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Phenotypic expression, natural history and risk stratification of cardiomyopathy caused by Filamin C truncating variants

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Abstract

Background.—Filamin C truncating variants (*FLNCtv*) cause a form of arrhythmogenic cardiomyopathy (ACM): the mode of presentation, natural history and risk stratification of *FLNCtv* remain incompletely explored. We sought 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 ten 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), non-arrhythmic death/HT/LVAD and SCD/major ventricular arrhythmias (SCD/MVA). Previously established cohorts of 46 patients with *LMNA* and 60 with *DSP*-related ACM were used for prognostic comparison.

Results.—Eighty-five patients carrying *FLNCtv* were included (42±15 years, 53% males, 45% probands). Phenotypes were heterogeneous at presentation: 49% dilated cardiomyopathy, 25% arrhythmogenic left dominant cardiomyopathy, 3% arrhythmogenic right ventricular cardiomyopathy. Left ventricular ejection fraction (LVEF) 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%) non-arrhythmic death/HT/LVAD and 23 (27%) SCD/MVA. The SCD/MVA incidence of *FLNCtv* carriers did not significantly differ from *LMNA* carriers and *DSP* carriers. In *FLNCtv* carriers, LVEF was associated with the risk of D/HT/LVAD and non-arrhythmic death/HT/LVAD.

Conclusions.—Among patients referred to tertiary referral centers, *FLNCtv* ACM is phenotypically heterogeneous and characterized by high risk of life-threatening arrhythmias, which does not seem to be associated with the severity of LV dysfunction.

Keywords

FLNC gene; genotype-phenotype correlation; prognosis; arrhythmogenic cardiomyopathy; sudden cardiac death; heart failure

Introduction

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]. Recently, truncating variants in the filamin C gene (*FLNCtv*) have 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

Patients with *FLNCtv* were collected from ten 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. In order to minimize the possibility of unintentionally sharing information that can be used to re-identify private information and considering the different institutional review boards policies of the participating centers, the datasets 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 online 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 I in the Supplement). To maintain a conservative approach, only 'pathogenic' and 'likely pathogenic' truncating variants were considered, while missense variants and 'variants of uncertain significance' were excluded from the analysis. Probands and available family members carriers of 'pathogenic' or 'likely pathogenic' *FLNCtv* were included in the registry. Additional variants of interest inherent to other cardiomyopathies related genes were also reported and patients considered as carriers of multiple mutations.

Phenotypic characterization

Demographic, clinical and therapeutic information were 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 non-sustained ventricular tachycardia [NSVT]), and atrial fibrillation/atrial flutter. Age of onset was defined based on clinical diagnosis. Data from 12-lead electrocardiograms (ECG), Holter ECG monitoring and signal-averaged electrocardiograms (SAECG) were recorded. Late potentials were determined by SAECG 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=(right ventricular end-diastolic area - right ventricular end-systolic area)/right ventricular 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).

Based on their presenting phenotypes, patients with *FLNCtv* were classified into six mutually exclusive phenotypic categories based on 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 (TFC)[13]; ALVC phenotype was defined as DCM presentation not fulfilling TFC for ARVC and with ≥1 of the following: SCD/major ventricular arrhythmias (MVA) (resuscitated cardiac arrest, sustained VT, appropriate ICD interventions), unexplained syncope, SVT, ≥1000 premature ventricular contractions (PVCs)/24 hours, ≥50 couplets/24 hours[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 above were classified as ‘minor phenotype’. Finally, patients without any cardiac pathological finding were considered unaffected.

Study outcomes

The study outcomes were: 1) all-cause mortality/heart transplantation/left ventricular assist device implantation (D/HT/LVAD); 2) non-arrhythmic death (including HF death and death not due to SCD)/HT/LVAD; 3) SCD/major ventricular arrhythmias (MVA). MVA included ventricular fibrillation, sustained VT (lasting >30 s or with hemodynamic instability) and appropriate ICD interventions (shock or anti-tachycardia pacing on ventricular fibrillation or sustained VT) (SCD/MVA). SCD was defined as witnessed SCD with or without documented ventricular fibrillation, death within 1 h of acute symptoms, or

nocturnal death with no antecedent history of immediate worsening symptoms. In addition, incident bradyarrhythmias (i.e. sick sinus syndrome, atrio-ventricular 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 three participating Centers (University Hospital of Trieste, University of Colorado Cardiovascular Institute, 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 (IQR), or counts and percentage, as appropriate. Comparisons between groups were made by the analysis of variance (ANOVA) test on continuous variables using the Brown-Forsythe statistic when the assumption of equal variances did not hold or the nonparametric Mann-Whitney test; the chi-square test or the Fisher’s 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 (CIF) for non-arrhythmic death/HT/LVAD and SCD/MVA were estimated for *FLNCtv* carriers, *LMNA* variants carriers and *DSP* variants carriers and compared by the log rank test. As 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 i.e. use a robust sandwich estimator for the standard error[16, 17].

