

FLNC-related myopathy: a description of 27 patients from 21 unrelated families

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Abstract

Myofibrillar myopathies are inherited neuromuscular disorders characterized by protein aggregation and myofibrillar disorganization. *FLNC*-related myopathy, a subtype of MFM, encompasses a broad clinical spectrum ranging from limb-girdle and distal myopathies to isolated cardiomyopathy. We retrospectively collected a cohort of 27 patients with genetically confirmed *FLNC*-related myopathy. Mean age at first symptoms and diagnosis was 40 ± 14 and 54 ± 17 years, respectively. Among the 27 patients, 13 (48%) had proximal muscle weakness only, 3 (11%) had distal muscle weakness only, 9 (33%) had both proximal and distal weakness, and 2 (8%) had no limb weakness. Axial weakness was identified in 16 patients (59%), facial weakness in 4 patients (15%), cardiac involvement such as cardiomyopathies (hypertrophic or dilated) in 13 patients (48%), and conduction and rhythm disorders requiring an implantable cardioverter defibrillator in 2 patients. Mean value of forced vital capacity was $85 \pm 28\%$ and 3 patients with sleep apnea syndrome required nocturnal CPAP. Muscle magnetic resonance imaging showed fatty replacement mainly in thigh muscles affecting the posterior compartment, pelvic girdle, and paravertebral muscles. Mean creatine kinase value was 502 ± 436 U/L. Muscle biopsy showed muscle fiber size variability, intracytoplasmic protein aggregates, internalized nuclei, rimmed vacuoles and type 1 muscle fiber predominance. *FLNC* gene analysis identified heterozygous missense and nonsense variants in 22 (81%) and 3 (11%) patients respectively, and a complex deletion insertion variant in 2 patients (7%). This study reports one of the largest multicenter cohorts of *FLNC*-related myopathy, confirming that the disease most frequently presents as an adult-onset proximal myopathy with frequent cardiac involvement. We also identified a relatively consistent MRI pattern mainly involving the posterior thigh and paravertebral muscles. Despite the predominance of missense *FLNC* variants, substantial clinical and pathological heterogeneity was observed, with no clear genotype–phenotype correlation.

Introduction

Myofibrillar myopathies (MFM) have been traditionally defined as a group of inherited neuromuscular disorders sharing distinctive features on muscle biopsies: hyaline and amorphous aggregates and inclusions on Gömöri trichrome (GT) staining reflecting areas of myofibrillar dissolution, abnormal accumulations of multiple proteins as demonstrated by immunostaining and myofibrillar disorganization originating at the Z-line with electron microscopy (EM) ultrastructural studies [1, 2]. This histopathological pattern led to the “MFM” entity in 1996 [3, 4]. The term “myofibrillar myopathy”, however, remains primarily descriptive and encompasses a pathologically heterogeneous group of disorders, while myofibrillar disruption itself is not disease-specific. Advances in molecular genetics have progressively shifted the classification of these disorders from a predominantly morphology-based approach toward one integrating their underlying molecular mechanisms. Recently, a mechanism-based definition centered on Z-disk disruption and defective Z-disk protein homeostasis has been proposed, distinguishing MFM primarily related to Z-disk dysfunction, for which the term “Z-disk-opathies” has been suggested, from other myopathies that may exhibit overlapping myofibrillar pathology [5].

To date, several genes have been reported to be associated with MFM, including *BAG3*, *CRYAB*, *DES*, *DNAJB6*, *FLNC*, *LDB3*, and *MYOT*, whereas other genetically distinct myopathies, such as those related to *PLEC* and *SVIL*, may exhibit overlapping MFM pathology according to the recently proposed mechanism-based classification (Table 1) [5–15]. Myopathies associated with the *GNE* and *VCP* genes are not strictly considered as MFM but are often ruled out as differential diagnoses due to some common clinical and histopathological features [2, 5, 16–19, 20].

Table 1
Main clinical features of genes associated with myofibrillar myopathy and myofibrillar pathology.
Inspired from [2], [5–8, 15]

Gene	Protein / mechanistic category	Heredity	Age at onset	Phenotype
<i>DES</i>	Z-disk/intermediate filament structural protein	AD/AR	28 ± 10.1 years	Distal myopathy > proximal, cardiopathy, respiratory failure
<i>MYOT</i>	Z-disk structural/scaffolding protein	AD/AR	58 ± 8.7 years	Limb girdle muscular dystrophy, myalgia, arrhythmia (when recessive)
<i>LDB3</i> (ZASP)	Z-disk structural/scaffolding protein	AD	56 ± 7.1 years	Distal myopathy > proximal, cardiopathy, few neuropathies reported [9]
<i>FLNC</i>	Z-disk/cytoskeletal structural protein	AD	Adulthood	Proximal myopathy > distal, cardiopathy, respiratory failure [10, 11]
<i>FHL1</i>	Z-disk-associated structural/signaling protein	X-linked	Early childhood Adulthood (rare)	Emery-Dreyfus muscular dystrophy (rigid spine syndrome, tendinous retractions, scapulo-peroneal myopathy, cardiac conduction disease)
<i>CRYAB</i>	Molecular chaperone / protein quality control	AD	Adulthood	Distal myopathy > proximal, cardiopathy, cataract, respiratory failure
		AR	Early childhood	Axial and limbs involvement (muscle weakness and rigidity), respiratory failure
<i>BAG3</i>	Chaperone-assisted selective autophagy / protein quality control	AD	Late childhood	Proximo-distal myopathy, axonal neuropathy with giant axons [12], cardiopathy
<i>DNAJB6</i>	Molecular chaperone / protein quality control	AD	Adulthood	Limb girdle muscular dystrophy, proximal myopathy > distal, axonal neuropathy [13], [14]
<i>HSPB8</i>	Molecular chaperone / protein quality control	AD	Early adulthood	Distal myopathy > proximal, Charcot-Marie-Tooth, distal axonal neuropathy [14]
<i>PLEC</i>	Cytolinker connecting cytoskeleton and membrane-associated structures	AR	Neonatal Childhood Adulthood	Epidermolysis bullosa simplex, Teeth skin and hair abnormalities

AD: autosomal dominant; **AR:** autosomal recessive; **CMT:** Charcot–Marie–Tooth disease; **MFM:** myofibrillar myopathy.

Gene	Protein / mechanistic category	Heredity	Age at onset	Phenotype
				Proximo-distal myopathy, cardiopathy, cataract
<i>SVIL</i>	Actin-associated cytoskeletal protein	AR	Childhood	Myopathy with predominantly proximal weakness; variable cardiac involvement
AD: autosomal dominant; AR: autosomal recessive; CMT: Charcot–Marie–Tooth disease; MFM: myofibrillar myopathy.				

