Clinical and genetic yield of familial screening after a sudden unexplained death at a young age

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Editorial
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ABSTRACT

Background: In a population under 45 years of age, the predominant causes of sudden cardiac death (SCD) are inherited cardiac diseases. Determining the underlying cause may help identify relatives at risk and prevent further events but is more difficult if an autopsy has not been performed.

Aims: We aimed to assess the diagnostic value of clinical and genetic screening in relatives of young non-autopsied sudden unexplained death (SUD) victims.

Material and methods: Eighty-seven relatives of 65 young non-autopsied SUD victims from 39 families were evaluated from 2016 to 2019. The relatives underwent extensive noninvasive cardiac workup. Genetic examinations were performed in 39 families.

Results: The definite diagnoses were made in 17 of 39 (44%) families. Cardiomyopathies were identified in 10 families (5 hypertrophic, 4 dilated, and 1 arrhythmogenic), followed by long QT syndrome (5 families). In 3 families, probable diagnoses were made, whereas in 20 families no diagnosis was achieved. In total, definite and probable diagnoses were made in 18 and 5 patients, respectively. All affected relatives were offered medical management, one of them died of heart failure and one underwent transplantation during the median follow-up of 3 years. Disease-causing variants were found in 7 of 39 (18%) probands; all in families with a definite diagnosis. Variants of unknown significance were found in 2 probands.

Conclusion: Screening of relatives of SUD victims is warranted and may save lives, even if it is not guided by autopsy results. Genetic testing in families without the disease phenotype has little effectiveness.

Key words: cardiomyopathy, family screening, genetic testing, primary electric disease, sudden death

INTRODUCTION

Sudden cardiac deaths (SCD) constitute up to 20% of all deaths in Europe and approximately half of all cardiovascular deaths [1, 2]. SCD is relatively rare in individuals aged <35 with an incidence of 2.8 per 10 000 per year [3]. This incidence significantly increases with age due to the higher prevalence of coronary artery disease (CAD), which accounts for the majority of SCD [4]. In young people, SCD is predominantly attributed to structural non-ischemic heart diseases and primary electric

WHAT'S NEW?

There is very little research on the effectiveness of screening of families of non-autopsied sudden-death victims even though it is a common clinical situation. In our study on families of young sudden-death victims, we established a definite clinical diagnosis in nearly half of the families, and in one-fifth of them, a genetic diagnosis was made. Although cardiomyopathies and inherited arrhythmia syndromes were most commonly identified, our findings underlie that inherited vasculopathy should also be taken into consideration as a cause of sudden deaths. Of note, the study shows that screening may be beneficial not only in healthy relatives but also in those with other disorders that obscure identification of cardiac disease. Genetic testing in families without the disease phenotype has little effectiveness.

diseases [5–7], both with a frequent genetic basis. Along with the undeniable great psychological and economic impact on the family of the sudden loss of a close family member, there is a strong possibility of relatives inheriting the causative monogenic disease [8]. Therefore, screening of living first-degree relatives is strongly recommended to avert further tragic events. Several studies have already shown the efficacy of such an approach, where diagnoses could be established in 16%–53% of families [4, 8, 9]. The probability of finding the causative disease is higher when an autopsy with toxicological tests is performed, which helps to exclude non-cardiac causes and guide further screening of relatives towards either structural heart disease or, in the case of a negative autopsy, primary electric disease. However, in many countries, autopsies are not routinely performed, even in the case of young victims. Kjerrumgaard et al. [9] have shown that the diagnostic yield in families of non-autopsied sudden unexplained death (SUD) victims did not exceed 20%, but the age limit was not applied in their study, thus a higher proportion of CAD could have led to underestimation of the results. Our study aimed to assess the diagnostic value of clinical and genetic screening in relatives of young non-autopsied victims of SUD.

MATERIAL AND METHODS

Definitions

SUD was defined as a natural death that occurred within 1 hour of the onset of symptoms, during sleep, or within 24 hours after being seen alive and healthy and was unexplained because an autopsy was not performed, and no disease that could underlie SUD had been previously diagnosed. Deaths of infants were not included in this study. The SUD victim, whose death prompted their family to undertake screening was named as the reference SUD victim. Additional SUD victims were included to the second degree of consanguinity.

Probands were first-degree relatives of the reference SUD victims who were selected for genetic testing with next-generation sequencing (NGS). Preference was given to relatives who, based on clinical screening, were diagnosed with a disease of probably genetic origin, or in whom such a disease could be suspected with the highest probability. In the case of families with several SUDs, based on pedigree analysis, preference was given to the relatives who, assuming a common genetic background of the SUDs, would be obligate carriers.

