Abstract/Resumen: Fragile X Syndrome (FXS), the most common heritable form of intellectual disability (ID), is usually due to a CGG expansion, named full mutation (> 200 CGG repeats) in the FMR1 gene, located in Xq27.3. This mutation leads to hypermethylation of the promoter silencing it and lowering the expression levels of the FMRP protein, involved in synaptic plasticity and maturation. The mothers of children with FXS generally have an X chromosome with a premutation (55-200 repeats) or, less frequently, a full mutation. In 2 % of the cases, the absence of FMRP is due to single nucleotide variants or deletions. We present the case of a 3 years-old male child (who presented ID, language development delay, autism, hyperactivity, hyperlaxity, prominent ears, high palate, surgically resolved hypospadias and left testicle in elevation), and his mother (with ID without dysmorphisms), who were tested for FXS. Fluorescent PCR, TP-PCR with the AmplideX FMR1 PCR kit (Asuragen) and MS-MLPA (ME029-B3 FMR1/AFF2 kit, MRC Holland) were performed for both of them. Fluorescent PCR did not show amplification product for the child's sample and capillary electrophoresis of the fluorescent PCR from the mother's sample showed a single peak of 33 triplets. Unexpectedly, the TP-PCR also showed no amplification for the child and a normal pattern of 33 repetitions for the mother. Finally, the MLPA showed a deletion of at least 1.05 Mb in the Xq27.3-q28 region, involving entire FMR1 and exons 1 to 14 of AFF2 (NM_002025.3), both in the child and his mother. No mosaicism was observed. So, the mother presented one allele with 33 repeats and another with deletion of FMR1. Her son inherited the allele with the deletion, probably resulting in no FMRP protein levels. Although the MS-MLPA for FMR1 is usually used to assess the methylation state of its promoter, in this case, this technique helped to evidence the presence of a deletion, a very rare molecular cause of FXS, reaching to an accurate diagnosis.

0700 - APPLICATION OF LDL GENETIC RISK SCORE IN PATIENTS WITH HYPERCHOLESTEROLEMIA TO EVALUATE A POLYGENIC ORIGIN CAUSES

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Abstract/Resumen: High LDL-cholesterol (LDL-c) values may be due to monogenic variants in the LDLR, APOB, PCSK9 or LDLRAP1 genes, leading to Familial Hypercholesterolemia (FH); or to a polygenic origin arising from polymorphisms in different genes related to cholesterol metabolism. Two genetic risk scores (GRS) are the most widely used, one in Canada (SNPs: 11) and the other in European population (SNPs: 6). Here we present the application of the European GRS in a sample of hypercholesterolemic patients in the province of Buenos Aires from the FH DaVinci study. The 6 SNPs of the GRS were obtained from the VCF files or by Sanger sequences, from 116 index cases with clinical evaluation (DCLN score) and genetic studies of FH. Twentyu eight % showed a positive GRS. The mean value was: 0.68 ± 1.72, median=0.704, mode=0.760. The quartiles values were: Q1= 0.581, Q2= 0.704 and Q3= 0.798. The SNP with the strongest effect on the score was the rs6511720 G allele on the LDLR gene (frequency 0.95). Four groups were considered: with monogenic origin (22); non-monogenic and GRS- (62); non-monogenic and GRS+ (26); and both monogenic and GRS+ (6). DLCN score was: 9.14 ± 2.98; 6.47 ± 2.53; 6.72 ± 1.90 and 10.71 ± 3.15 respectively, (ANOVA p<0.001), no differences were observed for: GRS+ vs. GRS- and for monogenic vs. both monogenic and GRS+. The mean LDL-c was: 269.36 ± 100.06; 188.17 ± 78.80; 218.30 ± 56.70 and 278.43 ± 93.14 respectively (ANOVA p<0.001), no differences were observed for GRS+ vs. GRS- .The GRS showed a sensitivity of 39 % and specificity of 81 % using a cut-off value of > 0.76. We conclude that hypercholesterolemic individuals from this sample of our population, with positive polygenic GRS showed lower values of DCLN clinical score compared to those with a monogenic origin, levels of LDL-c are higher for those with monogenic origin, and that it would be preferable to apply the GRS in a healthy group to assess their ability to discriminate polygenic causes in our population.

0709 - COPY NUMBER VARIANTS IN CHILDREN WITH INTELLECTUAL DISABILITY/GLOBAL DEVELOPMENTAL DELAY, DYSMORPHIC FEATURES AND/OR CONGENITAL ANOMALIES.

