Filamin-C variant-associated cardiomyopathy: A pooled analysis of individual patient data to evaluate the clinical profile and risk of sudden cardiac death

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BACKGROUND Mutations in filamin-C (FLNC) are involved in the pathogenesis of arrhythmogenic cardiomyopathy (ACM) and dilated cardiomyopathy (DCM), and have been associated with a left ventricular (LV) phenotype, characterized by nonischemic LV fibrosis, ventricular arrhythmias, and sudden cardiac death (SCD).

OBJECTIVE The purpose of this study was to investigate the prevalence of FLNC variants in a gene-negative ACM population and to evaluate the clinical phenotype and SCD risk factors in FLNC-associated cardiomyopathies.

METHODS ACM probands who tested negative for mutations in ACM-related genes underwent FLNC genetic screening. Clinical and genetic data were collected and pooled together with those of previously published FLNC-ACM and FLNC-DCM patients.

RESULTS In a cohort of 270 gene-elusive ACM probands, 12 (4.4%) had FLNC variants, and 13 additional family members carried the same mutation. Eighteen FLNC variant carriers (72%) had a diagnosis of ACM (72% male; mean age 45 years). On pooled analysis, 145 patients with FLNC-associated cardiomyopathies were included. Electrocardiographic (ECG) low QRS voltages were detected in 37%, and T-wave inversion (TWI) in inferolateral/lateral leads in 24%. Among 67 patients who had cardiac magnetic resonance (CMR), LV nonischemic late gadolinium enhancement (LGE) was found in 75%. SCD occurred in 28 patients (19%), 15 of whom showed LV nonischemic LGE/fibrosis. Compared with patients with no SCD, those who experienced SCD more frequently had inferolateral/lateral TWI (P = .013) and LV LGE/fibrosis (P = .033).

CONCLUSION Clinical phenotype of FLNC cardiomyopathies is characterized by late-onset presentation and typical ECG and CMR features. SCD is associated with the presence of LV LGE/fibrosis but not with severe LV systolic dysfunction.

KEYWORDS Arrhythmogenic cardiomyopathy; Cardiac magnetic resonance; Dilated cardiomyopathy; Filamin-C; Sudden cardiac death

Introduction

Arrhythmogenic cardiomyopathy (ACM) is a rare inherited heart muscle disease characterized by myocardial scar, systolic right ventricular (RV) and/or left ventricular (LV) dysfunction, and malignant ventricular arrhythmias (VAs).1–3 The hallmark of ACM is the replacement of ventricular myocardium by fibrofatty tissue, which progresses over time.1–3 Approximately one-half of ACM patients harbor genetic variants in genes encoding major components of the cardiac desmosomes, although mutations in nondesmosomal genes have been also described in association with ACM.3,4 Among them, mutations in gene
encoding filamin-C (\textit{FLNC}), traditionally linked to myofibrillar myopathy (MIM\#609524) and hypertrophic cardiomyopathy (MIM\#617047), are raising particular interest given their possible involvement in the pathogenesis of a peculiar LV phenotype, characterized by extensive nonischemic LV fibrosis, life-threatening VAs, and sudden cardiac death (SCD).\textsuperscript{7–10} This FLNC-associated phenotype combined with the cellular function of the protein, which serves as a structural actin cross-linker between sarcomeric Z-disc and sarcolemma, is increasingly recognized as a blend of dilated cardiomyopathy (DCM) and ACM.\textsuperscript{9,10} Notwithstanding, the presence of \textit{FLNC} variants in the context of a largely fibrotic LV seems to have significant implications for treatment of these patients, because their arrhythmic and SCD risk seem unrelated to the degree of systolic dysfunction.\textsuperscript{5,9,10}

Here we present a genotype-phenotype study focused on \textit{FLNC} variants, with the aim of reporting their prevalence in our ACM population from a tertiary referral hospital. Moreover, by pooling individual patient data from the published series of \textit{FLNC}-related ACM/DCM, we aimed to characterize their clinical phenotype, arrhythmic outcome, and SCD risk factors.

