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Myofibrillar myopathies: new developments

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Abstract

Purpose of review—Myofibrillar myopathies (MFMs) are a heterogeneous group of skeletal and cardiac muscle diseases. In this review, we highlight recent discoveries of new genes and disease mechanisms involved in this group of disorders.

Recent findings—The advent of next-generation sequencing technology, laser microdissection and mass spectrometry-based proteomics has facilitated the discovery of new MFM causative genes and pathomechanisms. New mutations have also been discovered in ‘older’ genes, helping to find a classification niche for MFM-linked disorders showing variant phenotypes. Cell transfection experiments using primary cultured myoblasts and newer animal models provide insights into the pathogenesis of MFMs.

Summary—An increasing number of genes are involved in the causation of variant subtypes of MFM. The application of modern technologies in combination with classical histopathological and ultrastructural studies is helping to establish the molecular diagnosis and reach a better understanding of the pathogenic mechanisms of each MFM subtype, thus putting an emphasis on the development of specific means for prevention and therapy of these incapacitating and frequently fatal diseases.

Keywords

hereditary myopathy with early respiratory failure; laser microdissection; myofibrillar myopathy; next generation sequencing; proteomics; reducing body myopathy

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Conflicts of interest

There are no conflicts of interest.

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INTRODUCTION

Myofibrillar myopathies (MFMs) are a genetically heterogeneous group of skeletal and cardiac muscle disorders characterized by focal dissolution of myofibrils and aggregation of degraded myofibrillar products into inclusions containing desmin and a number of other proteins [1]. A major morphological feature unifying these genetically diverse disorders is that myofibrillar degeneration starts at or close to the Z-disc of the sarcomere [1,2]. Regarding its major pathogenic mechanisms, MFM is also part of a group recently designated as protein aggregate myopathies (PAM) [3,4]. The use of new technologies, including next-generation sequencing, laser microdissection and mass spectrometry-based proteomics followed by gene sequencing, has recently helped to identify disease causative genes in a fraction of patients and will hopefully enlarge the spectrum of MFM causative genes in the very near future. This should increase the reliability of diagnostic procedures and aid develoment of therapeutic options for each MFM subtype. A number of detailed reviews focusing on MFMs have been published over the past 2–5 years [2,5–7]. This review summarizes the latest relevant advances in the field.

NOVEL MYOFIBRILLAR MYOPATHY SUBTYPES

Most recently, genetic causes of two disorders have been identified: reducing body myopathy (RBM) and hereditary myopathy with early respiratory failure (HMERF), both considered to be new members of MFM.

Reducing body myopathy

RBM, originally described by Brooke and Neville [8], is a rare congenital disorder defined by the presence of intracytoplasmic inclusions that reduce nitroblue tetrazolium (NBT) and thus stain strongly with menadione-NBT. In 2008, a very elegant work using laser microdissection followed by proteomic analysis resulted in the identification of FHL1 as the most abundant protein within the reducing bodies [9]. Subsequently, mutations in *FHL1* on chromosome Xq27.2 were discovered in affected children [9]. RBM manifests with a range of phenotypes extending from early onset fatal conditions to milder disorders manifesting in childhood or adulthood [9–13]. Besides RBM, mutations in *FHL1* have been identified in patients with several other X-linked disorders including X-linked myopathy with postural muscle atrophy and muscle hypertrophy [14], scapuloperoneal myopathy [15], rigid spine syndrome [16], Emery–Dreifuss muscular dystrophy [17], hypertrophic cardiomyopathy [18] and some other overlapping conditions. Reducing bodies have been detected in severe childhood-onset and juvenile-onset cases of RBM caused by mutations in the second LIM domain of FHL1 [12,13], but lately they were also identified in late-onset cases with mutations in the C-terminal domain [19■]. Besides FHL1, which constitutes the most abundant protein found in reducing bodies, immunohistochemical analyses have led to the identification of several other proteins within or surrounding the reducing bodies, including desmin and myotilin [9–12,19■,20–22], allowing classification of this entity as a PAM. Moreover, early Z-line abnormalities, Z-line streaming and reducing body material arising from the level of the Z-line and spreading under the sarcolemma and within the myofibrils to form reducing bodies [10,11,19■,20,21], as revealed by electron microscopy (EM) analysis,

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are other features that make the relationship to MFM certain, although the histochemical, immunohistochemical and ultrastructural characteristics are profoundly different from the other MFM subtypes.