The univariate Cox model (D/HT/LVAD) and the cause-specific Cox model (non-arrhythmic 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 non-linear. To avoid bias due 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 I in the Supplement 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 I in the Supplement).

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 old: 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 vs 42±16 years, p=0.854) and gender (male sex 51% vs 70%, p=0.250) between affected and unaffected individuals. Thirty-two percent of subjects had HF-related symptoms (NYHA class >1), 22% had a history of syncope. Negative anterior T-waves (V1-V4) 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, six (12%) with isolated RV dysfunction, 19 (38%) with isolated LV dysfunction and 14 subjects (28%) with preserved biventricular function. Mild LV hypertrophy was found in 11% of cases. Baseline therapy included 64% of carriers on betablockers, 57% on ACE-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 to relatives presented significantly more negative anterior T-waves, NSVT and pathological echocardiographic findings. They were also more likely to be treated with antineurohormonal drugs. Finally, phenotype presentation did not significantly differ according to *FLNCtv* variant location (Table II in the Supplement).

Cardiac MRI patterns of *FLNCtv*

There were 43 (51%) *FLNCtv* carriers with available CMR studies, of which 23 (53%) had evidence of LGE with no differences between probands and family members (44% vs 56%, p=0.738). Figure 3A shows the CMR features of a *FLNCtv* carrier (proband, male, 48 years old) in early stage of disease (CMR LVEF=54%), with subepicardial “ring-like” LGE indicated by the arrows. Figure 3B reports the characteristics of LGE location, distribution and pattern in the CMR subgroup. All except one 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 IQR 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 I in the Supplement, 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: −0.06–0.03, p=0.5 and −0.04, 95%CI: −0.11–0.02, p=0.2, respectively).

Study endpoints and prognostic stratification

Over a median follow-up of 61 months (IQR 10–139), 19 carriers (15 probands, 4 non-probands, 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 non-probands, 15% of the total cohort) non-arrhythmic death/HT/LVAD (5 deaths, 3 HT, 5 LVAD; median age 51, range 48–61) and 23 (15 probands, 8 non-probands, 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 to patients with no outcome, patients experiencing D/HT/LVAD and patients experiencing non-arrhythmic 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-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 to patients not suffering the arrhythmic outcome concerned the higher rate of probands (65% vs 37%, p=0.021) and of NSVT (82% vs 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 non-arrhythmic 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 one appropriate ICD shock) had LVEF >50%. Their mean age at inclusion was 45±5 years, two were males, one a proband. All were considered affected (2 ARVC, 1 ALVC, 3 minor phenotype).

We then compared *FLNCtv* carriers to two 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, *vs. FLNCtv* p=0.936; *DSP* carriers mean age 38±14, vs *FLNCtv* p=0.055). *LMNA* carriers had a lower LVEF (*LMNA* carriers mean LVEF 34±13%, *vs. FLNCtv*, p=0.024; *DSP* carriers mean LVEF 43±15, vs *FLNCtv* p=0.779). As shown in Figure 5, compared to *LMNA* carriers, *FLNCtv* carriers experienced a lower risk of D/HT/LVAD (p=0.017) and non-arrhythmic death/HT/LVAD (p=0.006), but the risk of SCD/MVA was not significantly different (p=0.318), whereas compared to DSP carriers, *FLNCtv* carriers experienced a similar risk of D/HT/LVAD (p=0.732), non-arrhythmic 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 II in the Supplement). Finally, during follow-up, 2 incident bradyarrhythmias (both first degree atrioventricular blocks) were reported in the *FLNCtv* carriers, compared to 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 (e.g. biventricular, ALVC); 2) LVEF is associated with the risk of D/HT/LVAD and non-arrhythmic 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

FLNCtvs are an important cause of DCM, accounting for 2% to 4% of DCM patients, and 6% of those with an arrhythmogenic phenotype[5, 6]. The FLNC protein is composed of an ABD domain, which is critical for actin crosslinking, a series of 24 Ig-like domains divided into ROD1 and ROD2 subdomains and a dimerization domain (Figure 1). In our study, *FLNCtvs* 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 one 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. in hypertrophic cardiomyopathy caused by *MYBPC3* mutations[20] where *MYBPC3tvs* were homogeneously distributed throughout the gene, in contrast to non-truncating *MYBPC3* pathogenic variants that instead, clustered in specific protein domains. Similarly, the severity of the phenotype and outcome were independent of location of the *MYBPC3* truncating variants.