### Methods

#### Study population and cardiomyopathy evaluation

This is an observational, single-center, retrospective study from the Clinical Genetic Center of Arrhythmic Cardiomyopathies, University Hospital of Padua, Italy. All patients provided written informed consent before inclusion in the study, in accordance with the protocol approved by the regional ethics committee. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Of all consecutive index cases who tested negative for likely pathogenic/pathogenic mutations in ACM-related genes, we reanalyzed the DNA searching for genetic variants in \textit{FLNC}. All of these patients were referred to our tertiary center between January 2011 and January 2021 and had a definite, borderline, or possible diagnosis of ACM according to the 2010 Task Force diagnostic criteria.\textsuperscript{11} A reclassification according to the recently published ACM 2020 Padua Criteria was also performed, particularly in the presence of biventricular or left-dominant phenotypic variants.\textsuperscript{12}

Detailed clinical evaluation included medical and family history, 12-lead electrocardiogram (ECG), 24-hour ambulatory ECG, 2-dimensional transthoracic echocardiogram, and cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE). Technical equipment and protocols of each routine investigation have been reported in detail elsewhere.\textsuperscript{13,14} When appropriate, genetic testing and clinical phenotyping were extended to consenting family members.

In the setting of SCD and/or heart transplantation, the heart was studied according to the Guidelines of the Association for European Cardiovascular Pathology.\textsuperscript{15}

### Search strategies and selection criteria

Electronic search engines included PubMed/Medline and Scopus for the following search keyword strings: (filamin-c) OR FLNC AND arrhythmogenic cardiomyopathy and (filamin-c) OR FLNC AND dilated cardiomyopathy. Other keyword strings also were tested: (filamin-c) OR FLNC AND ARVC/D, (filamin-c) OR FLNC AND ARVD/C, (filamin-c) OR FLNC AND ACM, (filamin-c) OR FLNC AND AC, (filamin-c) OR FLNC AND DCM. We carefully reviewed reference lists of original publications and review articles for missing studies. Duplicates were eliminated. All studies were filtered independently by 2 reviewers (RC, KP), and occasional disagreements were settled by an additional author (BB).

Only original peer-reviewed articles published since the first description of \textit{FLNC} in 2000\textsuperscript{16} providing accurate phenotypic data of patients with \textit{FLNC} were considered. If the same cohort was reported by multiple studies, only the first study published or the one containing more clinical details was included. If multiple and discordant diagnostic criteria for ACM were applied to the same cohort, then the study was excluded from the analysis. Healthy \textit{FLNC} variant carriers (genotype+/phenotype–) were excluded. Patients with \textit{FLNC}-associated hypertrophic and restrictive cardiomyopathy were not object of this analysis.

### Pooled clinical data analysis

Published individual patient data together with data of our cohort were used for the pooled analyses. Data extracted included demographics, ECG and cardiac imaging (echocardiogram and CMR) characteristics, phenotype diagnosis, arrhythmic history, and outcome. Among ECG characteristics, the presence/absence of low QRS voltages, $V_1$–$V_3$, or inferolateral/lateral T-wave inversion (TWI) were considered only when adequately reported. Among imaging features, RV involvement was considered in the presence of RV criteria for ACM (or when adequately reported) or LV dilatation in the presence of LV end-diastolic diameter $\geq55$ mm by echocardiogram (or when adequately specified). Left ventricular ejection fraction (LVEF) from CMR imaging (or echocardiogram, when CMR was not available) was considered. The phenotype diagnosis (ACM or DCM) was that reported in each study for each patient. Presence of $>500$ premature ventricular beats (PVBs) in 24 hours, sustained ventricular tachycardia, SCD, cardiac death, or cardiac transplantation were considered when adequately reported. SCD composite endpoint included SCD, aborted cardiac arrest, and implanted cardioverter-defibrillator intervention on ventricular fibrillation.

### Allele threshold for variants inclusion

The minor allele frequency threshold to consider a variant clinically relevant was $<0.01\%$, as the estimated prevalence of the disease ranges between 1:2000 and 1:5000. Moreover, we also considered the frequency of the most recurrent ACM variant (PKP2: c.2146-1G>C) and the algorithm proposed...
by Whiffin et al., which estimates the expected frequency of ACM variants at $6.7 \times 10^{-5}$ ($4.1-9.2 \times 10^{-5}$).

### Statistical analysis

Statistical analysis is reported in the Supplemental Methods.

