Review Article

Filamin C and Cardiomyopathies: Linking Genetic Variants to Their Phenotypic Impact

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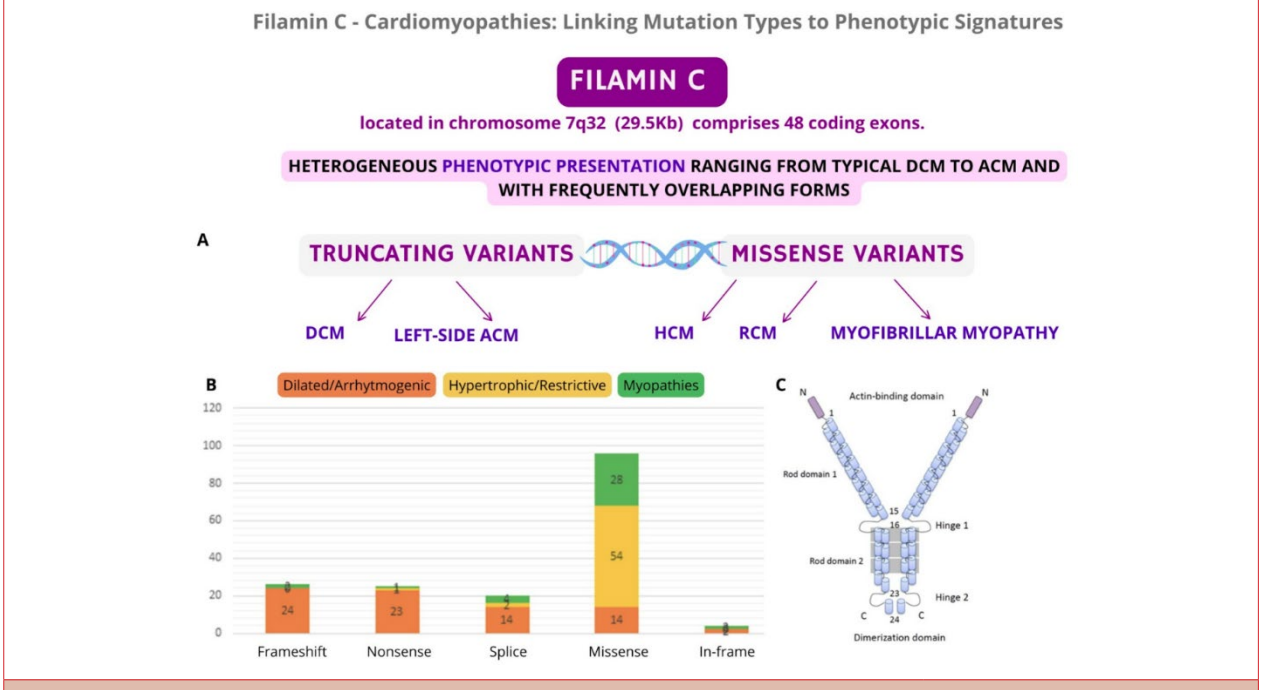
Central Illustration: Filamin C and Cardiomyopathies: Linking Genetic Variants to Their Phenotypic Impact



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A) Filamin C Cardiomyopathies: Overview of genetic variants in association with their cardiac phenotype. Adapted from Verdonschot JAJ et al. and Razinia Z et al.[1,3] B) Graph showing mutation types and cardiac phenotypes. C) Protein structure encoded by the FLNC gene and its respective domains. ACM: arrhythmogenic cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy.

Keywords

Filamins; Dilated Cardiomyopathy; Arrhythmogenic Right Ventricular Dysplasia; Hypertrophic Cardiomyopathy; Restrictive Cardiomyopathy

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Abstract

Filamin C (FLNC) plays a critical role in maintaining the structural integrity of muscle cells, particularly within the cardiac sarcomere. Pathogenic variants in the *FLNC* gene are increasingly recognized as significant contributors to a diverse range of cardiomyopathies, including dilated (DCM), hypertrophic (HCM), arrhythmogenic (ACM), and restrictive cardiomyopathy (RCM). This review explores the genotype-phenotype correlations in FLNC-related cardiomyopathies, emphasizing how the type and location of genetic variants influence the clinical presentation.

