Review Article

The Multiple Faces of Cardiomyopathy Due to Filamin C Gene Variants (*FLNC*)

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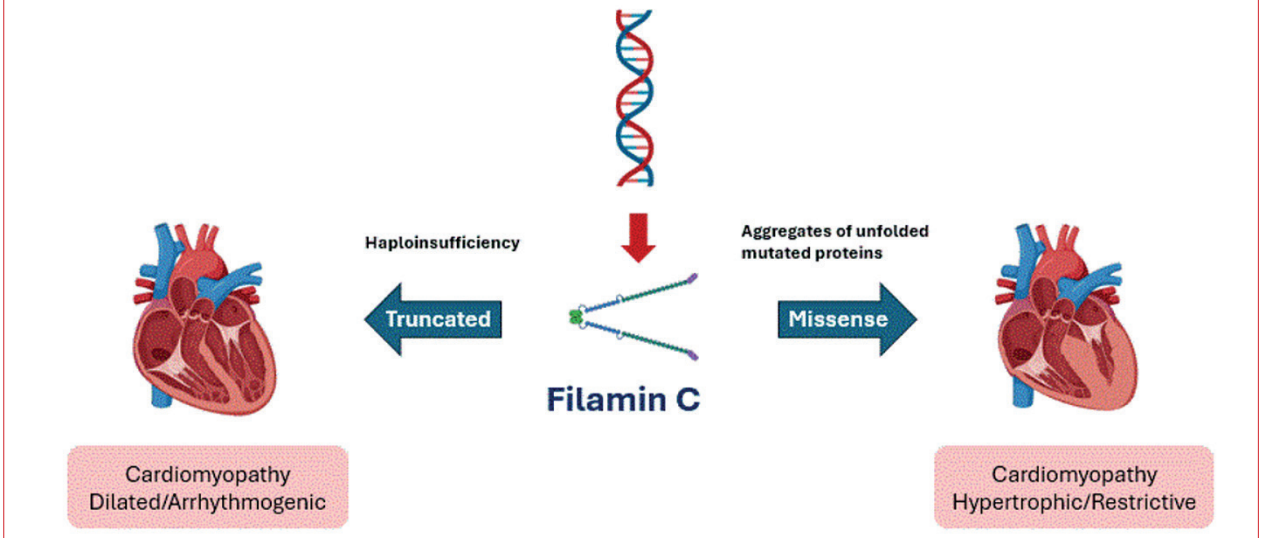
Central Illustration: The Multiple Faces of Cardiomyopathy Due to Filamin C Gene Variants (*FLNC*)



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Truncating and missense variants and the different phenotypes of cardiomyopathy due to variants in the FLNC gene.

Abstract

Filamin C is an essential protein for the integrity of the sarcomere and cytoskeleton of cardiomyocytes. Pathogenic variants in the *FLNC* gene are associated with a wide range of cardiomyopathies and may present distinct phenotypes depending on the type of genetic alteration. Truncated variants are frequently associated with dilated and arrhythmogenic cardiomyopathy, while missense variants are more related to hypertrophic and restrictive forms. These phenotypic differences reflect the molecular and structural impact of the *FLNC* variant on filamin C protein, with direct implications for clinical management. Diagnosis and risk stratification are challenging, requiring a multimodal approach that integrates clinical, genetic, and imaging data, especially cardiac magnetic resonance imaging, which is essential for the detection of myocardial fibrosis and for prognostic assessment. Recent evidence indicates that pathogenic *FLNC* variants have also been rarely associated with severe acute myocarditis, often presenting with malignant ventricular arrhythmias and systolic dysfunction. Accurate diagnosis, continuous monitoring, and family counseling are essential to define the best therapeutic

Keywords

Filamins; Cardiomyopathies; Sudden Cardiac Death.

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and prognostic approach for patients, especially those at high risk of sudden cardiac death (SCD), thus allowing personalized and preventive interventions.

