Inherited Cardiac Disorders: Identification of known and novel disease-associated genetic variants in the Cretan population

E Tzagkaraki1, A Batas1, I Anastasiou2, A Patrianakos3, F Parthenakis2, G Kochiadakis1, K Stratakis1, N Tavernarakis1, E Linardaki1,2

1Diagnostic Genetics and Precision Medicine Unit, Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology of Hellas, Heraklion 71003, Crete, Greece
2Cardiology Department, Heraklion University Hospital, Stavrika, P.O. Box 1352, Heraklion, Crete, Greece

*Presenting author: Emvoria Tzagkaraki, email: emvoria_tzagkaraki@imbb.forth.gr. *Corresponding author: Emmanouela Linardaki, email: emmanouela_linardaki@imbb.forth.gr

Introduction

- Inherited Cardiac Disorders (CD) are a group of rare genetic diseases that constitute a major cause of sudden cardiac death and Heart Failure.
- Pathogenic mutations in genes encoding cardiac sarcomere proteins, cytoskeletal proteins and desmosomal proteins have been associated with Inherited Cardiac Disorders.
- The majority of these conditions are inherited in an autosomal dominant manner.
- The island of Crete may exhibit mutational hotspot patterns due to its relative geographical “isolation”.

Aim

- Establish a genetic diagnosis in patients with CD from Crete.
- Determine the diagnostic yield and genetic diversity of CD cohorts.
- Confirm a clinical diagnosis in relatives or identify asymptomatic relatives who are at risk.

Methods

- 48 index patients (probands) (21 HCM, 18 DCM/HNDC, 2 ACM, 3 Channelopathies, 1 HCM/ACM overlap phenotype, 1 mild DCM features that suffered aborted SCD likely attributed to drug-induced QT-interval prolongation, as well as 2 SCD).
- Genomic DNA analyzed using NGS panel Extended Cardiac Solution by Sophia Genetics (complete coding sequence of 128 clinically relevant genes).
- Bioinformatics analysis: SophiaDDTM platform (Sophia Genetics).
- Clinical curation according to the American College of Medical Genetics and Genomics (ACMG) criteria [1].
- Pathogenic (P) and/or Likely Pathogenic (LP) variants verified by Sanger Sequencing.
- Family studies: 84 first, second and third degree relatives of P/LP positive probands screened with Sanger sequencing.
- Cascade screening included relatives of 7 P/LP positive probands (3 AC, 2 ATTR-CM, 1 Channelpathy and 1 HCM) that had been previously genotyped elsewhere.

Results

- Ten probands carried P/LP variants that had not been previously reported in the literature.
- A novel variant in gene MYBPC3 (NM_000256: c.3784_3795del (p.A1262_E1265del)) was identified in 6/17 gene positive HCM probands of proximal geographic origin (4 unrelated and 2 half siblings), indicating a mutational hotspot in Crete and a possible founder effect of this variant in the Cretan population.
- Seven more unrelated HCM probands carried the known LP variant MYH7 - NM_000257:c.1063G>A (p.A35ST), suggestive of a second mutational hotspot.

Discussion

- Crete has always been a natural terrain of rare inherited diseases due to its natural geographical isolation, which may promote the emergence of Inherited Cardiac Disorders.
- Genetic Diagnosis was established in 54% of tested probands using the 128 gene NGS panel.
- Our studies revealed 2 mutational hotspots in HCM, one of which involved a previously unreported MYBPC3 mutation.
- Family Cascade screening revealed the presence of a P/LP variant in 27 healthy asymptomatic individuals, highlighting the importance of family genetic screening in early diagnosis and clinical intervention.

Acknowledgments

This work was funded by the National Network of Precision Medicine in Cardiology and Prevention of SCD in the Young, in the framework of Work Package 1 (Hellenic Research Network for the Genetics of Human Cardiovascular Disease and the Prevention of Sudden Juvenile Death - Hellenic Precision Medicine Research Network for Neurodegenerative Diseases), of the project “Infrastructures for National Research Networks for Precision Medicine and Climate Change” no. 2018E01S00001 of the GSRT National Public Investments Program.

References