Study design

We conducted a single-center prospective study that enrolled patients who presented between 2016 and 2019 because of SUD of one or more of their first-degree relatives aged 1–45. Among them, we included patients with a history of cardiovascular events or with cardiovascular abnormalities if no diagnosis of hereditary cardiovascular disease had been established, e.g. unexplained sudden cardiac arrest (SCA) or mild left ventricular systolic dysfunction of unclear etiology. Upon visits of consecutive relatives, we obtained available relevant information regarding the SUD victims' health status and circumstances of their deaths in an attempt to identify potential causes of death. For every family, a three-to-four-generation pedigree tree was drawn. We sought to invite all available first-degree relatives of SUD victims'. More distant relatives were also invited in accordance with the principles of cascade screening or when the family history suggested the possibility of a genetically determined cardiovascular disease. This research was funded by the National Institute of Cardiology, Warsaw, Poland (statutory grant No: 2.9/II/17). It was conducted in accordance with the Declaration of Helsinki and approved by the Local Bioethics Committee. Informed consent was obtained from all subjects.

Clinical assessment

As a minimum, clinical screening included a detailed review of medical history, clinical examination, electrocardiogram (ECG) with standard and high-precordial leads, transthoracic echocardiogram, and routine blood testing. Twenty-four-hour ECG Holter monitoring was offered to everyone. Initial findings prompted further tests, including cardiac magnetic resonance, exercise stress testing, and sodium channel blocker tests (the flowchart in Figure 1). Our diagnostic approach was broad, not only aimed at cardiomyopathies or arrhythmic syndromes (class III and VI according to the classification of rare cardiovascular diseases and disorders), which are often responsible for sudden deaths of young people but also at other syndromes, including aortopathy (class I) [10, 11].

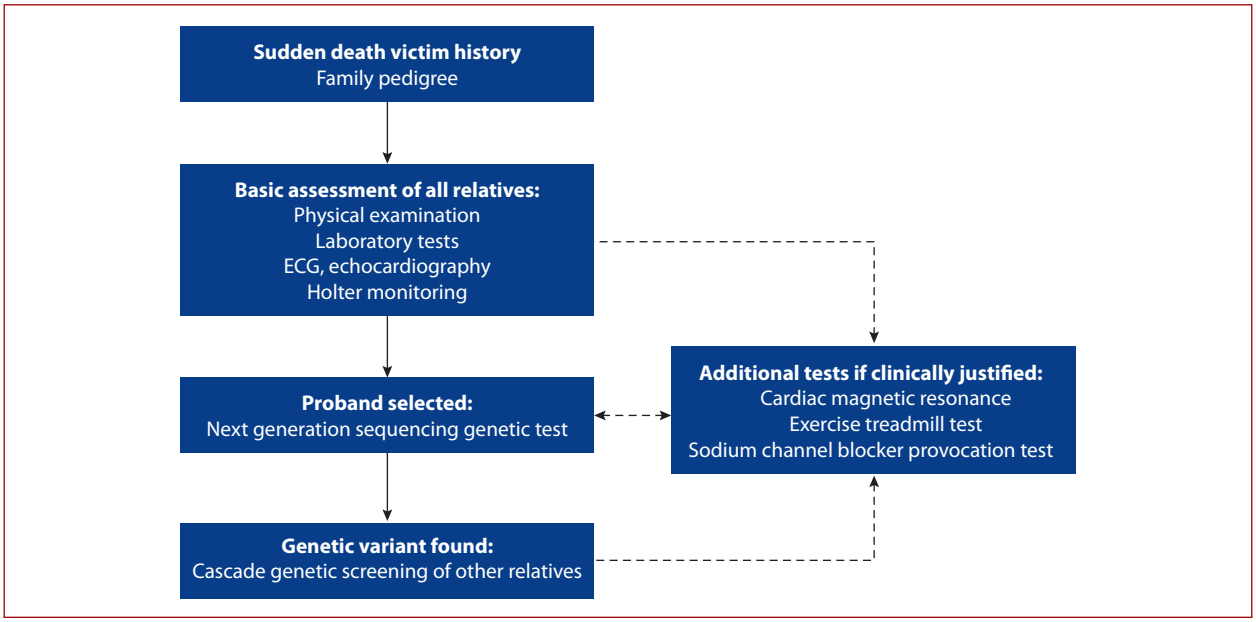

Figure 1. Design of the study on familial screening after sudden unexplained death at a young age

Table 1. Basic characteristics of sudden unexplained death victims within examined families