Introduction

Filamins participate in the preservation of cellular three-dimensional structure and architecture. In particular, filamin C (*FLNC*) is expressed in striated cells of skeletal muscle and cardiac muscle, and is an essential protein in the stabilization of the sarcomere and the integrity of the cellular cytoskeleton by binding actin filaments to plasma adhesion receptors on the cell membrane.[1,2] The protein is encoded by the *FLNC* gene, present on chromosome 7, and the first description of a pathological condition related to a variant present in the gene was published in 2005, in which members of a family of German origin presented myofibrillar pathology manifested by progressive musculoskeletal weakness.[3] Another 31 patients from four German families affected by pathogenic variants in the *FLNC* gene with a myofibrillar myopathy phenotype had one-third of them with cardiac abnormalities indicative of cardiovascular involvement by filaminopathy.[4]

The first report of an isolated cardiac phenotype was in 2014, in patients with hypertrophic cardiomyopathy (HCM).[5] Since then, other phenotypes of cardiomyopathies (dilated, arrhythmogenic, and restrictive) associated with variants in the *FLNC* gene have been described, with some carriers exhibiting phenotype changes as the disease naturally progresses.[6-9]

The growing knowledge of pathogenic variants in genes related to different cardiomyopathies, combined with greater access to genetic testing, reinforces the role of genetics in myocardial diseases. *FLNC* gene variants are particularly relevant due to their diverse phenotypic manifestations and potential malignant course. This article aims to review the participation of filamin C in the structure and function of cardiomyocytes, the pathogenic variants in its gene, and the pathogenesis associated with them, typical characteristics in imaging exams, and risk stratification of its carriers.

Clinical Case

A 37-year-old woman complained of palpitations since adolescence and was initially diagnosed with benign ventricular extrasystoles, without structural cardiac alterations. Despite the use of multiple antiarrhythmic medications, the symptoms persisted. Family history: father with sudden death (SD) at 34 years of age; grandmother with SD before age 50; 35-year-old brother with similar symptoms and at 33 years of age had a stroke.

During the etiological investigation of the ventricular extrasystole, an electrocardiogram (ECG) was performed, which showed sinus rhythm and low QRS voltage in peripheral leads. Doppler echocardiogram (ECHO): diffuse hypokinesia with systolic dysfunction with left ventricular ejection fraction (LVEF) by Teichholz method at 39%; 24-hour Holter monitoring with findings of frequent ventricular extrasystoles: 4339 isolated, 112 pairs and 2 episodes of non-sustained ventricular tachycardia (NSVT); exercise test: episode of NSVT; cardiac magnetic resonance imaging (CMR): extensive foci of late enhancement of diffuse midwall and subepicardial distribution, compatible with non-ischemic fibrosis (Figure 1). PET-CT with 18F-FDG ruled out the hypothesis of sarcoidosis or active myocarditis.

Due to the clinical suspicion of arrhythmogenic cardiomyopathy, she underwent genetic sequencing (NGS), which detected a probably pathogenic variant in the FLNC in heterozygosis: NM_001458.4:c.6663_6664del;p.(Phe2222Trpfs*22).

After her diagnosis, her brother underwent CMR, which showed the presence of fibrosis with a non-ischemic

