ABSTRACTS COLLECTION

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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

testing units but are computationally intensive and with performances that depend on window sizes. The filtering of variants is also often focused on coding parts, leaving out functionally relevant intronic variants.

Methods: We used pathogenicity scores observed in GnomAD to define testing units and to optimize the filtering of variants included in rare variant association tests. Using case-control exome sequence data on Moyamoya disease, we compared our proposed strategy to the classical gene-based analysis and to WGScan, a sliding window procedure. We evaluated the performances of these different strategies to detect the known signal on RNF213 by burden tests.

Results and conclusions: Our strategy and the sliding window approach were more efficient than the gene-based approach to detect the signal. They were able to delimit a restricted candidate region within the gene. Moreover, our region-based strategy to filter variants outperformed classical filtering strategies. These encouraging results suggest that a similar approach could also be used in the non-coding regions of the genome where we dramatically lack of functional annotations to define testing units and select qualifying variants.

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P24.051.B Genome-wide association study of smoking behaviors in a Chinese population of Taiwan

Ming-Wei Lin[1], *Chia-Yen Wu*[1], *Pei-Yu Weng*[1], *Ting-Yi Wu*[2], *Yi-Ying Wu*[1], *Chih-Kuan Lai*[3], *Kuang-Chieh Hsueh*[4], *I-Fan Liu*[5], *Hsin-Bang Leu*[6], *Li-Shiun Chen*[7], *Ivy Yi-Wen Tsai*[8], *Kung-Yee Liang*[9]

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Introduction: Tobacco smoking is one of the major risk factors for many chronic diseases and is the leading cause of preventable death in the world. Smoking behavior is a complex, multifactorial trait with both genetic and environmental factors contributing to the various phenotypes. The aims of this study were to conduct a genome-wide association study (GWAS) on smoking behaviors and to investigate the association between genes, smoking behaviors and their impact on the cardiovascular outcomes in a Chinese population of Taiwan.

Methods: We have enrolled 860 ever-smoking subjects recruited from the Healthcare Center and the Department of Family Medicine in the Taipei Veterans General Hospital, and the Department of Cardiology in the Cheng Hsin Hospital. Each participant was followed-up every six month by telephone interview with a structural questionnaire to obtain the information of their smoking status, smoking quantities, quitting attempt, and major cardiovascular events in subsequent one year. The Infinium CoreExome-24 BeadChips (Illumina, San Diego, CA) were used for the genome-wide association study. The PLINK program was used for the analysis of genome-wide association study.

Results: We identified several novel genes, including *RIT2, CLYBL, NFAM1, LRRC8E, FAM129B, HACD1, STK32A, CCDC88C, LINC01804, PCAT2, ASIC2, CNTNAP2*, were associated with smoking cessation at 6 months (with p-value 1×10^{-4}). Further studies to confirm our preliminary findings are warranted.

Conclusion: Our results identified several novel genes might be associated with smoking cessation in a Chinese population of Taiwan. Further study with larger sample is required to replicate our preliminary findings. Grant No: MOST 109-2314-B-010-045-

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P24.052.C Trans-ancestry GWAS of 118,780 individuals reveals biological mechanisms underlying the spatial QRS-T angle, a marker of arrhythmogenesis

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Background: The spatial QRS-T angle (spQRSTa), the angle between QRS and T-wave spatial vectors, is an established predictor for risk of arrhythmia and sudden cardiac death (SCD). However, the biological mechanism remains unclear. We sought to identify novel candidate genes associated with the spQRSTa, to improve our understanding of the underlying biology.

Methods: We performed a trans-ancestry meta-analysis of genome-wide association studies (15) imputed with 1000G / HRC reference panels, comprising 118,780 individuals (81.3% European, 10.7% Hispanic and 7% African). Genetic correlation with other electrocardiogram traits was estimated using linkage disequilibrium score regression. Gene prioritization and gene-set enrichment was performed using DEPICT.

Results: We identified 61 independent loci (58 novel) in the trans-ancestry meta-analysis and an additional novel locus in African and Hispanic ancestry-specific analyses. Percent variance explained by lead variants was 3.4% (2.5% increase by novel loci). Heritability in Europeans (UK-Biobank) was 22.3%. Genetic correlation with PR, QRS, JT and QT was low ($r_g = -0.06$, 0.12). Top gene-ontology terms included cardiac/muscle cell differentiation and chamber morphogenesis. At 11 loci, candidate genes had established relationships with cardiomyopathies in humans, including *MYH7* and *TNNT2*. At other loci, genes have roles in cardiac cell proliferation (*CENPA, ERBB4*), embryonic development (*PITX2, WNT2*), arterial development (*ALDH1A2*) and angiogenesis (*ANGPT1*).