Truncating variants are primarily associated with DCM and ACM, characterized by a high risk of arrhythmic events and severe outcomes, while *missense* variants often lead to HCM and RCM, with unique phenotypic features. The review also discusses the inheritance patterns, molecular mechanisms, and clinical phenotypes of *FLNC*-associated myopathies, highlighting the need for genetic testing in risk stratification and management. Future perspectives emphasize the importance of expanding research into the underlying mechanisms of *FLNC* variants and their interactions with other genetic and environmental factors. This integrated understanding is critical for improving the clinical management of patients with *FLNC*-related cardiomyopathies.

Introduction

In an era of precision medicine, understanding the complexities of genetic cardiomyopathies is crucial for enhancing the effectiveness of cardiology care and providing individualized patient management. As the field of cardiology advances, understanding the genotype-phenotype correlations in cardiomyopathies has become increasingly important. Specific genetic variants are linked to distinct clinical outcomes. The integration of genetic testing into clinical practice offers the potential for more accurate risk stratification, allowing cardiologists to personalize treatment strategies for patients with cardiomyopathies. Filamin C (FLNC) is a key cytoskeletal protein essential for maintaining the structural integrity of muscle cells, particularly within the cardiac sarcomere. In recent years, pathogenic variants in the *FLNC* gene have emerged as significant contributors to a diverse array of cardiomyopathies, including dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (ACM), and restrictive cardiomyopathy (RCM). These conditions, which often present with variable and overlapping clinical features, pose significant challenges for clinicians in terms of diagnosis, prognosis, and management. This review aims to provide an in-depth analysis of how these genetic alterations influence disease manifestations and clinical outcomes, with an emphasis on their relevance to precision medicine.

Gene *FLNC* and structural role of Filamin C

The gene *FLNC* is located in chromosome 7q32.1, stretches over 29.5Kb of genomic DNA, and comprises 48 coding exons in the canonical transcript (ENST00000325888.13/NM_001458.5).[1] *FLNC* tissue expression is increased predominantly in skeletal muscle, left ventricle (LV), and atrial appendage, as indicated in Figure 1. The *FLNC* encodes the protein filamin C, a sarcomeric muscle-specific protein involved in myocyte differentiation and muscle function, by interacting with proteins of both the Z-disc and the sarcolemma. Filamin C plays a critical role in preserving the structural integrity of the sarcomere by crosslinking actin filaments and anchoring sarcolemmal proteins[1] to the cytoskeleton in cardiac and skeletal muscle cells.[2] The protein is composed of an amino-terminal actin-binding domain and an ROD of 24 Ig-like domains, which are connected by flexible hinge regions between domains 15 and 16 (hinge 1) and domains 23 and 24 (hinge 2).[3] The Ig-like domains are subdivided into ROD1 and ROD2, which bind to different ligands due to organizational differences.[1] The dimerization of two identical filamin proteins occurs via the Ig-like 2 domain and is required for appropriate function.[1]

Inheritance patterns and disease mechanisms of *FLNC* variants

Cardiomyopathies associated with the Filamin C gene can exhibit various patterns of inheritance, including both autosomal recessive and autosomal dominant patterns.[4] While *FLNC* was initially linked with dominant forms of myopathy and cardiomyopathy, two cases reported biallelic variants in this gene in association with isolated myopathy or cardiomyopathy. Recessive *FLNC* variants have been reported in patients with the phenotype of both cardiomyopathy and myopathy.[4] Nevertheless, gene curations in OMIM and ClinGen databases do not include autosomal recessive patterns yet. The phenotype associated with *FLNC* variants is highly heterogeneous, with recessive forms generally exhibiting earlier onset and increased severity.[4] *FLNC* is highly intolerant for loss-of-function variants,[1] whereas haploinsufficiency has been suggested as the most probable reason for the disease phenotype in a number of patients with *FLNC*-induced myopathy.[5]

Heterozygous variants in *FLNC* were initially only linked with isolated skeletal and myofibrillar myopathy.[4] The initial descriptions of *FLNC* variants were primarily related to myopathies associated with skeletal muscle disease, as a particular form of myofibrillar myopathy. Cardiac involvement was mentioned without specific features. This picture evolved, and now it is recognized that Filamin C is widely expressed in cardiac myocytes, and different genetic variants appear to be associated with specific cardiomyopathy phenotypes.

