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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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BioTherapeutics, Santhera Pharmaceuticals, and Chiesi.

P07.035.A Investigation of the role of the DNM2 gene in mitochondrial dynamics by siRNA gene silencing

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Background/Objectives: The Dynamin2 protein (DNM2) has diverse roles in cell functions, including in clathrin mediated endocytosis at the plasma membrane and together with DRP1, in mitochondrial division. DNM2 depletion blocks mitochondrial division and results in an elongated, hyper-fused mitochondrial network.

Methods: The silencing was performed for 72 hours. The efficiency of siRNA gene silencing was analysed by real-time PCR and Western blotting. RNA sequencing was performed on the properly transfected samples on Illumina NextSeq platform. The bioinformatics analysis focusing on mRNA expression changes.

Results: Gene silencing of siRNA was performed in 3 parallel measurements with 3 different siRNAs. Scrambled siRNA and non-transfected HeLa cells were used as controls for the experiments. After a bioinformatical analysis very strong significance for 12 genes were found. These genes are involved in regulation of cytoskeletal function and trafficking, muscle function, and steroid biogenesis.

Conclusion: In DNM2 depletion samples, the downregulation of the FBLIM1, KRT13, KRT19, TMEM139, TMEM45A genes are involved in cytoskeletal function and trafficking, so they might be indirectly modify mitochondrial dynamics. TNNC1 plays a major role in the regulation of muscle function, so the decrease in expression found may be related to the formation of centronuclear nuclei. CYP4F3 gene expression was also significantly decreased. It is a monooxidase involved in cholesterol and steroid biosynthesis. Its relationship with DNM2 is currently in question. A validaton of RNASeq results currently in process.

References: -.

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Conflict of Interest: None declared.

P07.036.B Correlation between GLA rare variants and phenotype in Hungarian patients with Fabry disease

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Background/Objectives: Fabry disease (FD) is the second most common metabolic disorder with high morbidity and mortality. Hundreds of mutations and non-coding haplotypes in the *GLA* gene have been described; however, many are variants of unknown significance, prompting doubts about the diagnosis and treatment.

Methods: We identified *GLA* mutations in patients with suspicion of FD in Hungary for the last couple of decades. Identification of patients' genotype was done with Sanger sequencing. Patients tested were participating in FD screening projects or showed typical signs of FD or had low enzyme activity. The detected variants were classified using the current ACMG guideline, Fabry databases and literature.

Results: We found 24 different rare variants in 51 patients overall, of which 16 were classified as pathogenic, 4 likely pathogenic and 4 likely benign. Of the identified variants, 13 cause classic and 7 later onset phenotype. We also identified 2 variants that have conflicting interpretations of pathogenicity. Four of the damaging rare variants were only found in Hungarian patients so far.

Conclusion: We present a descriptive clinical study including 51 patients with 24 different *GLA* variants. We identified 4 novel rare damaging variants of the *GLA* gene. In order to better characterise VUS, not only probands but also all asymptomatic variant carriers from Fabry families should be followed prospectively. Data sharing has great importance. These data, in the future, will help to distinguish symptoms attributable to FD from nonspecific comorbidities in benign *GLA* variants carriers.

References:.

Grants: Nothing to disclose.

Conflict of Interest: None declared.

P07.037.C Molecular diagnosis of Fabry disease in patients with chronic renal failure of unknown etiology

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Background/Objectives: Fabry disease (FD) is a rare X-linked disorder caused by variants in the *GLA* gene leading to the deficiency of lysosomal α-galactosidase-A and progressive accumulation of globotriaosylceramide affecting the heart, nervous system, and kidneys. FD has overlapping phenotypes and often remains undiagnosed. Therefore, the precise molecular-genetic diagnosis and the earliest possible treatment are essential to avoid significant disease progression.

Methods: We analyzed 95 (34 female and 61 male) hemodialysis patients with clinical suspicion of FD using Sanger sequencing of all coding exons (7) and flanking intron regions of the *GLA* gene, and measured the relative expression of the *GLA* gene in available samples.

Results: The genetic analysis revealed 3 patients with a missense variant (p.Asp313Tyr), and 10 patients with combinations of non-coding variants, described as complex intronic haplotypes (ClHs). ClH1 (c.-10C>T, c.370-81_370-77delCAGCC, c.640-16A>G,

c.1000-22C>T), the most frequent haplotype, was detected in 7 (7.4%) patients. Lyso-Gb3 biomarker levels were within the normal range in each tested patient. However, RT-qPCR analysis revealed decreased relative expression of *GLA* gene in PBMC of 2 female patients with CIH1 and one female patient carrying only c.-10C>T variant by 9,1%, 7,4%, 46,3%, respectively, pointing out that further analyses are needed to confirm/exclude FD in these patients.