### Results

#### FLNC variants in the Padua cohort

Two hundred seventy gene-elusive ACM index cases with genetic testing detected 12 FLNC rare variants (4.4%) (Table 1), including 7 “radical” variants (4 deletions/insertions, 2 nonsense and 1 splice site variants) classified as pathogenic/likely pathogenic (P/LP), and 5 missense variants (minor allele frequency <0.1%) classified as variants of unknown significance according to American College of Medical Genetics and Genomics recommendations. In order to avoid overestimating genetic variants causality in FLNC, radical variants prevalence was compared in our ACM cohort vs gnomAD control v2.1.1 database, showing 76.55-fold (32.65–178.7, $P < .0001$) enrichment.

Cascade genetic screening was feasible in 5 of the 12 families (Figure 1); 13 of the 24 family members (54%) tested carried a FLNC genetic variant (9 radical variants, FLNC-R; 4 missense FLNC-M). Overall clinical reassessment was performed in 25 FLNC variant carriers (FLNC+: 25/36 [69%]), both index cases ($n = 12$) and relatives ($n = 13$).

#### FLNC variant carriers’ clinical phenotype

FLNC+ index cases had a mean age of 51 ± 16 years (range 17–66 years), and 4 of 12 reported a family history for undefined nonischemic cardiomyopathy (Families A, C, D, L). In Family C, the father’s proband had a nonischemic cardio-myopathy and received an implantable cardioverter-defibrillator for secondary prevention. In family L, the paternal cousin of the proband (Figure 2) underwent cardiac transplantation at age of 34 years due to arrhythmic storm in mildly dilated LV (Figure 3).

#### Table 1. FLNC variants identified in patients of the Padua cohort

| No. | g.DNA | c.DNA | AA change | dbsNP ID | MAF (gnomAD) | ACMG |
|-----|-------|-------|-----------|----------|--------------|------|
| 1   | g.128478819C>G | c.1373C>G | p.Pro658Arg | rs7734005500 | // | VUS |
| 2   | g.128493639 | c.6325A>G | p.Ile2109Val | rs755736125 | ALL:0.002% | VUS |
| 3   | g.128488758 | c.4727C>G | pThr1575Ser | rs737294794 | ALL:0.0016% | VUS |
| 4   | g.128482300C>G | c.2137C>G | p.Pro713Ala | rs771843379 | ALL:0.000402% | VUS |
| 5   | g.128475622G>C | c.595G>C | p.Ala199Pro | // | // | VUS |
| 6   | g.128492728C>T | c.5926C>T | p.Gln1976* | // | // | P |
| 7   | g.128485300 | c.3781G>T | p.Glu1261* | // | // | P |
| 8   | g.128480675_128480676insT | c.1623_1624insT | p.Pro542Serfs*21 | // | // | P |
| 9   | g.128481258_128481262del | c.1848_1852delCAAT | p.Ile616Metfs*2 | // | // | P |
| 10  | g.128490538 | c.5398+1G>T | p.? | // | // | P |
| 11  | g.128494689dupG | c.7037dup | p.Leu2347Profs*9 | // | // | P |
| 12  | g.128475403delAAACT | c.376_392delAACCTGA | p.Asn126GlyfsTer20 | // | // | P |

AA = amino acid change; ACMG = American College of Medical Genetics and Genomics classification; c.DNA = coding exon localization; dbsNP = Single Nucleotide Polymorphism Database; FLNC = filamin-C; g.DNA = genomic DNA localization; LP = likely pathogenic; MAF = minor allele frequency; P = pathogenic; VUS = variant of unknown significance.

Detailed clinical and histopathological findings of the FLNC+ probands are given in Table 2 and Supplemental Table 1.

Based on the 2010 Task Force diagnostic criteria, a diagnosis of definite in 4, borderline in 5, and possible in 9 ACMs was achieved, whereas classification according to the 2020 Padua Criteria was right dominant in 4 (22%), left dominant in 10 (56%), and biventricular in 4 (22%).

Because 18 patients fulfilled criteria for ACM diagnosis, the disease penetrance in all FLNC carriers was therefore incomplete and estimated 72% (18/25) and 79% (15/19) in patients older than ≥35 years. As such, we recalculated the allele frequency threshold of FLNC genetic variants using the algorithm of Whiffin et al. and penetrance of about 70%. The estimated threshold for a putative causative FLNC variant in ACM is $4.65 \times 10^{-5}$ (2.84–6.38 $\times 10^{-5}$), which is slightly lower compared to the frequency of desmosomal variants with 30%–50% penetrance.

