Postmortem genetic testing following sudden cardiac death using a cardiomyopathy and arrhythmia next-generation sequencing panel

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Introduction

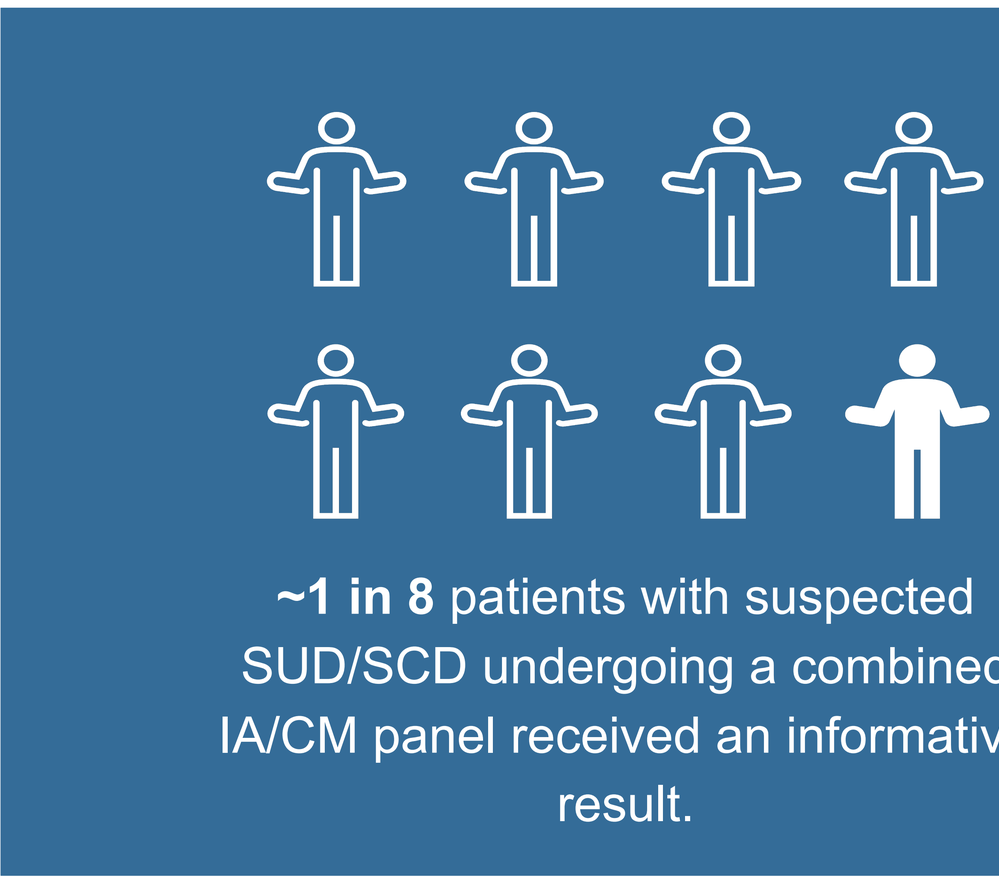
- Multiple professional societies recommend tiered genetic testing for patients with sudden cardiac death (SCD), starting with inherited arrhythmia (IA)/channelopathy genes followed by cardiomyopathy (CM) genes.[1] Best practices dictate that testing is done using a sample from the deceased individual, which is considered a precious sample.
- Given the overlap in these genes' clinical presentations and to maximize breadth of testing using a single potentially precious sample, a broader testing approach may be more effective.
- We describe the postmortem findings in a sub-cohort of SCD or sudden unexplained death (SUD) patients who underwent comprehensive testing with an IA/CM next-generation sequencing (NGS) panel to evaluate the utility of broad testing for this population.

Methods

- Test requisition forms (TRFs) of patients aged ≥ 1 year receiving an IA/CM NGS multigene panel were searched with the terms "deceased" and "death" to identify those with suspected SCD/SUD.
- The NGS panel included up to 223 genes associated with IA/channelopathies and CM clinical presentations that predispose to sudden death.
- TRFs were also examined for notes on cardiac structural findings.
- An informative case was defined as the identification of a likely pathogenic (LP) or pathogenic (P) variant(s), consistent with the patient's reported phenotype and inheritance.
- A Fisher's Exact test was used to determine statistical significance of the yield in 3 patient age groups. A P-value of <0.05 or <0.0125 (Bonferroni correction), as appropriate, was considered statistically significant.