Although some MFM, related to *BAG3* and *DES* genes, can present at a very young age, symptom onset in most patients with MFM occurs between the fourth and sixth decades of life, with diverse phenotypes such as distal myopathy, limb girdle muscle dystrophy (LGMD) and scapuloperoneal syndrome, with typically neither facial nor bulbar involvement [5]. Besides skeletal muscle involvement, the prominence of other organ involvement depends on the affected gene: cardiomyopathies (*DES*, *BAG3*, *ZASP*, *CRYAB*, *FHL1*), respiratory failure (*FHL1*, *BAG3*, *FLNC*), epidermolysis bullosa simplex (*PLEC*), myalgias (*FHL1*), joint contractures (*FHL1*, *BAG3*), polyneuropathies (*BAG3*, *CRYAB*, *HSPB8*), and cataract (*CRYAB*) [2, 5–7, 20].

Filamin C, encoded by the *FLNC* gene located on chromosome 7q32.1 (OMIM 102565), is the muscle isoform of an actin-crosslinking protein family which binds to F-actin, Z-disk components, and to many other proteins such as *BAG3*, titin, myotilin and sarcoglycans [22, 23]. Filamin C is predominantly expressed in the cardiac and skeletal muscles. The N-terminal extremity encompasses two calponin-homologous actin-binding domains (CH1 and CH2) followed by 24 immunoglobulin-like rod domains (R1 to R24) until the C-terminal extremity. There are two hinge domains which are calpain sensitive (H1 and H2) and allow filamin flexibility (Fig. 1). The R24 domain mediates filamin dimerization and allows V-shape conformation thanks to the H1 and H2 domains. Thus, there are 5 main functional domains within filamin C: actin-binding domain (CH1, CH2), ROD1 domain (R1 to R15), ROD2 domain (R16 to R23), the dimerization domain (R24) and 2 hinges. Numerous proteins interact with filamin C through its ROD domains, thus connecting and organizing the actin cytoskeleton within the cell [23, 24].

An MFM linked to an *FLNC* variant was first reported in 2005 in a German family of 17 individuals with an autosomal dominant inherited LGMD phenotype, with cardiac and respiratory involvement [10]. Shortly after, three more families were reported with the same *FLNC* variant [11], accounting for 31 patients in total. Since then, several small cohorts of patients with *FLNC* myopathies have been reported associated with LGMD [20, 25–27], distal myopathy [28–30], or rigid spine syndrome with multiple joint contractures [31–33]. Mutations in *FLNC* are also involved in isolated cardiomyopathies, either hypertrophic or dilated [34–39].

Therefore, large multicenter cohorts of patients with *FLNC*-related myopathies are rare and there is still a need to collect more cases to have accurate epidemiological data, thereby facilitating its diagnosis. Here, we present a detailed description of 27 patients (belonging to 21 families) linked to *FLNC* variants.

Materials and Methods

Data on clinical examination, biological samples, electrophysiology, imaging, muscle biopsies, and genetics were collected retrospectively from the medical records of patients referred to 10 reference centers for neuromuscular diseases in France (Pitié-Salpêtrière Hospital, Raymond-Poincaré Hospital, Henri Mondor Hospital, Lyon University Hospital, Lille University Hospital, Brest University Hospital, Nancy University Hospital, Nantes University Hospital, Bordeaux University Hospital, and Strasbourg University Hospital). Data from the first medical evaluation conducted between 2018 and 2023 were considered. All patients with pathogenic *FLNC* variants and compatible clinical findings were included. When available, Medical Research Council (MRC) muscle testing scores were collected. Cardiac involvement was assessed either by electrocardiography (ECG), transthoracic cardiac ultrasound, or cardiac magnetic resonance imaging (MRI). Respiratory involvement was assessed by vital capacity (VC) value on pulmonary function tests. Whenever possible, detailed results of electroneuromyography (ENMG), muscle MRI or computed tomography (CT) scan, genetic testing for *FLNC* gene, and muscle biopsies were retrieved.

Statistical analysis

Descriptive statistics were used to summarize demographic, clinical, electrophysiological, imaging, histopathological, and genetic data. Continuous variables are presented as mean $\pm$ standard deviation (SD) and median where relevant, while categorical variables are reported as counts and percentages. For variables with missing data, descriptive statistics were calculated based on the number of patients with available data. Given the descriptive nature of the study, no inferential statistical analyses were performed.

Results

Patients and phenotypes

Twenty-seven patients with genetically confirmed *FLNC*-related myopathy (13 men, 14 women; male/female sex ratio: 0.9) from 21 families were included in this study (Table 2). First symptoms began at the age of 40 ± 14 years, mainly with lower limb muscle weakness ($n = 16$, 60%), myalgia ($n = 5$, 19%), and palpitations ($n = 3$, 11%) revealing an underlying cardiac arrhythmia. Dilated cardiomyopathy ($n = 1$) and restricted hypertrophic cardiomyopathy ($n = 1$) revealed the disease in 2 patients. One patient was initially referred for Charcot–Marie–Tooth (CMT) neuropathy ($n = 1$). The mean age at diagnosis was 54 ± 17 years.

Skeletal muscle involvement

The distribution of phenotypes is detailed in Fig. 2. Several phenotypes can be highlighted:

- Exclusively proximal: 13 patients (48%) had a purely proximal muscle weakness. Among these 13 patients, axial involvement was found in 9 (69%), facial involvement in 2 (15%), cardiac involvement in 5 (38%). Patients with exclusively proximal weakness had no respiratory involvement;
- Exclusively distal: 3 patients (11%) had a purely distal muscle weakness. Among these 3 patients, axial weakness was found in 1 patient (33%), cardiac involvement in 1 patient (33%), and respiratory involvement in 1 patient (33%). Patients in this group had no facial involvement;
- Proximal and distal: 9 patients (33%) had both proximal and distal muscle weakness. Among these 9 patients, axial weakness was found in 5 (56%), facial weakness in 2 (22%), cardiac involvement in 5 (56%), and respiratory involvement in 2 (22%);
- No limb weakness: 2 patients (8%) had no limb weakness. Both these patients had cardiac involvement (100%). One had axial weakness (50%).

Moreover, we also found scapula winging in 6 patients (22%) and calf hypertrophy in 4 patients (15%). The patient (#14) initially referred for CMT had *pes cavus*, claw toes, and distal vasomotor disorders of the legs with distal proprioceptive sensory loss in the lower limbs and absence of ankle jerk reflexes. However, he had mild proximal weakness of the upper limbs, distal weakness of both upper and lower limbs, intrinsic hand muscle atrophy, and distal sensory loss. ENMG showed a sensory axonal lower-limb neuropathy of the legs. A custom genes panel for CMT disclosed no pathogenic variant. Creatine kinase (CK) values at initial evaluation were available for 19 patients. The mean CK value was 502 ± 436 U/L.