#### Pooled analysis of patients with FLNC variant ACM- and DCM-associated cardiomyopathy

The initial search identified 51 studies that fully examined patients carrying FLNC variants and affected by ACM and/or DCM. Eight records satisfied the inclusion criteria for analysis (Supplemental Figure 1). Among the 160 FLNC+ carriers identified, 42 patients with a diagnosis of ACM (22 index cases and 20 family members) and 85 with DCM (48 index cases and 37 family members) were included for analysis. Among ACM patients, the diagnosis provided was definite in 11, borderline in 6, and possible in 25. A left-dominant phenotype was described in 28 (67%).

The results of the pooled genotype-phenotype analysis of all FLNC cardiomyopathy patients ($n = 18 + 12$) are given in Table 3 and Supplemental Table 2.

In terms of outcome, the SCD composite endpoint occurred in 28 patients (20%), of whom 6/6 CMR and 9/9 postmortem analyses showed LV nonischemic fibrosis. Compared with patient who did not experience the SCD...
composite endpoint, patients who did more frequently had low QRS voltages ($P = .013$), inferolateral/lateral TWI ($P = .010$), and LV LGE/fibrosis ($P = .033$). Frequent PVBs, LV dilation, and LVEF <35% were not associated with the SCD composite endpoint ($P = .116$, $P = .804$, and $P = .835$, respectively) (Figure 4). Results of univariate and multivariable logistic regression analyses focused on clinical predictors of the SCD composite endpoint are given in Supplemental Table 2.

**FLNC variants protein domains analysis**

In total, 64 unique different variants, 54 radical and 10 missense (Supplemental Table 3), were described in 160 FLNC+ carriers (144 FLNC-R and 16 FLNC-M) for which gene region localization was evaluated (Figure 5 and Supplemental Figure 2). About one-half of these variants (32/64 [50%]) were clustered on the ROD1 domain; the remaining 32 were distributed all along FLNC. Specifically, 11 were localized between N-terminal actin-binding

![Image](https://example.com/image1)

**Figure 1** Pedigrees of families with filamin-C (FLNC) variants. Squares indicate males; circles indicate females; slashes indicate deceased individuals; black symbols indicate in vivo or postmortem diagnosis of FLNC cardiomyopathy; (+/-) indicates heterozygous carrier; arrows indicate the index case in each family.

![Image](https://example.com/image2)

**Figure 2** Electrocardiographic and cardiac magnetic resonance (CMR) features of Family L proband (III:1). A: Basal electrocardiogram showing low voltages in limb leads and flattened T waves in the inferolateral leads. B: Postcontrast CMR images in short-axis view showing normal left ventricular (LV) cavity size and subepicardial late gadolinium enhancement (white arrows) involving the LV inferolateral wall.
domains, 20 on the ROD2 domain, and 1 variant in the C-terminal dimerization domain. Of note, none of the variants was located in the hinge domains, and when considering the length of each domain no significant distribution was observed. Further description of this analysis is given in the Supplemental Results.

Discussion

Only a handful of studies have investigated cardiomyopathy-related FLNC variants in single cases/families and smaller/larger cohorts.\textsuperscript{5–10} However, large-scale studies are totally missing and as such fail to determine specific diagnostic clues associated with a specific disease phenotype (either ACM- or DCM-related). This is the first independent replication study of FLNC rare variants that aimed to pool data from all available studies matching our stringent quality criteria.

The main results of our study are as follows. (1) Novel FLNC variants were detected in about 4% of gene-elusive ACM index cases with late disease onset (after 40 years). (2) The most common ACM disease phenotype was the left-dominant one, identified in more than one-half of FLNC-associated ACM, but right-dominant forms also were also described. (3) The clinical phenotype of patients with FLNC-associated cardiomyopathy was characterized by ECG abnormalities such as low QRS voltages and inferolateral/lateral TWI, frequent and complex VAs, and extensive nonischemic LV LGE/myocardial fibrosis on CMR or postmortem analysis. (4) Risk factors associated with SCD were the presence of ECG inferolateral/lateral TWI and LV LGE/fibrosis, but not LV dilation or severe LV systolic dysfunction.

