Genetic arrhythmias complicating patients with dilated cardiomyopathy

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BACKGROUND Sudden cardiac death due to malignant arrhythmias is a common cause of death in dilated cardiomyopathy (DCM). Whether genetic variants increase the risk of arrhythmias in DCM is unknown.

OBJECTIVE The purpose of this study was to investigate the genetic causes of arrhythmias in DCM patients.

METHODS Whole-exome sequencing and high-depth targeted next-generation sequencing (142-gene panel) were used. Eight specific DCM pedigrees with arrhythmias and 2 separate cohorts of 1232 consecutive unrelated sporadic DCM patients from 3 medical centers (550 in the discovery cohort, 682 in the replication cohort) were analyzed; 470 (250 in the discovery cohort, 220 in the replication cohort) suffered from arrhythmias (DCM-A group) and 762 (300 in the discovery cohort, 462 in the replication cohort) did not (DCM-NA group). All identified causative variants were Sanger sequenced to eliminate false-positive results and then screened in 700 unrelated matched arrhythmia- and DCM-free healthy controls.

RESULTS We identified long QT syndrome (LQTS)-causative variants that independently cosegregated in 2 unrelated DCM-LQTS pedigrees. Pathogenic variants in arrhythmia-related genes (ion channelopathies) were identified in 4.9% (23/470) of sporadic DCM-A patients (4.0% in the discovery cohort, 5.9% in the replication cohort) but only 0.1% (1/762) of sporadic DCM-NA patients ($P = 2.16 \times 10^{-9}$). These arrhythmia-related pathogenic variants included long QT syndrome, atrial fibrillation, sick sinus syndrome, cardiac conduction disease, and Brugada syndrome.

CONCLUSION Some arrhythmias in DCM patients are caused by arrhythmia-related pathogenic variants. For DCM patients with explicit arrhythmias, arrhythmia-causative genetic screening may help to explain the etiology and decision-making.

KEYWORDS Arrhythmia; Dilated cardiomyopathy; Genetic diagnosis; Next-generation sequencing; Whole-exome sequencing

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Introduction

Dilated cardiomyopathy (DCM), which has a prevalence of approximately 1:250 in the general population,[1] represents the most common cardiomyopathy and is a leading cause of heart failure and sudden cardiac death (SCD).[2–4] From 30%–50% of DCM cases may be explained by genetic causes,[5] which can be divided into familial and sporadic forms.[2,6] DCM-causing variants have been found in >50 genes, and most identified pathogenic variants often are unique to families.[1] Based on these findings, recent

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guidelines recommend genetic counseling for DCM patients and their first-degree relatives.[6,7]

Unpredictable SCD is one of the most common lethal complications in DCM patients.[8] The primary mechanism causing SCD in many, if not all, cases is arrhythmia (eg, sustained or recurrent ventricular arrhythmia).[9] Currently, the implantable cardioverter-defibrillator (ICD) is the most effective treatment of malignant arrhythmias related to SCD.[10,11] In addition, the current guidelines for ICD implantation in DCM patients are mainly based on left ventricular ejection fraction and New York Heart Association functional class.[12–14] However, approximately 80% of patients with DCM and left ventricular ejection fraction ≤35% who underwent ICD implantation did not receive therapeutic intervention during 5-year follow-up.[8,11]

Physicians and guidelines usually regarded malignant arrhythmias as a random complication secondary to DCM.[5–7] However, previous studies reported that the risk of SCD caused by arrhythmias is significantly higher in patients with DCM due to a lamin A/C (*LMNA*) pathogenic variant than in patients with DCM due to variants in other genes.[8,15–17] Additionally, compared to other genes, *LMNA* is associated with more malignant disease.[18] Unfortunately, the genetic cause of most SCD-related malignant arrhythmias in DCM patients remains elusive.[8]

We have 2 hypotheses about the genetic bases of predictable arrhythmias in DCM. Hypothesis 1: Some arrhythmias in DCM may be caused by independent non-DCM genetic abnormalities (eg, ion channelopathy variants) (DCM and arrhythmia: ≥2 genetic causes). Hypothesis 2: Some arrhythmias in DCM are related to a single DCM-related genetic reason (eg, *LMNA* mutations) (DCM and arrhythmia: 1 genetic cause). To date, no previous study has systemically explored these 2 hypotheses with regard to malignant arrhythmias in DCM patients. The goal of this study was to investigate these 2 kinds of potential complex genetic etiology of malignant arrhythmia in a large cohort of DCM patients.

