetermined movement disorder. WES was performed in all patients after an initial consultation in our genomic counselling outpatient clinic. After the initial bioinformatics processing all the variants found were filtered and prioritized according to the phenotype presented using the Ingenuity Variant Analysis (QIAGEN) software.

Results: Overall we have identified ten different variants, which explain the phenotype in 14 of the 19 patients. In three patients the putative causal variant (PCV) was present in homozygosis (*GBA2* and *GRN*), in eight patients in heterozygosity (*SPAST*, *SPG7*, *PSEN1*, *SYP* and *WDR45*), two were X-linked variants in hemizygosis (*WDR45* and *SYP*), and two PCV (in *TPP1*) were found in a compound heterozigous patient. Among the ten PCV, eight were single nucleotide variants and two were indels. According to the ACMG classification, five PCVs were classified as 'variants of unknown significance' (*GBA2*, *SPG7*, *TPP1* and *WDR45*), two were interpreted as 'probably pathogenic' (*GRN* and *PSEN1*) and only three were classified as 'pathogenic' (*TPP1*, *SPAST* and *SYP*). In addition, we found that four PCVs identified in the present study have not been previously reported in public genomic databases or in the medical literature.

Conclusions: We found that the diagnostic yield of WES in our sample with neurogenetic disorders was =73.7%. It is well known that the effectiveness of WES, as a diagnostic tool, is largely dependent on the characteristic of patients to which the test is applied. In our sample, the high diagnostic yield is due, at least in part, to the monogenic nature of the phenotypes studied, most of which showing a clear familial recurrence. Despite this advantage, some challenges persist, such as the indirect (or probabilistic) process by which the evaluation of pathogenicity of variants is performed and the large volume of variants of unknown significance found. However, such difficulties are likely to be minimized in the future, as the scientific community share genomic and phenotypic data in public databases. It is also worth mentioning that in addition to the diagnostic utility of WES, it has an important contribution for expanding phenotypes, uncover new disease-causing genes and to the better understanding of genotype-phenotype associations.

ONCOGENÉTICA

Código #13363

Título: Análise da mutação p.Arg337His (R337H) no gene TP53 em mulheres com câncer de mama diagnosticadas com 50 anos ou menos avaliadas no ambulatório de Oncogenética do Hospital de Clínicas de Porto Alegre

Autores: Yasminne M. de A. Rocha, Camila M. Bittar, Cristina B. Netto, Gustavo Stumpf, Patricia Silva, Patricia Ashton-Prolla

Instituição dos Autores: Laboratório de Medicina Genômica, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Objetivos:
A Síndrome de Li-Fraumeni (LFS) e a variante Síndrome de Li-Fraumeni-Like (LFL), são doenças autossômicas dominantes associadas a mutações germinativas no gene *TP53* e caracterizadas por predisposição ao desenvolvimento de um amplo espectro de tumores em idade precoce. Os tumores mais comuns relacionados à SLF são sarcomas ósseos e de partes moles, tumores cerebrais, carcinoma adrenocortical, leucemias e cânceres de mama pré-menopáusicos. A mutação p.Arg337His (R337H) em *TP53* é uma mutação fundadora com uma prevalência populacional de 0.3% no Sul do Brasil. Indivíduos com esta mutação também têm maior risco para uma ampla gama de tumores do espectro típico da LFS. Em 2014, uma prevalência de R337H de até 12,1% foi descrita em mulheres não selecionadas para história familiar com câncer de mama pré-menopausico recrutadas em diferentes regiões do país. O objetivo do presente estudo foi analisar a prevalência da mutação R337H em mulheres que apresentaram câncer de mama com idade menor ou igual a 50 anos, com e sem história sugestiva de LFL/LFS.

Metodologia/Resultados/Discussão:
303 mulheres com diagnóstico confirmado de câncer de mama, atendidas no ambulatório de Oncogenética do HCPA foram testadas para a mutação R337H no gene *TP53*. História familiar autorreferida de câncer foi coletada de cada paciente. As 303 mulheres testadas, foram divididas em dois grupos: grupo (1) foi composto de 40 mulheres com critérios de Chompret para a síndrome e grupo (2) 263 mulheres sem critérios de Chompret. Na amostra total, foram identificadas 7 portadoras da mutação (2,31%). Quando os grupos foram analisados separadamente, a prevalência foi 2,5% (grupo 1, 1 portadora) e 2,29% (grupo 2, 6 portadoras). Embora a prevalência encontrada no presente estudo tenha sido menor que a publicada anteriormente, estudos adicionais com número maior de participantes são necessários para definição da real prevalência da mutação na região.

Código #13495

Título: ANÁLISE DA TERAPIA CIRÚRGICA EM PACIENTES COM CÂNCER DE MAMA FAMILIAL-HEREDITÁRIO EM PROGRAMA DE ACONSELHAMENTO GENÉTICO NO BRASIL.

Autores: Lucas Amadeus Porpino Sales; Jéssica Dayanna Landivar Coutinho; Diana Taissa Sampaio Marinho Navarro; Ana Rafaela de Souza Timóteo; Tirzah Braz Petta Lajus

Instituição dos Autores: Departamento de Biologia Celular e Genética da Universidade Federal do Rio Grande e Liga Norteriograndense contra o Câncer. Natal/RN

Objetivos: Traçar o perfil dos tipos de procedimentos cirúrgicos realizados em pacientes norteriograndenses submetidos a sequenciamento genético visando o rastreamento de mutações germinativas relacionadas à predisposição de câncer de mama familial-hereditário.

Metodologia: Foi feito um estudo prospectivo e longitudinal de pacientes do Ambulatório de Aconselhamento Genético (AG) da Liga Norteriograndense Contra o Câncer no estado do Rio Grande do Norte. Foi realizada triagem ambulatorial e análise de prontuários a fim de averiguar o critério de inclusão para estudo de síndrome de câncer de mama familial-hereditário, com base nos critérios estabelecidos pelos protocolos internacionais. Após obedecer pelo menos um dos critérios, o paciente foi convidado a participar do estudo, assinando um TCLE e através da coleta de 5ml sangue periférico para extração de DNA genômico e posterior seqüenciamento *Next GenerationSequencing (NGS)* em plataforma multigênica *PGM ION*. O trabalho foi aprovado pela resolução 44217315.6.00000.5293 e recebeu financiamento CNPq.

Resultados: Ao todo foram enquadrados 163 pacientes com risco de câncer de mama familial-hereditário, dos quais cento e sessenta eram do sexo feminino (98,16%) e três eram do sexo masculino (1,84%), com uma média de idade 41,77 anos. Desse total, cento e vinte e quatro (76,07%) dos pacientes tiveram diagnóstico de uma ou mais neoplasia maligna, dos quais cento e vinte e três (99,16%) eram do sexo feminino e um paciente era do sexo masculino (0,81%). Entre toda a amostra do estudo, uma quantidade de vinte e sete pessoas (16,54%) apresentaram mutações em algum gene que confere suscetibilidade ao câncer de mama hereditário, ocorrendo a seguinte distribuição: doze deles possuíam mutações no gene BRCA1 (44,44%), sete deles tinham mutações em BRCA2 (25,93%), quatro carregavam no gene ATM (14,81%), um paciente apresentava mutação ATR (3,70%), um paciente em CDH1 (3,70%), um paciente com MLH1 (3,70%) e outro em MSH6 (3,70%). Dos pacientes que tiveram mutação, vinte e quatro (88,89%) apresentaram um ou mais diagnósticos de carcinomas mamários e três (11,11%) são considerados assintomáticos para a doença. Entre os pacientes que apresentaram mutação sete pacientes realizaram mastectomia radical unilateral (29,17%), quatro pacientes realizaram mastectomia radical unilateral com reconstrução (16,67%), quadrantectomia com esvaziamento axilar, quadrantectomia sem esvaziamento axilar foram realizadas por três pacientes cada uma (12,50%). Mastectomia radical unilateral com reconstrução e esvaziamento e quadrantectomia com mastectomia radical foram realizados em dois pacientes cada (8,33%). Mastectomia radical com esvaziamento, mastectomia radical bilateral e mastectomia bilateral simples e radical foram feitas em um paciente com mutação cada (4,33%). Foi encontrada uma correlação positiva entre a existência de mutação germinativa e a prática do esvaziamento axilar ($p<0.05$). A realização de tratamento radioterápico interferiu na não realização de procedimento de reconstrução mamária ($p <0.05$).

Conclusão: As informações sobre a conduta cirúrgica no câncer de mama-familial hereditário no Brasil são escassas, de modo que o estudo é uma iniciativa pioneira na avaliação desse tipo de conduta na população. Além disso, a profilaxia cirúrgica e a reconstrução mamária nos pacientes encontrados, considerada baixa, pode refletir características sociais, econômicas e estruturais do sistema de saúde público brasileiro, mas também um grau de interferência da condição clínica do paciente na adoção desses procedimentos cirúrgicos.

Código #13298

Title: ANALYSIS OF THE DATA FROM THE CANCER GENOME ATLAS (TCGA) ON POSSIBLE BIOMARKERS FOR THERAPY WITH PARP INHIBITORS

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Objectives: At the moment, little is known about the percentage of patients who could benefit from the use of PARP inhibitors if an individual with mutations in other genes of the Homologous Recombination Repair (HRR) pathway also responds to these compounds. As objective of this study was to evaluate the percentage of patients who could benefit from the use of PARP inhibitors based on the frequency of mutation in the HRR genes in the TCGA database in breast, ovarian, prostate and pancreatic tumors.

Methods: Mutation frequency of in 33 genes of the HRR pathway was analyzed in the TCGA data through the cBioPortal (cbioportal.org). These genes are: *ATM, BARD1, BRCA1, BRCA2, BRCC3, DMC1, FAM175A, FEN1, H2AFX, LIG4, MDC1, MRE11A, NBN, PRKDC, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54, RAD54L, RBBP8, RNF8, SMC1, UBE2N, UIMC1, XRCC2, XRCC3, XRCC4, XRCC5,* and *XRCC6*.

Results: From this list of 33 HRR-related genes, in Ovarian Serous Tumours, 316 cases were analyzed and 30.7% of them were mutated. Regarding Breast Invasive Carcinoma, 817 cases were considered and 14.8% were mutated. The fraction of pancreatic and prostate mutated adenocarcinomas was 13.3% from a total of 150 cases and 11.1% from 333 evaluated cases respectively. When we look at each gene we have as the four most expressively altered genes (except *BRCA1* and *BRCA2*), for breast cancer, *ATM* with 2.1% of mutations, *PRKDC* 1.7%, *ATRX* 1.7% and *SMC1A* 1.1%. For ovarian cancer we get the percentage of *PRKDC* 2.5%, *ATM* 1.3%, *UIMC1* 1.3% and *SMC1A* 1.3%. For pancreatic cancer we have *ATM* 3%, *RBBP8* 2%, *PRKDC* 2% and *RAD54L* 2%. Lastly, for prostate cancer we have *ATM* 4%, *MDC1* 0.9%, *PRKDC* 0.9% and *RNF8* 0.9%.

Conclusion: The *ATM* and *PRKDC* genes appear as good candidates to be included in clinical trials with PARP inhibitors, since the number of patients with breast, ovarian, prostate and pancreatic tumors and with mutations in one of these two genes are relatively high. This study has support from FAPESP.

Código #13382

Assessing response to anti-cancer drugs treatment in cancer stem cell from oral squamous cell carcinoma

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Objectives: Cancer Stem Cells (CSCs) are responsible for sustaining tumor growth, resistance to conventional therapies and disease recurrence. Then, the aim of the current study was to identify and separate CSC through CD44, CD133 and CD117 markers and evaluate the effectiveness of anti-cancer drugs in head and neck cancer (HNC) stem cell and HNC non stem cell.

Materials and Methods: HN13 (oral cavity carcinoma) cell line was incubated at 37°C in 5% CO_2. CD44+, CD133+ and CD117+ cells were isolated by fluorescence-activated cell sorting flow cytometric using BD Biosciences FACS Aria. The $CD44^+/CD133^+/CD117^+$ subpopulation was considered as CSCs and $CD44^-/CD133^-/CD117^-$ subpopulation non-CSC and both were cultured and exposed for 24h to anti-cancer treatment with 0.02mg/ml of Cisplatin, 0.37mg/ml of 5-Fluorouracil, 0.06mg/ml of Cetuximab, 0.05mg/ml of Paclitaxel and 0.06mg/ml of Cetuximab combined with 0.05mg/ml Paclitaxel. $CD44^+/CD133^+/CD117^+$ and $CD44^-/CD133^-/CD117^-$ cells untreated were considered as control. Cell viability was determined by trypan blue exclusion. Mann-Whitney test was used for statistical analyzes and the significance level was 0.05.

Results: Cetuximab and 5-Fluorouracil has promising antitumor activity in $CD44^-/CD133^-/CD117^-$ subpopulation ($p<0.03$ for both drugs). However, for $CD44^+/CD133^+/CD117^+$ subpopulation was observed no significant statistical (Cetuximab: $p=0.33$ and 5-Fluorouracil: $p=0.66$). In addition, in both subpopulations for Paclitaxel, Cisplatin and Cetuximab combined with Paclitaxel were found no significant statistical ($p>0.1$ for non-CSC and CSC).

Conclusão: The Cetuximab and 5-Fluorouracil treatment appears to have effect on elimination of $CD44^-/CD133^-/CD117^-$ subpopulation in HNC. However, the same treatment no decreased the number of living CSC of HNC. Therefore, our outcomes suggest that Cetuximab and 5-Fluorouracil treatment have no effect in CSC and could be clarifying the resistance to anti-cancer drugs. Moreover, Paclitaxel, Cisplatin and Cetuximab in combination with Paclitaxel show no effectiveness in $CD44^+/CD133^+/CD117^+$ and $CD44^-/CD133^-/CD117^-$ subpopulations in HNC eradication.

Grants: São Paulo Research Foundation (FAPESP 2014/15009-6 and 2015/04403-8), CAPES and CNPq; Support: Base Hospital, FUNFARME-FAMERP.

Código #13410

Título: **ASSOCIATIONS BETWEEN SINGLE NUCLEOTIDE POLYMORPHISM *IL10G-1082A, IL10C-819T, IL10C-592A, -511(IL1BF1), -31(IL1BE1)* ALLELES AND SUSCEPTIBILITY TO GASTRIC CANCER IN A POPULATION FROM NORTH OF BRAZIL.**

Autores: *Gabriela Oliveira Esteves[1]; Yaisa Castro[2]; Darlen Cardoso de Carvalho[1,2;] Pablo Pinto[2]; Roberta Borges Andrade[1,2;] Ney Pereira Carneiro dos Santos[1,2]; Paulo Assumpção[2]; Sidney Santos[1,2]; Ândrea Ribeiro-dos-Santos*[, 1,2]

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Objetivos: Gastric Cancer (GC) is one of the most common causes of cancer-related deaths. Despite an overall decrease in the incidence of it in recent years (2001-2016), this disease is still responsible for more than 700,000 deaths for year. Levels of IL10 and IL-1 production are important in immune regulation. The choice of interleukins was due to both having antagonist effects. IL1B is related to the inflammatory response in initial gastric inflammatory process in the presence of *H. pylori.* IL10 is associated with several autoimmune diseases and many types of cancer, including gastric cancer. In this susceptibility study, the polymorphism investigate were interleukin genes *IL10G-1082A, IL10C-819T, IL10C-592A, -511(IL1BF1)* e *-31(IL1BE1)* on samples of patients with gastric cancer and patients without cancer.

Metodologia: 216 individuals were investigated (case group 100 patients diagnosed with gastric cancer, and 116 individuals without cancer), met in the Hospital Universitário João de Barros Barreto/UFPA - Pará, Brazil). Analysis of the molecular polymorphisms was performed by real-time PCR with Taqman ® probes.

Resultados: The results of the haplotype distribution analyzes, considering the gene *IL10* (IL10G-1082A, IL10C-819T, IL10C-592A) confirmed again the genotypes connected to the low production of IL-10 (ACC/ACC, ACA/ACA, ACC/ATA, ACC/ATC, ATA/ATA) as protection factor to gastric cancer (p 2.96E-06; OR= 7.88[3.450-19.743]). In contrast, the genotypes associated with the intermediate and high production of IL-10 (ACA / GCC, ACA / GTC, ATC / GTC, ATC / GCC, ATA / GCC, GTC / GTC, GCC / GCA) were significant in the case sample's group. Four haplotypes *-511(IL1BF1)* and *-31(IL1BE1)* were found for the case and control groups. The most frequent haplotype in the groups was GA, observed in 47% of the case group and 53% in the control group. The least frequent haplotype was AA, present in 3% of the case group and 1% of the control group. There were no statistical differences between the groups for any of the haplotypes found. These results suggest that these genotypes are associated with one risk factor against gastric cancer.

Conclusão: We concluded that patients who presented the haplotypes in IL10 (ACC / ACC, ACA / ACA, ACC / ATA, ACC / ATC, ATA / ATA) related to low production of this interleukine are less susceptible to the development of gastric cancer, Polymorphisms factor of protection to the disease.

Key words: Gastric cancer; Polymorphisms; Interleukin; Ancestry.

Supported by: RPGPH (Rede de Pesquisa em Genomica Populacional Humana) 3381/2013 CAPES/BioComputacional; FAPESPA (Fundacão Amazonia Paraense de Amparo à Pesquisa) ICAAF 083/2013; CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico); Bolsa CNPq/Produtividade 304413/2015-1 - Dr. Ândrea Ribeiro-dos-Santos; Bolsa CNPq/Produtividade 305258/2013-3 - Ph.D. Sidney Santos; FADESP/PROPESP/UFPA (Universidade Federal do Pará).

Código #12622

Título: ASSOCIATIONS OF RB1 GENETIC VARIANTS WITH CLINICAL TRAITS IN RETINOBLASTOMA PATIENTS FROM A BRAZILIAN SERVICE (INCA - RIO DE JANEIRO).

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Instituição dos Autores: 1- Instituto Nacional do Cancer (INCA), Rio de Janeiro - RJ, Brasil. 2- Universidade do Grande Rio (UNIGRANRIO), Rio de Janeiro - RJ, Brasil.3- Hospital Universitário Gaffrée e Guinle (HUGG), Rio de Janeiro - RJ, Brasil. 4- Fundação Oswaldo Cruz (FIOCRUZ), Rio de Janeiro - RJ, Brasil.

Objetivos: To estimate the frequency of genetic variants in *RB1* gene and to test possible associations with different clinical traits, in patients with Retinoblastoma (RB) diagnosis referred to INCA's Clinical Genetics Clinics.

Metodologia: Retrospective chart review of 206 patients was performed. So far we reviewed three continuous traits – age of diagnosis (DX), age of first symptom (1S) and lag-time between 1S and DX (LAG) – and the following categorical traits: laterality, survival, family history of RB, family history of other cancers, intra/extraocular tumors, enucleation, radio/chemotherapy, secondary tumors, and change in laterality or intra/extraocular tumors. We performed complete Sanger sequencing and/or Multiplex Ligation-dependent Probe Amplification (MLPA) of *RB1* gene from blood samples of 127 patients. *RB1* molecular diagnosis was defined as Positive (pathogenic variant in Sanger sequencing and/or MLPA abnormality) or Inconclusive (variants with benign or unknown clinical significance). To test the effects of *RB1* molecular diagnosis, laterality and survival on the square root (SQRT) of each continuous trait we used three-way ANOVA. Chi-square tests were used to test possible associations between pairs of categorical traits (alpha adjusted for multiple testing).

Resultados: ANOVA of SQRT age data showed that patients with bilateral RB have, on average, significant earlier diagnosis (DX = 11.5m ± 0.3) and first symptom (1S = 4.7m ± 0.3) than unilateral ones (DX = 26.4m ± 0.2; 1S = 15.7m ± 0.4); $P < 0.01$. Patients with pathogenic variants also presented significant earlier DX average (11.0m ± 0.3) than inconclusive ones (23.2m ± 0.3); $P < 0.05$. These results are in accordance with RB literature. Significant effect of survival was found only for LAG time, in which deceased patients had greater LAG average (10.3m ± 0.4) than living/non-determined ones (4.7m ± 0.1); $P < 0.01$. Chi-square tests were non-significant for all pairs of categorical traits (alpha = 0.01), except for: *RB1* molecular diagnosis (M) x laterality; M x family history of RB; M x change in laterality; survival x intra/extraocular tumors. For instance, pathogenic variants were associated with higher frequency of bilateral tumors (31 cases) than unilateral ones (18 cases). Most frequent types of pathogenic *RB1* variants were nonsense (20 cases) and splicing variants (9 cases). Interestingly, all

patients with splicing variants also had bilateral tumors. We are currently reviewing other chart data, like focality and tumor staging, as well as finishing Sanger sequencing and MLPA analysis of remainder patients, which might bring more information about the effects of *RB1* molecular diagnosis on clinical traits.

Conclusão: Frequencies of *RB1* genetic variants were similar to those in RB literature. Pathogenic variants were more frequent in patients with bilateral tumors. And a possible trend in which patients with splicing variants develop bilateral RB was detected.

Código #13354

Título: Avaliação da heterogeneidade tumoral para o gene *PIK3CA* em câncer de mama.

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Objetivos: Em busca de avaliar parâmetros de heterogeneidade intertumoral, objetivou-se identificar a presença de mutações no gene Fosfatidilinositol-4,5-bisfosfato 3-quinase alfa (*PIK3CA*) em amostras de câncer de mama metastáticos.

Metodologia: Treze casos de mulheres com câncer de mama metastático foram selecionados para o estudo e submetidos a avaliação de quatro mutações no gene *PIK3CA* (p.E542K, p.E545K, p.H1047L e p.H1047R) para uma amostra de tumor primário e uma amostra de tumor metastático. Todas as amostras foram previamente avaliadas e tiveram suas áreas de interesse demarcadas por médico patologista e, a partir desta marcação, foram retirados do bloco de parafina cerca de 35 mg de material tumoral. A extração do material genético foi realizada com o kit comercial *Wizard® Genomic DNA Purification* (Promega®, Wisconsin, EUA), conforme instruções do fabricante, após, a concentração de DNA genômico foi ajustada para 20 ng/µl. As amostras foram submetidas à avaliação das quatro sondas selecionadas, bem como, uma sonda de gene humano de referência. Os experimentos foram realizados no equipamento *7500 Fast Real-Time PCR System* utilizando TaqMan® Genotyping Master Mix e sondas TaqMan®, todos obtidos da *Life Technologies®* (California, EUA*)* e seguindo as especificações do fabricante.

Resultados: Foi detectada alta incidência de mutações em *PIK3CA* nas amostras metastáticas, estando presente em 8 dos 13 casos avaliados (61,5%). A heterogeneidade intertumoral esteve presente em 53,8% das amostras avaliadas, sendo que a mutação E545K foi a mais prevalente (87,5%), seguida da H1047R (37,5%). Nos casos heterogêneos, os sítios metastáticos com maior prevalência de mutação foram os linfonodos axilares e fígado (28,6%), seguido de bexiga, sistema nervoso central e peritônio (14,3%).

Conclusão: Para câncer de mama, alterações no gene *PIK3CA* são muito frequentes, perdendo apenas para mudanças no gene repressor tumoral P53, o que explica a presença de alterações em mais da metade dos casos avaliados no estudo. Além disso, as mutações mais frequentes estão nos *hostpots* localizados no éxon 9 e 20, sendo que a alteração E545K - que se mostrou mais prevalente - já foi relacionada com aumento nas atividades celulares de oncogênese. Logo, os resultados se mostraram promissores para continuarmos os estudos avaliando outras mutações importantes que podem estar associadas com as do gene *PIK3CA* e, futuramente, auxiliar em uma conduta clínica mais efetiva para cada paciente.

Código #13591

***BRCA1* and *BRCA2* mutational profile and the utility of international testing criteria in Hereditary Breast and Ovarian Cancer (HBOC) probands from Southern Brazil**

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Germline mutations in *BRCA1* and *BRCA2* (*BRCA*) are the main cause of Hereditary Breast and Ovarian Cancer syndrome (HBOC). In this study we evaluated the mutational profile and prevalence of *BRCA* mutations among probands fulfilling the NCCN HBOC testing criteria. Moreover, we characterized the clinical profile of these individuals and explored the performance of international testing criteria. We found a mutation prevalence of 19.1% among 418 probands, and seven novel frameshift mutations. Variants of uncertain significance were found in 5.74% individuals. For each proband, we evaluated 50 testing criteria plus scores of mutation prediction. Twenty-five reached a significant (P≤0.05) odds-ratio (OR) of carrying a mutation. Mutation prevalence among each criteria ranged from 22.1% to 55.6%, and criteria with the highest ORs were those related to triple-negative BC or ovarian cancer. Fourteen criteria had a highly significant OR (P ≤ 0.001) for being a mutation carrier: at a cutoff point ≥ four criteria, the sensitivity is 83.8%, and the specificity is 53.5% (P ≤ 0.001) for being a carrier. This is the largest Brazilian comprehensive *BRCA* study and the first to analyze the clinical criteria related to these families, and we demonstrated that many non-NCCN criteria reached higher mutational prevalence and OR. Identify the most appropriated criteria for each population is essential to design a rational approach for genetic testing, saving costs to the health system. This allows the prioritization of high-risk individuals using highly specific criteria, and it can be a first step to offer testing in low-incoming countries.

Código #13248

Title: Concordance between MSI and IHC in the Universal Screening Tumor at Barretos Cancer Hospital, a Public Health Cancer Center in Brazil.

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Objectives: The objective of this project was to show the experience of a Public Health System Hospital from Brazil in the identification of patients/families at-risk for Lynch Syndrome (LS). Individuals with LS have an increased risk of colorectal cancer, endometrial, ovarian and others. The detection has evolved from a clinical diagnosis to tumor-based screening. Given its importance in clinical practice, 5 years ago the Barretos Cancer Hospital implemented a molecular screening approach to identify patients at-risk for LS.

Methods: For the purpose of this work, pentaplex mononucleotide PCR for MSI was compared to IHC of MMR genes in a cohort with clinical criteria (Amsterdam and Bethesda), cancer family history or early onset of colorectal cancer patients. Additional molecular testing including tumor *BRAF* mutation analysis and *MLH1* hypermethylation testing was performed to exclude LS. Molecular genetic testing was performed for all patients with altered MSI and/or IHC. We calculated Cohen´s Kappa Statistic to define the accuracy and sensitivity of MMR IHC and MSI assays.

Results: 344 LS suspect patients (families) were evaluated, 18 and 24 were *BRAF* V600E and *MLH1* methylation tumor positive, respectively. Nine cases present inconclusive MSI and/or IHC and were excluded. Comparison of both MSI and IHC status was complete for 293 cases (Normal MSI/IHC: 200 cases; Discordant MSI/IHC result: 22 cases; Abnormal MSI/IHC: 71 cases). Overall agreement between methods was 92.5% (Kappa coefficient= 0.81). The genetic testing was performed for 93 patients, of which 54 (58%) had pathogenic mutation in one of the MMR genes. The sensitivity and PPV (Predictive Positive Value) were 85% and 62% for MSI, and 96% and 52% for IHC respectively. Considering MSI and IHC results together, the sensitivity for LS identification was 96%.

Conclusion: The results shows that both, MSI testing and IHC presented high sensitivity to the identification of families at-risk for LS. Our experience highlights the importance of adoption of these screening methods in the clinical practice, especially in public health centers and in underdeveloped countries with limited financial resources to performed molecular genetic testing.

Código #13321

Título: EXAMES DE *EGFR* EM CÂNCER DE PULMÃO: FREQUENCIA DE POLIMORFISMOS POSITIVOS ENCONTRADOS EM PACIENTES AVALIADOS NO LABORATÓRIO DIAGNOSE.

Autores: Jovana Mandelli, Edinéia Zimmermann, Letícia Guerra, Roxane Susin Miranda.

Instituição dos Autores: Laboratório Diagnose Genética Médica e Biologia Molecular, Brasil.

Objetivos: Avaliar a presença de polimorfismos no gene receptor do fator de crescimento epidérmico (*EGFR*) em pacientes com câncer de pulmão. Identificar a frequência dos polimorfismos encontrados, comparando as mesmas com frequências conhecidas.

Metodologia: Exames analisados entre 2011 e 2016. As amostras avaliadas foram obtidas de biópsia inserida em formol tamponado no momento da coleta e incluídas em parafina. A partir da marcação da área tumoral de interesse, feita por médico patologista, realizou-se um corte de aproximadamente 35 mg. A extração do DNA foi executada com o kit *Wizard® Genomic DNA Purification* (Promega), utilizando-se as recomendações do fabricante. São reconhecidas mutações em 4 éxons no EGFR: uma deleção de 9-15 nucleotídeos no éxon 19 (presente em 48,2% dos casos mutados), duas mutações pontuais no éxon 21 (42,7%), além de mutações pontuais no éxon 18 (3,2%) e inserções de nucleotídeos no éxon 20 (3,7%). A análise dos polimorfismos foi realizada com o equipamento 7500 Fast Real-Time PCR System utilizando TaqMan® Genotyping Master Mix, *primers* e sondas TaqMan®, todos da *Applied Biosystems (Foster City, CA)*, seguindo as recomendações do fabricante. Para a avaliação da presença de polimorfismos foi utilizada uma sonda TaqMan® de referência. A análise foi realizada com o *Software 7500 v2.0.*6 (*Thermo Fisher Scientific).*

Resultados: Em 167 amostras avaliadas no período de 2011-2016 foram encontrados 52 (31%) casos com polimorfismos no gene *EGFR*. Os polimorfismos encontrados foram: 20 casos em L858R (38,5%), 17 casos em deleções no éxon 19 (32,7%), 4 casos em G719C (7,7%), 4 casos em G719S (7,7%), 3 casos em T790M (5,8%) e 1 caso em G719A, L861Q, H773_v774insH e V769_D77insASV (1,9%).

Conclusão: Os resultados obtidos são compatíveis com as frequências encontradas em diversos estudos, que apresentam os polimorfismos de deleção no éxon 19 e L858R os de maior prevalência, cerca de 71% (Bacchi et al., 2012).

Referências bibliográficas: Bacchi CE et al. Epidermal growth factor receptor and KRAS mutations in Brazilian lung cancer patients. Clinics (Sao Paulo). 2012;67(5):419-24.

Código #14334

Title: Expression of stem cell markers, OCT4 and NANOG in cutaneous melanoma samples.

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Institution of Authors: Universidade Federal de Goiás - UFG; Centro Universitário de Anápolis – UniEvangélica; Hospital Araújo Jorge – Associação do Combate ao Câncer – Goiânia – GO.

Objectives: To evaluate by immunohistochemistry the presence of the OCT4 and NANOG proteins in samples of cutaneous melanoma of patients attended at a public service in Goiânia - GO.

Methodology: We selected 102 cases from the Pathology Sector of Hospital Araújo Jorge, diagnosed between 2004 and 2008. The study was approved by the Research Ethics Committee. Nuclear and cytoplasmic marking was considered according to the cutoff calculated by the ROC curve. Statistical analysis was performed by SPSS® for Windows®, version 16.0. The Univariate Analysis (Odds Ratio with 95% confidence interval) was adopted, using the chi-square test ($\chi 2$) and Fisher's Exact test. Survival analysis was performed using log-rank tests and illustrated with Kaplan-Meier graphs. The significance level was 5% ($p < 0.05$) for all analyzes.

Results: Of the 102 cases evaluated, 62.7% were female and 37.3% male; With mean age of 57.2 years and 63.1 years respectively ($p = 0.0026$). The most prevalent age at diagnosis of melanoma was in the age group 51 to 70 years. The primary site most affected by melanoma was the trunk. According to the Breslow index, lesions with ≤1.0mm predominated in 40 individuals (39.2%), followed by lesions> 4.0mm with 24 cases (23.5%). According to the Clark level, 30 cases (29.4%) were classified in level IV. Survival for patients with cutaneous melanoma was 73%. There were metastases in 47% of the cases and the main sites of localization were: lymph nodes, brain, skin and lung. Hyperexpression of OCT4 (nuclear) was observed in 49% of the cases. The presence of metastasis was observed in 84% of cases with positive marking for OCT4 ($p \leq 0.0001$). Most of the verified cases of death, due to melanoma death, showed positive nuclear OCT4 marking ($p \leq 0.0001$). Hyperexpression of OCT4 (cytoplasm) was observed in 41.2% of the cases. And hyperexpression of NANOG (cytoplasm) was observed in 82.25% of the cases. For verified cases of death, due to melanoma death, 32.5% of the cases presented positive immunoblotting for NANOG (cytoplasm) ($p = 0.030$).

Conclusion: We propose here that hyperexpression of these genes that are related to pluripotency OCT4 and NANOG would be a good marker of tumor stem cells. It was evidenced that the hyperexpression of these genes presented a greater invasiveness and aggressiveness of the melanoma, being possible to suggest that the tumor stem cells would be related to the biological behavior of this neoplasm.

Código #12641

Title: *FANCD2* and *BRCA1* have differential expression among DNA repair genes in breast cancer patients.

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Objectives: The Nucleotide Excision Repair (NER) and Fanconi anemia DNA repair (FA-BRCA) pathways operate in the repair of DNA interstrand crosslinks (ICLs) and a variety of other DNA lesions, as DNA adducts, thymine dimmers and 6,4-photoproducts. Expression analyses of DNA repair genes often result in clinically relevant data, highlighting mechanisms related to tumor progression and drug response that may be used to develop appropriate therapeutic strategies. If these genes are hyper-expressed in some tumors relative to others, this may suggest that therapeutic strategies that induce DNA lesions that are repaired by these pathways are not suitable for these tumors, because these lesions can be more efficiently repaired. Moreover, if these genes are expressed at lower levels in tumors compared to non-compromised tissues, this may demonstrate that this is one of the mechanisms that increase tumor progression-related genomic instability, which may be useful in developing new molecular therapies that are more specific and efficient. The main goal of the present study was to evaluate the mRNA expression profile of important *NER* and *FA-BRCA* genes in a well-characterized sample of primary invasive breast tumors compared to a group of non-compromised tissues of the breast.

Methods: We evaluated the mRNA expression of four genes involved in NER pathway (*ERCC1, XPA, XPF* and *XPG)* and six genes involved in FA-BRCA pathway *(FANCA, C, D2, F, BRCA1* and *PALB2*) using reverse transcribed quantitative PCR (RT-qPCR) in 46 fresh primary invasive ductal carcinomas (IDC) and ten normal samples collected from the non-compromised contralateral breast. Correlations with the clinico-pathological parameters were also determined (intrinsic subtypes, age at diagnosis, tumor size, lymph-node metastasis, histological grade, estrogen e progesterone receptors status, ERBB2 expression). Non-parametric tests were chosen to analyze gene expression in the various groups.

Results: *FANCD2* gene expression was twice greater in tumors than in the non-compromised group ($p = 0.02$). When samples were classified according to the intrinsic subtypes of breast cancer, *BRCA1* gene expression was three times lower in the Luminal-B group than in the Luminal-A group ($p = 0.01$). The differences in expression among the other genes were not statistically significant.

Conclusion: The increased expression of *FANCD2* in tumors may indicate activation of the FA-BRCA pathway, which contributes to the carcinogenic process and has been correlated with resistance to chemotherapeutic agents. The loss of *BRCA1* expression in the Luminal-B group may indicate that the

use of cisplatin-based adjuvant therapies is preferable and that the use of taxane-based therapies should be avoided due to the risk of drug resistance. It is important to expand the number of samples used in this study, performing correlation analyses with drug response and survival prognostic factors.

Key-words: breast cancer, DNA repair, gene expression, FANCD2, BRCA1.

Funding source: Fundação Araucária-CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico).

Código #13417

Frequência de neoplasias observadas em heredogramas estendidos de famílias com síndrome de Li-Fraumeni – estudo preliminar

A Síndrome de Li-Fraumeni (SLF), associada a mutação germinativa no gene *TP53*, leva à predisposição a múltiplos tumores em crianças e adultos. Os grandes estudos de penetrância das diversas mutações em *TP53* (PMID: ao selecionarem apenas indivíduos testados, deixam de considerar informações relevantes da história familiar contidas no heredograma. Além disso, o pequeno número de indivíduos testados por família e a alta proporção de indivíduos afetados por câncer nestes estudos pode levar a uma superestimativa da penetrância destas variantes. No sul do Brasil, o caso peculiar da mutação fundadora p.Arg337His (prevalente em 0,3% da população) suscita mais controvérsia, uma vez que sua penetrância é descrita como mais tardia, ou mesmo menor que aquela de outras mutações.

Objetivos: Fazer levantamento dos tumores descritos em famílias com SLF acompanhadas no Departamento de Oncogenética do Hospital de Câncer de Barretos. Comparar a incidência cumulativa de câncer entre famílias contendo portadores de mutação p.Arg337His e famílias contendo portadores de outras mutações em *TP53*.

Metodologia: Revisão de registros de família com coleta de dados retrospectiva dos heredogramas, do lado da família portador da mutação. O acompanhamento das famílias ocorreu de agosto/2011 a março/2017.

Resultados: Em um universo amostral de 1889 indivíduos (911 mulheres, 778 homens e 200 de gênero não especificado no heredograma), provenientes de 70 famílias, foram identificados 466 casos de câncer. Os diagnósticos mais frequentes no sexo feminino foram os carcinomas de mama (119 casos), colorretal (19 casos) e sarcomas de partes moles (19 casos). No sexo masculino, os casos mais comuns foram de estômago (23 casos), próstata (21 casos), pulmão (20 casos) e sarcoma de partes moles (17 casos). Em indivíduos com idade ≤ 25 anos, a ordem de ocorrência foi: carcinoma adrenocortical (20 casos), sistema nervoso central (7 casos) e leucemias (7 casos). A frequência de tumores não apresentou diferença estatística entre as famílias contendo mutação p.Arg337His (55 famílias) e aquelas com outras mutações em *TP53* (15 famílias), tanto na avaliação geral, quanto na avaliação ajustada para gênero ou para o subgrupo ≤ 25 anos.