**FLNC-related cardiomyopathy: prevalence and disease penetrance**

In this study, among 270 genotype-negative ACM index cases, 12 FLNC novel variants (4.4%) were identified (7 radical, 5 variants of unknown significance). This finding, combined with that of other case series reporting FLNC mutations in 3% to 7.5% of gene-elusive ACM patients,\textsuperscript{5,6} confirmed the link between FLNC and ACM, and the possible role of FLNC variants in the pathogenesis of the disease. Filamin C is an actin cross-linking protein localized in the intercalated discs of both cardiac and skeletal muscle cells, which is encoded by a 48-exon gene situated in chromosome 7q32-35.\textsuperscript{18} Its main function is the binding of actin rods in the adherens junction, which are the structures that, together with desmosomes, contribute to maintenance of the cellular integrity and force transduction of tissues exposed to mechanical stress.\textsuperscript{18,19} Mutations in FLNC may affect filamin C protein function and produce adherens junction abnormalities, which, as occurs with abnormal desmosomes,\textsuperscript{1,3} may confer a predisposition over time to

![Figure 3](image-url)
| Family | Index case | Sex | Radical variant | Age (y) | ECG low QRS voltages | ECG TWI V1–V3 | ECG TWI inferolateral/lateral leads | Major arrhythmias/24-h PVB count | Abnormal echo results | CMR LVEF (%) | CMR LV dilation | CMR RVEF (%) | CMR RV dilation | CMR LV LGE | ACM phenotype |
|--------|------------|-----|-----------------|--------|----------------------|--------------|------------------------------------|-------------------------------|---------------------|--------------|----------------|--------------|----------------|------------|---------------|
| A, III-8 | + | M | + | 63 | + | – | + | sVT | + | 45 | – | N* | – | N/A | LD ACM |
| A, III-9 | – | F | + | 68 | – | – | – | – | – | 69 | – | 60 | – | + | LD ACM |
| A, IV-2 | – | F | + | 32 | – | – | – | – | – | 55 | – | 56 | – | – | – |
| A, IV-3 | – | M | + | 31 | – | – | – | 673 | – | 58 | – | 55 | – | + | LD ACM |
| A, IV-4 | – | F | + | 36 | – | – | – | – | – | 55 | – | 52 | – | – | – |
| A, IV-7 | – | M | + | 43 | – | – | – | 1133 | – | 59 | – | 59 | – | + | LD ACM |
| A, IV-8 | – | M | + | 35 | + | + | + | sVT | + | 49 | – | 69 | – | + | LD ACM |
| A, V-2 | – | M | + | 12 | – | – | – | – | – | 60* | – | N* | – | N/A | – |
| B, II-2 | + | M | – | 65 | + | – | – | sVT | + | 70 | – | 43 | – | – | RD ACM |
| B, II-4 | – | M | – | 67 | – | – | – | N/A | – | 65* | – | N* | – | N/A | – |
| B, II-8 | – | F | – | 52 | – | – | – | N/A | – | 71 | – | 65 | – | – | – |
| B, III-1 | – | F | – | 39 | – | – | – | N/A | – | 64* | – | N* | – | N/A | – |
| B, III-2 | – | F | – | 33 | – | – | – | N/A | – | 63 | – | 65 | – | – | – |
| C, II-2 | + | M | + | 17 | N/A | N/A | N/A | SCD | N/A | N/A | N/A | N/A | N/A | N/A | LD ACM |
| C, I-2 | – | M | + | 63 | – | – | – | sVT | – | 52 | – | 56 | – | + | LD ACM |
| D | + | F | + | 66 | – | + | + | Rare | + | 66 | – | 45 | – | – | RD ACM |
| E | + | M | – | 40 | – | + | – | 4439 | + | 60 | – | 16 | + | – | RD ACM |
| F | + | F | – | 43 | – | + | + | Aborted SCD | + | 66 | – | 33 | + | – | BIV ACM |
| G | + | M | + | 57 | – | – | – | nsVT | + | 46 | – | 49 | – | + | BIV ACM |
| H | + | M | – | 56 | + | – | – | sVT | + | 55 | – | 37 | – | – | RD ACM |
| I | + | M | – | 64 | + | + | + | sVT | + | 44 | – | 35 | + | + | BIV ACM |
| L, III-1 | + | M | + | 43 | – | – | – | nsVT | – | 58 | – | 61 | – | – | + | LD ACM |
| L, III-4 | + | M | + | 25 | – | – | + | sVT | + | 30* | + | N* | – | N/A | LD ACM |
| M | + | F | + | 35 | – | + | – | nsVT | + | 39 | – | 56 | – | + | LD ACM |
| N | + | F | + | 42 | + | – | + | nsVT | + | 34 | – | 44 | – | + | BIV ACM |

* + = positive/present; – = negative/absent; ACM = arrhythmogenic cardiomyopathy; BIV = biventricular; CMR = cardiac magnetic resonance; ECG = electrocardiogram; echo = echocardiogram; F = female; FLNC = filamin-C; LD = left dominant; LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; M = male; N = normal; N/A = not available; nsVT = nonsustained ventricular tachycardia; PVB = premature ventricular beat; RD = right dominant; RV = right ventricle; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; sVT = sustained ventricular tachycardia; TWI = T-wave inversion.