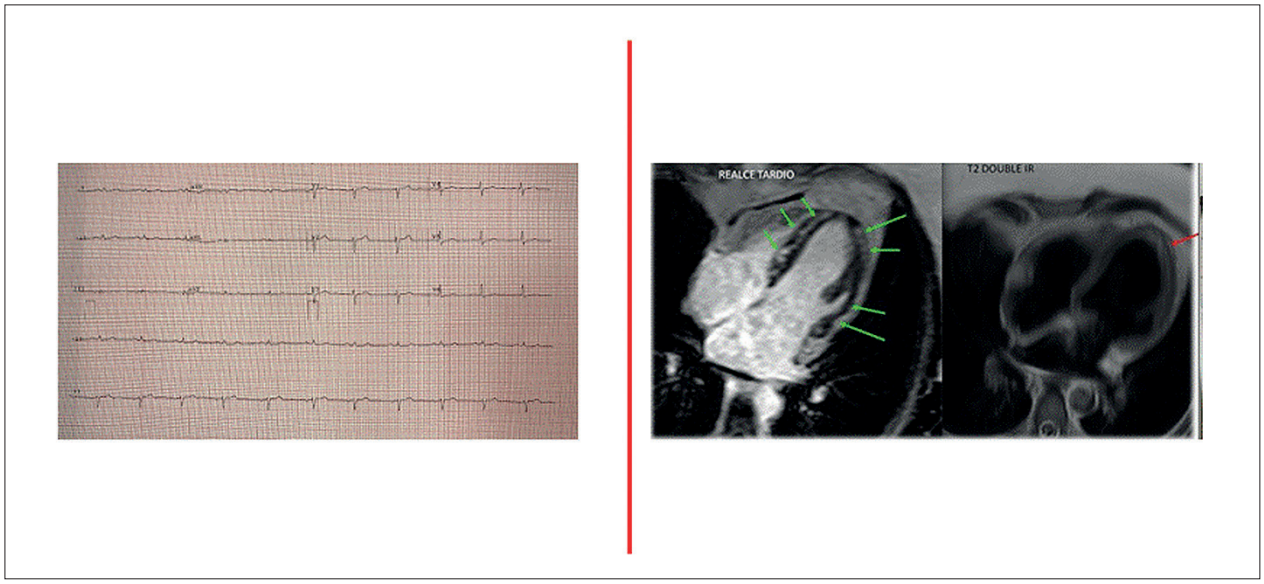

Figure 1 – *Electrocardiogram (low voltage in peripheral leads) and cardiac magnetic resonance (arrows highlighting non-ischemic, midwall late enhancement).*

distribution pattern. A 24-hour Holter and exercise test showed ventricular extrasystoles and episodes of NSVT. He underwent the Sanger technique, through family screening, which confirmed the presence of the same variant in the *FLNC*. After genetic diagnosis, both patients underwent an implantable cardioverter defibrillator (ICD) as primary prophylaxis for SCD.

Genetic aspects of FLNC variants

FLNC is an essential structural protein that plays a crucial role in maintaining the mechanical and functional integrity of the cardiomyocyte cytoskeleton. Encoded by the *FLNC* gene, located on chromosome 7q32.1, this protein is responsible for the intertwining of actin filaments and the regulation of interactions between structural and signaling proteins, promoting sarcomere stability and coordinated muscle function.[10]

Pathogenic variants in the *FLNC* gene can be classified into two main groups: truncating and missense. While both classes result in severe functional alterations in the protein, they contribute differently to a range of clinical phenotypes, from inherited cardiomyopathies to skeletal muscle diseases. Truncating variants include nonsense variants, which often result in the production of shortened proteins. These variants are mainly associated with arrhythmogenic and dilated cardiomyopathies. The molecular impact includes impairment of cytoskeletal organization and activation of apoptotic processes in the cardiomyocyte, leading to contractile dysfunction and cardiac remodeling.[7,11] One example is the p.W2710X variant, which leads to the loss of the terminal 16 amino acids of filamin C, impairing its dimerization capacity. This deficiency results in the formation of protein aggregates containing the abnormal form of filamin C and other Z-disc proteins, characterizing myofibrillar myopathies.[12] Additionally, truncating variants, such as p.Arg650X and Val2715fs87X, are associated with high penetrance, early onset of symptoms, and increased risk of SCD, with a mean age of fatal events of approximately 42 years.[7,13]

Missense variants cause amino acid substitutions, most frequently associated with HCM and overlapping phenotypes, including restrictive cardiomyopathy. These variants alter the three-dimensional structure of the protein, impairing its interaction with cytoskeletal components and cellular signaling pathways. One example is the p.A1186V variant, implicated in early-onset restrictive cardiomyopathies, often accompanied by severe heart failure (HF).[14] Studies show that missense variants affecting the ROD2 domain of filamin C are more likely to generate protein aggregates. These aggregates, composed of dysfunctional proteins, activate cellular stress pathways, such as the ubiquitin-proteasome system and autophagy, exacerbating myofibrillar degeneration and contributing to a more severe clinical phenotype.[1,15]