For instance, the variant *FLNC* c.2389+1C > A affecting the donor splice site at the end of exon 15 causes exon skipping, creating a stop codon and, consequently, a truncated protein. This haploinsufficiency leads to a decreased amount of Filamin-C protein associated with highly penetrant and more aggressive phenotypes.[4,6]

In the next session, we will systematically review the correlation between variants on *FLNC* and the phenotypic markers, which are helping to elucidate the main clinical features of Filamin C-induced cardiomyopathies.

Variant-Specific phenotypic expression in *FLNC*-Related cardiomyopathies

Genotype-phenotype correlation in *FLNC*-related cardiomyopathies is dependent on the nature of the protein modification due to the type and site of the pathogenic genetic variant. For instance, truncating *FLNC* variants, caused by *frameshift*, *nonsense*, and *splice-site* variants, typically manifest as DCM or ACM,[2,7-10] whereas

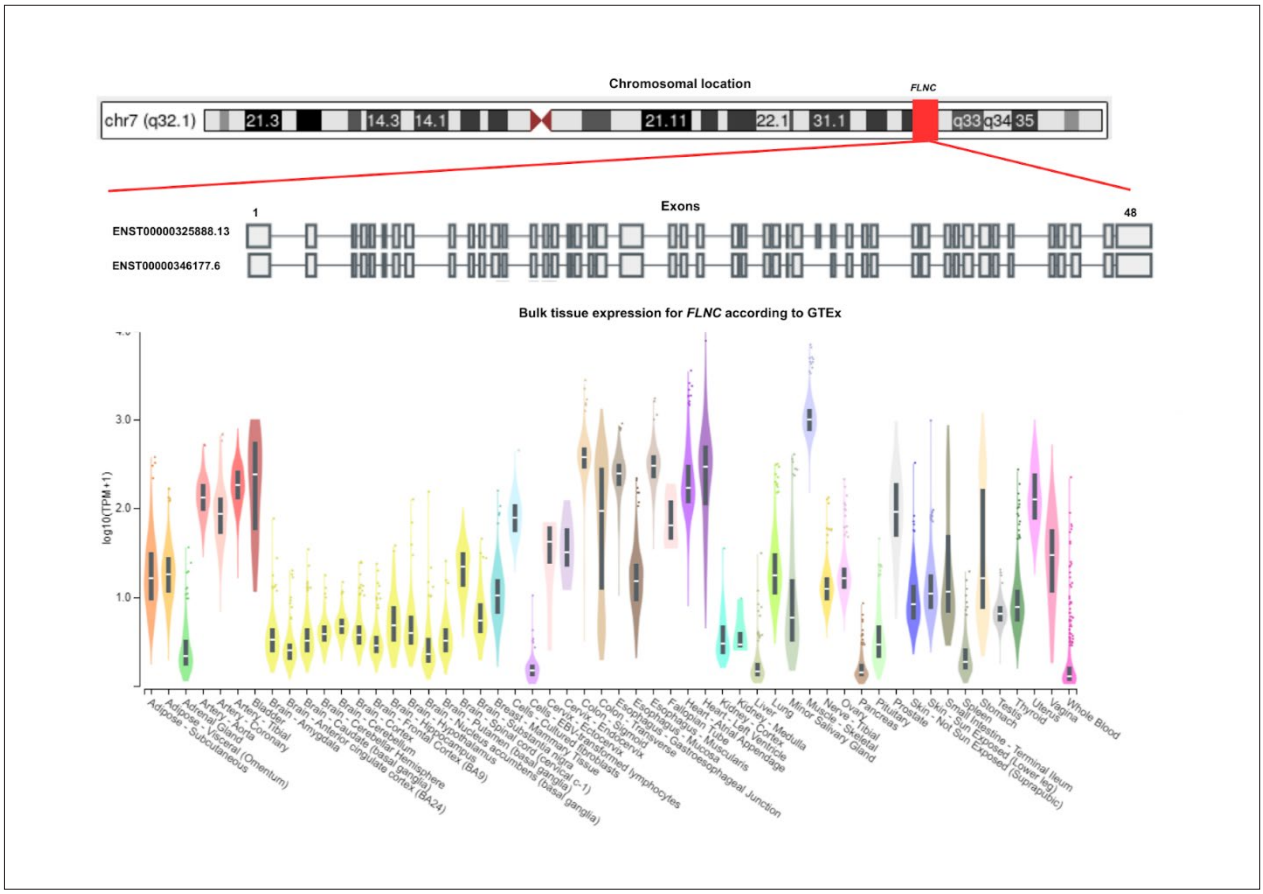

Figure 1 – *Chromosomal location of FLNC gene in 7q32.1, the transcripts including the canonical and the shorter transcript and bulk tissue expression of FLNC according to GTEx, indicating increased expression in skeletal muscle and heart.*

FLNC-related HCM or RCM phenotypes are usually linked to changes in the protein caused by *missense* genetic variants.[1,11,12] The overview of genetic variants in association with their cardiac phenotype is summarized in Central Illustration.

Truncating *FLNC* variants: Association with DCM and ACM

As mentioned, *FLNC* truncating variants (*FLNC*tv) are associated with haploinsufficiency and DCM and left-side ACM,[2] and the location of the variant seems not to modify the severity of the phenotype as reports of *FLNC*tv include variants spread across various exons.[1,9,10] The variants predicted to result in a premature stop codon are enriched in DCM, and the prevalence of *FLNC* variants in patients with DCM ranges from 1% to 5%.[2,8,13,14]

Missense FLNC variants: Links to HCM and RCM

FLNC missense variants are mainly associated with HCM and RCM with a varying prevalence from 1.3% to 8.7% in HCM cohorts.[11-13,15] Of note, *FLNC missense* HCM variants show a clustering in the ROD2 domain of the gene, suggesting a possible hotspot and indicating that the location of the variant might influence the development of this specific phenotype.[1] *Missense* variants in other domains, albeit less common, have also been reported.[1]