*Assessed with echocardiogram.
disruption of intercellular anchoring, eventually leading to myocyte detachment, cell death, and subsequent fibrofatty replacement. Recent experimental data demonstrated the detrimental effects of filamin C loss in morphology and function in FLNC cardiomyocyte-specific knockout models. Based on these findings, it seems reasonable to consider FLNC among causative ACM-related genes to be included in clinical gene panels when ACM is investigated.

Cascade genetic screening performed in 5 families of the Padua FLNC cohort identified 13 more FLNC carriers among family members, 5 of whom fulfilled diagnostic criteria for ACM. Accordingly, ACM disease penetrance was estimated about 70% and was critically age dependent due to a net increase of ACM diagnosis in ≥35-year-old FLNC carriers. As such, FLNC ACM seems to become clinically overt later in lifetime than what it is expected from desmosomal variant carriers (<35 years). This finding has crucial implications in clinical practice because it suggests the need for longer follow-up, especially in family members, to identify disease signs and allow prompt adoption of preventive measures and treatments.

### FLNC variant–associated ACM

We found that the most frequent ACM disease phenotype associated with FLNC variants was the left-dominant phenotype, diagnosed in >50% of FLNC-associated ACM, in keeping with recent studies. FLNC patients from the Padua cohort with left-dominant or biventricular phenotype exhibited nonischemic LGE/fibrosis affecting the subepicardial or midmyocardial layers of the LV free wall at CMR (Figure 2). However, in contrast with recent studies, the so-called “ring-like” pattern, that is, circumferential LGE of the LV free wall and septum in the short-axis view, was observed only in 2 of 11 patients (Family A, IV-8; Family N). This observation together with common identification of a right-dominant ACM phenotype (4/18) in the Padua cohort suggests high variability of FLNC variants in disease expressivity.

Among the 12 living ACM patients with LV disease, 50% did not have LV systolic dysfunction and regional LV wall-motion abnormalities (40% of echocardiographic results were unremarkable). This is a key diagnostic aspect and must be considered when dealing with ACM patients, especially family members. In fact, a limited extent of fibrofatty scars to subepicardial or midmyocardial layers of LV may not be sufficient to alter its regional (and global) function and can be undetectable by echocardiography. For this reason, CMR should be always offered to FLNC+ family members, irrespective of echocardiographic results.

### Clinical phenotype of FLNC variant–associated ACM and DCM

FLNC variants have been linked to extracardiac conditions such as distal and myofibrillar skeletal myopathy and other cardiac disorders. In our study, we focused on the association of FLNC mutations with the wide phenotypic spectrum of ACM, which recognizes not only right-dominant but also biventricular and left-dominant variants. However,

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**Table 3** Demographic and clinical profile of patients with FLNC cardiomyopathy (pooled analysis)