Methods

Details on all methods are given in the Supplemental Methods. Characterization of the 1232 DCM patients and 700 healthy controls is given in Supplemental Table S1 and of the 142 gene panels for targeted sequencing in Supplemental Table S2.

Results

Clinical characterization of sequencing cohorts of the 1232 DCM patients and 700 healthy controls is given in Supplemental Table S1 and of the quality of whole-exome sequencing is given in Supplemental Table S3. For further details, see the Supplemental Results.

Pathogenic arrhythmia-causative variants in sporadic DCM cohorts

In the discovery cohort, we identified pathogenic arrhythmia-causative variants in 4.0% (10/250) of patients having DCM with arrhythmia (DCM-A), but we did not identify such variants in the 300 patients having DCM with no arrhythmia (DCM-NA) ($P = 5.01 \times 10^{-4}$). Similarly, in the replication cohort, we identified pathogenic arrhythmia-causative variants in 5.9% (13/220) of DCM-A patients, and we identified 1 arrhythmia-causative pathogenic variants in 1 of 462 patients in the DCM-NA group ($P = 1.08 \times 10^{-6}$). In total, we identified pathogenic arrhythmia-causative variants in 4.9% (23/470) of DCM-A patients and 0.1% (1/762) of DCM-NA patients ($P = 2.16 \times 10^{-9}$) (Tables 1 and 2).

Clinical characterization of sporadic arrhythmia-causative variants carriers

Among the 23 arrhythmia-causative variants identified in DCM-A patients, we identified long QT syndrome (LQTS), atrial fibrillation (AF), sick sinus syndrome, Brugada syndrome, and cardiac conduction disease (Table 2). None of these patients has mitral stenosis or restrictive cardiomyopathy phenotype.

We confirmed 12 previously reported definite pathogenic variants for late-onset AF in 12 sporadic DCM patients with AF. Their average age at AF onset was 55 years old (youngest onset age was 45 years). Interestingly, the carrier of the identified reported pathogenic variant (p.Thr527Met-*KCNA5* for AF) in the 762 DCM-NA patients was a 38-year-old young man. Furthermore, we found that patients with AF have a larger proportion of left atrial enlargement.

We identified pathogenic variants in 5 LQTS-related genes in 7 unrelated sporadic DCM patients with LQTS. All 7 sporadic LQTS patients suffered from cardiac syncope. A 36-year-old man with DCM combined with Brugada syndrome often suffered from cardiac syncope in bed since the age of 20 years. This patient had an ICD implanted 2 years ago. We identified a female patient having DCM combined with *SCN5A*-related cardiac conduction disease. She was diagnosed with third-degree atrioventricular block (AVB) at age 27 years. We identified compounded novel pathogenic *TRMP4* variants (p.Phe617Serfs, c.1849_1849delT; p.Glu996Glyfs,

Table 1 Burden test of pathogenic variants in sporadic DCM cases

	DCM-A		DCM-NA		
	Pathogenic alleles	Wild-type alleles	Pathogenic alleles	Wild-type alleles	*P* value
Discovery cohort	10	490	0	600	5.01×10^{-4}
Replication cohort	14	426	1	923	1.08×10^{-6}
Two cohorts combined	24	916	1	1523	2.16×10^{-9}

DCM-A = dilated cardiomyopathy with arrhythmia; DCM-NA = dilated cardiomyopathy with no arrhythmia.

