

Received: 2021.04.10

Accepted: 2021.07.16

Available online: 2021.08.06

Published: 2021.09.16

# Cardiomyopathy, Proximal Myopathy, Camptocormia, and Novel Filamin C (FLNC) Variant: A Case Report

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

AEF 1 **Sara Jasmin Hooshmand**  
ADE 1 **Raghav Govindarajan**  
DE 2 **Brian P. Bostick**

1 Department of Neurology, School of Medicine, University of Missouri, Columbia, MO, USA

2 Division of Cardiovascular Medicine, School of Medicine, University of Missouri, Columbia, MO, USA

**Corresponding Author:** Sara Jasmin Hooshmand, e-mail: [sjh4k8@health.missouri.edu](mailto:sjh4k8@health.missouri.edu)

**Conflict of interest:** None declared

**Patient:** Male, 56-year-old  
**Final Diagnosis:** Camptocormia • cardiomyopathy • proximal myopathy  
**Symptoms:** Truncal weakness • weakness  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Neurology

**Objective:** Rare coexistence of disease or pathology  
**Background:** Filamin C (FLNC) is an actin crosslinking protein that provides structural support for the sarcomere. The exact function of FLNC is unknown; however, mutations have been reported in myopathies and cardiomyopathies, but rarely both. In this paper, we describe a case of adult-onset camptocormia, proximal myopathy, and cardiomyopathy and an intronic FLNC mutation.

**Case Report:** A 56-year-old man was referred to the neurology clinic for truncal weakness. The patient reported having curvature of his spine, which he said his mother also had prior to her dying suddenly due to a “cardiac issue.” The patient was found to have fatty infiltration of the periscapular and paraspinal muscles. Additionally, electromyography revealed irritable myopathy of the paraspinal muscles, and an echocardiogram revealed an ejection fraction of 40%. A genetic panel conducted through PerkinElmer Genomics revealed a heterozygous mutation c.1210+3A>G in the intron region of FLNC. Due to his low ejection fraction and family history of sudden cardiac death, he received an implantable cardioverter-defibrillator and began carvedilol. The patient received physical therapy for camptocormia.

**Conclusions:** The variability in genotypic-phenotypic relationships of FLNC mutations is a growing area of research. It is important to increase awareness to further the development of gene-targeted therapies. We hope this unique clinical presentation of co-occurring skeletal and cardiomyopathy secondary to an intronic mutation will increase awareness of the broad phenotypic spectrum of FLNC mutations.

**Keywords:** Cardiomyopathy, Dilated • FLNC Protein, Human

**Abbreviations:** FLNC – Filamin C; MRC – medical research council grading; MRI – magnetic resonance imaging

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/932648>



1193



—



2



14



## Background

Filamin C is a protein encoded by the FLNC gene. This actin crosslinking structural protein has a role in anchoring cells to the extracellular matrix and is involved in signaling pathways [1,2]. FLNC is primarily expressed in skeletal and cardiac muscle. Variants of FLNC mutations were originally described in cases of skeletal myopathies, and, more recently, specific variants have been described in cases of isolated, familial cardiomyopathies [3-9].

This paper describes a case of dilated cardiomyopathy, proximal myopathy with camptocormia, and an intronic mutation of the FLNC gene. Although there have been many reports of FLNC-associated cardiac and skeletal myopathies, it is less common to see cardiac and skeletal involvement co-occurring in a single individual [10]. Our case adds to the growing literature of the variability in the genotypic-phenotypic relationship of FLNC mutation.

## Case Report

A 56-year-old man presented after being evaluated by the orthopedic surgery department for right hip pain. Upon evaluation, the patient was incidentally found to have atrophy of his back and truncal weakness, which resulted in a referral to the neurology clinic. He had a history of osteoarthritis, hypertension, diabetes, and obstructive sleep apnea. He was treated with amlodipine and hydrochlorothiazide for hypertension and metformin for diabetes. He was poorly compliant with his continuous positive airway pressure due to fear of acquiring an infection. He reported chewing tobacco, rarely drinking alcohol, and working full time in the steel industry.

He reported his mother had developed similar spine curvature and died suddenly at age 66 from a "cardiac problem." The patient's brother had an aortic dissection at the age of 40 and underwent a surgical repair. There was no genetic testing of his family members or any known skeletal or cardiac myopathies to the patient's knowledge.

The patient reported noticing muscular weakness in his chest and upper back, causing him to walk with an abnormal posture for the past 6 years. Despite his posture, he reported being able to continue performing physical activities in the steel industry with minimal limitations. The patient denied any palpitations, lightheadedness, syncope, chest pain, dyspnea, and paroxysmal nocturnal dyspnea upon evaluation.