Conclusion: Because the effects of CIHs are not yet fully understood, our work highlights the importance of analyzing intronic regions of the *GLA* gene as genetic modifiers and the need to include expression analysis in the diagnostic algorithm.

References:.

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Conflict of Interest: None declared.

P07.038.D An unusual case of combined hypolipidaemia and premature peripheral vascular disease

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Background/Objectives: Monogenic hypobetalipoproteinemias include a heterogeneous group of disorders characterized by very low plasma levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and apolipoprotein B (apoB) that are relatively uncommon in general population. It is thought that low LDL can protect from CVD, but this is not what we found in a case we present. We report on a 57 years old male patient (with BMI 21 kg/m^2) with combined hypolipidaemia who presented with premature peripheral vascular disease. We also presented his two sons aged 32 and 27 years, who also manifested tendency to low lipid levels.

Methods: We used Illumina exome analysis in all three individuals. Variant filtering by QCI was performed using two different approaches: one based on candidate genes and the other one based on clinical symptoms.

Results: No *pathogenic* or *likely pathogenic* variants within main hypocholesterolaemia/dyslipidaemia candidate genes (*ANGPTL3, SAR1B, APOB*, *PCSK9* or *MTTP*) were found in any of them. However, all three individuals share a novel *ABCA1* variant, possibly responsible for decreased HDL levels. The proband and one of his sons share also the splicing variant rs138326449 within the *APOC3* gene, shown to be associated with decreased TG levels.

Conclusion: We can hypothesize that in our patient despite his low TGs and LDL levels obtained thanks to the presence of the protective *APOC3* variant, atherosclerosis developed due to the impaired cholesterol efflux caused by *ABCA1* variant.

References:.

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Conflict of Interest: None declared.

P07.039.A Untreated PKU patients without intellectual disability: SHANK gene family as a candidate modifier

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Background/Objectives: Phenylketonuria (PKU) is an inborn error of metabolism caused by variants in the phenylalanine hydroxylase (PAH) gene. Although PKU is a monogenic disease, decades of research and clinical practice have shown that the correlation between the genotype and corresponding phenotype is not simple at all. Attempts have been made to discover modifier genes for PKU cognitive phenotype but without any success so far.

Methods: We conducted whole genome sequencing of 4 subjects from unrelated non-consanguineous families who presented with pathogenic mutations in the PAH gene, high blood phenylalanine concentrations and near-normal cognitive development despite no treatment.

Results: We used cross sample analysis to select genes common for more than one patient. Thus, the SHANK gene family emerged as the only relevant gene family with variants detected in 3 of 4 analyzed patients. We detected two novel variants, p.Pro1591Ala in SHANK1 and p.Asp18Asn in SHANK2, as well as SHANK2:p.Gly46Ser, SHANK2:p.Pro1388_Phe1389insLeuPro and SHANK3:p.Pro1716Thr variants that were previously described. Computational analysis indicated that the identified variants do not abolish the function of SHANK proteins. However, changes in posttranslational modifications of SHANK proteins could influence functioning of the glutamatergic synapses, cytoskeleton regulation and contribute to maintaining optimal synaptic density and number of dendritic spines.

Conclusion: Our findings are linking SHANK gene family and brain plasticity in PKU for the first time. We hypothesize that variant SHANK proteins maintain optimal synaptic density and number of dendritic spines under high concentrations of phenylalanine and could have protective modifying effect on cognitive development of PKU patients.

References:.

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Conflict of Interest: None declared.

P07.040.B Clinical, genetic and therapeutic aspects in Menkes disease: study of a French cohort and systematic literature review

Paul Rollier[1;2], *Marie-Pierre Moizard[3;4], Annick Toutain[5], Sophie Blesson[5], Eric Bieth[6], Chrystèle Bonnemains[7], Aline Cano[8], Brigitte Chabrol[8], Annabelle Chaussenot[9], Léna Damaj[10], François Feillet[7], Sylvie Joriot[11], Manoelle Kossorotoff[12], Christian Richelme[13], Dominique Bonneau[14], Sylvie Odent[1], Magalie Barth[14]*

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