Characterization of cardiomyopathy phenotypes in *FLNC* variants

We have seen that the *FLNC* gene is associated with different forms of autosomal dominant cardiomyopathy, including DCM, HCM, RCM forms, and myofibrillar myopathy.[11] *FLNC*tv cardiomyopathy appears to be a disease with heterogeneous phenotypic presentation ranging from typical DCM to ACM and with frequently overlapping forms.[10]

Dilated cardiomyopathy

DCM is characterized by left ventricular dilation and systolic dysfunction that cannot be explained by abnormal loading conditions or coronary artery disease.[16] The etiology of DCM is heterogeneous, encompassing both acquired and inherited causes and may involve a complex interplay between genetic and acquired factors. Notably, 30% of DCM cases are linked to rare pathogenic variants.[17] Titin is the most frequently affected gene,[18,19] followed by *DSP,*

MYH7, LMNA, BAG3, TNNT2, TNNC1, TNNI3, PLN, ACTC1, ACTN2, NEXN, JPH2, SCN5A, TPM1, RBM20, DES, FLNC and *VCL*.[20]

DCM individuals with pathogenic or likely pathogenic genetic variants experience worse clinical outcomes and a higher incidence of major arrhythmic events compared to genotype-negative patients, especially with a left ventricular ejection fraction (LVEF) ≤ 35%. Certain genotypes, particularly those involving nuclear envelope, desmosomal, and cytoskeletal proteins, carry an elevated risk of arrhythmic events regardless of LVEF. Variants in *FLNC* have also been associated with increased arrhythmic risk.[17]

Accordingly, genetic testing can be instrumental in considering prophylactic cardiac defibrillator (ICD) implantation in DCM, and an ICD should be contemplated for genotype-positive DCM patients.[17] In this regard, ICDs should be considered for primary prevention in DCM patients harboring high-risk genetic variants (*LMNA, EMD, TMEM43, DSP, RBM20, PLN, FLNCtv)*, even at LVEF thresholds above 35%, especially when additional risk factors are present (example nonsustained ventricular tachycardia, increased ventricular ectopic beats, male sex, significant late gadolinium enhancement, specific genetic variant.[16,17] When the two copies of the *FLNC* gene are affected, in biallelic variants, the phenotype is devastating with end-stage heart failure, as seen in children with congenital DCM.[5]