Table 2 Pathogenic variants in arrhythmia-causative genes (ion channelopathy genes) identified in 1232 sporadic DCM patients and 8 pedigrees

Inheritance mode	Sex	Age* (y)	Arrhythmia type	LVEDd (mm)	LAD (mm)	LVEF (%)	IVSd (mm)	LVPWd (mm)	CS	PM/ ICD	Gene	Protein change	Coding change	ExAC Total	ExAC East Asian
Sporadic	F	56	AF	61	58	45	10	10	Y	N	*KCNA5*	p.Ala576Val	c.1727C>T	3.3×10^{-5}	3.5×10^{-4}
Sporadic	M	63	AF	59	47	29	10	10	N	N	*KCNA5*	p.Ala576Val	c.1727C>T	3.3×10^{-5}	3.5×10^{-4}
Sporadic	M	38	—	55	30	45	11	10	N	N	*KCNA5*	p.Thr527Met	c.1580C>T	2.4×10^{-4}	2.5×10^{-3}
Sporadic	M	45	AF	59	57	30	10	10	N	N	*KCNA5*	p.Thr527Met	c.1580C>T	2.4×10^{-4}	2.5×10^{-3}
Sporadic	M	60	AF	82	52	29	12	12	Y	Y	*KCNA5*	p.Thr527Met	c.1580C>T	2.4×10^{-4}	2.5×10^{-3}
Sporadic	M	33	LQTS	70	37	28	12	12	Y	N	*KCNA5*	p.Thr527Met	c.1580C>T	2.4×10^{-4}	2.5×10^{-3}
Sporadic	F	58	LQTS	60	50	40	9	9	Y	N	*KCNA5*	p.Thr527Met	c.1580C>T	2.4×10^{-4}	2.5×10^{-3}
P1:III:5	F	29	LQTS	51	35	45	9	9	Y	N	*KCNE1*	p.Ala8Val	c.23C>T	1.3×10^{-4}	9.3×10^{-4}
P1:III:3	F	34	LQTS	55	36	44	9	9	Y	N	*KCNE1*	p.Ala8Val	c.23C>T	1.3×10^{-4}	9.3×10^{-4}
P1:II:3	F	57	LQTS	66	52	23	7	9	Y	Y	*KCNE1*	p.Ala8Val	c.23C>T	1.3×10^{-4}	9.3×10^{-4}
Sporadic	M	65	LQTS	75	42	19	10	10	Y	N	*KCNE1*	p.Ser74Leu	c.221C>T	1.7×10^{-5}	3.0×10^{-5}
Sporadic	M	56	AF	60	45	40	9	9	N	N	*KCNE2*	p.Arg27Cys	c.79C>T	7.4×10^{-5}	4.5×10^{-4}
Sporadic	F	61	AF	59	35	36	9	9	Y	N	*KCNE2*	p.Arg27Cys	c.79C>T	7.4×10^{-5}	4.5×10^{-4}
Sporadic	F	62	AF	65	38	25	8	8	N	N	*KCNE2*	p.Arg27Cys	c.79C>T	7.4×10^{-5}	4.5×10^{-4}
Sporadic	F	62	AF	71	52	18	7	7	Y	Y	*KCNE2*	p.Arg27Cys	c.79C>T	7.4×10^{-5}	4.5×10^{-4}
Sporadic	F	47	AF, SSS	59	46	45	11	10	Y	Y	*KCNE2*	p.Arg27Cys	c.79C>T	7.4×10^{-5}	4.5×10^{-4}
Sporadic	F	45	LQTS	60	43	26	9	8	Y	N	*KCNH2*	p.Arg948Cys	c.2842C>T	1.2×10^{-4}	2.3×10^{-4}
Sporadic	F	31	LQTS	64	45	24	10	10	Y	N	*KCNH2*	p.Gln1141Profs	c.3419_3420insG	Novel	Novel
Sporadic	M	60	AF	62	59	45	9	9	Y	N	*KCNJ2*	p.Val93Ile	c.277G>A	1.2×10^{-4}	3.0×10^{-4}
Sporadic	F	48	AF	75	51	27	9	8	N	N	*KCNJ5*	p.Gly387Arg	c.1159G>C	1.4×10^{-4}	1.9×10^{-3}
Sporadic	F	50	AF	72	46	20	9	9	N	N	*KCNJ5*	p.Gly387Arg	c.1159G>C	1.4×10^{-4}	1.9×10^{-3}
P2:III:4	M	20	LQTS	55	25	37	7	7	Y	N	*KCNJ5*	p.Gly387Arg	c.1159G>C	1.4×10^{-4}	1.9×10^{-3}
Sporadic	M	24	LQTS	68	40	27	10	10	Y	N	*KCNJ5*	p.Gly387Arg	c.1159G>C	1.4×10^{-4}	1.9×10^{-3}
Sporadic	M	13	LQTS	56	30	39	9	9	Y	N	*KCNQ1*	p.Arg451Trp	c.1351C>T	Novel	Novel
Sporadic	F	27	CCD	57	27	45	9	9	Y	Y	*SCN5A*	p.Arg1632His	c.4892G>A	Novel	Novel
Sporadic	M	36	BRS	56	46	64	9	9	Y	Y	*SCN5A*	p.Gly292Ser	c.874G>A	1.7×10^{-5}	2.3×10^{-4}
Sporadic	M	54	SSS	62	51	40	11	10	Y	Y	*TRPM4*	p.Phe617Serfs	c.1849_1849delT	Novel	Novel
												p.Glu996Glyfs	c.2985_3012del28bp	Novel	Novel

