Preventing Sudden Cardiac Death(?): Exome Secondary Findings in Cardiovascular Genes

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BACKGROUND

- Studies have shown the risk of sudden cardiac death (SCD) in inherited cardiovascular disorders to be higher in patients with certain gene defects[1,2]. Genetic screening may thus be a useful tool in early detection of these potentially deadly conditions.
- Clinical diagnostic exome sequencing (DES) of trios presents an opportunity for clinical laboratories to inform probands and their relatives of genetic findings which may increase their risk of SCD.
- The American College of Medical Genetics and Genomics (ACMG) has previously recommended 31 (now 30) cardiovascular-related genes for inclusion in DES secondary findings reports[3,4].
- This study aimed to characterize the prevalence and spectrum of mutations within these 31 genes, in order to begin evaluating the utility of cardiac secondary findings in preventing sudden death.

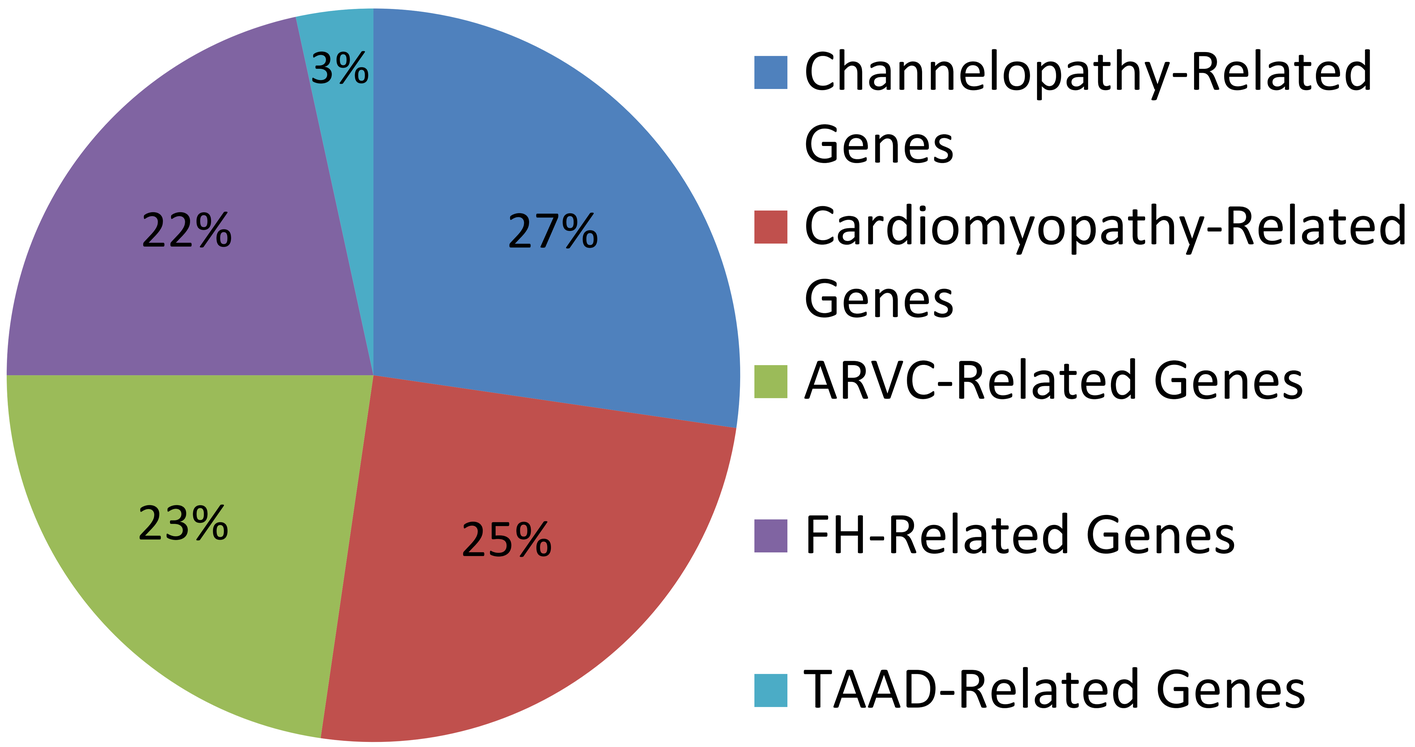
CARDIOVASCULAR SECONDARY FINDINGS GENES REPORTED

Inherited Cardiac Condition	Genes Identified (# of pts.)
Channelopathies	*SCN5A* (13), *KCNQ1* (9), *KCNH2* (2)
Cardiomyopathies	*TNNT2* (7), *MYBPC3* (6), *MYH7* (6), *TNNI3* (1), *LMNA* (1), *GLA* (1)
ARVC	*DSG2* (10), *DSP* (6), *PKP2* (4)
Familial Hypercholesterolemia (FH)	*LDLR* (15), *APOB* (4)
TAAD-Related Disorders	*FBN1* (1), *MYLK* (2)

METHODS

- In an unselected sample of 5,349 probands and relatives referred for clinical DES who opted to receive ACMG-recommended secondary findings, results were evaluated for the presence of pathogenic mutations or likely pathogenic variants in 31 ACMG-defined genes related to inherited cardiovascular disorders[3,4].
- DES and variant analysis was performed as previously described in the literature[5].
- A review of medical records submitted to our clinical laboratory was conducted for all probands and relatives on which cardiovascular-related secondary findings were reported.

DISTRIBUTION OF CARDIOVASCULAR SECONDARY FINDINGS



RESULTS

- **88 of 5,349** patients (**1.6%**), including 46 probands and 42 first-degree relatives, were found to harbor a total of 56 pathogenic mutations or likely pathogenic variants in ACMG-defined cardiovascular secondary genes.
  - There were 18 families in our cardiac secondary findings cohort with a parent-child combination who shared the same alteration
- Per available medical records review, only 3 of the 88 positive patients had a clinical or family history of symptoms seen in diseases with which their reported gene has been associated in the medical literature.
  - 1 proband with a p.R278C secondary finding in the *TNNT2* gene had a clinical history of heart palpitations and syncope.
  - 1 proband with a p.Q1667* secondary finding in the *DSP* gene had a mother with a history of syncope.
  - 1 proband with a p.E1823Hfs*10 secondary finding in the *SCN5A* gene had a father with a history of unspecified heart problems.

TAKE-HOME POINTS

- Overall, slightly less than 1 in 60 individuals who underwent DES had an incidental cardiac secondary finding. Thus, we have identified a substantial cohort of patients who may be at higher risk for development of symptoms related to sudden cardiac death. Life-saving clinical screening and medical intervention may be indicated for these patients.
- Cardiac DES secondary findings were evenly spread amongst genes related to inherited arrhythmias, cardiomyopathies, and familial hypercholesterolemia, all of which can lead to sudden cardiac death when left untreated.
- Secondary findings far exceeded expected disease prevalence rates for channelopathies, HCM, and ARVC.
- Further research is needed to determine referral patterns for a cardiovascular workup, long-term manifestations of disease, and overall outcomes for patients and relatives in which secondary findings were reported.

Comparison of Disease Prevalence in Medical Literature and DES Cohort

From Medical Literature	From DES Cohort
Channelopathies (LQTS) - **1:2,534**[6]	Channelopathies (LQTS) - **1:223**
Cardiomyopathies (HCM) - **1:500**[7]	Cardiomyopathies (HCM) - **1:255**
ARVC - **1:1,000**[8]	ARVC - **1:267**
Familial Hypercholesterolemia - **1:250**[9]	Familial Hypercholesterolemia - **1:282**

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