The *FLNC p.Ile1937Asn* variant is associated with full disease penetrance HCM and a phenotype characterized by severe hypertrophy and outcomes. Fifty percent of the patients harboring this variant displayed end-stage heart failure, requiring transplantation, and one-third of the family members presented sudden cardiac death (SCD). Other particular features of *FLNC-p.Ile1937Asn* include an early disease onset (mean age of 19 years) and the development of a marked atrial myopathy with severe atrial dilatation with remodeling and multiple complex atrial arrhythmias.[21]

Arrhythmogenic cardiomyopathy

ACM is a genetic disorder characterized by high risks of life-threatening ventricular arrhythmias, SCD, and progressive heart failure.[22]

The prevalence of pathogenic variants in ACM can reach 50%, with the most commonly identified genes being desmosomal (*PKP2, DSP, DSG2, DSC2, JUP*) followed by *TTN, FLNC, LMNA, DES, BAG3, PLN, TMEM43*, and RNA binding motif protein 20 (*RBM20*).[22,23]

The phenotype ACM appears as an overlapping of dilated and arrhythmogenic cardiomyopathies, characterized by variable degrees of LV dilation and systolic dysfunction, prominent subepicardial and/or intramyocardial fibrosis of the LV, frequent ventricular arrhythmias, and SCD.[2] LV myocardial fibrosis is mainly subepicardial with inferoposterolateral distribution.[2] The classic right predominant form of ACM has not been observed in cardiomyopathies caused by *FLNC*tv. The cardiac conduction abnormalities appear to fall between the severe conduction defects observed in laminopathies and the absence of such defects seen in desmosomal ACM. *FLNC*-associated DCM is more malignant, characterized by ventricular arrhythmias, myocardial fibrosis, and a high risk of SCD.[2] The average age of onset is in the fourth decade of life, with the presence of inferolateral negative T waves on the electrocardiogram, mild to moderate LV dysfunction, regional dyskinesia, and the ring-like scar pattern in the LV.[2]

The presence of certain ACM features, such as frequent premature ventricular complexes, nonsustained ventricular tachycardia (NSVT), or negative anterior T waves, raises suspicion for an underlying *FLNC*tv.[10] Additionally, low-voltage ECG findings may serve as a diagnostic marker.[24] Low-voltage QRS complexes are a risk marker for arrhythmic events in ACM[25] and may also be relevant for *FLNC*-related cardiomyopathies.

There is a strong correlation between LV dysfunction and an increased risk of adverse heart failure outcomes, such as heart failure-related mortality, heart transplantation, and the use of LV assist devices. However, arrhythmic events, including SCD and major ventricular arrhythmias, occur independently of low LVEF.[10] The hallmark of the phenotype is ventricular arrhythmias, which are independent of the degree of LV dysfunction, as indicated by the lack of correlation with LVEF.[10] This lack of correlation highlights the need for alternative strategies to stratify the arrhythmic risk and the importance of identifying novel biomarkers to predict arrhythmic risk.

*FLNC*tv has a significant risk for life-threatening ventricular arrhythmias, including SCD and major ventricular arrhythmias, compared to other high-risk genes, such as *LMNA* and *DSP*.[2]

The 2019 Heart Rhythm Society consensus guidelines on ACM included the *FLNC*, suggesting it be considered a high-risk marker for SCD.[22] Genetic-specific recommendations of ICD have been included in the most recent guidelines. There are specific recommendations for primary prevention of SCD in these patients when LVEF is lower than 45% (Class of Recommendation IIa).[26]

Genetic variants are associated with an increased risk of SCD when pathogenic or likely pathogenic variants are detected in specific high-risk genes: *FLNC, DES, DSP, PLN, LMNA, TMEM43, RMB20*.[22] Recent evidence suggests that phenotype plays a role in SCD risk, with patients harboring disease-causing variants in *PLN, DSP, LMNA, FLNC, TMEM43*, and *RBM20* having a substantially higher rate of major arrhythmic events than other causes of DCM regardless of LVEF.[16]