The heterogeneous phenotypic presentation of *FLNCtv*

The causal relation between *FLNC* variants and cardiomyopathy was initially found by family cosegregation studies, animal models[8] and in a large dataset 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., only half of the relatives harboring the mutation presented with reduced LVEF[6]. Finally, two 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 indeed, 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 bi-ventricular systolic dysfunction (Figure 2). It has been reported that missense *FLNC* variants are associated with hypertrophy besides typical DCM[18]. Interestingly, in our cohort presence of a mild LV hypertrophy was found in 11% of cases. However, more importantly, hallmark of the phenotype were ventricular arrhythmias, which were independent of the degree of LV dysfunction as indicated by the lack of correlation with LVEF. Therefore, 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 electrocardiogram as a potential diagnostic feature[21]. Our observations support the emerging concept that specific genes (i.e. 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 years median interval from baseline to revaluation, LVEF remained stable in the majority of patients, with no significant variations overtime.

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. Notably, CMR features were consistent with the data recently reported by Augusto et al., showing a subepicardial pattern and inferoposterolateral distribution as the more frequent characteristics of LGE in FLNCtv and DSP ACM[24]. 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. Interestingly, in the study by Ortiz-Genga et al. of a heterogeneous cohort of ~3,000 patients with different inherited cardiovascular diseases, carriers of *FLNCtv* experiencing SCD had reduced LVEF and the recent study by Akthar et al. suggested that higher LVEF values than those currently recommended for primary prevention ICD were associated with increased arrhythmic risk[25]. 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 NYHA class were, respectively, lower and more severe in patients experiencing D/HT/LVAD and non-arrhythmic death/HT/LVAD. As summarized in Figure 4, LVEF was associated with the risk of D/HT/LVAD and of non-arrhythmic death/HT/LVAD but not with the risk of SCD/MVA, suggesting that SCD-prevention for *FLNCtv* patients might not rely exclusively on reduced LVEF, similar to observations in others ACM[5, 28]. Alternative variables deserve to be explored in order to improve

the arrhythmic risk stratification process. In our cohort, for instance, the prevalence of NSVT was significantly higher in patients experiencing SCD/MVA. Finally, we compared the outcome of *FLNCtv* to *LMNA* and *DSP*, two established models of ACM with high risk of arrhythmic and non-arrhythmic events and, particularly for *DSP*, similarities with *FLNC* in phenotypic presentation[5, 22, 24, 29]. *FLNCtv* carriers showed a similar risk of non-arrhythmic related outcomes compared to *DSP*, such as irreversible HF, need of HT or LV assist devices, but lower compared to *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 II in the Supplement). Since LMNA mutations are associated with AV 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 hypotheses-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 Caucasian 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. Finally, imaging studies performed in each center were not reviewed by an independent core-laboratory and the inter-center 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 recently 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*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS:

ACM	Arrhythmogenic Cardiomyopathy
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
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

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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 ventricle 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 (i.e. high risk of life-threatening arrhythmias) support the use of genetic testing particularly 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.