Results

- Overall, 174 patients undergoing NGS multigene panel testing were suspected of SCD/SUD; 12% (21/174) received an informative result (Table 1).
- The yield of testing was statistically significant between all 3 age groups, $P<0.0125$ (Table1).
- Of those with an informative result, 33% (7/21) were explained by IA/channelopathy genes, 38% (8/21) by CM genes, and 29% (6/21) by syndromic, metabolic, myopathic, or mitochondrial genes that can present with CM. The distribution of LP/P variants by gene is illustrated in Figure 1.
- An additional 3% of all patients had a suspicious variant of uncertain significance, which has the potential to be upgraded with follow up family member testing.
- Among 118 TRFs mentioning cardiac structural findings, 63% (74/118) were noted to have cardiac structural findings (on autopsy or prior to death) and 37% (44/118) noted an absence of these findings.
- The yield of testing in the group with an absence of cardiac structural findings was not significantly different than the yield of testing in patients with cardiac structural findings (16%, 7/44 vs 12% 9/74, $P<0.05$).
- Of patients with no mention of cardiac structural findings and an informative result, 86% (6/7) had an LP/P variant in a gene associated with a cardiomyopathy presentation (Figure 2).



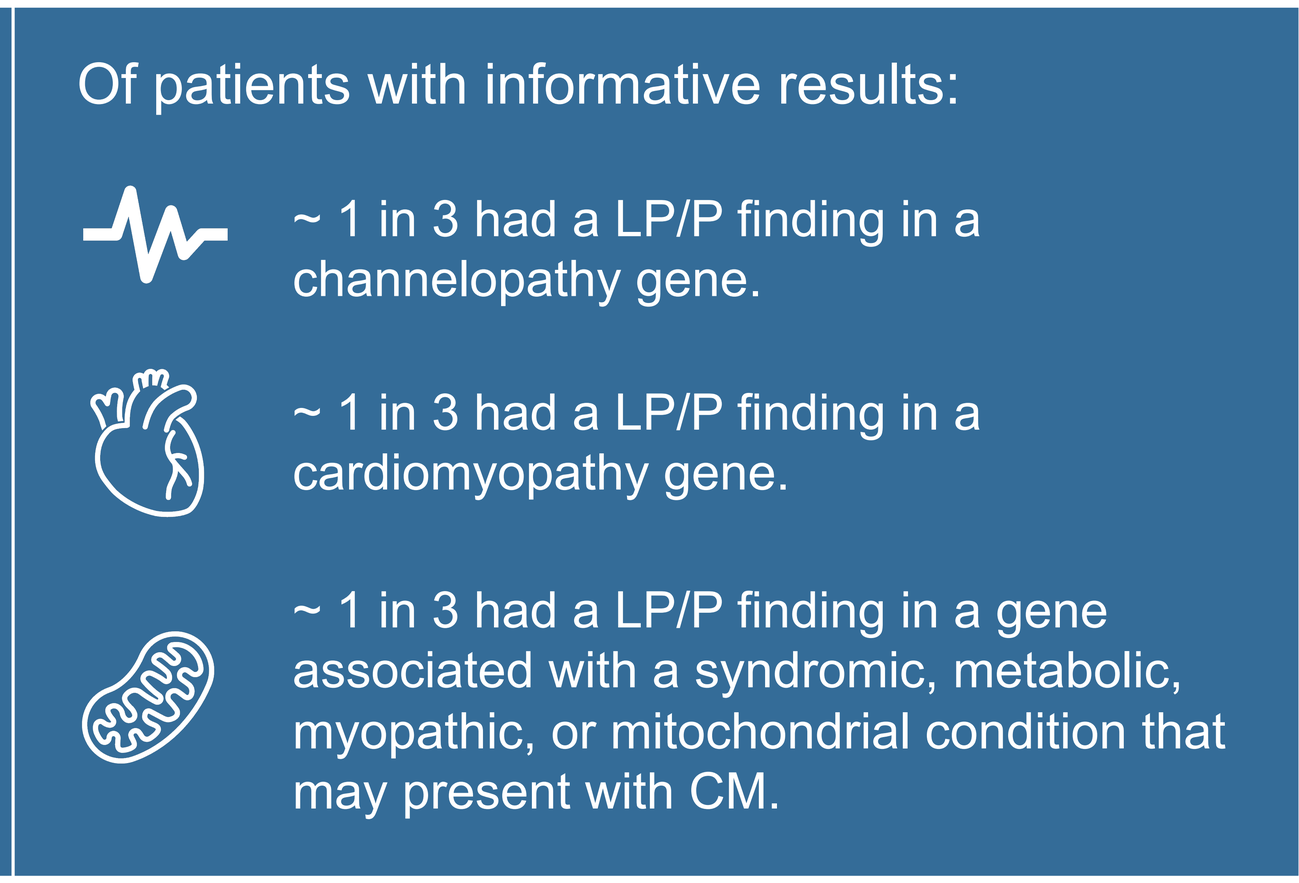
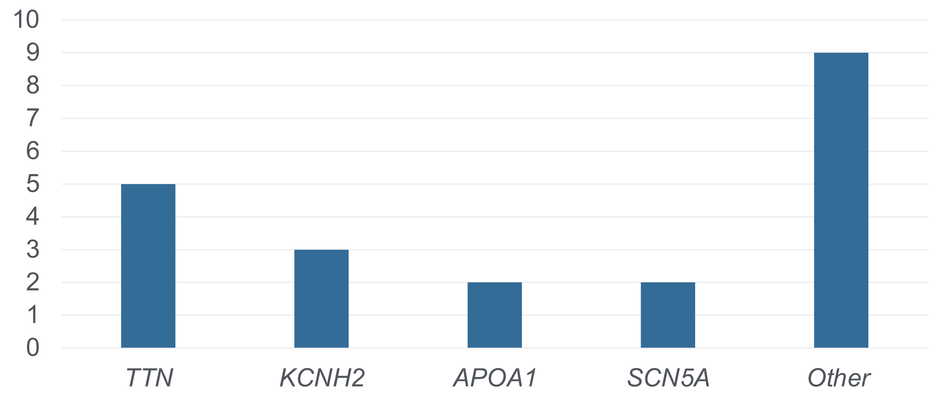


