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

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Introduction

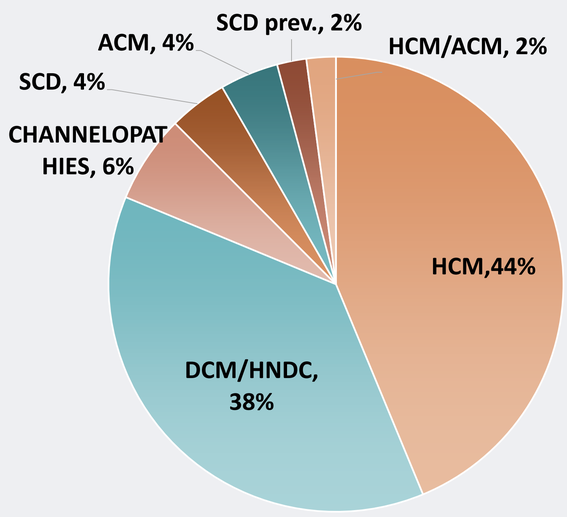
- Inherited Cardiac Disorders (CD) are a group of rare genetic diseases that constitute a major cause of sudden cardiac death and Heart Failure.
- Pathogenic mutations in genes encoding cardiac sarcomere proteins, cytoskeletal proteins and desmosomal proteins have been associated with Inherited Cardiac 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

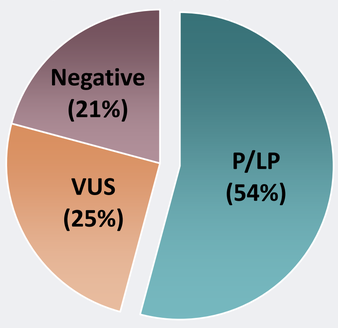
- 48 index patients (probands) (21 HCM, 18 DCM/HNDC, 2 ACM, 3 Channelopathies, 1 HCM/ACM overlap phenotype, 1 mild DCM features that suffered aborted SCD likely attributed to drug-induced QT-interval prolongation, as well as 2 SCD).
- genomic DNA analyzed using NGS panel *Extended Cardio Solution* by Sophia Genetics™ (complete coding sequence of 128 clinically relevant genes).
- Bioinformatics analysis: *SophiaDDM™* 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 Channelopathy and 1 HCM) that had been previously genotyped elsewhere.



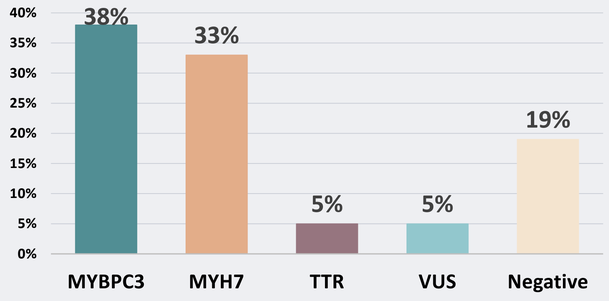
Disease distribution in the proband group
HCM: Hypertrophic Cardiomyopathy
DCM: Dilated Cardiomyopathy
ACM: Arrhythmogenic Cardiomyopathy
SCD: Sudden Cardiac Death
SCD prev. : SCD prevented
HNDC: Hypertrophic non- dilated CM.

Results

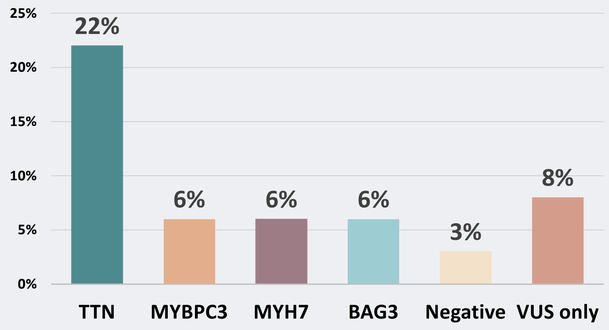
A) Overall Genetic Diagnostic Yield: The genetic analysis revealed a P/LP mutation in 26/48 probands (54%) with CD.



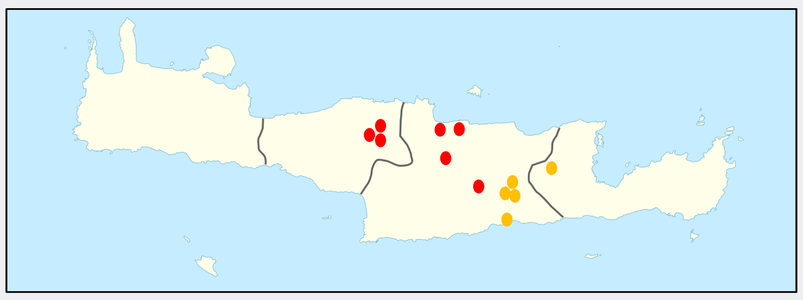
B) HCM genetic diagnostic yield was 76%. Most frequently mutated genes: MYBPC3 (38%) and MYH7 (33%), in line with international literature.



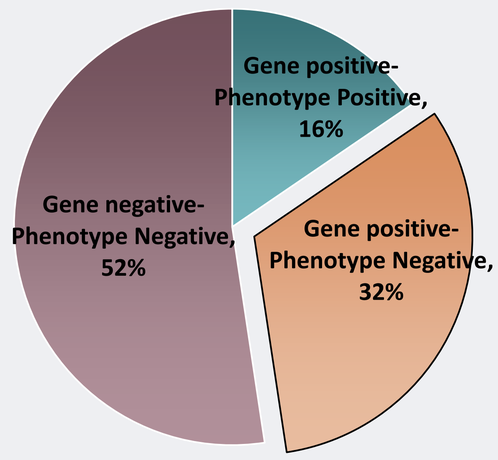
C) DCM/HNDC genetic diagnostic yield was 39%. Most frequently mutated gene: TTN (22%).



- Ten probands carried P/LP variants that had not been previously reported in the literature.
- A **novel LP 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.A355T), suggestive of a second mutational hotspot.



Mutational hotspots of HCM in Crete
- MYBPC3, NM_000256:c.3784_3795del (p.A1262_E1265del) - novel variant
- MYH7 - NM_000257:c.1063G>A (p.A355T) - known variant



Family Cascade Screening:
40/84 family members (48%) tested positive for the family mutation
44/84 tested negative (52%). All 44 gene - negative family members are healthy individuals (Gene Negative-Phenotype negative)
27 out of the 40 positive family members, are healthy asymptomatic individuals with a genetic finding associated with the inherited cardiac disease (Gene Positive-Phenotype Negative, 32%).
All Phenotype Positive members are also Gene Positive (16%).

- In 2 families with SCD we identified the genetic cause in the deceased probands; family cascade screening in one of these families, revealed the pathogenic variant in one of the two healthy daughters of the proband.

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

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References

[1] Richards, S., et al (2015). Genetics in Medicine 17, 405-423