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Abstract/Resumen: Chromosomal microarray analysis (CMA) has emerged as a major tool to identify clinically relevant copy number variants (CNV) in children with intellectual disability/developmental delay (ID/DD), autism spectrum disorders (ASD) and multiple congenital anomalies (MCA).The aim of this study is to present the spectrum of anomalies detected by CMA in patients with ID/DD, dimorphism and/or MCA in whom standard karyotyping analysis had shown normal results. CMA analysis was performed in 56 patients using two microarray platforms: Sure Print G3 ISCA v2 8x60K or Baylor CGH 8x60K (Agilent). Pathogenic or likely pathogenic CNVs were identified in 12 cases (21.4 %), a variant of uncertain significance (VOUS) was detected in 1 patient (1.8 %) and 3 patients (5.3 %) showed likely benign CNVs. Microdeletions were observed in 11 cases and only in one patient a microduplication syndrome was identified. Regarding deletions, 7 cases were associated with known syndromes, 2 patients showed intragenic deletions involving DYRK1A and SCL9A6 genes respectively, one patient presented an uncommon chromosome 19q13.12-q13-2 deletion, and a mosaic deletion of 18.3 Mb on chromosome 20 was observed in one case. CNVs detected in our cohort ranged from 8 Kb to 6.6 Mb regardless the mosaicism case. The resolution of 8x60K microarrays format used in this study demonstrated to be useful and offered an excellent diagnostic yield in patients with ID/DD, dysmorphic features and/or MCA. In addition, it provided a low rate of VOUS detection which may be difficult to interpret and may represent a counseling challenge. In conclusion, this study emphasizes the usefulness of CMA in detecting genomic imbalances in this group of patients with normal standard karyotype.

0902 - IMPLICATION OF GLUTATHIONE S-TRANSFERASES GENE VARIANTS ON ACUTE INTERMITTENT PORPHYRIA ONSET.

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CIPYP-UBA-CONICET (1); CIPYP - UBA-CONICET Y FCEN, UBA (2)

Abstract/Resumen: Acute intermittent porphyria (AIP) is a result of a partial and primary deficiency in Porphobilinogen deaminase (PBG-D), the third enzyme in the heme pathway. The presence of the mutation is not enough for the manifestation of AIP which can be triggered by therapeutic drugs, so genetic variants in cell detoxification system could be involved in AIP onset. Glutathione-S-transferases (GST) are Phase II enzymes involved in detoxification of reactive oxygen species, environmental carcinogens, metabolism of steroid hormones and chemotherapeutic agents. Some polymorphisms in this gene, GSTT1 null, GSTM1 null and GSTP1 (rs1695, c.313 A>G), alter GST activity affecting hormones and xenobiotics levels. The aim

was to analyze these variants in relation with AIP manifestation. The study was performed in control individuals (non porphyric) and in AIP patients carrying PBG-D mutation who at the moment of the diagnosis were symptomatics (S-AIP) or without clinical/biochemical alterations (latent group, L-AIP). GSTT1 and GSTM1 were amplified by multiplex PCR; GSTP1 variant by PCR-RFLP. The deletion frequencies in homozygosis for GSTT1 null were: 8.3 (control), 20.5 (S-AIP) and 6.1 % (L-AIP). Frequencies for GSTM1 null were: 41.7 (control), 51.3 (S-AIP) and 45.5 % (L-AIP). In S-AIP, null GSTT1 frequency was significantly high respect to control ($p<0.05$) and L-AIP ($p<0.01$); GSTM1 gene frequency were higher but no significant than the other cohorts. GSTs null variants are considered of risk. GSTP1 allelic frequencies for non-wild type (G) variant were: 0.42 (control), 0.47 (S-AIP), 0.35 (L-AIP). GG genotype frequency in GSTP1 was significantly high in S-AIP respect to others groups ($p<0.01$). When the combination of GSTM1/GSTT1/GSTP1 were calculated, a high frequency for the presence of 2 risk variants was observed for the S-AIP group respect to L-AIP and Control. In conclusion, results here presented would suggest a possible implication of GSTs in AIP onset.