The patient's mental status examination was intact, the patient's language was comprehensible with fluency intact, and no hypophonia was present. The patient's physical examination

was notable for significant flexion of the thoracolumbar spine on upright posture, which resolved in the supine position. There was atrophy of the pectoralis, paravertebral, and hip muscles. The patient had normal musculature of his extremities. Cranial nerves were intact, except for cranial nerve XI, which was grade 3 of 5 for strength bilaterally. Hip flexion, knee flexion, and knee extensor were MRC grade 4 of 5 bilaterally. The patient's reflexes were 2+ bilaterally throughout the examination. The patient was unable to perform tandem gait. There was palmoplantar keratoderma on his hands.

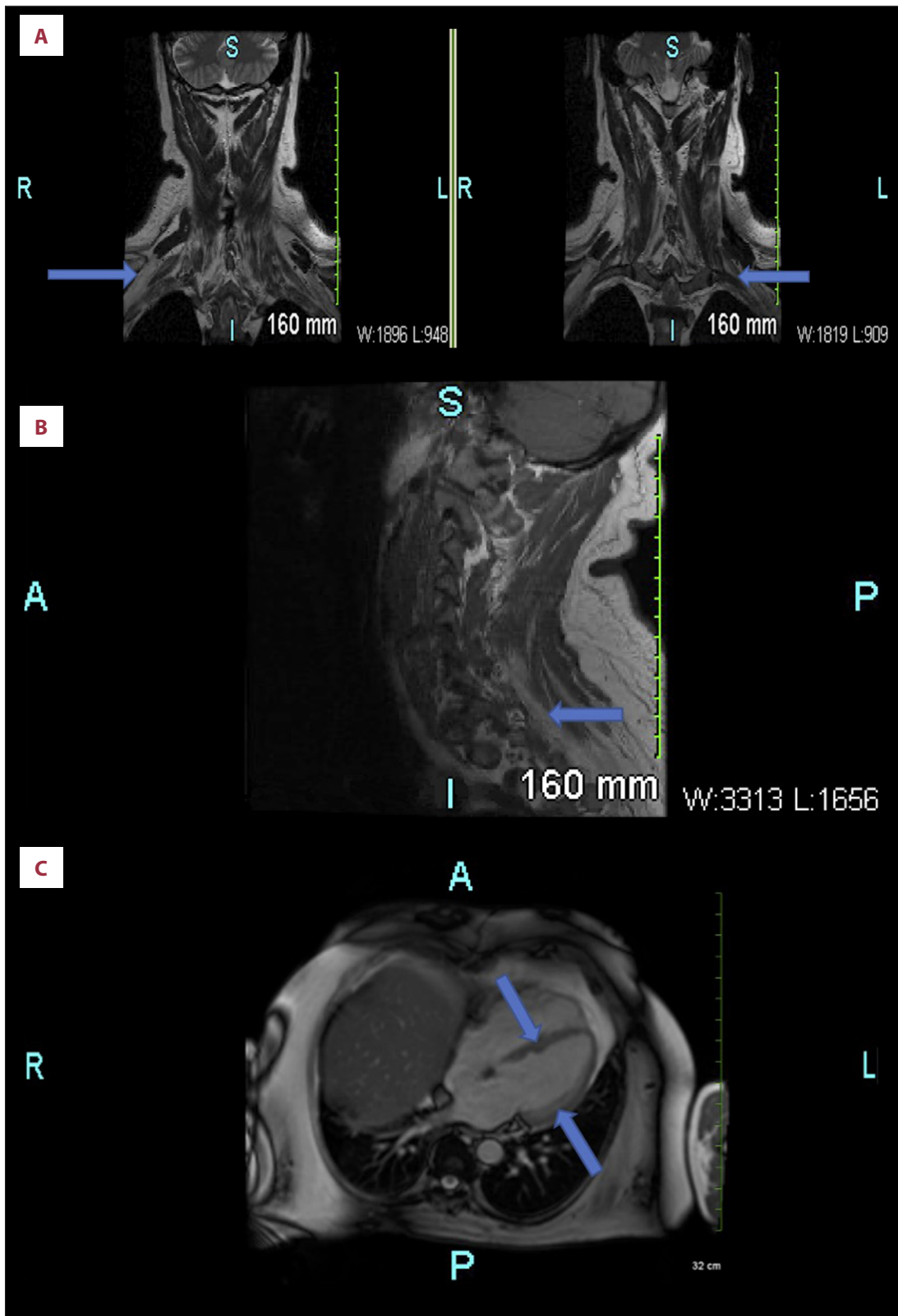
There was no elevation of creatinine kinase at 0.70 mg/dL (reference range, 0.70-1.20 mg/dL). The patient underwent magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine, which revealed asymmetrical fatty infiltration of the periscapular and paraspinal muscles (Figure 1A, 1B). Electromyography showed irritable myopathy in the paraspinal muscles with early recruitment in the deltoid, biceps, and hip flexors. Echocardiogram revealed a left ventricular ejection fraction of 40% with akinesis in the inferior basal septal segment. The cardiac MRI revealed biventricular dilation with reduced systolic function. There was severe hypokinesis of the basal inferoseptum and inferolateral wall, with late gadolinium enhancement suggestive of nonspecific fibrosis (Figure 1C). An electrocardiogram showed sinus rhythm and left anterior fascicular block. A coronary angiography showed nonobstructive coronary artery disease. The patient underwent Holter monitoring, which revealed 9% premature ventricular contractions. The pulmonary function test revealed a forced vital capacity (FVC) of 40% predicted. He was started on a Trilogy ventilator.

