Phenotypic Expression, Natural History, and Risk Stratification of Cardiomyopathy Caused by Filamin C Truncating Variants

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BACKGROUND: Filamin C truncating variants (*FLNCtv*) cause a form of arrhythmogenic cardiomyopathy: the mode of presentation, natural history, and risk stratification of *FLNCtv* remain incompletely explored. We aimed to develop a risk profile for refractory heart failure and life-threatening arrhythmias in a multicenter cohort of *FLNCtv* carriers.

METHODS: *FLNCtv* carriers were identified from 10 tertiary care centers for genetic cardiomyopathies. Clinical and outcome data were compiled. Composite outcomes were all-cause mortality/heart transplantation/left ventricle assist device (D/HT/LVAD), nonarrhythmic death/HT/LVAD, and sudden cardiac death/major ventricular arrhythmias. Previously established cohorts of 46 patients with *LMNA* and 60 with *DSP*-related arrhythmogenic cardiomyopathies were used for prognostic comparison.

RESULTS: Eighty-five patients carrying *FLNCtv* were included (42±15 years, 53% men, 45% probands). Phenotypes were heterogeneous at presentation: 49% dilated cardiomyopathy, 25% arrhythmogenic left dominant cardiomyopathy, 3% arrhythmogenic right ventricular cardiomyopathy. Left ventricular ejection fraction was <50% in 64% of carriers and 34% had right ventricular fractional area changes (RVFAC=(right ventricular end-diastolic area – right ventricular end-systolic area)/right ventricular end-diastolic area) <35%. During follow-up (median time 61 months), 19 (22%) carriers experienced D/HT/LVAD, 13 (15%) experienced nonarrhythmic death/HT/LVAD, and 23 (27%) experienced sudden cardiac death/major ventricular arrhythmias. The sudden cardiac death/major ventricular arrhythmias incidence of *FLNCtv* carriers did not significantly differ from *LMNA* carriers and *DSP* carriers. In *FLNCtv* carriers, left ventricular ejection fraction was associated with the risk of D/HT/LVAD and nonarrhythmic death/HT/LVAD.

CONCLUSIONS: Among patients referred to tertiary referral centers, *FLNCtv* arrhythmogenic cardiomyopathy is phenotypically heterogeneous and characterized by a high risk of life-threatening arrhythmias, which does not seem to be associated with the severity of left ventricular dysfunction.

Key Words: arrhythmogenic right ventricular dysplasia ■ death, sudden, cardiac ■ FLNC protein, human ■ heart failure ■ outcome studies ■ prognosis

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Clinical Perspective

What Is New?

- Filamin C truncating variants (*FLNCtv*) cause a high-risk arrhythmogenic cardiomyopathy with heterogeneous phenotypic presentations.
- Outcome exposure is mainly characterized by life-threatening arrhythmias.
- Left ventricular ejection fraction does not seem to be associated with the risk of life-threatening arrhythmias in carriers of *FLNCtv*

What Are the Clinical Implications?

- Prognostic implications of *FLNCtv* (ie, high risk of life-threatening arrhythmias) support the use of genetic testing, especially in patients with features that are suspicious of an underlying *FLNCtv.*
- Besides left ventricular ejection fraction, alternative cumulative risk factors may aid the risk stratification of *FLNCtv* carriers and the adoption of strategies for the prevention of sudden cardiac death.

Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
ARVC	arrhythmogenic right ventricular cardiomyopathy/dysplasia
D/HT/LVAD	all-cause mortality/heart transplantation/left ventricular assist device
DCM	dilated cardiomyopathy
HF	heart failure
ICD	implantable cardioverter-defibrillator
LV	left ventricle
LVEF	left ventricular ejection fraction
RV	right ventricle
SCD/MVA	sudden cardiac death/major ventricular arrhythmias

Arrhythmogenic cardiomyopathy (ACM) is a genetic disorder characterized by high risks of life-threatening ventricular arrhythmias, sudden cardiac death (SCD), and progressive heart failure (HF).[1,2] The expression of ACM encompasses a wide phenotypic spectrum ranging from classical dilated cardiomyopathy (DCM) to typical arrhythmogenic right ventricular cardiomyopathy (ARVC) with frequently overlapping features.[2–5] Truncating variants in the filamin C gene (*FLNCtv*) have recently been found to cause ACM with high penetrance, variable phenotypic presentation, and prominent ventricular arrhythmias.[6–9] *FLNC* encodes a striated muscle protein that cross-links actin and anchors cell membrane proteins to the cytoskeleton, sarcolemma, and sarcomere Z-disk.[10,11] The clinical spectrum of *FLNCtv* ACM remains incompletely defined and the natural history and prognosis are largely unexplored. In this study, we analyzed longitudinal clinical data from a large multicenter cohort of *FLNCtv* carriers to define the clinical features of *FLNCtv*-related cardiomyopathy and the correlations between genotype and phenotype. Factors associated with adverse outcomes were determined to inform on the risk stratification of *FLNCtv* carriers.

METHODS

International *FLNCtv* Registry

The records of patients with *FLNCtv* were collected from 10 international tertiary care centers with expertise in the management of inherited cardiomyopathies: University Hospital of Trieste, University of Colorado Cardiovascular Institute, Victor Chang Cardiac Research Institute, Utrecht and Amsterdam University Medical Centers, Brigham and Women's Hospital, University Hospital of Udine, Johns Hopkins University, Stanford Center for Inherited Cardiovascular Disease, and National Center for Cardiovascular Diseases in Beijing. Data were anonymized and stored in a shared database to create an International Registry of patients with *FLNCtv.* Institutional review boards approved the study and informed consent was obtained under the institutional review board policies of the hospital administration. Demographic, clinical, imaging, and genetic data were retrospectively analyzed by each participating center. To minimize the possibility of unintentionally sharing information that can be used to reidentify private information and considering the different institutional review board policies of the participating centers, the data sets generated for this study will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The authors declare that all supporting methods are available within the article (and in the Supplemental Material).

Molecular Genetics and Definition of Genetic Variants

Genetic testing was done through the participating sites by Next Generation and Sanger sequencing in a clinical or research laboratory. Variants were classified as pathogenic or likely pathogenic according to the American College of Medical Genetics criteria[12] (Table S1). To maintain a conservative approach, only pathogenic and likely pathogenic truncating variants were considered, whereas missense variants and variants of uncertain significance were excluded from the analysis. Probands and available family members who were carriers of pathogenic or likely pathogenic *FLNCtv* were included in the registry. Additional variants of interest inherent to other cardiomyopathy-related genes were also reported and patients considered as carriers of multiple mutations.