Extramuscular involvement

Cardiac involvement was found in 13 patients (48%). For 5 patients (18%, #16, #17, #18, #22, and #24), cardiac involvement was the first symptom. Conduction disorders were observed in 4 patients: right bundle branch block in patient #23, left anterior fascicular block in 3 patients (#15, #20, and #9), requiring an implantable cardioverter defibrillator (ICD) as primary prevention for cardiac rhythm disorder in patients #15 and #20. Rhythm disorders were observed in 3 patients (#16, #17, and #18), hypertrophic cardiomyopathy (HCM, septal and laterobasal) in 4 patients (#23, #21, #15, and #22), and dilated cardiomyopathy (DCM) in 2 patients (#4 and #24). Left ventricular ejection fraction (LVEF) was obtained for 11 patients, with a mean value of $63 \pm 8\%$.

Vital capacity, expressed as a percentage of the predicted value, was available for 9 patients, with a mean of $85 \pm 28\%$. These values were under 80% for 3 patients (#21, #15, and #23). Clinically, 6 patients (25%) complained of dyspnea and 3 patients had sleep apnea syndrome requiring CPAP nocturnal noninvasive ventilation (#8, #21, and #15) with predicted VC values of 86%, 54%, and 40%, respectively.

No cognitive impairment nor psychomotor delay was found. Cerebral MRI was available for 2 patients and showed no abnormalities. Gastrointestinal disorders were identified in 2 patients (7%) as chronic diarrhea and fecal incontinence.

ENMG

ENMG data were obtained for 18 patients. Nerve conduction studies were normal in all patients except one (#14), who was initially diagnosed with CMT disease as he presented an axonal sensory neuropathy and a neurogenic pattern on needle ENMG. Needle ENMG was normal in 4 patients (22%) and disclosed a myogenic pattern in 13 patients (72%). Detailed ENMG findings were available for 5 patients and showed distal myogenic signs in all limbs, especially in anterior tibialis, and fibrillations could be found in abductor pollicis brevis, quadriceps, gastrocnemius medialis, deltoids and anterior tibialis, quadriceps and the posterior compartment of thighs.

Muscle imaging

Muscle imaging results were available in 17 patients, including 14 MRI examinations and 3 CT-scans (Fig. 3 and Fig. 4). Thighs muscles were involved in 12 patients (71%), mostly affecting the posterior compartment in 8 patients (47%) with fatty replacement of the semitendinosus, semimembranosus, and biceps femoris muscles. The quadriceps muscle was involved in 6 patients (35%). The adductor longus muscle was affected in 3 patients (17%). The gluteus minimus, gluteus medius, and iliopsoas muscles were involved in 9 patients (53%). Leg muscles were involved in 6 patients (35%), affecting in all cases the triceps surae and tibialis anterior muscles. Sartorius muscle involvement was found in one patient (#13). The gracilis muscle was always spared. The lumbar paravertebral muscles were affected in 6 patients (35%).

Disease progression

Six patients (22%) required motor aids after a variable period of disease progression.

Two patients (7%) became wheelchair-dependent during follow-up: patient #21 after 54 years of disease progression, following a stroke, and patient #7 after 19 years of disease progression.

Walking canes were needed for 4 patients (15.8%, patients #1, #8, #9, and #11), after a mean disease progression of 10 years. The other patients were still able to walk unaided.

Muscle biopsies

A muscle biopsy report was available for 13 patients (Fig. 5). Biopsy sites included the deltoid in 6 patients (46%), quadriceps in 3 patients (23%), tibialis anterior in 1 patient (8%), and fibularis longus in 1 patient (8%), while the biopsy site was unknown in the remaining 2 patients (15%).

The distribution of histopathological features among the 13 patients was as follows: 100% muscle fiber size variability, 62% internalized nuclei, 62% intracytoplasmic aggregates, 62% type 1 muscle fiber predominance, 54% rimmed or non-rimmed vacuoles, 46% oxidative abnormalities, 46% amorphous and

hyalin foci, 38% fibrosis, and 31% necrosis and regeneration. No inflammatory infiltration was found. Two main histological patterns were observed: a myofibrillar pattern with desmin aggregates confirmed by EM or immunohistochemistry (7 patients) and non-specific myopathic pattern (4 patients). One patient (#13) showed an intermediate pattern with oxidative changes but no desmin aggregates. One atypical histopathological phenotype was also found, characterized by the presence of rods and ring fibers for patient #4. EM was available for five patients, including four with a myofibrillar phenotype and patient #4 (Fig. 6). It consistently revealed varying degrees of myofibrillar disorganization accompanied by autophagic vacuolar structures. In patient #4, EM confirmed the presence of both nemaline rods and ring fibers (Fig. 6c–d). In patients with the myofibrillar subtype, electron-dense protein aggregates were observed, including desmin-positive deposits as well as filamentous aggregates, predominantly located in the subsarcolemmal region, in three cases.

Genetic variants

Among the 27 patients, 20 different genetic variants were identified in *FLNC* gene (NM_001458.4, hg19, Table 2). Among the 21 families, three were represented by multiple affected individuals included in the cohort. Within each of these families, affected members harbored the same *FLNC* variant: c.533T > C, p.(Ile178Thr) in patients #2 and #3 (family B); c.2794T > G, p.(Tyr932Asp) in patients #8, #9, #10, and #11 (family G); and c.3646T > A, p.(Tyr1216Asn) in patients #16, #17, and #18 (family L). The c.2794T > G, p.(Tyr932Asp) variant was also identified in patient #12 (family H), representing an independent occurrence in an unrelated family. In two additional families, paternal inheritance was documented, although the transmitting fathers were not included in the cohort. Missense variants were identified in 22 patients (81%), nonsense in 3 patients (11%), and deletion/insertion (c.8034_8041delinsAAGGCCCCAGGT and c.630_635delinsGAACGCCTC) in 2 patients (7%). The inheritance pattern was autosomal dominant in all cases. Three variant clusters were identified for missense variants, localized either at the N-terminal extremity (within domains CH1, CH2, and R1), at its center (R9 to R14), or at the C-terminal extremity (R24) (Fig. 1).

Variants found in patients requiring ICD (patients #15 and #20) were localized at the center of the protein: a missense variant in R10 and a non-sense variant in R12. Dilated cardiomyopathy (patients #4 and #24) was associated with missense variants located at different regions of the protein, at the N-terminal and C-terminal regions, respectively. Hypertrophic cardiomyopathy (patients #23, #21, #15, and #22) was associated with missense variants distributed across several domains of the protein. Variants associated with restrictive respiratory failure (patients #23 and #21) were missense variants, localized respectively in the R10 and R14 domains.

Variants associated with myopathy did not show any preferential localization within the protein. Apart from the non-sense variants in the middle of the protein that seem to be more associated with severe arrhythmias requiring ICD, no clear genotype–phenotype correlations emerged.