	All n = 65	Reference n = 39	Other n = 26	*P*-value
Male sex	49 (75%)	30 (77%)	19 (73%)	0.72
Age at death, years	36 (9)	33 (7)	39 (9)	0.002
Known death circumstances	25 (38%)	16 (41%)	9 (35%)	0.60
Death during exercise/stress	9 (14%)	6 (15%)	3 (12%)	0.66
Death at rest/sleep	16 (25%)	10 (26%)	6 (23%)	0.81

Number of subjects is expressed as n (%). Continuous variables are shown as means (standard deviations). The reference victim denotes an individual whose death prompted the family to undertake screening

Diagnostic criteria consistent with the current European Society of Cardiology guidelines were used [4]. If all required criteria were not met, a diagnosis was defined as probable. If at least one of the relatives had confirmed inherited disease, which fulfilled standard criteria, the family diagnosis was considered established. All affected patients were offered a follow-up and treatment, and healthy relatives were offered periodic screening.

Genetic testing

DNA samples from probands were examined by NGS using a custom panel TruSight Cardio, including 174 genes associated with 17 cardiac syndromes, including cardiomyopathies, arrhythmias, and aortopathies (details in Supplementary material, *Tables S1* and *S2*). Variants identified with NGS were followed up in probands and relatives with Sanger sequencing. Baseline analysis of NGS results was based on searching for genetic variants with very low frequency (<0.001) and high bioinformatic prediction scores with special regard to phenotypically consistent genes. The frequencies of variants were compared with the GnomAD database, Phase 3 of 1000 Genomes, and NHLBI GO Exome Sequencing Project (ESP) 6500 and POL400 (in-house database of >400 ethnically matched exomes). For the bioinformatic prediction of variant pathogenicity, the combined score from 13 prediction tools (including PolyPhen2, SIFT, and CADD) was used. All identified variants were classified according to the American College of Medical Genetics and Genomics guidelines [12].

Statistical analysis

Data were presented as counts (percentages), means (standard deviation), or medians (25^{th}–75^{th} percentile). Group comparisons were made using the χ^2 test, Fisher's exact test, Student's t-test, or Wilcoxon two-sample test. Significance was assumed at a *P*-value of <0.05. Statistical analyses were performed using SAS 9.4 (Durham, NC, US).

RESULTS

Basic data of SUD victims

SUD victims (Table 1) were predominantly male (75%). Their death occurred at a mean age of 36 years, significantly earlier than in the reference victims (33 vs. 39 years; *P* <0.01). The circumstances of death could be established in 38% of cases: it occurred during sleep in 8 (12%) patients, at rest in 8 (12%), during exercise in 6 (9%), and it was related to stress in 3 (5%).

Table 2. Baseline characteristics of the screened relatives of the sudden unexplained death victims

	All n = 87	Probands n = 39	Other n = 48	*P*-value
Age, years	37 (15)	38 (14)	36 (16)	0.60
Male sex	38 (44%)	18 (46%)	20 (42%)	0.68
Symptoms				
Asymptomatic	46 (53%)	13 (33%)	33 (69%)	0.001
Palpitations	21 (24%)	14 (36%)	7 (15%)	0.02
Faintness	11 (13%)	7 (18%)	4 (8%)	0.21
Syncope	10 (11%)	7 (18%)	3 (6%)	0.10
Arrhythmias and conduction disturbances				
Ventricular arrhythmia	15 (17%)	8 (21%)	7 (15%)	0.47
Atrial fibrillation	3 (3%)	1 (3%)	2 (4%)	1.00
Atrioventricular block	4 (5%)	2 (5%)	2 (4%)	0.65

Number of subjects is expressed as n (%). Continuous variables are shown as means (SDs). Probands denote those family members in whom the diagnosis of a cardiovascular disorder of probably genetic origin was either established or seemed most likely and who were selected for next-generation sequencing

Characteristics of the screened families

We enrolled 87 patients from 39 families. There was one case of SUD in 22 (56.5%) families, two cases in 11 (28%) families, and three or more cases in 6 (15.5%) families. Only one family member participated in the study in the case of 16 (41%) families, two members — in the case of 10 (26%) families, three — in 7 (18%) families, and more than 3 — in 6 (15%) families. Among the patients screened, there were 12 parents of the reference SUD victims (median age 59 [55–64] years), 32 siblings (median age 35 [28–42] years), and 27 children (median age 34 [23–46] years). Importantly, based on the pedigree analyses, there were 47 alive first-degree relatives of SUD victims eligible for the screening who did not take part in the study (range 0–7 per family), which means we could only examine 60% of the living first-degree relatives.