A genetic panel conducted through PerkinElmer Genomics revealed a heterozygous mutation c.1210+3A>G in the intron region 7 of FLNC (Figure 2). A FSHD1 Southern blot test (Quest Diagnostics) was negative. A muscle biopsy was deferred due to higher risk of cardiopulmonary complications given his low ejection fraction and low FVC.

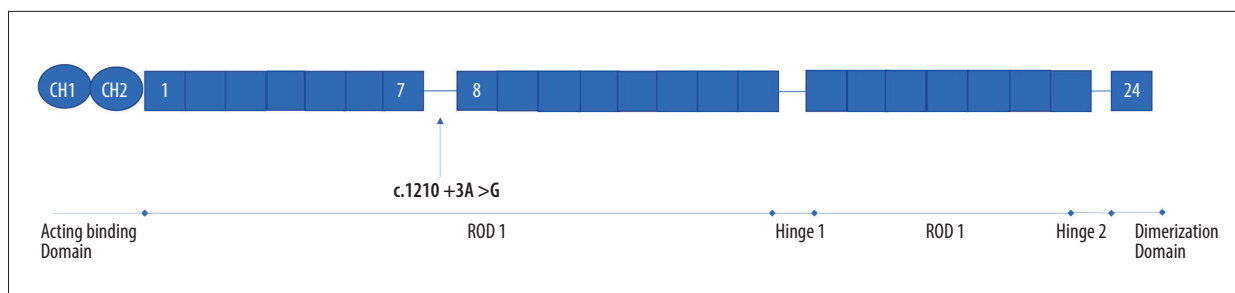
The patient was referred to the physical medicine and rehabilitation departments for his camptocormia. Our patient's heart failure was New York Heart Association class I. Given his family history of sudden cardiac death and the presence of a FLNC mutation, he received a single-chamber implantable cardioverter-defibrillator placement for primary prevention. He was also started on carvedilol 12.5 mg twice daily.

## Discussion

Filamin C, encoded by the FLNC gene, is an emerging cause of cardiac or skeletal myopathies [3-9]. Previous studies demonstrated the effect of FLNC splice-site mutations on sarcomere structures [3-12]. However, these mutations phenotypically



**Figure 1.** (A) Coronal T2 section showing fibrofatty infiltration of proximal muscles (arrows). (B) Sagittal T2 section showing fibrofatty changes in the paraspinal muscles (arrow). (C) Cross sectional T2 image showing biventricular dilation with fibrosis in the basal septum and inferolateral wall (arrows) of the heart.



**Figure 2.** Schematic representation of FLNC gene with the reported intronic mutation labeled between exon 7 and exon 8.

presented as isolated cases of cardiomyopathy [3-9]. Our patient's co-occurring skeletal and cardiac myopathy, possible familial involvement, and genomic evidence supports a mechanism of a novel intronic FLNC splice-site mutation.

While we cannot be certain of the effect the FLNC mutation (c. 1210+3A>G), the substitution of A with a G3 nucleotide after exon 7 in the intronic region of the ROD1 domain has been shown to disrupt RNA splicing. This can result in a loss of function truncated splice variant that predisposes patients to dilated cardiomyopathy [3]. In addition, splice variants in the ROD1 domain have been associated with proximal myopathies, as seen in our patient, although camptocormia had not been previously described. It remains unclear if camptocormia is a phenotypic presentation of the FLNC variant or is due to another etiology. Clinical, laboratory, and genetic testing have ruled out other causes of camptocormia.