AF = atrial fibrillation; BRS = Brugada syndrome; CCD = cardiac conduction disease; CS = cardiac syncope; ExAC = reported global risk allele frequency in the Exome Aggregation Consortium database; IVSd = interventricular septum thickness at end-diastole; LAD = left atrial diameter; LQTS = long QT syndrome; LVEDd = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVPWd = left ventricular posterior wall thickness at end-diastole; PM/ICD = pacemaker/implantable cardioverter-defibrillator implantation; SSS = sick sinus syndrome.

*Age at dilated cardiomyopathy (DCM) diagnosis.

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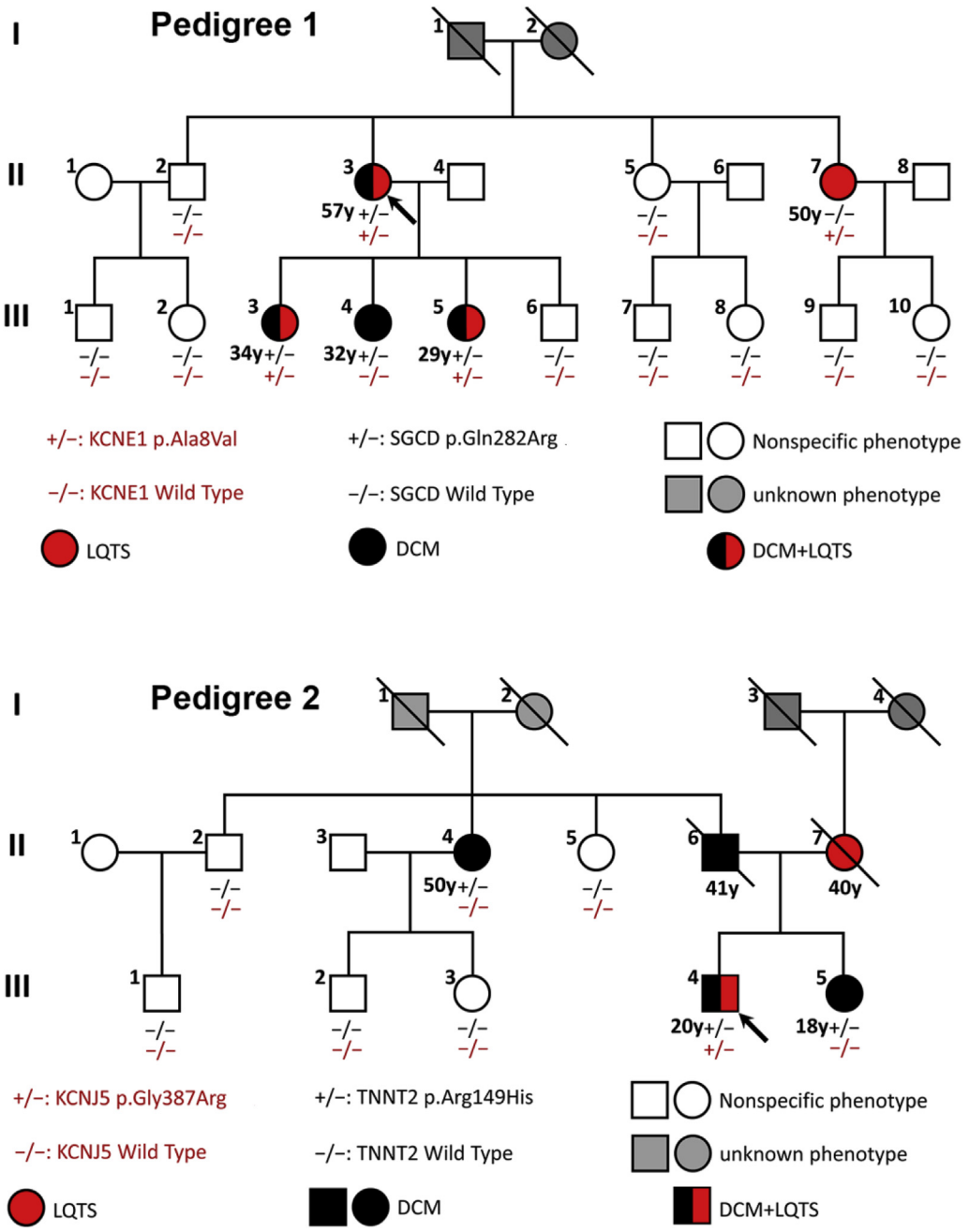