Myocarditis, by clinical and histological criteria, is a common presentation in patients with *FLNC* pathogenic variants.[26] Arrhythmic risk and the risk of SCD appear to be elevated during periods of myocardial inflammation in patients with *FLNC* variants.[26]

The prevalence of pathogenic variants reaches up to 50% of ACM of myocarditis cases, depending on the population studied, with the most commonly identified genes being desmoplakin, titin, *FLNC*, and RNA binding motif protein 20 (*RBM20*).[23] In a cohort of 21 cases of recurrent myocarditis,

it was found that approximately one-third of patients displayed a previously unknown pathogenic or likely pathogenic variant, mostly affecting the *DSP* gene.[27]

Hypertrophic cardiomyopathy

HCM is a common inherited heart disease characterized predominantly by LV hypertrophy in the absence of another cardiac, systemic, or metabolic disease capable of producing the magnitude of hypertrophy evident in a given patient and for which a disease-causing sarcomere (or sarcomere-related) variant is identified, or genetic etiology remains unresolved.[16]

HCM is considered to be an inherited disease with an autosomal dominant inheritance pattern. Several genes, mostly encoding sarcomere proteins, account for more than half of HCM cases.[15] *FLNC missense* variants have been associated with HCM phenotype since the cosegregation of the variant p.Ala1539Thr with HCM, which later found six additional *FLNC missense* variants segregating with the disease in eight families.[11] These authors also demonstrated that *FLNC* variants affect cardiac muscle structure, showing that histological analysis of cardiac muscle revealed marked sarcomeric abnormalities, including myofibrillar disarray, sarcomeric aggregates, and fibrosis not observed in control hearts from either three HCM patients without variants in *FLNC* or from a healthy subject.[11] These *missense* variants are distributed in various domains of the filamin C protein; however, as previously stated, there appears to be a *cluster* in ROD2.1.[15] *FLNC*-related cardiomyopathy patients rarely display skeletal myopathy. The patients affected by *FLNC missense* variants show a higher risk of SCD than patients with HCM without pathogenic variants.[15] Although *FLNC* variants account for only 2% of variant-positive HCM cases, the affected individuals frequently present severe phenotypes and severe clinical outcomes.[11-13,15]

Although some studies have linked *missense* variants in the *FLNC* to HCM, the prevalence of these *FLNC missense* variants in population databases is significantly higher (4%) than expected based on the known prevalence of HCM (0.2%). Consequently, *FLNC* variants are common in both HCM patients and healthy individuals, and initially, this matter raised questions about the association of these variants with clinical manifestations and prognosis in HCM patients. A large-scale screening of *FLNC* in 448 HCM patients and 450 healthy controls study identified 20 *FLNC* candidate variants (1 *nonsense* and 19 *missense*). The pathogenicity analyses classified 6 of the candidate variants as likely pathogenic, 10 as variants of uncertain significance, and 4 as likely benign. The authors proposed that *FLNC missense* variants can be likely associated with the development of HCM phenotype.[12]

A novel *FLNC* variant *p.(Ile1937Asn)* has been identified in a large family of French-Canadian descent with excellent segregation data. The clinical characterization data show that none of the affected patients presented LV dynamic obstruction. The HCM phenotype is characterized by septal or diffuse LV hypertrophy, and there are no cases of isolated apical HCM or LV apical aneurysms.[21]

Restrictive cardiomyopathy

RCM is a rare form of cardiac muscle disease characterized by ventricular diastolic dysfunction with preserved systolic function.[28] Genetic analyses uncovered various candidate pathogenic gene variants in RCM patients, including *TNNI3*, *TNNT2*, *MYL2*, *FLNC*, and *MYH7*.[28-30]

Restricting LV filling patterns were observed early in the disease course. Previous studies showed that restrictive forms of HCM represent an uncommon subtype accounting for about 1.5% of HCM cases.[21,31]

