ABSTRACTS COLLECTION

Abstracts from the 55th European Society of Human Genetics (ESHG) Conference: Hybrid Posters

European Journal of Human Genetics (2023) 31:345–709; https://doi.org/10.1038/s41431-023-01338-4

© The Author(s), under exclusive licence to European Society of Human Genetics 2023

Volume 31 | Supplement S1

Vienna, Austria

June 11-14, 2022

Sponsorship: Publication of this supplement was sponsored by the European Society of Human Genetics. All content was reviewed and approved by the ESHG Scientific Programme Committee, which held full responsibility for the abstract selections.

Disclosure Information: In order to help readers, form their own judgments of potential bias in published abstracts, authors are asked to declare any competing financial interests.

Contributions of up to EUR 10 000.- (Ten thousand Euros, or equivalent value in kind) per year per company are considered "Modest". Contributions above EUR 10 000.- per year are considered "Significant".

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

P01

REPRODUCTIVE GENETICS

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

Irene Tiemann-Boege[1], *Ingrid Hartl*[1], *Sofia Moura*[1], *Renato Salazar*[1]

[1]*Biophysics, Linz, Austria.*

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.

References: 1 Arnheim, N. et al. Annu Rev Genomics Hum Genet 2016.
2 Goriely, A. et al. Am J Hum Genet 2012.
3 Shinde, D. N. et al. Hum Mol Genet 2013.
4 Kennedy, S. R. et al. PLoS Genet 2013.
5 Salk, J. J. et al. Nat Rev Genet 2018.
6 Salazar, R. et al. bioRxiv 2021.04.26.441422 2022.
7 Lanzerstorfer, P. et al. PLoS One 2014.
8 Motsch, V. et al. Sci Rep 2019.

Grants: FWFW1250, FWFP30867000, REGGEN ATCZ207.

Conflict of Interest: Irene Tiemann-Boege Johannes Kepler University Linz, principal investigator, Ingrid Hartl Johannes Kepler University Linz, Sofia Moura: None declared, Renato Salazar: None declared.

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

Jason Kunisaki[1], *Suchita Lulla*[1], *Xichen Nie*[2], *Joemy Ramsay*[3], *Yixuan Guo*[2], *Joshua Horns*[3], *Jim Hotaling*[3], *Kenneth Aston*[3], *Aaron Quinlan*[1,4]

[1]*University of Utah School of Medicine, Human Genetics, Salt Lake City, United States;* [2]*University of Utah School of Medicine, Oncological Sciences, Salt Lake City, United States;* [3]*University of Utah School of Medicine, Surgery, Salt Lake City, United States;* [4]*University of Utah School of Medicine, Biomedical Informatics, Salt Lake City, United States.*

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

ventricular noncompaction (DCM/LVNC), 22 - arrhythmogenic right ventricular cardiomyopathy (ARVC), 7 – sudden infant death (SIDS) and 11 - acute aortic dissection were diagnosed. Positive family history (pFH) of cardiac disease or SCD was identified in 27/115 (23.4 %; median age 41.0 years) of victims, whereas in cases without pFH their median age was significantly lower – 30.0 years. Molecular aetiology (i.e. presence of Class 4 -5 variants) was detected in a total 21/106 cases (19.8%) in *RYR2, KCNH2, KCNQ1, SCN5A, FLNC, GLA, TTN, TNNT2, RBM 20, MYPN, MYBPC3, FHL1, TGFBR1* and *COL3A1*. Diagnostic yield in cases with pFA reached 13/27 cases (48.1 %).

Conclusion: We demonstrate the utility of post mortem cardiogenetic examination in individuals older than 40 years of age.

References:.

Grants: NV18-02-00237 and the Czech SCD Research Consortium.

Conflict of Interest: None declared.

P06.036.B Molecular analysis of cardiomyopathies using next generation sequencing technologies in Slovak patients

Jarmila Bernasovská[1], *Iveta Boronova*[1], *Michaela Zigová*[1], *Eva Petrejčíková*[1]

[1]*University of Presov, Institute of Biology, Presova, Slovakia.*

Background/Objectives: The aim of the study was to analyze a panel of genes associated with dilated or hypertrophic cardiomyopathy based on previously published results in order to identify the subjects at risk.

Methods: The method of next-generation sequencing by IlluminaHiSeq 2500 platform was used to detect sequence variants in 28 individuals diagnosed with dilated or hypertrophic cardiomyopathy. Detected variants were filtered and the functional impact of amino acid changes was predicted by computational programs.

Results: DNA samples of the 28 patients were analyzed by whole exome sequencing. We identified six nonsynonymous variants that were shown to be pathogenic in all used prediction softwares: rs3744998 (EPG5), rs11551768 (MGME1), rs148374985 (MURC), rs78461695 (PLEC), rs17158558 (RET) and rs2295190 (SYNE1). Two of the analyzed sequence variants had minor allele frequency (MAF)<0.01: rs148374985 (MURC), rs34580776 (MYBPC3).