Discussão: A ocorrência de tumores relativos à SLF em indivíduos não testados é obviamente útil ao fornecer critérios para a indicação de teste molecular em determinada família. Na dificuldade de ampla oferta do exame, lançamos mão dos relatos contidos nos heredogramas para obter indícios de que o fenótipo associado à mutação p.Arg337His não difere daquele visto em outras mutações detectadas em nossa casuística. Análise prospectiva dos indivíduos portadores e não portadores em famílias afetadas, em estudos colaborativos multicêntricos, é fundamental para maiores esclarecimentos acerca dos fenótipos associados a mutação germinativa em *TP53*.

Código #13293

Title: Gene expression computational analysis of possible biomarker of gastrointestinal tumors

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Aim: To compare *TULP3* expression levels between tumoral and non-tumoral adjacent tissues in different types of carcinomas of gastrointestinal organs such as Esophageal Carcinoma (ESCA), Gastric Cancer (GC) and Colorectal Cancer (CC).

Methods: Gene expression (GE) data from patient biopsies were obtained from GEOdatabase and TCGA public repositories. GEOdatasets were downloaded under accession numbers GSE26886 and GSE1420 for ESCA, GSE79973 and GSE33335 for GC and, GSE21510 and GSE24514 for CC. Data from TCGA comprised ESCA, STAD, COAD and READ studies (Stomach, Colon and Rectum Adenocarcinomas, respectively). GE raw data were normalized using *affy, limma* or *oligo BioConductor* R-packages. To select a single probe to represent a gene, we used JetSet score for *Affymetrix* microarrays. Data normality assumptions were verified and appropriate statistical test was chosen. Survival analysis was performed using *survival* R-package. Analyzes were performed in R 3.2.3 software. Prognostic value of *TULP3* expression was analyzed in GC using Kaplan-Meier Plotter tool (KMplotter), a manually curated database, different from all studies downloaded for this work.

Results: *TULP3* GE comparison between groups for ESCA (p=3.21e-06), GSE26886 (p=2.03e-06) and GSE1420 (p=0.01) showed significant statistical differences. In ESCA, *TULP3* GE could differentiate Esophageal Adenocarcinoma (ADC) from Esophageal Squamous Cell Carcinoma (SCC); in GSE26886, GE was different for Barret's Esophagus and in GSE1420, was different for non-tumoral group. Survival analysis for ADC assigned a bad prognosis for patients who had high *TULP3* levels (log2<4.36) (p=0.03, HR=2.11(1.05-4.21)), while for SCC, a poor prognosis was associated with low *TULP3* GE (log2>4.84) (p=0.03, HR=0.46(0.22-0.94)). *TULP3* comparison between groups for STAD (p=0.02) and GSE33335 (p=1.55e-09) were statistically significant and showed that GC groups have a higher expression than non-GCs. Survival analysis for Diffuse and NOS (Not Otherwise Specified) type of STAD assigned bad prognosis for patients with high *TULP3* levels (log2<4.91) (p=0.04, HR=2.93(1-8.54)) and (log2<5.05) (p=3e-04, HR=3.42(1.69-7.00)), respectively. KMplotter revealed a bad prognosis for patients with high *TULP3* expression (p=0.006, HR=1.97(1.21-3.22)) in GSE62254 dataset. Additionally, KMplotter analysis for Diffuse type in the same dataset assigned bad prognosis for patients with high *TULP3* levels (p=0.013, HR=2.22(1.17-4.23)). *TULP3* comparisons between groups for COAD (p=3.54e-12), READ (p=0.0045), GSE21510 (p=4.99e-06) and GSE24514 (p=0.006) were statistically significant and also revealed a higher *TULP3* expression in tumoral groups than in

non-tumoral ones. A poor prognosis in COAD and READ studies was associated with patients with low *TULP3* expression (log2<-0.781) (p=0.009, HR=0.37(0.17-0.80)) and (log2<4.55) (p=0.02, HR=0.35(0.13-0.89)), respectively.

Conclusion: These preliminary results highlight *TULP3* as a possible prognostic biomarker.

Código #13409

Title: GENETIC ADVICE IN BREAST CANCER AND / OR OVARIAN: CONTRIBUTIONS OF PSYCHOLOGY

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Objectives: To present the contributions of psychology department to the genetic counseling group and to present an overview of the population served at HCIII / INCA and their expectations regarding the predictive test.

Methodology: the institution's clinical staff perform the referral of patients, and / or relatives, to Genetic Counseling (GA), which includes the various direct care professionals. The first consultation is scheduled with the geneticists, who will evaluate the indication, following the medical criteria for predictive testing. Those who had their indication confirmed are forwarded to a psychological evaluation. In the first interview, is searched to know what are the personal motivation, for beyond the medical indication and, the knowledge degree of and/or expectation about the possible results and implications in everyday life. Evaluate the patient/family cognitive ability. Collect the previous story of psychiatric disorder, such as depression, schizophrenia, panic disorders or any other that, without stabilization possibility that can indicate that it will create a difficult in the elaboration process of whatever is the result of the test and that will interfere, in a harmful way, In the way of life.

Results: Clinical praxis demonstrates that the population served reports that there is an expectation that the forward to the GA and, and as a consequence, the testing, ensure to know the cause of the Cancer and a control/guarantee of a possible relapse. After that, the speeches is about the heredity, that is, they seek not only to know about the mutation but also to ensure that their next generations will not be reached. Then we see a concern for self-care and on the other that can generate diverse behaviors that can interfere in the familiar ties. There is speech whose expectation is *related* with the guarantee of a prophylactic surgery, especially that one is associated with the mastectomy.

Conclusion: Although based on an objectification, the expectation and confirmation of the presence of a Genetic alteration, by itself, is capable of producing both organic and psychic effects. This way the AG presents a meeting of subjective questions with the concepts of probabilities. With the Technical-scientific advancing and the Age of globalization, in which the information transits almost instantaneously, do not prevent patients and families from building expectations that we cannot yet respond to, especially concerning cure or non-recurrence. We remember that we deal with types of cancers that affect in an incisive way the various roles that the woman plays in the present day. Hence, the Importance of the GA team for breast and / or ovary cancer has resumed in the last three years its multi professional character. In this team, the consultations are not the only moments

of deliberation about testing, as well the reporting the results. There is a construction that is based on Spaces of learning and discussion of clinical cases. The learning about genetics and questions about subjectivity, as advocated by the American Society of Human Genetics in defining AG. The universe of this work is intense in front of a population of a Reference Center, in function this the researches of post-test is still ongoing.

Código #13256

Genetic alterations detected by comparative genomic hybridization in BRCAX breast and ovarian cancers of Brazilian population

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Abstract

Objectives: The aim of this study was to identify the causal or contributing factors associated with BRCAX tumors. For that, we performed chromosomal and subchromosomal copy number alterations analysis in tumor samples from Brazilian women without *BRCA1*/*BRCA2* germline mutations with family history strongly suggestive of HBOC. This cases are grouped as BRCAX category and very little is known about the genetic bases of these tumors, even though morphological studies have shown that these tumors are histologically heterogeneous, with varying levels of estrogen and progesterone receptors.

Methods: The SurePrint G3 Unrestricted CGH 8×60K microarray (Agilent) were used to detect the most frequent gains and losses in formalin-fixed paraffin-embedded (FFPE) tumors. A cohort of 31 Brazilian women at-risk for HBOC (27 breast and 4 ovarian cancers) and without mutations in *BRCA1*/*BRCA2* were included following criteria: patients diagnosed with breast/ovarian cancer at an early age (<55 years) and absence of male BC.

Results: In the present study, it was found 20 gained regions and 31 losses in BRCAX tumors by GISTIC algorithm. The more frequent gains observed in ovarian cases were 8q24.13 and 8p12-p11.23 and losses of 8p23.3, 10q26.3, 15q11.1 and 16q23.1 in BRCAX cases, similarly to other previous studies. However, it was found new regions associated with family history of ovarian cancer as for example the loss of 22q13.31-13.32 in 100% of ovarian cancers. Regarding breast cancer cases, the more frequent gains observed were 1q21.2, 6p22.1 and 8q24.13 and losses 8p23.3 and 17p13.1-p12 in BRCAX cases, similarly to other previous studies. Gain of Xq26 and loss of Xp22.32-22.31 were most frequently in ovarian cancer 100%, compared with breast cases 26% (P=*0.01* for both regions). Loss of 22q13.31-13.32 were detected more often in ovarian (100%) than in breast cancer (40%) (*P*=0.05). This region was also clinically associated with the presence of ovarian family history at 75% of cases (*P*=0.03).

Conclusions: Despite of the poor quality of FFPE samples, the results from this study show alterations in concordance with previous findings from the literature also analyzing BRCAX families. In addition, we identify new altered regions of BRCAX that showed significant association with family history of ovarian cancer. Further studies are necessary to integrate these findings with other molecular alterations to better understand the BRCAX heterogeneous subtype of hereditary tumors.

Keywords: BRCAX, hereditary breast cancer, hereditary ovarian cancer, hereditary breast and ovarian cancer predisposition syndrome, CNV alterations.

Código #14316

Title: Genetic predisposition of *CIITA* polymorphisms with Disability progression markers in multiple sclerosis patients

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Objectives: Multiple sclerosis (MS) is the most prevalent autoimmune inflammatory demyelinating disease of the central nervous system (CNS) in young adults. The natural history of MS has been charted extensively, but there are no easy-to-use references of disability outcomes that would enable individual patients to determine how their disability compares to others with similar disease duration. The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in MS and monitoring changes in the level of disability over time. To date, association of many genes polymorphisms with the prevalence and progression of the disease have been investigated. In the present study, the impact of *CIITA* -168A/G (rs3087456) and *CIITA* Gly500Ala (rs4774) polymorphisms on the risk of disability progression (EDSS>3) in MS was evaluated in a sample of the Rio de Janeiro.

Methodology: All patients were followed up and clinically reassessed at three-month intervals in the outpatient clinic of the CNS Idiopathic Inflammatory Demyelinating Diseases Unit for UFRJ. Genotyping was performed on 114 patients underwent clinical evaluations using EDSS. Genomic DNA was extracted from blood collected on filter paper (Flinders Technology Associates) according to Bereczky *et al* between January 2010 and July 2015. In order to genotype the polymorphisms; we used the SNPlexTM Genotyping System 48-plex technology and ABI3730xl equipment (Applied Biosystems, Foster City, CA, USA). We used the GeneMapper v.4.0 Software (Applied Biosystems, Foster City, CA, USA) to identify the SNP genotypes from fluorescence signals. Allelic and genotypic frequencies were calculated by direct gene counting. Logistic regression analyses were used to calculate corresponding *P*-values for the association of each genotype and It has been achieved EDSS3 <3 and ≥3, while controlling for the confounding effects of sex and disease duration.

Results: The distribution of allelic frequencies of the *CIITA* -168A/G and *CIITA* Gly500Ala in our studied population were 0.12 and 0.16 respectively. Applying a Multinomial Logistic Regression it has been observed an association between the *CIITA* -168A/G (*P*=0.007) and *CIITA* Gly500Ala (*P*=0.005) and a possible development of EDDS ≥3.

Conclusion: *CIITA* is a 42-kb gene locating on chromosome 16p13 and encodes the non-DNA-binding coactivator for MHCII. *CIITA* plays a vital role in inflammatory response and in T cell-dependent immunity. In this study, the frequencies and statistical results may be suffering an effect of small sample size, but this is a pilot study and is the first study related to the potential association of

polymorphisms in *CIITA* gene disability progression markers. Indeed, in a nearby study with a larger population there is a change of statistical relevance between the comparisons of these genotypes frequencies.

Código #13308

Title: IDENTIFICATION AND ANALYSIS OF VARIANTES IN *ATM* IN INDIVIDUALS AT RISK FOR HEREDITARY BREAST CANCER.

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Abstract:
Goals: Breast cancer (BC) is the most common neoplasia in women, and it can be caused by mutations in high penetrance genes (*BRCA1* and *BRCA2*), characterizing Hereditary Breast and Ovarian Cancer (HBOC) Syndrome. However, genes with moderate penetrance also contribute for cancer, such as *ATM*, with a relative risk of 2.3 for the development of BC. *ATM* is compound by 62 exons translated, codifying a protein involved in monitoring and DNA repair. Considering the difficulty of sequencing the whole gene, due to its size, this work aims to search *hotspots* regions in *ATM*, estimating the prevalence of pathogenic variants and elucidating the significance of variants of uncertain significance (VUS) *in silico.*

Methods: *Hotspot* regions were identified through literature review. Non-related individuals with HBOC clinical criteria (NCCN) were selected after sign free and informed consent (CEP-HCPA 04/170, 03/018, 11/0427 e 10/0521). Genomic DNA was obtained from peripheral blood and exons 26, 37, 41 and 49 were amplified by PCR, followed by sequencing by capillary electrophoresis (Sanger). *In silico* tools and comparative modeling were used for analysis of VUS. Chi-square test were used for statistical analysis and calculated by SPSS software (v. 19, IBM Company).

Results: We included 111 subjects, of which 101 had personal history of BC. The rest present diagnosis for other neoplasia, but family history of breast cancer. The age of first diagnosis was 41.22. We found 13 variants in the regions sequenced: five variants were intronics and eight, contained in exon 26, 37, 41 and 49. Between exonics variants, two variants were VUS, three were not identified in ClinVar database and three, benign. Allelic and genotypic frequencies were calculated for each variant and compared with 1000 Genomes and ExAC Browser. Four variants presented a significant different frequency when compared with the control population frequency. VUS were evaluated by tools of mutational effect and comparative modeling, and c.6025C>T presents a possible pathogenic significance.

Conclusions: This was the first study in Brazil to evaluate the mutational spectrum of *ATM* gene in individuals at risk of hereditary BC. It was identified a high frequency of VUS and additional analyses are necessary to establish the pathogenicity of these variants.

Código #13316

Title: IDENTIFICATION OF PATHOGENIC RAD51C MUTATIONIN THE CLEAR CELL RENAL CELL CARCINOMA

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Objective: Description of a patient diagnosed with clear cell renal cell carcinoma (CCRCC), with pathogenic RAD51C mutation, as a new variant recognized in CCRCC.

Methodology: Descriptive case report through clinical exams such as magnetic resonance imaging, ophthalmologic and neurological exam, histopathological nephrectomy and molecular analysis. In order to obtain genetic data, VHL gene sequencing was performed by MagNa Pure / Roche platform, followed by sequencing of 79 genes related to hereditary cancer (Invitae- Multi-Cancer Panel / Illumina Technologies).

Results: Male patient, 41 years old, hypertensive, with a family history of cancer (father: prostate cancer; paternal grandmother: intestine cancer, brother: CCRCC). Magnetic resonance imaging of the upper abdomen showed a nodule at the upper pole, measuring about 1cm. After the histopathological assessment of the nodule collected in the partial nephrectomy, CRCC was appointed as cause. Due to the family history of cancer, suspicion of Von Hippel Lindau Syndrome (VHLS) was raised, but the ophthalmological and neurological evaluation did not present alterations, besides the absence of pheochromocytoma. For confirmation, the VHL gene sequencing was performed and no alteration was found, thus discarding the diagnosis of VHLS. The patient then performed the sequencing panel, where a heterozygous mutation was found in exon 5 of the RAD51C gene, c.709C> T (p.Arg237 *). After the diagnosis, RAD51C gene sequencing was performed in his brother, where this variant was not found.

Conclusion: The patient described herein has a genetic variant on the RAD51C gene that was previously associated with breast and ovary tumors. Such gene has a function on the DNA's repair system and its overexpression leads to tumor progression. The c.709C> T variant creates a premature stop code, leading to the absence or incomplete formation of the protein and consequent loss of function, thus being considered pathogenic. In 5% of cases, CCRCC is associated with hereditary syndromes, such as VHLS. In addition to specific pathological features, VHLS is characterized by mutations in the VHL gene. However, in the case described, no variation was found, thus eliminating this diagnosis. Therefore, based on the genetic evaluation of the patient and the brother, it is not possible to characterize them with a predisposition to hereditary syndrome, however the occurrence of a tumor with high frequency in the population, with a pathogenic mutation not yet described for such lesion, is verified.

Código #13305

Title: IDENTIFICATION OF THE POLYMORPHISMS IN THE UPSTREAM REGULATORY REGION - 5'URR OF THE *HLA-G* GENE IN PATIENTS WITH BREAST CANCER IN SANTA CATARINA

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Aim: To investigate polymorphisms of the promoter region (5'URR) *HLA-G* gene in women with breast cancer and with no evidence of mammary carcinoma, in order to obtain informative parameters for diagnosis and prognosis population of Santa Catarina. Observe the variability of the 5'URR of *HLA-G*, calculate the allelic and genotype frequencies of the polymorphic *loci* found in the 5'URR of *HLA-G* in patients with breast cancer *versus* controls and verify whether there is an association within alleles and genotypes with breast cancer.

Methodology: We investigated 50 samples of breast cancer patients (cases) in treatment at the University Hospital Professor Polydoro Ernani de São Thiago (HU - UFSC) and 50 samples from women with no evidence of breast cancer (control). The extraction of the genomic DNA from the samples using the Salting Out method was done. The region was amplified by polymerase chain reaction (PCR), confirmed in 1% agarose gel and afterwards sequenced. Estimates of the allele and genotype frequencies of each *locus*, in cases and controls were made by the GENEPOP version 4.2. The association analysis were verified by using the Odds Ratio (OR) indicator, 95% confidence interval (CI) and p=0.05 as the limit value of significance (HDS Epimax).

Results: Through the analysis of the DNA sequences of the *HLA-G* 5'URR, 21 polymorphic sites were identified. Among these, the following associations were observed for the polymorphisms -689A>G alleles A (OR=0.084 p=0.000) and G (OR=11.963 p=0.000), A/A (OR=0.070 p=0.000) and G/A genotypes (OR=7.5 p=0.003); -633G>A A/A genotype (OR=0.356 p=0.039); -486A>C alleles A(OR=2.308 p=0.010) and C (OR=0.433 p=0.010), the C/A (OR=3.469 p=0.029) and C/C genotypes (OR=0.279 p=0.006); -483A>G alleles A (OR=4.164 p=0.011) and G (OR=0.240 p=0.011); -443G>A alleles A (OR=3.337 p=0.057) and G (OR=0.3 p=0.057); -400G>A alleles A (OR=9,764 p=0.021) and G (OR=0.102 p=0.021); -256TC>T alleles C (OR=0.406 p=0.008) and T (OR=2.464 p=0.008), the T/T genotype (OR=2.955 p=0.034); -201G>A alleles A (OR=0.246 p=0.000) and G (OR=4.070 p=0.000) and the A/A (OR=0.237 p=0.005) and G/G genotypes (OR=3,962 p=0.005).

Conclusion: The -689A>G A, -486A>C C, -443G>A G, -400G>A G, -256TC>T C alleles at 5'URR were more frequent in controls and are associated with the protective effect against the development of the disease, and also, these homozygous alleles confer protection. When considering the -633G>A

polymorphism, the A/A genotype has a protective effect. The heterozygotes for the -689A>G A/G and -486A>C A/C sites represent a risk for the development of breast cancer, as well as the alleles -483A>G A e -201G>A G more frequent in patients. The *HLA-G* polymorphisms are associated to various disorders, among these, to tumors. The sites of variation of 5'URR may imply in the regulation of gene expression, as these polymorphisms are inside or close to the transcriptional regulatory elements.

Código #13207

Impact of Genetic Counseling and Genetic Testing on High-Risk Hereditary Breast and Ovarian Cancer (HBOC)

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Objectives: To evaluate the impact of genetic counseling (GC) and genetic testing (GT) on a convenience sample of families at-risk for hereditary breast and ovarian cancer from the Department of Oncogenetics from Barretos Cancer Hospital.

Methods: The study has four moments: M1- Before GC; M2- After GC session and blood drawn for GT; M3- after GT result, and M4- performed 6 to 12 months after the result of GT. In M1 pedigree, genogram and ecomap were build and several questionnaires were applied (the Lerman's Cancer Worry (CWS), Cancer Awareness Needs Survey (CANS), Champion's Health Belief Model Scale (CHBMS), Scale Modes of Confronting Problems (EMEP), Hospital Anxiety and Depression Scale (HADS)). At M2 and M3 the HADS and CWS and CANS were re-applied. At M4 all the questionnaires were applied over again and the pedigree, genogram and ecomap were re-build. In this study, the significance of 0.05 was considered. In addition, qualitative analysis was performed based on the Grounded Theory.

Results: 40 women were included in the study and have M1 and M2 completed. Of them, 6 have pathogenic mutation, 20 are WT and 1 have a variant of unknown significance (total of 27 women completed M3). The mean age of the participants was 40 years old (SD = 9.77), and 34 (85%) had a diagnosis of breast cancer and 6 (15%) are distributed in ovarian cancer e bilateral breast cancer. The application of CANS showed risk perception for breast and ovarian cancer less than or equal the general population, even considering the family history of cancer and presence of mutation. The CHBMS showed a lower mean score in the susceptibility scale (7.6; SD = 2.92), showing that this group has low perception of their cancer risk. However, the CWS showed a greater concern to develop cancer in M1, M2 and M4. The average score calculations for anxiety and depression at all times did not have a significant difference, but more individualized analyzes, demonstrated the presence of cases with moderate to severe anxiety at all times. The EMEP showed that the participants have the strategy of coping with a problem through the search for religiosity. The genograms and ecomaps were categorized and common data were: 1-Conflicts with relatives of first degree, which might interfere in behaviors when the genetic test has a positive result causing an impediment in the preventive monitoring of the family since the dialogue can be difficult; 2-The proximity with first-degree relatives, which may facilitate the dynamics of the GC process; 3-The presence of religiosity, which may suggest that religiosity can be a positive factor for individuals to deal with the situation but it also might stop

the preventive attitude since the feeling of protection through religion is sufficient.

Conclusion: The obtained data demonstrate the need to understand all the GC and genetic test process that the individual can adequately follow prevention and control strategies. This study has support from FAPESP.

Código #13415

Título: **LIPOID PROTEINOSIS: CASE REPORT**

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Introduction: Lipoid Proteinosis (LP) or Urbach-Wiethe syndrome (OMIM 247100) is a rare (unknown prevalence) autosomal recessive genodermatosis caused by loss-of-function mutation in *ECM1* (Extracellular Matrix Protein 1) gene, 1q22, associated with hyaline-like material deposition that lead to multisystemic involvement. This gene has a role in physiology and homeostasis of the skin and many other tissues. In general, the patients develop a hoarseness voice since birth, multiple vesicles that can advance with crusts, and thickening of dermis caused by hyaline deposition. Seizures, memory impairment, alopecia and moniliform blefarosis can be part of clinical presentation.

Objective: Report a case of patient diagnosed with LP.

Methods: Case report.

Results: A 31-year-old female patient with hoarseness since birth, presented subcutaneous cystic lesions with white and thick secretion in the back, inguinal region, face and neck and areas with thickening of the skin. Two years ago she started to complain of short-term memory impairment. There were no reports of convulsive episodes or dysfunction of the salivary glands. Her parents are non consanguineous, but they are from the same small town in Bahia; there are no similar cases in the family, although her grandmother presented some cysts in the back without diagnosis. In the physical examination she had hoarseness; hypoplasia of the fifth toes; thickened regions on the skin, regions with scars some with discharge, and moniliform blefarosis. The diagnosis was established by Eosin-Hematoxylin and periodic acid-Schiff biopsy of thick skin on the back and eyelids has evidenced: dermal fibrotic scar skin and hyaline vessel wall thickening.

Conclusion: LP is a rare condition, with low rates of death, but it has a multisystemic presentation that may strongly impact quality of life. Therefore, it has to be known by physicians to promote an earlier diagnosis, unlike our patient, giving a better quality of life for these patients and appropriated management. This patient has a recent diognosis, so we don't have knowledge about her response to treatment with D-penicillamine, oral dimethyl sulfoxide, acitretin, topical corticosteroids, or carbon dioxide laser. The best treatment for her has not yet been defined and the patient reported the use of nonsteroidal anti-inflammatory drugs without a good response. Their parents are non consanguineous and probably there is

a founder effect, although she didn't Known other people from their family or in their city (Conceição de Coité) with a similar phenotype. Taking into account this possibility of a founding effect, that this condition is very rare, and knowing that the diagnosis can be late or even occur due to lack of suspicion, it is important to publicize this case to improve the suspicion of this diagnosis and thus the management.

Código #13314

Título: Malignant neoplasms in patients with Neurofibromatosis type 1: retrospective cases reviews.

Autores: Bárbara Nasr[1], Ana Carolina Bonini[1], Mireille Gomes[1], Anna Cláudia Evangelista[1].

Instituição dos autores: 1. Instituto Nacional de Câncer José Alencar Gomes da Silva.

Aim: The purpose of current study is describe types of cancer associated with NF1 in 28 patients referred to INCA's Clinical Genetics Clinics for genetic counseling. The association between NF1 and malignant tumors has been widely described; the most common reported associations are with gliomas, malignant peripheral nerve sheath tumors, leukemia, pheochromocytoma and rhabdomyosarcoma. Concerning the association between NF1 and breast cancer, only a few cases have been reported. Methods: We performed a retrospective chart review of twenty-eight patients with NF1 at INCA's Clinical Genetics Clinics for genetic counseling. So far, we analyzed age of diagnosis, family history, physical exam and evolution for cancer. Results: The mean age of NF1 diagnosis was 64, 93 months (SD: 63, 18 months, minimum 1 month and maximum 192 months of age). Eleven patients were diagnosed with central nervous system tumor; 5 with optic gliomas, 2 astrocytoma, 2 posterior fossa tumor, 1 medial fossa tumor and 1 mesencephalon, thalamus and optic pathways. We identified a total of four different tumors types: malignant astrocytoma (2), neurofibrosarcoma (1), rhabdomyosarcoma (1) and breast cancer (2). Regarding to family history, 2 patients had first degree relatives with breast cancer. Discussion and Conclusion: The types of cancer found in our sample were similar to those found in the medical literature. Even if the association between breast cancer and NF1 is rarely reported, the few studies found in the literature suggest that women with NF1 are at a higher risk of developing breast cancer when compared to the general population. Interestingly, *NF1* gene and *BRCA1* gene are both located in the peri-centromeric region of the long arm of chromosome 17 and about 28% of sporadic breast cancers are missing at least one copy of the *NF1* gene, either due to deletion or mutation. The findings of the above-mentioned reports and other published data justify the requirement of specific screening programs for breast cancer in NF1 patients. Moreover, cancer management in this population is not well defined; especially when some available data suggests that the risks of fibrosarcomas are increased by radiation when a conservative approach is chosen for this population. Counseling of patients and their families should provide a realistic overview of possible clinical complications, while emphasizing that most individuals with NF1 have healthy and productive lives.

Código #13328

MICROSSATELLITE INSTABILITY IDENTIFICATION IN A SAMPLE OF ENDOMETRIOID CARCINOMA OF ENDOMETRIUM WITH POSITIVE IMMUNOHISTOCHEMISTRY FOR MLH1, MSH2, MSH6 AND PMS2

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Objective: To determine the occurrence of microsatellite instability (MSI) cases of endometrioid carcinoma of endometrium with presence of MLH1, MSH2, MSH6 and PMS2 proteins identified by immunohistochemistry (IHC) reactions.

Methods: The sample consisted of 43 cases of endometrioid carcinoma of endometrium with biopsies preserved in paraffin blocks stored at the Pathology Service of the Ribeirão Preto Clinics Hospital, collected between 2005 and 2016. All biopsies selected were positive for MLH1, MSH2, MSH6 and PMS2 proteins, identified by IHC reactions. DNA was extracted from normal and tumor samples in each case. The MSI status was analysed using a panel of five mononucleotide microsatellite markers (BAT26, BAT25, NR21, NR24 and NR270) in a fluorescent multiplex PCR-based assay followed by capillary electrophoresis separation and analysis of the output data with PeakScanner v.1.0 software. The markers that showed amplified alleles in tumor DNA, not observed in the respective normal tissue DNA, were considered unstable. Tumors were classified as: High Instability (when two or more of the five markers showed instability); Low Instability (when only one of the markers was unstable) and Stable (when none of the markers showed instability).

Results: Of the 43 cases evaluated, four (9.30%) presented microsatellite instability, all of them classified as High Instability.

Conclusion: More than half of the women with Lynch Syndrome (LS), an autosomal dominant condition predisposing to tumors - particularly colorectal and endometrial - , develop endometrial cancer as the“sentinel cancer”. The data from this study showed that a screening approach to LS from endometrial cancer, composed only by the immunohistochemistry technique, is not sufficient to detect all the probable carriers of this syndrome, emphasizing the use of MSI analysis as a complement to the IHC in the investigation process of SL. [Financial Support: CAPES, CNPq, AND FAEPA].

XXIX CONGRESSO BRASILEIRO
GENÉTICA MÉDICA 2017
Bento Gonçalves | 20 a 23 de junho
Da Pesquisa à Prática Clínica

Fellinievents

Código #12634

Título: MODULAÇÃO DE GENES DA VIA HORMONAL DE CÉLULAS TUMORAIS DE CÂNCER DE MAMA APÓS TRATAMENTO COM O EXTRATO DE *Azadirachta indica*.

Autores: Deisi L. Braga; Sara T.S. Mota; Mariana A.P. Zóia; Lara Vecchi; Antonielle O. Cordeiro; Bruno H. S. Dias; Jimi Nakajima; Cristina R. Fürstenau; Luiz R. Goulart; Thaise G. Araújo.

Instituição dos Autores: UFU-Universidade Federal de Uberlândia, Laboratório de Nanobiotecnologia e Laboratório de Genética e Biotecnologia

Objetivos: O Câncer de Mama (CM) é uma doença que engloba inúmeras entidades com características biológicas e comportamentais diferentes, que são favorecidas por sua complexidade molecular. A *Azadirachta indica* (nim) tem sido utilizada em diversas patologias, com potencial aplicação no tratamento do câncer, uma vez que apresenta compostos fenólicos. O presente estudo objetivou avaliar a resposta das linhagens MCF-10, MCF-7 e MDA-MB231 aos extratos etanólicos das folhas de *Azadirachta indica* (EEFN) obtidos por solventes diclorometano (DCM) e acetato de etíla (AE), seguida da quantificação da expressão dos genes *ESR1, ESR2, AR, AR-V7, AR-V4* e *AR-V1*(via hormonal).

Metodologia: Os fenóis totais foram determinados conforme o método de Folin-Ciocalteau, com uma maior quantidade verificada em DCM (P<0,0001). Ensaios de MTT foram realizados nas três linhagens em tratamentos de 24 e 48 horas e a extração do mRNA ocorreu antes e após o tratamento por 48 horas, com as concentrações de 0,03125 µg/mL para DCM e 1,0 µg/mL para AE, definidas por MTT. Os fenóis totais foram determinados conforme o método de Folin-Ciocalteau, com uma maior quantidade verificada em DCM (P<0,0001). Ensaios de MTT foram realizados nas três linhagens em tratamentos de 24 e 48 horas e a extração do mRNA ocorreu antes e após o tratamento por 48 horas, com as concentrações de 0,03125 µg/mL para DCM e 1,0 µg/mL para AE, definidas por MTT.

Resultados: Verificou-se um perfil transcricional esperado dos genes de interesse nas linhagens estudadas sem tratamento. No tratamento com EEFN/DCM houve aumento da expressão dos genes *AR-V1, AR-V4, AR-V7* (em MDA-MB231 P<0,05) e a redução na expressão do *AR* e *ESR2*. A expressão do gene ESR1 aumentou na linhagem MCF-7 e reduziu em MDA-MB231. O tratamento com EEFN/AE mostrou aumento do gene *AR-V4* e a redução na expressão da *AR-V1* e *AR*. Os genes *ESR1* e *ESR2* tiveram sua expressão aumentada na linhagem MCF-7 e reduzida em MDA-MB231, enquanto o gene *AR-V7* (P<0,01) aumentou em MDA-MB231 e reduziram na linhagem MCF-7.

Conclusão: Os resultados mostram efeito diferencial do EEFN nas linhagens tumorais. As respostas encontradas com o gene *ESR2* em MCF-7 e *AR-V7* em MDA-MB231 apontam um possível alvo terapêutico do EEFN no CM.

Código #13375

Molecular characterization of colorectal cancer patients diagnosed at young age.

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The study aimed to identify patients / families at risk for Lynch Syndrome (LS) through molecular, histopathological and family history. We included 257 patients diagnosed with colorectal câncer (CRC) under the age of 50, treated at the Hospital de Cancer de Barretos, from 2006 to 2010. We performed a retrospective collection of family history and histopathological data, and analyzed the presence and frequency of the p.V600E mutation in the *BRAF* gene, microsatellite instability (MSI) and methylation of the *MLH1* gene. 257 patients were tested for presence of the p.V600E mutation. Of these, we obtained 238 results, with a minimum age of 19 years, maximum of 50 years and mean of 41.3 years at diagnosis (SD = 6.81). The 16 patients mutated (6.7%) for p.V600E had a mean age of 42.7 years and no positive first-degree family history for LS associated tumors. Among the 222 wild type (WT) (93.3%), the mean age was 41.2 years and 8.2% had a first-degree positive family history for tumors associated with LS. MSI analysis was performed for 200 patients. We identified 155 MSS patients (77.5%), 30 MSI-High (15%) and 15 MSI-Low (7.5%). MSS patients had a mean age of 42.1 years, versus 39.2 years for MSI-High and 43.46 years for MSI-Low (p = 0.035). 7 MSI-High patients had a family history suggestive of LS as well as 6 MSS patients. A suggestive family history of LS was not observed in patients with MSI-Low tumor (p = 0.002). Comparing results of the p.V600E mutation in the *BRAF* gene with the MSI, we found that among the 183 *BRAF* WT cases, 138 were MSS (75.4%), 30 MSI-High (16.4%), 15 MSI-Low (8.2%). The 14 cases mutated were MSS (100%) (p = 0.183). As for methylation of the *MLH1* gene, among the 177 analyzed samples, 170 were unmethylated and 7 methylated. The mean age at the unmethylated diagnosis was 41.5 years and the methylated was 39.3 years (p = 0.195). As regards the presence of the p.V600E mutation in the *BRAF* gene and the presence and absence of *MLH1* gene methylation, we found 158 unmethylated (92.9%) and 7 methylated (100%) with WT result for *BRAF* and 12 unmethylated (7 , 1%) with mutated *BRAF*. Comparing the methylation of the *MLH1* gene with MSI, 97 (75.8%) of the unmethylated patients were MSS, 20 (15.6%) MSI-High and 11 (8.6%) MSI-Low. Among the methylated patients 1 (16.7%) was MSS and 5 (83.3%) MSI-High. Relating the results of *BRAF*, MSI and methylation, we found 20 patients with LS characteristics (*BRAF* WT, MSI-High, unmethylated). We hope that the characterization of these patients may contribute to the identification of patients / families at risk of hereditary CRC, decreasing the expenses with expensive and unnecessary genetic tests, besides enabling the identified patients will be directed to specific programs of monitoring and treatment.

Código #12642

Title: *PCA3* complexes in prostate malignant transformation

Autors: Matheus Alves Ribeiro[1], Adriana Freitas Neves[2], Nilson Nicolau Júnior[3], Douglas Alexsander Alves[1], Sara Teixeira Soares Mota[1], Luiz Ricardo Goulart[4,5], Thaise Gonçalves Araújo[1]

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Objetives: *PCA3* gene has been characterized as antisense to the human homolog of the Drosophila prune gene (*PRUNE2*), associated with the loss of prostate homeostasis, resulting in malignant transformation. Defined as long non-coding RNA (lncRNA), PCA3 binds to intron 6 of the pre-mRNA of *PRUNE2* which is later regulated by ADAR (adenosine deaminase-no-RNA) family enzyme. Although *PCA3* has been well accepted clinically as a diagnostic tool, its molecular biology has not yet been elucidated. This work aimed to depict the entire complex (*PCA3*-*PRUNE2*-ADAR1) and its implications in neoplastic process.

Methodology: Modeling of RNA-RNA interaction prediction (RRIP) was performed by in silico methods with the programs SimRNA and intaRNA. Unprecedented modeling of the ADAR1 protein binding site was supported by Modeller-HHPred, Robetta and Rosetta software. Thousands of predictions were generated, of which the best was ranked by the dDFire program.

Results: Currently, PCA3 is the most specific biomarker for CaP, and elucidating the molecular behavior of this gene in tumor cells is essential for understanding prostate carcinogenesis. For *PCA3-PRUNE2* complex, the RRIP proposed the most stable binding location. Considering ADAR1 modeling, the 10 best archetypes were selected. Our results had demonstrated new possible targets for prostate cancer treatment and new insights to better understand malignant transformation.

Conclusion: The successful modeling of ADAR1 on the binding-site of *PCA3-PRUNE2* complex, and the RRIP for RNA molecules, created new strategies for prostate cancer management. Combined efforts and multiple analyzes are crucial to develop new study strategies, including bioinformatics and molecular assays, to unravel the possible implications of *PCA3* in prostate cancer.

Código #13272

Título: *POLQ* GERMLINE MUTATIONS IN PATIENTS WITH BILATERAL BREAST CANCER: A POTENTIAL NEW DIAGNOSTIC MARKER

Autores: Tiago Finger Andreis[1,2]; Ana Paula Carneiro Brandalize[1,3]; Patricia Ashton-Prolla[1,2]

Instituição dos Autores: [1] Laboratório de Medicina Genômica, HCPA/POA; [2] Programa de Pós-Graduação em Ciências Médicas, UFRGS; [3] Faculdade de Medicina, UFPR.