Discussion

We here describe one of the largest cohorts of patients with *FLNC*-related myopathy. The clinical spectrum of *FLNC*-related disorders has historically been described through cohorts ascertained either for cardiomyopathy or for skeletal myopathy, leading to the distinction between predominantly cardiac, predominantly skeletal muscle, and combined phenotypes. However, the boundaries between these presentations remain difficult to define because detailed neuromuscular assessment has not always been systematically performed in cardiology-based cohorts, and our findings further illustrate this phenotypic overlap. Skeletal muscle involvement was variable, with distal, proximodistal, and proximal patterns of weakness, the latter being the most frequent. Scapula winging was not as frequent as that reported in other cohorts [40]. On the other hand, paravertebral muscle involvement was identified in approximately one-third of our patients, and facial muscle weakness was occasional, as previously reported [15, 24, 25].

Nearly half of our patients had a cardiac involvement, including dilated or hypertrophic cardiomyopathy, arrhythmia, and conduction blocks sometimes requiring ICD, associated with muscle weakness. *FLNC* variants have mostly been reported associated with myopathies, but recent studies show they can also be associated with cardiac phenotypes [39, 41]. In a large study, DNA analysis of 1150 unrelated index patients with isolated cardiomyopathy showed that only 28 patients (2.4%) had an *FLNC* pathogenic variant, leading to a prevalence of 1% to 8% depending on the cardiomyopathy subtype [41]. Genotype–phenotype correlations in *FLNC*-related disorders are not yet clear, although some authors have claimed emerging correlations and proposed simplified ones [34]. For instance, missense variants associated with hypertrophic cardiomyopathy have been reported to cluster preferentially within the ROD2 domain [34]. Our study is to some extent in line with this finding as two patients with hypertrophic cardiomyopathy harbored a missense variant in the ROD2 domain, although a variant located in the ROD1 domain was also identified in a patient with cardiomyopathy. As previously reported, arrhythmogenic and dilated cardiomyopathies appear to be more frequently associated with truncating variants, with no preferential localization within the protein [34]. Even though our study shows that ICD was associated with a truncating variant in the ROD1 domain, it was also associated with a missense variant. Genetic variants linked to cardiac involvement were identified across multiple domains of the filamin C protein, with no apparent clustering.

More recently, *FLNC*-related early onset cytoplasmic myopathy caused by the variant p.Ala1186Val was reported to be associated with prominent joint contractures, rigid spine, and severe respiratory involvement [33]. Within MFM, some entities are responsible for severe respiratory failure, such as desminopathies [42], which do not seem to be the hallmark of *FLNC*-related myopathy in our cohort.

Nocturnal ventilation was required for obstructive apnea syndrome in 3 of our patients, 2 of whom had a restrictive respiratory failure. There are discrepancies regarding the frequency of respiratory failure in *FLNC*-related myopathy, which was sometimes reported as occasional [16] or absent [25, 26, 28, 29]. In contrast, Kley et al. published a cohort of 31 patients, all bearing the same heterozygous frameshift variant p.(Trp2710*); half of whom had severe respiratory involvement, leading to the death of 2 patients at 64 and 54 years old (age at onset 45 and 44 years, respectively [15]). In our cohort, this variant was

found in a female patient who showed no respiratory or cardiac symptoms, either when her condition began at age 45 or at the time of diagnosis at age 57, thus suggesting that factors other than the *FLNC* variant itself may contribute to respiratory involvement. Given the relatively high prevalence of CMT (approximately 1 in 2,500 [43, 44]), patient #14 may have had coexisting CMT2 and *FLNC*-related myopathy; accordingly, the presence of neurogenic features on ENMG should prompt clinicians to investigate an additional or alternative diagnosis rather than attributing these findings solely to *FLNC*-related myopathy. A recognizable pattern on muscle MRI was identified, with fatty replacement in the biceps femoris, semimembranosus, and semitendinosus muscles, the gracilis muscle being consistently spared and sartorius involvement being uncommon, which has also been reported elsewhere [38]. Half of our patients had fatty replacement within the gluteus minimus and medius muscles as well as the iliopsoas muscles. Leg muscles were not always affected but, whenever they were, the triceps surae muscles consistently showed abnormalities. Approximately one-third of our patients had fatty replacement of the quadriceps muscles. Muscle MRI can thus be a great help for the differential diagnosis with other MFM subtypes, such as desminopathies, which show involvement of the long fibular and gracilis muscles, but also with other limb girdle myopathies, such as calpain 3-related myopathy, which generally displays medial gastrocnemius and soleus muscle abnormalities, and fukutin-related protein myopathy, which shows gracilis muscle hypertrophy [45]. Like facio-scapulo-humeral dystrophic myopathy, *FLNC*-related myopathies may show proximal muscle weakness and affect facial muscles. However, unlike facio-scapulo-humeral dystrophic myopathy, the classic asymmetric fatty involvement is not observed.

In patient #14, the *FLNC* variant was classified as likely pathogenic despite a normal muscle MRI at age 18, warranting longitudinal EMG and MRI follow-up to assess the development of *FLNC*-related myopathy. Muscle biopsies from patients with *FLNC*-related myopathy show a broad histopathological spectrum, encompassing mild myopathic changes, oxidative staining abnormalities without protein aggregates, and alterations characterized by Z-disc-related protein aggregates and myofibrillar disorganization, the latter being the most frequently observed pattern [15]. These histological patterns have been comprehensively characterized by Fürst et al. and correlated with the mutational site within the *FLNC* gene, with variants in Ig-like domain usually being associated with protein aggregation and myofibrillar abnormalities [40]. However, in our cohort, most patients who underwent muscle biopsy harbored variants within Ig-like domains, and no consistent relationship between Ig-like domains variant localization and histopathological features emerged. Moreover, the three histopathological patterns proposed by Fürst et al. may not fully reflect the morphological spectrum of *FLNC*-related myopathy, as a distinct phenotype resembling nemaline myopathy and characterized by rods and ring fibers has recently been reported [46, 47]. In fact, similar histopathological features were observed in patient #4 of our cohort, further supporting and extending these recent observations. The recognition of this morphological presentation is particularly relevant to the differential diagnosis of myopathies with nemaline bodies and should prompt consideration of *FLNC* among the underlying genetic causes. Both our patient and the cases previously reported carried variants within the N-terminal actin-binding domain, indicating a potential genotype–phenotype correlation in this subgroup that warrants

confirmation in larger series [46, 47]. Given the direct role of this domain in binding filamentous actin, its involvement in patients displaying rods and ring fibers is of particular interest, although the underlying pathophysiological mechanism remains to be elucidated [23]. Protein aggregates can be further characterized by immunohistochemistry, showing multicomponent deposits of desmin, myotilin, α B-crystallin, and other Z-disc/cytoskeletal proteins.

