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P01

REPRODUCTIVE GENETICS

P01.001A An unusual number of high mutations expand in the male germline in tyrosine kinase receptors

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Background/Objectives: The higher risk of older fathers having an affected offspring with early or late-onset rare disorders has been quite unsettling; but unfortunately, the methods have been limited to better characterize this phenomenon. So far, studies have focused on well-characterized mutations mainly identified in the receptor tyrosine kinase receptor (RTK) signalling pathway [1-3].

Methods: The establishment of duplex sequencing opened exciting new possibilities in ultra-rare variant detection with a very high accuracy for a sequencing-based method [4, 5]. This is the first study that has used this sequencing approach to explore this type of mutagenesis directly in sperm in the FGFR3 gene.

Results: We found mutations associated with congenital disorders at increased frequencies and identified new unreported selfish mutations expanding with age [6]. We further characterized the expansion of these in the male germline with droplet digital PCR and analysed the change in receptor signalling [7, 8].

Conclusion: Our work sheds light into different mutational mechanisms potentially affecting the receptor kinase activity.

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P01.002.B Using accurate duplex sequencing to explore the connection between elevated germline mutation rates, sperm selection, and male (sub)fertility

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Background/Objectives: Elevated germline de novo mutation rates can impact health and fertility, especially in the context of male subfertility. In 2020, we associated elevated paternal germline mutation rates with reduced lifespans, mirroring the somatic theory of aging. Similarly, studies of subfertile men report elevated individual and familial cancer risks compared to

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Background/Objectives: Differences of sex development (DSD) are heterogeneous conditions affecting the development of chromosomal, gonadal or anatomical sex. Although over 75 genes have been associated with DSD, the diagnostic yield of whole exome sequencing (WES) studies is typically not higher than 35% in a clinical setting. Here, we investigated the benefits of WES for the genetic diagnosis in patients with DSD.

Methods: Between 2016 and 2022, 144 unrelated index patients with a clinical diagnosis of DSD or the broader DSD umbrella underwent WES-based panel testing interrogating the coding regions of 130 genes implicated in DSD, primary ovarian insufficiency and hypogonadotropic hypogonadism. Variants were extracted and classified according to the ACMG guidelines. Copy number variant (CNV) analysis was performed using the ExomeDepth algorithm.

Results: In 13% of patients, we identified a likely pathogenic (LP) or pathogenic (P) rare variant in 12 distinct DSD genes, including *AR* (6), *NR5A1* (2), *WT1* (2), *ATRX*, *CYP21A2*, *DHX37*, *HSD3B2*, *HSD17B3*, *RXFP2*, *SRD5A2*, *SRY*, and *TXNRD2*. The majority are sequence variants; four defects are CNVs identified using ExomeDepth. Interestingly, in two brothers displaying bilateral cryptorchidism and infertility an intragenic *RXFP2* deletion was found to occur in *trans* with a heterozygous missense variant, corroborating its role in familial bilateral cryptorchidism.

Conclusion: We demonstrate the benefit of WES-based genetic testing of DSD in a clinical context. The low detection rate emphasizes the need for more stringent inclusion criteria on the one hand and for advanced genome analysis to solve missing heritability in this condition.

References:.

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Conflict of Interest: None declared.

P04.028.C Unique pipeline for the assessment of novel genetic variants leads to confirmation of PCD diagnosis

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Background/Objectives: Primary ciliary dyskinesia (PCD) is a disease caused by impaired ciliary motility and mainly affects the lungs and reproductive organs. Inheritance is autosomal recessive and X-linked with more than 40 disease-causing genes, wherefore PCD patients have diverse clinical manifestations, thus making diagnosis difficult. The utility of next-generation sequencing (NGS) technology for diagnostic purposes allows a better understanding of the PCD genetic background. However, the identification of specific disease-causing variants is challenging. The objective of this study was to create a unique guideline that will enable the standardization of the assessment of novel variants within PCD associated genes.

Methods: The study included designing a pipeline for the classification of the rare genetic variants detected using NGS. The pipeline included in silico (translation, 3D-model, protein-protein interactions, sequence conservation, posttranslational modifications) and functional analysis (expressional analysis, Western Blot) of the variants.

Results: The designed pipeline consists of three steps: sequencing, detection, and identification of genes/variants; classification of variants according to their effect; and variant characterization using in silico structural and functional analysis. The pipeline was validated by the analysis of the variants detected in a disease-causing gene (*DNAI1*) and the novel candidate gene (*SPAG16*).

Conclusion: The application of the pipeline resulted in the identification of disease-causing variants, as well as pathogenicity validation, through the analysis on transcriptional, translational, and posttranslational levels.The application of created pipeline leads to the confirmation of PCD diagnosis and enables a shift from candidate to disease-causing gene.

References:.

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Conflict of Interest: None declared.

P04.029.D TSHB R75G is a founder variant and prevalent cause of low or undetectable TSH in Indian Jews

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Background/Objectives: Bi-allelic loss-of-function mutations in *TSHB*, encoding the beta-subunit of TSH, cause congenital hypothyroidism. Homozygosity for the TSHB p.R75G variant, previously described in South Asian individuals, does not alter TSH function, but abrogates its detection by some immune-detection-based platforms, leading to erroneous diagnosis of hyperthyroidism. We set out to identify and determine carrier rate of the p.R75G variant among clinically euthyroid Bene Israel Indian Jews, to examine possible founder origin of this variant worldwide and to determine phenotypic effects of its heterozygosity.

Methods: Molecular genetic studies of Bene Israel Jews and comparative studies with South Asian cohort were performed. TSHB p.R75G variant was tested by Sanger sequencing and RFLP. Haplotype analysis in the vicinity of the *TSHB* gene was performed using SNP arrays.

Results: Clinically euthyroid individuals with low or undetectable TSH levels from three apparently unrelated Israeli Jewish families of Bene Israel ethnicity, originating from the Mumbai region of India, were found heterozygous or homozygous for the p.R75G TSHB variant. Extremely high carrier rate of p.R75G TSHB in Bene Israel Indian Jews (~4%) was observed. A haplotype block of 239.7kB in the vicinity of *TSHB* shared by Bene Israel and individuals of South Asian origin was detected.

Conclusion: Our findings highlight the high prevalence of the R75G TSHB variant in euthyroid Bene Israel Indian Jews, demonstrate that heterozygosity of this variant can cause erroneous detection of subnormal TSH levels, and show that R75G TSHB is an ancient founder variant, delineating shared ancestry of its carriers.

References:.

Grants:.