Figure 1 Pedigrees of DCM patients with ion channelopathy–related arrhythmia. Pedigrees of 2 DCM families with LQTS. Proband is indicated with an *arrow*. *Circle* indicates female; *square* indicates male; *open symbol* indicates nonspecific phenotype; *closed symbol* indicates DCM affected; *diagonal line* indicates deceased; *solid red symbol* indicates LQTS affected. +/− and −/− signs indicate presence or absence of a pathogenic variant, respectively. DCM = dilated cardiomyopathy; LQTS = long QT syndrome.

c.2985_3012del28bp) in a 54-year-old DCM patient with sick sinus syndrome (Table 2).

Pedigree 1: LQTS-DCM

This is a 3-generation DCM pedigree with LQTS (Figure 1). Four family members (P1:II:3, P1:III:3, P1:III:4, P1:III:5) presented with DCM, and 4 patients (P1:II:3, P1:II:7, P1:III:3, P1:III:5) suffered from torsades de pointes–related cardiac syncope. The proband (P1:II:3) was a 64-year-old woman diagnosed with DCM 7 years ago. Her QTc was >600 ms on repeated 12-lead electrocardiograms (ECGs) and in the absence of a secondary cause of QT prolongation. She suffered from cardiac syncope 4 times and was treated with an ICD.

A reported definitive pathogenic heterozygous variant, *KCNE1*-p.Ala8Val, and a novel pathogenic heterozygous variant, *SGCD*-p.Gln282Arg, were identified in the proband.

