ABSTRACTS COLLECTION

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Presenting author names **are bolded** in the contributor lists.

E-POSTERS

P01 Reproductive Genetics/Prenatal Genetics

P01.001.A Frequency of Y chromosome microdeletions in Turkish infertile men: Single Center Experience

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Objective: Y chromosome microdeletions are the leading genetic cause of male infertility and their detection is clinically relevant for appropriate genetic counseling. Y chromosome includes genes for testicular development and spermatogenesis. The aim of this study was to establish the frequency of the Y chromosome microdeletions in Turkish infertile men who referred to our center with severe oligozoospermia and azoospermia.

Materials and Methods: In our study, 396 infertile men referred to İstanbul University- Cerrahpaşa, Cerrahpaşa Medical Faculty Department of Medical Genetics (GETAM) between 2016 to 2020 with azoospermia/severe oligospermia. We evaluated microdeletions of the Y-chromosome STS markers AZFa, AZFb and AZFc, ZFX/ZFY, terminal sY160 regions by using DNA Fragment analysis.

Results: Among the 396 infertile men, we determined 30 cases of Y chromosome micro- deletions (7.57%). Among 30 cases, AZFc microdeletions were found in 18 cases (60%), AZFa microdeletions in 4 cases (13.3%), AZFb microdeletions in 1 case (3.3%), AZFa,b,c in 4 cases (13.3%), AZFb,c in 3 cases (10%). Our findings are consistent with the literature.

Conclusion: Our results are similar to the previous studies which have mostly reported a frequency of less than 10% for Y chromosome microdeletions. The etiology of infertility remains unknown and novel genes other than y chromosome microdeletions should be identified with high throughput techniques.

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P01.002.B Serotonin transporter 5-HTTLPR genotypes and trinucleotide repeats of androgen receptor exert a combinatorial effect on hormonal milieu in patients with lifelong premature ejaculation

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Premature ejaculation is one of the most common sexual disorders in men due to the uncontrolled modulation of spinal reflexes. In this study, we investigate the combinatorial effects of trinucleotide repeats of androgen receptor and allelic variants of the 5-HTTLPR gene on sex steroids, hypophyseal hormones, sexual performance, and premature ejaculation assessment parameters among evidence-based lifelong premature ejaculation subjects. A total of 271 patients consulting for evidence-based lifelong premature ejaculatory dysfunction were selected in this study. The control group consists of 155 men with normal IELT (>4 min). The study revealed that the subjects who have the highest (≥26) CAG stretch depicted significantly higher serum oxytocin levels

located in four new loci. We prioritized the genes in known CAD loci. Usually, the gene closest to the top GWAS signal is interpreted as the causal gene. We showed that only 50% of validated genes were the closest to the top signal at each locus. For 19 known CAD loci, we showed that the probably causal genes are more distant from the top GWAS signal.

Conclusions: We identified 65 genes that contribute to CAD with their within-gene variants and prioritized genes in known CAD loci. This work was supported by the Ministry of Education and Science of the RF (project 0259-2021-0009/-17-117092070032-4).

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P24.013.D Genome-wide association study of estradiol levels, and the causal effect of estradiol on bone mineral density

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Estrogen is the primary female sex hormone and plays an important role for skeletal health in both sexes. Several enzymes are involved in estradiol metabolism but few genome-wide association studies (GWAS) have been performed to characterize the genetic contribution to variation in estrogen levels.

We performed GWAS for estradiol in males (N = 147,690) and females (N = 163,985) from UK Biobank (UKB). Estradiol was analyzed as a binary phenotype; above/below detection limit (175 pmol/L). We further estimated the causal effect of estradiol on bone mineral density (BMD) using Mendelian randomization.

We identified 14 independent loci associated ($P < 5x10^{-8}$) with estradiol levels in males, of which one (*CYP3A7*) was genome-wide, and another seven were nominally ($P < 0.05$) significant in females. In addition, one female specific locus was identified. Most candidate genes have functions that are relevant to estrogen metabolism and have not been discussed in relation to estradiol levels in previous GWAS. For example, *SRD5A2*, which encodes a steroid 5-alpha reductase that is involved in processing androgens, and *UGT3A1* and *UGT2B7* which encode enzymes likely to be involved in estradiol elimination. The allele that tags the O blood group at the *ABO* locus, was associated with higher estradiol levels.

We further applied Mendelian Randomization to identify a causal effect of estradiol on bone mass density, both in males (beta = 0.099, $P = 1.58x10^{-11}$) and, for the first time, in females (beta = 0.15, $P = 7.48x10^{-6}$). Our findings further support the importance of the body's own estrogen to maintain skeletal health in males and in females.

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P24.015.B Genetic variability of 6p22.1 in sepsis susceptibility: a fine mapping association study of the HLA

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Introduction: Sepsis is a severe inflammatory response to infections with a high death rate. We previously conducted the first GWAS of copy number variations in 839 sepsis cases from the Gen-Sep Network and 1,453 controls, highlighting 6p22.1 as one of the significant loci linked to sepsis susceptibility. Due its importance in inflammatory and immunological diseases, here we performed a fine mapping of the Human Leukocyte Antigen (HLA) region contained in that locus.

Methods: We used SHAPEIT v2.837 for phasing the haplotypes and Impute2 to impute the classic HLA alleles, amino acids, and single nucleotide polymorphisms (SNPs). Association analyses were performed by logistic regressions using EPACTs v3.2.6. A Bonferroni correction was applied to identify significant classic HLA alleles ($p < 2.58E\text{-}4$) and amino acids ($p < 4.91E\text{-}5$). For SNPs, a significance threshold was established at $p < 1.50E\text{-}5$ based on the number of independent variants.

Results and conclusions: We analyzed a total of 194 classic HLA alleles, 1,019 amino acids and 10,919 SNPs. None of the classic HLA alleles ($p_{lowest} = 0.01$), amino acids ($p_{lowest} = 0.01$), or SNPs ($p_{lowest} = 9.84E\text{-}4$) were significantly associated with sepsis. Given the complexity of this phenotype, these results suggest that the HLA genetic variation is not a major driver of sepsis susceptibility or has a modest effect size.

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