Influence of location and age

The severity of *FLNC* variants is closely linked to their specific location within the gene and the carrier's age. Alterations in the C-terminal end of the protein are associated with more severe phenotypes, including increased risk of cardiac fibrosis, ventricular dilation, and malignant arrhythmias.[7,16] While truncating variants have greater penetrance in middle-aged adults, some missense variants manifest in childhood. For example, the FLNC-Ile1937Asn alteration causes end-stage HF in young patients, with a mean age of symptom onset of 19 years.[16,17]

Molecular impact and cardiac remodeling

At the molecular level, pathogenic variants in the *FLNC* gene trigger dysregulation of mechanical stress pathways and sarcomere disorganization. This leads to progressive myocardial fibrosis, left ventricular dilation, and eventual loss of contractile function. The formation of toxic protein aggregates in the cytoplasm aggravates cellular dysfunction and increases susceptibility to local inflammatory events.[16,17]

Advances in NGS have allowed the identification of variants of uncertain clinical significance (VUS) in the *FLNC* gene, especially in families with a history of cardiomyopathy. Genotype-phenotype correlation studies, combined with protein structural analysis, have been instrumental in reclassifying many of these variants as benign or pathogenic.[1]

Clinical and imaging aspects of *FLNC* variants

In Roman mythology, the god Janus, a deity with two different symmetrically opposed faces, represents the duality and transitions of the universe.[18] Similarly, the molecular etiology, characterized by the presence of pathogenic variants in the *FLNC* gene – whether truncated or missense –, contributes to a broad phenotypic diversity, encompassing hypertrophic, restrictive, arrhythmogenic, and dilated cardiomyopathies, in addition to possible overlaps between these phenotypes[19] (Central Illustration).

Although initially described as a pathogenic variant in patients with myofibrillar myopathy, its most prevalent association was found to be with isolated cardiomyopathy. However, some cohorts have demonstrated myopathy associated with cardiomyopathy in some clusters of families carrying *FLNC* variants.[4] Patients with skeletal myofibrillar myopathy frequently present missense and indel variants, manifesting slowly progressive proximal muscle weakness in isolation or associated with hypertrophic or restrictive cardiomyopathy. Less frequently, frameshift and nonsense variants that result in truncated proteins cause arrhythmogenic or dilated cardiomyopathy and myofibrillar structural derangement with muscle atrophy.[20]

Electrocardiogram

The main abnormalities in carriers of pathogenic variants of the *FLNC* gene are low voltage, changes in ventricular repolarization, and ventricular arrhythmias.

In a cohort of 145 patients with heart disease associated with *FLNC*, the prevalence of low voltage on the ECG was 37% and T wave inversion in inferolateral and lateral leads was 24%.[21] There was a correlation between the presence of changes in ventricular repolarization and an increased risk for SCD. Another 167 consecutive patients with truncating variants of *FLNC*, 95.7% of whom were in sinus rhythm, 4.5%

had complete left bundle branch block, 23.9% had abnormal T wave inversion, and 22.3% had low QRS voltage.[22]

A cohort study assessing the relationship between truncating *FLNC* variants and the risk of arrhythmogenic or high-risk dilated cardiomyopathy in 28 probands and 54 relatives found that 82% of affected patients exhibited ventricular arrhythmias, primarily NSVT and frequent ventricular extrasystoles (>500/24h).[7]

FLNC and cardiomyopathy phenotypes

Knowledge of the multiple facets of cardiomyopathy due to *FLNC* variants comes mainly from observational studies of patients with cardiomyopathies related to variants of this gene. A common factor in these observational studies is the use of CMR as an imaging method.

CMR has become an indispensable pillar in cardiology, particularly regarding cardiomyopathies, with implications for diagnosis and prognosis. The presence, extent, and distribution pattern of myocardial fibrosis detected by late gadolinium enhancement provide prognostic information independent of LVEF. A common distribution pattern of late enhancement in genetic cardiomyopathies is the ring-like pattern, characterized by the presence of late enhancement in the midwall-epicardium involving at least three contiguous segments in the same short-axis view.[23,24] Ring-like scarring is considered a highly specific feature of arrhythmogenic LV cardiomyopathy and represents an important diagnostic criterion in the recently published European Task Force Consensus Report.[25] It is associated with a high rate of malignant ventricular arrhythmias when compared with other LGE distribution patterns, and an additional risk may be observed in patients who, in addition to this pattern, present with an ECG with Q waves in the anterior wall, QRS widening, and ECHO with increased LV end-diastolic volume index.[23] In addition, it is known that the particularly high risk of malignant arrhythmic events in the presence of a ring-like pattern is independent of the total late enhancement burden and LVEF, which would be risk factors commonly used in the prognostic evaluation of other etiologies.[23,24]

