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Spectrum of genetic variants and yield of genetic testing in Slovenian probands with suspected cardiomyopathies surviving sudden cardiac arrest

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Abstract

Background Cardiomyopathies (CMs) present phenotypically on a spectrum and in a proportion of patients the initial presentation is sudden cardiac arrest (SCA). Studies performing genetic screening of SCA survivors have identified (likely) pathogenic (LP/P) variants in 2–50% of probands, with mean cohort ages ranging from 28 to 64 years. Due to inconsistent data in the literature, our study aimed to genetically characterise Slovenian SCA survivors with clinically confirmed/suspected cardiomyopathy (CM). The present study included 29 probands (17 women, 59%) with clinically confirmed/suspected CM who survived SCA and were referred to the Clinical Institute of Genomic Medicine for genetic testing between January 2010 and July 2024. The majority of probands (23; 79%) underwent whole exome sequencing, and the remainder either clinical exome (5; 17%) or panel sequencing (1; 4%). Genetic data were analysed following ACMG/AMP guidelines and ACGS recommendations.

Results Probands survived SCA at a mean age of 49 ± 17 years (range 15–71), and 12 (41%) were < 50 years old. The majority had clinically confirmed/suspected arrhythmogenic (10; 34.5%) or dilated (9; 31.0%) CM, while the remainder had clinically undefined (5; 17.2%), hypertrophic (4; 13.8%), or non-compaction (1; 3.4%) CM.

Seven LP/P variants in CM-related genes were identified in eight (28.6%) probands. In addition, 16 variants of uncertain significance (VUS) were identified in 12 (41.3%) probands.

Probands' age at SCA did not significantly affect the yield, as LP/P variants were identified in four probands < 50 years at SCA and in four > 50 years ($p = 0.56$), nor did the positive family history of heart disease ($p = 0.55$) or sudden cardiac death ($p = 0.43$).

There were also no significant differences in probands' age and test outcome, as the mean age of patients with LP/P variants was 46 ± 21 years, those with the VUS(s) were 45 ± 15 years, and those without candidate variant(s) were 55 ± 12 years ($p = 0.41$).

Conclusions LP/P variants were identified in almost one-third of Slovenian SCA survivors with clinically confirmed/suspected CM. Genetic testing of SCA survivors with structural clinical findings provides additional confirmation of the clinical diagnosis and a basis for identifying relatives at risk of heart disease, allowing for better management.

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Keywords Sudden cardiac arrest, Genetic testing, Molecular pathology, (likely) pathogenic variants, Hereditary cardiomyopathy

Background

Cardiomyopathies (CMs) are defined as diseases of the myocardium in which the structure and function of the heart muscle is abnormal, but not as a result of coronary artery disease, hypertension, valvular disease, or congenital heart disease (Elliott et al. 2007; Arbelo et al. 2023). CMs may be genetically predisposed, and pathogenic variants associated with CMs have been shown to have incomplete, age-dependent penetrance and variable disease expression, meaning that not all individuals with the variant actually develop the disease phenotype or express it in the same way and to the same degree. Therefore, in a small proportion of patients, the onset of the disease is sudden and severe and presents as sudden cardiac arrest (SCA) (Martinez et al. 2021).

If any type of hereditary cardiomyopathy (CM) is suspected in a SCA survivor, genetic testing using phenotype-specific gene panels is recommended (Wilde et al. 2022). Studies have been conducted to evaluate the yield of genetic testing in these individuals (Mellor et al. 2017; Giudicessi and Ackerman 2018; Asatryan et al. 2019; Rucinski et al. 2020), but they have been heterogeneous in terms of the diagnostic gene panel used and the patient inclusion criteria for the presence of myocardial abnormalities. As a result, the difference in the (likely) pathogenic (LP/P) variant yield varied widely, from 2 to 50% (Mellor et al. 2017; Giudicessi and Ackerman 2018; Rucinski et al. 2020), and an estimate of the LP/P variant yield in SCA survivors with suspected inherited CM remained unknown.