Table 3 Pathogenic *LMNA* variants identified in sporadic or familial patients

Mode	Sex	Age* (y)	Arrhythmia type	Cardiomyopathy Type	LVEDd (mm)	LAD (mm)	LVEF (%)	IVSd (mm)	LVPWd (mm)	CS	PM/ ICD	Protein change	Coding change	ExAC Total	ExAC East Asian
P3:II:3	F	53	AF, bradycardia	DCM	55	43	58	9	9	Y	Y	p.Pro485fs	c.1446_1447insT	Novel	Novel
P3:II:5	F	50	AF, bradycardia	DCM	59	42	55	9	9	Y	Y	p.Pro485fs	c.1446_1447insT	Novel	Novel
P3:III:4	M	25	AF	DCM	59	40	60	9	9	N	N	p.Pro485fs	c.1446_1447insT	Novel	Novel
P4:II:4	F	60	AF, bradycardia	DCM	55	35	56	9	9	Y	Y	p.Arg419fs	c.1249_1249delA	Novel	Novel
P4:II:8	F	44	AF, bradycardia	DCM	55	34	54	10	10	Y	Y	p.Arg419fs	c.1249_1249delA	Novel	Novel
P5:I:2	F	69	VF, VT	DCM	62	42	35	10	10	Y	Y	p.Arg571Cys	c.1711C>T	5.7×10^{-5}	1.6×10^{-4}
P5:II:1	M	44	VF, VT	DCM	56	40	58	9	9	Y	N	p.Arg571Cys	c.1711C>T	5.7×10^{-5}	1.6×10^{-4}
P6:III:1	F	45	AF	DCM	59	42	47	9	10	N	N	p.Arg190Trp	c.568C>T	Novel	Novel
P6:III:6	M	39	AF	DCM	53	39	29	8	8	N	N	p.Arg190Trp	c.568C>T	Novel	Novel
Sporadic	F	49	AF	DCM	55	45	45	9	9	N	N	p.Arg190Trp	c.568C>T	Novel	Novel
P7:II3	F	68	AVB	DCM	52	43	49	10	10	Y	Y	p.Arg321Ter	c.961C>T	Novel	Novel
P7:III:2	M	45	AVB	DCM	54	35	55	10	9	Y	N	p.Arg321Ter	c.961C>T	Novel	Novel
P7:III:3	F	38	AVB	DCM	53	33	58	9	9	N	N	p.Arg321Ter	c.961C>T	Novel	Novel
P8:II:1	M	24	AF, AVB, VT	DCM	55	35	28	9	9	Y	N	p.Ser94Pro	c.280T>C	Novel	Novel
Sporadic	M	52	—	DCM, LVNC	54	40	45	10	10	N	N	p.Arg225Ter	c.673C>T	Novel	Novel
P14:II:6	F	55	AF, bradycardia	—	45	34	60	9	9	Y	Y	p.Trp498Ter	c.1494G>A	Novel	Novel
Sporadic	M	49	AF, AVB, VT	DCM	58	43	37	9	9	Y	Y	p.Ala9fs	c.21_22delGC	Novel	Novel
Sporadic	M	41	VT	DCM	60	45	40	9	9	Y	Y	p.Leu59Pro	c.176T>C	Novel	Novel
Sporadic	M	41	AF, VF, VT,	DCM	63	43	36	11	10	Y	N	p.Arg349Trp	c.1045C>T	Novel	Novel

AVB = atrioventricular block; LVNC = left ventricular noncompaction; VF = ventricular fibrillation; VT = ventricular tachycardia.
*Age at DCM diagnosis.

Previous case reports and functional studies demonstrated that *KCNE1*-p.Ala8Val was responsible for LQTS type 5.[19–22] The *KCNE1*-p.Ala8Val specifically disrupted *hERG* 1b function and reduced cardiac I_{Kr}, which represent a potential mechanism underlying inherited LQTS.[19,22] We found that the 2 variants cosegregated independently in the pedigree. Three patients (P1:II:3; P1:III:3, P1:III:5) had both variants and had similar clinical features. Patient P1:III:4 had only the heterozygous *SGCD*-p.Gln282Arg variant, presented with a normal QTc, and did not have a history of syncope. Patient P1:III:7 had only the heterozygous *KCNE1*-p.Ala8Val variant. Her QTc was ≥500 ms on repeated 12-lead ECGs, and she had experienced 3 cardiac syncopes. Echocardiography showed normal chamber size in this patient.

Pedigree 2: LQTS-DCM

In this pedigree, 4 family members (P2:II:4, P2:II:6, P2:III:4, P2:III:5) presented with DCM (Figure 1). Both parents (P2:II:6, P2:II:7) suffered from SCD at approximately 40 years. The mother (P2:II:7) had a history of cardiac syncope. Echocardiography showed she had a normal chamber size. The proband's QTc was >500 ms on repeated ECGs and in the absence of a secondary cause of QT prolongation.