Although still imprecise, some observational studies have sought to estimate the prevalence of *FLNC* variants in the population with cardiomyopathies. In a cohort that evaluated the presence of truncated variants of the *FLNC* gene in 2877 patients with hereditary heart diseases, the prevalence was 3.9%, 3.2% and 2.2% for dilated, arrhythmogenic, and restrictive cardiomyopathy, respectively, and there were no cases of HCM. There was high penetrance (97%) in patients over 40 years of age who presented with the following main symptoms: dyspnea on exertion and palpitations. Most affected patients (probands and relatives with truncated variants) presented ventricular dilation, LVEF < 55% and delayed enhancement mainly in the epicardial region of the left ventricle (LV) on CMR. This phenotype was associated with a high potential for malignant arrhythmias, with 40 SCD in 21 of the 28 families analyzed. Structural alterations in the right ventricle (RV) occurred in a minority of cases. Of these, all also had LV involvement. No patient presented clinically relevant skeletal myopathy.[7]

In another cohort of 1150 patients, which evaluated the prevalence of pathogenic variants of *FLNC* and their genotype-phenotype correlation in different cardiomyopathies, 1.3% of patients had a hypertrophic phenotype, 3% had dilated phenotypes, and 8% had restrictive phenotypes. Carriers of truncating variants exclusively exhibited the dilated phenotype, while missense variants were associated with the hypertrophic phenotype. There was no manifestation of skeletal myopathy in any of the cases.[26] Indeed, in light of current evidence, the hypertrophic phenotype is infrequent in carriers of *FLNC* variants, and in most of these cases, the presentation is with mild symptoms, non-severe forms, and incomplete penetrance.[27]

A combined analysis of individual data from 145 patients with arrhythmogenic and/or dilated cardiomyopathy associated with *FLNC* evaluated the clinical profile and factors related to the risk of SCD.[21] The main findings of this study were: (1) predominance of arrhythmogenic LV cardiomyopathy (67%), but RV dominance forms were also found; (2) most patients (75%) had late enhancement suggestive of non-ischemic pattern myocardial fibrosis on CMR; (3) SCD occurred in 19% (28/145) of individuals and was associated with the presence of repolarization changes in inferolateral/lateral leads on the ECG and late enhancement/myocardial fibrosis in the LV; (4) frequent ventricular extrasystoles, LV dilation and LVEF < 35% were not associated with the SCD outcome. The lack of correlation between LVEF and the risk of serious arrhythmic events was validated in another observational study in which the frequency of malignant ventricular arrhythmia (SCD, aborted SCD, ICD shock, and sustained ventricular tachycardia) was similar in the group with mild to moderate LV dysfunction when compared to the group with LVEF ≤ 35% assessed by ECHO.[22]

A summary of the main findings of these retrospective cohorts is presented in Table 1.

Another important use of CMR is in the differential diagnosis between genetic cardiomyopathies that may present different patterns of delayed enhancement distribution. Figure 2 describes the distribution pattern of delayed enhancement of some of the main variants related to genetic cardiomyopathies.[28-31]

A cohort study compared the role of CMR in carriers of truncated *FLNC* and titin (*TTN*) variants, two of the main causes of genetic cardiomyopathy in patients with dilated cardiomyopathy and arrhythmogenic cardiomyopathy phenotypes.[32] The frequency and extent of myocardial fibrosis, assessed by the delayed enhancement technique, were significantly higher in carriers of *FLNC* variants than in carriers of *TTN* variants. There was also a difference in relation to the location of the area of fibrosis. In carriers of *FLNC* variants, there was a predominance of non-ischemic fibrosis, i.e., epicardial, midwall, or a combination of both, in the inferior and lateral region of the LV. In contrast, in carriers of *TTN*, the interventricular septum was the most affected region. The ring-like distribution pattern was found in 84% of the *FLNC* group and in only one patient with a truncated *TTN* variant, thus being a useful tool in