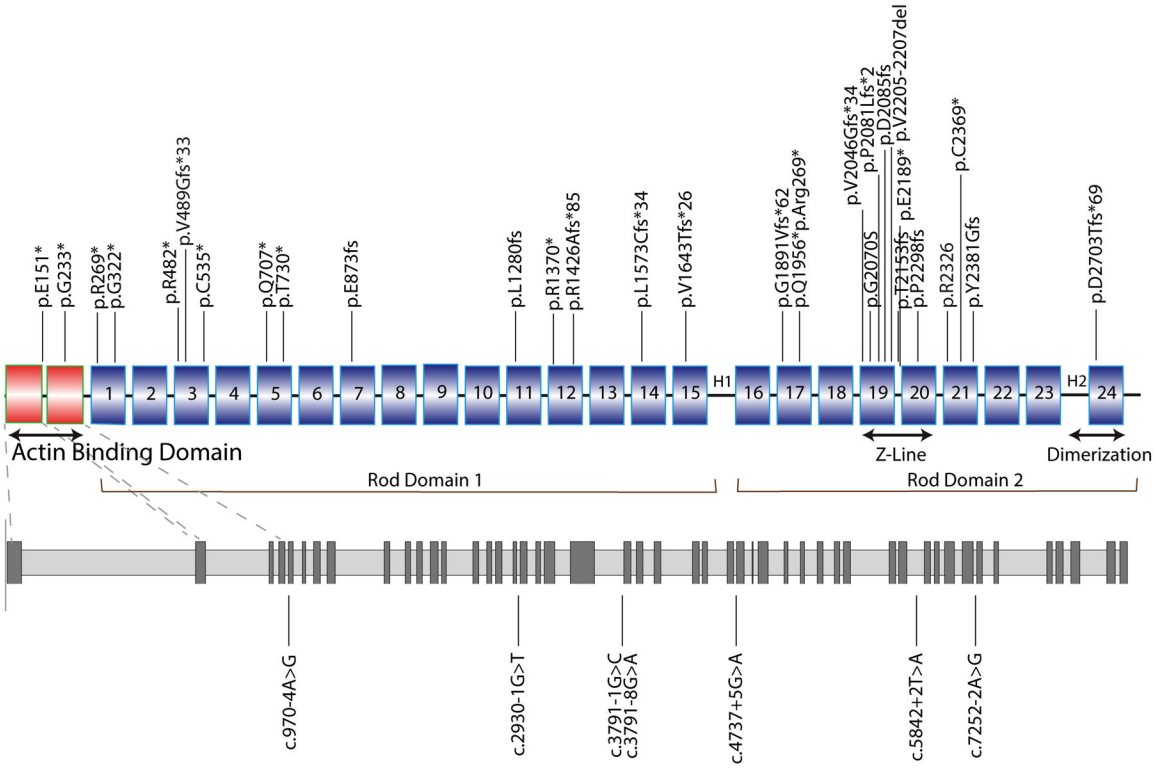

Figure 1. Mapping of *FLNCtv* variants.

Diagrams representing the structure of FLNC and the distribution of *FLNCtv* variants. *FLNCtv* were distributed across all gene 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, Ig-like domains; H1 and H2, hinge domains.