Electron microscopy, performed mainly in biopsies showing protein aggregates and myofibrillar disorganization, provided further characterization. Ultrastructural abnormalities ranged from focal Z-disc abnormalities to extensive myofibrillar disorganization and were associated with electron-dense, granular, or filamentous material (Fig. 6). These findings are consistent with the ultrastructural spectrum previously reported in *FLNC*-related myopathy, including Z-disc streaming and disruption, accumulation of granulofilamentous material, and autophagic vacuolar changes [15]. To explain the mechanism of *FLNC* disease, some hypotheses have already been investigated. Among them, impaired autophagy has emerged as a potential contributor. Ruparelia et al. demonstrated autophagic dysfunction in genetically modified zebrafish models carrying *FLNC* variants [48], in line with the EM findings from muscle biopsy samples of our cohort. They first showed that the filamin C protein with the p.(Trp2710*) variant can partially restore an *FLNC* knock-out genotype, demonstrating the remaining activity of this truncating variant. Moreover, they showed the sequestration of BAG3 chaperone-protein within the aggregates, which in turn impaired proper protein folding, leading to more aggregates over time. Hyperactivation of the autophagy with drugs (such as carbamazepine, rapamycin, or spermidine) significantly decreased these aggregates. For instance, rapamycin has already been used for inclusion body myositis [49]. These studies may therefore open the way for future therapeutic trials in *FLNC*-related diseases.

Conclusions

Due to its rarity, *FLNC*-related myopathy is often described and reported within a family harboring the same genetic variant, leading to a homogenous phenotype within the published patients [15, 16, 25]. The phenotype may vary and encompasses limb-girdle, distal, or proximodistal myopathy. Our cohort included diverse, unrelated patients with different genotypes, accounting for the clinical variability. Nevertheless, our findings indicate that *FLNC*-related myopathy mainly presents as a proximal adult-onset myopathy with cardiac involvement, while initial respiratory failure is uncommon. Individuals diagnosed with *FLNC*-related myopathy are advised to receive routine cardiac evaluations, which should include as a minimum, an annual electrocardiogram and cardiac ultrasound conducted by a cardiologist. Conversely, patients with apparently isolated cardiac disease should undergo neuromuscular assessment at diagnosis and periodically thereafter. Within our cohort, no definitive mutation hot-spot has been identified, and further investigation is required to elucidate phenotype–genotype correlations.

Abbreviations

MFM
myofibrillar myopathies

GT
Gömöri's trichrome
LGMD
limb girdle muscle dystrophy
MRC
Medical Research Council
ECG
electrocardiography
MRI
magnetic resonance imaging
VC
vital capacity
CPAP
continuous positive airways pressure
ENMG
electroneuromyography
CT
computerized tomography
CMT
Charcot–Marie–Tooth
ICD
implantable cardioverter defibrillator
HCM
hypertrophic cardiomyopathy
DCM
dilated cardiomyopathy
LVEF
left ventricular ejection fraction
CK
creatine kinase
EM
electron microscopy
NADH-TR
nicotinamide adenine dinucleotide–tetrazolium reductase

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with French regulations governing retrospective observational research and was approved by the French data protection authority (CNIL; authorization

#20240329143041, recorded on 29 March 2024). Informed consent to participate was not required due to the retrospective nature of the study and the use of anonymized data.

Competing interests

The authors declare that they have no competing financial or non-financial interests related to this work.

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Author Contribution

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- Manh-Louis NGUYEN and Béatrice LABELLA contributed equally to the writing and editing of the article.

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Data Availability

Excel tables were use to report patients informations and to do descriptive statistics only.

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Table

Table 2 is available in the Supplementary Files section.

Figures

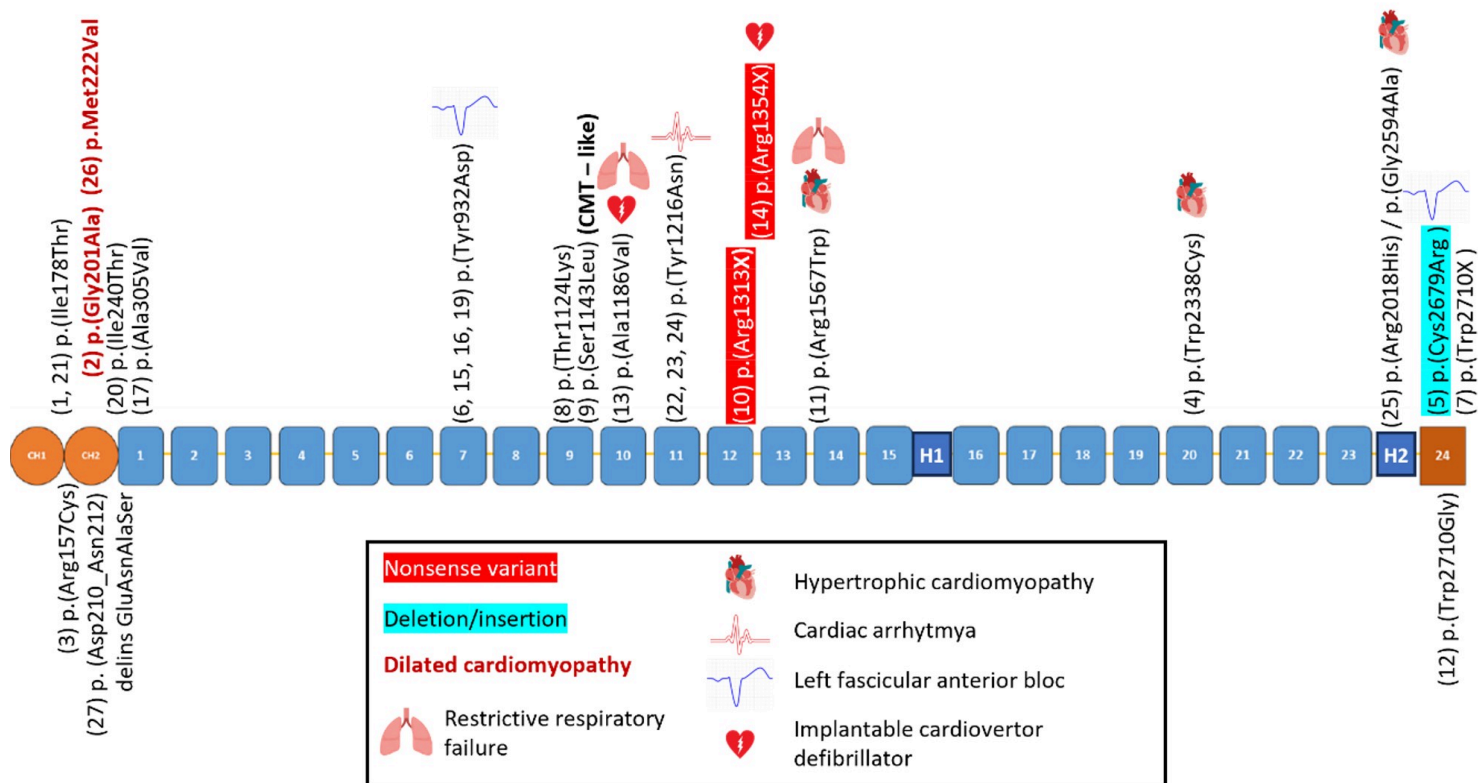
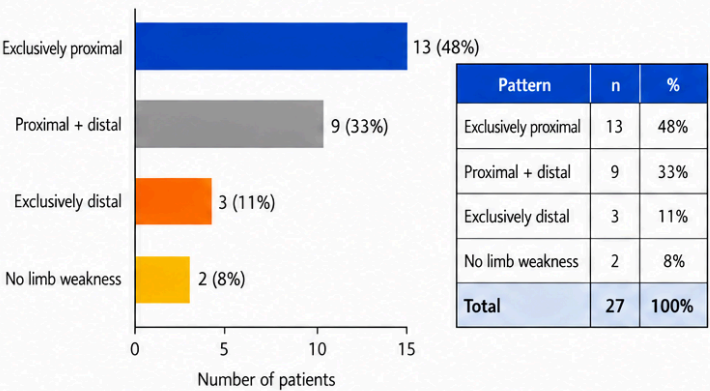