Characteristics and diagnostic workup of the study participants

The mean age of the screened relatives at the initial visit was 36 years, 38 (44%) of them were male (Table 2). Forty-three (49%) patients reported symptoms of potentially cardiac origin, the most common of which were heart palpitations (21 patients) and fainting (11 patients).

Several patients included in the study had a relevant medical history, but no diagnosis of hereditary cardiovascular disease was established. Two of them survived SCA a few months earlier. Another patient had a history of bilateral carotid artery dissection. A 29-year-old woman had mild left ventricular systolic dysfunction, and a 35-year-old patient with impaired physical capacity and severe bronchial asthma had been diagnosed with left ventricular hypertrophy a year earlier.

Fifteen patients had ventricular arrhythmia: 2 had a history of ventricular fibrillation, and the rest had arrhythmia detected on Holter monitoring, understood as a ventricular ectopy burden of >500/24 h or non-sustained ventricular tachycardia. Atrial fibrillation was found in 3 patients and atrioventricular block in 4 patients: the first degree in 2 patients and complete in 2 patients.

Comorbidities were infrequent. Well-established cardiovascular risk factors, including obesity (20%), dyslipidemia (31%), and hypertension (22%) were the most prevalent (Supplementary material, *Table S3*).

All patients had ECG and echocardiography performed, 26 had cardiac magnetic resonance, 56 had Holter monitoring, and 23 underwent exercise stress testing. The sodium channel blocker test was performed in 4 patients.

Results of familial screening

Upon the first visit or during follow-up, definite and probable diagnoses of inherited cardiovascular disease were reached in 17 and 3 families, respectively (Figure 2; selected diagnostic findings see Figure 3). In one of the families, 2 different diagnoses were made, one definite and one probable (Figure 4D). In all but two cases, both the definite and probable diagnoses were established in the probands.

The most common diagnoses were cardiomyopathies, namely hypertrophic (HCM), dilated (DCM), and arrhythmogenic right ventricular (ARVC) cardiomyopathies found in 5, 4, and 1 families, respectively. Long QT syndrome (LQTS) was diagnosed in 5 families. We also diagnosed progressive cardiac conduction disease and vascular Ehlers-Danlos syndrome (vEDS). In 3 families, probable diagnoses of inherited disorders could be made. They included short QT syndrome (persistent corrected QT of ~350 ms in an individual with no syncope), HCM (unexplained interventricular septum thickening to 14 mm), and Brugada syndrome (type 3 Brugada pattern on standard ECG, a history of syncope and a negative provocation test with flecainide).

In total, definite and probable diagnoses were made in 18 and 5 patients, respectively. Sixteen patients (including 7 probands) had only one visit to our center, and 71 patients had a median follow-up of 3.1 (1.5–5.0) years. One of them died due to rapidly progressive refractory heart failure, and another one, with obstructive HCM and restrictive filling pattern, required heart transplantation. One patient had ventricular arrhythmia ablation. Eight patients received an implantable cardioverter-defibrillator (ICD), and one had a pacemaker implanted.