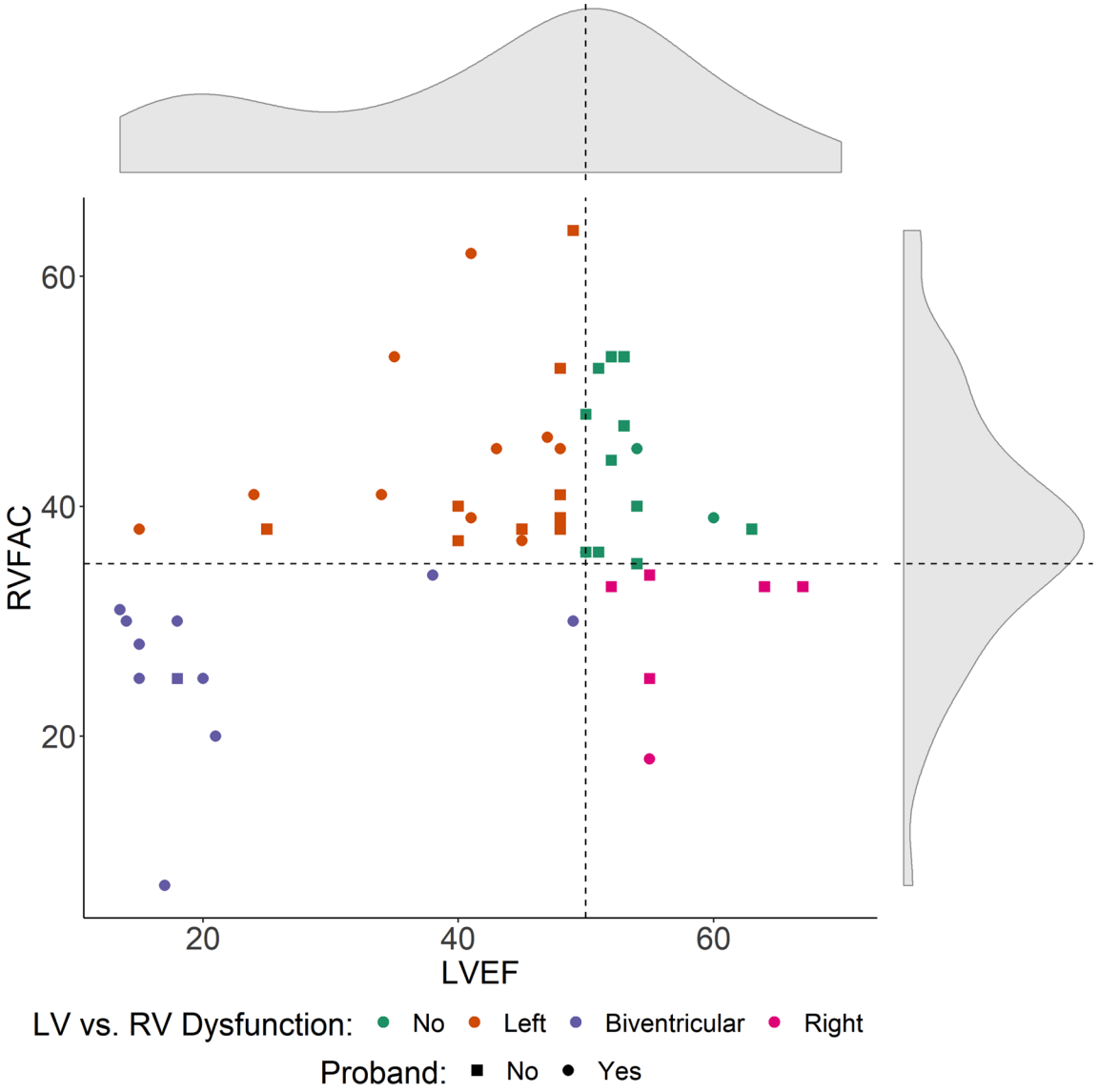

Figure 2. Distribution of right and left ventricular function in FLNCtv carriers.

The *FLNCtv* population showed a wide distribution of RV and LV dysfunction. Dashed lines mark the cut-offs defining LV dysfunction (LVEF<50%) and RV dysfunction (RVFAC<35%). LVEF=left ventricular ejection fraction, RVFAC=right ventricle fractional area change, RV= right ventricular.

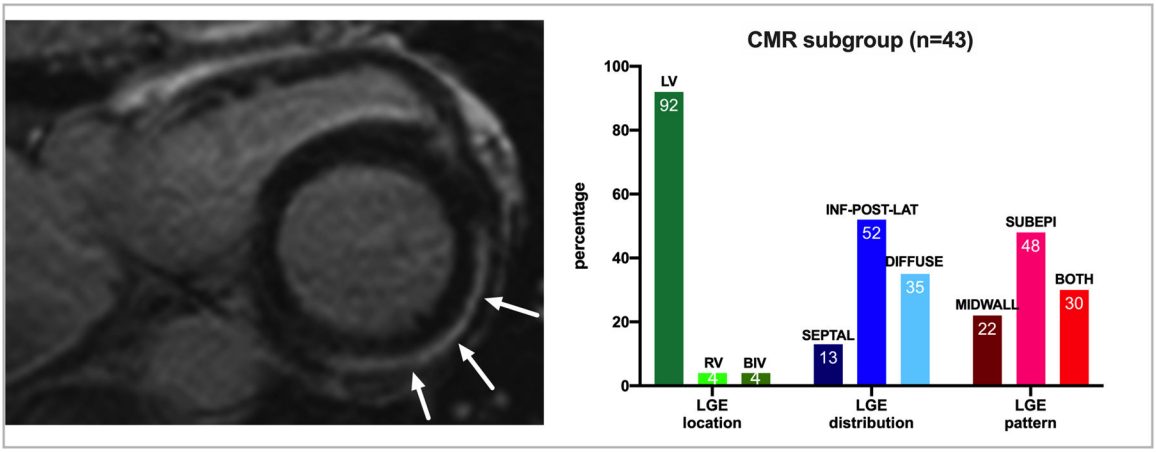

Figure 3. Characteristics of LGE in carriers of *FLNCtv*.

Left panel shows the typical subepicardial "ring-like" distribution of LGE in a carrier of *FLNCtv* (male, 48 years old, LVEF 54%), involving the inferior, posterior and lateral wall. Right panel summarizes the distribution of LGE in the 43 *FLNCtv* carriers with available cardiac magnetic resonance (CMR). Percentages are reported within bars.