Table 1. Patient demographics and yield of results

Demographic	% of cohort (# of patients)	% with informative result (n)
Male	65% (n=113)	8% (n=9)
Female	35% (n=61)	18% (n=11)
Pediatric (1-17 yrs)	13% (n=22)	9% (n=2)[b]
Young adult (18-40 yrs)	59% (n=103)	17% (n=18)[b]
Older adult (>40 yrs)[a]	N/A	N/A[b]

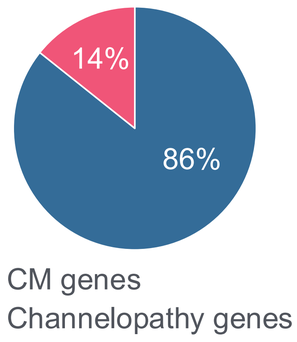
a. Data regarding the older adult subgroup cannot be represented due to small numbers and the potential for patient identification. b. Statistically significant.

Figure 1. Distribution of LP/P variants by gene



"Other" includes genes with <2 cases: *DSG2, FLNC, KCNQ1, PKP2, PTPN11, RBCK1, RYR2, MT-ND1, SLC22A5*

Figure 2. Distribution of genes in patients with a noted absence of structural findings



Conclusion

- **In 2/3 of patients with informative results, LP/P variants were identified in genes associated with CM (isolated, metabolic, myopathic or mitochondrial).**
- **The yield of genetic testing in this cohort is on the lower limit of what has previously been reported in the literature (12%-27%)[2,3,4].**
- **Most (86%) LP/P variants identified in patients with informative results and a noted absence of cardiac structural findings were in genes associated with CM.**
- **These findings support a broad testing approach for patients with SCD/SUD.**

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Conflict of interest statement: All authors are employed by Blueprint Genetics.

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