Phenotypic Characterization

Demographic, clinical, and therapeutic information was collected at study entry (baseline) and detailed information on family history of cardiomyopathies and SCD were recorded. Clinical data included HF symptoms (New York Heart Association functional class), history of unexplained syncope at enrollment

(likely secondary to arrhythmic cause), presence of ventricular arrhythmias (SCD, resuscitated cardiac arrest, sustained ventricular tachycardia [VT], and nonsustained ventricular tachycardia [NSVT]), and atrial fibrillation/atrial flutter. Age of onset was defined on the basis of clinical diagnosis. Data from 12-lead ECGs, Holter ECG monitoring, and signal-averaged ECGs were recorded. Late potentials were determined by signal-averaged ECGs as currently recommended by the 2010 revised Task Force Criteria.[13]

Echocardiographic biventricular dimensions and systolic function were assessed at transthoracic echocardiography as currently recommended by international guidelines.[14] Left ventricle (LV) and right ventricle (RV) systolic dysfunction were defined by LV ejection fraction (LVEF) <50% and RV fractional area change (RVFAC=(RV end-diastolic area – RV end-systolic area)/RV end-diastolic area) <35%, respectively. For the subgroup of patients with available cardiac magnetic resonance (CMR) images, we analyzed the presence, localization (LV, RV, or biventricular), distribution (septal, inferoposterolateral, or both), and pattern (midwall, subepicardial, or both) of late gadolinium enhancement (LGE).

On the basis of their presenting phenotypes, patients with *FLNCtv* were classified into 6 mutually exclusive phenotypic categories on the basis of current international consensus guidance[2]: DCM, ARVC (definite, borderline, or possible), arrhythmogenic left dominant cardiomyopathy (ALVC), biventricular ARVC, minor phenotype, and unaffected. The DCM phenotype was defined by a LVEF <50% in the absence of any known possible cause of LV dysfunction[15]; ARVC phenotype was defined according to the 2010 Task Force Criteria[13]; ALVC phenotype was defined as DCM presentation not fulfilling Task Force Criteria for ARVC and with ≥1 of the following: SCD/major ventricular arrhythmias (MVA; resuscitated cardiac arrest, sustained VT, appropriate implantable cardioverter defibrillator [ICD] interventions), unexplained syncope, ≥1000 premature ventricular contractions/24 h, ≥50 couplets/24 h[2,3]; biventricular ARVC was defined as definite ARVC plus LVEF <50%.[2] Patients with isolated or multiple pathological findings insufficient to fulfill the criteria for any of the phenotypes defined here were classified as minor phenotype. Last, patients without any cardiac pathological finding were considered unaffected.

Study Outcomes

The study outcomes were as follows: (1) all-cause mortality/heart transplantation/left ventricular assist device implantation (D/HT/LVAD); (2) nonarrhythmic death (including HF death and death not attributable to SCD)/HT/LVAD; (3) SCD/MVAs. MVA included ventricular fibrillation, sustained VT (lasting >30 s or with hemodynamic instability), and appropriate ICD interventions (shock or antitachycardia pacing on ventricular fibrillation or sustained VT; SCD/MVA). SCD was defined as witnessed SCD with or without documented ventricular fibrillation, death within 1 hour of acute symptoms, or nocturnal death with no antecedent history of immediate worsening symptoms. In addition, incident bradyarrhythmias (ie, sick sinus syndrome, atrioventricular blocks, permanent pacemaker/ICD implantation for pacing indications) were recorded. The follow-up date for analysis ended at the date of the first outcome or at the last available contact with the patient. A cohort of 46 carriers with pathogenic or likely pathogenic *LMNA* variants and a cohort of 60 carriers with pathogenic or likely pathogenic *DSP* variants from 3 participating centers (University Hospital of Trieste, University of Colorado Cardiovascular Institute, and Brigham and Women's Hospital), representing arrhythmia-prone populations, were used as comparisons.

Statistical Analysis

Variables were expressed as mean±SD, median and interquartile range, or counts and percentage, as appropriate. Comparisons between groups were made by the ANOVA test on continuous variables using the Brown-Forsythe statistic when the assumption of equal variances did not hold or the nonparametric Mann-Whitney *U* test; the χ^2 test or the Fisher exact test were calculated for discrete variables. Two independent linear regression models were used to quantify changes of LVEF at follow-up in the overall cohort and in patients with baseline LVEF≥50% and <50%, respectively. Kaplan-Meier curves for D/HT/LVAD and cumulative incidence function for nonarrhythmic death/HT/LVAD and SCD/MVA were estimated for *FLNCtv* carriers, *LMNA* variant carriers, and *DSP* variant carriers and compared by the log rank test. Because some patients were grouped as families, in all survival analyses we reported *P* values derived from Cox regression models with the family code as a cluster indicator, that is, we used a robust sandwich estimator for the standard error.[16,17]

The univariate Cox model (D/HT/LVAD) and the cause-specific Cox model (nonarrhythmic death/HT/LVAD and SCD/MVA) were used to assess the association between LVEF and the outcomes. A restricted cubic spline transform (*termplot* function from the R survival package) was used when the association between LVEF and the outcome was nonlinear. To avoid bias attributable to baseline characteristics missing not at random, multiple imputation (n=5) was performed using predictive mean matching (*mice* package). A *P* value <0.05 was considered statistically significant. Statistical analyses were performed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characterization and Mapping of *FLNC* Truncating Variants

The study included 85 carriers of *FLNCtv* from 49 families (see Table S1 for the complete list of variants and cases contribution for each participating center), of whom 38 (45%) were probands. *FLNCtv* variants included nonsense variants, splice site variants, and insertion/deletion (indel) variants that resulted in downstream premature stop codons. The percentage of variants distribution is reported in Table 1. As shown in Figure 1, variants were distributed throughout the protein, with an apparent cluster in the Z-disk interacting region (Ig-like 19–21) of the rod domain 2. Two patients (2.4%) had additional pathogenetic/likely pathogenetic variants on different genes than *FLNC* (*TTN c.76115_76116insA, p.Asn25372Lysfs*5, and PPA2 c.514G>A, p.(Glu172Lys)*; see Table S1).