|                         | Overall sample (n = 145) | ACM (n = 60) | DCM (n = 85) | P value |
|-------------------------|--------------------------|-------------|-------------|---------|
| Age (y)                 | 43 ± 16                  | 48 ± 17     | 40 ± 14     | .017    |
| ≥35 y                   | 101 (70)                 | 45 (75)     | 56 (66)     | .274    |
| Male sex                | 89 (61)                  | 40 (67)     | 49 (58)     | .302    |
| Proband                 | 81 (56)                  | 33 (55)     | 48 (57)     | .867    |
| Radical variant         | 133 (92)                 | 49 (82)     | 84 (99)     | <.001   |
| Electrocardiographic characteristics |                      |             |             |         |
| Low (<0.5 mV) QRS voltages in limb leads | 40/109 (37) | 19/46 (41) | 21/63 (33) | .426    |
| TWI in V1–V3 ± V6       | 11/120 (9)               | 9/56 (16)   | 2/66 (3)    | .023    |
| TWI in inferolateral/lateral leads | 29/120 (24) | 19/56 (34) | 10/66 (16) | .032    |
| Arrhythmic history      |                         |             |             |         |
| Frequent PVB (>500/24 h) | 94/119 (79) | 41/53 (77) | 53/66 (80) | .821    |
| Sustained VT            | 30/107 (28)              | 15/53 (28)  | 15/54 (28)  | 1       |
| Cardiac imaging findings |                         |             |             |         |
| LV dilation             | 69/131 (53)              | 15/57 (26)  | 54/74 (73)  | <.001   |
| LVEF (%)                | 42 ± 14                  | 51 ± 11     | 36 ± 12     | <.001   |
| LVEF ≤35%               | 43/137 (29)              | 5/57 (9)    | 38/80 (48)  | <.001   |
| RV involvement          | 36/117 (31)              | 19/57 (33)  | 17/60 (28)  | .689    |
| LV LGE                  | 50/67 (75)               | 38/44 (86)  | 12/23 (52)  | .004    |
| Full heart histopathological analysis |             |             |             |         |
| LV fibrosis             | 11/12 (92)               | 7/7 (100)   | 4/5 (80)    | .217    |
| Outcome                 |                         |             |             |         |
| SCD composite endpoint  | 28 (19)                  | 10 (17)     | 18 (21)     | .498    |
| Cardiac transplantation/heart failure death | 8 (6) | 1 (2) | 7 (8) | .088    |

Values are given as n (%) or mean ± SD unless otherwise indicated.

DCM = dilated cardiomyopathy; VT = ventricular tachycardia; other abbreviations as in Table 2.
these last 2 ACM phenotypes can overlap with that of DCM due to the possible occurrence in both conditions of myocardial scarring, LV systolic dysfunction, and malignant VAs, making differential diagnosis sometimes challenging. For this reason, our pooled analysis included FLNC patients with either ACM or DCM phenotype in order to investigate differences and similarities of clinical features involved in the diagnosis, management, and risk stratification strategies. Our data showed that low QRS voltages on ECG, possibly reflecting loss of viable myocardium, were detected in 37% of FLNC patients. Electrical instability, represented by frequent PVBs and sustained ventricular tachycardia, was frequently observed, with no significant differences between the 2 phenotypes. LV nonischemic myocardial fibrosis evidenced by CMR was common (75%) and was significantly more prevalent in ACM patients. Noteworthy, due to the dominant LV involvement, RV endomyocardial biopsy can be negative in terms of fibrofatty replacement detection but reveals cardiomyopathic changes that are shared by ACM and DCM.

**FLNC and SCD**

SCD events have been frequently reported in studies involving FLNC cohorts. In DCM and ACM populations, SCD occurred as the presenting symptom in 5% of cases and during follow-up in 15% of cases. However, risk factors for SCD have not further investigated. In our

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**Figure 4** Bar chart showing clinical differences in filamin-C (FLNC) cardiomyopathy patients who reached or did not reach the sudden cardiac death (SCD) composite endpoint. LV = left ventricle; LVEF = left ventricular ejection fraction; PVB premature ventricular beat; RV = right ventricle; TWI = T-wave inversion.

**Figure 5** Variants localization in the filamin-C (FLNC) gene.
study, we showed that the detection of low QRS voltages in limb leads, ECG TWI in inferolateral/lateral leads, and LV LGE/fibrosis can help identify FLNC patient at higher risk for SCD. Importantly, as recently demonstrated for patients with desmoplakin mutations, LVEF <35% also seems not to be a marker of higher SCD risk in FLNC patients. Larger multicentric FLNC cohorts are needed to extend and improve SCD risk stratification in these patients.

**Study limitations**

This study is limited by the small number of recruited FLNC missense variant carriers, which in part could be linked to the low frequency of FLNC variants in ACM and DCM populations and to the high genetic heterogeneity that characterizes these disorders. Indeed, variant types and locations were unable to explain phenotypic variability, and cosegregation studies were limited due to the small size of families.

**Conclusion**

FLNC-associated cardiomyopathy is characterized by late onset and mostly left-dominant phenotype. Typical ECG abnormalities consist of low QRS voltages and inferolateral/lateral TWI and frequent and complex VAs. Nonischemic LV scar is detectable by CMR or postmortem analysis. The presence of low QRS voltages in limb leads, inferolateral/lateral TWI, and LV LGE/fibrosis, but not LV dilation or severe systolic dysfunction, is associated with SCD.

**Appendix**

**Supplementary data**

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.09.029.

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