Genetic findings in a cohort of over 1,800 patients tested with a combined cardiomyopathy and arrhythmia panel

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Introduction

Multiple societies recommend genetic testing for patients with inherited arrhythmias (IAs) and/or cardiomyopathies (CMs)[1,2]. Identifying the underlying genetic cause can inform management, assist with the surveillance of extra-cardiac features, and may determine clinical trial eligibility. Among patients with a clinical suspicion of IAs and/or CMs, both nuclear and mitochondrial DNA (mtDNA) genes have not been extensively studied. We describe the genetic findings of patients with a clinical suspicion of IAs and/or CMs who were evaluated using a broad, combined IA and CM next-generation sequencing (NGS) panel that included both nuclear and mtDNA genes to demonstrate utility of this testing for these patients.

Methods

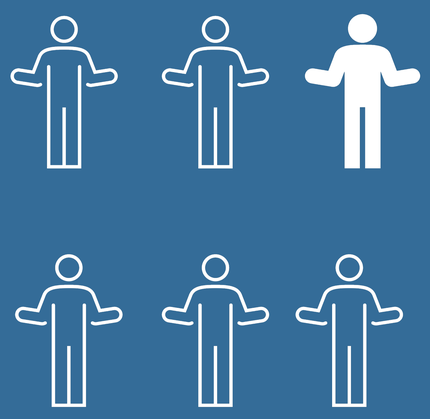
This retrospective review included deidentified patients suspected of having an IA, CM and/or complex cardiovascular phenotype, based on the test requisition form, who underwent genetic testing with a combined IA and CM panel. Testing included analysis of both sequence and copy number variants (CNVs) in up to 260 genes and up to 199 non-coding variants in these genes from a validated assay. Almost two-thirds (1,211/1,883) of patients tested had mtDNA genes included on their panel. Variant interpretation was performed in accordance with ACMG/AMP guidelines. An informative result in a nuclear gene was defined as the identification of a pathogenic (P) or likely pathogenic (LP) variant(s) consistent with the patient's reported phenotype and disease inheritance. An informative result in a mtDNA gene was defined as a P/LP variant with >5% heteroplasmy consistent with the patient's reported phenotype. Chi-square analysis was used to determine statistical significance; a P-value <0.05 was considered significant.

Results

A total of 1,883 index patients underwent testing; 81.1% (1,527/1,883) were adults (≥18 years of age at the time of testing). Over half were male (58.5%, n=1,101). The median age at the time of testing was 41 years (range: prenatal to 100 years). An informative result was identified in 17.7% of patients (333/1,883). Patients tested in childhood (fetuses excluded, n=7) were more likely to receive an informative result (22.9%, 80/349) than those tested in adulthood (16.5%, 252/1,527) (P<0.05, chi-square statistic 8.0379) (Table 1). In total, 352 LP/P variants were identified in 59 different genes. Of those patients with informative results, 9.3% (31/333) had a LP/P variant in a gene associated with either a metabolic, myopathic, mitochondrial or syndromic condition (Table 2).

For pediatric patients, 90 LP/P variants were identified in 80 patients, including 3 (3.8%) with LP/P variants in two different autosomal dominant genes. For adult patients, 262 LP/P variants were identified in 252 patients, with 3 patients (1.2%) having variants in more than one gene, suggestive of a dual diagnosis. LP/P variants in *MYBPC3* were the most common finding in children (10.0% of all LP/P variants, 9/90), followed by *RYR2, KCNH2,* and *MYH7* (each 7.8%, 7/90 of all LP/P variants) (Figure 1). LP/P variants in *TTN* were the most common finding in adults (15.6% of all LP/P variants, 41/262), followed by *MYBPC3* (7.6% of all LP/P variants, 20/262), *LMNA* (6.9% of all LP/P variants, 18/262), and *MYH7* (5.7% of all LP/P variants, 15/262) (Figure 2).