Objetivos: Patients with hereditary cancer syndromes can carry mutations in genes associated with double-strand breaks (DBS) repair. A high expression of DNA polymerase theta (Pol Θ), a translesion DNA synthesis (TLS) polymerase, is associated with a poor clinical outcome in breast, lung and colon cancer. Recent studies reveled its role in the repairing process of DBS. Pol Θ also influences in the timing of replication initiation in human cells and its overexpression may lead to chromosomal instability. In a case-control study of our research group, a single-nucleotide polymorphism (SNP) in the promoter region of the gene *POLQ*, was associated with bilateral breast cancer (BBC) cases. This study aims to identify and characterize germline mutations in *POLQ*.

Metodologia: Thirty-two female patients diagnosed with BBC were recruited in the hospitals Moinhos de Vento and Hospital de Clínicas de Porto Alegre, both located in southern Brazil. gDNA were extracted from blood samples and then sequenced using the Ion Personal Genome Machine (PGM) System. Data analysis, alignment to the hg19 human reference genome and variant calling was done using the Torrent Suit Software (Life Technologies). Variants were then annotated using the Ion Reporter software (Life Technologies). We found a total of 31 variants, but only 27 were considered for *in silico* analysis due to low coverage or unbalance allele ratio in the annotated variants. For non-synonymous exonic variants we used two *online* tools: Mutation Taster, which runs several tests to estimate mutation impact in protein and DNA level; and Mutation Assessor, which predict the impact of substitutions based on evolutionary conservation of the affected amino acid in protein homologs. We also used three meta-predictors: Predict SNP; Condel; and Meta-SNP, which base their deleterious potential scores according to a consensus between two or more prediction algorithms.

Resultados: We found two potentially pathogenic exonic variants distributed in three patients: V310G and A2464T. The patient carrying the V310G variant developed a synchronous BBC in her 26 years old and has a family history of breast and central nervous system cancers. Interestingly, she was also diagnosed with a *BRCA1* mutation (c.5266dupC), associated with a hereditary cancer-predisposition. One patient with the A2464T variant developed metachronous BBC in her 48 and 49 years old, but apparently has no family history of cancer. The other patient carrying the A2464T variant developed metachronous BBC in her 38 and 59 years old with a family history of stomach and lung cancer in early ages.

Conclusão: Indeed, these rare variants may constitute a new and not yet described important component to the development of BBC since Pol Θ is involved both in DBS and TLS repair. Although the functional effects of these variants can be predicted in silico with very high reliability, its effects on protein function need to be determined.

Código #13307

Title: POLYMORPHISMS OF THE UPSTREAM REGULATORY REGION- 5'URR OF THE *HLA-G* GENE IN PATIENTS WITH CERVICAL CANCER AND INFECTED BY HPV

Authors: Clisten Fátima Staffen [a]; Mari Dalva Staffen [a]; Emily Bruna Justino [a]; Lorena Mendes Maia [b]; Cinthya Regina de Medeiros Borém [b]; Istéfani Luciene Dayse da Silva [b]; Adriana das Dores Vítor [b]; Ilíada Rainha de Souza [a]; Renata Toscano Simões [b]; Yara Costa Netto Muniz [a].

Author`s Institution: [a] Laboratory of Genetic Polymorphisms, Federal University of Santa Catarina, Brazil; [b] Institute of Education and Research - IEP, Santa Casa Postgraduate and Research Center of Belo Horizonte, Brazil

Aim: To genotype the promoting region polymorphisms (5'URR) of the *HLA-G* gene in patients with cervical cancer and controls, in those with no history of the disease, to better understand the action of this gene in the pathogenesis of the disease. Observe the variability of the 5'URR in patients and controls. Calculate the allelic and genotypic frequencies of the variation points found in the 5'URR. To determine whether there is an association of alleles and genotypes with the disease studied.

Methodology: The sample consisted of 50 patients with cervical cancer, being treated at Santa Casa de Belo Horizonte / MG (IEP / SCBH) and 50 women with no evidence of carcinoma. The genomic DNA of the samples was extracted by the Salting Out method, the region was amplified by polymerase chain reaction (PCR), confirmed in 1% agarose gel and sequenced afterwards. Based in the cases and control data, allelic and genotypic frequencies were calculated using the GENEPOP version 4.2 program. Through the HDS Epimax program, the Odds Ratio (OR) was calculated, with a confidence interval (CI) of 95% and p=0.05 as the limit value of significance, and the association of polymorphisms with the disease was analyzed.

Results: Of the 21 polymorphic sites analyzed in this study, in the 5'URR, 9 SNPs presented significant values, among them the -725G>C>T allele T (OR=7.00 p=0.009) and the T/C genotype (OR=5,256 p=0.053); -689A>G alleles A(OR=0.112 p=0.000) and G (OR=8.906 p=0.000), the A/A (OR=0.106 p=0.001) and G/A genotypes (OR=5.586 p=0.014); -633G>A the A/A (OR=0.366 p=0.046) and G/A genotypes (OR=2,489 p=0.054); -509C>G alleles G (OR=11.182 p=0.001) and C (OR=0.098 p=0.001); C/G (OR=25.389 p=0.029) and C/C genotypes (OR=0.050 p=0.001); -486A> C alleles A (OR=2,727 p=0.002) and C (OR=0.367 p=0.002) and C/C genotype (OR=0.244 p=0.003); -400G>A alleles A (OR=17,775 p=0.001) and G (OR=0.056 p=0.001) and the G/G genotype (OR=0.089 p=0.015); -369C>A alleles A (OR=3.115 p=0.002) and C (OR=0.321 p=0.002), the A/A (OR=2.862 p=0.037) and C/C genotypes (OR=0.119 p=0.008); -284G>A alleles A (OR=2.456 p=0.016) and G (OR=0.407 p=0.016); -201G>A alleles A (OR=0.214 p=0.000) and G (OR=4.675 p=0.000), A/A (OR=0.235 p=0.006) and G/G genotypes (OR=5,145 p=0.002).

Conclusion:

The *loci* -725 T allele, T/C genotype, -369 A allele, A/A genotype and -201 G allele and G/G genotype, are more frequent in patients and associated with the risk of developing the disease. The loci -689 A allele, A/A genotype, -633 A/A genotype, -509 and -486 C allele and C/C genotype, -400 and -284 G allele and G/G genotype, are more frequent in controls, conferring a protective effect, and the heterozygous genotypes for the -689, -633 and -509 positions present a risk for the development of the disease. In cervical cancer, HPV infection is a risk factor for the development of the disease and some polymorphisms in the 5'URR of *HLA-G* can regulate transcription levels and thus, be associated with the disease.

Código #13337

Title: Prevalence of Pathogenic/Likely Pathogenic and unknown clinical significance variants among 385 patients referred for NGS-based Multigene Hereditary Cancer Panel

Geórgia Fernanda de Oliveira[1]; Laís Rodrigues Moura[1]; Jobson Ferraz do Nascimento[1]; Danilo Luiz Soares Barbosa[1]; Mariana Rezende Bandeira de Melo[1]; Cheysa Arielly Biondo[1]; Nara Diniz Soares Pessoa[1]; Rodrigo Bertollo de Alexandre[1]; Marcel Caraciolo[1]; João Bosco Oliveira Filho[1]

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Objectives: To evaluate the prevalence of pathogenic, likely pathogenic and unknown clinical significance variants (VUS) among patients tested with a multigene hereditary cancer risk panel at Genomika Diagnósticos and to highlight the most frequently affected genes.

Methods: For this study, we used our internal database (Gensoft) to compile the results of 385 patients previously tested for the genes APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51, RAD51C, RAD51D, RB1, RET, STK11, TP53 and VHL at Genomika Diagnósticos between March 2016 and February 2017. The majority of the patients had personal or family history of cancer. The regions analyzed were sequenced for germline variants using a dual-library next-generation sequencing (NGS) based method that guarantees 100% coverage of exons and flanking intronic regions at a minimum depth of 50x reads per base. Bases not passing this depth threshold were resequenced by NGS or Sanger methods. In addition, the pathogenic Alu insertion in the exon 3 of BRCA2 was investigated by PCR followed by gel electrophoresis. All pathogenic/likely pathogenic results were confirmed with a second technique.

Results: Our results demonstrated that 58 (15%) of the assessed patients harbored one or more pathogenic or likely pathogenic variants of clinical importance in one or more genes. Among those, 28 (48%) had BRCA1 or BRCA2 pathogenic variants, and this represents 7.2% of the total individuals. The prevalence of VUS in the whole cohort was 33% (129 individuals), with 16 patients (4,1%) harboring VUS in the BRCA1 or BRCA2 genes, 32 individuals in ATM (8,3%) and 81 (21%) in other genes. Our VUS rates are comparable to those recently published (Lisa R , Genetics in Medicine, 2015), which demonstrated a 34.7% VUS rate using a 29 gene panel in 2056 patients. The remaining 52% of our patients harbored only benign or likely benign variants.

Conclusions: The use of a multigene cancer panel doubles the positivity rate (15%) in comparison to using only a BRCA1/2 dual gene panel (7.2%). Our BRCA1/2 VUS rates are low (4,1%), in line with the best centers. On the other side, the VUS rates go up, as the number of genes increases.

Código #13335

Prevalence of positive findings with the use of a NGS-based RNA and DNA sequencing multigene panel in solid tumors for therapy guidance

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Objectives: We aimed to investigate the prevalence of positive findings in solid tumors using a next-generation sequencing (NGS)-based RNA and DNA sequencing multigene panel in different types of cancers.

Methods: For this study, we used an internal database (Gensoft) for compilation of the results of 86 patients previously tested for mutations at Genomika Diagnósticos between March 2016 and March 2017. Data were generated from results obtained through NGS using the Ion Torrent Oncomine ™ Focus Assay platform. Data about cancer types, positive/negative frequency and affected genes were listed. We analyzed the presence of variants such as hotspots, SNVs, indels, CNVs and gene fusions among 52 genes evaluated by the platform. The results of the sequencing were analyzed with the Oncomine™ Knowledgebase Reporter software to verify possible therapies for each case.

Results: Our results showed that 62 patients (72.09%) were positive for mutations, while 17 patients (19.76%) were negative for any variants. Seven cases (8.13%) were considered inconclusive due to insufficient tumor percentage or unsatisfactory genetic material quality for the study. Lung adenocarcinoma was the most frequent type of cancer tested, accounting for 61.62% of the cases. Among these, 40 (75%) of the cases were positive, with 26 variants guiding therapy. Variants were found in the genes KRAS (24.52%), EGFR (20.75%), MET (20.75%), ALK (11.32%), PIK3CA (5.66%), CTNNB1 (5.66%), as well as ERBB2, NRAS, ROS1, RET, CDK4 and BRAF genes. Finding of fusion genes involving ROS1 and ALK indicate drugs such as crizotinib, while variants found in EGFR indicate treatment with drugs such as Afatinib, Erlotinib and Gefitinib, with the exception of exon 20 insertions, which may contraindicate therapy with tyrosine kinase inhibitors. Colorectal cancer was the second most frequent cancer type (11.62%). In the patients with this tumor, variants in the KRAS, NRAS, ERBB2, CTNNB1 and PIK3CA genes were found, and KRAS was the most frequently affected gene (60%), with several therapies contraindicated for these cases (Cetuximabe and Panitumumabe). Other cancers represented 26.74% of the cohort and variants were found in several genes, including IDH1, KRAS, ERBB2, FGFR1, EGFR and MET.

Conclusion: These results indicate that a NGS multigene panel for the detection of SNVs, CNVs, indels and fusion events in solid tumors have a high positivity rate and low failure rate, with most findings guiding the therapy to be used. This type of assay can be very useful clinically, allowing a personalized medicine.

Código #13339

PROFILE OF KRAS AND NRAS MUTATIONS IN PATIENTS WITH COLORECTAL CANCER: RESULTS OF 1392 CASES

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[1]Genomika Diagnósticos, Brasil.

Objectives: We aimed to evaluate the degree of positivity for KRAS/NRAS mutations and summarize the main variants found in patients with metastatic colorectal cancer (mCRC) evaluated at Genomika Diagnósticos.

Methods: For this study, we used an internal database (Gensoft) for compilation of the results of 1392 patient previously tested for KRAS/NRAS mutations at Genomika Diagnósticos between September 2013 and March 2017. The regions analyzed were the codons 12 and 13 (exon 2), 59 and 61 (exon 3) and codons 117 and 146 (exon 4) of KRAS and NRAS that were sequenced for somatic mutations using a next-generation platform. We considered as a positive result the presence of variant with a minimum allele frequency of 10% in the analyzed region. All variants were checked in databases and bioinformatics tools to evaluate their impact in therapy response. According to the status of each gene, we separated the patients in three groups: KRAS positive, NRAS positive and negative patients. Patients with gain-of-function mutations in KRAS or NRAS have a poor response to the conventional therapy with anti-EGFR monoclonal antibodies, while wild-type patients are candidates for use of those therapies. We also summarized the main variants found in these patients and the frequency of affected codon.

Results: Our results showed that 777 patients (55.82%) were negative for KRAS/NRAS mutations, while 558 patients (40.09%) were positive for KRAS mutations and 55 patients (3.95%) were positive for NRAS mutations in the codons analyzed. Among the KRAS positive group, the main variants reported were the c.35G>A (p.G12D) (30.34%) and the c.38G>A (p.G13D) (17.77%). The most common variants found in the NRAS positive group was c.35G>A (p.G12D), identified in 11 patients (20%) followed by 7 patients (12.73%) that presented the variant c.182A>T (p.Q61L). The KRAS variants frequency in the codons 12, 13, 59, 61, 117 and 146 was 63.31%, 22.66%, 1.08%, 5.76%, 0.72% and 6.47%, respectively. For the NRAS group, only the codons 12, 13 59 and 61 were affected with a frequency of 16.36%, 52.73%, 5.45% and 25.45%. Additionally, we reported two patients that presented the KRAS variants c.38G>A (p.G13D) and c.35G>A (p.G12D) concomitantly. We also reported two patients with mutations in both genes, one of these had the KRAS variant c.35G>C (p.G12A) and NRAS c.35G>T (p.G12V); the second patient was positive for KRAS c.35G>T (p.12V) and NRAS c.436G>A (p.A146T).

Conclusion: According to our results, 44.22% of the patients were positive for variants in KRAS and/or NRAS and are contraindicated for use of therapies with anti-EGFR drugs. Our results corroborate the current literature which also stipulates an average of 40-45% of positivity for KRAS and 1-6% for NRAS mutations in patients with CRC. This study also reinforces the importance of determining the KRAS/NRAS status for therapeutic decisions in patients with mCRC.

Código #13288

RECOGNIZING HISTORIES: THE KNOWLEDGE OF HEALTH PROFESSIONALS ABOUT HEREDITARY CANCER – A preliminary data.

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Objectives: The aim of this study was to assess the knowledge regarding hereditary cancer of health professionals from primary care (basic health units of Barretos, a city in the state of Sao Paulo, Brazil) and tertiary care (Hospital de Cancer de Barretos, in the state of São Paulo, Brazil).

Methods: The study involved the application of a questionnaire on basics knowledge concepts related to hereditary cancer and oncogenetics aspects. This instrument were applied anonymously in physicians and nurses from different medical specialties from Barretos Cancer Hospital and a Barretos Primary Care Unity. Also, the community health agents from a primary health care unit were included since they are the first access for the population to the public health service.

Results: 90 professionals answered the questionnaire, being that 10 (11.1%) of primary care (3 physicians, 3 nurses and 4 community health agents) and 80 (88.9%) of tertiary care (70 physician of various oncologic specialties and 10 nurses). Of the total surveyed, 67% had professional specializations in Oncology and 10% performed genetic specializations. The concept of hereditary cancer among participants, in general, is reported as genetic inheritance. When questioned if they are used to ask about family history of cancer 78 (86.7%) answered affirmatively (4 physicians, 4 nurses and one community health agent do not ask, two participants did not answered). The results also showed that 4 (3.6%) physicians use to draw the pedigree and 8 (7.2%) participants don't know what a pedigree is (7 physicians and 1 nurse from tertiary care). Regarding to the criteria that may lead to suspicion of hereditary cancer, we found that 78 (70.2%) of the participants responded that rare cancer is not enough to know if it is a hereditary cancer case. Most participants, 77 (69.3%), answered that a case of cancer diagnosed aged less than 55 years is not enough for diagnosis of hereditary cancer. With respect to family history 37 (33%) ask the history of cancer to the patients until the third generation, 21 (18.9%) until the second generation; 11 (9.9%) ask until the second generation and 10 (9%) question only the first generation. Still with respect to data concern about family history, 15 (13.5%) of participants responded that the fact that the maternal grandmother and the mother of an individual have had cancer, does not cause an increase in the risk of cancer. It is important to emphasizes that one nurse from the primary care unit does not know what oncogenetics is.

Conclusion: The data obtained until now, show that there is a need for health-care professionals receive guidelines to correctly identify patients with hereditary cancer risk and guide them to the oncogenetics service. High-risk patients can benefit from screening strategies as well as receive appropriate guidelines regarding prevention and control strategies.

Código #13268

Título: *STAT3* as promising chemoresistance biomarker associated with CD44$^{+/high}$/CD24$^{-/low}$/ALDH^{+} BCSCs-like subset of triple-negative breast cancer (TNBC) cell line

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Instituição dos Autores: [1]Serviço de Biologia Celular da Fundação Ezequiel Dias, [2]Instituto de Ciências Biológicas e Saúde do Centro Universitário UNA, [3]Departamento de Patologia Geral do Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil.

Objectives: We searched for potential predictive markers of chemoresistance in CSCs of triple-negative (TNBC) breast cancer cell line classified as claudin-low subtype.

Methods: Doxorubicin (DOX) was tested for cytotoxic activity against BT-549 human TNBC breast cancer cell line and BT-549 tumorspheres (BT-549 TS). Cytotoxicity analyze was performed by MTT assay. BT-549 TS were examined for CD44, CD24 and ALDH markers by flow cytometry. DOX-treated and untreated BT-549 TS had EGF pathway associated genes expression analyzed by RT-qPCR. Statistical tests used were non-parametric Mann-Whitney for independent samples and Kruskal-Wallis.

Results: BT-549 presents BCSCs-like subset determined by CD44+/high/CD24-/low/ALDH1+ phenotype. CD44+/high/CD24-/low/ALDH+ BCSCs-like subset presented the majority of the genes analyzed downregulated and only 3 genes were upregulated after DOX treatment. Among the upregulated genes MAPK3, PRKCZ and STAT3, the last one presented higher level of upregulation in DOX-treated CD44+/high/CD24-/low/ALDH+ BCSCs-like subset.

Conclusions: The identification of biomarkers that predict antitumor responses is at the top of cancer research priorities. STAT3 stood out as molecular signature in CD44+/high/CD24-/low/ALDH1+ BCSCs-like subset obtained from TNBC BT-549 cell line related to DOX-resistance. The majority of evaluated genes in EGF pathway seems not have association with DOX-resistance presented in ours CD44+/high/CD24-/low/ALDH1+ BCSCs-like subset.

Código #12670

Title: THE INFLUENCE OF A *DRD4 GENE POLYMORPHISM ON SUBSTANCE USE DISORDERS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADULTS.*

Authors: Marina Debon[a,b], Cristina Winkler[a,b], Djenifer B. Kappel[a,b], Bruna S. da Silva[a,b], Diego L. Rovaris[a,b], Jaqueline B. Schuch[a,b], Breno Sanvicente-Vieira[e], Lisia von Diemen[d], Felix H. P. Kessler[d], Rodrigo Grassi-Oliveira[e], Luis A. Rohde[b,c], Eugenio H. Grevet[b,c], Claiton H. D. Bau[a,b].

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Objectives: Most individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) present one or more psychiatric comorbidities and Substance Use Disorders (SUD) are some of the most frequent in adults. The dopaminergic system is related to the pathogenesis of externalizing disorders, which includes both ADHD and SUD. Thus, the aim of this study was to evaluate the effects of the 120 bp tandem duplication of the *DRD4* gene in the susceptibility to ADHD in adults and to crack/cocaine addiction, as well as to evaluate the associated comorbidities in these two independent samples.

Methods: The sample is composed by 554 adults with ADHD, 296 crack/cocaine addicts and 634 blood donors as control group. Association analysis for primary outcomes and comorbidities were performed using binary logistic regression.

Results: Regarding susceptibility to ADHD and crack/cocaine addiction, we did not observe a significant association between the 120 bp duplication polymorphism and the disorders ($p = 0.669$, $OR = 0.95$; $p = 0.559$, $OR = 1.167$; respectively). However, evaluating the presence of comorbid SUD within the ADHD sample, it was observed that short allele carriers are at higher risk of developing SUD than homozygotes for the long allele ($p = 0.023$; $OR = 1.679$) and this effect was stronger for non-alcohol substance use ($p = 0.010$; $OR = 2.085$).

Conclusion: Our results suggest that the short allele of the 120 bp tandem duplication of *DRD4* gene influences the susceptibility to SUD when in simultaneous presence of ADHD.

Código #13247

Title: Validation of Digital PCR to identify *EGFR* somatic mutations of lung cancer.

Authors: Tamyres Mingorance Carvalho; Renata Montoro Dourado; Cesar Augusto Barros Duarte; Irina Nastassja Riediger; Sueli Massumi Nakatani; Angelica Beatle Winter Boldt.

Institutions: Universidade Federal do Paraná, Curitiba, Brasil. Laboratório Genoprimer, Curitiba, Brasil.

Key-words: digital PCR, *EGFR*, lung cancer, castPCR.

Objectives: Lung carcinoma and colorectal cancer are the most common malignancies worldwide. These diseases mainly involve somatically acquired mutations, identified by molecular tests, widely used for laboratory diagnosis. Direct DNA sequencing is considered as the gold standard test for identification of mutations, but this technique can be laborious, time consuming and expensive. Because tumor specific mutations can drive therapeutic decisions, alternative methods have been developed to detect common cancer genetic alterations. Digital PCR (dPCR) is a group of molecular techniques for nucleic acid detection and quantification. It offers an alternative method that facilitates quantification of rare genetic variants. In this study, we aim to validate a diagnostic system based on sealed chip technology digital PCR (*QuantStudio 3D (Thermo Fischer Scientific)* to detect most common *EGFR* mutations associated with lung carcinoma

Methods: We analyzed a panel of well-established *EGFR* mutations in lung tumor paraffin embedded samples. We followed the MIQE guideline (*Minimal information for publication of quantitative digital PCR experiments*) and performed an analytical sensitivity test, which comprises linearity tests, defining limits of detection (LOD) and quantification (LOQ), as well as precision and specificity tests. We also analyzed clinical sensitivity, which compares the obtained results of dPCR experiments with other methods, such as DNA sequencing and competitive allele-specific TaqMan® real-time PCR (castPCR, *(Thermo Fischer Scientific, Waltham, Ma, USA)*,

Results: We compared the results of dPCR assays with castPCR for 58 lung carcinoma tumor paraffin embedded samples, for the most common *EGFR* mutations: p.L858R and the exon 19 deletion (Del19), p.T790M, p.L861Q, p.G719A, p.G719A, p.G719S and p.S768I. Except for p.G719C, dPCR has shown greater sensitivity to detect mutations on the samples of this study. The mutations of samples with lower than 1% mutated cells were only observed with dPCR assays. No sample was observed mutations, when performed by Sanger Sequencing, probably because in Sanger sequencing are necessary more than 20% of mutations to can be detected.

Conclusion: In summary, we found advantages of dPCR to detect *EGFR* mutations, with sensitivity around 1-0,1% amounts of mutated cells. We believe that these results will be replicable to detect rare mutations in other tumor samples, as well. These analyses will help to develop a more sensitive diagnostic method and to improve treatment and prognosis of such diseases.

Financial Support:

TERATOGENESE E MUTAGENESE

Código #12774

Title: CARTPT GENE ANALYSES IN COCAINE ADDICTED MOTHERS AND THEIR RESPECTIVE CHILDREN WITH COCAINE PRENATAL EXPOSURE

Authors: Bruna Duarte Rengel[1,3]; Thayne Woycinck Kowalski[1,2,3]; Alejandra Roja Gomez[1,2,3]; Claudia Maciel Szobot[4]; Lavínia Schuler Faccini[1,2,3,5]; Fernanda Sales Luiz Vianna[1,2,3]

Institutions: [1]Laboratory of Medical Genetics and Evolution, Genetics Department, Federal University of Rio Grande do Sul; [2]Post-Graduation Program in Genetics and Molecular Biology, Federal University of Rio Grande do Sul; [3]National Institute of Medical Populational Genetics (INAGEMP); [4]Psychiatry Service, Clinical Hospital of Porto Alegre; [5]Medical Genetics Service, Clinical Hospital of Porto Alegre

Objectives: The aim of this study was to evaluate genetic susceptibility variants in *CARTPT* gene in crack/cocaine addiction. *CARTPT* codifies CART (cocaine and amphetamine regulated transcript) peptides, which are neuromodulators involved mainly in feeding, drug reward and addiction. *CARTPT* mRNA levels are up regulated by cocaine administration, suggesting its role in the reward system. *CARTPT* has 3 exons and 2 introns and it is located in 5q13.2 region. Hence, in this study we analyzed the *CARTPT* gene in crack/cocaine addicted mothers and their respective children, with prenatal exposure and compared with a non-exposed group of non-users (mothers and children).

Methodology: DNA samples were collected from mother's whole blood and children's umbilical cord blood. DNA extraction was performed using Puregene Blood kit (Qiagen). PCR and subsequent Sanger sequencing was performed, comprising exons 1, 2 and 3 of *CARTPT*, together with a portion of adjacent introns. CodonCode Aligner program was used to read the DNA sequence. Haploview 4.2 software was used to analyze the linkage disequilibrium. Haplotypes were inferred by Phase 2.1.1 tool. Statistical analysis was performed in SPSS v.18, to compare allelic, genotypic and haplotypic frequencies between affected and non-affected mother groups, and their children. This study was registered in Ethics Comittee of Hospital de Clínicas de Porto Alegre by the number 11-0095.

Results: Until the present moment, we sequenced the exon 2 of 70 samples, including 30 exposed (15 children and 15 mothers) and 40 non-exposed (13 children and 27 mothers). We observed six polymorphisms previously described in genomic databases, four in exon 2 and two in intron 1. All the polymorphisms were in Hardy-Weinberg Equilibrium. In intron 1 the polymorphisms observed were rs796075849 and rs114374940. In exon 2 were rs11575893, rs2239670, rs16871443 and rs140190376. Polymorphisms rs11575893 and rs2239670 were previously associated with dependence to psychostimulant substances. Genotypic and allelic frequencies did not differ statistically between exposed and non-exposed groups ($p>0.05$). Haplotypic frequency was also statistically similar between the groups, although one haplotype has been only identified in affected children when compared to non-affected children ($p=0.055$).

Conclusion: This is a preliminary report of *CARTPT* sequencing in crack/cocaine addicted mothers and exposed children. Until this moment, we did not identify a risk or protective allele in exon 2, although it is probably due to small sample number. Comparison between genetic variants and clinical manifestations will be performed after the whole sample is sequenced. Further analysis will also evaluate haplotypic differences between the groups. Exons 1 and 3 will also be sequenced, and a methylation evaluation will be performed, regarding a CpG island located in exon 2. Therefore, new results are expected with the analyses in perspective.

Código #13181

TITLE: The role of *ESCO2*, *TBX5* and *SALL4* genes in the susceptibility to thalidomide embryopathy.

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Objectives: Thalidomide is a drug that causes thalidomide embryopathy (TE) in about 20-50% of embryos exposed during pregnancy. Given the similarity of phenotypic characteristics, TE is considered a phenocopy of three genetic syndromes. In the present study we aimed to investigate the genes associated with these syndromes - *ESCO2*, *SALL4* and *TBX5* genes - in the susceptibility to TE and to specific endophenotypes seen in affected individuals.

Methodology: Twenty-nine subjects affected by TE were included in this study. Saliva was collected through Oragene-DNA OG-500 (DNA Genotek) and DNA was obtained according to the manufacturer's instructions. Exons, flanking introns and untranslated regions of *ESCO2*, *SALL4* and *TBX5* genes were sequenced through next generation sequencing by semiconductor chip Ion Torrent™ technology (Thermo Fisher Scientific, USA). *In silico* analyses of the variants found were performed. All statistical analyses were evaluated in SPSS® program, version 20 (SPSS, IBM, USA).

Results: Forty-one gene variants were identified, 11 (27%) in *ESCO2*, 14 (34%) in *SALL4* and 16 (39%) in *TBX5*. One variant in *ESCO2* and one in *TBX5* have not been previously described in genomic databases. Twelve (29%) were rare variants (MAF <0.01). We compared the frequencies of our sample with data from the European population of 1000 Genomes Project. Allelic and genotypic frequencies were significantly different between the groups only to one 3'UTR variant (rs62498042) of *ESCO2* gene ($p<0.001$). *In silico* analysis suggested splicing affected by this variant; however, there are no reports in literature of its functional role or association with any disease. Some variants identified were previously evaluated in cardiovascular diseases or cardiac malformations. In this sample, there was no association between these variants and an increased risk for such conditions. *In silico* analyses were performed to evaluate the potential of all variants found for functional alterations in the protein or for changes in splicing sites, or transcription factors and miRNAs binding sites. Many variants were considered to have such potential; however, it was not possible to correlate them with decay of mRNA, alternative isoforms or decrease of these genes expression. Moreover, experimental assays and validation of these variants are required in order to understand their actual biological role in the proteins activities, in the molecular mechanism of congenital anomalies development and in thalidomide teratogenesis.

Conclusion: It was not possible to demonstrate the involvement of these genes with greater susceptibility to TE or diseases and malformations seen in affected individuals. Despite this, the approach used here brought more knowledge of these genes and perspectives to the understanding of TE etiology and these syndromes etiology.

Key words: Duane-radial ray syndrome, Holt-Oram syndrome, Okihiro syndrome, Phenocopy, Roberts syndrome, Susceptibility, Thalidomide embryopathy

Financial Support: CNPq, INaGeMP, FIPE/HCPA, UFRGS

CASOS CLÍNICOS

Código #13324

Título: HUNTINGTON'S DISEASE: DIFFERENT ASPECTS OF FAMILY DYNAMIC FROM MOLECULAR DIAGNOSIS

Autores: Alice Salgueiro Nascimento Marinho; Wilen Norat Siqueira; Carolina Mazza de Menezes; Clarissa Maria Motta Stofell de Siqueira; Marina Kossmann Ferraz; Olavo Ferreira de Siqueira; Leda Maria Neumann Keim; Edna Corrêa Moreira; Fernando Regla Vargas

Instituição dos Autores: Serviço de Genética Médica, Hospital Universitário Gaffrée e Guinle, Universidade Federal do Estado do Rio de Janeiro, Brasil.

Objetivos: The goal of this study is to describe the psychosocial mechanisms used in the family dynamic to deal with results of the molecular test

Metodologia: The qualitative method was adopted. A clinical case study was carried out. The data collection was done by analyzing records of the multiprofessional team. The analysis from a psychosocial point of view, aims to meet an ethical demand from the medical genetics itself to discuss and reflect on the implications of the use of diagnostic technologies, identifying the emotional factors that motivate patients to look for the service and analyzing the psychological reactions of the patients and their relatives facing the results of the molecular test, in its manifested and latent aspects. From the genetic and therapeutic point of the view, the analysis identifies aspects of molecular and differential diagnosis in each of the case and describes the therapeutic procedures used to reduce the symptoms.

Resultados: The case study illustrated how the access to molecular testing and genetic information related to family risk resignify the doubts, the uncertainties, and the vulnerabilities, and reconfigure the family dynamic. Over the period between the emergence of the first symptoms of Huntington's disease (HD) and the access to the results of the molecular test, changes in the family dynamic occur as a strategy for coping with the disease. At the heart of these family reconfigurations emerge issues such as: transmission risk, reproductive project, use of predictive test. The way each family deals with those issues is more related to family experiences to deals with illness itself than with the number of the CAG repetitions found in the genetic testing.

Conclusão: It concludes that from psychosocial point of the view, the individuals who undergo genetic risk situation tend to confront these situations with the gradual stress level in order to adapted to a new condition and, in the specific case of Huntington's disease, this process will rely more on the quality of the family and therapeutic supports available than on individual capacity. Knowing the mechanisms used by the families as strategies to face DH favors the care planning by health teams in medical genetics.

Código #13357

Myeloid leukemia and Prader-Willi syndrome – A case report.

Autores: Anna Cláudia Evangelista Dos Santos1; Bárbara Nasr1; Ana Carolina Bonini1; Mireille Gomes1; Manuella P.P. Siqueira1; Catielly Ferreira Rocha2; Carmem Lucia Antão Paiva2; Suely Rodrigues dos Santos2; Fernando Regla Vargas2.

Instituição dos autores: 1. Instituto Nacional de Câncer José Alencar Gomes da Silva. 2. Departamento de Genética e Biologia Molecular– UNIRIO.

A 6-year-old boy was referred to INCA's Clinical Genetics because of dysmorphic features. He had acute leukemia at 4 years-old. Clinical exam demonstrated mental retardation, short stature, obesity, unilateral chryptorchidism, and small hands and feet. Hypotonia at birth, hyperphagia, compulsive nails picking, and food-seeking behaviors were also noted. This features suggested Prader-Willi syndrome (PWS). DNA methylation studies on chromosome 15 were performed and methylation test of *Small Nuclear Ribonucleoprotein-associated Protein N* (*SNRPN*) revealed uniparental disomy. There are only a few reports (three cases) of acute myeloid leukemia associated with PWS.

Código #13386

Título: HIPOFOSFATASIA RELATO DE CASO

Autores: Ananias Nogueira Mendes[4], Cleiton Fantin[2] , Denise Corrêa Benzaquem[2], Vânia Mesquita Gadelha Prazeres[1,3,4], Marcela Figueiredo Conceição Azevedo[3]

Instituição dos Autores:[1]Ambulatório de Genética Médica da Associação de Pais e Amigos dos Excepcionais/APAE-AM,[2]Laboratório de Citogenética da Universidade do Estado do Amazonas. [3]Universidade Federal do Amazonas/Departamento de Saúde Materno Infantil/Ambulatório Araújo Lima,[4]Universidade do Estado do Amazonas/Residência Médica em Pediatria

Objetivos: O objetivo deste trabalho é relatar um caso clínico de Hipofosfatasia, com ênfase nas características físicas e exames laboratoriais. A paciente foi atendida no ambulatório de genética médica da Associação de Pais e Amigos dos Excepcionais de Manaus (APAE/Manaus).

Metodologia: Para o relato de caso foram realizadas anamnese, cariótipo com banda G de sangue periférico, dosagem de Vitamina B6 e Fosfatase Alcalina e exame de ressonância.

Resultados: A.M.M.S, 9 anos, pais não consanguíneos, sem doenças ósseas na família, possui mais uma irmã por parte de mãe. Gravidez sem intercorrencias, parto distócico, a termo. RN AIG sem intercorrencia, a mãe relata primeira internação da criança aos 15 dias de vida devido á convulsão e tratou até os 3 anos de idade. Mãe relata várias internações devido à infecção respiratória. Apresenta leve atraso no desenvolvimento neuropsicomotor e foi diagnosticada com cranioestenose em exame de imagem SNC. Evoluiu com baixa estatura e fez reposição hormonal com acompanhamento de endocrinologista pediatra sem sucesso. Ao exame físico além da baixa estatura, nota-se dolicocefalia, bossa frontal, tíbias encurvadas e grande comprometimento odontológico com muitas cáries precoces e perda dos dentes. Avaliação laboratorial: Cariótipo de sangue periférico Banda G 46, XX (normal); ressonância de crânio: cranioestenose, calcificação comprometimento globos pálidos e substancias branca subcortical; dosagem de Fosfatase Alcalina: 63/L (N=69-325)em uso de GH; dosagem de Vitamina B6: 27, 4 (5,2-34,1).A mãe e a irmã mais nova também apresentaram resultado de FosfataseAlacalina abaixo do esperado para idade.

Conclusão: O fenótipo clínico e diagnóstico laboratorial da paciente é compatível com Hipofosfatasia.

CASOS CLÍNICOS CITOGENÉTICA

Código #13371

Title: CHROMOSOME 15 RING: CASE REPORT AND IMPORTANCE OF KARYOTYPE

Authors: Erica Erica Aires Gil; Erica Aires Gil;João Ivanildo da Costa Ferreira Neri;Geísa pereira Januário;victor de Lima Soares;Gioconda Dias Rodrigues Leão; Roberto chaves de Vasconcelos; Andrea Luciana Araujo da Cunha Fernandes;Adriana Damasceno Pereira Pinto Cirne;Maria Beatriz Alves da Costa; Geraldo Barroso Cavalcanti Junior

Institution of Authors: DNA Center Clinical and Laboratory, Natal-RN, Brazil.

Case Summary:

Objectives: To report the case of a patient with chromosome 15 ring.

Methods: case report.