The aim of the present study was to investigate the molecular pathology of Slovenian probands who had survived SCA and received a clinical diagnosis of confirmed/suspected CM after the event.

Methods

An in-house Mendelian disease registry was screened to identify probands who had survived SCA and were suspected of having a hereditary CM. Genetic, clinical, and genealogical data were collected.

Study cohort

The Clinical Institute of Genomic Medicine (CIGM) maintains a Mendelian disease registry with exome/genome sequencing results from approximately 15,000 probands. We searched for probands referred to CIGM between January 2010 and July 2024 who survived SCA, which was the first presentation of clinically confirmed or suspected CM.

Sequencing and bioinformatic analysis

Genetic analysis in the form of exome sequencing was performed in all probands as previously described (Maver et al. 2016; Bergant et al. 2018). The majority of probands (23; 79%) underwent whole exome sequencing (between January 2019 and July 2024), while the remainder underwent either clinical exome (5; 17%) (between January 2015 and December 2018) or target panel sequencing (1; 4%) (between January 2010 and December 2014). The median minimum exome coverage was 100x, and over 98% of targets had at least 10×coverage. The targeted panel sequencing analysis was performed at GENDIA (Genetic Diagnostic Network, Antwerp, Belgium), while whole and clinical exome sequencing was performed at CIGM. To ensure the most up-to-date classification of variants, the genetic data of the selected probands were re-interpreted at CIGM prior to the study using the PanelApp Sudden Unexplained Death or Survivors of a Cardiac Event gene panel (version: 19.73), which contains 54 genes. The variants were classified according to the ACMG/AMP guidelines and the ACGS recommendation (Richards et al. 2015; Durkie et al. 2024).

Clinical information and genealogy

The medical records of each proband were retrospectively reviewed to determine the type of suspected/confirmed CM and the age of SCA. Three-generation pedigrees were available for 26 of the 29 probands and were examined to identify any family history of any potentially inherited heart disease or sudden cardiac death (SCD).

Results

Twenty-nine probands were identified, of whom 17 (59%) were female. The mean age at the time of SCA was 49 ± 17 years (range 15–71 years). Twelve (41%) probands were younger than 50 years at the time of SCA. Most probands had clinically confirmed/suspected either arrhythmogenic (10; 34.5%) or dilated (9; 31.0%) CM and a smaller proportion had CM of unknown aetiology (5; 17.2%), hypertrophic CM (4; 13.8%), or non-compaction CM (1; 3.4%). Sixteen (55.2%) probands had a family history of heart disease and 10 (34.5%) had a family history of sudden cardiac death.

Seven LP/P variants were identified in 8 (28.6%) probands (Table 1). In addition, 16 variants of uncertain significance were identified in 12 (41.3%) probands in whom no LP/P variants were identified (Table 2).

No statistically significant difference ($p=0.56$) was observed in the yield of LP/P variants between probands who survived SCA before 50 years of age and those who survived SCA after 50 years of age (4/12 vs. 4/16, respectively). There was no statistical difference in the age of the probands at the time of SCA and the yield (46 ± 21 years in probands with LP/P, 45 ± 15 years in probands with the variant of uncertain significance (VUS) and 55 ± 12 years in probands with negative results, p-value = 0.41). The outcome of LP/P variants was not significantly different between patients with positive or negative family history of heart disease ($p=0.55$) and sudden cardiac death ($p=0.43$).

Discussion

This study investigated the molecular pathology of Slovenian probands who survived SCA and received a clinical diagnosis of confirmed/suspected CM after the event. The results highlight the importance of genetic testing in these individuals, as more than a quarter were found to

Table 1 Characteristics of probands with (likely) pathogenic variants and identified variants