Conclusions: These analyses highlight the sarcomeric assembly, cardiac development and vasculogenesis as key contributors to the spQRSTa. The findings provide insight into possible mechanisms underlying the association with risk of arrhythmogenesis and SCD. W.J.Young is funded by the Medical Research Council (Grant code MR/R017468/1)

W.J. Young: None. **P.B. Munroe:** None. **L. Tereshchenko:** None.

P24.053.D A Genome-Wide Association Study of Copy Number Variants of sepsis susceptibility

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Introduction: Sepsis is a severe inflammatory response to infections and a major cause of death and healthcare expenditure worldwide. To date, no genome-wide association study (GWAS) has been conducted for sepsis susceptibility. Here, we provide the results of the first GWAS of Copy Number Variants (CNVs) in sepsis patients.

Methods: We conducted a one-stage GWAS of CNVs in 839 sepsis cases from the Gen-Sep Network and 1453 controls genotyped with the Axiom Genome-Wide CEU 1 Array (Thermo Fisher Scientific). We used the software PennCNV for variant calling, and ParseCNV and PLINK v1.9 for association testing of common CNVs (>1% frequency), adjusting the models for gender, age, and the first two principal components of genetic variation. A Bonferroni adjustment was applied correcting for the number of tested CNVs to declare significance ($p < 3.6E-5$).

Results and conclusions: Four CNVs, including one deletion in 6p22.1 ($p = 2.94E-5$) and three duplications in 1q21.1 ($p = 1.43E-8$), 9p11.2-q21.11 ($p = 8.31E-8$), and 15q11.1-11.2 ($p = 1.46E-05$) regions, were significantly associated with sepsis susceptibility. The deletion is found in the Human Leukocyte Antigen (HLA) region, which plays a central role in many inflammatory and immunological diseases. Our findings revealed structural variants associated with sepsis susceptibility and provided the basis for further fine-mapping studies at these loci.

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P24.054.A Genetic dissection of Cloninger's Temperament and Character Inventory, TCI, in an Italian isolate

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Personality has a fundamental role in underlying a series of psychiatric symptoms. Thus, an accurate assessment of personality and temperament is essential to search for possible correlations of higher-order behaviours with the underlying biology (genes).

Five hundred eighty-seven adult individuals (331 females-256 males) from Friuli Venezia Giulia Genetic Park were included in the study. All subjects completed the TCI scales to assess the four temperament dimensions (harm avoidance (HA), novelty seeking (NS), reward dependence (RD) and persistence (P)), and the three character dimensions (self-directedness (SD), cooperativeness (C) and self-transcendence (ST)). GWAS was performed for each scale using an additive model. Age, sex, education level (for NS, SD and C) and anxiety and depression status (for HA) were added as covariates.GWAS on TCI scales led to the identification of several genes with a significant or suggestive p-value, expressed in the brain and/or already associated with psychiatric disorders. In particular, for NS scales, *MAGI2* (p-value $= 9.14x10^{-8}$), broadly expressed in the brain and already associated with schizophrenia and major depressive disorder, and *CNTN4* (p-value $= 3.39x10^{-7}$), previously associated with neurobehavioral phenotypes. As regards to HA scales, *BTBD3* ($p = 2.152x10^{-8}$) already linked to obsessive-compulsive disorder and *SIAH1* implicated in Parkinson's disease (p-value $= 8.52x10^{-6}$). Concerning RD scales, *PARK2*, associated with young-adult onset Parkinson (p-value $= 8.27x10^{-9}$).

Results: demonstrated a series of GWAS significant/suggestive associations between TCI scales and genetic background. Additional studies are needed to further confirm present results and better elucidate the role of the genes here identified.

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P24.055.B High-resolution genetic maps provide new insights into mitochondrial dysfunction in Type 2 diabetes

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Introduction: Mitochondrial dysfunction is well-known to co-occur with Type 2 diabetes (T2D); a reflection of this is the fact that multiple T2D drugs and treatments target the mitochondria. However, there is an ongoing question as to what extent genetic mechanisms contribute to this process, particularly since T2D onset can itself impact mitochondrial function. Characterising these mechanisms is complicated by risk variants occurring in (1) large blocks of linkage disequilibrium (LD) and (2) non-coding regulatory elements.

Materials and Methods: Here, we use expression quantitative trait loci (eQTL) to investigate >260 genetic risk loci significantly associated with T2D risk in 5,800 T2D cases, for evidence of regulating the expression levels of nuclear-encoded mitochondrial genes (NEMGs) in adipose tissue. T2D loci and eQTL were mapped