Case: L.M.M., female, sixteen years old, was referred for delay in her neuropsychomotor development and suspected syndromic feature. She is the eldest daughter, in the offspring of two, of non-consanguineous couple, who denies related cases in the family. Metrorrhagia in a small amount in the first trimester of gestation and intrauterine growth retardation was referred and motive of cesarean delivery. Esophageal atresia was observed at birth and corrected at second day of life. At the age of two, because she was very small, she began to follow up with several specialists. At the physical examination, it was observed short stature with apparently short limbs and small hands and feet, microcephaly with low hairline at the back of the head, prominent forehead and triangular face, ocular hypertelorism, prominent and enlarged nose, small and slightly dysmorphic ears, hypoplasia of 4th and 5th metacarpals and thumbs, large **cafe au lait spots** on the trunk and generalized mild hypotonia. As complementary investigation, were performed thyroid and ovarian hormonal profiles, electroencephalogram, chest and lumbar spine radiographs and hands with a bone age, and abdominal and pelvic ultrasound, all with results compatible with normality, and karyotype from peripheral blood with G-band that confirmed chromosome 15 ring [46, XX, r (15) (p11.2; q26)].

Discussion: Chromosome 15 ring is a rare condition that results from loss (deletion) of genetic material from both ends of the 15th chromosome and a joining of the ends to form a ring. In most cases, it is caused by spontaneous (de novo) errors very early in embryonic development and its variability of associated symptoms and findings may depend upon the amount and location of genetic material lost from the 15th chromosome, the stability of the ring chromosome during subsequent cellular divisions, or other factors.

Conclusion: Genetic counseling was performed with parents, being considered fundamental her accompaniment in a service where she can receive psychological support and develop activities of psychopedagogical, phonological and occupational therapy stimulation, in order to minimize the alterations presented by her in these areas, besides the medical follow-up necessary for her conditions. This case is brought to the congress to reinforce the importance that the traditional karyotype exam still has as an aid in the diagnosis of syndromic conditions, especially when correctly requested and performed.

Código #13369

Title: DOUBLE AUTOSOMAL TRANSLOCATION APPARENTLY BALANCED IN BOY WITH DISMORPHYSMS AND NEUROPSICOMOTOR DELAY: CASE FOR DISCUSSION

Authors: Erica Aires Gil; Erica Aires Gil;João Ivanildo da Costa Ferreira Neri;Geísa pereira Januário; Taissa maria de oliveira moura;victor de Lima Soares;Gioconda Dias Rodrigues Leão; Roberto chaves de Vasconcelos; Andrea Luciana Araujo da Cunha Fernandes;Maria Beatriz Alves da Costa;Geraldo Barroso Cavalcanti Junior

Institution of Authors: DNA Center Clinical and Laboratory, Natal-RN, Brazil.

Case Summary:

Objectives: Bring for discussionthe case of a patient with double autosomal translocation apparently balanced in boy with dismorphysms and neuropsicomotor delay.

Methods: case report.

Case: J.G.M.D., male, two years old, referred to the service due to neuropsychomotor delay and suspicion of syndromic feature. He is the youngest in an offspring of three of non-consanguineous couple, who denies similar cases in the family. The mother reported two metrorrhagias (1st and 3rd trimesters), cesarean delivery for tubal ligation, with good fetal development conditions (Apgar 8/8). He presented moderate global hypotonia from the beginning, began physiotherapy at 7 months and followed up with neuropediatra from the 9th. Physical examination revealed a broad forehead, rarefaction of the lateral thirds of the eyelids, hypertelorism, long eyelashes, wide palpebral clefts with eversion of the external third, lower eyelids, low set ears, short columella, short neck, mild global hypotonia. The neuropediatrician suspected of metabolic condition, however, the whole profile of amino acids, muscle enzymes, sugars and lipids was normal. In view of the interesting dysmorphic aspect, we requested a peripheral blood karyotype that detected the presence of an autosomal double translocation [46,XY,t(2;3)(q31q37?;q23q29?),t(4;22)(q13?;q25q35?)].

Discussion: Balanced chromosomal translocations have a frequency of 0.3% in the general population. Double balanced translocations are particularly rare and the risk of a fetus with unbalanced chromosomal anomaly is greater than for single translocation carriers. The majority of reports describing more than one translocation have indicated de novo origin of the rearrangements, but a few familial cases have been documented. Because it is a family in need, the parents' karyotype was requested in public service and we are waiting for the result. We hope to count on the collaboration of colleagues from other service to elucidate this case in the event that the parental karyotypes are normal.

Código #13351

TÍTULO: Isocromossomo X em paciente masculino: relato de caso

AUTORES: Ilara Pires dos Santos[1], Dione Fernandes Tavares[1], Esmeralda Santos Alves[2], Neulice Correia Barros[2], Paula Brito Corrêia[2], Angelina Xavier Acosta[1], Joanna Góes Castro Meira[2]

INSTITUIÇÃO DOS AUTORES: Faculdade de Medicina da Universidade Federal da Bahia[1]; Serviço de Genética Médica do Hospital Universitário Profº Edgar Santos[2]

INTRODUÇÃO: O isocromossomo Xq (iXq) é uma alteração estrutural causada quando a divisão dos centrômeros dá-se transversalmente, quando deveria ocorrer longitudinalmente, levando à duplicação do braço longo (Xq) do X e perda do braço curto (Xp). A presença do iXq é comum em pacientes com síndrome de Turner (TS), entretanto, é aparentemente rara em homens. Até agora, foram relatados poucos pacientes do sexo masculino com iXq, principalmente na síndrome de Klinefelter (KS). Nesses relatos, observou-se que os pacientes apresentam as principais manifestações clínicas de KS. Na TS, aproximadamente 12 a 20% das afetadas apresentam em seu cariótipo o iXq. Classicamente, associa-se a presença de iXq na TS à menor incidência de anomalias congênitas e à alta taxa de doenças auto-imunes como doença de Crohn e tireoidite, além de perda auditiva e alterações linfáticas. Sabe-se que a baixa estatura da síndrome de Turner está ligada à haploinsuficiência do gene *SHOX* do braço curto do cromossomo X, logo, a baixa estatura ocorre também nos casos de TS com iXq. Paradoxalmente, a presença do iXq no sexo masculino, não associado à TS, não está bem esclarecido devido à raridade destes casos. O objetivo deste trabalho é descrever o caso de um paciente masculino com iXq.

METODOLOGIA: Revisão de prontuário médico e revisão bibliográfica.

RESULTADOS: Paciente JMSB, 10 meses, sexo masculino, segundo filho de uma G2P2A0. Nasceu por PSAC, com 38 semanas, pesando 2,720 kg, com 48 cm de estatura. Genitora informa ter feito pré-natal, com sorologias normais. USG morfológica mostrou artéria umbilical única. Nega exposição a teratógenos ou consanguinidade parental. Ao nascimento, apresentava 4 dentes neonatais e CIA (comunicação interatrial). Evoluiu com atraso global no desenvolvimento neuropsicomotor, sendo que aos 10 meses ainda não senta com apoio. Ao exame físico: Paciente alerta, hipotônico, baixo peso e estatura, microcefalia relativa, epicanto bilateral, nariz pequeno com narinas antevertidas, lobo de orelhas pequenos com chanfradura em orelha esquerda, hipoplasia de face média, boca pequena com palato estreito, mamilos hipoplásicos (invertidos), calcanhares proeminentes. Genitália externa masculina com pênis de tamanho reduzido, escroto bipartido. Entre os exames complementares realizados, o ECG de repouso evidenciou dilatação de átrio direito; Ecocardiograma detectou CIA, dilatação moderada do átrio direito. Ultrassonografia transfontanela demonstrou discreta ectasia de do ventrículo lateral esquerdo e afilamento de corpo caloso. O cariótipo de sangue periférico detectou isocromossomo de Xq: 46,Y,i(X)(q10).

CONCLUSÃO: Devido a escassez de pacientes relatados com um cariótipo 46,Y,i(X)(q10), é provável que o espectro clínico não tenha sido elucidado. Somente através da avaliação de um grupo maior de

tais pacientes poderá ser fornecida uma melhor avaliação do prognóstico e possíveis complicações que devem ser investigadas nesses pacientes.

Código #13161

Title: MED13L SYNDROME (MIM 616789): CASE REPORT AND PHENOTYPE CHARACTERIZATION.

Authors: Thais Arbocese Zanolla[1], Eduardo Perrone[1], Ana Beatriz Alvarez Perez[1]

Authors Institution: 1. Universidade Federal de São Paulo (UNIFESP)

Purpose:
To report a MED13L gene microdeletion case, delineate the phenotype and highlight the importance of SNP array for diagnostic elucidation.

Methods:
The patient was followed at the Medical Genetics Ambulatory. Our evaluation included anamnesis, morphological and physical examination, and audiovisual records. Proband and parental SNP-arrays were performed.

Results:
A 4-year old male was referred for evaluation due to a clinical suspicion of Prader-Willi syndrome. The pregnancy was uneventful, except for third trimester maternal hypertension. Our patient was the only affected child of non-consanguineous parents. Birth length was 49cm (25−50th centile), weight was 3305g (25-50th centile) and occipitofrontal head circumference (OFC) was 35cm (25-50th centile). At birth, the patient presented with hypospadias, and during the neonatal period, showed hypotonia and poor suck. At our evaluation, he showed global developmental delay, language milestones delay and abnormal behavioral phenotype, characterized by eating compulsive behavior tantrum, stubbornness and poor eye contact. Anthropometric evaluation was not performed because child had aversion to touch. Based on these behavior abnormalities, he was diagnosed with Autism Spectrum Disorder (ASD) and neurodevelopment delay. There was no familial history. Morphological examination revealed obesity, brachycephaly, facial asymmetry, almond-shaped palpebral fissures, prominent nasal bridge with low hanging columella, prominent lips with down-turned corners of the mouth, macrostomia and tapering fingers. Echocardiography revealed a structurally normal heart. Cranial magnetic resonance showed symmetrical ectasia of the perivascular cerebrospinal fluid in the bilateral parietal substance. Karyotype G band was 46,XY. Fragile X molecular evaluation revealed a normal number of CGG trinucleotide repeats. The proband's SNP - array identified four copy number variations (CNV's). Three were maternally inherited, and one was a de novo CNV[arr[hg19]12q24.21(116,463,228-116,650,609)X1dn]. This CNV comprises and disrupts MED13L gene. The phenotype of our patient was consistent with MED13L syndrome phenotype as previously described in literature.

Código #13230

Microdeletion of 9q34.3 causes a new Neurodevelopmental Disorder: Description of a first Brazilian patient with Kleefstra syndrome

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Kleefstra syndrome (KS) (OMIM 610253), also known as 9q subtelomeric deletion syndrome, is a rare chromosomal disorder, with about a 100 patients described worldwide. KS IS clinically characterized by childhood hypotonia, moderate to severe intellectual disabilities, distinct facial features (flat face with hypertelorism, synophrys, anteverted nares, everted lower lip, carp mouth with macroglossia) and speech delay. In addition, congenital heart defects, genital, ear and eye anomalies, recurrent infections, feeding problems, seizures, and behavioral such as temper tantrums, aggression, impulsivity and autistic features have been associated with this disorder. Approximately 75% of the patients have a small interstitial deletion at 9q34.3 and the remaining patients have a heterozygous intragenic pathogenic variant in *EHMT1 (*Euchromatic Histone Methyltransferase 1). We describe a new patient diagnosed with KS characterized by microarray technology. The patient is a 17-yo female patient who was the fourth-born child to a healthy and unrelated 29-year-old father and 28-year-old mother. The pregnancy was uncomplicated and she was born at term by spontaneous vaginal delivery. There was no previous history of genetic diseases in either of the parental families. Her birth weight was 3,300g (25–50th percentile), her height 46 cm (10th percentile) and her occipital-frontal circumference (OFC) 32 cm (10th percentile) with description of hypotonia. Her developmental milestones were delayed and she showed autistic features including behavioral problems (auto aggression), speech impairment and stereotyped and repetitive body movements such as hand flapping. On her physical evaluation, she presented with proportionate short stature, microbrachicephaly, midface hypoplasia, prognathism, carp mouth, arachnodactyly and joint laxity. Electroencephalogram (EEG) showed multifocal epileptiforme discharges and the brain MRI showed persistence of the cavum septum pellucidum. Auditory evaluation, karyotype and molecular investigation for Angelman syndrome (SNPRN methylation) were normal. A chromosomal microarray analysis was performed using CytoSNP array 850K BeadChip (Illumina®) and an interstitial 273 kb deletion was identified at 9q34.3. To the best of our knowledge, this is the first report in a Brazilian patient and, consistent with the majority of patients in the literature, the presented case showed a 9q34.3 deletion that included the *EHMT1* gene. Many patients with neurodevelopmental disorders and few dysmorphisms fail to be diagnosed due to the limited resolution of older genetic test methodologies. The clinical impact of higher resolution microarray technology has allowed the physicians in reaching an accurate diagnosis and understanding of underlying mechanisms and adequate genetic counselling.

Apoio: FAEPA/CAPES

Código #14335

Título: PACIENTE COM OSTEOCONRODISPLASIA E MIELODISPLASIA – RELATO DE CASO

Autores: Miriam de Melo Melquíades[1], Thais Bomfim Teixeira[1], Anita Frisanco Oliveira[1], Glaucia R. C. Murra[1], Elvira D. Velloso[2], Luis Fernando Lopes[1], Henrique C. R. Galvão[1]

Instituição dos Autores: [1]Hospital de Câncer de Barretos; [2]Hospital Israelita Albert Einstein

Resumo do caso: BCA, 4 anos à época da primeira consulta (DN: 04/11/2011), natural de Taubaté-SP. Trigemelar (fertilização *in vitro*, pai com oligospermia) de casal não consanguíneo. História familiar sem outros dados relevantes.

Mãe nega infecções ou comorbidades durante gestação.

Nascida de parto cesáreo, com 35 semanas. Permaneceu internada por 28 dias devido a cardiopatia congênita (sem necessidade de abordagem cirúrgica, sic), displasia de coluna, hipoplasia de quadril e pé torto congênito bilateralmente.

Em acompanhamento, desde então, com ortopedistas subespecialistas. Submetida a cirurgia para correção dos pés tortos aos 2 anos de idade. Em avaliação pré-anestésica foi detectada plaquetopenia (100.000/ml). A partir do terceiro ano de vida, apresentou episódios recorrentes de infecção (otite, amigdalite, infecção urinária), associados a leucopenia e neutropenia. Avaliação de biópsia de medula óssea foi sugestiva de síndrome mielodisplásica (SMD), tendo sido a paciente encaminhada para avaliação pelo Grupo Cooperativo Brasileiro de Síndromes Mielodisplásicas em Pediatria. Após três avaliações medulares, no intervalo de 10 meses, foram evidenciadas alterações displásicas no mielograma, expressão anômala de CD56 em toda linhagem mielóide, diminuição dos precursores mieloides e ausência de precursores linfoides B; biópsia de medula óssea hipocelular, com desarranjos arquiteturais nas séries eritrocitica e granulocitica. Esses achados associados à piora hematológica da paciente, levaram o grupo a concluir tratar-se de síndrome mielodisplásica – citopenia refratária. A paciente segue em acompanhamento clínico, sem neutropenia ou necessidade transfisional, com hematologista na origem.

Ao exame físico, apresenta sobrancelhas espessas, cílios longos, olhos amendoados, fissuras palpebrais inclinadas para cima, tronco curto, escoliose grave, pelve estreita, dedos das mãos longos e em espátula, genu valgo, pés tortos com evidência de abordagem cirúrgica e uso de tutor. Sem déficits cognitivos.

Exames complementares realizados: Radiografias: escoliose grave, platispondilia, vértebras malformadas, luxação de quadril, fossas acetabulares rasas e irregulares

Cariótipo de sangue periférico (realizado em unidade neonatal, durante propedêutica de dismorfismos): 46,XX,t(2;9)(q21;q21.2)

Cariótipo de medula (realizado durante propedêutica de SMD): 46,XX,t(2;9)(q13;q13)

Cariótipo do pai: 46,XY

Cariótipo da mãe: 46,XX

Array-CGH: não foram detectados ganhos ou perdas dos segmentos cromossômicos.

BMO: Hipocelular para idade (20%), relação G:E 2:1, com desarranjos arquiteturais nas séries ertotrocitica e granulocítica e ausência de megacariócitos.

Hipóteses diagnósticas: Síndrome espôndilo-metafisária + SMD a/e

Síndrome de Schwachmann-Diamond (???)

Conclusões: Associação entre os achados clínicos não encontrada na literatura.

Translocação cromossômica balanceada (conferida por a-CGH) sem correspondente sindrômico descrito.

Material adicional: Fotos da paciente, radiografias, cariótipo, lâminas de biópsia de medula óssea

Código #13413

Título: PSEUDOISODICÊNTRICO DE X NÃO MOSAICO : RELATO DE CASO.

Authors: José Francisco da Silva Franco [1]; Adriana Bortolai [2]

Institution: 1 Hospital Sabará-SP, USP-IPEN Centro de Biotecnologia; **2** Hospital do Servidor Público Estadual de São Paulo "Francisco Morato de Oliveira", Brasil.

Objective: To report a clinical case of a patient referred for evaluation by complaint of short stature with chromosomal alteration (pseudoisodiccentric) and review the literature.

Methodology: Analysis of medical records of a clinical case attended ambulatory of medical genetics at Hospital Infantil Sabara- SP. Evaluation of karyotype, microarray and other laboratory tests.

Results: LRT, 6 years old, daughter of non-consanguineous parents, pregnant and delivery was without complications, child was born 40 weeks, weighting 2370g, mesuring 44.5cm, cephalic perimeter(CP) = 32.4cm, neuropsychomotor development was without change. The physical examination showed a height of 115cm (P10), weight 18.5 kg (P10), CP 49cm (P10), hoarse voice, widened nasal root, discreetly rounded ears, slight pronation limitation and supination of the left forearm, neck slightly shortened. The karyotype showed structural alteration of the X chromosome (pseudoisodiccentric with deletion of the Xq27.2q28 region). Microarray showed on the X chromosome, a duplication of 139.6 MB involving 836 genes and loss of 178 genes in 14.5MB of the end region of the long arm of X chromossome. Karyotype of parents without change. Radiography of bone age 3.1 SD below average. Echocardiography, ultrasonography, MRI of the turcica sela, and thyroid function without alteration.

Conclusion: There are few cases reported at the literature that show patients with pseudoisodicentric X chromosomes although they generally occur in mosaic form (Xp) and (Xq). The patient presents an atypical case because her karyotype with the pseudoisodicentric is in non-mosaic form. Although the results of the Microarray show that 551 genes from the duplicated region and 113 from the deleted region are reported in ®OMIM, the patient has a mild phenotype, probably explained by the preferential deviation of X inactivation with structural alteration, which can be proven with other methodologies and justifying a better correlation genotype/phenotype of this case.

Código #14371

Título: Relato de Caso de Lipofuscinose Ceróide Neuronal tipo 2

Autores: Maria Denise Fernandes Carvalho de Andrade; Krishnamurti de Morais Carvalho; Isabella Fernandes Carvalho; Norma Martins de Menezes Morais ; Ellaine Dóris Fernandes Carvalho

Instituição dos Autores: Universidade Federal do Ceará, Hospital Universitário Walter Cantídio e Maternidade Escola Assis Chateaubriand); Universidade Estadual do Ceará e Unichristus

Resumo do caso:

Patient Information: female, 9 years old, third grade (but she does not read or write) **Gestational Data:** No problems at birth.

Medical History: According to the mother, she was **healthy until 4 years old when she started to have Seizures** (general tonic-clonic). After the crises she started vomiting and had postictal state for about 20 minutes. After that the mother noticed that the child had **difficulty to walk and stand up**. She had also **difficulty to make sentences and sometimes spoke nonsense words.** Since the event, the patient started to have seizures with a **five months apart frequency even with the medication.** The last crisis ocurred at december 2013. The mother reports **progressive cognitve and motor delay specially after 2014 and in May 2016 she had difficulty of walking** and needed help (with frequent falls). The patient **was hospitalized at July 2016 for more exams** and elucidation of the medical chart

Main Sign and Symtoms: **Seizures** (general tonic-clonic), **dislalia, dysathria, apraxia, ataxia, difficulty of concentration, difficulty to obey commands,** apparently **sensibility is preserved, global muscular strength lowered**, walks with bended knees and **needs help to walk, tetraparesis, weakness of muscle mainly at the right side and feet inversion**. **Exalted reflexes at the right side**. **Apparently there was no damage at ocular movements (ophthalmologist could not be precise about it) and it was not possible to evaluate visual perceptiveness.**

There was no other history of the disease in the family. She doesn´t know informations about the father´s family. She denies consanguinity.

Main Laboratory Tests: Alkaline Phosphatase: 532; GGT: 42; BD: 0,09; BI: 0,2; Albumin: 3,9; HDL: 50; LDL: 126; TG: 91; IgA: 149; **Lactate: 3,06 (até 2,4);** TSH: 0,91; FT4: 7,18; IgE: 21; serum cooper: 87,6; Venous Ceruloplasmin: 43,4; urinary copper: 68;

MRI (July 2016): alteration of signal of rear periventricular white matter, cortic-spinal tracts and pulvinar thalamus. Along with the clinical data provided, we can consider the possible diagnosisof a disease of a demyelinating metabolic/leukodystrophies nature (Krabbe´s Disease? Metacromatic?). Corelate with clinic – laboratory data. Signs of cortical-subcortical atophy of the brain and pontomesencephalic.

The enzymatic assay of the enzyme tripeptidyl peptidase was performed on a patient's leukocyte sample at the Medical Genetics Service of the Hospital das Clínicas do Rio Grande do Sul and was undetectable. The results obtained in the sample were compatible with Neuronal Ceroid Lipofuscinosis

2. Currently, we are accompanying the patient with a multidisciplinary team (phonoaudiology, physiotherapy, occupational therapy), taking care of the airway for the risk of aspiration and request videodeglutograma. Myoclonic epilepsy is being managed by the neurologist. Molecular analysis is also being sought and genetic counseling conducted with family members.

There is still no treatment available in Brazil but the medication is in the approval phase by the FDA.

Código #14320

Título: RELATO DE CASO E CORRELAÇÃO GENÓTIPO-FENÓTIPO DA DELEÇÃO 15q21.2q22.2

Autores: Luciana Mota Bispo; Joana Rosa Marques Prota; Carlos Eduardo Steiner; Antonia Paula Marques de Faria.

Instituição dos Autores: Universidade Estadual de Campinas - UNICAMP.

Resumo do caso: Propósito do sexo masculino, sete anos, encaminhado ao serviço de genética clínica para investigação diagnóstica devido a atraso de desenvolvimento neuropsicomotor, segundo filho de pais jovens hígidos e não consanguíneos, nascido de parto cesáreo (indicação: pós-datismo), evoluiu com hipotonia e sucção débil no período neonatal. Sem antecedentes familiais relevantes. Além retardo de desenvolvimento, o exame físico revelou obesidade, baixa implantação de cabelos na nuca, fendas palpebrais estreitas e oblíquas para cima, prega epicântica interna e ptose palpebral bilateral, filtro curto, incisivos centrais proeminentes. Realizados exame de cariótipo, teste molecular para síndrome do X frágil e pesquisa de rearranjos subteloméricos pela técnica de MLPA, todos sem alterações. Pela associação de deficiência intelectual e obesidade, também foram consideradas as hipóteses das síndromes de Prader Willi e Cohen, afastadas com base na evolução fenotípica, sendo mantido seguimento clínico anual. Após dez anos, realizada hibridização genômica em arrays (SNP-array) que identificou uma deleção intersticial de 6,9MB em 15q21.2q22.2 classificada como patogênica.
Exames complementares: Cariótipo de sangue periférico (bandamento G, 600 bandas por lote haplóide, 16 células analisadas): 46,XY.
Análise do gene *FMR1* por *Southern Blotting*: Padrão indicativo de repetições CGG dentro da normalidade.
Pesquisa de rearranjos subteloméricos pela técnica de MLPA (Salsa MLPA P036 MRC Holland): Dentro da normalidade.
Hibridização genômica em arrays (SNP-array): arr[GRch37]15q21.2q22.2(52654281-59511540)x1.

Hipótese diagnóstica: Deficiência intelectual, obesidade e sinais *minor* associados a deleção 15q21.2q22.2

Conclusões: As deleções intersticiais do cromossomo 15 que não envolvem a região crítica de Prader Willi e Angelman são eventos raros e dificilmente diagnosticados antes do advento da hibridização genômica em *arrays*. Cerca de quatorze casos foram registrados na literatura com deleção envolvendo a região 15q21.1q22.2, sendo ao menos um deles parte de um rearranjo complexo envolvendo perda e ganho de outras regiões cromossômicas. Em 2005, tais casos foram revistos, na tentativa de estabelecer um padrão fenotípico que caracterizasse uma nova síndrome de microdeleção. No entanto, apesar de algumas similaridades, o número reduzido de casos e a inespecificidade dos dismorfismos, além da heterogeneidade da investigação citogenética e molecular, dificulta a caracterização de um fenótipo clinicamente reconhecível e do estabelecimento da região crítica responsável por tal fenótipo. Ressalta-se então a importância de registrar e

compartilhar os achados clínicos e citogenômicos em bases de dados públicos no intuito de acelerar a correlação genótipo-fenótipo e possibilitar o reconhecimento de novos quadros sindrômicos, contribuindo assim tanto para facilitar o diagnóstico clínico-laboratorial dos pacientes, quanto para a caracterização de novos fenótipos e a interpretação dos achados laboratoriais oriundos das novas ferramentas citogenômicas, como o hibridização genômica em arrays.

Material adicional: Fotos

Código #13311

Title: TESTICULAR SEX DIFFERENTIATION DISORDER: CASE REPORT OF XX MALE.

Authors: Ana Maria Figuerêdo de Carvalho Barbosa; Bethânia de Araújo da Silva Amaral; Amanda de Lima Schuler Borges, Marina Araújo Fonzar Hernandes; Rodrigo Neves Florencio; João Bosco de Oliveira Filho.

Authors' Institutions: Genomika Diagnósticos - Recife, Pernambuco, Brazil.

Objectives: The presence of the XX male syndrome or testicular sex differentiation disorder was evaluated in a 23-year-old man with complete masculinization, but complaining of infertility resulting from azoospermia and cryptorchidism.

Methodology: The conventional and molecular cytogenetic study was carried out through the band G and band C karyotyping, fluorescent *in situ* hybridization (FISH) using SRY gene probe and CGH+SNP microarray. Further was also performed the screening for AZF microdeletions using PCR**.**

Results: The band G karyotyping showed a 46,XX karyotype with increase in length of heterochromatin in long arm of chromosome 1 and addition of unknown origin in long arm of chromosome 9. Band C results confirmed the presence of increased heterochromatin for chromosome 1 and showed that the addition long arm of chromosome 9 represented another increase of heterochromatin region. CGH+SNP microarray did not show any other alteration then the absence of the chromosome Y and the presence of two X chromosomes. FISH analysis showed presence of SRY gene on one of the X chromosomes and PCR analysis for the three azoospermia factor regions (AZFa, AZFb and AZFc) showed absence of any Y-chromosome derivated material from these regions.

Conclusion: The patient here described is a case of XX male sex reversal syndrome SRY-positive, one of the rarest sex chromosomal aberrations that have been clinically seen. The genetic investigation of SRY gene in patients with infertility it's important to determinate the prognosis and treatment to be followed. Thus The 46,XX sex differentiation disorder it is a very rare condition, incident in 1/20,000-30,000 newborn boys, it could have a higher frequency on human reproduction centers.

Código #14328

Título: TRANSLOCAÇÃO BALANCEADA ENTRE 10q22.3 E 17q25 EM PACIENTE XX COM FENÓTIPO MASCULINO.

Autores: Jessica Cavalcante dos Santos de Paiva[1]; Maria Juliana Rodovalho Doriqui[2], Ingrid Araújo de Oliveira[2], Maria do Perpétuo Socorro Balby Pires[2], Liana Moraes Leite[2] , Elis Vanessa de Lima Silva[1], Antônio Augusto Lima Teixeira Júnior[1], Fabrício Maciel Soares[1], Vanessa Ribeiro Moreira[1], Silma Regina Ferreira Pereira[1].

Instituição dos Autores: 1. Universidade Federal do Maranhão, Brasil; 2.Hospital Infantil Dr. Juvêncio Matos.

Resumo do caso: sexo masculino, primeiro filho de pais jovens, não consanguíneos. Mãe fez 8consultas prenatais, exames bioquímicos e 2ecografias não detectaram alterações. Refere que apresentou edema em membros inferiores, parestesia em mãos, amniorrexe prematura (4dias antes do parto). Foi realizada cesárea, com 39semanas, paciente apresentou peso adequado para a idade gestacional, Apgar 7/8. Evoluiu com desconforto respiratório, necessitou manobras de reanimação; não conseguiu sugar seio materno, recebeu alta aos 3 dias de vida, com leite Nestogeno em mamadeira. Aos 4 dias, a mãe percebeu regurgitações pelo nariz e observou que o filho apresentava fenda palatina posterior. Avaliado por Cirurgia Bucomaxilofacial aos 2anos e 2meses, programando correção cirúrgica; encaminhado para avaliação por Cardiopediatria, Genética Médica. Quanto aos marcos do desenvolvimento neuropsicomotor, o paciente andou sem apoio com 14meses e falou primeiras palavras com cerca de 1 ano e meio. Ao exame clínico-dismorfológico, aos 3 anos e 1 mês, com 9900g (<p3), comprimento de 88cm (<p3), perímetro cefálico de 48,5cm (p25), foram observados baixo ganho ponderoestatural, linguagem verbal de difícil compreensão, interage bem, marcha atípica, nariz com ponta bulbosa, orelhas baixo implantadas, rodadas posteriormente, antihélices proeminentes, fenda palatina posterior, retrognatia; tórax, coluna, abdome, membros e pele/fâneros sem alterações aparentemente significativas; genitália masculina, pênis com meato uretral tópico, presença de *cordee*, gônadas palpáveis em bolsa escrotal bilateralmente. Exames complementares realizados: cariótipo 46,XX,t(10;17)(q22.3;q25), cariótipo materno 46,XX (aguardando pai comparecer para coletar amostra); análise molecular não detectou presença de genes SRY, DAZ, AMGY; triagem neonatal, avaliação oftalmológica e cardiológica normais.

Hipóteses diagnósticas: paciente com baixo ganho ponderoestatural, anomalia no desenvolvimento sexual (sexo reverso), fenda palatina posterior e dismorfias craniofaciais com translocação cromossômica aparentemente balanceada - t(10;17)(q22.3;q25). Conclusões: a translocação entre os braços longos dos cromossomos 10 e 17 é rara; não sendo encontrado caso semelhante na literatura. Houve provavelmente disrupção gênica nos pontos de quebra, podendo indicar genes candidatos para a cascata de determinação sexual; bem como para formação do palato. Em 17q25.3 foi mapeado o gene CBX2, cujas mutações em ambos os alelos estão relacionadas a fenótipo de sexo reverso em indivíduos 46,XY (Phenotype MIM number 613080). Contíguos ao gene supracitado, estão os genes CBX8 e CBX4, também de regiões genômicas altamente conservadas, e para os quais ainda não há alterações fenotípicas

claramente definidas. Ressalta-se que em humanos, o gene SOX9 está localizado em 17q24, próximo ao ponto de quebra observado pela análise citogenética convencional no presente caso.

Este gene é expresso nos testículos em desenvolvimento (em baixos níveis nos primórdios gonadais femininos e masculinos e sua expressão persiste nas células de Sertoli, desaparecendo no tecido ovariano) e em condensações mesenquimais precursoras de cartilagens e ossos. Dados experimentais sugerem que o gene *SOX9* é um gene determinante testicular; há ainda descrição de caso de sexo reverso 46,XX associado à duplicação da região genômica contendo o gene *SOX9*, sugerindo que a expressão aumentada do gene poderia determinar o desenvolvimento da gônada masculina na ausência do gene *SRY*. Portanto é recomendável a investigação detalhada da região envolvida na translocação, além da definição sobre tratar-se ou não de rearranjo novo ou herdado; fundamentais para o aconselhamento genético adequado.

Material adicional: (cariótipos, fotos)

Código #14340

Título: TRISSOMIA PARCIAL DE CROMOSSOMO 15 E MONOSSOMIA PARCIAL DE CROMOSSOMO X.

Autores: Fabrício Maciel Soares[1], Elis Vanessa de Lima Silva[1]; Jéssica Cavalcante dos Santos de Paiva[1]; Antônio Augusto Lima Teixeira Júnior[1]; Maria Juliana Rodovalho Doriqui[2].

Instituição dos Autores: 1. Universidade Federal do Maranhão, São Luís – MA, Brasil. 2. Hospital Infantil Dr. Juvêncio Matos. Laboratório Hermes Pardini, Hospital de Clínicas da Universidade de São Paulo, Brasil.

Resumo do caso: Paciente, sexo feminino, primeira filha de pais jovens, não consanguíneos, com diagnóstico pré-natal de dilatação de vias urinárias. Nega intercorrências durante gestação ou parto (nasceu de parto cesáreo, a termo, com 2740g, 47cm, perímetro cefálico e Apgar ignorados), alta aos 3dias. Aos 4 dias, evoluiu com desconforto respiratório, sendo diagnosticado defeito parcial do septo atrioventricular (corrigido cirurgicamente aos 15 meses), programando ainda correção de estenose aórtica supravalvar. Relato de atraso no desenvolvimento neuropsicomotor (sustento cefálico com 5meses; sentou com apoio 1ano; andou sem apoio com cerca 1ano 9meses, primeiras palavras com cerca de um ano, evoluiu com atraso de fala). Ao exame dismorfológico foram observados: filtro nasolabial longo, ausência de outras dismorfias faciais aparentemente significativas, tórax alargado, membros simétricos, persistência dos coxins fetais, hipoplasia ungueal, genitália feminina anatômica; com 1ano e 8meses Peso: 9335g (<p3), medindo 77cm (p5) Perímetro Cefálico (PC): 49cm (p90); aos 4anos e 6meses com 14900g (p10/25), 99cm (p10), PC: 52,5cm (p50/97), distância Intermamilar: 12,5cm (p25/50). Exames complementares realizados: triagem neonatal, IgA, IgG, IgE, proteínas totais e frações, função tireoidiana, ferro, ferritina, triglicerídeos, ácido úrico, antitransglutaminase IgA, IgF1, AST, ALT, VHS, glicemia, uréia, creatinina, hemograma, lipidograma, cálcio, cintilografia renal, eletroencefalografia, todos dentro da normalidade. Ecocardiograma evidenciou defeito de septo atrioventricular parcial. Tomografia de crânio mostrou dilatação dos ventrículos supratentoriais sem sinais hipertensivos; alargamento de sulcos e cisternas basais. Ecografia pélvica: útero normal para idade e ovários não visualizados. Cariótipo 46,X,der(X)t(X;15)(q24;q11.2)[30]; cariótipo materno normal. CGH Array (CytoSure 180k) revelou presença de uma duplicação de braço longo do cromossomo 15 (cerca de 79Mb) e uma deleção do braço longo do cromossomo X (64Mb – até a banda Xq21.31), ambas classificadas como patogênicas. Estudo molecular para síndrome de Prader Willi e Angelman confirmou a duplicação em heterozigose de 33 sondas consecutivas (L00865-L12924); alteração no status de metilação devido a uma diminuição de digestão nas ilhas CpG-SNRPN também foi observado, sendo compatível com duplicação em 15q11.2 de herança materna. Hipóteses diagnósticas: Translocação X;autossomo (Q95.3), *de novo,* não balanceada levando à trissomia parcial de cromossomo 15, monossomia parcial de braço longo de cromossomo X. Conclusões: Translocações X;autossomo são raras. Quando não balanceadas, como no presente caso, geralmente produz uma inativação parcial do cromossomo X alterado; atenuando dessa forma os efeitos da trissomia, ainda que não a anule, devido a inativação do autossomo ser descontínua e incompleta. No caso relatado, observam-se monossomia parcial do braço longo do cromossomo X e trissomia quase completa do cromossomo 15. As monossomias parciais do cromossomo X, cursam

com variantes da Síndrome de Ullrich-Turner, enquanto as trissomias parciais de cromossomo 15 são responsáveis por um espectro a depender também da região envolvida - sendo descritas dismorfias craniofaciais tais como filtro nasolabial longo, nariz proeminente, palato alto, pescoço curto, cardiopatia, deficiência intelectual, epilepsia, comportamento do espectro autista. Um caso semelhante ao da propósita, com t(X;15)(q22;q11.2) e fenótipo discreto, foi descrito (Am J Med Genet A. 2006 Mar 1;140(5):442-52).

Material adicional – cariótipo, fotos.

CASO CLÍNICO COM DIAGNÓSTICO

Código #13246

Title: Adams Oliver syndrome with pulmonary hypertension: a case report.

Authors: Manuella Galvão de Oliveira 1; Ricardo Henrique Almeida Barbosa 1; Luiza Virmond 1; Eduardo Perrone 1; Maria de Fátima de Faria Soares 1; Ana Beatriz Alvarez Perez 1

Authors Institutions: 1.Universidade Federal de São Paulo

Purpose: To report a patient with a clinical diagnosis of Adams Olivers Syndrome, including pulmonary hypertension, and to compare this case with previous reports in the literature.

Method: Clinical and radiological evaluation of patient referred from Pediatric Cardiology due to dysmorphic features and pulmonary hypertension.

Results: Our proband was a 13-year- old boy, born to nonconsanguineous parents. There was no familial history of genetic disease (the parents and sibship were not affected), and antenatal history was unremarkable. At birth, the patient presented with aplasia cutis congenita (parietal area of skull), vertex skull defect and terminal transverse foot defect. The neurodevelopment was normal. Meanwhile, he was diagnosed with atopic dermatitis and asthma, showing progressive worsening despite being treated. Most recently, he was diagnosed with pulmonary hypertension. The patient also had cutis marmorata telangiectasica congenital and others morphological findings compatible with Adams Oliver Syndrome. In the literature, only 8 cases of this disease were described with pulmonary hypertension. A plausible etiology for pulmonary hypertension could be related to vascular disruption due to peripheral vascular narrowing. This mechanism could also explain the other congenital defects presented in the patient (aplasia cutis and terminal transverse foot defect).