Hereditary myopathy with early respiratory failure

HMERF is an autosomal dominant disease characterized by proximal and distal muscle weakness associated with respiratory insufficiency and involvement of neck flexors early in the disease course [23]. A p.R32450W mutation in the kinase domain of titin was identified in Swedish families, originally described by Edström [24]. A novel p.C30071R *TTN* mutation was recently detected by next-generation sequencing as the cause of HMERF in several new North European families [25■■,26■■]. Subsequently, a number of additional *TTN* mutations, all of them in the A-band *TTN* domain, were identified in HMERF families of divergent geographical origins [27■–30■]. The age at onset ranges from 13 to 71 years [25■■,26■■,29■]; initial symptoms are variable, but ultimately nearly all patients develop significant distal and proximal weakness. Respiratory function is affected early and undergoes a gradual deterioration over time [25■■,26■■,27■–30■].

The morphological phenotype is in most cases consistent with MFM. Histopathological analysis highlights cytoplasmic bodies as the most relevant finding. EM studies revealed extensive myofibrillar changes with Z-disc streaming and myofibrillar disruption (Figs 1 and 2). Accumulation of various proteins including desmin, myotilin, and filamin C in the abnormal fibers was also reported [25■■,26■■,27■–30■]. These histopathological and ultrastructural features justify that HMERF associated with mutation in the A-band of titin is classified as MFM-titinopathy. However, the presence of cytoplasmic bodies as the morphological hallmark in HMERF distinguishies HMERF from other MFM subtypes.

Proteomic analysis in MFM

Proteomic analysis has become a valuable method in MFM research. It enables highly sensitive detection and quantitation of proteins even in very small samples [19■,31■–33■]. Laser microdissection selectively collects aggregates from abnormal muscle fibers and control samples from normal appearing fibers of the same biopsy (Fig. 3). Mass spectrometry-based quantitative proteomic analysis of these paired samples allows identification of proteins that are overrepresented in aggregates. This approach has provided new insights into the composition of pathological protein aggregates in several MFM subtypes [19■,31■–33■], and has revealed significant differences between the MFM subtypes regarding the accumulation ratio and the abundance of proteins in aggregates (Fig. 3), to the extent that the subtype-specific proteomic profiles can be successfully used for differential diagnosis [32■,33■].

The finding that the disease-causing proteins show stronger accumulation in filaminopathy, desminopathy and RBM [19■,31■–33■] suggests that proteins overrepresented in aggregates of patients with so far unsolved MFM-related conditions are the potential disease-causing candidates. Next-generation sequencing can in this situation be used to search for mutations in genes encoding these proteins.

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PROGRESS IN STUDIES OF THE PREVIOUSLY IDENTIFIED MYOFIBRILLAR MYOPATHIES

Mutations in sarcomeric and Z-disc-supporting cytoskeletal proteins, desmin (*DES*), αB-crystallin (*CRYAB*), myotilin (*MYOT*), Z band alternatively spliced PDZ-containing protein (*ZASP*), filamin C (*FLNC*) and Bcl-2-associated athanogene-3 (*BAG3*) have previously been identified in patients with MFM (Table 1).

Desminopathy

MFM resulting from mutations in desmin (*DES*) is the most common and best studied subtype of MFM [34–36,37■■]. Thus far, 67 disease-causing *DES* mutations have been reported [37■■]. Clinical manifestations of desminopathy are heterogeneous. Skeletal myopathy is often associated with cardiac involvement: this has recently been the subject of extended studies [38,39■] stressing the need for close cardiac monitoring in desminopathy patients. Desmin mutations have recently been found in a subset of patients suffering from arrhythmogenic right ventricular cardiomyopathy [40]. Also, exome sequencing identified a *DES* mutation in affected members of a Swedish family with MFM and arrhythmogenic right ventricular cardiomyopathy [41■], previously reported by Melberg *et al.* [42].