Figure 1

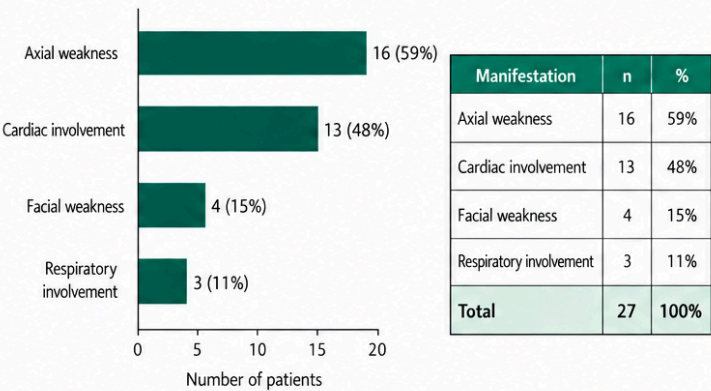
Diagram of *FLNC* domains with the distribution of the genetic variants in our cohort. Blue squares represent immunoglobulin-like repeated domains.

Spectrum of Limb Weakness and Associated Manifestations in FLNC Patients (N = 27)

A Distribution of limb weakness patterns (N = 27)



B Associated manifestations in the total cohort (N = 27)



C Manifestations according to limb weakness pattern

		Limb weakness pattern									
		Exclusively proximal n = 13		Proximal + distal n = 9		Exclusively distal n = 3		No limb weakness n = 2		Total cohort N = 27	
		n	%	n	%	n	%	n	%	n	%
	Axial weakness	9	69%	5	56%	1	33%	1	50%	16	59%
	Cardiac involvement	5	38%	5	56%	1	33%	2	100%	13	48%
	Facial weakness	2	15%	2	22%	0	0%	0	0%	4	15%
	Respiratory involvement	3	23%	2	22%	1	33%	0	0%	3	11%

Values are n (%). Percentages are calculated within each limb weakness subgroup and in the total cohort (N = 27).

Figure 2

Phenotypes distribution.

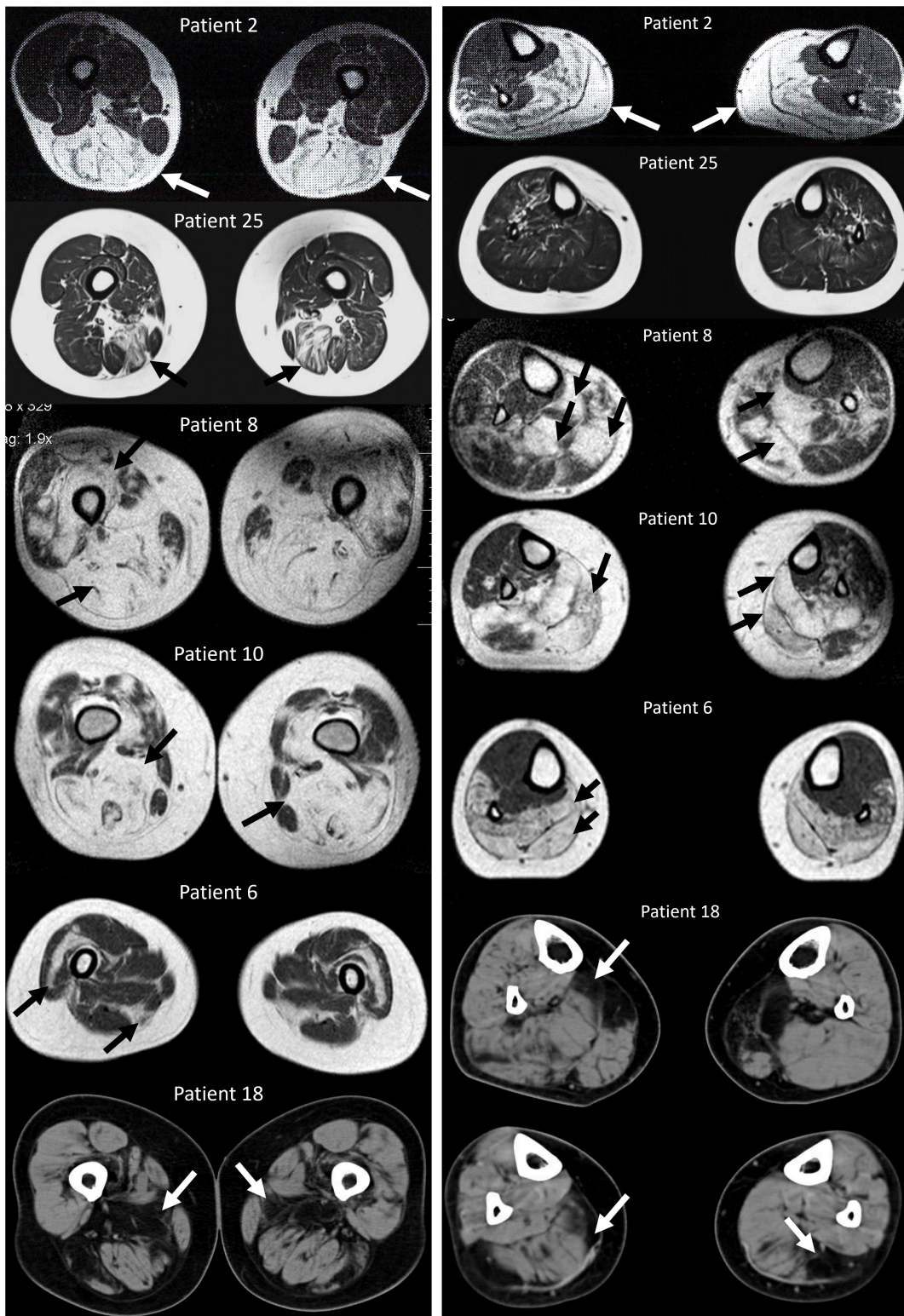


Figure 3

T1-weighted muscle MRI and muscle CT-scan (patient #18) of thighs (left) and legs (right). Hyperintensity signal in MRI images and CT-scan hypodensity (arrows) reflect fatty replacement of muscles, mainly in the posterior compartment of the thigh (patients #2 and #25) and to a lesser extent the anterior compartments (patients #8, #10, and #6).