0918 - ATM KINASE ACTIVITY PROMOTES THE REMOVAL OF ETOPOSIDE-INDUCED TOP2A CLEAVAGE COMPLEXES THROUGH TDP1 FUNCTION

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Abstract/Resumen: The Top2 poison Etoposide (ETO) stabilizes a covalent intermediate Top2-DNA, which represent a protein blockage of DNA ends. Tyrosil-DNA-Phosphodiesterase 1 (TDP1) can remove phosphodiester bonds between proteins and the phosphate group of DNA to allow the repair of blocked DNA ends. We determined the role of TDP1 in the removal of abortive Top2A-DNA complexes (ccTop2A) during different metabolic processes of DNA. A possible regulatory effect of ATM on the TDP1-dependent ccTop2A removal was also analyzed. The study was performed in a HeLa TDP1-knock down cell line (TDP1kd) by assessing ETO-induced ccTop2A by flow cytometry. We showed that TDP1kd cells accumulated higher amounts of abortive ccTop2A than control (NS) cells after 1 h exposure to ETO ($p<0.05$, t-test). In addition, pre-incubation of TDP1kd cells with the proteasome inhibitor Bortezomib (Btz, 2.5 μM) gave rise to similar levels of ETO-induced ccTop2A than those found in NS cells treated with Btz+ETO and ETO-treated TDP1kd cells. This suggests a proteasome-dependent activity of TDP1 in the removal of ccTop2A. TDP1kd cells showed higher levels of ETO-induced ccTop2A in the S-phase compared to NS ($p<0.05$), which correlated with increased DNA damage signals (γH2AX) by 2 h. No significant differences were found in ETO-induced ccTop2A levels in NS and TDP1kd cells after pre-treatment with the transcriptional inhibitor DRB (300 μM)+ETO compared with ETO alone. On the other hand, pre-treatment with an ATM kinase inhibitor (KU55933, 10 μM) resulted in higher accumulation of ETO-induced ccTop2A in both NS and TDP1kd cells ($p<0.05$), without evidence of synergistic or additive effect; thus suggesting both enzymes are involved in the same pathway. Together, our results demonstrate that TDP1-mediated removal of ETO-induced ccTop2A occurs during DNA replication and is dependent on proteasome activity. Similarly, we showed the kinase activity of ATM promotes the removal of abortive ccTop2A by the same pathway that TDP1 does.

0940 - VARIATION OF THE ABSOLUTE TELOMERE LENGTH AFTER DIFFERENT TREATMENT IN PATIENTS WITH OBESITY

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Abstract/Resumen: Overweight and obesity are one important risk factors for mortality in the world. Telomeric length is considered a marker of cell aging and is closely related to biological situations like oxidative stress and inflammation. Our objective was to analyze different treatments on absolute telomere length (aTL) in obese patients. We studied a group of 21 patients with obesity treated with diet, physical exercise and pharmacological treatment and a group of 31 obese patients with indication of bariatric surgery. The biochemical-clinical characteristics were measured and we evaluated the difference in their absolute telomere length after 6 months of intervention. aTL was determined in genomic DNA extracted from peripheral blood leukocytes by the method of absolute quantification by quantitative real-time PCR. Statistical analysis was carried out by SPSS with a significance level of 0.05. We observed by linear regression a negative association between the variation of aTL between basal time and after 6 months and age in all patients with obesity ($p= 0.03$). A change in telomere length significantly correlates with weight loss ($p= 0.01$) and decrease in BMI ($p<0.01$), and depended on the type of treatment ($p<0.01$) and with the incidence of T2DM ($p= 0.02$). The significant increase in aTL in patients with an indication of bariatric surgery ($p<0.01$), was attributed to a significant correlation found with the greatest decreases in the levels of inflammation measured by PCR-us ($p<0.01$). In patients undergoing pharmacological treatment we only found a significant positive association between the variation of aTL after treatment and the dose of metformin ($p= 0.01$). The treatments had different effects on the absolute length of the telomere in obese patients. We show the impact of inflammatory status and high doses of metformin on telomere length.

Metabolismo y Nutrición / Metabolism and Nutrition I

Chairs: Marcelo Choi | Miriam Wald

0060 - CHRONIC ADMINISTRATION OF HIGH FRUCTOSE-HIGH FAT DIETS INCREASES ABDOMINAL ADIPOSE TISSUE AND LIVER WEIGHT BUT NOT BODY MASS IN RATS

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Abstract/Resumen: Diets in industrialized nations have shifted to increased consumption of fructose and saturated fat. These diets are linked with metabolic complications such as metabolic syndrome (MS). Fructose is a lipogenic substrate which can induce metabolic alterations in the liver and has increasingly been used as a sweetener since the introduction of high-fructose corn Syrup in soft drinks and other carbohydrate-sweetened beverages. Similar effects are not observed with the administration of other simple sugars such as glucose. In animal models, the administration of high fructose -10 % fructose in drinking water- and fat -20 %- (known as Western diet –WD-), induce features of MS including weight gain, insulin resistance, hypertriglyceridemia, hypertension, abdominal obesity and non-alcoholic fatty liver disease (NAFLD) among other pathological alterations. The objetive of this work was designed to evaluate body composition modification in long term administration of WD to male Wistar rats. Animals were exposed from 6 to 24 weeks of age to a standard diet –SD- (n= 8) or WD (n= 8). Every 6 weeks