Proband	Gender	Age at SCA [years]	(Sub)clinical phenotype	Variant	Variant type	Classification
1	F	15	ACM	*DSP*:c.3793G > T	Nonsense	P
				DSP:c.6577G > A	Missense	VUS
2	M	63	ACM	*DSP*:c.3793G > T	Nonsense	P
3	M	65	DCM	*TTN*:c.12478del	Frameshift	P
4	F	40	DCM	*DSP*:c.621G > A	Missense	LP
				DSP:c.3346 T > C		VUS
5	F	71	HCM	*ALPK3*:c.432_435dup	Frameshift	LP
6	M	21	HCM	*PRKAG2*:c.905G > A	Missense	P
7	F	30	HCM	*MYH7*:c.2225C > A	Missense	LP
8	F	63	NCC	*TNNT2*:c.445C > T	Missense	LP
				MYBPC3:c.1828G > C	Missense	VUS

ACM arrhythmogenic cardiomyopathy, *DCM* dilated cardiomyopathy, *F* female, *HCM* hypertrophic cardiomyopathy, *LP* likely pathogenic, *M* male, *NCC* noncompaction cardiomyopathy, *P* pathogenic, *SCA* sudden cardiac arrest, *VUS* variant of uncertain significance

Table 2 Variants of uncertain significance detected in probands and characteristics of the probands

Proband	Gender	Age at SCA [years]	(Sub)clinical phenotype	Variant	Variant type
9	F	32	ACM	*FPGT-TNNI3K*:c.2337C > A	Missense
10	M	32	ACM	*DES*:c.1123C > T	Missense
				DSP:c.5062G > A	Missense
				CACNA1C:c.202G > A	Missense
11	M	22	ACM	*TTN*:c.16516G > T	Nonsense
12	F	20	ACM	*TTN*:c.12614 T > C	Missense
13	M	51	ACM	*KCNE3*:c.248G > A	Missense
14	M	66	DCM	*MYPN*:c.3160G > A	Missense
15	F	39	DCM	*GPD1L*:c.560A > G	Missense
16	F	60	DCM	*TTN*:c.103360del	Frameshift
17	M	52	DCM	*TTN*:c.79606_79618del	Frameshift
				LMNA:c.1195C > T	Missense
				MYH7:c.728G > A	Missense
18	F	53	CM UA	*MYH7*:c.5333A > C	Missense
19	M	59	CM UA	*KCNH2*:c.526C > T	Missense
20	F	59	CM UA	*SCN5A*:c.6034C > T	Missense

ACM arrhythmogenic cardiomyopathy, *CM UA* cardiomyopathy of undefined aetiology, *DCM* dilated cardiomyopathy, *F* female, *M* male, *SCA* sudden cardiac arrest

have an LP/P variant. Detection of such variants in the proband allows cascade family screening, which is most important to identify relatives with the LP/P variant who can then be regularly evaluated by a cardiologist to prevent major adverse cardiac events. In addition, LP/P variants in certain desmosomal (e.g., *DSP*, *DSG2*, *DSC2*, *PKP2*), nuclear envelope (e.g., *LMNA*, *EMD*, *TMEM43*) and cytoskeletal (e.g., *TTN*) genes have recently been associated with a higher risk of major arrhythmic events. Identifying patients with high-risk genotypes helps to tailor their management, as they are at higher risk of the adverse cardiac event with less prominent phenotypes.

The average age of the probands studied at the time of SCA was 49 years, which is within the range of 28 to 64 years reported in previous studies (Mellor et al. 2017; Giudicessi and Ackerman 2018; Asatryan et al. 2019; Rucinski et al. 2020). More than half of them had a family history of heart disease and more than a third had one or more relatives who had died suddenly. However, we did not observe a significant association between a positive family history of SCD and the yield of genetic testing, as previously reported (Mellor et al. 2017). Previous studies have given mixed results as to whether there is a significant correlation between age at SCA and the yield of genetic testing, with one study in favor (Rucinski et al. 2020) and three against (Mellor et al. 2017; Giudicessi and Ackerman 2018; Asatryan et al. 2019). We did not find a significant association.