Conclusions: Clinical genetic evaluation was essential in determining the etiology of pulmonary hypertension, diagnostic elucidation and appropriate genetic counseling. Lack of knowledge about the findings of the syndrome may delay the diagnosis, such as in the case described. This case illustrates the need to investigate cardiovascular abnormalities in patients presenting with aplasia cutis and transverse terminal limb defects as soon as they are identified, since delaying the diagnosis and treatment of pulmonary hypertension causes irreversible damage to patients' quality of life and may cause death due to complications from pulmonary hypertension

Código #14178

Título: Alterações esqueléticas atípicas associadas à distribuição seguimentar de pêlos e manchas hipercrômicas.

Autores: Deivid Calebe de Souza, Clarissa Gondim Picanço de Albuquerque, Carlos Henrique Paiva Grangeiro, Tatiana Mozer Joaquim, Thaliane Buranello, Lucimar Aparecida F Laureano, Sara Reis Teixeira, Lucia Regina Martelli.

Instituição: Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (HCFMRP-USP).

Resumo: JRD, masculino, 54 anos, casado, 4 filhos, aposentado pelo INSS (ex-segurança), católico, natural de Araguarí-MG e procedente de Ribeirão Preto-SP. Encaminhado pela Unidade Básica de Saúde por deformidades em mãos, alteração na distribuição de pilificação, manchas hipercrômicas desde nascimento, coxartrose bilateral em idade precoce. Hipertenso desde 35 anos, 6 abordagens cirúrgicas em quadril por artrose primária bilateral desde 36 anos, história de trombose de subclávia esquerda aos 50 anos. Filho de pais não consanguíneos, sem casos semelhantes na família. Ao exame: estatura 168,5cm (P10-25), peso 93kg, IMC: 33, PC 57,5cm (p90-97), apresenta pilificação presente apenas em hemitórax D e membro inferior E, respeitando a linha média. Lesões hipercrômicas, maculares, lineares, iniciando em 3^{o} QDD e progredindo para palma de mão, poupam antebraço e braço D, mácula numular em tórax D, com pigmentação em folha, vasos arboriformes (CBC superficial pigmentado à dermatoscopia); lesões hipercrômicas lineares na face posterior de perna D até atingir o pé; assimetria das mãos (D<E) com polissindactilia pré-axial D, encurtamento de 1º, 2º e 5º QDDs à D e 3º à E, com sindactilia cutânea parcial de 3º e 4º QDDs à E, discreta hipertrofia de MSD, múltiplas pápulas em região de axila direita e marcha claudicante.

Exames complementares: Radiografia de mãos e pés evidencia: polissindactilia pré-axial com encurtamento e alargamento de todos os ossos do 1º raio à D, falange média de 2º raio é curta e alargada, o mesmo acontece com a falange proximal do 3º raio, apresenta ainda 5º metacarpo curto à D e encurtamento de falange média e 3º raio à E; encurtamento de 2º metatarsos bilateralmente; raio X de quadril evidencia extenso desgaste ósseo, a descrição fica comprometida devido às repetidas abordagens cirúrgicas (não possuímos radiografias prévias à colocação das próteses); o exame citogenético a partir de cultura temporária de linfócitos e fibroblastos (foram realizadas culturas de pele dos quatro membros) resultou em: 46, XY inv(9)(p13q21), biópsia de lesão de tórax D: CBC pigmentado e biópsia de lesão em perna D: presença de lesão sugestiva de amiloidose. Outros exames complementares (Ressonância de encéfalo, revisão de lâmina de biópsia, radiografias, exame oftalmológico e odontológico) já foram solicitados.

Hipóteses diagnósticas: Síndrome de Happle-Tinshert, Gorlin, Proteus

Conclusão: A Síndrome de Happle-Tinshert se caracteriza pela presença de hamartoma folicular basalóide unilateral segmentar que segue as linhas de Blaschko, distrofia de unhas, polidactilia, hemihipertrofia, hipotricose ou hipertricose, hipopigmentação e hiperpigmentação da pele, além de anomalias esqueléticas e cerebrais. Existem apenas 12 casos descritos na literatura, sendo todos os relatos esporádicos. A etiologia da síndrome ainda é desconhecida, mas acredita-se que a origem seja um mosaicismo.

Material adicional: Cariótipo de cultura de linfócitos e fibroblastos, radiografias, anatomopatológico e fotografias.

Código #13292
Title: AUTOSOMAL RECESSIVE OMODYSPLASIA:PRENATAL AND POSTNATAL FEATURES

Authors: Tales Shinji Sawakuchi Minei, Ramon Magalhães Mendonça Vilela, William Osamu Toda Kisaki, Tális Manoel Strack Lima, André Campos da Cunha**,** Gisele Calai, Jamile Dutra Correia, Paulo Ricardo Gazzola Zen, Rafael Fabiano Machado Rosa*.

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Objectives: Our aim was to report the prenatal and postnatal findings of a patient with autosomal recessive omodysplasia.

Methods: It was made the report of the fetus/child with a literature review.

Results: The pregnant woman presented 38 years and she was in her seventh pregnancy. She was initially assessed in fetal medicine at the hospital at 29 weeks and 6 days of gestation due to obstetric ultrasound showing short femur and humerus. The pregnancy was uneventful. Her husband presented 40 years of age and was healthy and non-consanguineous. Family history was positive for a maternal uncle with nanism. Fetal ultrasound performed at 29 weeks and 6 days of pregnancy showed reduced amniotic fluid and important rhizomelic shortening of the limbs. The humerus measured 1.8 cm and the femur 2.4 cm. The hands and feet, as well as the face and thorax seemed normal. Bone mineralization was also normal. At this point, achondroplasia/hypochondroplasia emerged as diagnostic hypotheses. GTG-Banding karyotype performed through cordocentesis revealed a normal chromosomal constitution (46,XY). Fetal echocardiography was also normal. The ultrasound performed at 35 weeks and 6 days of gestation revealed femur measuring 3.4 cm. The estimated fetal weight was 1,441 grams. The patient was born through vaginal delivery, at 37 weeks and 4 days of gestation, weighing 2,320 grams, measuring 40 cm, with head circumference of 33 cm and Apgar scores of 9 at first minute and 10 at fifth. He presented micromelia with important rhizomelic shortening of the upper and lower limbs, normal thorax and some dysmorphia: nevus flammeus at nose and glabella, small mouth, micrognathia, small ears with overfolded helix, bilateral single palmar crease and cryptochid testis.

Conclusion: Autosomal recessive omodysplasiais considered a rare skeletal dysplasia characterized by severe micromelia with shortening and distal tapering of the humeri and femora. The clinical data added to the radiological features (that included radial head dislocations) of our patient were consistent with the diagnosis of autosomal recessive omodysplasia. There are few reports in the literature of prenatal features of patients with this genetic condition. In prenatal, autosomal recessive omodysplasia has also been confused with other syndromes, as diastrophic dysplasia, due to the similarity of the findings. The definition of the diagnosis has important implications over the genetic counseling.

Código #13237

Título: Case Report: Child with Beta-Ketothiolase Deficiency

Autores: Alice Aguiar Crispim; Maria Teresa Alves da Silva Rosa; Karine Santielle Pereira Malheiros, Romina Soledad Heredia Garcia Silva; Bárbara Cátia Martins da Silva.

Instituição dos Autores: NUGEN-Núcleo de Genética Médica, Hospital de Apoio de Brasília, Brasília-DF, Brasil; HMIB- Hospital Materno Infantil Brasília, Brasília-DF, Brasil.

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Resumo do caso: This is a female newborn, first child of consanguineous parents, referred to our service with 27 days of life due to alteration of metilmalonilcarnitina/hidroxi-isovalerilcarnitina (C4DC/C5OH) in the neonatal screening test. Born late preterm with 36 weeks and 5 days of gestation because of premature rupture of membranes. She had normal weight, length and cephalic perimeter at birth. Had elevation of C4DC/C5OH in the two first blood spot test without any remarks in physical examination. The first hypothesis was organic acidemia of B12 vitamin deficiency. In follow-up evaluations she had adequate growth and development, but persisted with elevation of C4DC/C5OH and biochemistry with hypovitaminosis B12 vitamin, and was prescribed vitamins and ferrous sulfate.

At 1 year old she was admitted at hospital with respiratory distress and pneumonia was suspected. Evolved to worsen respiratory discomfort and hyperglycemia despite adequate therapeutic measures. Laboratory analysis showed leukocytosis with neutrophilia, metabolic acidosis with and high anion gap, partially improved with bicarbonate reposition. Zero protein intake, L-carnitine, and hydroxycobalmin was prescribed. Organic acids presented significant excretion of tiglilglycine and 2-methyl-3-hidroxybutyric acid and 2 methylacetic acid and expressive ketonuria and latic aciduria was observed, which confirmed beta- ketothiolase deficiency. After confirmatory diagnosis, cyanocobalamin, biotin, riboflavin, folic acid and limited protein intake with isoleucine-free metabolic formula were prescribed, with clinical improvement and ambulatory follow up.

Discussion/Conclusion: Through the neonatal screening test there was a suspicion of organic acidemia, which was evident because of metabolic descompensation with pulmonary infection. Urinary organic acids were essential for confirmation of beta ketothiolase deficiency. The treatment requiring limited protein intake with isoleucine-free metabolic formula and reposition of vitamins. A multidisciplinary team with pediatricians, geneticists and nutritionists is essential to ensure a favorable clinical evolution of these patients.

Additional material: We do have photographs of the pacient.

Código #12610

Título: CASE REPORT: MOTHER AND DAUGHTER WITH FBN1 MUTATION RESULTING IN ACROMICRIC DYSPLASIA

Autores: Ana Carolina Rathsam Leite; Talyta de Matos Cano; Graziela Paronetto Machado Antonialli; Gerson da Silva Carvalho; Cristina Touguinha Neves Medina; Maria Terezinha de Oliveira Cardoso; Robert Edward Pogue

Instituição dos Autores: Secretaria de Estado de Saúde do distrito Federal /NUGEN – Núcleo de Genética, Hospital de Apoio de Brasília, Brasil; Universidade Católica de Brasília, Brasil.

Case Presentation: This is a 9-year-old female referred to our service for investigation of disproportionate short stature. She was the first child of nonconsanguineous parents, born preterm with 36 weeks of gestation because of gestational hypertension. She had normal weight, length and cephalic perimeter at birth and there was no relevant events during her childhood. She achieved the milestones at normal age, was never seriously ill, had no cognitive impairment. Physical examination revealed short stature, a round face, well-defined eyebrows, epicanthal folds, bulbous nose, anteverted nostrils, hypoplasia of the midface, thin upper lip and long philtrum. She also had small hands and feet, stiff joints and camptodactyly of the hands. It was noticed that the mother, the great grandmother and an aunt of the patient also had short stature with the same dysmorphic features. Only the mother had mild intellectual disability. The child presented one episode of loss of consciousness at age 7. EEG's reveled epileptiform discharges compatible with focal epilepsy, but she never needed the use of antiepileptic drugs because there was no recurrence or other clinical implications. Magnetic resonance imaging and CT were normal. Hearing evaluation did not show any disturbance. The echocardiogram revealed mild stenosis of the pulmonary valve. Abdominal echography demonstrated renal lithiasis. Radiographic studies showed delayed bone age and cone-shaped epiphyses. Her karyotype was 46, XX. She also was submitted to CHG-array analysis which did not show any alterations. A gene panel sequencing for osseous dysplasias discovered a heterozygous variant in the FBN1 gene: c.5284C>T; p.Gly1762Ser, associated with Geleophisic dysplasia type 2 (GD). The same mutation was found in the mother of this patient.

Discussion/ Conclusions: Initially we received the exam result suggesting that it was geleophysic dysplasia, however the patient fits much better in the description of acromicric dysplasia (AD) despite the cardiac involvement. There is no evidence that the nature of mutations identified in GD is different from the mutations identified in AD. Therefore, both conditions are allelic and have overlapping features, so it is necessary to understand the criteria to establish the correct diagnosis. Short statute, joint limitations, short hands and feet, skin thickening, delayed bone age, cone-shaped epiphyses, shortened long tubular bones, and ovoid vertebral bodies are present in either AD or GD. Nevertheless, each one of these two types of acromelic dysplasia have some peculiarities that allow them to be distinguished.

Additional Material: We do have photographs of the mother and daughter, as well as their radiographies.

Código #13333

Título: CASE REPORT: SCHWARTZ-JAMPEL SYNDROME

Autores: Cleiton Fantin[1] ,Denise C. Benzaquem[1], Vânia Mesquita Gadelha Prazeres[2].

Instituição dos Autores: [1]Laboratório de Citogenética da Universidade do Estado do Amazonas.[2]Universidade Federal do Amazonas/Departamento de Saúde Materno Infantil .

Objectives: This study aims to report the case of a patient with a clinical diagnosis of SJ seen at the medical genetics outpatient clinic of the Association of Parents and Friends of the Exceptional Manaus (APAE / Manaus).

Methodology: Information was obtained through consultations and revision of the chart as well as the photographic and radiographic record. A retrospective and observational study was carried out to collect information about the evolution of the clinical picture and the main complications of the patient.

RESULTS: DNO, 5 years old, the seventh daughter of a non-consanguineous young couple, from a population isolated from the interior of Amazonas . Pregnancy, childbirth and neonatal without intercurrences, the couple has 7 children in all, the third (male) with intellectual disability and the oldest male also has behavioral changes. The patient started the clinical picture at 9 months of age, when muscle contracture was noticed after intramuscular injection stimulation due to acute viral illness. It evolved with progressive worsening of muscle contractions, difficulty in gaining weight and short stature. It is found in Z-score -3 for height. The physical examination showed short stature, permanently contracted facies, giving impression of crying, palpebral ptosis muscular hypertrophy, hyporeflexia, characteristic posture with rigid and flexed articulation. The Rx presents flattening of vertebral bodies, Irregular epiphyses hip dysplasia. Conclusion: The clinical phenotype described above, besides the characteristics of skeletal dysplasia and with myotonia correspond to the Diagnosis of Schwartz-Jampel syndrome.

Código #14315

Title: Clinical and Genetic features in a Brazilian patient with Cerebral Cavernous Malformations.

Authors: Fabrícia Lima Fontes-Dantas[1], Jorge Paes Barreto Marcondes de Souza [1, 2], Marcelo Chagas Muniz [2], Soniza Vieira Alves-Leon[1, 2].

Authors Institution: 1-Programa de Pós Graduação em Neurologia da Universidade Federal do Estado do Rio de Janeiro (UNIRIO). 2- Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro.

Case Report: An eight-year-old Caucasian (self-declaration) girl came for a neurological evaluation. The patient was admitted to our institution with acute ataxia and diplopia, which improved in a few days. Brain Magnetic resonance image (MRI) showed great hemorrhage in the brainstem. She presented new small episodes of hemorrhage with less expressive symptoms a few months later. MRI with a higher sensitivity to hemosiderin (SWI?) demonstrated that she had numerous lesions beyond those found in the brainstem. Diagnosis of cerebral cavernous malformation (CCM) was established on the basis of cerebral MRI and clinical data. In March 2011, with twenty-six years old, the *CCM1* gene was sequenced by Prevention Genetics (USA) using the ABI 3130xl platform (Applied Biosystems) from blood samples, and no variation was detected. In 2013, the same company sequenced the *CCM2* and *CCM3* genes and as result were identified the *CCM2* c.915 G>A and *CCM3* c.475-2 A>G mutations in heterozygosis. The patient has MRI for all the evolution of her case and control of the progression of lesions. She had three recent cerebral hemorrhages (out brainstem), with seizures, associated with the use of oral contraceptives for the treatment of ovarian cysts. Since then, she remains asymptomatic, using two anticonvulsants. Due to CCMs phenotypic expression be variable between the affected members of the same family, molecular analysis should be extended to disclose unaffected parents and genetic risk in subjects who are either asymptomatic or possible silent lesions. Her parents and her only sister had their *CCM1, CCM2* and *CCM3* genes sequenced and as result they did not present any variation in these genes. Additionally, MRI of the brain doesn't reveal lesions or hemorrhages in these family members. CCMs are vascular abnormalities that may cause seizures, headaches, intracerebral hemorrhages, and focal neurological deficits that can be found in sporadic or familial form, with an autosomal dominant inheritance. CCMs have been reported to be linked to three chromosomal loci, and loss-of-function mutations have been identified in *CCM1*, *CCM2*, and *CCM3* genes, which encode the protein skrev/rap1 interacting trapped1 (KRIT1), malcavernin (MGC4607), and programmed cell death 10 (PDCD10) respectively. These proteins are involved in regulation of angiogenesis and stress response. Nevertheless, CCMs are characterized by an incomplete disease penetrance with up to 30–45% of all patients remaining asymptomatic. Although genotype-phenotype correlations for *CCM1* and *CCM2* mutations are still unclear, a great aggressiveness and an early onset were observed in *CCM3* mutations carriers. In our proband, molecular analyzes indicated a de novo *CCM2* synonymous mutation c.915G>A (rs2289367, p.T305T), with benign clinical significance. In addition, the sequencing of *CCM3* revealed de novo splice site mutation c.475-2 A>G (p.A119Gfs*42). This variation promotes the production of a truncated protein. The variations found suggest a non-Mendelian inheritance since the proband did not inherit any allele from parents. Probably, the *CCM3* c.475-2 A>G mutation affect αG-helix of the focal

adhesion targeting (FAT)-homology domain, which is responsible for direct interaction with MGC4607 and with paxillin. This interaction is essential for cell-cell junctions regulation, cell-extracellular matrix adhesion, cell cycle regulation, proliferation and migration of cells and cell cycle regulation. This report emphasizes the need of understanding the mutations in *CCM* genes and the associated phenotypes, which is beneficial for the genetic counseling of patients and your families. The most important benefit of predictive genetic testing would be the exclusion of a mutation carrier status, which reduces the fear of presenting serious complications and performing unnecessary MRI.

Imagens das ressonâncias magnéticas, laudos de testes genéticos e heredograma disponíveis.

Código #13344

Título: COMPLICAÇÃO MATERNA EM GESTANTE COM ATAXIA CEREBELAR TIPO 2: RELATO DE CASO

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Objetivos: Este trabalho tem como objetivo descrever as complicações ocorridas durante o período gestacional de uma mulher com ataxia cerebelar tipo 2.

Metodologia: Relato de caso. Os dados foram coletados por meio de consulta às anotações contidas no cartão da gestante, entrevista norteada por um instrumento previamente testado e resultados de exames complementares de imagens, sangue e urina. A paciente é participante voluntária de pesquisa desenvolvida pelo Laboratório de Genética Humana – LGH da Universidade Federal de Rondônia – UNIR, cujo objetivo é identificar, realizar diagnóstico molecular e acompanhar clinicamente pacientes com Doenças Neurodegenerativas Raras – DNRs.

Resultados: Trata-se de uma mulher de 33 anos, com diagnóstico clínico e análise de segregação familiar compatível com Ataxia Cerebelar Tipo 2, com início dos sintomas há 8 anos. Durante sua primeira gestação ocorrida em 2016, apresentava como sintomas da DNR, agrafia, disfagia, disartria, dismetria, marcha atáxica com ampliação da base de sustentação, passos irregulares, lentos, deambulação somente com auxílio e vertigens. Confirmada atrofia cerebelar difusa em ressonância magnética. Como complicações da gestação apresentou obesidade, elevação dos níveis pressóricos necessitando da utilização de metildopa para controle, diabetes gestacional de difícil controle glicêmico e a partir da 33ª semana gestacional, anasarca. Devido ao agravamento do quadro clínico com pico hipertensivo, anasarca e proteinúria, caracterizando pré-eclampsia grave, a gestação foi interrompida por meio de cesariana no início da 37ª semana gestacional. O recém-nascido (RN) nasceu com 2,860 kg, 47 cm de estatura com Apgar de 4 e 9 no primeiro e quinto minutos, respectivamente. Nos primeiros 15 dias de vida o mesmo manifestou vários episódios de hipoglicemia, com valores glicêmicos chegando a 17mg/dl, com sintomas como letargia, taquipnéia e cianose, necessitando de intervenção terapêutica imediata. Atualmente encontra-se com desenvolvimento correspondente para a idade e a puérpera apresenta os sintomas já descritos anteriormente agora com manifestação mais acentuada, acarretando dificuldade na realização das atividades de vida diária –AIVDs assim como nos cuidados com seu filho.

Conclusão: Considerando que as DNRs como a Ataxia Cerebelar comprometem sobremaneira o estado físico e psicológico do paciente, aliada as profundas mudanças fisiológicas, emocionais e sociais que são naturais do processo gestacional, fica evidente que a gravidez nesses casos é de grande risco para o binômio mãe-filho. Ressalta-se a importância do aconselhamento genético para a

preservação da vida da mãe e para a redução do risco de transmissão da doença para as gerações seguintes. Também se destaca a necessidade de maiores pesquisas com este enfoque de forma a elucidar a predisposição, que parece existir, da ocorrência de doenças específicas da gravidez, como diabetes gestacional e pré-eclâmpsia, em mulheres com DNRs.

Código #13329

Título: Cutis Laxa syndrome associated with unusual benign tumors and liver findings

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Objetivos: This report aims to describe an uncommon association of cutis laxa syndrome with chronic liver disease and benign tumor findings.

Metodologia: This report was based on medical notes.

Resultados: Female patient was referred to genetics evaluation at age 21 months with clinical diagnosis of cutis laxa syndrome. Proband was born after an uneventful term pregnancy; with 6 month of pregnancy the mother was inpatient for two days due to risk of premature labor. C-section was performed, birth weight 3,100 g; birth length 44 cm; uneventful neonatal period. Patient had a normal psychomotor development. Physical exam: weight (P75), height (P25-50), head circumference (P3-10); sagging, wrinkled skin, hooked nose, long philtrum, several verrucoid lesions on the face and extremities, presented hair loss and bilateral small palpable lumps on the occipital bone. Normal intelligence in childhood, mild cognitive deterioration developed later. Delayed tooth eruption. At age 17 she presented with elevated liver enzymes, liver biopsy showed perisinusoidal fibrosis with reverse lobulation. Normal brain MRI. Corpus callosum dysgenesis. Normal ceruloplasmin. Pleural biopsy revealed chronic granulomatous pleuritis associated with tuberculosis. At age 21 diagnosed with dermatofibroma. At age 22 she was diagnosed with leiomyomatous tumor (low grade mesechymal neoplasia ?) in the left shoulder.

Conclusão: This patient presents infrequent findings, not related to the syndrome in question based on the literature.

Código #14338

Título: Deficiência de ECHS1, uma rara causa de síndrome de Leigh diagnosticada por sequenciamento completo do exoma e análise funcional.

Autores: Bibiana Mello de Oliveira; Helena Fussiger; Ana Paula Kurz de Boer; Felipe de Siqueira Toledo Koerich Kahl; Claudia Fernandes Lorea; Carolina Fischinger Moura de Souza; Jonas Alex Morales Saute.

Instituição dos Autores: Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Resumo do caso: Paciente de 5 anos, do sexo masculino, em investigação ambulatorial de quadro de regressão de desenvolvimento neuropsicomotor, crises convulsivas e sinais piramidais. Apresentou desenvolvimento adequado até 1 ano e 6 meses de vida, quando iniciou quadro epiléptico e evoluiu com regressão de marcos do desenvolvimento previamente adquiridos. História pré e perinatal não evidenciou dados sugestivos de insulto ou intercorrências. É o quarto filho de pais não consanguíneos, sem recorrência de quadros semelhantes na irmandade. Ao exame apresentava estrabismo convergente, hipotonia axial, hipertonia e hiperreflexia apendicular, reflexo cutâneo-plantar extensor, movimentos coreoatetóticos e contratura de aquileus. Investigação laboratorial evidenciou aumento dos níveis de ácido 3-OH-isovalérico e 3-metil-glutacônico urinários, além de intermediários do Ciclo de Krebs. Lactato sérico mostrou-se aumentado em duas coletas diferentes. Realizou extensa investigação metabólica complementar, com demais exames dentro dos valores da normalidade. Realizou ressonância magnética de crânio com espectrometria aos 2 anos, com alteração de sinal e redução volumétrica dos núcleos da base, sugestiva de doença mitocondrial, apesar da ausência de pico de lactato. A avaliação oftalmológica foi normal aos 2 anos e em reavaliação, aos 4 anos, apresentava palidez de papilas ópticas bilateralmente. Considerando a hipótese clínica de encefalopatia mitocondrial com fenótipo sugestivo de síndrome de Leigh, foi solicitado sequenciamento completo do exoma (WES). O WES identificou duas variantes em *trans* (heterozigose composta) no gene *ECHS1* (c.394G>A - variante patogênica - e c.713C>G - variante de significado incerto), confirmado por análise dos pais. A proteína codificada por este gene é a Enoil-CoA hidratase de cadeia curta mitocondrial (ECHS1), uma enzima multifuncional da matriz mitocondrial que atua no metabolismo de ácidos graxos de cadeia curta e aminoácidos de cadeia ramificada. Os dados clínicos disponíveis na literatura até o presente momento são limitados, e os casos descritos são compatíveis com o quadro de encefalopatia mitocondrial. Em quatro casos foi descrita cardiomiopatia. Após resultado da investigação molecular, foi realizado aconselhamento pós-teste e indicada investigação complementar através de avaliação da atividade enzimática. A atividade da ECHS1 em fibroblastos do paciente estava três vezes abaixo do limite inferior da normalidade, confirmando o diagnóstico de síndrome de Leigh por deficiência de ECSH1. A síndrome de Leigh é a apresentação mais frequente de encefalopatia mitocondrial de início na infância, tendo atualmente mais de 75 genes associados a este fenótipo, codificados tanto pelo genoma nuclear quanto mitocondrial. O WES com ou sem análise do genoma mitocondrial parece ser uma estratégia adequada para avaliação de pacientes com suspeita de síndrome de Leigh.

A confirmação diagnóstica possibilita adequado manejo e aconselhamento genético para as famílias.

Material adicional: Neuroimagens (Ressonância magnética de crânio com espectroscopia de prótons); Resultado de sequenciamento completo de exoma; Resultado de análise enzimática

Código #14319

Title: Dropped head syndrome as a manifestation of Charcot-Marie-Tooth disease type 4C: a case report

Authors: Camila Maria de Oliveira[1], Helena Fussiger[1,3], Ana Paula Kurz de Boer[1], Laura Bannach Jardim[1,2,3,4], Jonas Alex Morales Saute[1,2].

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Clinical data: An 11-year-old boy born to consanguineous parents presented with predominantly proximal muscle weakness and atrophy with facial involvement, including bilateral palpebral ptosis, associated with dropped head and severe scoliosis. Other signs were hypotonia, generalized areflexia, impaired vibration sense, tongue fasciculations, divergent strabismus and sialorrhea. Symptoms started at the age of 3 with frequent falls and foot torsions. At the age of 6, he needed walking aids and at the age of 8 he was wheelchair-dependent. Pregnancy, delivery and neuropsychomotor development were normal. No similar cases were reported in the family.

Diagnostic work-up: Nerve conduction velocities were markedly reduced, compatible with a sensorimotor demyelinating polyneuropathy. Normal blood levels of creatine kinase, lactate, β-galactosidase, galactocerebrosidase, arylsulfase A and VLCFA were found. Urinary sulfatides chromatography and serum transferrin isoelectric focusing were normal. A comprehensive multigene next-generation sequencing panel for CMT was ordered (Invitae, USA) revealing the homozygous pathogenic missense mutation c.1969G>A (p.Glu657Lys) in *SH3TC2*.

Differential diagnosis: Considering the clinical picture of early-onset proximal muscle weakness with facial involvement and dropped head and the history of consanguineous parents, our first hypotheses were congenital myopathy or myasthenic syndromes. However, as nerve conduction studies consistently suggested a demyelinating polyneuropathy, an atypical form of Charcot-Marie-Tooth disease type 4 (CMT4) became the leading hypothesis in the differential diagnosis. CMT4 is a group of demyelinating autosomal recessive neuropathies caused by mutations in at least 11 different genes with significant clinical heterogeneity.

Conclusions: The multigene next-generation sequencing panel for CMT revealed the homozygous pathogenic missense mutation c.1969G>A (p.Glu657Lys) in *SH3TC2*, thus confirming CMT4C diagnosis. This variant disrupts SH3TC2 cellular localization, protein-protein interaction and function and has been previously reported as associated with CMT4C phenotype. The present report adds dropped head as a disease feature and raises the importance of considering early-onset inherited neuropathies in the differential diagnosis of patients with proximal muscle wasting associated with dropped head syndrome.

Additional material: Video, pictures.

Código #14342

Title: Early initiation of elosulfase alpha is associated to better outcomes in Mucopolysaccharidosis IVA (MPS IVA).

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Authors Institution: Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil. Universidade Federal do Rio Grande do Sul, Rio Grande do sul, Brasil.

Case Report: We report 2 patients with MPS IVA disease from the same family, consanguineous parents, and analyze their differences regarding disease severity considering the different ages at ERT start. Patient 1: male, 8 years old. He started walking at the age of 1 year and 4 months. At 2 years of age, prominent skeletal abnormalities were noticed. He was diagnosed with MPS IVA at the age of 6 years, Quantitative GAGs 335 ug/mg (VR 53-115 ug/mg of Cr), GAGs electrophoresis showed Keratan Sulfate, Galactose-6-sulfate Sulfatase indetectable and started elosulfase alpha infusions when 8 years old. Molecular exam *GALNS* gene showed c.Gly301Cys (p.Gly301Cys) in homozygosis. He is currently well, but with prominent skeletal abnormalities and a very short stature (Z-score -6.4). His MRI shows cervical stenosis, without cord compression. Patient 2: a first cousin of patient 1, male, 2 years old. He was diagnosed with MPS IVA at the age of 8 months, Quantitative GAGs 232 ug/mg (VR 133-274 ug/mg of Cr), GAGs electrophoresis showed Keratan Sulfate, Galactose-6-sulfate Sulfatase 4,4 nmoles/h/protein (VR 58-242 nmoles/h/protein) and started the ERT at 18 months of age. Molecular exam *GALNS* gene showed c.Gly301Cys (p.Gly301Cys) in homozygosis. His current length Z score is -0.9. Moreover, in spite of having signs of cord compression, he had a marked improvement of his mobility after ERT and physical therapy. Conclusion: While individual differences may also be important even in related patients, these cases are in accordance to the concept that early initiation of ERT is associated to better outcomes in MPS IVA. Additional material: patients pictures, Hip and Spine X – ray and Brain and Spine MRI.

Código #13358

Title: Hereditary predisposition to pheochromocytoma: report of a family with mutations in two genes and management considerations

Authors: Fernanda Teresa de Lima[1,3]; Larissa Barbosa de Lima[2]; Daíse Moreno Sás[2]; Camila Maida de Pontes[1]; Eliana Maria Monteiro Caran[1]

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Case report: A family of three siblings accompanied in a pediatric children's hospital is reported, two with suprarenal pheochromocytoma and one with intermittent arterial hypertension. The children are the offspring of a young non-consanguineous couple. The father presented right suprarenal pheochromocytoma at the age of 8 years and left suprarenal pheochromocytoma at age 17, on the latter occasion with pulmonary metastases, and at 32 years was diagnosed with thyroid cancer, neuroendocrine tumor of the pancreas and tumor of Sertoli cells. He was submitted to pancreatectomy and right orchiectomy, evolving with retro-gastric abscess, septic shock, and death. There was not enough time for anatomopathological investigation of the thyroid tumor. The eldest son presented pheochromocytoma at 12 years, being submitted to left adrenalectomy. The younger son presented pheochromocytoma at 6 years of age, treated with right adrenalectomy and the middle child presented with intermittent arterial hypertension, being in clinical follow-up and drug treatment for hypertension. In view of family history, hereditary predisposition to pheochromocytoma was suspected. As the molecular tests for mutation identification are unavailable in the Brazilian Unified Health System, the family obtained a donation, and the three siblings were tested with a multigene panel at the same time. This identified mutations in two genes associated with hereditary predisposition to pheochromocytoma. In the two brothers with pheochromocytoma, the same variant was identified in heterozygosis, in exon 1 of the *VHL* gene, c.340G> A (p.Gly114Ser), classified as pathogenic. The *VHL* gene causes von Hippel-Lindau disease (VHL), associated with pancreatic endocrine tumors and pheochromocytoma. Families with VHL and pheochromocytoma are classified as type 2, more commonly associated with missense mutations. The mutation at codon 114 is considered a mutation that changes a deep protein residue, although in the literature it is the missense mutations that alter surface protein residues that are most correlated with pheochromocytoma. In the sibling with intermittent systemic arterial hypertension, a heterozygous variant was identified in exon 5 of the *SDHC* gene, c.263C> A (p.Ser88Ter), which leads to a truncated protein, classified as probably pathogenic variant. The C subunit of the succinate dehydrogenase, *SDHC* gene, is a gene associated with three entities linked to a predisposition to pheochromocytoma and gastrointestinal stromal tumors: Carney-Startakis syndrome, familial gastrointestinal stromal tumors and familial paragangliomas. The latter is also associated with thyroid cancer of the papillary subtype. None of the mutated genes found are associated with Sertoli cell tumors.

Conclusions: Hereditary predisposition to pheochromocytoma is rare. Two genes involved in this predisposition are mutated in the same family, reported above. The mutation found in the *VHL* gene is normally associated with a lower predisposition to pheochromocytoma, contrary to what is observed in this family. This generates considerations about the impact that genotype-phenotype correlations may have on disease management. The implication of paternal tumors and of the different mutations found, raises controversies in the definition of oncological prevention and surveillance for the boys, and considerations for the genetic counseling of other family members.

Additional material - pedigree, pathology reports, abdominal tomography, molecular test result.

Código #14148

Título: LEUCOENCEFALOPATIA DO ADULTO COM ESFEROIDES AXONAIS E GLIA PIGMENTAR: UMA CAUSA RARA DE DEMÊNCIA RAPIDAMENTE PROGRESSIVA NO ADULTO

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Instituição dos Autores: Serviço de Neurogenética, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Resumo do caso: Paciente feminina, de 46 anos, natural de Duque de Caxias/ RJ, procedente de Porto Alegre, primeiro grau completo, começou com quadro de alteração de humor (sintomas depressivos), em julho de 2016. Iniciou acompanhamento psiquiátrico e uso de medicamentos antidepressivos, mas sem resposta clínica. Os sintomas pioraram progressivamente, evoluindo para quadro demencial após quatro meses. Simultaneamente, teve dois episódios de crise convulsiva tônico-clônica generalizada, internando em Hospital Terciário para investigação. Recebeu pulsoterapia com metilprednisolona por suspeita de encefalite de Hashimoto, tendo em vista que estava em tratamento de hipotireoidismo. Não obteve resposta a este tratamento e teve alta com suspeita de doença psiquiátrica. Após, um mês, devido à piora progressiva, internou novamente. Neste momento, ao exame físico, apresentava afasia mista, apraxia de marcha e sinais de liberação piramidal. Realizou RMN de crânio que evidenciou, em T2 e FLAIR, hipersinal de substância branca com predomínio em região frontal, além de algumas áreas com restrição na difusão. Sem história de consanguinidade entre os pais (ambos provenientes de diferentes estados). A mãe tem 77 anos35, é hígida e nega história de quadros semelhantes em sua família. O pai faleceu os 55 anos por morte violenta, e não se tem dados da história familiar do mesmo. A paciente é a irmã mais velha de uma prole de três irmãos, sendo que o irmão mais velho, de 48 anos, tem iniciou com quadro demencial progressivo aos 38 anos, atualmente acamado. Já havia sido avaliado por outra equipe e tido o diagnóstico de Marchiafava Bignami (desmielinização e necrose do corpo caloso e substancia branca periventricular, principalmente associada a desnutrição e etilismo). No entanto, além de quadro clínico semelhante, a imagem de RNM de crânio do irmão apresentava padrão muito parecido com o da paciente. Dessa forma, pela história de demência rapidamente progressiva, leucodistrofia de predomínio frontal e história familiar positiva, foram realizados os seguintes exames complementares: punção lombar com diferencial celular, glicorraquia e proteinorraquia - que não mostraram alterações - dosagem de galactocerebrosidase, arilsulfatase A, cromatografia de sulfatídeos e ácidos orgânicos na urina – também normais – descartando encefalites, doença de Krabbe, Leucodistrofia Metacromatica e acidemias orgânicas, respectivamente. Assim, pelas principais hipóteses diagnósticas de doença de Alexander e Leucoencefalopatia do Adulto com Esferoides Axonais e Glia Pigmentar (ALSP) , foi solicitado painel de leucodistrofias que evidenciou mutação p.Ala781Val, em heterozigose, no gene *CSF1R*, confirmando o diagnóstico de ALSP.

Esta é uma doença de herança autossômica dominante, caracterizada por leucodistrofia de predomínio em região anterior e quadro clínico de demência rapidamente progressiva geralmente na quarta década de vida, atualmente sem tratamento específico. A penetrância é incompleta, mas não há estimativa calculada ainda. O gene mutado codifica receptor de superfície para a citocina CSF-1, responsável pela sobrevivência, proliferação e função de células mononucleares, incluindo as microgliais. .Este foi realizado com os três filhos da paciente, adultos e assintomáticos.

Material adicional:

RNM de crânio da paciente e do irmão.