We identified a reported definitive LQTS pathogenic heterozygous variant, *KCNJ5*-p.Gly387Arg,[23,24] and a novel heterozygous likely pathogenic DCM variant, *TNNT2*-p.Arg149His, in the proband. Two patients (P2:II:4; P2:III:5) had only the *TNNT2*-p.Arg149His variant and presented with DCM having normal ECG features. We speculate that the proband inherited the *KCNJ5*-p.Gly387Arg variant from his mother and the *TNNT2*-p.Arg149His variant from his father.

Pathogenic variants in *LMNA*

Previous repeated studies revealed that DCM patients carrying pathogenic *LMNA* variants present with a high risk for arrhythmias.[25] In the 1232 sporadic DCM patients, we identified 3 previously reported definitive *LMNA* pathogenic variants and a novel pathogenic variant **(PVS1+PS4+PM4)** in 4 of 470 sporadic DCM-A patients with explicit arrhythmia (AF, AVB, ventricular fibrillation, ventricular tachycardia), respectively. In these 4 patients, we did not identify extra pathogenic arrhythmia-causative variants or pathogenic DCM-related variants. We also identified a reported definitive *LMNA* pathogenic variant in a 52-year-old male DCM-NA patient without arrhythmia ($P = .006$). By pedigree analysis, we identified pathogenic *LMNA* variants in 6 DCM families with explicit arrhythmia (pedigrees 3–8; Table 3, Supplemental Figure S1, and Supplemental Results).

CNV identification

We analyzed the potential pathogenic copy number variations (CNVs) in all DCM- and ion channelopathy–related genes by using sequencing data after the CNV workflow. However, no potential pathogenic CNVs were identified after quantitative real-time polymerase chain reaction of the DNA.

Discussion

To our knowledge, this is the first study to comprehensively investigate the genetic basis of arrhythmia in DCM patients. Using strict criteria, in 2 separate large DCM cohorts (550 discovery cohort: 250 DCM-A + 300 DCM-NA; 682 replication cohort: 220 DCM-A + 462 DCM-NA), we identified 23 pathogenic variants in 4.9% (23/470) of DCM-A patients and identified a pathogenic variant in 0.1% (1/762) of DCM-NA patients. Using burden test, we demonstrated that arrhythmia-causative pathogenic variants play an important role in arrhythmia in DCM (DCM-A) ($P = 2.16 \times 10^{-9}$). In pedigree analysis, we identified definitive pathogenic LQTS variants in 2 extra DCM-LQTS families and found they cosegregated independently with the DCM-causative variants in the pedigrees. This evidence supports our hypothesis 1. Some arrhythmias in DCM patients have an explicit DCM-independent genetic basis in arrhythmia-caused genes and probably increase the risk of SCD (DCM and arrhythmia: ≥2 genetic causes).

Similar to previous studies,[8,15,17,18] we identified more pathogenic *LMNA* variants responsible for both DCM and arrhythmia (AVB, AF, ventricular tachycardia) phenotypes in sporadic DCM-A cohorts than in DCM-NA cohorts ($P = .006$). We also identified pathogenic variants in 6 unrelated compounded phenotype pedigrees. This evidence supports our hypothesis 2.Some arrhythmias in DCM can be explained by a single DCM-related genetic variant (eg, *LMNA* mutations) (DCM and arrhythmia: 1 genetic cause).

For DCM patients with late-onset AF or LQTS, we identified 4 "hotspot" reported pathogenic variants (*KCNA5*-p.Ala576Val,[26] *KCNA5*-p.Thr527Met,[26–28] *KCNE2*-p.Arg27Cys, *KCNJ5*-p.Gly387Arg[24,29]). Interestingly, unrelated DCM patients were positive for the same pathogenic variants. To investigate where these shared pathogenic variants come from, we performed haplotype analysis flanking the targets. Finally, geographic and haplotype analyses suggest that these "hotspot" pathogenic variants are founder mutations. The different carriers may inherit them from a same recent ancestor.