The first recessive desmin-null mutation was reported in two siblings manifesting with a progressive myopathy, muscle fatigue, swallowing difficulties and respiratory restriction. Affected muscles showed myopathic abnormalities and cytochrome c oxidase (COX)-deficient fibers but no MFM pathology. Desmin expression was completely absent on immunostaining and western blot [43■■]. Laser microdissection of skeletal muscle and mass spectrometry-based proteomics allowed identification of a *DES* mutation in another family affected by skeletal and cardiac myopathy with conduction defects [44■]. The disease in this family was previously mistakenly linked to a 6q23 locus and designated as limb–girdle muscular dystrophy (LGMD) 1D/1E.

Transfection experiments, animal models and in-vitro assembly studies have been carried out to investigate the pathogenesis of desminopathy (reviewed in [37■■]). Abnormal desmin filament elasticity has been postulated as a contributory mechanism of disease progression. A recent study performed in primary cultured myoblasts obtained from a patient revealed abnormal mechanical properties of affected muscle cells, which acquire increased stiffness and higher vulnerability to mechanical stretch [45■].

A useful disease model has been generated by inoculating adeno-associated virus vectors carrying mutant desmin cDNA into the anterior tibialis muscle of a mouse. The results demonstrate mutation-dependent effects on muscle regeneration, distribution of fiber size and generation of muscle force [46■]. This technology may help to assess the level of pathogenicity of various desmin mutations.

αB-crystallinopathy

αB-crystallinopathy represents an infrequent subtype of MFM. A heterozygous *CRYAB* p.R120G mutation was identified in a large French family presenting with proximal upper

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limb and distal lower limb weakness, involvement of the velopharyngeal muscles, respiratory failure, cardiopathy and lens opacities. Granulofilamentous material, the characteristic ultrastructural feature of desmin deposits, has for the first time been described in this family [47,48]. Analysis of a second kindred manifesting identical symptoms [49■] caused by a novel D109H *CRYAB* mutation confirmed that αB-crystallinopathy is a multisystem disorder. A few further cases have been reported presenting in adulthood with muscle weakness and respiratory failure, or weakness and peripheral neuropathy but no cardiac involvement or lens opacities [50,51].

A knock-in mouse model for the *CRYAB* p.R120G mutation has been developed [52]; analysis of the affected tissues show the loss of αB-crystallin solubility and accumulation of protein aggregates in the lens and skeletal muscle, thus recapitulating many features of the human disease.

Recessive mutations in *CRYAB* have been identified as the cause of fatal infantile hypertonic muscular dystrophy described two decades ago in Canadian natives [53,54]. Affected children presented shortly after birth with severe weakness and hypertonia, predominantly in axial muscles, and progressive respiratory insufficiency leading to early death. Muscle biopsies showed typical features of MFM, although αB-crystallin was not detected in the inclusions by using monoclonal antibody that recognizes the entire protein [53,54].

Myotilinopathy

MFM resulting from *MYOT* mutations is a late-onset disorder presenting with distal weakness of lower limbs or limb–girdle weakness followed by distal muscle involvement [55–57]. Peripheral neuropathy, respiratory failure and cardiomyopathy are rare associated findings [56,57]. To date, 50 MFM patients from 40 unrelated families with *MYOT* mutations have been identified. All mutations except for one are located in exon 2 of the *MYOT* gene [56–58].

Recent studies in transfected COS7 cells and myotubes have demonstrated reduced myotilin degradation by the proteasome system and accumulation of mutant myotilin in the transfected cells, which perfectly explains the disease mechanisms in human myotilinopathy [59]. New observations support previous results from studies of human MFM muscle biopsies that suggested a major role for impaired protein degradation in the pathogenesis of MFM [60,61■].

The pathogenic effects of *MYOT* mutations *in vivo* were also studied by using electroporation to express mutant myotilin in mouse skeletal muscles; abnormal insoluble protein aggregates were similar to those observed in patients with myotilinopathy [62■].

ZASPopathy

The clinical and pathological phenotype in patients carrying *ZASP* mutations is similar to the one described in myotilinopathy. First clinical symptoms usually occur in the sixth decade, the disease progression is very slow and patients remain ambulatory until very late

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age. Peripheral neuropathy and cardiac involvement are associated features in a minority of cases [63,64].