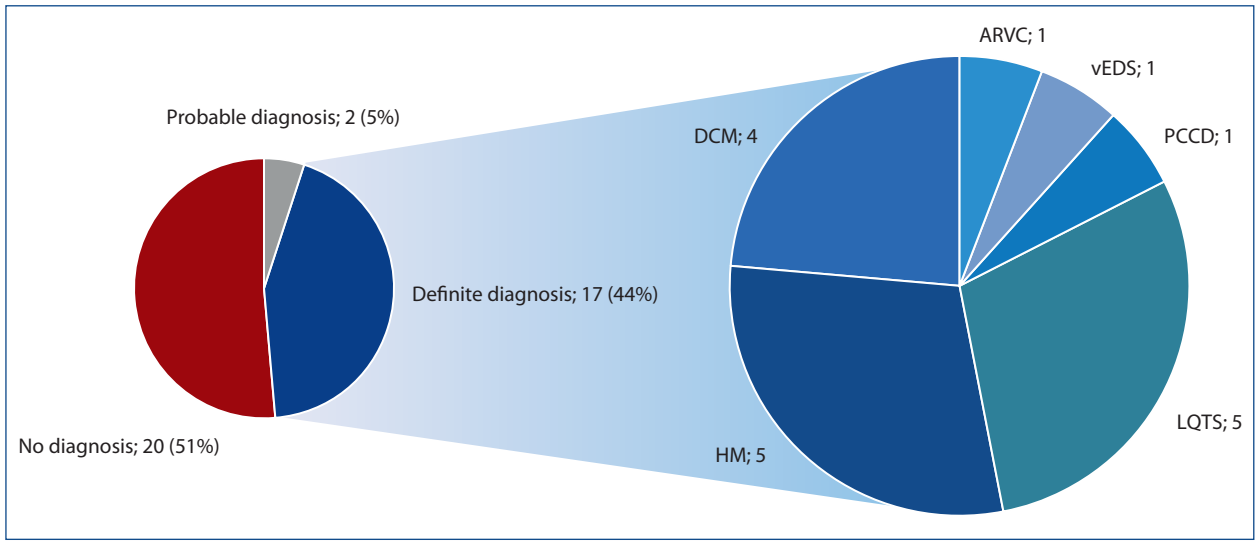

Figure 2. Diagnostic yield of the screening in the families of sudden unexpected death victims

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; PCCD, progressive cardiac conduction disease; vEDS, vascular Ehlers-Danlos syndrome

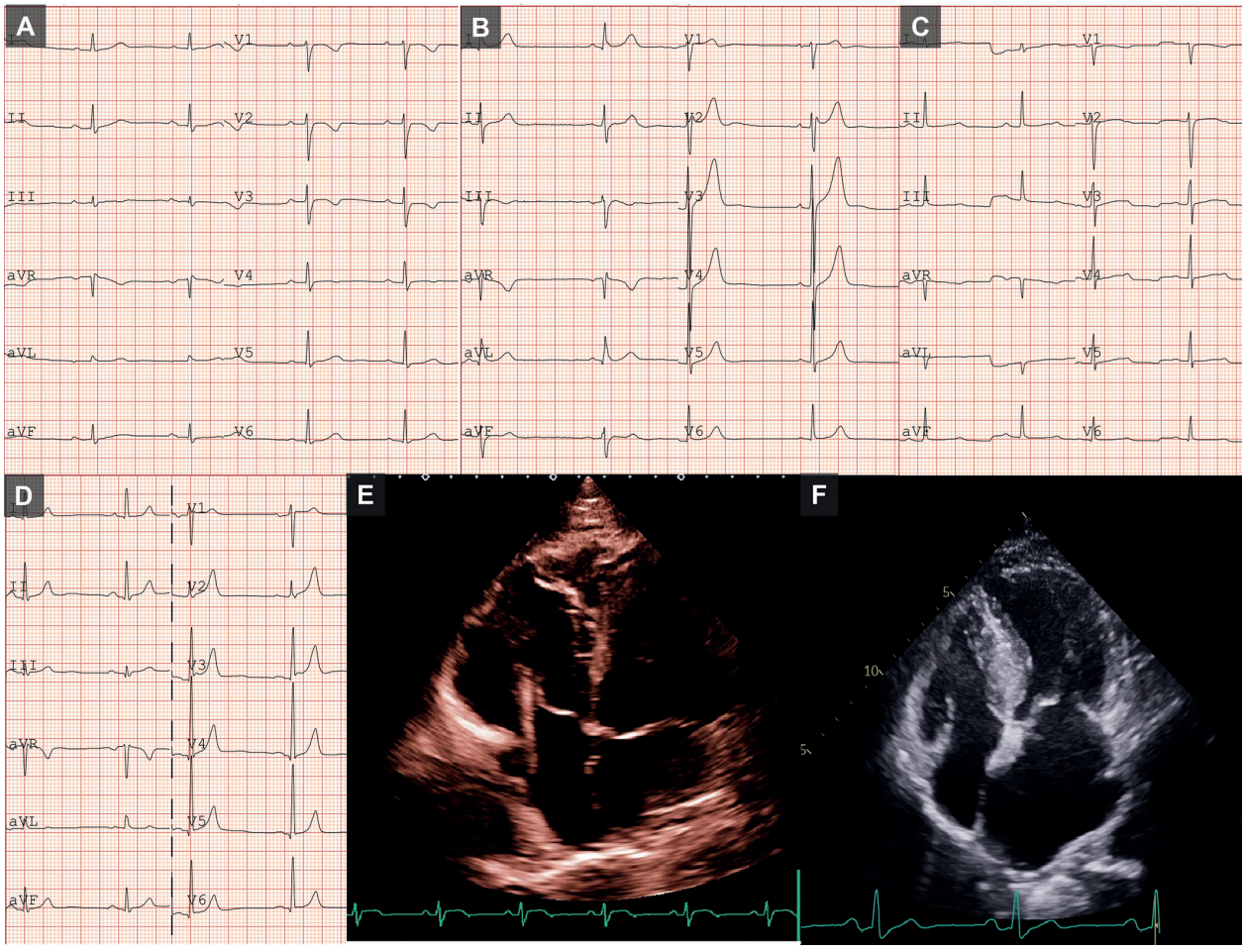

Figure 3. Examples of diagnostic findings in the screened individuals. **A.** ECG of a patient with arrhythmogenic right ventricular cardiomyopathy. **B.** Probable Brugada syndrome. **C.** Long QT syndrome. **D.** Probable short QT syndrome. **E.** Four-chamber view with features of arrhythmogenic right ventricular cardiomyopathy. **F.** Hypertrophic cardiomyopathy