Table 1 – Summary of major cohort studies of *FLNC* variants

Study	Objective of the study	Sample	Main findings
Ortiz-Genga et al.[7] (2016)	To evaluate the association of truncating *FLNC* variants with high-risk ACMP or DCMP phenotype	2877 people with hereditary heart disease	tvFLNC in 3.9% of DCMP, 3.2% of ACMP, 2.2% of RCMP carriers. SCD in 40 individuals from 21 of the 28 families analyzed with tvFLNC
Gómez et al.[27] (2017)	To assess the prevalence of *FLNC* variants in a sample of HCM carriers	448 HCM patients and 450 healthy controls	HCM x control group (3.1 x 0.2%) p= 0.007 HCM group: 20 variants in 22 patients (19 missense; 1 nonsense, being 6 PP, 10 VUS) Control group: 1 missense variant
Ader et al.[26] (2019)	To assess the prevalence of the *FLNC* variant in a sample of patients with cardiomyopathies	1150 patients with cardiomyopathies of different phenotypes	*FLNC* variants in 1.3% of HCM, 3% of DCMP, and 8% of RCMP patients
Akhtar et al.[22] (2021)	To assess risk factors associated with serious adverse events in patients with tvFLNC	167 tvFLNC carriers	Increased risk of serious adverse events in probands, presence of late enhancement on CMR, and reduction of LVEF > 10% compared to LVEF of 50%
Celeghin et al.[21] (2021)	To evaluate risk factors associated with SCD in carriers of *FLNC* variants	145 patients with DCMP and ACMP related to variants in *FLNC*	Increased risk associated with repolarization changes in inferolateral/lateral leads on ECG and late enhancement/myocardial fibrosis in the LV

FLNC*: filamin C; ACMP: arrhythmogenic cardiomyopathy; DCMP: dilated cardiomyopathy; tvFLNC: truncating variants of FLNC; HCM: hypertrophic cardiomyopathy; PP: likely pathogenic; VUS: variant of undetermined significance; RCMP: restrictive cardiomyopathy; CMR: cardiac magnetic resonance imaging; LVEF: left ventricular ejection fraction; SCD: sudden cardiac death; ECG: electrocardiogram; LV: left ventricle.*