Conclusion: Our data support the potential role of the detected variants in pathogenesis of dilated or hypertrophic cardiomyopathy; however, the possibility that these variants might not be true disease-causing variants but are susceptibility alleles that require additional mutations or injury to cause the clinical phenotype of disease must be considered.

References: Rocarati,M.,Latronico,M.V.G.,Musumeci,M. et al.: Unexpectedly low mutation rates in beta-myosin heavy chain and cardiac miosin finding protein genes in Italian patients with hypertrophic cardiomyopathy. J Cell Physiol, 226,2894-2900, 2011.

Yamada T, Nomura S. Recent Findings Related to Cardiomyopathy and Genetics. Int J Mol Sci. 2021 Nov 20;22(22):12522. https://doi.org/10.3390/ijms222212522. PMID: 34830403; PMCID: PMC8623065.

Grants: KEGA 032PU-4/2021.

Conflict of Interest: None declared.

P06.037.C Aortic rupture force in mice modelling hereditary aortic diseases

Nicolo Dubacher[1;2], *Kaori Sugiyama*[3;4], *Jeffrey Smith*[5], *Vanessa Nussbaumer*[1], *Sylvan Caspar*[1], ***Marc Schönholzer***[1], *Janine Meienberg*[1], *Hiromi Yanagisawa*[3], *Mary Sheppard*[6;7], *Gabor Matyas*[1;8]

[1]*Center for Cardiovascular Genetics and Gene Diagnostics, Swiss Foundation for People with Rare Diseases, Schlieren-Zurich, Switzerland;* [2]*Translational Cardiovascular Technologies, Department of Health Sciences, ETH Zurich, Zurich, Switzerland;* [3]*Life Science Center for Survival Dynamics, Tsukuba Advanced Research Alliance, University of Tsukuba, Tsukuba, Japan;* [4]*Institute For Advanced Research of Biosystem Dynamics, Research Institute for Science and Engineering, Waseda University, Tokyo, Japan;* [5]*Saha Cardiovascular Research Center, University of Kentucky, Lexington, United States;* [6]*Department of Family and Community Medicine, University of Kentucky, Lexington, United States;* [7]*Saha Aortic Center, University of Kentucky, Lexington, United States;* [8]*Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland.*

Background/Objectives: Individuals suffering from hereditary aortic diseases (ADs) are at increased risk for aortic dissections and ruptures. We established an objective approach to measure the rupture force of the murine thoracic aorta, thereby explaining the outcomes of clinical studies and assessing an added value of old drugs in vascular Ehlers-Danlos syndrome (vEDS). Here, we applied our approach to six additional mouse AD models.

Methods: We used two mouse models for Marfan syndrome (MFS) as well as one smooth-muscle-cell-specific *Efemp2* knockout (SMKO) and three CRISPR/Cas9-engineered knock-in models (*Ltbp1*, *Mfap4*, and *Timp1*). Moreover, one mouse MFS model was subjected to 4-week-long losartan treatment previously shown to reduce aneurysm growth. As previously described, 1.5-mm-long sections of the murine thoracic aorta were mounted on a tissue puller and uniaxially stretched until rupture.

Results: The aortic rupture force was significantly lower in both MFS and SMKO models, but mice with knock-in mutations in the genes *Ltbp1*, *Mfap4*, and *Timp1* did not present with an impaired aortic integrity. As expected, the losartan treatment of MFS-modelling mice led to the reduction of aneurysm formation, which, surprisingly, had no impact on the aortic rupture force.

Conclusion: We show for the first time that our read-out system is able to characterize the aortic biomechanical integrity of mice modelling not only vEDS but also related ADs. Furthermore, aneurysm progression alone may not be a sufficient read-out for aortic rupture, as blood-pressure-lowering therapies preventing aortic aneurysms might still not strengthen the weakened aortic wall. These results may contribute to better medical therapies of hereditary ADs.

References:.

Grants:.

Conflict of Interest: None declared.

P06.038.D Functional characterization of iPSC-derived cardiomyocytes from Brugada syndrome patients of a genetically unresolved family reveals distinct underlying mechanisms

Dogan Akdeniz[1], *Aleksandra Nijak*[1], *Eline Simons*[1], *Bert Vandendriessche*[1], *Dieter Van de Sande*[1], *Erik Fransen*[1], *Ewa Sieliwonczyk*[1], *Dorien Schepers*[1], *Dirk Snyders*[1], *Emeline Van Craenenbroeck*[2], *Johan Saenen*[2], *Alain Labro*[3], *Maaike Alaerts*[1], *Bart Loeys*[1]

[1]*University of Antwerp, Antwerp, Belgium;* [2]*Antwerp University Hospital, Edegem, Belgium;* [3]*Ghent University, Ghent, Belgium.*

Background/Objectives: Brugada syndrome (BrS) is an inherited cardiac arrhythmia characterized by a specific ECG pattern of ST-segment elevation, predisposition to ventricular fibrillation and sudden cardiac death. Over 20 genes have been associated with the disorder, however roughly 70% of patients remains without a genetic diagnosis.