Interestingly, Ortiz-Genga et al noted palmoplantar keratoderma segregation with the cardiac phenotype and FLNC mutations in 4 family members. These unique combination findings were identical to the patient described in our case report [5]. Furthermore, Deo et al investigated the cardiac phenotype in fish and demonstrated FLNC-b knockdown splice-site inhibition resulting in cardiomyopathy with ventricular delay in fish, as was seen in our patient [13].

Our report is limited because we did not have a muscle biopsy analysis to confirm a myofibrillary pattern, although electrodiagnostic and muscle MRI results confirmed a proximal myopathy. While the patient had a family history of cardiovascular

disease, further segregation of this genetic variation was limited by the lack of gene testing among family members, who would not consent for gene testing. This is a common clinical scenario and has been reported in genetic conditions as well [14]. We hope that the distinct clinical, imaging, electrodiagnostic, laboratory, and genetic characterization of this patient will increase awareness of the broad phenotypic spectrum of FLNC mutations and genetic cardiomyopathies.

## Conclusions

Variants in FLNC can lead to myopathies and cardiomyopathies. The difference in phenotypes can be partly explained by the pathomechanism and location with the gene. Splice-site changes resulting in truncating variants can lead to a dilated cardiomyopathy with proximal myopathy. We hope this unique clinical presentation of co-occurring proximal myopathy and dilated cardiomyopathy with camptocormia will increase awareness of the broad phenotypic spectrum of FLNC mutations and genetic cardiomyopathies.

## Conflicts of Interest

None declared.

## Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

## References:

1. Thompson TG, Chan YM, Hack AA, et al. Filamin 2 (FLN2): A muscle-specific sarcoglycan interacting protein. *J Cell Biol.* 2000;148(1):115-26
2. Gonzalez-Morales N, Holenka TK, Schock F. Filamin actin-binding and titin-binding fulfill distinct functions in z-disc cohesion. *PLoS Genet.* 2017;13(7):e1006880
3. Verdonchot J, Vanhoutte E, Claes GR, et al. A mutation update for the FLNC gene in myopathies and cardiomyopathies. *Hum Mutat.* 2020;41(6):1091-11
4. Begay RL, Graw SL, Sinagra G, et al. Filamin C truncation mutations are associated with arrhythmogenic dilated cardiomyopathy and changes in the cell-cell adhesion structures. *JACC Clin Electrophysiol.* 2018;4(4):504-14
5. Ortiz-Genga MF, Cuenca S, Dal Ferro M, et al. Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. *J Am Coll Cardiol.* 2016;68(22):2440-51
6. Valdés-Mas R, Gutiérrez-Fernández A, Gómez J, et al. Mutations in filamin C cause a new form of familial hypertrophic cardiomyopathy. *Nat Commun.* 2014; 5:5326
7. Gómez J, Lorca R, Reguero JR, et al. Screening of the filamin C gene in a large cohort of hypertrophic cardiomyopathy patients. *Circ Cardiovasc Genet.* 2017;10:e001584

8. Janin A, N'Guyen K, Habib G, et al. Truncating mutations on myofibrillar myopathies causing genes as prevalent molecular explanations on patients with dilated cardiomyopathy. *Clin Genet.* 2017;92(6):616-23
9. Brodehl A, Ferrier RA, Hamilton SJ, et al. FORGE Canada Consortium. Mutations in FLNC are associated with familial restrictive cardiomyopathy. *Hum Mutat.* 2016;37:269-79
10. Vorgerd M, van der Ven PF, Bruchertseifer V, et al. A mutation in the dimerization domain of filamin c causes a novel type of autosomal dominant myofibrillar myopathy. *Am J Hum Genet.* 2005; 77:297-304
11. Friedman JH. Episodic camptocormia in PD. *Mov Disord.* 2001;16:1201
12. Golbus JR, Puckelwartz MJ, Dellefave-Castillo L. Targeted analysis of whole genome sequence data to diagnose genetic cardiomyopathy. *Circ Cardiovasc Genet.* 2014;7:751-59
13. Deo RC, Musso G, Tasan M, et al. Prioritizing causal disease genes using unbiased genomic features. *Genome Biol.* 2014;15(12):534
14. Hoffman-Andrews L. The known unknown: The challenges of genetic variants of uncertain significance in clinical practice. *J Law Biosci.* 2018;4(3):648-57