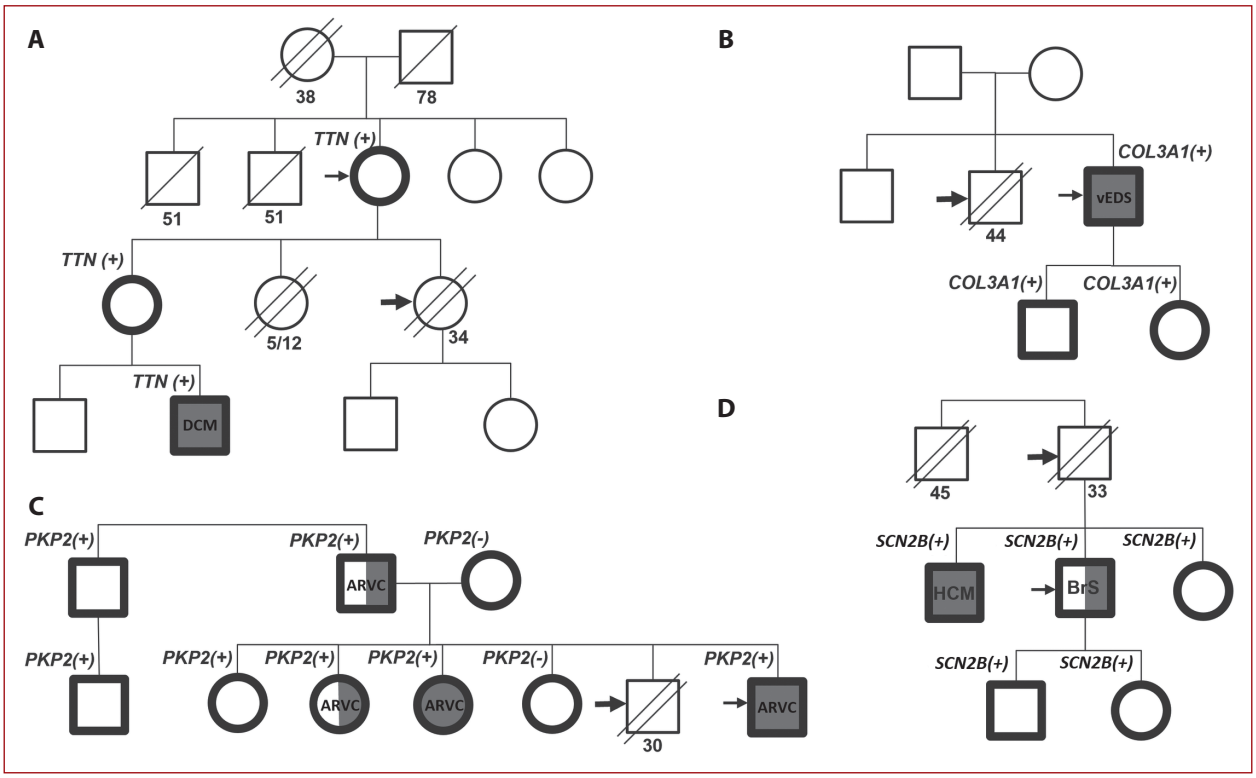

Figure 4. Sample pedigree trees of screened families. **A.** Family with the diagnosis of dilated cardiomyopathy and a *TTN* truncating variant (NM_001267550.2: c.93166C>T). **B.** Family with the diagnosis of arrhythmogenic right ventricular cardiomyopathy and a *PKP2* variant. **C.** Family with the diagnosis of vascular Ehlers-Danlos syndrome and a *COL3A1* variant. **D.** Family with a definite diagnosis of hypertrophic cardiomyopathy, a probable diagnosis of Brugada syndrome, and an *SCN2B* variant of unknown significance
Legend: squares denote males, circles — females; crossed symbols — deceased family members, double-crossed symbols — sudden death victims, numbers denote age at death in years; thin-outlined symbols — out-of-study relatives, thick-outlined symbols — relatives screened in the study, grey-colored symbol — definite disease diagnosis, semi-colored symbol — probable disease diagnosis, *gene*(+) — variant carriers, *gene*(–) — variant carriership excluded, thick arrow — reference victim, thin arrow — proband

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome, DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; vEDS, vascular Ehlers-Danlos syndrome

We found that, among various characteristics of the studied families, SUD victims, and probands, the presence of symptoms in probands and a history of ≥2 SUDs in the family were associated with a greater chance of diagnostic success (Supplementary material, *Table S4*).