Recently, the p.D117N *ZASP* variant previously found to be associated with dilated cardiomyopathy was reported in a mother and child with symptoms of skeletal myopathy [65]. Three muscle biopsies performed in the mother showed neurogenic features but no MFM pathology, making it uncertain if the p.D117N *ZASP* variant was the cause of myopathy in this family.

A new p.V566M *ZASP* mutation was identified in a single case of sporadic inclusion body myositis (sIBM) diagnosed according to the existing diagnostic criteria [66]. This is not surprising because some of the pathological features of sIBM overlap with those encountered in MFM, although large protein aggregates and major sarcomere disorganization are not usually seen in sIBM.

MFM-filaminopathy

MFM-filaminopathy is characterized by adult-onset predominantly proximal weakness with involvement of respiratory muscles and cardiac abnormalities [61■,67,68■]. The p.W2710X mutation located in the dimerization domain of filamin C was recently identified as a mutational hotspot [61■]. Late-onset cerebellar ataxia has been reported in one sporadic patient with *FLNC* p.T241M mutation, but a causal relationship with filaminopathy is unclear [69]. Established cell culture models show significant protein aggregation and are applicable for testing therapeutic approaches [61■]. Two reported fish models [70,71] relate rather to distal myopathy caused by haploinsufficiency than MFM-filaminopathy.

BAG3-myopathy

Mutations in BAG3 cause a rare subtype of MFM; only 12 patients, all carrying the same p.P209L recurrent de-novo mutation transmitted from a mosaic parent, have been reported to date [72–75]. Unlike other subtypes of MFM, BAG3-myopathy manifests during the first decade of life with rapidly progressive limb and axial muscle weakness, contractures, hypertrophic cardiomyopathy and respiratory insufficiency. A characteristic feature of the disease is the association with peripheral neuropathy that may in some patients be the initial clinical manifestation [75]. Nerve biopsies reveal a loss of myelinated fibers and the presence of giant axons with thin myelin sheets as characteristic features [73,75]. Muscle biopsies are consistent with MFM, sometimes associated with signs of chronic denervation.

DIAGNOSIS

The diagnosis of MFM is based on muscle biopsy findings that demonstrate characteristic aggregates containing desmin and other proteins as revealed by immunohistochemistry [1,2] (Fig. 1). By EM, the initial abnormalities are often localized at or close to the Z-lines (Fig. 2). This is followed by disruption of sarcomeres that become replaced by degraded material which accumulates in various patterns [2,5,76,77]. In spite of myopathological similarities, individual MFM subtypes have distinct clinical morphological and muscle imaging features [76–78]. A summary of MFM gene-dependent phenotypic features is provided in Table 1. Genetic testing is essential for establishing an accurate diagnosis of MFM, providing

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appropriate genetic counseling, and timely prevention of cardiac arrhythmia and heart failure.

CONCLUSION

The latest discoveries in the field of MFM have led to the identification of new genes and disease mechanisms involved in the causation of this group of disorders. Further molecular studies of MFMs in combination with classical myopathological approaches will potentially result in improvements in diagnosis and the development of subtype-specific prevention and therapy.

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KEY POINTS

- Mutations in eight genes are now known to cause MFMs, skeletal and cardiac muscle disorders characterized by focal dissolution of myofibrils and aggregation of degraded myofibrillar products into proteinacious aggregates.
- The discovery of the latest two genes, *FHL1* and *TTN*, the identification of new mutations in the previously identified MFM genes and the elucidation of disease mechanisms were achieved by the use of novel technologies: next-generation sequencing, laser microdissection and mass spectrometry-based proteomics.
- Molecular studies of large groups of patients with MFMs helped to outline new MFM phenotypes such as arrhythmogenic right ventricular cardiomyopathy and find a classification niche for other diseases having features of MFMs.
- Progress in molecular studies of MFMs in combination with classical morphological and ultrastructural approaches leads to improvements in diagnostics and opens up the prospects for the development of subtype-specific prevention and therapy.