Likely pathogenic or pathogenic variants were identified in almost one third of the Slovenian probands. The LP/P variants in the *DSP* gene were found together in three out of eight probands with ACM and DCM phenotypes. A recent study of more than 250 patients with LP/P *DSP* variants showed that they have a high risk of developing malignant ventricular arrhythmias (Gasperetti et al. 2024). The *DSP*:c.3793G > T identified in two SCA survivors is a recurrent pathogenic nonsense variant in the local region that has been extensively characterised genetically and phenotypically (Vodnjov et al. 2024). Another LP/P *DSP* variant identified is the nonsense *DSP*:c.621G > A. The pathogenicity of this variant is supported by the fact that it was not identified in gnomAD controls and is expected to cause pathogenicity by truncating the protein product of the gene.

Two probands had two variants in the *DSP* gene, one classified as LP/P and one as VUS. Both survived SCA at (relatively) young ages. A study evaluating the clinical outcome of patients with two or more variants in the desmosomal genes found that patients with multiple LP/P variants were more likely to develop ventricular arrhythmias, heart failure or death than patients with one LP/P and one VUS or (likely) benign (LB/B) variant and were significantly younger than the latter two groups (Nagyova et al. 2023). Our probands had SCA at 15 or 40 years of age, and a (relatively) young age of event could be the result of either environmental or genetic factors, as there is insufficient evidence to rule out the possible pathogenic effect of the other two *DSP* variants currently classified as VUS.

According to international cardio-genetic guidelines, genetic testing for channelopathy and cardiomyopathy-associated genes may be considered in survivors of unexplained SCA with no upper age limit. Here, we identified a heterozygous predicted loss-of-function LP variant in the *ALPK3* gene in the patient who developed SCA in her seventh decade of life. Such variants have recently been found to be strongly associated with HCM and with disease onset at a later age (Herkert et al. 2020; Lopes et al. 2021; Hespe et al. 2025). Identification of the variant in one patient allowed cascade testing of relatives to ensure regular cardiologic evaluation of those with the variant (Wilde et al. 2022; Arbelo et al. 2023). Our results support the fact that genetic testing of unexpected SCA survivors with suspected underlying HCM is indeed beneficial for the management of the survivor and their family.

In probands with either hypertrophic, dilated, arrhythmogenic or non-compaction CM, a LP/P variant was identified in 33% of probands. However, no LP/P variants were identified in probands referred for CM of unknown aetiology, supporting the finding that genetic testing yields a higher proportion of LP/P variants in SCA survivors with a more refined definition of the phenotype rather than a less specific clinical diagnosis of heart disease (Giudicessi and Ackerman 2018).

The limitations of the study are its retrospective nature and the relatively small number of probands tested at a single diagnostic centre. However, as SCA is a serious manifestation of heart disease and the genetic basis is not well understood, the results of our study are of great relevance to the community.

Conclusion

The present study has identified a molecular pathology in almost one third of the Slovenian probands who survived SCA and had post-event clinical findings suggestive of hereditary CM. Genetic testing of SCA survivors with structural clinical findings provides additional confirmation of the clinical diagnosis and a basis for identifying pre-symptomatic relatives at risk of heart disease, allowing for better management.

Abbreviations

ACM	Arrhythmogenic cardiomyopathy
CMs	Cardiomyopathies
CMUA	Cardiomyopathy of undefined aetiology
DCM	Dilated cardiomyopathy
F	Female

LB/B	Likely benign/benign
LP/P	Likely pathogenic/pathogenic
M	Male
SCA	Sudden cardiac arrest
VUS	Variants of uncertain significance

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Authors' contributions
The study was conceived and designed by NV, KW and BP. AM processed the sequencing data. NV analysed the sequencing and clinical data and drafted the first draft of the manuscript. All authors contributed to revising the manuscript and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study adhered to the Declaration of Helsinki and was approved by the National Medical Ethics Committee of Slovenia (Approval No. 0120–71/2022/3, dated 28/03/2022). All study participants gave informed consent during the pre-genetic testing process for their anonymised data to be used for research purposes.

Consent for publication
All study participants gave informed consent during the pre-genetic testing process for their anonymized data to be published in the scientific literature.

Competing interests
The authors declare no competing interests.

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