Table 1. Baseline Clinical Characteristics of the Overall Cohort of *FLNC*-Truncating Mutations Carriers and Divided According to Proband Status

Baseline characteristics	Total n=85	Probands n=38 (45%)	Nonprobands n=47 (55%)	*P* value
Age, y	42±15	40±14	44±16	0.163
Male, % (n)	53 (45)	63 (24)	45 (21)	0.090
White, % (n)	99 (84)	97 (37)	100 (47)	0.263
Variant mapping, % (n)				0.822
Active binding domain	6 (5)	5 (2)	6 (3)	0.866
ROD1	47 (40)	53 (20)	43 (20)	
ROD2	44 (37)	40 (15)	47 (22)	
Z-disk	18 (15)	18 (7)	17 (8)	
Dimerization	4 (3)	3 (1)	4 (2)	
Family history cardiomyopathy, % (n)	81 (69)	61 (23)	100 (46)	<0.001
Family history sudden cardiac death, % (n)	52 (44)	34 (13)	66 (31)	0.004
Phenotype, % (n)				0.016
Dilated cardiomyopathy	49 (42)	53 (20)	47 (22)	
Arrhythmogenic right ventricular cardiomyopathy	3 (3)	3 (1)	4 (2)	
Arrhythmogenic left-dominant cardiomyopathy	25 (21)	37 (14)	15 (7)	
Biventricular arrhythmogenic right ventricular cardiomyopathy	1 (1)	3 (1)	0 (0)	
Minor phenotype	11 (9)	5 (2)	15 (7)	
Unaffected	11 (9)	0 (0)	19 (9)	
Creatine phosphokinase, U/L	80 (55–121)	75 (55–139)	94 (50–119)	0.713
Heart rate, bpm	72±21	73±21	71±21	0.567
Atrial fibrillation, % (n)	4 (3)	5 (2)	2 (1)	0.219
Left bundle-branch block, % (n)	8 (7)	8 (3)	9 (4)	0.871
NYHA class III or IV, % (n)	18 (15)	22 (8)	15 (7)	0.424
NYHA class I, % (n)	68 (57)	62 (23)	72 (34)	0.321
Negative anterior T waves, % (n)	21 (18)	39 (15)	7 (3)	<0.001
Premature ventricular complexes/24 h	3194±5443	4581±6913	1806±2994	0.108
Premature ventricular complexes>1000/24 h, % (n)	45 (18)	55 (11)	35 (7)	0.204
Positive late potentials, % (n)	8 (7)	5 (2)	11 (5)	0.370
Nonsustained ventricular tachycardia, % (n)	48 (28)	61 (19)	33 (9)	0.034
Echo LVEF, %*	43±15	33±14	51±12	<0.001
Echo LVEF <50, % (n.)	64 (52)	89 (33)	43 (19)	<0.001
Echo LVEF ≤35, % (n)	31 (25)	56 (21)	9 (4)	0.046
Echo left ventricular end-diastolic volume, mm	57±10	62±8	52±9	<0.001
Echo maximum wall thickness, mm	9±2	10±1	9±2	0.446
Echo left ventricular hypertrophy, %	11	6	14	0.270
Echo right ventricle fractional area change, %*	38±11	35±12	40±9	0.083
Echo right ventricle fractional area change <35, % (n)	34 (17)	46 (11)	23 (6)	0.090
Echo right ventricle wall motion abnormalities, % (n)	8 (4)	16 (4)	0 (0)	0.031
Echo mitral regurgitation, % (n)	44 (33)	58 (19)	33 (14)	0.036
Cardiac magnetic resonance late gadolinium enhancement, % (n)†	53 (23)	61 (8)	56 (14)	0.738
β-Blockers, % (n)	64 (52)	89 (31)	46 (21)	<0.001
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/ angiotensin receptor neprilysin inhibitors, % (n)	57 (46)	80 (28)	39 (18)	<0.001
Implantable cardioverter defibrillator, % (n)	14 (11)	20 (7)	9 (4)	0.152
Implantable cardioverter defibrillator at follow-up, % (n)	48 (39)	57 (21)	41 (18)	0.155

Values are reported as mean±SD, median and interquartile range, or percentage as appropriate. Echo indicates echocardiographic; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

*Missing data for LVEF=4 (5%), missing data for right ventricle fractional area change=35 (41%).

†Among the 43 patients with available cardiac magnetic resonance.

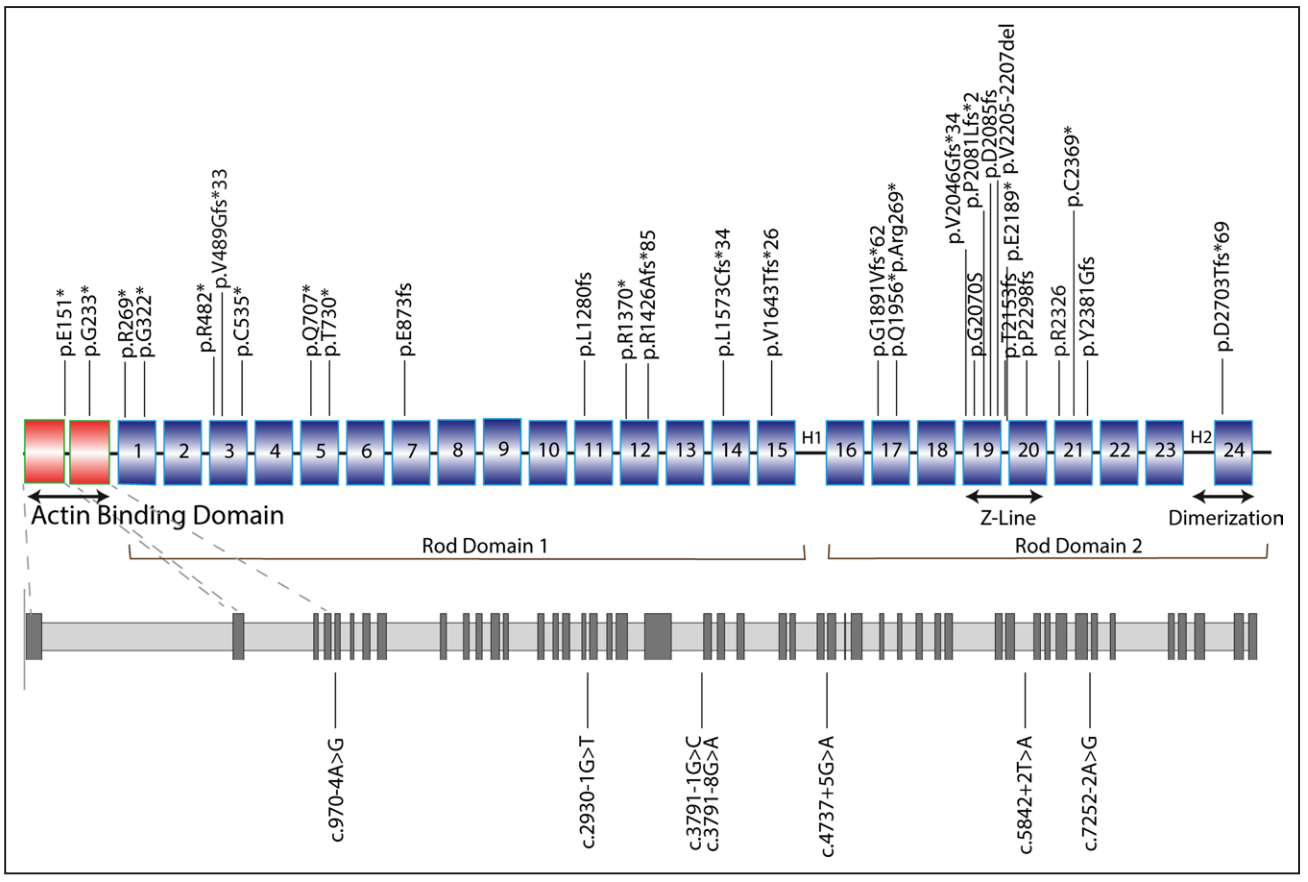

Figure 1. Mapping of *FLNCtv* variants.
Diagrams representing the structure of FLNC and the distribution of *FLNCtv* variants. *FLNCtv* were distributed across all gene and protein domains. However, clusters were noted in the actin binding domain (ABD domains 1 and 2) and in the Z-disk region (Ig-like 19–21) of the rod domain 2. Nonsense mutations and insertion/deletion (indel) variants are indicated in the upper scheme; splice site mutations in the lower (gray) scheme. 1 to 24 indicate Ig-like domains; and H1 and H2, hinge domains.

