ABSTRACTS COLLECTION

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P01

Reproductive Genetics

P01.002.B PPARG1 gene methylation in granulosa cells relation to hyperinsulinemia and hyperandrogenism in women with polycystic ovary syndrome

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Background/Objective: one of the most prevalence endocrine disorders in women is Polycystic Ovary Syndrome (PCOS). This syndrome is heterogeneous, and recent evidence suggested that epigenetic events could responsible for the occurrence of this syndrome. one of the most significant epigenetic modifications is DNA methylation, which could decrease gene expression. There is a close connection between energy metabolism and female fertility. PPARG gene plays an important role in lipid and glucose metabolism, and it shows significant role in the evolution of the reproductive system growth and development in embryonic stage. This study aimed to investigate the frequency PPARG1 gene methylation in granulosa cells in PCOS patients with hyperinsulinemia and hyperandrogenism.

Methods: The follicular fluid of 30 normal individuals, 25 women with polycystic ovary syndrome only, 20 PCO women with hyperandrogenism (HA), and 20 PCO women with insulin resistance (IR) were collected. After isolation of granulosa cells from follicular fluid, genomic DNA extracted and after bisulfite DNA treatment, CpG-rich region in PPARG1 gene promoter was selected and methylation-specific polymerase chain reaction (MS-PCR) was performed on bisulfite DNA.

Results: The results analysis revealed a significant difference between the methylation of the PPARG1 gene in four patient groups ($P < 0.005$), indicating that the PPARG1 gene promoter is hypermethylated more significantly in PCO-IR and PCO-HA patients.

Conclusion: The frequency of PPARG1 gene promoter methylation in PCO-IR and PCO-HA individuals were higher than in other groups. So higher methylation would decrease PPARG1 gene expression in ovary, which could cause PCO-IR and PCO-HA in women in reproductive age.

Conflict of Interest: None declared

P01.004.D Severe premature ovarian insufficiency: don't forget about men

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process, VC causes vascular stiffness increasing morbidity and mortality.

Material and Methods: Herein we investigated RUNX2 and IL-6/STAT3 signalling pathways through hsa-miR-30a-5p, hsa-miR-223-3p and downstream members of these pathways using RNA PCR technique. From the waste vascular tissue of 37 patients collected during renal transplantation operation expression levels of target miRNA and genes were analyzed with qRT-PCR at the Biorad Real time PCR platform.

Results: There were 8 females and 29 male patients with an average age of 36 +/− 14 years. For normalization of expression levels hsa-mir-145-5p was used as internal control which is expressed at vascular tissue at physiological condition.

Conclusion: We have detected that Hsa-miR-223-3p and Hsa-miR-30a-5p expressions were increased in vascular tissue of chronic renal failure patients effecting osteoblastic differentiation at the vascular tissue.

Conflict of Interest: None declared

P06.038.B Genetics of a rare and complexe congenital heart defect: the congenitally corrected transposition of the great arteries

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Congenitally corrected transposition of the great arteries (CCTGA), a complex and rare congenital heart disease, is laterality defect. The aim of this study is to understand the mechanisms and genes that control the alignment of cardiac chambers, and lead to the CCTGA. We analysed à cohort of 43 trios (41 sporadic cases and 2 familial cases) of non syndromic CCTGA by next generation sequencing analysis (whole-genome and whole-exome sequencing). Variant selection criteria were: rare (<1%), damaging (using SIFT and PolyPhen), the gene is known to play a role in heart morphogenesis. Under the hypothesis of Mendelian model with de novo genomic alterations, no major gene could be identified. Under the hypothesis of a complex model of inheritance with incomplete penetrance, a total gene set of 156 genes matched each of our selection criteria. The highly heterogeneous combinations of susceptibility rare variants, mostly inherited from the healthy mother and father respectively, functionally converge to give rise to the CCTGA phenotype. To prove that a given allele combination is associated with the CCTGA phenotype, we showed a highly significant enrichment of rare variants in cases, any given deleterious variant combination within the CCTGA gene set being specific to the affected individual. A replication of these results was obtained on another cohort of CCTGA simplex cases with statistical significance ($p = 0.04$, OR 1.5). These data contradict a monogenic mode of inheritance, favoring a polygenic origin of the disease where parents harbour a genetic predisposition (susceptibility alleles) and transmit this genetic risk to their offspring.

Conflict of Interest: None declared

P06.039.C Dose-effect of celiprolol in mice modelling vEDS

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Background/Objectives: Patients with vascular Ehlers-Danlos syndrome (vEDS) caused by pathogenic variants in the *COL3A1* gene are at increased risk of arterial events such as dissections and/or ruptures. In addition to preventive and emergency surgical interventions, the most important therapeutic modality is the use of antihypertensive drugs. Clinical and long-term observational studies showed the reduction of arterial events upon treatment with the beta-blocker celiprolol. Previously, we have demonstrated that celiprolol increases the reduced aortic rupture force in mice modelling vEDS. Recently, two other groups have reported conflicting results on survival of celiprolol-treated mice using different mouse vEDS models and celiprolol doses. Here, we therefore analysed the effects of different doses of celiprolol in our (i.e. the same) mouse vEDS model.

Methods: Four-week-old heterozygous *Col3a1*^{m1Lsmi} and wild-type mice of both sexes were treated with the three formerly studied doses of celiprolol for four weeks. Following treatment, plasma levels of celiprolol were measured using LC-MS/MS. The survival of animals per treatment group was also analysed.

Results: Mortality was clearly higher in heterozygous mice treated with higher doses of celiprolol compared to heterozygous mice treated with lower doses and wild-type mice. Furthermore, a trend towards higher plasma concentrations upon higher doses of celiprolol was observed.

Conclusions: There is currently no clinical consensus regarding the medical treatment of vEDS. Thus, it is important to explore the reason for the controversial results concerning the efficacy of celiprolol in mouse models of vEDS. Our results may help to clarify the clinical relevance of celiprolol in vEDS patients.

Conflict of Interest: None declared

P06.040.D FBN1 mutation profile in Korean patients with TAAD, : Data from AMC Hereditary Thoracic Aortic Aneurysm Registry

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Background: Marfan syndrome(MFS), caused by mutations in fibrillin-1(*FBN1*), is a relatively common hereditary connective tissue disorder. The thoracic aortic aneurysms and acute aortic dissections(TAAD) are the leading causes of mortality in MFS patients. This study investigated the spectrum of FBN1 variants in Korean patients with TAAD, and the genotype–phenotype correlations.

Methods: The study subject were enrolled from the Asan medical center(AMC) Hereditary Thoracic Aortic Aneurysm Registry between October 2016 and December 2021. MFS was diagnosed based on Ghent-criteria, clinical manifestations, and detection of *FBN1* mutations using Sanger sequencing, and Next-Generation Sequencing(NGS).

Results: Total 302 patients(M:F = 203:99) were enrolled in AMC Hereditary Thoracic Aortic Aneurysm Registry and family members(N = 70) were also performed FBN1 genetic test. Pathogenic variants(PV) of *FBN1* were detected in 50.3%(N = 152, M:F = 93:59). Most frequent type of PV was null variant(46.7%,