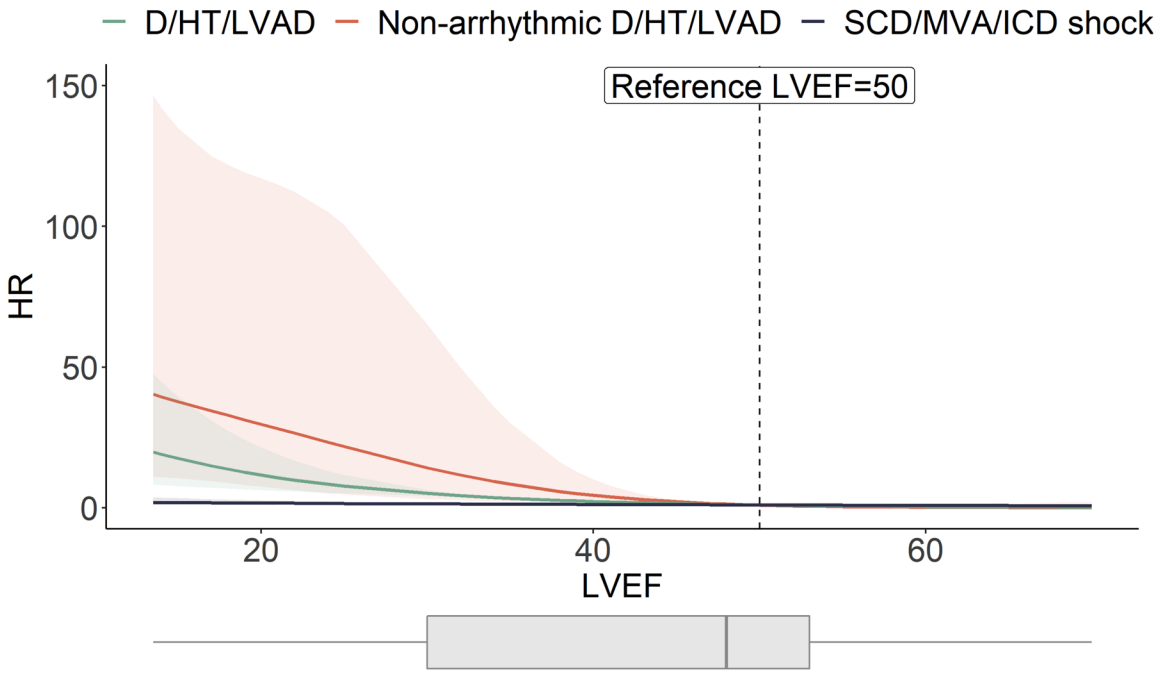

Figure 4. Association between LVEF and the study outcomes in the FLNCtv cohort.

In this high-risk population the burden of D/HT/LVAD and SCD/MVA was 22% and 27%, respectively, over a median ~5 years 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 non-arrhythmic 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 % confidence intervals.
D/HT/LVAD=all-cause mortality/heart transplantation/left ventricular assist device; HR=hazard ratio, LVEF=left ventricular ejection fraction; SCD/MVA=sudden cardiac death/ major ventricular arrhythmias.

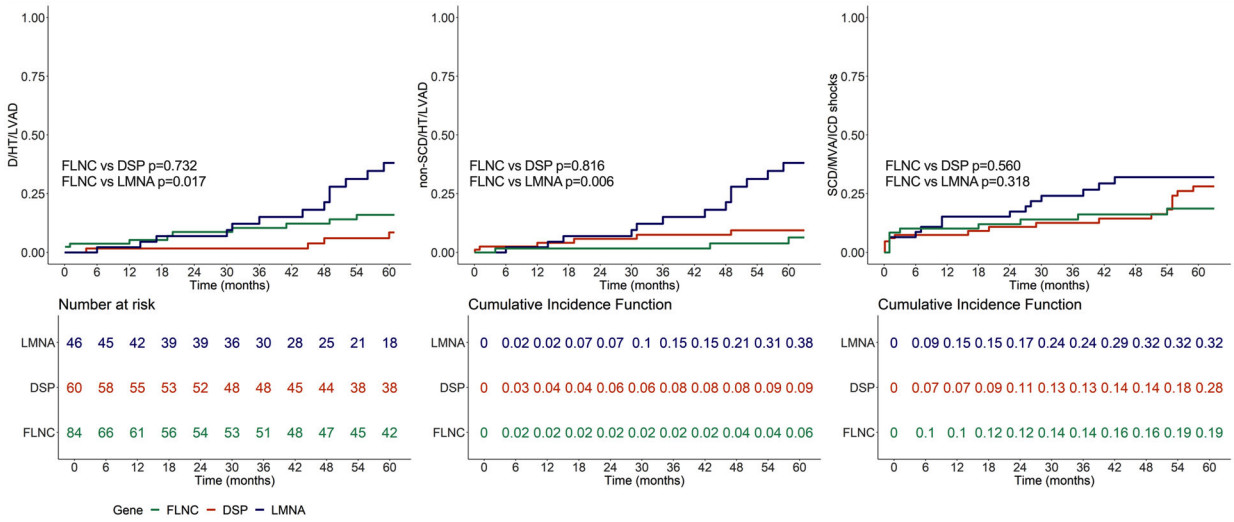

Figure 5. Comparison of outcome between the study population of *FLNCtv* carriers (n=85), *LMNA* mutation carriers (n=46) and *DSP* mutation carriers (n=60).