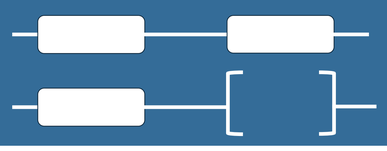
Among patients with an informative result in this cohort, 1.2% (4/333) had an LP/P deep-intronic variant and 4.5% (15/333) had an LP/P CNV. Four of these CNVs (26.7%) were single-exon deletions. Of the 1,211 patients who had mtDNA included in their test; 204 received an informative result and 4 (2.0%) had a LP/P variant in a mtDNA gene.



>1 in 6 patients in the cohort received an informative result

2% had LP/P mtDNA variants

~1% had LP/P non-coding variants



~1% had LP/P single-exon CNVs

Table 1. Patient demographics

Demographic	% of cohort (# of patients)	% with informative result (n)
Male*	58.5% (n=1,101)	16.7% (n=184)
Female*	41.3%% (n=777)	19.0 % (n=148)
Adult (≥18 yrs)	81.1% (n=1527)	16.5 % (n=252)^
Pediatric (<18 yrs)	18.5% (n=349)	22.9 % (n=80)^

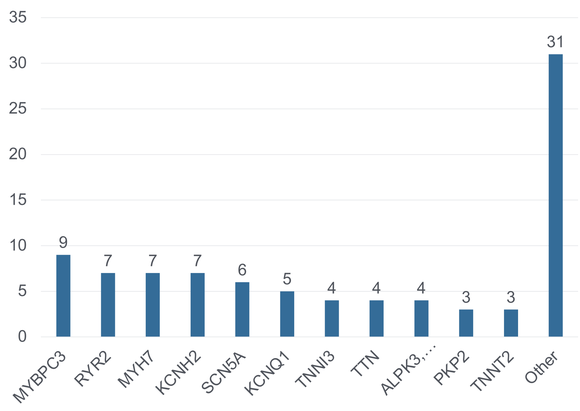
*Sex not known n=5; ^ compared for statistical significance, significant at P<.05, chi-square statistic 8.0379. Fetuses n=7 removed from the table.

Table 2. LP/P variants in genes associated with extra-cardiac features

Category	Number of patients	% of informative results (of 333)
Metabolic	16	4.8%
Myopathy	7	2.1%
Syndromic	4	1.2%
Mitochondrial	4	1.2%
Total	31	9.3%

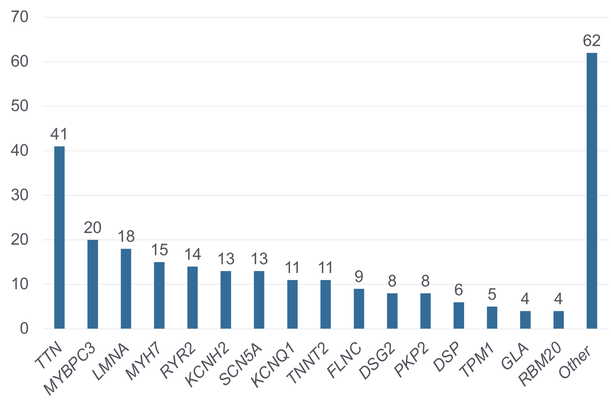
Metabolic genes: *TTR, SLC25A4, SLC22A5, APOA1, GLA, LAMP2, PRKAG2*; Myopathy genes: *ACTA1, FHL1, FKRP, RBCK1, DMD*; Syndromic genes: *LEMD2, NF1, PTPN11, KRAS*; Mitochondrial genes: *MT-TL1, MT-ND1.*

Figure 1. LP/P variant distribution in pediatric patients



"Other" includes genes with <3 cases. Percentages are rounded up to the whole number.

Figure 2. LP/P variant distribution in adult patients



"Other" includes genes with <4 cases. Percentages are rounded up to the whole number.

Conclusion

In this cohort, ~18% of patients received an informative result; the yield of testing was significantly higher in children than in adults.

LP/P variants in *MYBPC3* accounted for 8% of all informative results, which is significant given the recent availability of a gene-specific interventional clinical trial[3]. Over 9% of patients had a LP/P variant in a gene associated with extra-cardiac features.

Combined IA/CM NGS testing should include high-resolution CNV detection, non-coding variants, and mtDNA, as these combined explain 4% of all informative results.

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