Código #13359

LI-FRAUMENI SYNDROME: CASE REPORT AND LITERATURE REVIEWS

Autores: Hanny Kirszenworcel Pereira, Débora Block Sanderson, Eduardo Dallazen, Eliege Bortolini, Letícia Leão Alvarenga, Renata Sartor Fachinelli, André Anjos da Silva

Institucion: Univates

OBJECTIVES: This study was aimed to collect literature about a case report of the Li-Fraumeni Syndrome (LFS) and to actualize a literature review to amplify the knowledge of genetics.

METHODS: This case report is referent about LFS. To achieve the objectives of study, were utilized as data source, over and above fundation bibliographic, analyses of medical records of patient and familial record.

RESULTS: pacient female, 2 years and 3 months, foward to geneticist from oncopediatrician. initially with abdominal pain. In the investigation, laboratory tests revealed increase of serum cortisol, without other laboratory alterations. Imaging, computadorized tomography and ultrasound revealed right adrenal mass, with a diameter of 8.2 cm and irregular aspect, suggestive of carcinoma. It was treated surgically by means of resection of tumor. Adrenocortical carcinoma was diagnosed in the anatomopathological study. In the sequence, genetic research was performed, with complete sequencing of the TP53 gene, with SLF confirmed with clinical and molecular diagnosis, with mutation p.Arg337His (R337H)in heterozygosis. This dominant autosomal syndrome was inherited from the father, the R337H carrier after genetic examination in the parents. In the family history is still observed paternal grandmother deceased due to breast cancer and paternal great-aunt with breast cancer at an early age.

CONCLUSION: In this case report, associated with bibliographic search and analysis of the exams and family history, we can conclude that SLF is an autosomal dominant disease of hereditary character that increases the risk of an individual developing a wide variety of cancers. That is, individuals with this syndrome are prone to develop cancer early in relation to the general population. A significant portion of the pediatric population with carcino adrenocortical fulfills criteria for SLF, the R337H mutation already known to be common in southern Brazil. Therefore, the importance of genetic counseling is related to the knowledge of this syndrome by physicians, so that they refer their patients properly, as well as the understanding of medical students about the complexity of the case, thus helping in the training of professionals who know how to advise, and prevent complications of the disease.

Keywords: Li-Fraumeni syndrome; TP53 P.R337H mutation; Hereditary neoplastic syndrome

Código #13283

Title: MARFAN SYNDROME NEONATAL FORM: CASE REPORT IN RIO GRANDE DO NORTE

Authors: Hugo Macedo de Moura; Maria Antonia Ferreira Gomes; Lana Lira Cantidio de Medeiros; Francielly Tertulino Cunha; Luciana Emerenciano Silveira; Inayara Jade Nunes Silva; Luiz Guilherme dos Santos Pinheiro; Talita Maia Rêgo; Zêmia Maria Câmara Costa Ferreira; João Ivanildo da Costa Ferreira Neri

Institution of Authors: Centro de Reabilitação e Habilitação do Rio Grande do Norte (CERH-SESAP-RN) and Universidade Potiguar (UnP), Natal-RN, Brazil.

Case Summary:

Objectives: To report the case of a patient with the neonatal form of Marfan Syndrome.

Methods: case report.

Case: I.C.G.S., female, born in 01/17/2009, referred for diagnostic definition at age of 09 months. Youngest daughter in an offspring of four of non-consanguineous parents, without related cases in the family. Mother reported bleeds during gestation. Vaginal delivery, weight of 3370g, length of 51cm, cephalic perimeter of 35.5cm, Apgar score 7/9. At the physical examination, dolicocephaly, elongated face, deep-set eyes, apparent megalocornea, large and retroverted ears with poor relief, pectus carinatum with protruding xiphoid appendix, arachnodactylia in hands and feet, large feet, heart murmur were observed. Doppler echocardiography revealed significant dilatation of the aortic valve annulus and moderate dilatation of the ascending aorta, spinal radiography showed dextroconvex scoliosis.

Discussion: Signs observed in the patient are characteristic of the neonatal form of Marfan syndrome, a genetic disease, with an autosomal dominant inheritance pattern and associated with alterations in the synthesis of fibrillin type 1 (FBN-1). As parents do not present signs suggestive of this syndrome, genetic counseling was performed, reporting a negligible risk for recurrence of this condition in their future offspring and being, similar to the general population, the chance of having children with any other genetic abnormality.

Conclusion: Since the diagnosis, was suggested to the parents that the patient has been followed up with a pediatric cardiologist, orthopedist and ophthalmologist due to the cardiac, bone and ophthalmologic abnormalities that presented and / or may present. It was determined the family's permanent follow-up in her early years of life. Finally, it is important to note that, most of the time, Marfan syndrome does not present with mental retardation, suggesting a neurological evaluation if the pediatrician deems it necessary. This case clearly illustrates the importance of early diagnosis in

rare diseases, especially for those in whom the awareness of the fact associated with simple palliative care is critical to ensuring a quality patient's life when accurate treatment is not yet commercially available.

Código #13462

Title: MESOMELIC DYSPLASIA KANTAPUTRA TYPE SEGREGATING WITH ANTECIPATION IN A FAMILY

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Summary of the case: A male child from the inside São Paulo state and with Latin-European ethnic background was referred at age of 7 months because of limbs malformations. Prenatal was uneventful. Delivery was by cesarean section at 41 weeks. Anthropometric measures at birth were normal. Likewise, his motor development is normal. Parents are young and non-consanguineous, and a similar phenotype was referred and confirmed by clinical examination in his brother, mother and maternal grandmother. It was also referred, always on the maternal side, two affected uncles and a cousin. The clinical examination of the proband showed the following features: slight facial dysmorphism (midface hypoplasia, depressed nasal root, bulbous nasal tip, full cheeks), short and bowed forearms, and hands with hypothenar hypoplasia, camptodactyly and ulnar deviation of fingers. He also had bilateral calf muscle hypoplasia and non-reducible bilateral clubfoot. X-rays showed shortness of radius, ulna, tibia and fibula, including bowed radius, bilateral changes of the ulna, and thickness of fibulae. No other skeletal changes were observed. The brother, 10 years old, presented identical clinical and radiographic features with a normal cognitive development. The mother and grandmother phenotype were more slight and characterized by slightly short forearms, hands with hypothenar hypoplasia, and clinodactyly of the fifth finger. Mild hypoplasia of calf muscles observed in the mother was not seen in the grandmother. The proposed diagnosis was mesomelic dysplasia, Kantaputra type. The mesomelic dysplasias are a heterogeneous group of disorders characterized by predominant shortness of the middle limb segments. The molecular basis underlying most of them is poorly understood. Among the 11 conditions classified as mesomelic and rhizo-mesomelic dysplasias, the phenotype of the present family is similar with that presented by the individuals described by Kantaputra in 1992 in a Thai family with AD inheritance pattern. Those individuals presented short and bowed upper extremities, ulnar deviation of hands with camptodactyly, and short legs with feet in a characteristic extended position called “ballerina's foot”. This later feature is absent in the members of the present family. By the other hand, it was observed a generational worsening, similar to the anticipation phenomenon, in these individuals. So far, 32 persons from five families have been reported, and the locus for this condition has been mapped in 2q24-q32. In conclusion, we assumed the phenotype in the affected members of the present family can be interpreted as Mesomelic dysplasia, Kantaputra type, or, it could be a variant of this dysplasia. The discovery of the precise molecular basis will be necessary to better classify these phenotypes.

Additional material: Clinical photos and X-rays of patient, brother, mother, and grandmother.

Código #13403

Título: MOMO syndrome: A possible new case – report and clinical findings in a male patient

Autores: Cecília Oliveira Pinheiro[1]; Angelina Xavier Acosta[2]; Renata Santos Ribeiro Reis[2]; Dione Fernandes Tavares[1]; Joanna Goes Castro Meira[2]

Instituição dos Autores: Liga Acadêmica de Genética Médica da Universidade Federal da Bahia (LAGeM-UFBA)[1], Hospital Universitário Professor Edgard Santos (HUPES)[2]

Introduction: MOMO syndrome is a very rare genetic disorder of overgrowth characterized by four main features: macrosomia, obesity, macrocephaly and ocular abnormalities. With only nine cases reported in literature, of which seven remain suspect. This syndrome was originally described by Moretti-Ferreira *et al.* (1993), who suggested that it is linked to a new autosomal dominant mutation. Since then, its molecular etiology, inheritance pattern, penetrance, phenotypic expressivity, and recurrence risk remain unknown. However, Vu *et al.* (2012) studied a suspected case who had an inherited homozygous balanced reciprocal translocation (16;20)(q21;p11.2) and revealed a disruption of a novel gene located at 20p11.23, *LINC00237*. Currently, the diagnosis is made essentially by phenotype comparison, excluding other clinical causes of intellectual deficiency associated with obesity.

Objectives: To describe one clinical case of a male child with possible MOMO Syndrome who was examined at the Genetic Service of the University Hospital Professor Edgard Santos (HUPES) and compared with other cases reported in the literature.

Materials and Methods: Clinical report and literature review.

Results: MSS, male, 9 years old, born in Capim Grosso, Bahia, Brazil. His birth weight was 4080 g (97th centile), delivery was normal vaginal. In his medical history, the adoptive mother reported delayed neuropsychomotor development and intellectual disability. Consanguineous family medical history accused maternal alcohol abuse during pregnancy. Patient has behavioral disorder and epilepsy and is currently medicated with Topiramate, Aripiprazole and Risperidone. Anthropometric measurements showed: high stature (90-97th centile), severe obesity (BMI: 35.31), macrocephaly (>98th centile), brachycephaly, wide frontal, long nasal philtrum, wide nasal root, thick lips, high-arched palate, dental malocclusion, taurodontism, ocular hypertelorism, large ears (P>97%) with undeveloped helix, and short neck. The examination findings were: acanthosis nigricans in cervical and axillar regions, and bilateral lipomastia. Complimentary exams: IQ of 50, mental age compatible with a 2 years, 9 month old when he was 7 years, 8 months, indicating severe intellectual disability; ophthalmologic findings were strabismus and severe myopia; karyotype showed 46,XY; molecular tests for X-fragile (*FMR1* analysis) and Prader-Willi/Angelman syndrome were both negative.

Conclusions: This patient was clinically diagnosed with MOMO syndrome. His features are compatible with MOMO's phenotype, showing 66.7% of the abnormalities previously described in the other nine cases published. This case presents macrosomia, obesity, macrocephaly and

ocular abnormalities (severe myopia and strabismus in this instance), the four main characteristics of the syndrome. Our patient is a possible new case, the tenth reported in literature, the fourth in Brazil.

Key-words: MOMO Syndrome; Intellectual Disability; Macrosomia; Obesity, Macrocephaly; Ocular Abnormalities.

Código #13223

Title: Neuronal Ceroid Lipofuscinoses (LCN2). Case report

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Authors Institution: Ambulatório Erros Inatos do Metabolismo, Hospital Infantil Waldemar Monastier, Brasil.

Abstract: L.M.P.M., 11 years old, female, was born in Foz do Iguaçu, Paraná, previously healthy, when was three years old, after eight days of a level drop, began with myoclonic seizures, that got five minutes each one, presenting psychomotor regression after it. In spite of being treated with many kinds of anticonvulsants drugs, continue with daily myoclonic episodes. HF: Uncle's maternal grandfather with schizophrenia; paternal grandmother with psychiatric illness. AGO: G2 P0 C2 A0, normal first pregnancy, a healthy brother with 7 years old, without consanguinity. DPM: sat down with 7 months, walked and spoke with 12 months, with 3 years old began psychomotor regression, ataxia, dysarthria, dysphagia and with 6 years old stopped walking and talking. EF: W:35 kg, H:130 cm, CP:50 cm, visual loss, sialorrhea, axial hypotonia, spastic tetraplegia, pyramidal signs present, and frequent myoclonic seizures, gastrostomy and tracheostomy.

Exams: EEG: disorganized activity, frequent discharges of spike and waves in bilateral fronto-temporal regions. MRI: cerebral and cerebelar atrophy, bilateral hipersignal white matter. Oftalmologic valuation: bilateral optic atrophy. Skin biopsy: normal. Hexoaminidase A/B and total, Quitotriosidase, Beta galactosidase, Palmitoyl protein thioesterase, normals. Tripeptidyl Peptidase 1: 0,45 nmol/h/ml (NV: 4,0 a 23,0 nmol/h/ml)

Diagnoses hypotesis: Myoclonic epilepsy, Neuronal ceroid lipofuscinoses, Gangliosidoses, Doose syndrome, Mithochondrial Encephalopathy - MERRF, Progressive Myoclonic Epilepsy (Unverricht-Lundborg), Lafora Disease.

Conclusion: The neuronal ceroid lipufuscinoses are severe neurodegenerative lysosomal storage disorders of childhood characterized by accumulation of autofluorescent ceroid lipopigments in most cells. Since the first description, in 1826, many forms have been described, suggesting a genetically heterogeneous disease. The signs and symptoms presented by this child, associated with the enzymatic dosage of Tripeptidyl Peptidase 1: 0,45 nmol/h/ml (NV: 4,0 a 23,0 nmol/h/ml) confirmed diagnosis of LCN2. We have not had a specific treatment for this disease until recently, only symptomatic treatment (anticonvulsants and supportive care). Nowadays we have the possibility to use intracerebroventricular enzyme replacement therapy which, if started early can provide good results.
Adicional Material:Picures of the patient, enzymatic dosage, image exams and EEG.

Código #14343

Título: NOVA VARIANTE NO GENE *SETD5* ASSOCIADA A DEFICIÊNCIA INTELECTUAL (DI).

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Resumo do caso: Resumo dos dados clínicos incluíndo história familiar e exame: Paciente do sexo masculino, 36 anos, com dois irmãos saudáveis de pais não consanguíneos, foi clinicamente identificado com leve deficiência motora e intelectual, miopia e astigmatismo, porém sem causa conclusiva. O paciente apresenta parâmetros físicos normais, pesando 65kg, 178cm de altura e um perímetro cefálico de 57.5cm. A Ressonância Magnética Cerebral e o Ecodopplercardiograma de tórax não apresentam alterações morfológicas. Os testes metabólicos apresentaram-se normais.

Exames complementares realizados: O sequenciamento completo de exoma, foi realizado com o Nextera Exome Rapid Capture (Reads com 77 pb paired-end, cobertura: 97,47% no mínimo de 20 leituras) na plataforma Illumina HiSeq (Illumina, San Diego, CA). Para confirmação da mutação, tanto a amostra do paciente com dos pais foram analisados por sequenciamento de Sanger.

Hipóteses diagnósticas: O sequenciamento identificou uma variante, não previamente descrita, na posição Chr3: 9.517.294 A> AC (ou, alternativamente, c.3848_3849insC-CCDS46741.1) no gene SETD5 (Set protein 5, OMIM # 615743), causando a substituição de uma Serina por uma Leucina na posição 1286 e consequentemente um códon de parada prematuro (p.Ser1286Leu), na posição 1322. Estudos *in silico* indicam que esta mutação é provavelmente patogênica e com possível perda de função. Os pais nao apresentaram tal variante pelo sequenciamento de Sanger, sugerindo uma mutação *de novo* para o paciente em questão.

Conclusões: Embora raros, os pacientes com DI podem apresentar tanto pequenas como grandes deleções (até 12 Mb), substituições e inserções. Nossos resultados sugerem uma nova mutação *de novo* no gene SETD5 como a causa genética de DI neste paciente. Após revisão de literatura, é possível observar que o paciente apresenta um fenótipo mais leve, o que poderia ser justificado pela presença de grandes deleções, que englobam vários genes em pacientes severamente afetados. O SETD5 é altamente expresso no córtex cerebral, intestino e olho, mas seu papel exato ainda não é claro. Estudos recentes mostraram que SETD5 pode funcionar como regulador de transcrição, já que domínios semelhantes são frequentemente encontrados em proteínas nucleares que interagem com a cromatina. Apesar desta mutação criar um códon de parada prematuro, é provável que esta variante leve a uma perda parcial de função, visto que a mesma se encontra no final da proteína, o que pode explicar o fenótipo leve do paciente. Em conclusão, após sequenciamento completo do exoma, foi encontrada uma nova variante *de novo* provavelmente patogênica, como causa genética das disfunções motora e cognitiva deste paciente

Material adicional: Exames bioquímicos, imunológicos, hormonais, laudo neuropsicológico, exames ecocardiológicos e genéticos.

Código #14346

Título: OCT4/NANOG Expression in cutaneous melanoma

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Resumo do caso: Primary cutaneous melanoma incidence is growing and it appears as a public health problem. Recent evidence suggests a subset of cells within a tumor with "stem-like" characteristics. Cancer stem cells show low proliferative rates, high self-renewing capacity, propensity to differentiate into actively proliferating tumor cells, and resistance to chemotherapy or radiation. OCT4 is an 18-kDa POU-domain transcription factor encoded by the POU5F1 gene. Is involved in the initiation, maintenance, and differentiation of pluripotent and germline cells during normal development. NANOG plays a pivotal role in maintenance of pluripotency and self-renewal in embryonic stem cells. The encoded protein can block embryonic stem cell differentiation and can also autorepress its own expression in differentiating cells.
A male patient (CACV) 62 years old, and a female patient (DFP) 83 years old, was admitted to the Araujo Jorge Hospital, in Goiânia, GO, Brazil. CACV with a plantar melanoma (sole) and DFP with a melanoma on the trunk (chest) diagnosed. Both presented lymph node and brain metastasis, and died of melanoma. The diagnosis was made by histological examination of the paraffin sections stained with Haematoxylin – Eosin. Immunohistochemical study for OCT4 and NANOG expression was performed on formalin-fixed, paraffin-embedded tissues. The antibodies the rabbit monoclonal anti-OCT4 antibody and anti-NANOG antibody (Abcam), were used. The tumor infiltrated the subcutaneous fat (Clark's Level V) and showed features of Breslow's high-risk category (CACV with thickness 8mm, DFP with depth 5mm). These patients showed a positive immunostaining expression for both antibodies in nucleus and cytoplasm cell. Ectopic expression of *OCT4* or *NANOG* in somatic cells results in dedifferentiation, malignant transformation and causes dysplasia in epithelial tissue, demonstrating the oncogenic potential of pluripotency genes.

Keywords: Cancer stem cells, immunohistochemical, oncogenic potential, proliferating tumor cells.

Financiamento: CAPES.

Código #14325

Título: RELATO DE CASO: NECROSE ESTRIATAL AGUDA

Autores: Bethânia de Freitas Rodrigues Ribeiro[1], Luma Alves Fonseca[2], Bruna da Cruz Beyruth Borges[1], Flávia Fernandes Santos[1]

Instituição dos Autores: Secretaria de Estado de Saúde de Rio Branco – AC[1], Estudante do curso de medicina da UNINORTE[2]

Resumo do caso:

K.H.T.S, 8 anos, natural e procedente de Rio Branco – AC, filha única de casal jovem e não consanguíneo.

Avós maternos e paternos todos do Acre, mais distantes vindos de Pernambuco.Antecedentes obstétricos: gestação única sem intercorrências.

Parto: normal, à termo, Peso: 3230g, comprimento: 48 cm, perímetro cefálico: 33cm, APGAR: 9/9, apresentou boa sucção seio materno, alta com 1 dia de vida. Chorou ao nascer.

Desenvolvimento neuropsicomotor: sorriu com 3 meses, sentou com apoio com 6 meses quando já pegava objetos e levava à boca. Com 7 meses ficou doente e regrediu todo o desenvolvimento. Após sentou com 3 anos e andou com andador com 5 anos.

Com 11 meses foi encaminhada para a genética. A paciente sustentava a cabeça e apresentava sorriso social. Na ocasião foi encaminhada para reabilitação e iniciado investigação para erros inatos do metabolismo. Neste momento ficou com diagnóstico de paralisia cerebral distônica, hiperreflexa ou encefalopatia crônica não progressiva. Fazia uso de biperideno com melhora da distonia. Evoluiu gradativamente chegando a sentar com 3 anos e andar em andador com 5 anos.

Em Outubro de 2016 procurou pronto socorro pois paciente parou de andar e de deglutir. Mãe referia febre 38ºC por 2 dias, uma semana antes do quadro, fez uso apenas de antitérmico (dipirona). Primeiro parou de andar e 3 dias depois parou de se alimentar e começou a fazer movimentos nos olhos e face.

Foi avaliada pela neuropediatra cujo exame está descrito a seguir: regular estado geral, hipoativa, reativa, eupnéica, corada, hidratada, sem edemas, sem interagir com o examinador. Paciente acamada com tetraparesia espástica, arreflexia global nos 4 membros. Força muscular diminuída globalmente, sensibilidade preservada. Movimentação ocular constante, com nistagmo horizontal constante. Apresentando crises focais intermitentes em face. (vídeo)

A suspeita clínica era de encefalite, foi colhido exames laboratoriais e líquor: todos normais (lactato foi realizado no sangue e líquor normal).

Realizou tomografia de crânio na urgência onde foi evidenciado lesão em gânglios da base, tendo realizado ressonância magnética de crânio que evidenciou necrose estriatal aguda (imagens).

Após avaliação da imagem por diversos especialistas várias hipóteses foram surgindo e dentre elas que poderia se tratar de uma doença dos gânglios da base biotina-tiamina responsiva. Foi iniciado então altas doses de biotina e tiamina.

Ficou internada em unidade semi-intensiva do Hospital da Criança de Rio Branco não necessitando de suporte ventilatório porém a alimentação era por sonda nasoenteral. Permaneceu internada por um período de 40 dias tendo deixado o hospital sem crises convulsivas, ainda não deambulava e só se alimentava via sonda nasoenteral.

Após 4 meses em reabilitação recuperou parcialmente a marcha com apoio, retornou o contato visual, alimentação via oral pastosa (vídeo)

Atualmente em uso de: Akineton, clobazam, fenobarbital, carbamazepina, tiamina (900mg/dia), biotina (100mg/dia)

Exames complementares:

Perfil tandem quantitativo e ácidos orgânicos: 05/07/2011: normal

Ultrassonografia de abdome total: normal

Avaliação oftalmológica: refração, fundoscopia e lâmpada de fenda: normais

Sorologias: toxoplasmose, citomegalovirose, Epstein bar, sífilis e HIV negativas

Líquor: normal

Ressonância magnética de crânio com e sem contraste 30/10/2009: normal (imagens)

Ressonância magnética de crânio com e sem contraste 22/10/2016: alteração de sinal associado a efeito expansivo local nucleocapsular e substância negra bilaterais e simétrico, coroa radiada mais evidentes, à esquerda e substância branca periventricular bilateral (tenho as imagens)

Ressonância magnética de crânio com e sem contraste 17/03/2017: alteração de sinal com redução de volume dos núcleos da base bilateral podendo corresponder a doença metabólica (imagens)

Hipótese diagnóstica: Doença dos gânglios da base biotina- tiamina responsiva?

Perguntas: Mais alguma hipótese para este caso? Por quanto tempo ainda usar as medicações? Em quanto tempo pode-se reduzir a dose das vitaminas? A lesão tem que reduzir por completo?

Exames estão disponíveis: vídeos do paciente antes, após crise e após uso de biotina e tiamina, ressonância magnética de crânio antes da crise, na crise e 4 meses após a crise.

Código #14322

Título: RELATO DE CASO: DISTONIA DE TORÇÃO PRIMÁRIA COM DELEÇÃO GAG NO GENE DYT1

Autores: Bethânia de Freitas Rodrigues Ribeiro, Bruna da Cruz Beyruth Borges, Socorro Elizabeth Rodrigues de Souza

Instituição dos Autores: Secretaria de Estado de Saúde de Rio Branco - AC

Resumo do caso:

V.A.M, 14 anos, natural e procedente de Plácido de Castro – AC, filho de casal jovem e não consanguíneo (Mãe tem 42 anos e pai tem 48 anos).

Antecedentes obstétricos: 4 gestações (G1 aborto provocado, G2 faleceu com 3 dias de vida não sabe a causa, G3 paciente, G4 menino 8 anos. Refere que realizou pré-natal a partir de 2 meses de vida sem intercorrências

Parto: normal, à termo, Peso: 3300g, comprimento: 51 cm, perímetro cefálico: ?, APGAR: 8/10, apresentou boa sucção seio materno, alta com 1 dia de vida.

Desenvolvimento neuropsicomotor: andou com 9 meses, falou com 1 ano, tinha bom aproveitamento escolar até 2013.

Refere que em 2013 paciente iniciou com vários episódios de arritmia cardíaca e sudorese sendo encaminhado para avaliação com cardiopediatra tendo feito exames como eletrocardiograma, ecocardiograma todos normais. Evoluiu com dores em membros inferiores e quadril tendo sido encaminhado ao ortopedista onde realizou radiografias de membros inferiores todas normais.

Em 2014 começou a andar na ponta dos pés e apresentar movimentos involuntários nos dedos dos pés sendo encaminhado para avaliação com neurologia.

Em 2015 foi para Porto Velho – RO para avaliação com neurologia sendo realizado ressonância magnética de crânio e coluna total com resultado normal sendo encaminhado para seguimento com psicólogo.

Em 2016 foi encaminhado para psiquiatra, na ocasião os movimentos involuntários haviam piorado e progredido para coluna e membros superiores (paciente não conseguia mais se sentar), os movimentos só cessavam quando dormia.

Na avaliação do psiquiatra foi dado o diagnóstico de psicose sendo iniciado uso de sertralina, zolpidem, alprazolam, rivotril. O tratamento foi proposto para 3 meses. Não houve mudança com o tratamento apenas piora.

Em novembro de 2016 paciente internou no HUERB (Hospital de Urgência e Emergência de Rio Branco) na Clínica médica com distonia generalizada (vídeo), sendo transferido para o Hospital de Clínicas do Acre.

A avaliação do neuropediatria relatava que o paciente apresentava movimentação espontânea, movimentos distônicos difusos mais intensos em cervical, dorso. Estava emagrecido, com sudorese intensa, equilíbrio e coordenação alterados devido à presença de movimentação involuntária o que o impossibilitava de ficar em pé e deambular sem apoio. Sensibilidade preservada, força muscular grau V, preservada, reflexos profundos normais nos 4 membros, hipertonia global, hipotrofia generalizada.

Foi iniciado tratamento para distonia, sendo retirado todas as medicações anteriores. Inicialmente foi utilizado akineton, biperideno sem efeito, após GABA e L-DOPA sem efeito. Após 40 dias foi transferido para UTI pediátrica (em "status distônico") onde foi sedado, colocado em ventilação mecânica e colhido teste genético (Sequenciamento do EXOMA). Na UTI foi iniciado clobazam e Artane sem melhora do quadro. Paciente evoluiu para sonda nasoenteral e traqueostomia.

Foi preenchido TDF (Tratamento Fora do Domicílio) pois a suspeita era de Distonia de Torção Primária com indicação de implante de estimulação cerebral profunda (DBS), já que não havia respondido aos tratamentos medicamentosos e ainda se encontrava em "status distônico" necessitando ficar em coma induzido.

O paciente foi admitido na UTI do Hospital das Clínicas de São Paulo (12/01/2017) onde foi submetido à cirurgia de colocação do DBS em 12/01/2017. Após 30 dias paciente começou a se alimentar sozinho via oral, após 51 dias paciente voltou a deambular sozinho (vídeo). Ainda em seguimento ambulatorial no HC-USP.

Atualmente em uso de: metadona, biperideno, diazepam, blacofeno, omeprazol.

História familiar: irmão com 9 anos apresenta dor em membros inferiores, distonia em dedos dos pés com babinsky positivo bilateral e reflexos de membros inferiores exaltados. (iniciado investigação, aguardando exames)

Exames complementares:

Ressonância magnética de crânio com e sem contraste 03/12/2015 e 05/11/2016: normal

Ressonância magnética de coluna cervical com e sem contraste 13/08/2015 e 10/12/2015: normal

Ultrassonografia de abdome total 10/08/2016: normal

Avaliação oftalmológica: refração, fundoscopia e lâmpada de fenda: normais

Exames 14/07/2016: hemograma, função renal, glicemia, perfil lipídico, função hepática: normais

Exames 03/12/16: hemograma infeccioso, radiografia de tórax com pneumonia, função renal normal, função hepática normal, glicemia normal, CPK 1700 (reduziu à normalidade após coma induzido do paciente)

Sorologias: toxoplasmose, citomegalovirose, Epstein Baar, sífilis, HIV, hepatite B e C normais

Sequenciamento do Exoma: Foi identificada a variante TCTC>T (ou alternativamente c.907_909delGAG - ENST00000351698) em heterozigose no gene TOR1

Conclusões: O diagnóstico clinico e laboratorial foi de Distonia de Torção Primária ligada ao gene DYT1. Ela apresenta herança autossômica dominante, com maior prevalência entre os judeus Ashkenazi e com penetrância estimada entre 30% e 40%. Entre as distonias hereditárias representa a forma mais comum e mais grave. A maioria dos quadros se inicia por volta dos 9 anos de idade e alguns chegam a manifestar com 45 anos. A distonia inicialmente acomete o membro inferior ou superior e progride rapidamente para a forma generalizada, em alguns casos não responsiva ao tratamento medicamentoso, sendo nestes casos indicado o DBS. Neste paciente foi identificada a mutação clássica que é uma deleção de 3 pares de base (GAG) no gene. Neste caso, o irmão também realizou o teste genético pois apresenta distonia em dedos dos pés, mas estamos aguardando o resultado para realização do aconselhamento genético.

Material adicional, exames que estão disponíveis: vídeos do paciente antes, após tratamento medicamentoso e após tratamento DBS, ressonâncias magnéticas de crânio e coluna.

Código #13193

Título: Relato de recorrência familiar da malformação de Dandy-Walker

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Resumo do caso: A malformação de Dandy-Walker (MDW) afeta o desenvolvimento cerebral, principalmente o desenvolvimento do cerebelo, que é a parte do cérebro que coordena o movimento, resultando em problemas com o movimento, coordenação, intelecto, humor e outras funções neurológicas. Adicionalmente, problemas em outros sistemas podem incluir defeitos cardíacos, malformações do trato urogenital, dedos ou dedos extras (polidactilia) ou dedos ou dedos dos pés (sindactilia) ou características faciais anormais. Estima-se que a malformação de Dandy-Walker afete 1 em 10.000 a 30.000 recém-nascidos. A etiologia envolve uso de teratógenos, infecções virais, *diabetes mellitus* e mutações gênicas. Entretanto, a maioria dos casos da malformação Dandy-Walker são esporádicos, o que significa que ocorrem em pessoas sem história de transtorno em sua família. Uma pequena percentagem de casos parece ocorrer em famílias sem padrão claro de herança. Neste estudo, relata-se a ocorrência de dois irmãos com a malformação de Dandy-Walker com relatos prévios na linhagem materna da família. Caso 1: I.T.S, sexo masculino, branco. Antecedentes: Trata-se do 1º filho nascido à termo, de parto normal, diagnosticado com a MDW, veio falecer aos 2 anos e 8 meses, devida complicações da doença, o mesmo tinha fenda palatina, polidactilia e refluxo, ocasionando uma serie de problemas pulmonares. Caso 2: A.T.S. sexo feminino, branca, 15 anos. Antecedentes: Trata-se do 2º filho nascido a termo de parto normal, diagnosticado com a síndrome de Dandy-Walker no período gestacional de 4 meses, informação negligenciada pela mãe. Tirada da progenitora aos 3 meses devido a maus tratos. Hoje a mesma se encontra com a tia paterna, ao recebê-la observou que a criança não tinha contato visual e não tentava pegar objetos. Apresentava atraso no desenvolvimento neuropsicomotor, sentou aos 5 anos, andou aos 7 anos e fala muito pouco. Conclui-se que a intervenção correta da família como cuidadora é fundamental para evolução durante o tratamento, o prognóstico de desenvolvimento intelectual é variável e a longevidade depende da gravidade dos sinais da síndrome e da presença ou não de outras malformações e/ou doenças associadas. No estudo de caso apresentado há fortes indícios do componente genético na etiologia da MDW, merecendo destaque o ramo materno. Recomenda-se o aconselhamento genético para a família no sentido de prevenir a recorrência familiar.

Código #14341

Title: Report of a patient presenting Carbamoyl Phosphate Synthetase 1 (*CPS1*) deficiency – the first Brazilian case.

Authors: Renata Barreto Tenório; Carolina Fischinger Moura de Souza; Ana Paula Kurz de Boer; Kalina Carneiro Lopes; Valentina Coutinho Baldoto Gava Chakr, Paulo Roberto Antonacci Carvalho; Maria Antônia Mendonça Soledade, Marcela Cristina Weber Pasa; Ida Vanessa Doederlein Schwartz.

Authors' academic institution: Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul.

Case report: A male patient, the first child of a consanguineous couple, who was discharged from a hospital located at the countryside of Rio Grande do Sul, at 48 hours after birth. Prenatal period without intercurrences. One day after discharge, the child was readmitted due to hypoactivity, feeding difficulties, lethargy and tonic clonic generalized seizures. A full infection screening was performed and empirical antibiotics were initiated. The screening results were all negative and the neurological status rapidly deteriorated; the child went into a coma and needed assisted ventilation. At the age of 15 days, the cephalic perimeter had increased 5 cm (from 34 to 39 cm), suggesting cerebral edema. The possibility of an inborn error of metabolism (IEM) was suggested and initial evaluation was requested after consultation to SIEM - urine organic acids, lactate, ammonia, quantitative aminoacid analysis and acylcarnitines profile. Tests showed high serum ammonia (611 mmol/L), normal urine orotic acid, high alanine and low citrulline, suggesting an urea cycle disorder (UCD). The child was transferred to HCPA and managed with appropriate low-protein diet, nitrogen scavenger pharmacological therapy (sodium benzoate, which was replaced by phenylbutyrate once it was available), supplementation of arginine and citrulline, and measures to minimize catabolism. The clinical response was poor, the neurological status had little improvement and ammonia levels remained fluctuating. He also presented sustained normocytic normochromic anemia of unclear etiology. Sequence analysis for *NAGS* and *CPS1* deficiencies were requested. The child presented a novel homozygous deletion c.1424delG in exon 14 of *CPS1* gene, confirming the diagnosis of *CPS1* deficiency. After clinical deterioration, the child passed away before completing 6 months of age; genetic counseling was offered to the parents. *CPS1* deficiency is a rare urea cycle disorder often misdiagnosed. The prognosis is usually poor despite adequate management. The conclusive diagnosis is necessary for adequate genetic counseling.

Código #14339

Título: SÍNDROME DE DELEÇÃO 2q DISTAL, EM MOSAICO.

Autores: Antonio Augusto Lima Teixeira Júnior[1]; Martinha Elisa da Silva Matos[2], Patrícia da Silva Sousa[2], Mariana Ribeiro de Santana Leitão; Maria Juliana Rodovalho Doriqui[2]

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Resumo do caso: Sexo feminino, segunda gestação de pais jovens e não consanguíneos, abortamento espontâneo prévio de gestação gemelar monocoriônica e monoamniótica. Mãe, 31anos na época do parto, nega exposição a teratógenos, nega intercorrências durante gestação ou parto. Nascimento a termo, de parto cesáreo, com 2930g, 49cm, perímetro cefálico (PC) de 32cm e Apgar 09/10. Chorou ao nascer, mas apresentou dificuldade para sucção. Não foram detectadas anomalias congênitas. Recebeu alta da maternidade aos 2dias. Ao exame clínico-dismorfológico com 2anos e 3meses, peso de 8kg (<p3), comprimento de 80cm (<p3) e PC de 44cm (<p3); estado geral bom, corada, hidratada, eupnéica, hipotonia axial, sustentação cefálica incompleta, balbucia sons incompreensíveis, apresenta movimentos involuntários; microcrania, telecanto, raiz nasal baixa, orelhas baixo-implantadas; hipertelorismo mamilar, prega palmar de transição bilateral, frouxidão ligamentar acentuada, cutis marmorata; tórax, coluna, abdome e genitália, sem outras alterações significativas. Dentre os exames complementares realizados, a tomografia do crânio não revelou alterações, exceto por microcrania, cariótipo 46,XX,del(2)(q35)[28]/46,XX[2]. Ressonância magnética do encéfalo, radiografia de coluna e ecocardiograma, dentro da normalidade. Diagnóstico: Microcrania, baixo ganho ponderoestatural, atraso no desenvolvimento neuropsicomotor, secundários à monossomia parcial 2q distal, em mosaico. Conclusões: Tem sido descrita na literatura a síndrome de deleção 2q37, como um fenótipo de osteodistrofia hereditária de Albright-*like* (AHO-*like)*, cursando com atraso do desenvolvimento ou intelectual, baixa estatura (23% dos casos), tendência para a obesidade com a idade, braquimetafalangismo (50%). Sendo também frequentes: clinodactilia do quinto dedo e mãos/pés pequenos, sindactilia dos dedos das mãos e dos pés, persistência de coxins fetais, prega palmar única, microcefalia ou macrocefalia; face redonda, cabelos esparsos, fronte proeminente, fissuras palpebrais inclinadas para cima, olhos profundos, sobrancelhas espaçadas e arqueadas, hipoplasia da face média, ponte nasal baixa, hipoplasia alar, e columela proeminente, vermelhidão fina da delimitação dos lábios, palato alto e arqueado, mamilos supranumerários, hipertelorismo mamilar; eczemas frequentes. Foram descritas também malformações cardíacas congênitas, gastrointestinais (30%), genitourinárias (11%) e do sistema nervoso central (6%). Frequentemente presentes hipotonia, convulsões (35%), alterações do comportamento (30%). Comportamento repetitivo, graves deficiências de comunicação e interação social, movimentos estereotipados, agressividade intermitente, hiperatividade, déficit de atenção, doença obsessiva-compulsiva e distúrbios do sono são característicos de um subtipo de autismo associado com a delecção 2q37. A banda 2q37 contém três sub-bandas com mais de 80 genes localizados na região 2q37.1-q37.3. Algumas correlações genótipo-fenótipo foram identificadas incluindo uma região crítica para o fenótipo AHO-*like* e os genes candidatos para braquimetafalangismo, obesidade e do espectro do comportamento autista. A monossomia pode ser pura ou pode estar associada a desequilíbrios cromossômicos adicionais. Array é

justificável para o presente caso, visando melhor definição a respeito dos genes envolvidos na deleção e também para detectar eventuais rearranjos associados. O seguimento com equipe multiprofissional e aconselhamento genético são fundamentais na abordagem de pacientes com atraso do desenvolvimento, microcefalia ou outras anomalias congênitas. Embora, no presente caso, tenha sido observado mosaicismo, indício de mutação pós zigótica; considerando o baixo número de células normais foi solicitada análise citogenética da probanda em nova população de linfócitos para confirmação; devendo ser considerada se há necessidade de análise citogenética dos pais para orientações adequadas sobre o risco de recorrência.