Spectrum of Phenotypes in *FLNCtv* Cardiomyopathy

Table 1 shows the baseline characteristics of probands and relatives. Mean age at enrollment was 42±15 years (3 patients were <18 years of age: 12 months, 14 months, and 14 years, respectively), 53% were male, 99% were European ancestry. The most frequent phenotype at presentation was DCM (42 carriers, 49%) followed by ALVC (21 carriers, 25%), and ARVC (3 carriers, 3%). Nine *FLNCtv* carriers from 5 families (mean age 45±17 years, 67% males) were unaffected (11%). There were no differences in age (43±15 versus 42±16 years, P=0.854) and sex (male 51% versus 70%, P=0.250) between affected and unaffected individuals. Thirty-two percent of subjects had HF-related symptoms (New York Heart Association class >I), and 22% had a history of syncope. Negative anterior T waves (V_1 through V_4) were found in 21% of carriers; 48% had NSVT. Atrial fibrillation/atrial flutter at baseline was present in 4% of the study cohort. No skeletal muscle involvement was reported.

Mean LVEF and RVFAC were 43±15% and 38±11%, respectively; 64% of carriers had LVEF <50% and 34% had RVFAC <35%. Four carriers were missing data for LVEF (5%) and 35 were missing data for RVFAC (41%). Figure 2 shows the distribution of RV and LV dysfunction at enrollment among the 50 patients with both LVEF and RVFAC data available. Eleven (22%) subjects presented with biventricular dysfunction: 6 (12%) with isolated RV dysfunction, 19 (38%) with isolated LV dysfunction, and 14 (28%) with preserved biventricular function. Mild LV hypertrophy was found in 11% of cases. Baseline therapy included 64% of carriers on β-blockers, and 57% on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. In 14% of the cohort, ICDs were already implanted at the time of entry into the study, whereas a total of 48% had ICDs by the end of follow-up.

As shown in Table 1, probands compared with relatives presented significantly more negative anterior T waves, NSVT, and pathological echocardiographic findings. They were also more likely to be treated with antineurohormonal drugs. Last, phenotype presentation did not significantly differ according to *FLNCtv* variant location (Table S2).

CMR Patterns of *FLNCtv*

There were 43 (51%) *FLNCtv* carriers with available CMR studies, of which 23 (53%) had evidence of LGE

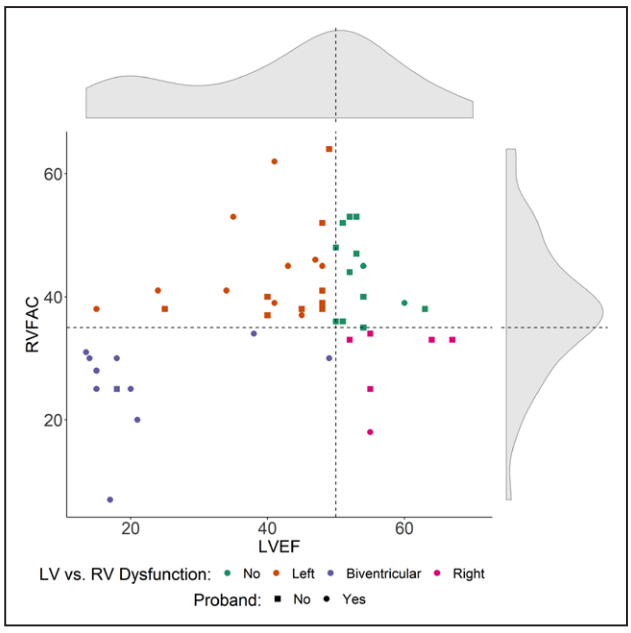

Figure 2. Distribution of right and left ventricular function in *FLNCtv* carriers.
The *FLNCtv* population showed a wide distribution of RV and LV dysfunction. Dashed lines mark the cutoffs defining LV dysfunction (LVEF<50%) and RV dysfunction (RVFAC<35%). LV indicates left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; and RVFAC, right ventricle fractional area change.

with no differences between probands and family members (44% versus 56%, *P*=0.738). Figure 3A shows the CMR features of a *FLNCtv* carrier (proband, male, 48 years of age) in the early stage of disease (CMR LVEF=54%), with subepicardial ringlike LGE indicated by the arrows. Figure 3B reports the characteristics of LGE location, distribution, and pattern in the CMR subgroup. All except 1 case had LV involvement, with the most frequent area of LGE signal distribution being the inferoposterolateral wall (12/23, 52% of LGE positive) and the most frequent LGE pattern was subepicardial (11/23, 48% of LGE positive).

Variable Longitudinal Echocardiographic Trends at Follow-Up

Echocardiographic measures at follow-up (median, 66 months; interquartile range, 19–126) were available in 68 carriers (80%) and are summarized in Table 2. At last follow-up, mean LVEF was 44±14% and mean RVFAC was 41±9%. As shown in Figure S1, in both the groups of patients with LVEF ≥50% and LVEF <50% at baseline, no significant mean change was observed during follow-up (coefficient of monthly mean change: −0.01 [95% CI, −0.06 to 0.03]; *P*=0.5 and −0.04 [95% CI, −0.11 to 0.02], *P*=0.2, respectively).

Study End Points and Prognostic Stratification

Over a median follow-up of 61 months (interquartile range, 10–139), 19 carriers (15 probands, 4 nonprobands, 22% of the total cohort) experienced D/HT/LVAD (11 deaths, 3 HT, 5 LVAD; median age 54; range, 47–66), 13 (10 probands, 3 nonprobands, 15% of the total cohort) nonarrhythmic death/HT/LVAD (5 deaths, 3 HT, 5 LVAD; median age 51; range, 48–61), and 23 (15 probands, 8 nonprobands, 27% of the total cohort) SCD/MVA (6 SCD, 6 sustained VT/ventricular fibrillation, 11 ICD interventions; median age 48; range, 44–60).