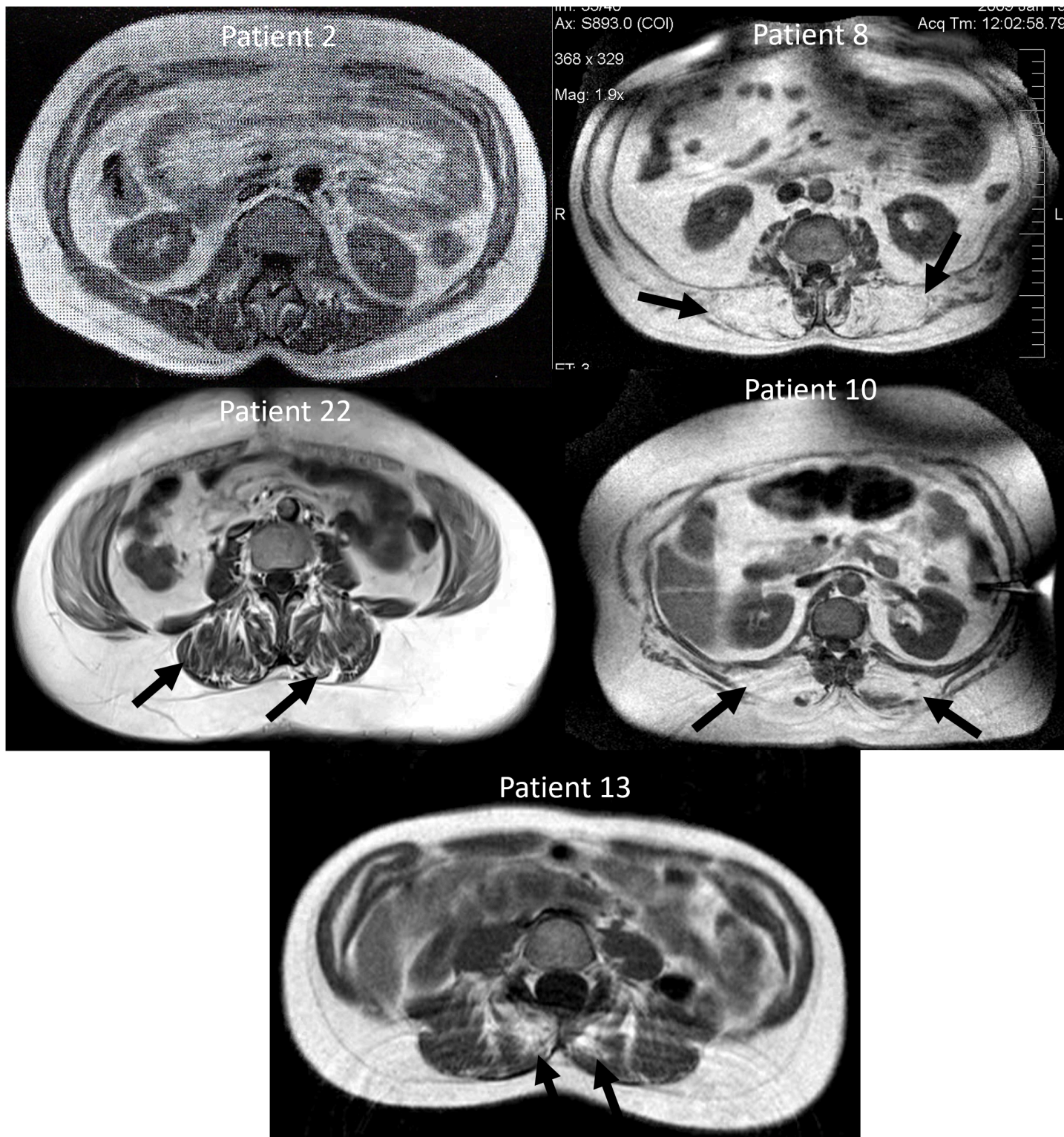


Figure 4

T1-weighted muscle MRI focused on paravertebral muscles (patients 2, 8, 10, 13 and 22). Hyperintensity shows fatty replacement of the paravertebral muscles (arrows).