Código #13259

Título: SÍNDROME DE KLEEFSTRA: RELATO DE CASO E REVISÃO DA LITERATURA.

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Objetivos: Relatar uma paciente do sexo feminino com microdeleção 9q34.3 associada a síndrome de Kleefstra.

Metodologia: Estudo descritivo tipo relato de caso.

Resultados: A propósita é 2ª filha de casal (mãe: 20 anos; pai: 43 anos), sadios e não consanguíneos. A criança nasceu após pré-natal sem intercorrências de parto normal a termo, apresentação cefálica; Apgar 9-9; PN= 2.725g; C=48 cm; PC=34,0 cm. Ao nascimento foi observada polidactilia pós-axial bilateral completa e hipotonia cervical. Evoluiu com RGE, atraso de DNPM, déficit de linguagem e déficit cognitivo. EF (3a7m): baixa estatura, fácies peculiar, microcefalia, hipoplasia do terço médio da face, epicanto bilateral; lábio superior em arco de cupido, sinal do polegar bilateral, hipotonia axial. RX crânio, esqueleto completo e IO, US abdome, rins e v. urinárias, Ecocardiograma RNM encéfalo-sem alterações. Cariótipo GTG: 46, XX. CGH: deleção de 1,25 mb que inclui o gene EHMT1, classificada como patogênica e duplicação 2q de 203 kb classificada como VUS. Cariótipo GTG dos pais: sem alterações.

Conclusões: A deleção 9q34.3 está associada à Síndrome de Kleefstra (SK)-OMIM 610253. Trata-se de cromossomopatia extremamente rara (prevalência inferior a 1: 200.000 -1M:1F). Há descrições de aproximadamente 100 pacientes na literatura. Os achados principais são anomalias congênitas múltiplas, atraso de DNPM, DM, atraso no desenvolvimento da linguagem, e dismorfismos craniofaciais. O fenótipo comportamental inclui estereotipias, transtorno do espectro autista e transtornos psiquiátricos. Os pacientes podem evoluir com crises convulsivas e distúrbios graves do sono. A SK é causada por haploinsuficiência no gene *EHMT1 (Euchromatin Histone Methyl Transferase 1)* que é um dos genes localizados na região 9q34.3. Na grande maioria dos pacientes relatados na literatura, a microdeleção ocorre *de novo.* O gene *EHMT1* codifica uma enzima que modifica a função da proteína histona, essencial para o desenvolvimento embrionário normal. As deleções mais extensas (>1mb) estão associadas a quadro clínico mais grave.

Código #14188

Título: Síndrome de LI-Fraumeni: relato de caso e considerações acerca do tratamento em gestante e da testagem preditiva em crianças pertencentes às famílias de risco

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Instituição dos Autores: [1]FCM- Faculdade de Ciências Médicas, Hospital Universitário Pedro Ernesto, Universidade Estadual do Rio de Janeiro, Brasil; [2]Hospital Israelita Albert Einstein - São Paulo, Brasil.

Resumo do caso: Paciente do sexo feminino, 39 anos, encaminhada pelo oncologista para diagnóstico e aconselhamento genético (AG) por histórico de adenocarcinoma primário de pulmão aos 37 anos, tratado com lobectomia direita e carcinoma ductal infiltrante de mama direita (MD), receptores de estrogênio +, HER 2+; diagnosticado 4 meses após, na 5ª semana de gestação. Realizada quadrantectomia e esvaziamento axilar ao diagnóstico e quimioterapia (QT), a partir do 2º trimestre, se estendendo no pós-parto com continuidade da quimioterapia, uso de Herceptin e Tamoxifeno; mastectomia da MD, esvaziamento profilático de mama esquerda com colocação de prótese mamária; radioterapia na MD. RNM de crânio mostrou imagem compatível com meningioma. Histórico familiar de pai e tio falecidos por câncer de próstata aos 69 anos e câncer de intestino entre 50 e 60 anos, respectivamente, e 1 irmão em tratamento de linfoma. A partir do uso dos Critérios de Chompret modificados, foi solicitado, mediante AG pré-teste, o teste da mutação R337H no éxon 10 do gene *TP53,* que foi positivo. No AG pós-teste foram iniciadas discussões com seu oncologista acerca de protocolos de rastreamento tumoral, e, solicitada, mediante assinatura de termo de consentimento informado, o teste da mutação p.R337H no gene *TP53* em seu filho aos 10 meses de vida, com resultado negativo.

Discussão: o câncer de mama durante a gravidez é uma situação clínica ainda incomum e de manejo clinico complexo; não há relatos semelhantes em pacientes com SLF. O uso da QT é mais seguro no 2º trimestre da gestação por risco menor de malformações fetais; onde os antracíclicos são as drogas mais estudadas e consideradas seguras. O aleitamento materno geralmente é proibido durante a QT. A mastectomia radical modificada é considerada o padrão de cuidado no 1o trimestre da gestação devido as potenciais consequências de se adiar a radioterapia após o parto, contraindicada na gravidez. A hormonioterapia adjuvante se indica no período pós-parto, pós conclusão da QT, frente aos riscos de defeitos congênitos e abortos espontâneos. Testagem preditiva em crianças possivelmente portadoras de mutações germinativas em *TP53*, apesar de controversa, pelos efeitos psicológicos a longo prazo ainda não bem esclarecidos, tem se mostrado encorajadora frente ao alto risco de desenvolvimento de câncer na infância nesta síndrome e possíveis benefícios do rastreamento precoce, especialmente em famílias com determinadas classes de mutações. A razão primária da realização do teste genético nesta criança, que não teve a capacidade de consentir, foi

prover benefício. O possível malefício da remoção da autonomia da criança foi suplantado pela retirada da angústia da dúvida (aboliu a incerteza e ansiedade parental) e pela possibilidade de oferta de um protocolo de rastreamento bastante precoce de carcinoma adrenocortical, caso a mutação tivesse sido detectada.

Código #14155

Título: SÍNDROME DE PAI – RELATO DE CASO

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Instituição dos Autores: IFF – Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, Fiocruz, Rio de Janeiro, Brasil

Resumo do caso: IMP, feminina, branca, 2 meses, encaminhada por fenda nasal e gengival. Primeira filha de casal não consanguíneo, mãe com 29 e pai com 37 anos ao nascimento. Pré-natal sem intercorrências, ultrassonografia morfológica com suspeita de agenesia de corpo caloso. Nasceu a termo/AIG. História familiar negativa para malformações, tem uma irmã saudável por parte de pai. Pais examinados: sem anormalidades. Exame físico: hipertelorismo ocular discreto, fenda gengival mediana com estrutura sacular de consistência mole na região da fenda e fenda nasal à esquerda com proeminência cutânea superior a ela. Sem outras dismorfias ou malformações. Peso, altura e PC normais. Feita cirurgia de correção das fendas com seis meses de idade com ótimo resultado. Última avaliação com um ano de idade, desenvolvimento normal.

Exames complementares:

RNM (aos 2 meses): Agenesia de corpo caloso com colpocefalia. Imagem alongada amorfa, com sinal semelhante ao da gordura em todas as sequências, localizada na linha média na topografia da fissura inter-hemisférica, associada a vascularização anômala de permeio, medindo aproximadamente 2,7x2,0x1,4 cm, podendo corresponder a lipoma. Os vasos anômalos podem corresponder a veias cerebrais internas e veias basais de Rosenthal, que drenam para a veia de Galeno em posição ectópica e mais alta que o usual em direção ao seio reto. Discreta hipoplasia e alteração rotacional dos hipocampos. Fenestração nasal à esquerda e imagem ovalada com intensidade de sinal semelhante ao da gordura em todas as sequências, superiormente à mesma que mede cerca de 1,2x0,8 cm, também podendo corresponder a lipoma ou dermóide, com pequena extensão intracraniana através do *foramen cecum*. Artéria cerebral anterior aparentemente única (ázigos). Impressão: agenesia de corpo caloso, lipoma da fissura inter-hemisférica com drenagem vascular anômala, lipoma ou dermóide nasal, associado a persistência do *foramen cecum* e fenda nasal à esquerda.

Cariótipo: 46, XX / Array-CGH: normal

Hipótese diagnóstica: síndrome de Pai

Conclusão: A síndrome de Pai é bastante rara e se caracteriza por hipertelorismo, fenda labial mediana, pólipos nasais e faciais, lipoma de corpo caloso e desenvolvimento psicomotor normal. A etiologia e o modo de herança são desconhecidos e a maioria dos casos é esporádica. Alguns relatos sugerem herança autossômica dominante e há um caso descrito com uma translocação X;16. O cariótipo e o array-CGH normais em nossa paciente permitiram excluir causa cromossômica, falando a favor de herança monogênica. Como os pais são normais e a herança proposta é AD, provavelmente trata-se de uma mutação nova. Feito aconselhamento genético de risco de recorrência provavelmente baixo para os pais da propósita. A paciente deve retornar ao serviço no final da adolescência para que seja feito o seu aconselhamento genético.

Material disponível para apresentação: fotos da paciente (pré e pós operatório) e ressonância de crânio.

Código #13273

Título: SÍNDROME DE VON HIPPEL-LINDAU - RELATO DE DOIS CASOS ATENDIDOS NO AMBULATÓRIO DE ONCOGENÉTICA DO HOSPITAL DE CLÍNICAS DE PORTO ALEGRE.

Autores: Daniele Konzen[1]; Cristina Brinckmann de Oliveira Netto[1]; Gustavo Stumpf da Silva[2]; Patrícia Ashton Prolla[1, 2];

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Resumo do caso:

Caso 1) Paciente feminina, 12 anos, com queixa de baixa acuidade visual há um ano. Encaminhada por oftalmologista ao ambulatório de oncogenética após diagnóstico de hemangioblastoma (HB) de retina em olho direito. Em consulta referiu história familiar de pai e avó paterna com diagnósticos de diferentes tumores: HB de retina, HB de cerebelo e carcinoma renal de células claras. Pela história pessoal e familiar de tumores pertencentes ao espectro da síndrome de Von Hippel-Lindau (VHL), foi solicitada análise molecular do gene *VHL*, sendo identificada a variante germinativa patogênica c.194C>G (p.Ser65Trp, éxon 1), confirmando o diagnóstico de VHL. A paciente manteve-se em seguimento e tratamento oftalmológico, recebendo após 7 meses o diagnóstico de HB de retina em olho esquerdo (BH de retina bilateral). Exames de seguimento solicitados no ambulatório de oncogenética (ecografia abdominal total e metanefrinas urinárias) retornaram sem alterações. Seu pai realizou posteriormente pesquisa de variante germinativa patogênica familiar c.194C>G (p.Ser65Trp, VHL éxon 1), confirmando também seu diagnóstico molecular.

Caso 2) Paciente masculino, 28 anos, em seguimento com oftalmologia há 9 anos por amaurose bilateral. Aos 19 anos, devido a um HB cerebelar tardiamente diagnosticado, desenvolveu atrofia óptica decorrente de hipertensão intracraniana. Aos 27 anos foi diagnosticado com HB de retina em 3 pontos do olho esquerdo e encaminhado para o ambulatório de oncogenética; paciente preenchia critérios clínicos para diagnósticos de VHL. Nega tumores do espectro VHL presentes em sua família. Em seguimento solicitou-se ecografia abdominal total e posteriormente tomografia abdominal para *screening* de carcinoma renal, sendo identificadas lesões renais bilaterais multifocais. O paciente foi submetido a nefrectomia total direita e a nefrectomia parcial esquerda, o exame anatomopatológico das peças das nefrectomias confirmou 6 focos de carcinoma renal de células claras (CRC).

Conclusões – A síndrome de VHL se trata de síndrome de predisposição hereditária ao câncer, com variabilidade fenotípica intra e interfamiliar com alta penetrância que confere risco aumentado de desenvolvimento de HB de retina, HB de sistema nervoso central, CRC, feocromocitomas, tumor neuroendócrino de pâncreas, entre outros. O seu diagnóstico precoce permite o adequado seguimento dos pacientes conforme faixa etária de aparecimento dos tumores; a detecção pré-sintomática dos tumores leva a uma diminuição das comorbidades decorrentes assim como da mortalidade. A possibilidade de realização de teste molecular em familiares em risco evita o fardo de uma possível rotina de seguimento desnecessária em pacientes que não herdaram a variante patogênica presente na família.

Código #14144

Título: SÍNDROME KEUTEL : PRIMEIRO RELATO DE CASO COM CONFIRMAÇÃO MOLECULAR EM PACIENTE BRASILEIRO.

Autores: Kelin Chen[1]; Eduardo Perrone[1]; Marco Antonio de Paula Ramos[1]; Maria de Fatima de Faria Soares[2]; Ana Beatriz Alvarez Perez[1]

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Resumo do caso: A estenose de artéria pulmonar (EAP), tanto de tronco como de ramos periféricos, é uma anomalia bem descrita na literatura apesar de pouco comum. Sua patogênese ainda não é completamente conhecida, todavia é frequentemente associada a defeitos cardíacos e também a síndromes genéticas como Alagille, Williams, Cutis Laxa, Ehlers-Danlos, Noonan e Silver-Russel. Uma paciente de 13 anos foi encaminhada ao serviço de Genética para investigação de possível EAP com associação sindrômica. Esta é primeira filha de casal consanguíneo e hígido, natural de Olindina-BA, sem história de risco gestacional ou neonatal, com crescimento e desenvolvimento neuropsicomotor adequados, diagnosticada com sopro cardíaco desde os 3 anos. Somente conseguiu realizar ecocardiograma aos 12 anos que evidenciou EAP, sendo encaminhada à Cardiopediatria que solicitou angiotomografia cardíaca com resultado de estenose de valva pulmonar e hipoplasia de tronco e ramos de artérias pulmonares. Ao exame físico, apresentava medidas antropométricas entre os percentis 50 e 75, sopro cardíaco, dismorfias faciais (orelhas rígidas, hipoplasia de face média, raiz nasal deprimida) e braquitelefalangismo. Foi solicitado raios-X de esqueleto que mostrou calcificações em orelha e em cartilagens laríngeas, assim como encurtamento de falanges distais das mãos e dos pés. Angiotomografia cardíaca também revelava sinais de calcificação em traqueia após revisão das imagens. Baseada nos achados clínicos e radiológicos foi aventada a hipótese de Síndrome de Keutel (SK). Foram solicitados de exames complementares: audiometria, prova de função pulmonar, angiotomografia de crânio, USG de tireóide, função tireoideana e sequenciamento do gene *MGP*. Este revelou variante em homozigose em *MGP* (c.2T>C;p.M1T;exon1), classificada como patogênica, confirmando-se o diagnóstico de SK.

Conclusões: SK é uma doença autossômica recessiva muito rara com frequência estimada de 1:1000000, caracterizada por calcificações anômalas em cartilagens, estenoses múltiplas de ramos periféricos das artérias pulmonares, déficit auditivo, hipoplasia de face média e braquitelefalangismo. Mutações em homozigose no gene *MGP* estão associadas à síndrome. Em revisão de artigos no PubMed usando-se o termo “Keutel Syndrome”, foram encontrados 38 artigos, 28 destes relatavam um total de 36 pacientes e descreviam 7 mutações em *MGP*. A maioria dos casos é de origem no Oriente Médio e nenhum brasileiro. O caso descrito assume grande importância por se tratar de um

diagnóstico diferencial na EAP, por ser o primeiro caso brasileiro, pela descrição de uma variante "novel" e pelo diagnóstico permitir que seja realizado o devido manejo clínico pois esta síndrome cursa com calcificações cerebrais, convulsões, surdez, infecções respiratórias de repetição, nódulos tireoideanos com risco de malignização, doença respiratória obstrutiva e alterações dermatológicas. E por fim, o diagnóstico permitirá o adequado aconselhamento genético devido ao risco de recorrência do quadro pelo padrão de herança autossômica recessiva.

Material adicional: fotos, raios-X de esqueleto, angiotomografia cardíaca, sequenciamento de *MGP*. Demais exames solicitados não foram realizados ainda pela paciente.

Código #14323

Título: THIAMINE DEFICIENCY IN A GSD Ia PATIENT: A CASE OF WERNICKE-KORSAKOFF SYNDROME.

Autores: Mariana Sbaraini da Silva; Berenice Lempek dos Santos; Ida Vanessa Doederlein Schwartz; Carolina Fischinger Moura de Souza.

Instituição dos Autores: Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Brasil.

Resumo do caso: 17 year old with GSD Ia (p.Val338Phe/p.Val338Phe), diagnosed at 1 month, receiving dietary treatment excluding sucrose and fructose associated with the use of UCCS every 4 hours. She has consanguineous parents and a sister with the same diagnosis since 8 months old.

The patient was admitted in the emergency presenting dizziness, epigastric pain, inappetence, vomiting and hypoglycemias (HGT 50) for about two weeks. Previously she had been eating less food and increasing starch doses in order to maintain the glucose and lose weight.

At the physical examination: HR 100bpm, RR 16 breaths pm, 140/70mmHg, lower limb edema (3+/4+) and extremity tremors. She had epigastric pain at profound palpation, palpable liver below 2cm of the costal margin and a negative Blumberg sign. At heart auscultation, she presented with a holosystolic murmur (2+/6+) in the mitral and tricuspid area.

The laboratorial exams showed normal levels of urea, creatinine, albumin and bilirubins; blood count, coagulation and thyroid exams within normal ranges. At an abdominal echography, the liver had an diffuse increase of echogenicity, with a echogenic nodular area of 1.1 cm in the right lobe (possible adenomas). She also did a upper digestive endoscopy with biopsy, without any abnormalities.

Hypothesis: Viral gastroenteritis

After a few days, she progressed with visual impartment, nystagmus, walking abnormalities and paresthesias. A head MRI was normal, as well as vitamin B12 levels (although low). She then presented heart failure and altered level of consciousness that culminated in an ICU admission, staying in mechanical ventilation for two days.

Hypothesis: Wernicke-Korsakoff Syndrome and Cardiovascular Beriberi

Large doses of IV thiamine were administered at ICU admission, and neurological and cardiological conditions improved rapidly. However, she continued with muscular pain without neuropathic pattern ou electromyography changes. She had normal CK levels and altered of aldolase.

A thigh MRI showed findings compatible with inflammatory muscle alterations (inflammatory myopathy).

Hypothesis: B1 deficiency myopathy

The patient maintained thiamine supplementation therapy after discharge, as well as B12. She continued with paresthesias and difficulty walking for another two months. After seven months she was fully recovered.

Conclusion: Vitamins are bioactive compounds that must be a part of any nutritional orientation. Due to a restricted diet, GSD patients have a higher risk to manifest vitamins deficiencies and should be carefully evaluated. This case shows a patient with thiamine deficiency due to low food intake while maintaining high supply of corn starch. She presented symptoms of Wernicke-Korsakoff Syndrome, evolved with signs of cardiovascular beriberi and then with B1 deficiency myopathy. The clinical manifestations regressed after vitamin supplementation. The relevance of this case report is to alert about vitamins deficiency - although easily treatable, it can lead to death, and patients with special diets must receive special attention.

Material adicional: Fotos, Exames laboratoriais, Ressonância de coxas/crânio/abdome, RX de trânsito intestinal.

Código #13327

Title: THORACO-OMPHALOPAGUS CONJOINED TWINS: IMPORTANCE OF THE PRENATAL DIAGNOSIS AND A MULTIDISCIPLINARY APPROACH

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Objectives: Our aim was to report the prenatal findings of a case ofthoraco-omphalopagus conjoined twins.

Methods: We made the description of the case along with a literature review.

Results: The mother was a 31 year-old pregnantwoman in her fourth gestation. She was referred to the fetal medicine service due to an ultrasound performed at 12 gestational weeks that found conjoined twins fused by the abdomen. This exam was repeated in the hospital at 14 gestational weeks, showing conjoined twins apparently fused by the thorax and upper abdomen. They apparently shared the heart and liver, however this interpretation was hindered by the early gestational age. There seemed to be only a single umbilical cord, which emerged caudally to the fetuses union. The umbilical arteries were observed emerging laterally to the bladders. It was a monochorionic and monoamniotic gestation. Echocardiography disclosed that the fetus at left had a normal heart and the fetus at right presented dextrocardia. The inter ventricular septum and the exit ways were not properly visualized. The morphologic ultrasound performed at 22 gestational weeks did not identify other malformations (normal cranium, limbs and spine). Two venous ducts were visualized. Four defined cavities were observed and the hearts were apparently connected by ventricles. The pericardium could not be defined. The echocardiography performed soon after revealed apparent heart communication between the right atrium of the fetus at right and the left atrium of the fetus at left. The fetus at left had tetralogy of Fallot with pulmonary atresia. There was a big interventricularperimembranous communication with a large aorta overriding the trabecular septum in 50% of its perimeter. Magnetic resonance imaging displayed conjoined twins fused by thorax and superior abdomen, above the umbilical cord insertion. The right hepatic lobe of the fetus at right was related to the left hepatic lobe of the fetus at left. There were two stomachs, two gallbladders and four kidneys.

Conclusion: Although conjoined twins are a rare condition, estimated in 1:75.000 births, their prenatal diagnosis is important. This allows the evaluation of the point of attachmentand its complexity, for, then, help in the management and prognosis determination. Because of this, the evaluation of these fetus always should be multidisciplinary, involving health professionals of different areas, as radiologists, obstetricians, pediatricians and pediatric surgeons.

Código #12296

TURCOT´S SYNDROME AND MEDULOLBLASTOMA SY: 3 CASE REPORT

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Key words: Turcot's syndrome; Medulloblastoma; FAP

Introduction: Turcot syndrome (1) is a hereditary predisposing cancer syndrome and is characterized clinically by the association of central nervous system tumor (medulloblastoma (2) or glioblastoma multiforme) and familial adenomatous polyposis (FAP) (3). Most of the patients present with a germ mutation of the APC gene on chromosome 5q21 (4). FAP is a hereditary condition in which practically 100% of the patients develop cancer of the colon, stomach and duodenum if they are not submitted to prophylactic colectomy. In young children there is an increased risk of developing hepatoblastoma and, in adolescents and adults, the risk of developing duodenal, thyroid, tumors, and brain tumors (5).

Objective: To describe 3 cases of patients with Turcot Syndrome treated at the Pediatric Oncology Service of the National Cancer Institute (INCA)

Methodology: Revision of medical records of patients enrolled in the Pediatric Service of the National Cancer Institute between 2000 and 2016.

Results: In the period 1997-2015, 126 cases of medulloblastoma were diagnosed in patients aged 0-18 years. Of these, three (2.5%) patients presented Turcot Syndrome.

Patient no. 1 diagnosed in 2000 with medulloblastoma, treated with surgery, radiotherapy and chemotherapy. At age 16, diagnosed with intestinal polyposis and submitted to colectomy. Retinal pigment epithelial hypertrophy in the fundoscopy. Family history: father died with gastric cancer. Performs annual colonoscopy. He's been in control of the brain tumor for 13 years.

Patient no. 2 diagnosed with medulloblastoma in 2001, at age 10, treated with surgery, radiotherapy and chemotherapy. Colonoscopy showing tubular adenomas and polyps. Family history: father, paternal grandfather and 4 paternal uncle with polyposis who evolved to colon adenocarcinoma. First-degree cousin treated at this hospital, diagnosed with hepatoblastoma and a deoid tumor, in addition to intestinal polyposis, submitted to total colectomy. Currently in the 14th year of control.

Patient no. 3 diagnosed in 2015 with medulloblastoma, operated and treated with radiotherapy. Currently undergoing chemotherapy. It presents FAP, being accompanied annually with colonoscopy and biopsies. Family history: mother and maternal aunt with colon cancer adenocarcinoma. Patients

are regularly followed up at the long-term follow-up clinics, ophthalmology and genetic counseling. To date, none of these patients developed colon cancer.

Conclusion: Due to the strong association between Turcot's Syndrome and colon cancer, it is necessary to identify this syndrome in patients with meduloblastoma, so that close follow-up with colonoscopies and biopsies of suspected lesions is performed. Family screening is also of fundamental importance for preventive measures.

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Código #14317

Título: VARIANTES GENÉTICAS NO GENE *RYR1* ASSOCIADAS A MIOPATIA DO CERNE CENTRAL (MCC), ATRAVÉS DE SEQUENCIAMENTO DIAGNÓSTICO DE EXOMA

Autores: Kássia Kramer, Nyasmin Mendes Anéli, Mônica Dayane Lammers, Heloisa Malakovski, João Marcos Soares Miranda Cordeiro, Sarah Franco Vieira de Oliveira Maciel

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Resumo do caso:

Dados clínicos: J.V.A., 7 anos de idade, sexo masculino, nascido em Chapecó (SC) em abril de 2010. A mãe refere pré-natal e parto cesáreo sem intercorrências, com sorologias e ultrassonografias normais. Aos 3 meses de vida, a criança iniciou quadro de hipotonia generalizada e atraso global no desenvolvimento neuropsicomotor. Como história mórbida familiar, uma prima materna com diagnóstico de Doença da urina do Xarope de Bordo. Aos um ano e 3 meses o paciente iniciou fisioterapia pelo método Bobath e fonoterapia, e passou a ser acompanhado por médico neurologista. Próximo aos 3 anos necessitou de andador por apresentar quadro de paralisia cerebral tetraparético ao exame físico, tendo iniciado tratamento com fenobarbital.

Exames complementares: Aos primeiros sintomas, a criança realizou exames laboratoriais, incluindo creatinofosfofoquinase, hormônios tiroidianos e sorologias, com resultados todos normais, exceto para citomegalovírus. Teste de BERA (*brain evoked response audiometry*) normal. Foi realizada Ressonância Nuclear Magnética do Encéfalo (RNM) com 1 ano e 8 meses, e posteriormente com 2 anos e 2 meses. Ambas indicaram redução da substância branca periventricular com dilatação dos ventrículos e redução volumétrica dos lobos frontal e temporal, além de afilamento difuso do corpo caloso, e não houve alterações significativas entre elas no intervalo de tempo realizado. Aos 4 anos e 3 meses, o Eletroencefalograma (EEG) apontou atividade paroxística epileptogênica nas regiões centro-temporais, independentes, com predomínio à esquerda, de severa intensidade. Foi sugerido realizar Sequenciamento Diagnóstico de Exoma (SDE). O primeiro laudo foi emitido em fevereiro de 2015 e não apontou variantes patogênicas que pudessem explicar o fenótipo apresentado. Após oito meses a mãe solicitou reanálise do exoma, e, utilizando novas técnicas bioinformáticas, o segundo laudo apontou três variantes genéticas com características patogênicas heterozigotas no gene do Receptor de Rianodina do Músculo Esquelético subtipo 1 (*RYR1*), duas herdadas em bloco de origem materna [c.7373G>A (p.Arg2458His) e c.7093G>A (p.Gly2365Arg)], e uma de origem paterna (c.13746+4C>G).

Hipóteses diagnósticas: Os exames sorológicos, genéticos e de imagem descartaram outras hipóteses, e o SDE indicou mutações patogênicas no gene *RYR1*, que estão associadas a Miopatia do Cerne Central (MCC), que causa hipotonia e atraso no desenvolvimento neuropsicomotor. Foi sugerido à família realização de biópsia muscular para confirmação histopatológica. A mãe relata que até o momento, a criança não realizou o referido exame.

Conclusões: O gene *RYR1* codifica um canal de liberação de cálcio situado no músculo esquelético. A variante materna c.7373G>A já havia sido descrita anteriormente em famílias com histórico de

hipertermia maligna (HM). Tanto J.V.A. quanto sua mãe podem estar predispostos a um episódio de HM caso venham a necessitar de anestesia geral, especialmente com uso de halotanos e succinilcolina. A família foi alertada para informar o anestesista deste risco em caso de necessidade cirúrgica, além de estimular familiares maternos a
realizar o exame diagnóstico de maneira preventiva. A outra variante materna, c.7093G>A, não havia sido descrita anteriormente como patogênica e foi analisada como de significado ainda desconhecido. A variante paterna, c.13746+4C>G foi descrita pela primeira vez no gene *RYR1*, com interpretação clínica complexa, podendo estar relacionada aos sintomas apresentados. Mais de 200 mutações já foram descritas no gene *RYR1*, algumas relacionadas à MCC, outras relacionadas a outras miopatias e HM, podendo ter concomitantemente duas dessas condições. As variantes em *RYR1* não explicam as alterações observadas na RNM, podendo estas corresponder a achados incidentais. Os pontos de interesse deste relato são a descrição clínica de caso de MCC, diagnóstico por SDE e indicação de nova mutação patogênica (c.13746+4C>G) em *RYR1*.

Material adicional: Fotos, EEG, RNM, laudo do SDE.

CASO CLÍNICO MOLECULAR

Código #13214

Title: A NOVEL MUTATION IN TRANSACTIVATION DOMAIN WITHIN *PAX6* GENE IN CONGENITAL ANIRIDIA

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Case Report: Aniridia is a rare congenital disorder characterized by iris hypoplasia and other structural and functional associated abnormalities. It can appear as an isolated anomaly or as a manifestation of a number of syndromes, such as WAGR and Gillespie. It affects about 1 in 64,000 to 96,000 livebirths. About 90% of the mutations causing aniridia occurs within the *PAX6* gene. In this study, we present a case of an individual affected by congenital aniridia. An affected individual and three non-affected relatives that live in a small town in Northeast Brazil, in the state of Alagoas. Patient was a 13 years old boy. Ophthalmological examination demonstrated total and bilateral aniridia and congenital cataract. He didn´t show genitourinary abnormalities, and behavior and neuro-psychomotor development were appropriate. It was a sporadic case, without report of ocular abnormalities in his family. His mother was 35 years old, and the two sisters were 12 years old and 1 year and 4 months, all healthy. The analysis of the *PAX6* gene showed a novel duplication of four nucleotides within the exon 11 (c.997_1000dupGACA), located within the transactivation domain of the transcription factor coded by this gene. This mutation was not described before and detected only in the affected boy, being absent in the two sisters and in the mother. The father was not available for genetic testing. Most of the *PAX6* mutations described until now exert their effect through a haploinsufficiency mechanism. In this case, the mutation affects the transactivation domain with both binding domains unaffected, and an alternative mechanism through a dominant-negative effect is proposed. Furthermore, mutants and normal proteins would compete for the same DNA binding site. Mutant ones are able to bind DNA but unable to activate the target genes transcription by preventing physical binding of the normal proteins and the correct gene activation. This type of *PAX6* mutation would be responsible for more severe expression of aniridia.

Supplemental Material: For the presentation, we have chromatograms from sequencing by Sanger method.

Código #13176

Título: CASO CLÍNICO: DOENÇA DE KRABBE, UMA NOVA MUTAÇÃO IDENTIFICADA.

Autores: Marta Wey Vieira; Franco Patriani D'andrea; Paula Maria Petro Mimura; Ana Carolina Zanin Moura; Gabriela Teixeira Araújo; Marina Helena Mariano; Débora Aparecida Rodrigueiro; Júlio Boschini Fillho.

Instituição dos Autores: Pontifícia Universidade Católica de São Paulo, FCMS-Faculdade de Ciências Médicas da Saúde de Sorocaba, Departamento de Medicina, Área de Pediatria.

Resumo do caso: D.L.G.V, nascimento 13/08/2014, 2 anos e 6 meses, sexo masculino, branco, natural e procedente de Capela do Alto – SP. Pai: G.F.A.V, 23 anos ; Mãe: C.F.S.G., 22 anos. Sem antecedentes familiais e pré-natais dignos de nota. Nasceu de parto cesáreo, pesou 3680g, comprimento 50 cm, PC: 37 cm, Apgar: 8/10; triagem auditiva normal, Capurro: 37 semanas 1/7. Seu desenvolvimento neuropsicomotor foi normal até aproximadamente 1 ano 7 meses. Paciente sem sinais dismorfológicos. Após completar 1 ano e 7 meses os pais observaram que o paciente começou com perda visual progressiva: parou de fixar o olhar e perdeu a noção espacial. Iniciou a investigação em consulta com diferentes oftalmologistas que nada identificaram. Com 1 ano e 8 meses apresentou quadro de infecção de vias aéreas superiores evoluindo em seguida com perda de força muscular em membros inferiores e perda da sustentação da cabeça. Em 15 dias houve parada na deambulação e após um mês começou a apresentar salivação excessiva, engasgos e disfagia progressiva, com interrupção abrupta na capacidade de se alimentar e de falar. Foi submetido à gastrostomia com 2 anos e 6 meses. Encaminhado para avaliação neurológica e genética-clínica sendo solicitado eletroencefalograma e RNM que evidenciou cegueira cortical e atrofia de substância branca. Então sob suspeita clínica de leucodistrofia foi solicitado Análise do Exoma para investigação de variantes genéticas que pudessem estar relacionadas, tendo sido identificado 2 variantes: variante no cromossomo 14, no gene GAL, c.1934T>G, promovendo substituição do aminoácido leucina na porção 645 por arginina – considerada definitivamente patogênica. (herdada da mãe); e presença da variante no cromossomo 14, no gene GALC,c.1690T>G, com substituição do aminoácido cisteína por glicina – ainda não relatada na literatura médica – considerada provavelmente patogênica (herdada do pai).

Hipóteses diagnósticas: Doença de Krabbe (CID: E75.2) decorrente de heterozigosidade composta.

Conclusões: A Doença de Krabbe (leucodistrofia de células globoides) é uma doença de depósito lisossomal com padrão de herança autossômico recessivo, relacionada à mutação no gene GALC localizado no cromossomo 14q31. Tem incidência de 1/100.000 nascidos vivos e são conhecidas mais de 60 mutações nesse gene. Contudo, uma das mutações genéticas encontrada neste paciente não havia sido antes identificada como patogênica. É uma doença de início insidioso de difícil identificação precoce. O prognóstico da doença é ruim quanto mais tardiamente for

identificada. Os pacientes evoluem com deterioração neurológica progressiva até coma e morte em poucos meses ou anos, fazendo-se necessário o diagnóstico precoce para instituição do tratamento em tempo hábil para ser efetivo. O tratamento baseia-se no transplante de medula ou de células tronco de cordão umbilical. Há novas frentes de pesquisa envolvendo a tecnologia do Gene Terapy para o tratamento da Doença de Krabbe. Estudos apontam alguns fatores de pior prognóstico e a efetividade do tratamento relacionada ao tempo de manifestação da doença.

Material adicional: Cópia do exame de Análise de Exoma.

Código #13374

Title: Molecular Clinical Case: Genetic Analysis of a Family with Keratoconus

Authors: Gabriela Elis Wachholz[1]; Thayne Woycinck Kowalski[1,2,3]; Otávio Magalhães[1,2,4]; Lavínia Schuler-Faccini[1,2,3,5].

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Case Description: Keratoconus is an eye disorder characterized by progressive distortion of the cornea. Both environmental and genetic factors have been implicated in its etiology. Our objective is to investigate the genetic basis of Keratoconus in a family by the identification of genetic variants of susceptibility, in candidates genes previously related to the condition, establishing a genotype-phenotype correlation. This project was approved by the Federal University of Rio Grande do Sul Ethical Committee. A family with diagnosis of Keratoconus, confirmed by ophtalmic clinical evaluation and cornea tomography, was recruited from Hospital Banco de Olhos of Porto Alegre. Saliva samples were collected with Oragene kit for DNA extraction. Whole exome sequence was performed in the platform *IlluminaHiSeq 3000* and the alignment was performed on software *Bowtie2*. The tools *Variant Effect Preditor (VEP*), *Variant Annotation* and *Analysis and Search Tool (VAAST*) were used to filter the variants. Sanger sequencing and subsequent analysis on software *CodonCodeAligne*r confirmed some regions of low coverage and new variants. The functional prediction of the variants was performed on *PolyPhen-2, PROVEAN, MutationTaster*e *Mutation Assessor* tools. This family was composed of the mother and her two daughters from a first marriage, and a pair of twins from a second marriage. The mother and her two daughters present Keratoconus in a severe degree and one of the twins does not have the clinical disease, just a forme fruste Keratoconus. The second twin was not diagnosed yet. A high number of missense polymorphisms, previously described in literature as associated to Keratoconus, was identified in the *COL4A3* and *COL4A4* genes. A missense variant in the filaggrin (*FLG*) gene, located in chromosome 1, was observed. This variant (rs151103850 C>T) was present in all individuals genotyped (mother and four children). One of the two twins is homozygote for the alternative allele (TT) and the other members are heterozygotes. The allele frequency is 0.013 (T), according to population data of the 1000Genomes project. This variant might affect the protein function in different levels, including alteration of the aminoacid chain or even in splicing sites, according to functional predictors. The variant was considered potentially deleterious to the *FLG* gene by these tools. Our initial hypothesis is that the identified variant in the *FLG* gene may be considered a susceptibility factor to Keratoconus in Brazil. In future, we aim to follow the clinical development of the twins, considering their genotypes differences; evaluated by Sanger sequencing genes which presented a low coveragein Exome data; and to recruit other patients to evaluate the polymorphisms encountered in *COL4A3* and *COL4A4* genes, regarding Brazilian Southern population.