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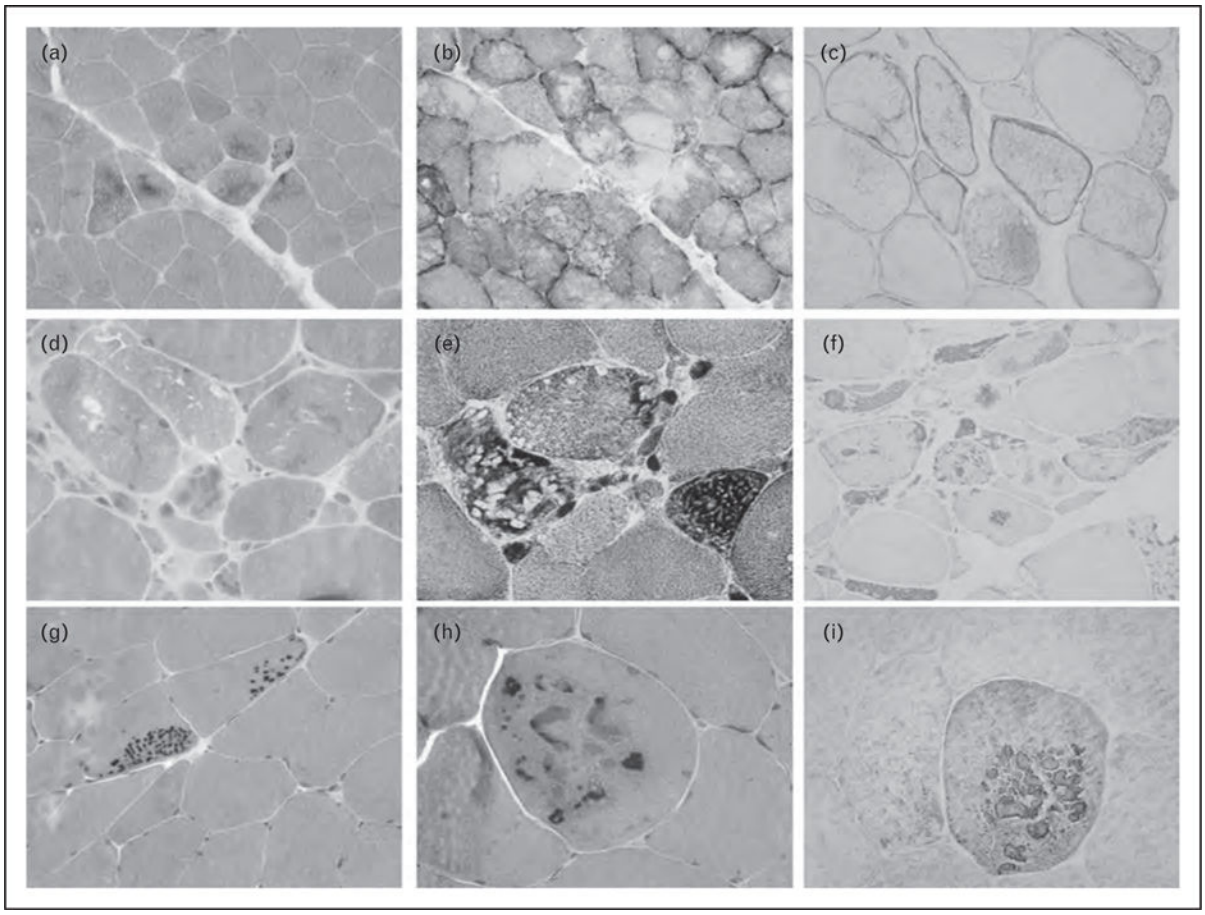

FIGURE 1.

Light microscopy analysis of muscle biopsy samples from myofibrillar myopathy patients with *DES*, *MYOT*, or *TTN* mutations. The most characteristic lesions in patients carrying mutations in *DES* (a–c) are the thin discrete patches of amorphous material forming diffuse networks in the cytoplasm (a). These inclusions are devoid of oxidative enzyme activity causing a 'rubbed-out' appearance (b), and display increased desmin immunoreactivity (c). Characteristic features of myotilinopathy (d–f) are polymorphous inclusions, spheroid bodies, and vacuoles. Some abnormal areas lack and some others show increased oxidative enzyme activity (e). Focal or diffuse myotilin-immunoreactive aggregates are seen in (f). In a patient with TTN-A-band MFM (g–i), abnormal fibers show collections of cytoplasmic bodies (g), or more diffuse and polymorphous inclusions (h) that display strong filamin C immunoreactivity (i).