Table 3 reports the main baseline characteristics of the study patients according to outcomes. Compared with patients with no outcome, patients experiencing D/HT/LVAD and patients experiencing nonarrhythmic death/HT/LVAD were more likely probands, reported less frequently a familial history of cardiomyopathy, had more severe symptoms, lower LVEF and larger LV end-

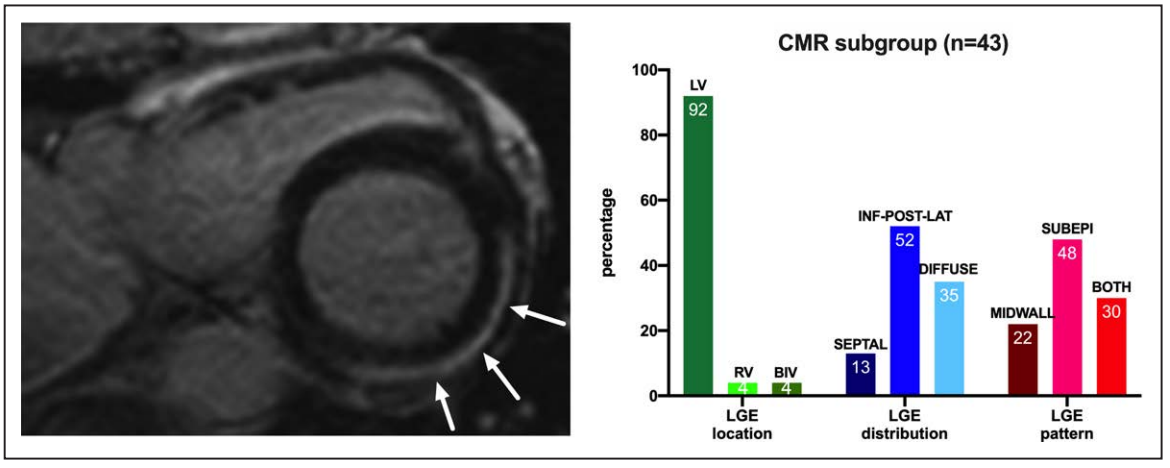

Figure 3. Characteristics of LGE in carriers of *FLNCtv*.
Left, Typical subepicardial ringlike distribution of LGE in a carrier of *FLNCtv* (male, 48 years of age, LVEF 54%), involving the inferior, posterior, and lateral wall. **Right**, Summary of the distribution of LGE in the 43 *FLNCtv* carriers with available cardiac magnetic resonance (CMR). Percentages are reported within bars. BIV indicates biventricular; INF-POST-LAT, inferoposterolateral; LGE, late gadolinium enhancement; RV, right ventricular; and SUBEPI, subepicardial.

Table 2. Main Echocardiographic Measures at Follow-Up in the Overall Subset of Patients With Available Follow-Up Reassessment and Divided According to Proband Status

Echocardiographic measures	Total n=68	Probands n=28 (57%)	Nonprobands n=21 (43%)	*P* value
Left ventricular ejection fraction, %	44±14	38±14	49±12	0.001
Left ventricular ejection fraction <50, %	57	78	39	0.001
Left ventricular ejection fraction ≤35, %	25	37	14	0.025
Left ventricular end-diastolic volume, mm	60±10	63±9	55±10	0.008
Right ventricle fractional area change, %	41±9	41±10	40±8	0.710
Right ventricle fractional area change <35, %	14	17	11	0.505
Mitral regurgitation, %	64	71	55	0.277

The median time was 66 months, and the interquartile range was 19–126.

diastolic diameter, left bundle-branch block, NSVT (for D/HT/LVAD only), and mitral regurgitation were more prevalent. In patients experiencing SCD/MVA, the only differences compared with patients not experiencing the arrhythmic outcome concerned the higher rate of probands (65% versus 37%, *P*=0.021) and NSVT (82% versus 34%, *P*=0.001). Of note, no differences were observed in the distribution of *FLNCtv* and, limited to the 43 patients with available CMR, in the presence or absence of LGE for any of the explored outcomes.

As shown in Figure 4, we found an increasing risk of D/HT/VAD and nonarrhythmic death/HT/VAD events with decreasing values of LVEF at baseline. In contrast, there was no significant association between LVEF and the risk of SCD/MVA (Figure 5). Of note, among patients experiencing SCD/MVA, 6 (23%, 5 aborted SCD/sustained VT, and 1 appropriate ICD shock) had LVEF >50%. Their mean age at inclusion was 45±5 years, 2 were men, 1 was a proband. All were considered affected (2 ARVC, 1 ALVC, 3 minor phenotype).

We then compared *FLNCtv* carriers with 2 separate populations of *LMNA* and *DSP* variant carriers as established models of ACM. At baseline, there was no difference in age of onset (*LMNA* carriers mean age 42±11 versus *FLNCtv P*=0.936; *DSP* carriers mean age 38±14 versus *FLNCtv P*=0.055). *LMNA* carriers had a lower LVEF (*LMNA* carriers mean LVEF 34±13% versus *FLNCtv*, *P*=0.024; *DSP* carriers mean LVEF 43±15 versus *FLNCtv P*=0.779). As shown in Figure 5, compared with *LMNA* carriers, *FLNCtv* carriers experienced a lower risk of D/HT/LVAD (*P*=0.017) and nonarrhythmic death/HT/LVAD (*P*=0.006), but the risk of SCD/MVA was not significantly different (*P*=0.318), whereas compared with *DSP* carriers, *FLNCtv* carriers experienced a similar risk of D/HT/LVAD (*P*=0.732), nonarrhythmic death/HT/LVAD (*P*=0.816), and SCD/MVA (*P*=0.560). The same results were obtained if only affected carriers (n=76 *FLNCtv*, n=43 *LMNA*, n=60 *DSP*) were considered for the outcome analysis (Figure S2). Finally, during follow-up, 2 incident bradyarrhythmias (both first-degree atrioventricular blocks) were reported in the *FLNCtv* carriers, compared with 6 incident bradyarrhythmias (3 first-degree atrioventricular blocks, 2 sick sinus syndromes, including 1 requiring pacemaker/ICD implantation) in the *LMNA* carriers.

DISCUSSION

In the present study, we report the comprehensive characterization of variants, phenotypes, and outcomes of *FLNCtv* cardiomyopathy in an international cohort of *FLNCtv* carriers from tertiary care centers. Key findings of our study are: (1) *FLNCtv* cardiomyopathy appears to be a disease with heterogeneous phenotypic presentation ranging from typical DCM to ARVC and with frequently overlapping forms (eg, biventricular, ALVC); (2) LVEF is associated with the risk of D/HT/LVAD and nonarrhythmic death/HT/LVAD but not with the risk of SCD/MVA, highlighting the need for alternative strategies of stratification of the arrhythmic risk in *FLNCtv*-related cardiomyopathy; (3) *FLNCtv* cardiomyopathy is associated with a high risk of ventricular arrhythmias, with frequencies of life-threatening ventricular arrhythmias not significantly different from *LMNA* and *DSP* cardiomyopathy.