Results of genetic testing

Within 39 families, 5 pathogenic (P), 2 likely pathogenic (LP), and 2 variants of unknown significance (VUS) were identified, all heterozygous, and 3 of them were novel (Table 3). They were found in genes associated with cardiomyopathies (*MYH7, LMNA, TTN, PKP2*), arrhythmic disorders (*KNCQ1, RYR2, SCN2B*), and vasculopathies (*COL3A1*), inherited in autosomal dominant manner. None of the probands had more than one variant in the tested genes. Overall, in 7 (41%) of 17 families with definite diagnoses, a causative P/LP variant was found. Notably, except for 1 VUS in *RYR2*, no genetic variants were found in families without a disease phenotype. It should be noted, however, that in the case of 2 families, genetic findings played a key role in making the diagnosis.

This applies to a 57-year-old male with bilateral carotid artery dissection and a family history of 2 SUDs (mother aged 24 and brother aged 44), in whom the identification of a pathogenic variant in *COL3A1* allowed for the diagnosis of vEDS (Figure 4C).

Another example is a family with 2 female SUDs in which two first-degree relatives presented with normal echocardiography and minor electrocardiographic abnormalities: non-sustained ventricular tachycardia on 24-hour Holter monitoring in a 67-year-old woman and right bundle branch block with a first-degree atrioventricular block on standard ECG in her daughter. NGS was performed on the mother, who would be an obligate carrier, assuming a common genetic background of both SUDs in the family (Figure 4A). A pathogenic p.Arg31056Ter *TTN* variant was identified. The clinical diagnosis was made, following cascade screening, in a 20-year-old male, the proband's grandson, and a nephew of the reference SUD victim, in whom the presence of the identified *TTN* variant and early-stage DCM were found.

The utility of cascade screening was demonstrated in the family, in which ARVC was found (Figure 4B). Of 9 screened family members, 6 carriers of a pathogenic variant in *PKP2* were identified. Two of them had full-blown ARVC with malignant arrhythmia and adequate ICD in-

Table 3. Variants in genes associated with cardiovascular disorders identified in the relatives of sudden unexplained death victims

Gene	Variant	Chromosomal locations	Protein	Type	Patho-genicity	Variant carriers	Affected relatives	SUDS in the family	Clinical diagnosis
MYH7	NM_000257.4: c.715G>A	chr14-23431602	p.Asp239 Asn	Missense	P	1	1	1	HCM
LMNA	NM_170707.4: c.575A>T	chr1-156134464	p.Asp192 Val	Missense	P	1	1	1	DCM
TTN	NM_001267550.2: c.93166C>T	chr2-178548460	p.Arg 31056Ter	Nonsense	P	3	1	2	DCM
TTN	NM_003319.4: c.16553-1G>C^{N}	chr2-178631301	-	Splicing	LP	1	1	1	DCM
PKP2	NM_004572.4: c.929_951dup	chr12-32877928	p.His318 TrpfsTer10	Frame-shift	P	6	4	1	ARVC
KNCQ1	NM_000218.3: c.728G>A	chr11-2572057	p.Arg116 His	Missense	P	1	1	3	LQTS
RYR2	NM_001035.3: c.5105A>G^{N}	chr1-237614233	p.Tyr1702 Cys	Missense	VUS	2	0	4	-
SCN2B	NM_004588.4:c. 625_626delAAinsCC	chr11-118166909	p.Asn209 Pro	Missense	VUS	5	1	3	BrS susp.
COL3A1	NM_000090.4: c.2338-1G>T^{N}	chr2-189001535	-	Aplicing	LP	3	1	2	vEDS

All the listed variants were heterozygous

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS susp., suspicion of Brugada syndrome; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LP, likely pathogenic; LQTS, long QT syndrome; ^{N}, novel; P, pathogenic; vEDS, vascular Ehlers-Danlos syndrome; VUS, variant of unknown significance

terventions, two other carriers had asymptomatic, borderline ARVC, and two were phenotype-negative.

Of the 2 VUSs, one was found in a patient with suspected Brugada syndrome (*SCN2B*), increasing the probability of the diagnosis, and the other one in a family with no clinical diagnosis (*RYR2*).