Left panel: all-cause mortality/heart transplantation/left ventricular assist device (D/HT/LVAD) in *FLNCtv* (green lines) vs *LMNA* (blue lines) *vs DSP* carriers (red line). Central panel: Cumulative Incidence Function (CIF) of non-arrhythmic death/HT/LVAD in *FLNCtv* vs *LMNA vs DSP* carriers. Right panel: CIF of sudden cardiac death/major ventricular arrhythmias (SCD/MVA) in *FLNCtv* vs *LMNA vs DSP* carriers. LMNA patients 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 three groups.

Table 1.

Baseline clinical characteristics of the overall cohort of *FLNC* truncating mutations carriers and divided according to proband status.

	total n=85	probands n=38 (45%)	non-probands n=47 (55%)	p-value
Age (years)	42±15	40±14	44±16	0.163
Male %(n.)	53 (45)	63 (24)	45 (21)	0.090
Caucasian %(n.)	99 (84)	97 (37)	100 (47)	0.263
Variant mapping %(n.)				0.822
ABD	6 (5)	5 (2)	6 (3)	
ROD1	47 (40)	53 (20)	43 (20)	
ROD2	44 (37)	40 (15)	47 (22)	
Z-disk	18 (15)	18 (7)	17 (8)	0.866
Dimerization	4 (3)	3 (1)	4 (2)	
Family history cardiomyopathy %(n.)	81 (69)	61 (23)	100 (46)	<0.001
Family history SCD %(n.)	52 (44)	34 (13)	66 (31)	0.004
Phenotype %(n.)				0.016
DCM	49 (42)	53 (20)	47 (22)	
ARVC	3 (3)	3 (1)	4 (2)	
ALVC	25 (21)	37 (14)	15 (7)	
Biventricular ARVC	1 (1)	3 (1)	0 (0)	
Minor phenotype	11 (9)	5 (2)	15 (7)	
Unaffected	11 (9)	0 (0)	19 (9)	
CPK (U/l)	80 (55–121)	75 (55–139)	94 (50–119)	0.713
HR (bpm)	72±21	73±21	71±21	0.567
AF %(n.)	4 (3)	5 (2)	2 (1)	0.219
LBBB %(n.)	8 (7)	8 (3)	9 (4)	0.871
NYHA 3–4 %(n.)	18 (15)	22 (8)	15 (7)	0.424
NYHA 1 %(n.)	68 (57)	62 (23)	72 (34)	0.321
Negative anterior T waves %(n.)	21 (18)	39 (15)	7 (3)	<0.001
PVCs/24h	3194±5443	4581±6913	1806±2994	0.108
PVCs>1000/24h %(n.)	45 (18)	55 (11)	35 (7)	0.204
Positive Late Potentials %(n.)	8 (7)	5 (2)	11 (5)	0.370
NSVT %(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 LVEDD (mm)	57±10	62±8	52±9	<0.001
Echo MWT (mm)	9±2	10±1	9±2	0.446
Echo LVH (%)	11	6	14	0.270

	total n=85	probands n=38 (45%)	non-probands n=47 (55%)	p-value
Echo RVFAC (%) *	38±11	35±12	40±9	0.083
Echo RVFAC<35 %(n.)	34 (17)	46 (11)	23 (6)	0.090
Echo RV WMA %(n.)	8 (4)	16 (4)	0 (0)	0.031
Echo MR %(n.)	44 (33)	58 (19)	33 (14)	0.036
CMR LGE %(n.) **	53 (23)	61 (8)	56 (14)	0.738
Beta-blockers %(n.)	64 (52)	89 (31)	46 (21)	<0.001
ACEi/ARB/ARNI %(n.)	57 (46)	80 (28)	39 (18)	<0.001
ICD %(n.)	14 (11)	20 (7)	9 (4)	0.152
ICD at follow-up %(n.)	48 (39)	57 (21)	41 (18)	0.155

ABD=active binding domain, SCD=sudden cardiac death, DCM=dilated cardiomyopathy, ARVC=arrhythmogenic right ventricular cardiomyopathy, ALVC=arrhythmogenic left-dominant cardiomyopathy, CPK=creatine phosphokinase, HR=heart rate, AF=atrial fibrillation, LBBB=left bundle branch block, NYHA=New York heart association, PVC=premature ventricular complex, NSVT=non-sustained ventricular tachycardia, LVEF=left ventricular ejection fraction, LVEDD=left ventricular end-diastolic volume, MWT=maximum wall thickness, LVH=left ventricular hypertrophy, RVFAC=right ventricle fractional area change, WMA=wall motion abnormalities, MR=mitral regurgitation, CMR=cardiac magnetic resonance imaging, LGE=late gadolinium enhancement, ACEi/ARB/ARNI=ACE-inhibitors/angiotensin receptor blockers/angiotensin receptor neprylisin inhibitors, ICD=implantable cardioverter defibrillator.