Regional Distribution of Variants Across the Gene Structure

*FLNCtv*s are an important cause of DCM, accounting for 2% to 4% of patients with DCM, and 6% of those with an arrhythmogenic phenotype.[5,6] The FLNC protein is composed of an ABD domain, which is critical for actin cross-linking, a series of 24 Ig-like domains divided into ROD1 and ROD2 subdomains and a dimerization domain (Figure 1). In our study, *FLNCtv*s were distributed across the whole gene, as reported by other investigators,[18] and we did not find an association between variant position and phenotype or prognosis, as was also observed in 1 small series.[19] These findings support the hypothesis that, in *FLNCtv* cardiomyopathy, the disease is the product of haploinsufficiency and that *FLNCtv* location does not modify the severity of the phenotype. It is noteworthy to mention that similar findings were recently reported by Helms et al[20] in hypertrophic cardiomyopathy

Table 3. Baseline Clinical Characteristics of *FLNC* Truncating Mutations Carriers Divided According to Study Outcomes

	All-cause mortality/heart transplantation/left ventricular assist device			Nonarrhythmic death/heart transplantation/left ventricular assist device			Sudden cardiac death/major ventricular arrhythmias		
	Outcome			Outcome			Outcome		
Baseline characteristics	Yes	No	*P* value	Yes	No	*P* value	Yes	No	*P* value
Age, y	45±18	42±14	0.485	43±20	42±14	0.943	45±11	42±16	0.424
Male, %	53	53	0.976	46	54	0.594	56	62	0.687
White, %	95	100	0.061	92	100	0.018	100	98	0.540
Proband, %	79	35	0.001	77	39	0.011	65	37	0.021
Variant mapping, %			0.689			0.610			0.458
Active binding domain	5	6		0	7		4	7	
ROD1	42	49		46	47		44	48	
ROD2	53	41		54	42		43	43	
Z-disk	21	17	0.659	15	18	0.816	17	18	0.970
Dimerization	0	4		0	4		9	2	
Family history cardiomyopathy, %	63	86	0.023	54	86	0.006	74	84	0.297
Family history sudden cardiac death, %	32	58	0.046	31	56	0.100	52	52	0.963
Phenotype, %			0.120			0.367			0.185
Dilated cardiomyopathy	63	46		69	46		48	50	
Arrhythmogenic right ventricular cardiomyopathy	0	5		0	4		9	1	
Arrhythmogenic left-dominant cardiomyopathy	37	21		31	24		35	21	
Biventricular	0	1		0	1		0	2	
Minor phenotype	0	14		0	12		9	11	
Unaffected	0	14		0	12		0	15	
Heart rate, beats per minute	74±23	71±20	0.668	74±26	71±20	0.718	70±17	72±22	0.615
Atrial fibrillation, %	32	14	0.076	32	15	0.186	30	13	0.065
Left bundle-branch block, %	22	5	0.017	25	6	0.026	4	10	0.407
NYHA class III or IV, %	42	10	0.002	46	13	0.004	13	20	0.479
NYHA class I, %	37	77	0.001	23	76	<0.001	74	66	0.466
Negative anterior T waves, %	32	19	0.220	23	21	0.875	26	20	0.523
Premature ventricular complexes/24 h	3987±8473	3054±4899	0.704	652±364	3476±5673	0.331	4642±6958	2773±4979	0.371
Positive late potentials, %	5	9	0.593	8	8	0.938	4	10	0.427
Nonsustained ventricular tachycardia, %	75	41	0.038	67	45	0.230	82	34	0.001
Echo left ventricular ejection fraction, %	30±12	46±15	<0.001	27±12	45±15	<0.001	40±14	43±16	0.360
Echo left ventricular ejection fraction <50, %	100	55	0.001	100	58	0.005	73	61	0.328
Echo left ventricular ejection fraction ≤35, %	65	22	0.001	67	25	0.004	36	29	0.513
Echo left ventricular end-diastolic volume, mm	67±6	54±9	<0.001	67±5	55±9	<0.001	59±11	56±9	0.279
Echo maximum wall thickness, mm	9±2	9±2	0.966	9±2	9±2	0.973	10±1	9±2	0.170
Echo left ventricular hypertrophy (%)	8	11	0.863	10	11	0.929	16	9	0.358
Echo right ventricle fractional area change, %	34±13	39±10	0.231	35±14	38±10	0.504	34±9	39±11	0.114
Echo right ventricle fractional area change <35, %	62	29	0.063	67	30	0.072	42	32	0.520
Echo right ventricle wall motion abnormalities, %	20	6	0.277	33	6	0.086	15	5	0.229
Echo mitral regurgitation, %	69	39	0.044	78	39	0.030	50	42	0.556
Cardiac magnetic resonance late gadolinium enhancement, % *	50	59	0.729	33	60	0.367	63	57	0.782

Values are reported as mean±SD, median and interquartile range, or percentage, as appropriate. Echo indicates echocardiographic; and NYHA, New York Heart Association.
*Among the 43 patients with available cardiac magnetic resonance.

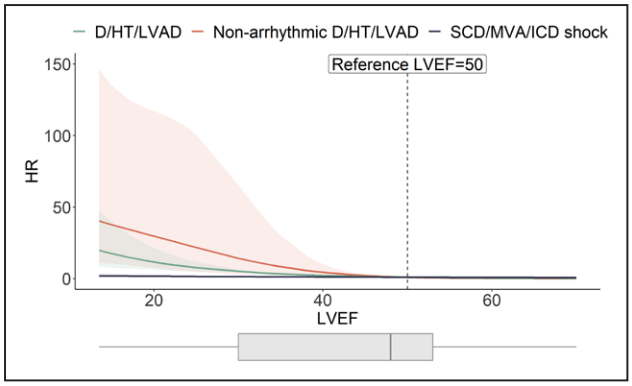

Figure 4. Association between LVEF and the study outcomes in the *FLNCtv* cohort.
In this high-risk population, the burden of D/HT/LVAD and SCD/MVA was 22% and 27%, respectively, over a median ≈5 years of follow-up. The association of LVEF with the study outcomes varies according to the type of outcome. As LVEF decreases, the HR for the outcomes D/HT/LVAD (green line) and nonarrhythmic death/HT/LVAD (orange line) get progressively higher, whereas no variation in risk was observed for the outcome SCD/MVA (blue line). Light painted areas indicate 95% CIs. D/HT/LVAD indicates all-cause mortality/heart transplantation/left ventricular assist device; HR, hazard ratio, ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; and SCD/MVA, sudden cardiac death/major ventricular arrhythmias.

caused by *MYBPC3* mutations where *MYBPC3tvs* were homogeneously distributed throughout the gene, in contrast to nontruncating *MYBPC3* pathogenic variants that, instead, clustered in specific protein domains. The severity of the phenotype and outcome were similarly independent of location of the *MYBPC3* truncating variants.