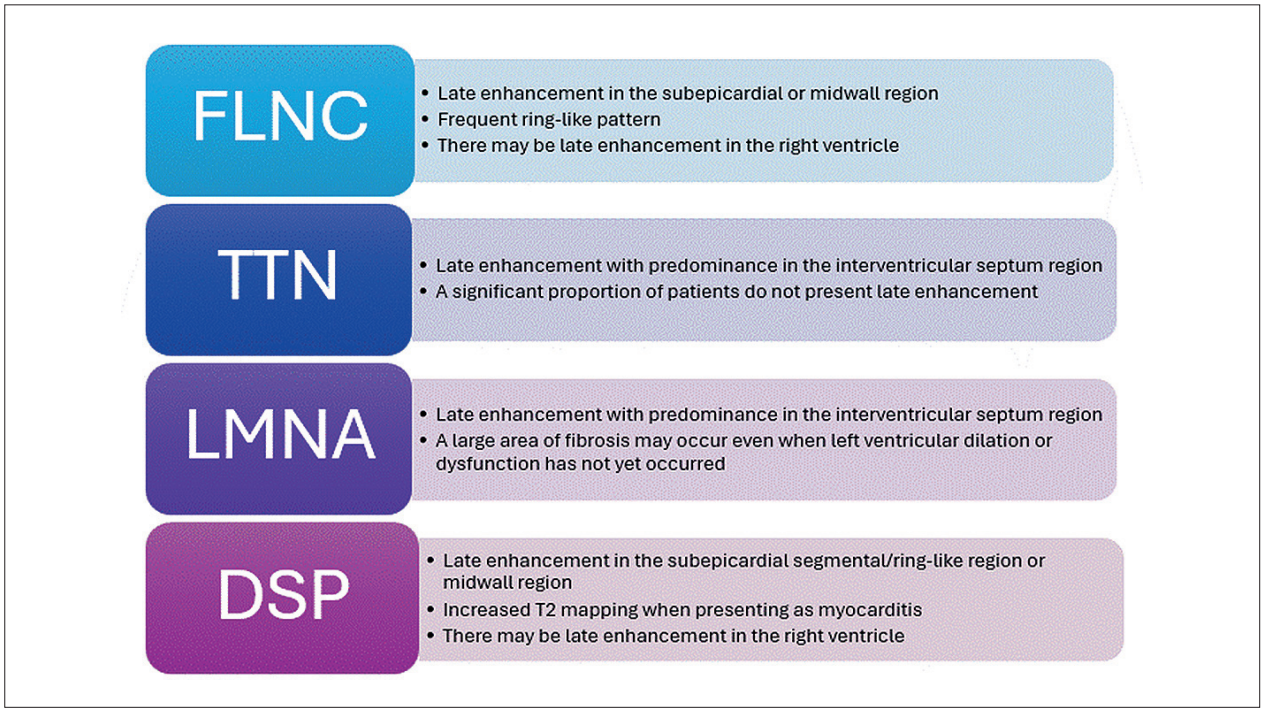

Figure 2 – *Differences in cardiac magnetic resonance imaging findings of genetic cardiomyopathies. Abbreviations:* FLNC*: Filamin C;* TTN*: Titin;* LMNA*: Lamin A/C;* DSP*: Desmoplakin.*

differentiating between the two. The phenotypic pattern of late ring-like enhancement is associated with an increased risk of malignant ventricular arrhythmias and SCD.[23,24]

FLNC and myocarditis

Myocarditis is an inflammatory heart disease of infectious or non-infectious etiology, such as induced by drug hypersensitivity, autoimmune disease, or immune-mediated disease related to vaccines. It presents a heterogeneous clinical presentation, ranging from asymptomatic/oligosymptomatic presentation to septic shock or SD.[33,34] Recent evidence suggests that greater susceptibility to myocarditis after exposure to external factors and the heterogeneity of clinical presentation may depend on a genetic predisposition.

Pathogenic/probably pathogenic variants of the *TTN* and *DSP* genes have been identified as the most prevalent in case series of patients affected by acute myocarditis.[35,36] Truncated variants of *FLNC* have also been described and are generally related to severe forms manifesting with malignant ventricular arrhythmias, alteration of left ventricular or biventricular systolic function, and SCD.[37-39]

There also appears to be a correlation with greater severity in carriers of genetic variants who present with acute myocarditis when compared to individuals who do not carry genetic variants who present with acute myocardial inflammatory disease, with a higher prevalence of acute HF, reduced LVEF, and malignant ventricular arrhythmias. [35,39] Therefore, patients who present with severe or recurrent acute myocarditis or who have a family history of non-ischemic cardiomyopathy or SD in young people should be investigated for the presence of associated genetic cardiomyopathy.[33-35,40]

FLNC and mitral valve prolapse

Mitral valve prolapse (MVP) has historically been considered a benign entity and is the most common valvular abnormality. Recently, a small subgroup of an arrhythmogenic form of this abnormality has attracted attention due to the risk of ventricular arrhythmias and SCD in its carriers.[41] In a case report study with familial segregation of relatives with a similar phenotype, through genetic testing with exome analysis, a new truncating variant related to the *FLNC* gene (p.Trp34*-FLNC) was identified in this family.[42] Affected patients presented prolapse of both leaflets, mitral annular disjunction, frequent and complex ventricular arrhythmias, and mild to moderate LV enlargement. Although this is the only report in the literature, it raises the possibility of future studies that may consolidate the association, in some cases, of both entities: cardiac manifestation due to a pathogenic variant in *FLNC* and Arrhythmogenic MVP Syndrome.