Values are reported as mean±standard deviation, median and interquartile range or percentage as appropriate.

* missing data for LVEF=4 (5%), missing data for RVFAC=35 (41%).

** among the 43 pts with available CMR.

Table 2.

Main echocardiographic measures at follow-up (median time 66 months, IQR 19–126) in the overall subset of patients with available follow-up reassessment and divided according to proband status.

	total n=68	probands n=28 (57%)	non-probands n=21 (43%)	p-value
Echo LVEF (%)	44±14	38±14	49±12	0.001
Echo LVEF <50 (%)	57	78	39	0.001
Echo LVEF ≦35 (%)	25	37	14	0.025
Echo LVEDD (mm)	60±10	63±9	55±10	0.008
Echo RVFAC (%)	41±9	41±10	40±8	0.710
Echo RVFAC<35 (%)	14	17	11	0.505
Echo MR (%)	64	71	55	0.277

For abbreviations see Table 1

Table 3.

Baseline clinical characteristics of *FLNC* truncating mutations carriers divided according to study outcomes.

	D/HT/LVAD			Non-arrhythmic death/HT/LVAD			SCD/MVA		
	Outcome Yes	**Outcome No**	**p-value**	**Outcome Yes**	**Outcome No**	**p-value**	**Outcome Yes**	**Outcome No**	**p-value**
Age (years)	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
Caucasian %	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
ABD	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 SCD %	32	58	0.046	31	56	0.100	52	52	0.963
Phenotype %			0.120			0.367			0.185
DCM	63	46		69	46		48	50	
ARVC	0	5		0	4		9	1	
ALVC	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	
HR (bpm)	74±23	71±20	0.668	74±26	71±20	0.718	70±17	72±22	0.615
AF %	32	14	0.076	32	15	0.186	30	13	0.065
LBBB %	22	5	0.017	25	6	0.026	4	10	0.407
NYHA 3–4 %	42	10	0.002	46	13	0.004	13	20	0.479
NYHA 1 %	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

	D/HT/LVAD			Non-arrhythmic death/HT/LVAD			SCD/MVA		
	Outcome Yes	Outcome No	p-value	Outcome Yes	Outcome No	p-value	Outcome Yes	Outcome No	p-value
PVCs/24h	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
NSVT %	75	41	0.038	67	45	0.230	82	34	0.001
Echo LVEF (%)	30±12	46±15	<0.001	27±12	45±15	<0.001	40±14	43±16	0.360
Echo LVEF <50 %	100	55	0.001	100	58	0.005	73	61	0.328
Echo LVEF ≦35 %	65	22	0.001	67	25	0.004	36	29	0.513
Echo LVEDD (mm)	67±6	54±9	<0.001	67±5	55±9	<0.001	59±11	56±9	0.279
Echo MWT (mm)	9±2	9±2	0.966	9±2	9±2	0.973	10±1	9±2	0.170
Echo LVH (%)	8	11	0.863	10	11	0.929	16	9	0.358
Echo RVFAC (%)	34±13	39±10	0.231	35±14	38±10	0.504	34±9	39±11	0.114
Echo RVFAC<35 %	62	29	0.063	67	30	0.072	42	32	0.520
Echo RV WMA %	20	6	0.277	33	6	0.086	15	5	0.229
Echo MR %	69	39	0.044	78	39	0.030	50	42	0.556
CMR LGE % **	50	59	0.729	33	60	0.367	63	57	0.782

D/HT/LVAD=death heart transplant/left ventricular assist device, non-SCD/HT/LVAD=non sudden cardiac death/heart transplant/left ventricular assist device, SCD/MVA=sudden cardiac death/major ventricular arrhythmias, ABD=active binding domain, SCD=sudden cardiac death, DCM=dilated cardiomyopathy, ARVC=arrhythmogenic right ventricular cardiomyopathy, ALVC=arrhythmogenic left-dominant cardiomyopathy, CPK=creatine phosphokinase, HR=heart rate, AF=atrial fibrillation, LBBB=left bundle branch block, NYHA=New York heart association, PVC=premature ventricular complex, NSVT=non-sustained ventricular tachycardia, LVEF=left ventricular ejection fraction, LVEDD=left ventricular end-diastolic volume, MWT=maximum wall thickness, LVH=left ventricular hypertrophy, RVFAC=right ventricle fractional area change, WMA=wall motion abnormalities, MR=mitral regurgitation, CMR=cardiac magnetic resonance imaging, LGE=late gadolinium enhancement.Values are reported as mean±standard deviation, median and interquartile range or percentage as appropriate.

** among the 43 pts with available CMR.