Adicional Material: Whole exome sequence results of mother and her two daughters; cornea tomography images of mother, her two daughters and one of the twins; sanger sequencing results of all family.

Código #14337

Título: UM NOVO FENÓTIPO ASSOCIADO AO GENE *HTT*?

Autores: Joana Rosa Marques Prota; Antonia Paula Marques-de-Faria; Benilton de Sá Carvalho; Iscia Lopes Cendes.

Instituição dos Autores: Universidade Estadual de Campinas - Unicamp.

Resumo do caso: Paciente do sexo masculino, 19 anos, primeiro filho de casal jovem, hígido e não consanguíneo, iniciou investigação no primeiro mês de vida pelo quadro de hipotonia generalizada, aparente microftalmia unilateral, micropênis e gônadas em canal inguinal. Mãe primigesta, nega intercorrências gestacionais, parto a termo, vaginal, classificado como recém-nascido a termo adequado para idade gestacional, com hipotonia neonatal. Evoluiu com atraso global de desenvolvimento; por ocasião da orquidopexia, realizada biopsia gonadal, indicativa de testículos pré-puberais. Como não apresentava dismorfismos relevantes, exceto a alteração ocular (descrita como *phthisis bulbi* em tomografia posterior), a hipótese inicial foi DDS XY sindrômico com hipogonadismo hipogonadotrófico de causa indeterminada, sendo recomendado seguimento clínico. Mesmo com terapias de apoio, o paciente manteve o atraso neuropsicomotor, consolidado com déficit intelectual e prejuízo significativo da linguagem oral, a despeito da audição íntegra. Além do exame de cariótipo, foi submetido a teste molecular para *FMR1*, pesquisa de rearranjos subteloméricos pela técnica de *MLPA*, *FISH* para 22q11.2 e *a-CGH*, todos sem alterações. Na adolescência, observado hábito eunucóide, piora da marcha com instabilidade, distonia de MMII e bradicinesia. Recentemente, o sequenciamento do exoma revelou heterozigose composta para variantes no gene *HTT;* uma delas corresponde a deleção de 1pb (classificada como provavelmente patogênica) e a outra é uma deleção "in- frame" interpretada como de "significado incerto", conforme a ACMG.

Hipótese diagnóstica: Quadro sindrômico associado a heterozigose composta em *HTT*

Conclusões: É sabido que expansões de trinucleotídeos em *HTT* causam doença de Huntington, condição neurodegenerativa de herança autossômica dominante caracterizada por demência, coréia e involução neurológica. No entanto, após o uso diagnóstico do exoma, outros fenótipos associados ao *HTT* começam a ser descritos, como o caso de três irmãos com atraso global de desenvolvimento e hipotonia central que progrediu para tetraparesia espástica e dificuldade alimentar, todos heterozigotos compostos para variantes "missense" em *HTT*. Em outra paciente com quadro clássico de síndrome de Rett, porém sem mutação em *MECP2*, *CDKL5*, *FOXG1* e a-CGH normal, o exoma identificou duas variantes "missense" em *HTT*. Apesar de algumas similaridades com os quadros neurológicos já descritos, não há descrição na literatura de quadro clínico malformativo associado ao gene *HTT* em humanos, entretanto, é conhecida a expressão embrionária do *HTT* e em animais há diversos fenótipos malformativos associados a tal gene.

Material adicional: Fotos

CASO CLÍNICO SEM DIAGNÓSTICO

Código #14309

Título: ALTERAÇÕES ESQUELÉTICAS ATÍPICAS ASSOCIADAS A DEFEITO DE PAREDE ABDOMINAL ANTERIOR, HIPOTROFIA MUSCULAR E FROUXIDÃO LIGAMENTAR FAMILIAR.

Autores: Clarissa Gondim Picanço de Albuquerque; Thereza Taylanne Souza Loureiro Cavalcanti; Natália Renault Quaresemin; Rayana Elias Maia; Jair Huber; Sara Reis Teixeira; Lucia Regina Martelli.

Instituição: Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (HCFMRP-USP).

Resumo: Relatamos caso familiar de alterações esqueléticas de arcos costais, esterno, escápulas e coluna associada a defeito de parede abdominal (onfalocele, diástase de músculos retos abdominais, hérnia umbilical e hérnia inguinal), hipotrofia muscular, frouxidão ligamentar, além de doença inflamatória crônica de vias aéreas (asma, rinite) e dismorfias. Esse caso engloba duas gerações que compreende uma paciente de 35 anos e seus dois filhos, sendo uma menina e um menino. Importante salientar que são filhos de pais diferentes e sem história de consanguinidade. Os pacientes apresentam quadro clínico bem semelhante, com pequenas particularidades entre eles. O caso índice é RVSP, feminina, 35 anos, que tem história de onfalocele relatada e hérnia inguinal bilateral corrigida nos primeiros dias de vida, submetida à amidalectomia e adenoidectomia, asma moderada e infecções recorrentes. Ao exame apresenta desproporção crânio-face, com face triangular, frontal amplo, cabelos de implantação alta, nariz afilado e pequeno, proeminência de maxila com má oclusão dentária, orelhas pequenas, baixo implantadas e rodadas posteriormente, pescoço curto, tórax estreito e alongado, escoliose, espaço interescapular estreito, retificação da lordose fisiológica lombar, cifose tóraco-lombar, hepatoesplenomegalia, diástase de retos abdominais, hipotrofia muscular e frouxidão ligamentar. EJSI, feminina, 9 anos, tem história de diástase de retos abdominais com hérnia umbilical e inguinal bilateral corrigidas, hipogamaglobulinemia transitória da infância, infecções recorrentes, rinite alérgica e asma moderada a grave, já realizou amidalectomia e adenoidectomia, tubo de aeração bilateral, além de uma dilatação pielocalicial à direita sem etiologia definida. Realizou cariótipo convencional que foi normal. Ao exame possui as mesmas dirmorfias que a mãe. AHSP, masculino, 3 anos e 2 meses, relato de quedas frequentes, história de hérnia inguinal bilateral e umbilical, em seguimento por rinite e asma persistente moderada, hipertrofia de adenoide. Ao exame apresenta frouxidão ligamentar importante em manguito rotador e dismorfias semelhantes, porém mais discretas que a mãe e a irmã, com preservação do espaço interescapular. Todos possuem prova de função pulmonar com distúrbio ventilatório restritivo. Apresentam estatura na média e desenvolvimento neuropsicomotor adequado.

Exames complementares: Os exames de imagens (radiografias, tomografia e ressonância) evidenciam, no caso índice, proeminência da maxila, costelas cervicais, alargamento e deformidade dos arcos costais posteriores com fusão em vários níveis bilateralmente, esterno com deformidade e alargamento látero-lateral, escoliose biconvexa, discreta diminuição dos espaços discais, retificação da lordose lombar fisiológica, discreto cifose tóraco-lombar, além de hipotrofia das musculaturas paravertebral e ílio-psoas e diástase de retos abdominais. As imagens radiográficas dos filhos são semelhantes, porém com achados mais discretos, sugerindo alterações ósseas progressivas.

Hipóteses diagnósticas: A esclarecer.

Conclusão: Acreditamos tratar-se de uma doença autossômica dominante, que envolva genes do grupo de doenças do tecido conjuntivo (tecido conjuntivo propriamente dito, ósseo, cartilaginoso e hematopoiético). Por se tratar de um quadro peculiar, o exoma seria fundamental na tentativa de se esclarecer a etiologia dessa doença e quem sabe descrever uma nova síndrome.

Material adicional: Exames de imagem, fotografias clínicas, fichas operatórias, audiometria, avaliação oftalmológica e ecocardiograma (em andamento)

Código #14183

Título: BAIXA ESTATURA DESPROPORCIONADA ASSOCIADA A DISTROFIA MUSCULAR DE PROVÁVEL HERANÇA AUTOSSÔMICA RECESSIVA: ASSOCIAÇÃO DE DOENÇAS OU UMA NOVA SÍNDROME?

Autores: Antonette Souto El Husny, Maria Suely Fernandes, Isabel Cristina Neves de Souza e Luis Heredero Baute.

Instituição dos Autores: Universidade Federal do Pará, Brasil.

Resumo do caso:
SCR, 18 anos, sexo feminino, foi avaliada por deficiência de crescimento e leve atraso de desenvolvimento desde os primeiros meses de vida. Nas primeiras avaliações já se observava desproporção de segmentos corporais com encurtamento de membros. Aos seis anos de idade evoluiu com perda de força muscular com piora progressiva, comprometendo inclusive as atividades escolares. Atualmente com progressão lenta. Seu exame físico exibe a baixa estatura desproporcionada com importante hipertrofia de panturrilhas e hiporreflexia difusa. Fáscies atípica com discreta hipoplasia de face média e órbitas rasas. Há perda precoce e atraumática de dentes, macroglossia aparente e acentuado encurtamento de 4º metacarpiano. Há também registro de visceromegalias em exames prévios. É filha de casal não consangüíneo, de uma prole de cinco filhos dentre os quais uma irmã, falecida aos 9 meses, apresentava fenótipo semelhante – baixa estatura e musculatura muito proeminente.

Exames complementares realizados:
Cariótipo 46,XX
CPK: 10.800 (infância) → 1900 (adolescência)
Radiografias com encurtamento de ossos longos, encurtamento de 2º, 3º e 4º metacarpianos, Quinto metacarpiano encurvado. Alargamento de 1º metatarso bilateralmente.
Biópsia muscular compatível com padrão distrófico (Centro de Estudos Genoma Humano), testes específicos para distrofina, calpaína, sarcoglicana, merosina e outros: normais.
Eletroneuromiografia com padrão de miopatia primária, simétrica e de predomínio proximal. (UNIFESP)
Ecografia pélvico - Ovários de volume aumentado e com textura micropolicística.
Avaliação endocrinológica e cardiológica normal.
Avaliação nefrológica por hematúria e dismorfismo eritrocitário na infância.
Avaliação com otorrinolaringologia por ser respiradora oral.
Avaliação oftalmológica com deficiência de convergência causando diplopia.

Hipóteses diagnósticas: DISPLASIA ESQUELÉTICA ASSOCIADA A DISTROFIA MUSCULAR A ESCLARECER.

Conclusões – Deseja-se discutir possíveis diagnósticos específicos e auxílios laboratoriais que possam orientar melhor a condução do caso e seu aconselhamento genético.

Material adicional: Fotos clínicas, radiografias, exames bioquímicos gerais, CPK biópia muscular, enmg.

Código #13447

Título: Caso clínico de paciente com dismorfias, deficiência intelectual e baixa estatura em investigação etiológica sem diagnóstico

Autores: Thiago Rodrigues Cavole; Maria de Fátima de Faria Soares; Ana Beatriz Alvarez Perez

Instituição dos Autores: Centro de Genética Médica da Universidade Federal de São Paulo, SP.

Resumo do caso:

Relatamos um paciente masculino de 16 anos encaminhado com hipótese inicial de Síndrome de Sanjad-Sakati, apresentando fácies dismórfica, associada à calcificações cerebrais e baixa estatura. Paciente é filho de pais não consanguíneos, com três irmãs hígidas, procedentes de Alagoas e descendente de ciganos egípcios pela linhagem paterna. Possui cariótipo por bandamento G normal, CGH-Array sem alterações significativas e sequenciamento do gene *TBCE* sem variantes encontradas. O paciente apresenta história pregressa de convulsões neonatais, hipocalcemia decorrente de hipoparatireoidismo diagnosticado aos 10 anos de idade, retardo de crescimento com estatura de 135 cm, perímetro cefálico de 48 cm e peso de 29 quilos (todas aferições menores que o percentil 3 das curvas de crescimento da OMS). Apresenta atraso do desenvolvimento neuropsicomotor com deficiência intelectual, microcefalia, rosto afilado, microftalmia, orelhas malformadas, nariz em aduncо e mãos e pés pequenos). O paciente possui tomografias computadorizadas de crânio indicavam progressivas e extensas calcificações cerebrais sugestivas do diagnóstico de hipoparatireoidismo, também sugerido por níveis baixos de paratormônio. Mantemos investigação para doença renal crônica e hipercalcemia secundária à reposição de cálcio.

Material adicional: Tomografia de crânio, pesquisa de microdeleções e microduplicações por CGH-Array, sequenciamento do gene *TBCE*

Código #13371

CASO SEM DIAGNÓSTICO : PACIENTE COM ATRASO DO DESENVOLVIMENTO NEUROPSICOMOTOR, DEFICIÊNCIA INTELECTUAL , COMPORTAMENTO AUTISTA, DISMORFIAS E CONSANGUINIDADE PARENTAL

Autores: Gabriela Gayer Scheibler; Joanna Goes Castro Meira; Angelina Xavier Acosta; Diego Miguel; Esmeralda Santos Alves; Paula Brito Correia

Instituição dos autores: Serviço de Genética Médica, Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia, Brasil

Resumo do caso: Paciente do sexo masculino, de 10 anos de idade, encaminhado para investigação genética por atraso do desenvolvimento neuropsicomotor, deficiência intelectual, dismorfias e craniossinostose sagital. Nascido de parto normal a termo, pesando 4100g, apresentou sucção débil ao nascimento e infecção neonatal, permanecendo na maternidade por 9 dias antes da alta hospitalar. Evoluiu com hipotonia e atraso dos marcos motores, com controle cervical apenas aos 6 meses de vida. Sentou sem apoio aos 10 meses, caminhou sem apoio aos 3 anos e não desenvolveu fala. Evoluiu com inúmeros episódios de tosse produtiva e febre, com diagnóstico de rinossinusite de repetição. Aos 10 anos, não controla esfíncteres, não fala e necessita de ajuda para o autocuidado. Os pais são primos em terceiro grau e não há casos semelhantes na família. Ao exame físico, apresenta peso e altura no limite inferior da normalidade, dolicocefalia com espessamento de sutura metópica e sagital, saliência de região supraorbitária, rarefação de sobrancelhas, epicanto, fendas palpebrais alongadas, leve eversão de terço lateral de pálpebras inferiores, hipertelorismo ocular, nariz pequeno e largo com ponte nasal baixa, filtro nasolabial longo e apagado, palato ogival, boca entreaberta com rima para baixo e proeminência de lábio superior, apêndice em região cervical esquerda, orelhas proeminentes e com implantação borderline, pescoço alado, mamilo extranumerário, hérnia umbilical redutível, polidactilia pós-axial bilateral corrigida, pés planos e desviados lateralmente, frouxidão ligamentar e acentuação das linhas de mãos e pés.

Exames complementares:
-Cariótipo : 46,XY
-TC Crânio (2013): redução do diâmetro biparietal para idade e sexo, questionável alteração de densidade parenquimatosa cerebral na região temporal esquerda.
-ECOTT(2012): normal
-Endonasofibroscopia (2012): sinusite crônica (discinesia ciliar?)
-USG ap urinário: normal

-IgA, IgE e hemograma normais
-Triagem básica EIM: normal

-Array CGH (2015): dup (x4)4p15.1, LOH (x2) 13q12.11-q13.1, LOH (x2) 18q12.1-q21.2 (alterações que não explicam o quadro clínico, conforme literatura disponível).
-Aguarda RNM de crânio
-Aguarda exoma

Hipóteses diagnósticas: Síndrome dismórfica a esclarecer (hipóteses iniciais de Sd. Kabuki, FG ou síndrome de microdeleção).
Au-Kline? Mutação de ponto em HNRNPK?

Conclusões: Quais as hipóteses diagnósticas?

Material adicional:
Fotos

Código #13336

Título: CASO SEM DIAGNÓSTICO: DISPLASIA TORÁCICA ASFIXIANTE DE JEUNE TIPO 3?

Autores: Ricardo H. Almeida Barbosa[1], Thiago Rodrigues Cavole[1], Ariane Falconi[2], Viviane N. Katz[2], Maria Fernanda Milanezi[2], Daniela Testoni[1], Eduardo Perrone[1], Maria de Fátima de Faria Soares[1,] Rita de Cássia Xavier Balda[1], Mirlene Cecilia S.P. Cernach[3].

Instituição dos Autores: 1- Universidade Federal de São Paulo; 2- Salomão Zoppi Diagnósticos; 3- Universidade Metropolitana de Santos

Resumo do caso: Paciente filha única, pais hígidos, não consanguíneos, sem história familiar de malformações ou doenças genéticas na família. Mãe primigesta. Sem intercorrências gestacionais. Ao ultrassom gestacional foram vistos RCIU e encurtamento dos ossos longos. Nascida de parto cesárea por apresentação pélvica, feminino, termo, AIG, APGAR 2/7, PN= 2880g, PC= 34,5 cm, CN= 45,5 cm. Exame físico: fronte proeminente, face plana, narinas antevertidas, pescoço curto, tórax estreito. Evoluiu com insuficiência respiratória grave e necessidade de ventilação mecânica prolongada, mantendo-se internada em UTI Neonatal. Sem história significativa de icterícia neonatal ou de doença renal.

Exames complementares: USTF e fundoscopia normais. Ecocardiograma dilatação de câmaras direitas com refluxo tricúspide moderado, hipertrofia de ventrículo direito e valva aórtica tricúspide. Ultrassom de abdome total sem alterações. Ultrassom rins e vias urinárias com nefrolitíase não obstrutiva à direita. Radiografia de esqueleto com fronte ampla, tórax estreito, 12 pares de costelas e, arcos costais anteriores encurtados. Vértebras normais. Horizontalização leve do sacro, ilíacos arredondados e encurtados, com irregularidades nas superfícies acetabulares (tridente acetabular). Irregularidades das cavidades glenoidais. Metáfises irregulares, em formato de taça, dos metacarpos. Discrepância entre idade óssea do carpo e falanges. Mãos com falanges curtas. Morfologia da porção proximal do fêmur incompatível com a faixa etária à custa de sinais que sugerem definição da região trocanteriana nos fêmures direito e esquerdo. Encurtamento mesomélico dos membros inferiores. Sequenciamento completo do exoma: encontrada a variante c.7175T>G (p.L2392W) no gene *DYNC2H1*, em heterozigose, classificada como provavelmente patogênica, e a variante sinônima c.11070 G>A (p.P3690P), em heterozigose e classificada como variante de significado incerto.

Hipótese diagnóstica: Displasia torácica asfixiante de Jeune do tipo 3? (JATD)

Conclusões: A JATD é uma síndrome geneticamente heterogênea e caracterizada por anomalias esqueléticas, principalmente em costelas e membros. A hipoplasia torácica está associada a infecções respiratórias recorrentes e em 60% dos casos com insuficiência respiratória letal. Faz parte do grupo

das ciliopatias esqueléticas e são associadas à disfunção primária dos cílios. Mutações em diferentes genes, que em comum, causam o fenótipo. Esses genes codificam proteínas que participam no transporte intraflagelar ciliar/ciliogênese causam o fenótipo. A presença de variantes patogênicas no gene *DYNC2H*1 em homozigose já foi demonstrada previamente em pacientes com JATD. A variante c.7175T>G está em *hot spot* e afeta um domínio importante da proteína enquanto a variante c.11070 G>A afeta uma região altamente conservada. Essa é uma doença autossômica recessiva, exigindo a presença de uma variante em homozigose ou duas variantes em heterozigose composta para um diagnóstico genético definitivo.

Material adicional: Fotografias, radiografias e dados do sequenciamento do exoma.

Código #14307

Título: DISPLASIA ESQUELÉTICA COM ALTERAÇÕES CRÂNIO FACIAIS E PROTUSÃO MAXILAR PROGRESSIVA.

Autores: Shélida Vasconcelos Braz [1,2], Paulo Marcio Yamaguti[3], Heliana Dantas Mestrinho[3], Daniel Rocha de Carvalho[4], Juliana Forte Mazzeu [2], Ana Carolina Acevedo[1].

Instituição dos Autores: : [1] Laboratório de Histolopatogia Oral, Faculdade de Ciências da Saúde, Universidade de Brasília-UnB, Brasil; [2] Laboratório de Genética Clínica, Faculdade de Medicina, Universidade de Brasília-UnB, Brasil; [3] Clínica de Pacientes Portadores de Anomalias Dentárias, Unidade de Saúde Bucal, Hospital Universitário de Brasília-HUB; [4] Associação das Pioneiras Sociais, Rede Sarah de Hospitais de Reabilitação.

Resumo do caso: Paciente do sexo masculino de 19 anos, filho de pais consanguíneos e único membro da família afetado. Apresenta quadro de deficiência intelectual, associada a epilepsia iniciada na lactância, infecções respiratórias de repetição e queixa de dor crônica em membros. Ao exame físico apresenta macrocefalia, hipertelorismo ocular, fendas palpebrais oblíquas para cima, nariz pequeno com narinas antervertidas. As alterações mais marcantes estão presentes na arcada dentária superior, com crescimento anormal da pré-maxila, má oclusão dentária, associada a um palato estreito, hiperplasia gengival e incisivos centrais superiores protuídos.

Exames bioquímicos de cálcio sérico; fosfatase alcalina; creatinina; elastina pancreática fecal e triagem para erros inatos do metabolismo apresentam valores dentro do padrão de referência, já os níveis de fósforo (4,77mg/dL); osteocalcinina (99,5ng/mL); PTH (90.2pg/mL) e cloro no suor (80.49 mEq/L- braço direito) e (73.56 mEq/L- braço esquerdo) apresentaram dosagem aumentada em comparação aos valores de referência.

Exames radiológicos mostraram espessamento difuso da calota craniana, osteopenia, aumento do diâmetro antero-posterior do tórax com abaulamento anterior do esterno, aumento do índice das regiões metadiafisárias distais dos fêmures e proximais das tíbias e dos úmeros, proeminência dos pólos inferiores das patelas. O ultrassom abdominal, mostra hepatomegalia moderada e esteatose hepática moderada grau II.

Avaliação do potencial evocado: normal.

Análise de cariótipo: 46, XY

Análise cromossômica por microarray : Normal

Hipóteses diagnósticas sugeridas: Displasia craniometadiafisária ou Displasia craniometafisária, hipovitaminose D.

Conclusões: Paciente que apresenta dismorfismos faciais com hiperplasia gengival intensa, protrusão progressiva da maxila, além de escoliose, hiperlordose, genu valgus, osteopenia, infecções respiratórias de repetição, atraso no desenvolvimento intelectual e epilepsia.

Apesar do teste de mensuração de cloro no suor ser positivo para fibrose cística, o paciente não apresenta sintomas atuais da doença. Até o presente momento tem diagnóstico presuntivo de displasia esquelética não classificada.

Material adicional: Os exames de laboratório, radiológico, citogenético e fotos do paciente estão disponíveis para a apresentação do caso clínico.

Código #14308

Título: Infant cobalamin deficiency presenting with pancytopenia and severe neurological signs, inborn metabolic error or acquired disorder?

Autores: Renata Lazari Sandoval, Ana Carolina Rathsam Leite, Graziela Paronetto Machado Antonialli, Alice Crispim, Ludmila Inácio de Lima Uchôa, Maria Teresa Alves da Silva Rosa.

Instituição dos Autores: Núcleo de Genética Médica da Secretaria de Saúde do DF.

Resumo do caso:

A 6-month-old boy was admitted to the emergency department of Hospital Materno Infantil de Brasília due to extreme pallor and global hypoactivity. Admission laboratory exams revealed hemoglobin 1.7, hematocrit 7.4%, leukocytes 7000 (neutrophils 7% = 490), platelets 105000, Coombs negative, normal hemoglobin electrophoresis, reticulocytes 0.3%, DHL 2453, AST 63, ALT 18, CKMB 87, arterial blood pH 7.4, PCO2 16.6, pO2 148 (in O2 support), BE -9.6, HCO3 17.4, anion gap 17.7. His axial and peripheral muscle tone was decreased, with frog-like posture of both legs. There was no visceromegalies. He got better after initial blood transfusions and started investigations for pancytopenia.

He was the first and only child of non-consanguineous parents. The mother was 30 years old, G1P1A0, and did not have any known comorbidities prior to gestation. She attended to pre-natal medical checkups properly and had no gestational complications except for an urinary infection treated in the 3rd trimester. He was born from elective cesarean delivery, full term, low weight (birth weight 2565 g, stature 45 cm, head circumference 34 cm), the 1-minute and 5-minute APGAR score were 5 and 9. There were no history of perinatal or neonatal complications and he was discharged from hospital with 2 days of life. He was exclusively breast-fed until 5 months of age. Neonatal screening performed in the private network at birth showed no abnormalities.

With three months of life the mother noticed hypoactivity /hypersomnolence, difficulty in swallowing, low weight gain, but the pediatrician said that there was nothing to worry at that time. At the age of 4 months, he presented with clinical symptoms compatible with viral infection (fever, diarrhea, dehydration). Previous symptoms as hypoactivity and hypersomnolence got worse after this infectious condition and it was noticed progressive pallor. At that time the hemoglobin was 10.9. At the age of 5 months he started complementary feeding, and at this point it was evident the neuropsychomotor development delay which started to be investigated. At 6 months he weighted of 5.6 kg (<p3) and his head circumference was 42.3 cm (p10).

A few days after the initial hospitalization he developed severe pancytopenia, seizures, and comatose state. Complementary exams showed homocysteine 183, methionine 6.9, Vit B12 83, ammonia 108, urinary methylmalonic acid - 2,662.6 mmol / mole creatinine (VR: <5.0). The serious clinical scenario and the presence of vitamin B12 deficiency conducted to the hypothesis of an inborn error of the

metabolism related to the metabolism of cobalamin (absorption? Transport? Intracellular metabolism-methylmalonic acidemia combined with homocystinuria defect C?). It was instituted targeted therapy (parenteral cobalamin replacement, oral replacement of folinic acid, L-carnitine, betaine).

After 10 days of vitamin replacement the hematological series were recovered, and the serum levels of homocysteine and vit B12 were normalized. But in the fifth day of replacement he developed involuntary movements (masticatory movements, clonus, myoclonus) that got worse with time. Cranial MRI excluded basal ganglia changes or other findings (thrombosis / stroke). The movement disorder was attributed to neurological recovery after repositions. A panel of mutations (NGS) was performed to investigate treatable inborn error of the metabolism including the evaluation of genes related to cobalamin metabolism (MMAA, MMAB, MMACHHC, LMBRD1, MTR, MTRR) and no pathogenic mutations were found in the analyzed genes. Although the mother had no history of prior comorbidities and was asymptomatic (without anemia or neurological symptoms), maternal laboratory investigation showed deficiency of vit B12 (29/12/16 = vit B12 192 homocysteine 56,7 and 08/02/17 = vit B12 146 homocysteine 69, methylmalonic acid-122.0 mmol / mole creatinine, anti-parietal cell antibody reagent, gastrin 377). High digestive endoscopy evidenced marked atrophic gastritis, and the biopsy revealed autoimmune atrophic gastritis, H. pylori negative.

The patient recovered completely the hematological levels but still have failure to thrive, development delay, epilepsy (daily quick crisis characterized by ocular deviation folowed by somnolence) and developed microcephaly. Considering this disclosure, the diagnosis of the patient was changed to neurological sequelae due to maternal deficiency of vitamin B12.

In babies exclusively fed with breast milk, the symptoms of vitamin B12 deficiency are observed in general between the 4th and the 12th months. The time of onset of clinical findings is correlated with vitamin B12 levels in breast milk and the mother´s serum, in addition to the vitamin stores of the baby at birth. As the clinical findings of vitamin B12 deficiency are non-specific, they may easily be overlooked by family physicians or paediatricians, which in turn leads to a delay in the diagnosis and more severe manifestations and sequelae. The most common presentation signs and symptoms in infants are diarrhea, vomiting, lethargy, developmental delay, pallor, hypotonia, irritability, encephalopathy, coma, microcephaly, which through the eyes of the medical geneticist may represent an inborn error of metabolism. The appearance of involuntary movements in B12 deficiency after some days of corrective treatment with cobalamin is a rare condition but there are some case reports.

Material adicional: vídeos do início do caso, do distúrbio de movimento após início da reposição vitamínica, vídeos do status atual.

Código #14326

Título: Onfalocele, hérnia diafragmática, coloboma de íris, agenesia de corpo caloso, consanguinidade parental. Síndrome de Donnai Barrow?

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Resumo do caso: segundo filho de pais consanguíneos (primos em primeiro grau), história de irmão com óbito neonatal devido anomalias congênitas; diagnóstico pré-natal de onfalocele, parto cesáreo, a termo, com 3400g, 50cm, perímetro cefálico (PC): 38,5cm, Apgar de 8/9; sendo a mãe submetida à laqueadura tubária por decisão médica. Foi transferido para UTI neonatal na capital do estado, realizada correção cirúrgica de onfalocele aos 3 dias, apresentou no dia seguinte parada cardiorrespiratória, necessitou reanimação. Após cerca de um mês fez correção de hérnia diafragmática. Avaliado por médica geneticista, ao exame clínico-dismorfológico observaram-se: cabelos direcionados para cima, fontanela anterior ampla, prolongando-se pela região metópica, normotensa, hipertelorismo ocular, fendas palpebrais oblíquas para baixo, coloboma de íris bilateral, dorso nasal curto, cicatrizes de correção de onfalocele e de hérnia diafragmática alargadas e, com pele delgada. À avaliação por Neuropediatria observados movimentos erráticos do olhar – opsoclônus, irritabilidade, agitação, hipotonia axial e apendicular. Exames complementares realizados: tomografia computadorizada de crânio mostrou paralelismo dos ventrículos laterais com mínima dilatação dos mesmos, sugestivo de agenesia de corpo caloso; ecocardiografia evidenciou apenas forame oval patente; rastreio de proteinúria mostrou-se positivo; sorologias (TORCHS) e cariótipo sem alterações. Ainda sem avaliação auditiva, perdeu seguimento devido dificuldades com tratamento fora de domicílio; sendo reinternado devido desnutrição, pneumonia e sepse aos 9meses. Hipóteses diagnósticas: onfalocele, hérnia diafragmática, agenesia de corpo caloso, coloboma de íris, dismorfias craniofaciais, pais consanguíneos, caso semelhante na irmandade a esclarecer - síndrome de Donnai Barrow? (SDB). Conclusões: A SDB tem padrão de herança autossômico recessivo, caracteriza-se por dismorfismo facial (hipertelorismo ocular, fontanela alargada), achados oculares (coloboma de íris, alta miopia, perda visual progressiva), perda auditiva neurossensorial, agenesia de corpo caloso, atraso no desenvolvimento, onfalocele, hérnia diafragmática, variabilidade fenotípica inter e intrafamilial. O diagnóstico é baseado em dados clínicos e de neuroimagem, constatação de padrão característico de proteínas de baixo peso molecular na eletroforese de proteínas na urina e, confirma-se por análise molecular para o gene LRP2, que codifica a proteína megalina. A SDB apresenta elevada morbimortalidade pré-natal e perinatal, porém os pacientes que sobrevivem por longo tempo necessitam de acompanhamento oftalmológico, auditivo e renal regulares, além de

estimulação precoce. Discussões marcantes sobre o presente caso, além das dificuldades de confirmação diagnóstica de pacientes com doenças raras pelo SUS, incluem: dificuldades para referenciamento e tratamento compartilhado desde período preconcepcional/ prenatal; falta de conhecimento adequado dos profissionais de saúde sobre aconselhamento genético; orientação para casais consanguíneos inclusive com possibilidades atuais de estudos genéticos de rastreio para doenças autossômicas recessivas; considerações a respeito de custoXbenefício de diagnóstico preimplantação e reprodução assistida para casais com risco aumentado para doenças genéticas.

Material adicional: (imagens de estudo radiológico e de citogenética, família optou por não autorizar fotos).

Código #14169

Título: Provável Síndrome de Ellis-van Creveld com Ectrodactilia

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Resumo do caso: Filho de casal jovem, não consanguíneo, a termo AIG nascido pela via de parto cesáreo, idade gestacional de 38 semanas e 5 dias, Apgar 9/9, peso de 3820 gramas, 47 cm de comprimento e perímetro cefálico de 39 cm. História familiar de irmã falecida aos 7 dias de vida com displasia esquelética, polidactilia e átrio único. Os exames ultrassonográficos pré-natais descreveram polidramnia, encurtamento dos ossos longos, ectrodactilia bilateral, polidactilia em mão esquerda e átrio único. Ecocardiografia fetal confirmou a presença de átrio único e presença de aorta ascendente hipoplásica. Ao exame clínico apresentava língua com nódulos; porção medial do lábio superior fundido com a gengiva; dentes neonatais; tórax estreito e curto; encurtamento de membros; mão esquerda com 3 dedos e fenda entre o segundo e terceiro quirodáctilos. Observou-se dedo acessório com implantação em metade do segundo quirodáctilo no eixo ulnar; mão direita com quatro quirodáctilos, sendo o segundo com dedo acessório com implantação em sua metade e sindactilia do segundo e quarto quirodáctilos. Fenda entre o segundo e terceiro quirodáctilos; calcâneo valgus bilateral; polidactilia pós-axial em pé esquerdo e micropênis. Paciente faleceu com treze dias de vida de insuficiência respiratória.

Exames complementares: Ecocardiograma pós-natal confirmou o átrio único, além de duas valvas AV com regurgitação moderada a direita e a esquerda. O canal arterial era amplo e com shunt D/E. Angiotomografia de tórax documentou ausência do septo interatrial sugerindo átrio único. Afilamento difuso da aorta transversa, com área focal de menor calibre em nível do istmo. Ectasia do tronco arterial pulmonar. Ultrassonografia transfontanela foi normal. USG de abdome total revelou ascite volumosa em todos os quadrantes da cavidade peritoneal. Radiografia de corpo inteiro realizado no leito demonstrou costelas curtas, encurtamento de ossos longos e esporões nos ossos ilíacos descritos na Síndrome de Ellis-van Creveld.

Hipótese diagnóstica: Síndrome de Ellis-van Creveld familiar

Conclusões: A síndrome de Ellis-van Creveld pode ser causada por mutações nos genes *EVC ou EVC2* localizados no cromossomo 4p16.2 sendo de padrão autossômico recessivo. Até o momento não foi descrito na literatura a ocorrência de ectrodactilia na síndrome.

Pontos de interesse para a discussão: Este trabalho tem como objetivo principal discutir se a ectrodactilia pode ocorrer na síndrome de Ellis-van Creveld, possibilitando o aconselhamento genético preciso e descrever um possível novo achado clínico na síndrome.

Material adicional: radiografias, ecocardiograma e fotos

Código #14167

Título: RELATO DE CASO: SÍNDROME DE CANTÚ EM PACIENTE DE 19 ANOS

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Resumo do caso: Paciente do sexo feminino, 19 anos, acompanhada nesta instituição desde os 10 dias de vida. Pais não-consanguíneos, nasceu de parto vaginal com 36 semanas de gestação, pesando 2640g, Apgar 4/8. Ao nascimento, observou-sefácies grosseira e hipertricosegeneralizada, principalmente em região dorsal. Passou por correção cirúrgica aos 12 dias de vida devido a persistência de canal arterial. Ecocardiograma transtorácico demonstrou hipertrofia concêntrica de ventrículo esquerdo, além de válvula pulmonar displásica e dilatação do tronco arterio-pulmonar, sem repercussões hemodinâmicas; diagnóstico de erros inatos do metabolismo afastado por exames complementares. Apresentou 13 episódios de pneumonia no primeiro ano de vida, com infecções respiratórias recorrentes até a presente data.

Em agosto de 2016, apresentou derrame pericárdico moderado, assintomática, sem sinais de restrição diastólica, diagnosticado através de ecocardiograma de rotina por conta de sua cardiomegalia. Realizou ressonância magnética cardíaca revelando derrame pericárdico importante associado a movimentação acentuada do coração durante a sístole e sem a visualização do pericárdio em alguns segmentos.

Densitometria óssea realizada em março de 2017 demonstrou osteoporose em coluna lombar (Z-Score -3,0) e densidade mineral óssea de corpo inteiro com Z-Score de -3,8. Radiografia de coluna total evidenciou escoliose torácica e lombar, área cardíaca aumentada, enquanto a de crânio demonstrou espessamento de calota craniana.

Ao exame clínico atual, apresenta hirsutismo frontal e em braços e pernas, fácies grosseira, ponte nasal alargada, lábios grandes e grossos. Não apresenta hipertrofia gengival, assim como lesão distal dos membros. É longilínea, com boa definição muscular. Desenvolvimento puberal de acordo com a idade cronológica. A ausculta cardíaca, apesar do derrame pericárdico, não é alterada. Déficit intelectual leve.

Exames realizados: Cariótipo (46, XX); ECO TT; RNM cardíaca; densitometria óssea; RX de coluna, crânio e mãos.

Hipóteses diagnósticas: A principal hipótese é a Síndrome de Cantú (OsteocondrodisplasiaHipertricótica, OMIM #239850), caracterizada por hipertricose congênita, cardiomegalia e osteocondrodisplasia. Ainda não realizou análise molecular dos genes ABCC9 ou KCNJ8.No entanto, durante o acompanhamento do caso, foram aventadas as possibilidades de MPS tipo III, Síndrome de Zimmermann-Laband, Síndrome de Coffin-Siris e Síndrome de Ambras.

Conclusões: Frente à nossa hipótese,é possível um protocolo para o diagnóstico clínico da Síndrome de Cantú? Como é o manejo do paciente na infância e na idade adulta? Importância do aconselhamento genético.

Material adicional: Fotos da paciente, exames de imagem.