Risk stratification of *FLNC* carriers

SCD is frequently reported in *FLNC* carriers, especially with truncating variants, and may be the initial presentation in 5% of cases or seen during clinical follow-up in 15% of patients.[21] Although LVEF ≤ 35% is an independent risk marker for cardiac death and all-cause death in several cardiomyopathies, some genetic etiologies, including *FLNC* variants, confer a higher risk of SCD, regardless of the LVEF value, suggesting that additional risk factors should be taken into account when deciding on the indication for an ICD.[8,22] The 2023 European Society of Cardiology Guideline on the management of cardiomyopathies endorses this approach with a recommendation IIa, level of evidence C that ICD implantation should be considered for primary prevention of SCD in patients with dilated cardiomyopathy with LVEF ≥ 35% and *FLNC* truncating variant genotype when in the presence of the following additional risk factors for SCD: delayed enhancement on CMR and LVEF < 45%.[43]

Among the clinical criteria described as risk predictors for SCD in patients with truncating variants in *FLNC*, the proband has a higher risk when compared to diagnosed family members, in addition to the presence of a family history of SCD being an important predictor of events.[8]

The ECG with characteristics that may be useful in the diagnostic suspicion also helps in the risk assessment for SCD when low QRS voltages of V1–V3 and T wave inversion are present in inferolateral/lateral leads, possibly correlating with myocardial scarring.[21,22] In addition, the presence of NSVT and high density of ventricular extrasystoles, which may be a reflection of electrical instability, also help to guide ICD implantation.[8,21]

Late enhancement CMR is the main imaging modality for risk stratification, as it provides confirmation of the presence of myocardial fibrosis and describes the extent and pattern of its scar distribution. The phenotypic pattern of delayed ring-like enhancement is associated with a higher risk of malignant ventricular arrhythmias and SCD, and is an important finding with prognostic value.[21,23,24]

Therefore, even with preserved LVEF, these factors should be considered together to determine the individual risk of adverse events.[21,22] Patients with variants in the *FLNC* gene should be stratified and monitored, for example, for indication of primary prophylaxis and adequate preventive follow-up. (Table 2).

Conclusion

Variants in the *FLNC* gene represent a clinical and diagnostic challenge due to their wide phenotypic heterogeneity and high risk of SCD, even in patients with preserved ejection fraction. Early identification of these variants, combined with advanced imaging tools and genetic testing, is crucial for risk stratification and implementation of preventive strategies. Management should be integrated, considering clinical, genetic, and structural aspects, to optimize the prevention of fatal events and improve the quality of life of carriers.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript and Critical revision of the manuscript for content: Nunes F, Couto RGT, Avila DX, Torbey AFM, Luciano KS, Figueiredo EL, Mesquita ET.

Table 2 – Risk factors for sudden cardiac death in carriers of pathogenic *FLNC* variants

	Risk	Action
Variant type	Truncated variant in *FLNC* is associated with arrhythmogenic left ventricular cardiomyopathy and increased risk of ventricular arrhythmias.	Genetic evaluation and counseling
Family history	Early SCD	Family screening and monitoring
Phenotype	Arrhythmogenic or dilated, often with left ventricular dysfunction	Transthoracic echocardiogram. Magnetic resonance imaging of the heart at rest with a ring-like distribution pattern
Arrhythmias	Documented ventricular fibrillation or SVT.	Holter or implantable devices. Electrophysiological study if necessary.
Electrocardiogram	Abnormalities such as inverted T wave, repolarization changes in inferolateral and lateral leads, low voltage, or bundle branch blocks. Ventricular extrasystoles in high incidence.	Periodic ECG
Syncope	Unexplained syncope may indicate high risk	Electrophysiological study
Ventricular dysfunction	Reduced LVEF implies high SCD risk	Consider ICD
Myocardial fibrosis	Fibrosis implies high risk	CMR and late enhancement monitoring, consider ICD
Exercise	High intensity implies high risk	Restriction of competitive physical activity
Dyspnea	Presence of heart failure	Optimized clinical management and regular follow-up

SVT: sustained ventricular tachycardia; LVEF: left ventricular ejection fraction; SCD: sudden cardiac death; ECG: electrocardiogram; CMR: cardiac magnetic resonance imaging; ICD: implantable cardioverter defibrillator.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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