The association between RCM and *FLNC* variants was described in association with phenotypes, including supraventricular arrhythmias, high prevalence of atrial fibrillation, atrial cardiomyopathies, diastolic dysfunction, and variable degrees of myopathy.[31-34]

A review of all previously *missense* variants in *FLNC* associated with RCM shows a "mutational" hotspot located at the Ig-like repeat domains 18 to 21, a key region for interactions with several structural and signaling proteins.[32,35]

Rare *missense* variants at the ROD2 domain of the *FLNC* gene, affecting Ig-like domains from 18 to 21 (d18-21), present a singular "saw-tooth myocardium" phenotype, consisting of a severe HCM/RCM phenotype with an unusual saw-tooth LV hypertrophy and deep myocardial recesses, HF symptoms and diastolic dysfunction.[36] This ROD2 domain is essential for *FLNC* dimerization and secondary protein structure acquisition.[1] This d18-21 *cluster* interacts with Z-disc proteins, muscle development, and contraction-related proteins and is a critical point for protein phosphorylation.[36] Therefore, *missense* variants in the ROD2 subdomain may precipitate a misfolded protein and impaired crosslinking, leading to sarcomere disarray and mechanotransduction impairment.[1,36]

In pediatric presentation of RCM, pathogenic or likely-pathogenic variants are identified in 50% of patients.[28] Heart failure symptoms develop at young ages, resulting in early heart transplantation.[33]

Skeletal and myofibrillar myopathies

The term filaminopathy was introduced after a truncating mutation in the dimerization domain *FLNC* was shown to be responsible for a devastating muscle disease.[35] Early symptoms of proximal muscle weakness precede distal and respiratory muscles that are affected by disease progression.[35] The symptoms usually present after the fourth decade of life, possibly as a result of time-related impairments in the machinery that is responsible for the disposal of damaged proteins.[35] Muscle biopsies demonstrate typical signs of myofibrillar myopathy, including disintegration of myofibrils and intracellular aggregation of proteins.[35] This formation of desmin-positive protein aggregates is required for the diagnosis of myofibrillar myopathy.[35]

Nonsense mutation in the ROD domain that leads to RNA instability, haploinsufficiency with decreased expression levels of *FLNC* in the muscle fibers, and myofibrillar abnormalities are associated with non-specific myopathic abnormalities without myofibrillar myopathy pathology.[35]

Myopathies features of *FLNC*-associated myofibrillar myopathy are the symmetrical involvement of proximal muscles in the lower extremities, respiratory weakness during the disease course, and a specific set of imaging characteristics for muscle involvement.[37] About one-third of the *FLNC* myofibrillar myopathy showed cardiac involvement. Distal myopathies due to *FLNC* variants are characterized by weakness in the hand and calf muscles with an onset in early adulthood. *FLNC* variants previously identified in myofibrillar myopathy are mostly non-loss-of-functions variants, including *missense* and *in-frame* indels. The mechanism of these variants for *FLNC*-induced myopathy is attributed to the aggregation of *FLNC* and *FLNC*-binding proteins in muscle and the sarcomere.[35] The different clinical phenotypes of myopathies are summarized in Table 1.

Cardiac magnetic resonance imaging and FLNC cardiomyopathies

Cardiac magnetic resonance imaging (CMR) is a powerful tool for assessing the impact of FLNC mutations on cardiac tissue. The CMR can provide detailed insights into myocardial structure and function. CMR allows for the precise assessment of myocardial fibrosis, wall motion abnormalities, and other pathophysiological changes that result from genetic cardiomyopathies. Particularly the use of late gadolinium enhancement (LGE) has emerged as a critical imaging technique for detecting areas of myocardial fibrosis, which is an important risk marker. By integrating genetic testing with CMR findings, clinicians can achieve a more precise understanding of the disease, enhancing risk prediction and informing individualized management strategies for patients with *FLNC*-related cardiomyopathies.[38]

