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

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ABSTRACT

Aim: Inherited Cardiac Disorders represent a group of rare genetic cardiac conditions that are the major cause of sudden cardiac death (SCD) and Heart Failure (HF) in people of all ages. The island of Crete may exhibit mutational hotspot patterns due to its relative geographical “isolation”. Our aim was to establish a genetic diagnosis in patients with Cardiomyopathies and Arrhythmias from Crete, determine the genetic diversity of this cohort and finally conduct family studies in order to confirm a clinical diagnosis in relatives or reveal asymptomatic carrier members.

Subjects and Methods: A total of 48 index patients (probands) with Cardiomyopathies and Arrhythmias were analyzed (21 HCM, 18 DCM/HNDC, 3 Channelopathies, 2 Arrhythmogenic Cardiomyopathies (AC), 2 SCD, 1 HCM/ACM and 1 SCD prevented with mild DCM features and LQTS after drug delivery). Genomic DNA was analyzed using a commercially available targeted NGS gene panel covering the complete coding sequence of 128 clinically relevant genes. Pathogenic (P) and/or Likely Pathogenic (LP) variants were verified by Sanger Sequencing. Family studies involved screening first, second and third degree relatives of P/LP positive probands. Cascade screening included relatives of 7 more positive probands that had been previously genotyped elsewhere.

Results: Our genetic studies revealed a P/LP mutation in 26/48 probands, a Variant of Uncertain Significance (VUS) in 12/48 probands, and no genetic finding in 10/48, conferring an overall genetic diagnostic yield of 54.2%. Variant NM_000256: c.3784_3795del p.(Ala1262_Glu1265del) in MYBPC3 gene was identified in 6/17 gene positive HCM patients of proximal geographic origin (4 unrelated and 2 half-blooded siblings), indicating mutational hotspot as well as 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.(Ala355Thr), suggestive of a second mutational hotspot in Crete. In the HCM subgroup of patients, genetic diagnostic yield was 76% (most frequently mutated genes: MYBPC3 and MYH7), in line with international literature. In the DCM subgroup genetic diagnostic yield was 39% (most frequently mutated gene: TTN). A total of 84 relatives were analyzed as part of family cascade screening; 40/84 tested positive for the family mutation. 27/40 positive family members, are healthy individuals. Conclusions: Our studies revealed at least 2 mutational hotspots in HCM, one of which involved a previously unreported MYBPC3 mutation. In the present study, the overall diagnostic genetic yield in each cardiomyopathy is in accordance with the literature. 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.