Heterogeneous Phenotypic Presentation of *FLNCtv*

The causal relation between *FLNC* variants and cardiomyopathy was initially found by family cosegregation studies, in animal models,[8] and in a large data set of patients with inherited cardiovascular disease.[6] Clinical presentation was more frequently DCM, but ALVC was also reported. Moreover, in the study of Ortiz-Genga et al,[6] only half of the relatives harboring the mutation presented with reduced LVEF. Lastly, 2 studies found overlap between DCM and ARVC in *FLNCtv* carriers.[7,9] Regardless of the subphenotypes and structural abnormalities at presentation, arrhythmogenicity is a constant feature of *FLNCtv* cardiomyopathies, and the 2019 Heart Rhythm Society consensus guidelines on ACM included *FLNC* among the genes responsible for arrhythmogenic cardiomyopathy and suggested they be considered high-risk markers for SCD.[2]

In our large cohort of *FLNCtv* carriers, only 11% of carriers showed no sign of myocardial involvement. The clinical-echocardiographic phenotype at presentation was heterogeneous, with left, right, or biventricular systolic dysfunction (Figure 2). It has been reported that missense *FLNC* variants are associated with hypertrophy besides typical DCM.[18] In our cohort, the presence of a mild LV hypertrophy was found in 11% of cases. However, more importantly, the hallmark of the phenotype was ventricular arrhythmias, which were independent of the degree of LV dysfunction, as indicated by the lack of correlation with LVEF. Therefore,

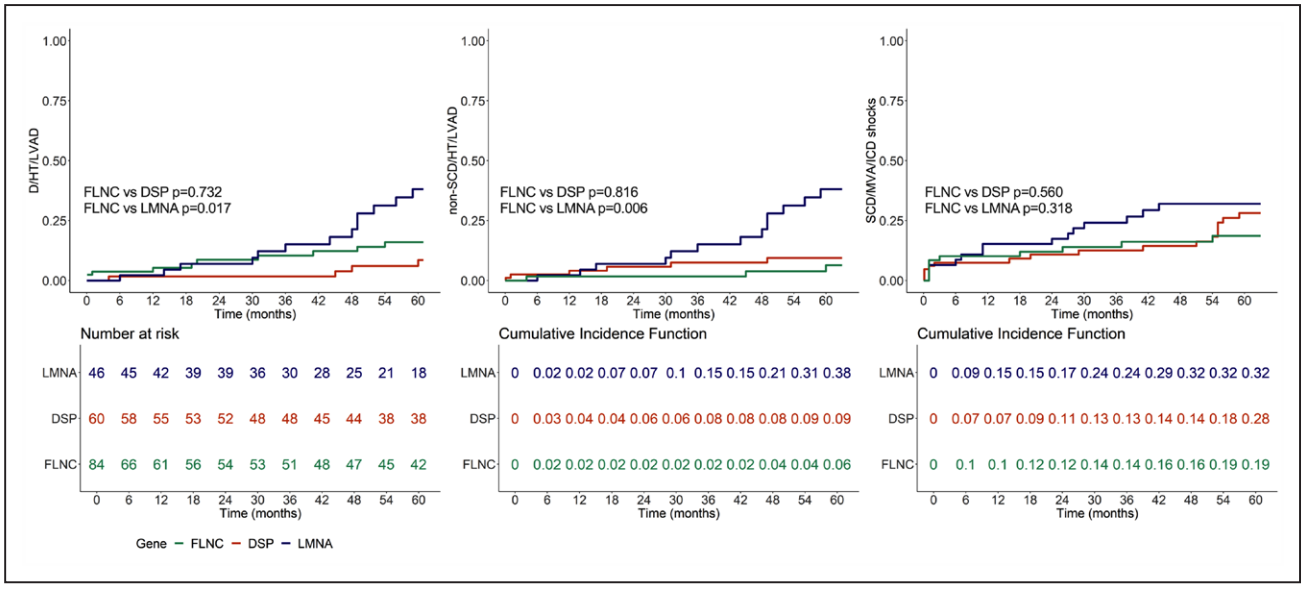

Figure 5. Comparison of outcome between the study population of *FLNCtv* carriers (n=85), *LMNA* mutation carriers (n=46), and *DSP* mutation carriers (n=60).
Left, All-cause mortality/heart transplantation/left ventricular assist device (D/HT/LVAD) in *FLNCtv* (green lines) versus *LMNA* (blue lines) versus *DSP* carriers (red line). **Center**, Cumulative incidence function of nonarrhythmic death/HT/LVAD in *FLNCtv* versus *LMNA* versus *DSP* carriers. **Right**, Cumulative incidence function of sudden cardiac death/major ventricular arrhythmias (SCD/MVA) in *FLNCtv* versus *LMNA* versus *DSP* carriers. Patients with *LMNA* showed a higher risk of D/HT/LVAD (*P*=0.017) and non-SCD/HT/LVAD (*P*=0.006), whereas the risk of SCD/MVA was comparable across the 3 groups. ICD indicates implantable cardioverter defibrillator.

the combined presence of some ACM features, such as frequent premature ventricular complex, NSVT, or negative anterior T waves, should raise the diagnostic suspicion of an underlying *FLNCtv*. A recent publication also noted the presence of a low-voltage ECG as a potential diagnostic feature.[21] Our observations support the emerging concept that specific genes (ie, desmosomal genes, *FLNC*, *PLN*, *RBM20*) demonstrate high variability in phenotypic expression and share a high risk of ventricular arrhythmias.[2,5–8,22,23]

In our series, echocardiographic follow-up was available in 68 patients. Despite the 5.5-year median interval from baseline to revaluation, LVEF remained stable in most patients, with no significant variations over time.

In the subgroup with available CMR data, we did not find an association between the presence of LGE and outcome, which could be explained by the limited number of observations and the proportional high overall rate of positive LGE. It is notable that CMR features were consistent with the data recently reported by Augusto et al[24] showing a subepicardial pattern and inferoposterolateral distribution as the more frequent characteristics of LGE in *FLNCtv* and *DSP* ACM. The typical subepicardial ring-like distribution of LGE seen in Figure 3 is another marker reported as a defining characteristic that leads one to consider the presence of *FLNCtv* and *DSP* cardiomyopathies.[24]