Clinical case with phenotype description

A 44-year-old patient experienced a cardiorespiratory arrest while his motorcycle was stationary at a traffic light. Other drivers observed the motorcycle tipping over and assisted with resuscitation maneuvers. The cardiorespiratory arrest occurred almost in front of the hospital, and the emergency rescue promptly transported the patient to the cardiological emergency department. A ventricular fibrillation rhythm was identified, and successful defibrillation was administered with successful recovery. The patient underwent coronary catheterization and did not exhibit obstructive coronary artery disease. Electrocardiogram showed sinus rhythm, low QRS voltage and T wave inversion in lateral leads and limb leads, and ventricular premature contractions (Figure 2). CMR revealed the presence of late gadolinium enhancement in a ring-like pattern on the inferior and lateral walls of the LV, along with borderline ventricular function, with an ejection fraction of 45%. The patient underwent implantation of an automatic cardioverter-defibrillator.

Conclusion

Clinical relevance of FLNC variants in cardiomyopathies

Pathogenic variants in the *FLNC* gene are associated with a spectrum of cardiomyopathy phenotypes, including dilated, arrhythmogenic, hypertrophic, and RCM. In practice, varying degrees of phenotypic overlap can be observed, particularly between DCM and ACM, as well as between HCM and RCM. Cardiac phenotypes of *FLNC* disease are related to a more aggressive clinical course, and this concern is not only limited to truncating *FLNC*-variants but can also be caused by *missense* variants, which are important for clinical management and outcomes in these patients.

Perspectives: Future directions in *FLNC* research and clinical management

This review highlights the need to expand the underlying mechanisms associated with *FLNC* variants, their types, and associated phenotypic presentations. The potential contribution of additional genetic variants and improved understanding of the complex interplay with other genetic and environmental factors are key challenges to be addressed.

Taken together, it is clear that individuals and families with high-risk hereditary cardiomyopathies require specialized integrated care to seamlessly incorporate the beneficial mounting genetic evidence to improve the risk stratification and management of these patients.

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Author Contributions

Conception and design of the research: Olivetti N, Linnenkamp B; Acquisition of data: Olivetti N, Pagotti M, Carvalho MLP, Andrade F, , Santos BM, Mizuta MH; Analysis and interpretation of the data: Pagotti M, Andrade F, Senra PM; Writing of the manuscript: Olivetti N, Linnenkamp B, Sacilotto L; Critical revision of the manuscript for content: Sacilotto L, Krieger JE, Santos BM, Mizuta MH.

Table 1 – FLNC Genetic variants type and myopathies features

Gene	Type of variant	Physiopathology	Clinical Phenotype
FLNC	*Missense* or *in frame* indels.	Formation of desmin-positive protein aggregates	myofibrillar myopathy
FLNC	*Nonsense*	Decreased expression levels of *FLNC* in the muscle fibers	distal myopathy

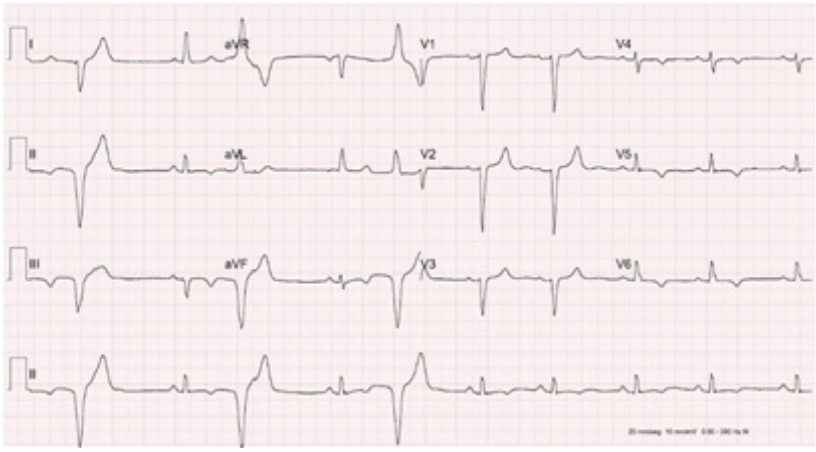

Figure 2 – *Electrocardiogram showing sinus rhythm, low QRS voltage, and T wave inversion in lateral leads and limb leads and ventricular premature contractions.*

Potential conflict of interest

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

Sources of funding

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Study association

This study is not associated with any thesis or dissertation work.

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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