The *KCNA5*-p.Thr527Met was identified as a pathogenic variant in 2 unrelated families with AF and 4 unrelated sporadic AF patients.[26–28] In these 3 investigations, repeated functional studies demonstrated a consistent loss-of-function effect of mutant *KCNA5* proteins on the ultrarapid activating delayed rectifier potassium currents, which links the mutation to AF and LQTS.[26–28] In our study, we identified this variant in 2 unrelated AF DCM-A patients and 2 unrelated LQTS DCM-A patients (average age of onset ~50 years) (Table 2). We also identified a 38-year-old *KCNA5*-p.Thr527Met carrier in the DCM-NA cohort. We speculate that this patient may develop AF in the future **(PS3+PS4+PP1+PP3+PP5).**

The *KCNE2*-p.Arg27Cys variant was reported as a pathogenic variant for AF in different families and repeated functional studies.[29–31] It has a gain-of-function effect on the *KCNQ1-KCNE2* channel and induces familial AF partially by enhancing the suppression of L-type Ca^{2+} current.[29–31]

We identified the *KCNE2*-p.Arg27Cys variant in 5 unrelated AF DCM-A patients (average age of onset ~55 years) **(PS3+PS4+PP3+PP5)**.

The *KCNJ5*-p.Gly387Arg variant was reported as a pathogenic variant for LQTS on the basis of multiple pedigree cosegregation analysis and repeated functional studies.[23,24] Yang et al[24] and Wang et al[32] studied a large 4-generation Chinese family segregating autosomal dominant LQTS. The 62-year-old proband manifested as LQTS and persistent AF. In the pedigree, 9 p.G387R positives also manifested as LQTS, and AF was also observed in 3 of them. Two younger p.G387R-positives were asymptomatic family members, indicating incomplete penetrance or age just too young to onset. Kokunai et al[23] identified this mutation in an unrelated 35-year-old man with hypokalemic periodic paralysis and LQTS. The *KCNJ5*-p.Gly387Arg caused a loss-of-function electrophysiological phenotype resulting from reduced plasma membrane expression, therefore inhibiting inwardly rectifying potassium channels **(PS3+PS4+PP1+PP3+PP5)**.[23,24] We identified this variant in a sporadic DCM-LQTS patient, a DCM-LQTS pedigree (pedigree 2), and 2 sporadic AF patients. Interestingly, we found that some patients who had the same causative variants developed overlapping syndromes of both AF and LQTS phenotypes (Table 2). These kinds of conditions have previously been reported; however, the potential mechanism is not yet clear.[33–35]

These arrhythmia-causative variants, either inherited from a previous generation or occurring as *de novo* variants, can be transmitted in the pedigree and further impact the clinical phenotype of DCM. SCD risk factor stratification models for DCM patients currently do not consider specific arrhythmia-causing genetic factors (ie, ion channelopathy–causative gene) or *LMNA* sequencing.[8] Because high-throughput next-generation sequencing is increasingly more powerful and available, we suggest that in DCM families with malignant arrhythmias, DCM-causative genes as well as other arrhythmia-causative genes should be screened (ie, full next-generation sequencing arrhythmia panels). Importantly, incorporating the arrhythmia-causative variant into an SCD risk factor stratification model may increase the accuracy of SCD prediction.

Study limitations

Lack of patients with a multiple ethnic background in our current study due to the geographic locations of the 3 medical centers is a limitation of this study. Therefore, our results represent only Han Chinese patients.

Clinical implications

Patients with DCM have significant risk for arrhythmic death. DCM may develop into an arrhythmogenic substrate itself, but other genetic factors may contribute as well. Additional screening of arrhythmia-susceptibility genes is warranted in DCM families with arrhythmias.

Conclusion

In this initial investigation of the genetic etiology of arrhythmia in DCM, ≈5% of arrhythmias is associated with specific pathogenic variants. This study highlighted the value of targeted sequencing in arrhythmia-causative genes and *LMNA* for future SCD risk factor stratification and genetic counseling for patients with DCM.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.09.012.

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