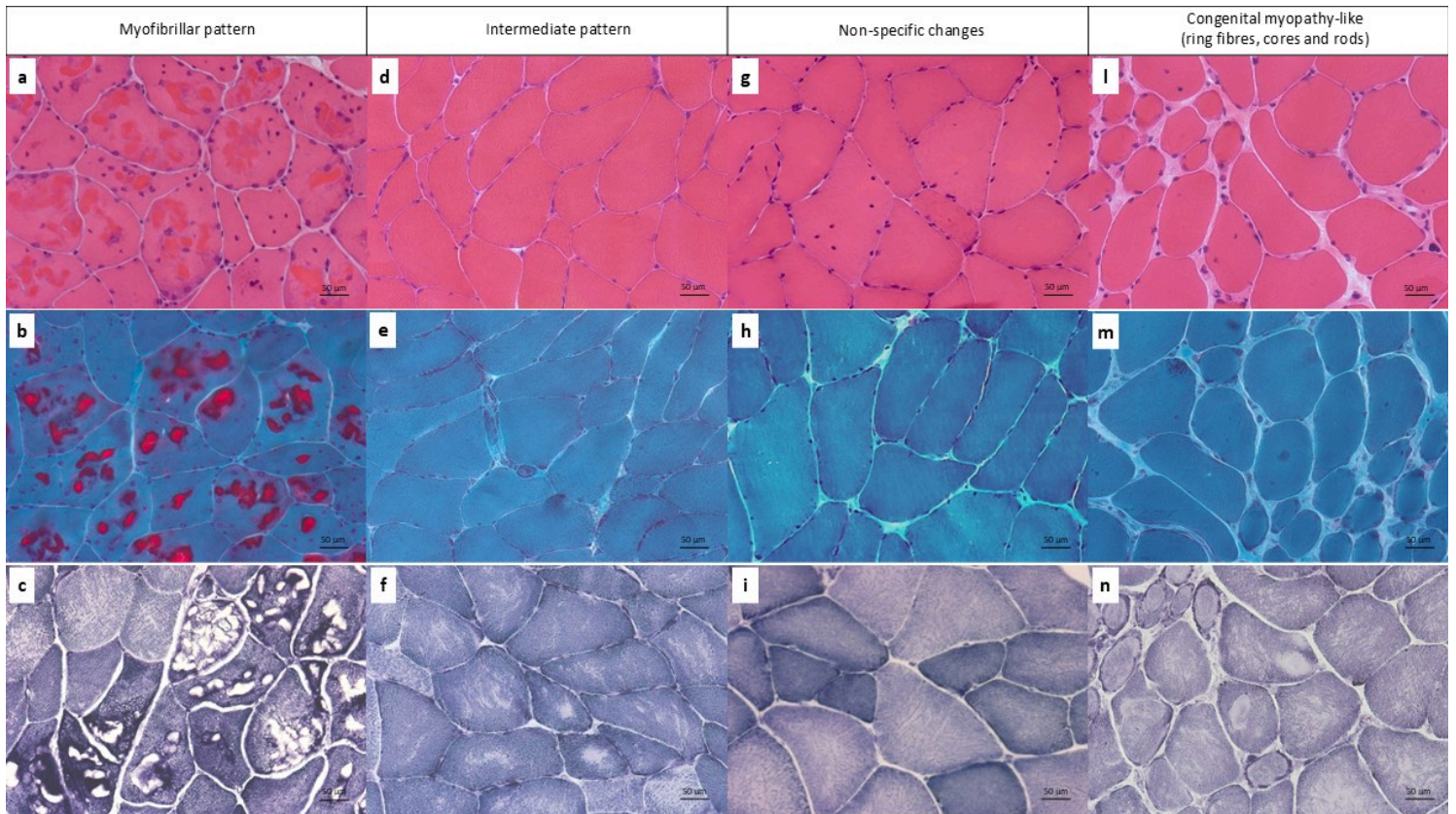


Figure 5

Muscle biopsies optical microcopy. Patient with myofibrillar histological pattern: hematoxylin eosin (a), Gömöri's trichrome (b), nicotinamide adenine dinucleotide–tetrazolium reductase (c, NADH-TR) showing a wide variation in fiber size, with many fibers containing hyaline and amorphous inclusions, some of them appearing as cytoplasmic bodies, resulting in a disruption of the myofibrillar array. Intermediate pattern: mild variability in fiber size with no increase of nuclear internalization nor inclusions (d,e). Some fibers may display myofibrillar disarray, such as cores (f). Non-specific changes: hematoxylin eosin (g), Gömöri's trichrome (h), NADH-TR (i) revealed only variability in fiber size with increased nuclear internalization. No protein aggregates or oxidative abnormalities were found. Nemaline-like pattern: variability in fiber size (l,m) and rare fibers with fuchsinophilic inclusions (m). In NADH-TR (n), a cluster of ring fibers was found along with some fibers showing oxidative abnormalities (cores). Scale bars: 50 µm.

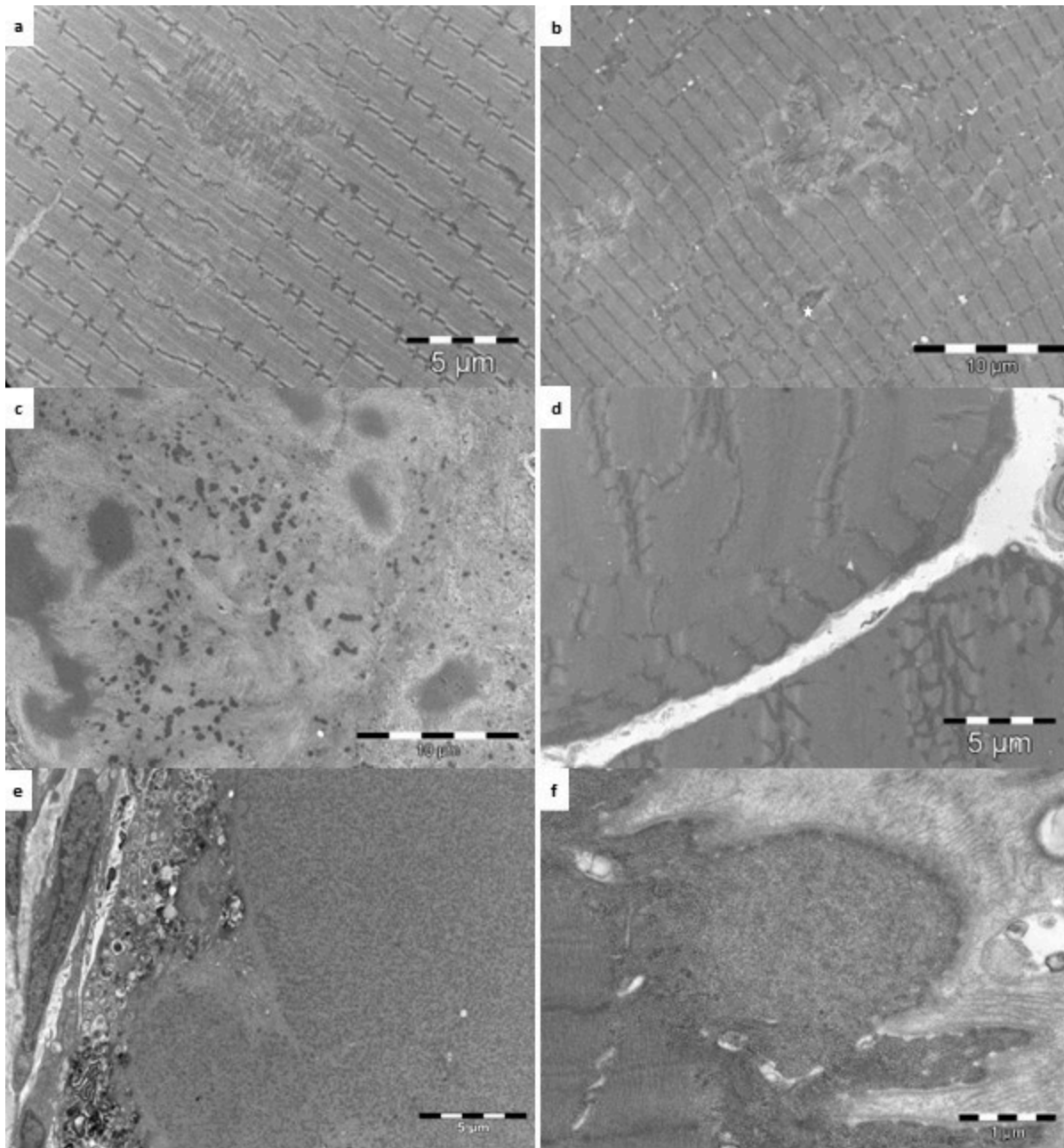


Figure 6

(a-b). Muscle biopsies electron microscopy showing mild to moderate disorganization, ranging from Z-line streaming (star) to disarray involving the size of around four sarcomeres. (c) Larger myofibrillar disorganization with multiple cytoplasmic bodies and rods. (d) Ring fiber. (e) Cytoplasmic desmin deposits and subsarcolemmal early to late autophagic structures. (f) Subsarcolemmal filamentous aggregates.

Supplementary Files

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- [Table2.docx](#)