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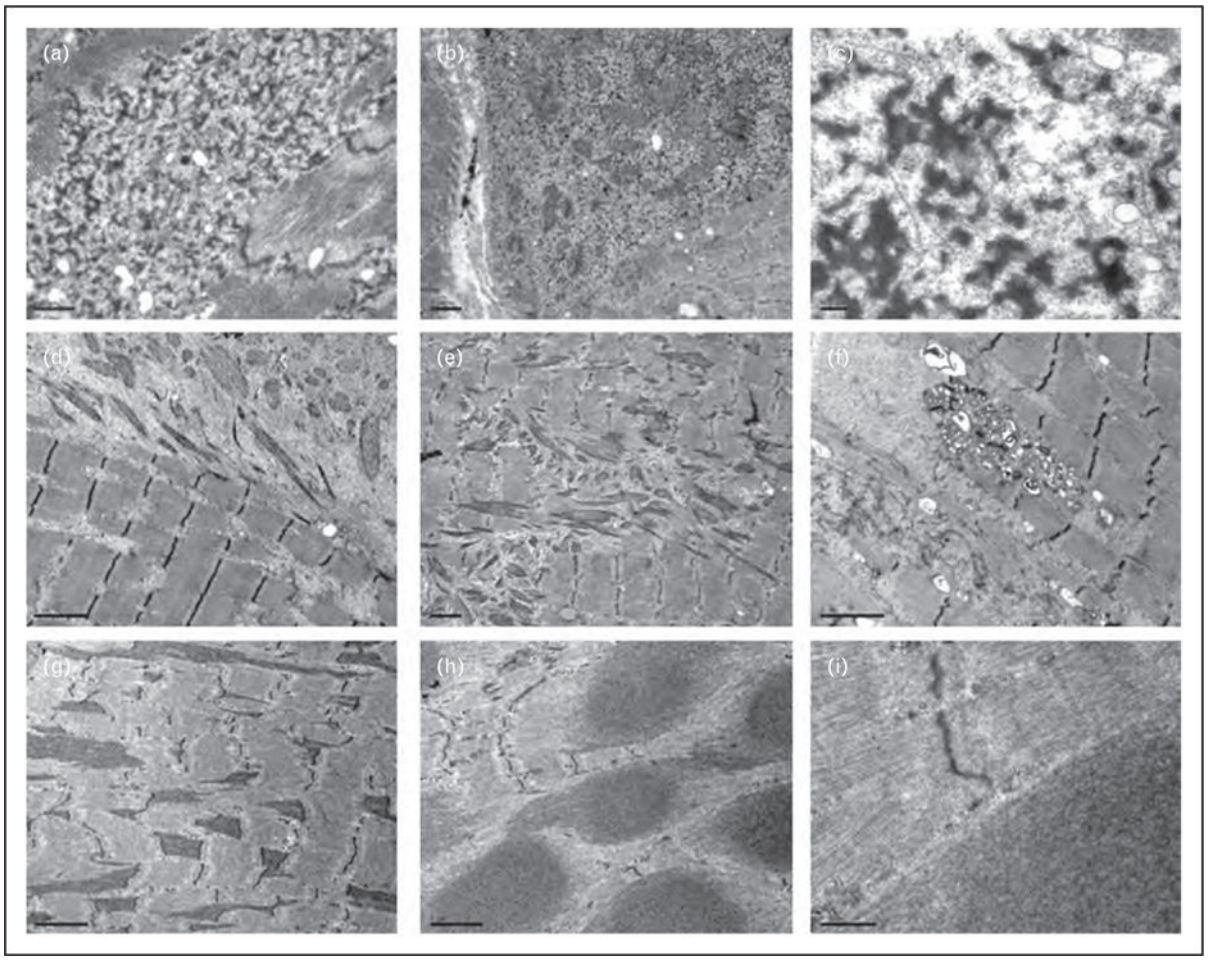

FIGURE 2.