DISCUSSION

In our study, a diagnosis of inherited cardiovascular disease could be established in 41% of families of non-autopsied SUD victims. P/LP variants in genes related to cardiovascular diseases could be identified in 18% of probands.

There is very little research on the effectiveness of screening of families of non-autopsied SUD victims, even though it is a common clinical situation. In a Danish study by Kjerrumgaard et al. [9], definite and probable inheritable cardiac diagnosis was established in 13% and 10% of families, respectively. As the age limit was not applied in their study, a higher proportion of CAD could significantly underestimate the results. In the study by Quenin et al. [13], a screening efficiency of 25% was achieved. Other studies focused on screening of families of SUD victims with a negative autopsy [14, 15], or irrespective of the autopsy findings [16], often guided by genetic testing of the deceased.

The most common diagnosis in our study were cardiomyopathies (HCM, followed by DCM and ARVC). Cardiomyopathies are an important cause of SCD among young active adults, responsible, respectively, for 41% of cases in the US National Registry of Sudden Death in Athletes [17]. Among cardiomyopathy-associated variants, we found a *MYH7* missense variant in relation to HCM, two *TTN* truncating variants and an *LMNA* variant in relation to DCM, and a *PKP2* truncating variant in relation to ARVC.

The p.Asp239Asn *MYH7* variant, located in the myosin head, a well-established functional domain and a mutational hot-spot, was related to HCM in several cases, in particular to early onset HCM [18] leading to end-stage heart failure [19]. We identified it in a 35-year-old female with a history of 2 SUDs in her family and HCM (Figure 3F) eventually treated with heart transplantation.

Although present in 1% of the normal population, *TTN* truncating variants are known as the most common cause of inherited DCM [20]. It is characterized by a milder course in females and often leads to severe ventricular arrhythmia as heart failure progresses [21, 22]. Interestingly, in the family with an identified *TTN* variant, the clinical diagnosis of DCM was made only in a second-degree relative of the reference SUD victim (Figure 4A). Two young females died suddenly in the family, in one of them binge drinking could be a potential trigger of the disease, as *TTN* truncating variants represent a prevalent genetic predisposition for alcohol-related cardiomyopathy [23]. Notably, SUD in a 33-year-old female was also reported in the family with the *TTN* p.Phe24259Leufs*51 variant [24]. Our study adds also a hint to the observations that *TTN* truncating variants may have early arrhythmogenic potential in young adult females.

Of particular importance is identification of a malignant p.Asp192Val variant in the *LMNA* gene since another amino acid substitution p.Asp192Gly in *LMNA* was shown to lead to obliteration of nuclear architecture, breakdown of the nuclei, and death due to heart failure [25]. SCD is common among *LMNA* mutation carriers [26, 27], and sometimes the diagnosis is made only after molecular autopsy [26].

We showed a variable course of ARVC in two generations of a family with a loss-of-function variant in

PKP2 (Figure 4B). This duplication of 23 base pairs causing a frameshift has not been clinically reported. Making a diagnosis of ARVC is of great importance since SCD may occur at an early phase of the disease and prophylactic ICD implantation guided by arrhythmic risk assessment may save lives [28, 29].

As in other studies on SUD or SCA [9, 13, 30, 31], another major group of diagnoses is inherited arrhythmia disorders. Genetic testing revealed two P/LP variants in related genes. The identification of the LQTS-related *KCNQ1* variant is very important as the 2022 European Society of Cardiology Guidelines recommend diagnosing LQTS in the presence of a pathogenic mutation, irrespective of the QT duration [4].

It is interesting that we identified a novel pathogenic variant in COL3A1. In vEDS, spontaneous ruptures of the aorta, arteries, and hollow organs can lead to sudden death [32]. The course of the disease is dependent on the type of pathogenic variant. Truncating variants, as identified in our study, show the most severe complications [33].

Study limitations

The study group size, although informative, is small, as a result of conducting this study in a single center. The diagnostic yield could be improved with a higher number of family members examined or if the scope of routinely performed diagnostic tests was more comprehensive (e.g., standard sodium channel blocker tests performed routinely and not only in selected patients). Also, the number of positive genetic test results may have been higher with the use of whole exome sequencing instead of a commercial cardiac panel or if all relatives had been examined with NGS.

Finally, although we were able to establish a diagnosis of hereditary cardiovascular disease in a significant proportion of the screened families, we must acknowledge that the actual cause of sudden deaths might have been different.

CONCLUSIONS

The study shows that screening of SUD victims' relatives is warranted and may save lives, even when it is not guided by autopsy results. Genetic testing in families without the disease phenotype has little effectiveness. Identification of the genetic background can help make the diagnosis and provide targeted care for at-risk family members.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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