Survival and Arrhythmogenicity

The 27% incidence of SCD/MVA observed in our population was comparable to previous series.[6–8] The >20% incidence of D/HT/LVAD that we observed was also remarkable. In the study by Ortiz-Genga et al[6] of a heterogeneous cohort of ≈3000 patients with different inherited cardiovascular diseases, carriers of *FLNCtv* experiencing SCD had reduced LVEF, and the recent study by Akthar et al[25] suggested that higher LVEF values than those currently recommended for primary prevention ICD were associated with increased arrhythmic risk. The most recent guidelines on ACM include LVEF as a criterion for the eligibility for primary prevention ICD.[2,26,27] In our cohort, known risk factors such as LVEF and New York Heart Association class were, respectively, lower and more severe in patients experiencing D/HT/LVAD and nonarrhythmic death/HT/LVAD. As summarized in Figure 4, LVEF was associated with the risk of D/HT/LVAD and of nonarrhythmic death/HT/LVAD but not with the risk of SCD/MVA, suggesting that SCD prevention for patients with *FLNCtv* might not rely exclusively on reduced LVEF, similar to observations in others with ACM.[5,28] Alternative variables warrant being explored to improve the arrhythmic risk stratification process. In our cohort, for instance, the prevalence of NSVT was significantly higher in patients experiencing SCD/MVA. Last, we compared the outcome of *FLNCtv* with the outcome of *LMNA* and *DSP*, 2 established models of ACM with high risk of arrhythmic and nonarrhythmic events and, in particular for *DSP*, similarities with *FLNC* in phenotypic presentation.[5,22,24,29] *FLNCtv* carriers showed a similar risk of non–arrhythmic-related outcomes compared with *DSP*, such as irreversible HF, need of HT or LVADs, but lower compared with *LMNA*. On the contrary, in *FLNCtv*, the risk of life-threatening ventricular arrhythmias (SCD/MVA) was not significantly different from *LMNA* and *DSP*, further emphasizing the dominant arrhythmogenic phenotype of *FLNCtv*. Limiting the analysis to affected carriers did not modify these findings (Figure S2). Because *LMNA* mutations are associated with atrioventricular nodal disease, we also compared the incidence of bradyarrhythmias in the *FLNC* and *LMNA* populations: unlike *LMNA* carriers, we observed a lower rate of incident bradyarrhythmias in the *FLNCtv* carriers, with no severe cases requiring permanent pacing. Although the size of the population and the observational nature of the data do not allow us to support causality, our observation can be considered as hypothesis generating and, if further confirmed in larger multicenter studies and in validation cohorts, could aid in a more accurate and more precise arrhythmic risk stratification of *FLNCtv* carriers.

Study Limitations

Despite the multicenter design to overcome limited experience of individual centers, the rarity of the disease leads to a small sample size that limits the power of our observations requiring validation in other cohorts. The enrollment in tertiary care centers for genetic cardiomyopathies allowed us to analyze the largest available cohort of *FLNCtv* carriers, but also represents potential selection and ascertainment biases that have to be considered in the interpretation of results. The enrolled population was nearly exclusively of White ancestry which limits the generalizability of our results to non-White populations and highlights the need to conduct similar studies in other less selected populations to comprehensively understand the *FLNC* genotype-phenotype relationships. The retrospective nature of the study means that some clinical data were not available in all the patients. Last, imaging studies performed at each center were not reviewed by an independent core laboratory, and the intercenter reproducibility was not tested.

Conclusions

FLNCtv are variants leading to a heterogeneous ACM clinical presentation with overlapping phenotypic aspects of DCM and ARVC. The frequent ventricular arrhythmias and the significant risk of arrhythmic-related major outcomes support the systematic screening of *FLNC* in clinical genetic cardiomyopathy panels. *FLNC* was re-

cently introduced in the new 2019 Heart Rhythm Society expert consensus statement on ACM with specific recommendations for primary prevention of SCD and ICD based exclusively on LVEF<45% (Class of Recommendation IIa).[2] Our findings confirm the high-risk phenotype of *FLNCtv* carriers. However, we show that, in these patients, an ICD might be considered regardless of the LVEF. The identification of alternative factors associated with increased risk of SCD/MVA, such as ventricular arrhythmias (NSVT), in larger dedicated studies will foster a precision medicine approach to the risk stratification of patients with *FLNCtv.*

ARTICLE INFORMATION

Received January 4, 2021; accepted September 7, 2021.

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Acknowledgments

Dr Giulia Barbati, Associate Professor of Biostatistics, University of Trieste, is gratefully acknowledged for her advice and supervision of data analysis. The authors are grateful to the patients and family members for their participation in these studies.

Sources of Funding

This study was supported by the following: National Institutes of Health (NIH) R01HL69071, R01HL116906, R01HL147064 and America Heart Association (AHA) 17GRNT33670495 to Dr Mestroni; NIH 1K23HI067915; NIH 2UM1HG006542 and R01HL109209 to Dr Taylor; CRTrieste Foundation and Cassa di Risparmio of Gorizia Foundation to Dr Sinagra. Dr McKenna was a UK National Institute for Health Research Senior Investigator. This work is also supported in part by a Trans-Atlantic Network of Excellence grant from the Fondation Leducq (14-CVD03), NIH/National Center for Advancing Translational Sciences Colorado Clinical and Translational Science Awards Grant UL1 TR002535 and UL1 TR001082, by the Netherlands Cardiovascular Research Initiative, an initiative with support of the Dutch Heart Foundation (grant CVON2015-12/2018-30 eDETECT/PREDICT2). Dr Te Riele is supported by the Dutch Heart Foundation (grant 2015T058) and the UMC Utrecht Fellowship Clinical Research Talent. Drs James and Calkins and C. Tichnell are supported by the Leonie-Wild Foundation, the Francis P. Chiaramonte Private Foundation, the Leyla Erkan Family Fund for ARVD Research, the Dr. Satish, Rupal, and Robin Shah ARVD Fund at Johns Hopkins, the Bogle Foundation, the Healing Hearts Foundation, the Campanella family, the Patrick J. Harrison Family, the Peter French Memorial Foundation and the Wilmerding Endowments. Dr Parikh is supported by the John Taylor Babbitt Foundation, The Sarnoff Cardiovascular Research Foundation, NIH K08 HL143185. Dr Ashley is supported by the NIH Common Fund U01HG007708, and NIH 1U24EB023674. Dr Fatkin is supported by the Victor Chang Cardiac Research Institute, National Health and Medical Research Council, Estate of the Late RT Hall. Dr Lakdawala is supported by the O'Hare Family Foundation for research on cardiolaminopathy.

Disclosures

Dr Judge has received payments as a consultant from 4D Molecular Therapeutics, ADRx Pharma, MyoKardia, and Pfizer, and has received research funding from Array Biopharma and Eidos Therapeutics, all of which are outside the scope of this work. Dr Lakdawala has received payments as a consultant from MyoKardia, Pfizer, Tenaya, and Array Biopharma, outside the scope of this work. Dr Calkins is a consultant for Medtronic Inc. and Abbott and receives research support from Boston Scientific Corp. C. Tichnell and Dr James receive salary support from this grant. B. Murray is a consultant for MyGeneCounsel. C. Reuter is a consultant for MyGeneCounsel. The remaining authors have nothing to disclose.

Supplemental Materials

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Figures S1 and S2
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