Characteristic ultrastructural findings in desminopathy (a–c), myotilinopathy (d–f), and TTN-A-band-myofibrillar myopathy (MFM) (g–i). In desminopathy, granulofilamentous material originating at the Z-disc level accumulates between the myofibrils (a). Large areas of the muscle fibers are occupied by a mixture of granulofilamentous material and electron dense filamentous inclusions (b). The granulofilamentous material is composed of electron-dense fine filaments and granular profiles (c). The typical features of myotilinopathy include dissolved myofibrils with disrupted Z-lines (d), abnormal fiber regions replaced by filamentous bundles of Z-disc origin, Z-like bodies and thin filaments (e), Z-disc extension, and collections of tubulofilaments and autophagic vacuoles (f). Muscle biopsy from a patient with TTN-A-band MFM shows semidense filamentous material arising perpendicularly to the Z-lines and extending to the entire sarcomere length (g); the same semidense material gives rise to globular inclusions that appear interspersed between preserved sarcomeres (h). A higher magnification shows that the inclusions originate at the Z-line level (i).

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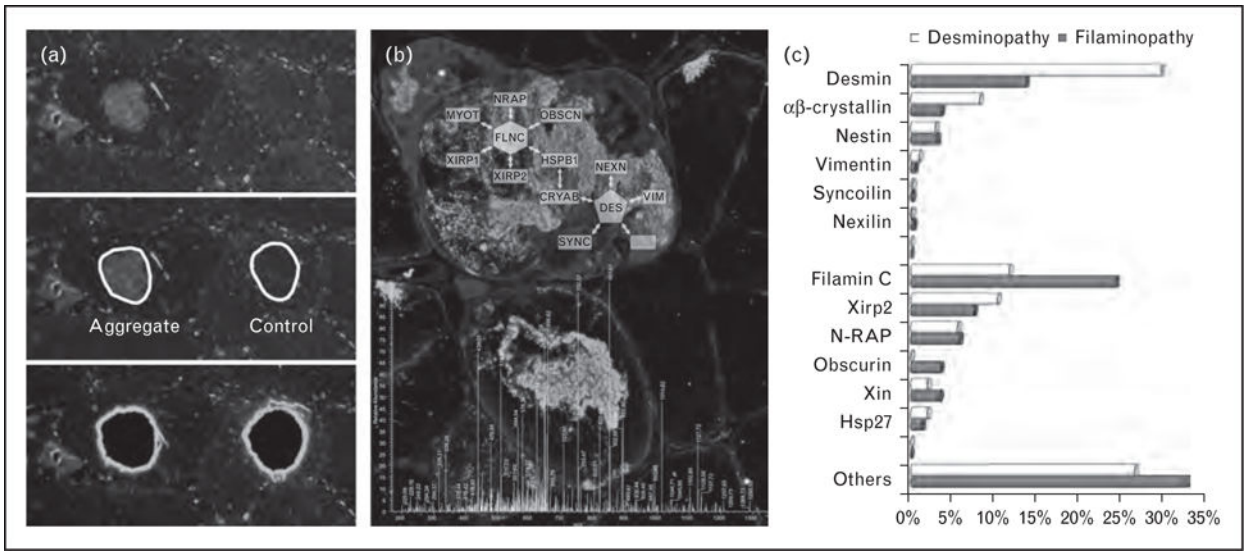

FIGURE 3.

Combined laser microdissection and mass spectrometry-based proteomic approach to deciphering the composition of aggregates in myofibrillar myopathy (MFM). (a) Laser microdissection of aggregate and control samples in skeletal muscle sections from MFM patients. Immunofluorescence staining using antibodies directed against myotilin localizes in areas of protein aggregation in abnormal fibers (upper section). Aggregates in abnormal fibers and control areas can be marked (middle section) and selectively collected by laser microdissection (lower section). (b) Analysis of filaminopathy samples by a label-free quantitative mass spectrometry approach [32■] revealed a significant over-representation of various proteins including desmin, filamin C and their binding partners (arrows). (c) Comparison of published data from proteomic analysis in desminopathy and filaminopathy [32■,33■]. The graph shows a selection of proteins (desmin, filamin C and their binding partners) accumulated in aggregates. Values based on the number of identified peptides assigned to the selected proteins were calculated as percentage of total peptides from proteins over-represented in aggregates with a ratio > 1.8 compared with control samples. Differences in abundance of proteins and accumulation ratios (not shown) allows definition of subtype-specific proteomic profiles.

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Table 1

Genes and proteins associated with MFMs

Gene	Disease	Inheritance pattern	Age of onset	Main clinical features	Key myopathology features	Other phenotypes/ other names for the disease
DES/desmin	Desminopathy	Dominant, *de novo*	Early/middle adulthood	Distal > proximal weakness, cardiopathy, respiratory insufficiency	Amorphous/granular aggregates, rimmed vacuoles, rubbed-out fibers, granulofilamentous material	LGMD 1E, dilated and restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy
	Desminopathy	Recessive	Infancy/childhood			
CRYAB/αB-crystallin	αB-crystallinopathy	Dominant	Middle adulthood	Distal > proximal weakness, cardiopathy, respiratory insufficiency, cataracts	Amorphous/granular aggregates, rimmed vacuoles, rubbed-out fibers, granulofilamentous material, apoptotic nuclear changes	
	αB-crystallinopathy	Recessive	Infancy	Limb and axial stiffness and weakness, respiratory failure	No full length αB-crystallin expression	
MYOT/myotilin	Myotilinopathy	Dominant	Middle/late adulthood	Distal and proximal weakness, cardiopathy and respiratory insufficiency in a minority of patients	Amorphous/granular aggregates, rimmed and nonrimmed vacuoles, Z-line streaming, filamentous bundles, tubulofilaments	LGMD 1A, spheroid body myopathy
ZASP	ZASPopathy	Dominant	Middle/late adulthood	Distal > proximal weakness, cardiopathy and neuropathy in a minority of patients	Amorphous/granular aggregates, rimmed and nonrimmed vacuoles, Z-line streaming, filamentous bundles, tubulofilaments	Dilated cardiomyopathy
FLNC[a]/filamin C	MFM-filaminopathy	Dominant	Middle adulthood	Proximal > distal weakness, respiratory failure, cardiopathy in a subset of patients	Amorphous/granular aggregates, rimmed vacuoles, granulofilamentous material, tubulofilaments	
BAG3/BAG3	BAG3-myopathy	*De novo*	Childhood	Proximal and distal weakness, respiratory insufficiency, hypertrophic cardiomyopathy, peripheral neuropathy	Amorphous/granular aggregates, rimmed vacuoles, granulofilamentous material, Z-line streaming, apoptotic nuclei, giant axonal neuropathy	
FHL1[b]/FHLl	Reducing body myopathy	X-linked	Infancy/childhood adulthood (rare)	Delayed motor milestones, proximal > distal weakness, scoliosis, contractures, rapid loss of ambulation, respiratory	Reducing bodies	Scapuloperoneal syndrome, X-linked myopathy with postural atrophy, Emery–Dreifuss muscular dystrophy, rigid spine

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Gene	Disease	Inheritance pattern	Age of onset	Main clinical features	Key myopathology features	Other phenotypes/ other names for the disease
				insufficiency, milder course in adult onset patients		syndrome, hypertrophic cardiomyopathy
TTN[c]/titin	Hereditary myopathy with early respiratory failure	Dominant	Young adults	Distal, proximal and neck weakness, early respiratory insufficiency	Cytoplasmic bodies, rimmed vacuoles	Tibial muscular dystrophy, LGMD 2J, autosomal recessive early-onset myopathy with fatal cardiomyopathy, dilated cardiomyopathy

LGMD, limb-girdle muscular dystrophy; MFM, myofibrillar myopathy.

[a]Filamin mutations causing MFM-filaminopathy are located in the rod domain of FLNC.

[b]Most of the mutations causing RBM are located in the LIM2 domain of FHL1.

[c]Mutations causing hereditary myopathy with early respiratory failure are located in the A-band domain or the kinase domain of TTN.

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