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## MYOFIBRILLAR MYOPATHIES

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### Abstract

**Purpose of review**—The aim of this communication is to provide an up-to-date overview of myofibrillar myopathies (MFMs).

**Recent findings**—The most important recent advance in the MFMs has been the identification of mutation Bag3 (Bcl-2-associated athanogene-3) as a new cause of MFM. Although, the typical clinical manifestations of MFMs are slowly progressive weakness, the patients with Bag3opathy may have had a rapidly progressive and more severe phenotype.

**Summary**—Several MFM disease genes have recently been recognized. The identified disease proteins (desmin,  $\alpha$ B-crystallin, myotilin, Zasp, filamin C, and Bag3) interact with components or with chaperones of the Z-disk. In each case the molecular defect leads to a largely stereotyped cascade of structural perturbation of the muscle fiber architecture.

### Keywords

Myofibrillar myopathy; desmin;  $\alpha$ B-crystallin; myotilin; Zasp; filamin C; Bag3; FHL1

### Introduction

The myofibrillar myopathies (MFMs) are a group of muscular dystrophies associated with common morphologic features [1,2]. These consist of myofibrillar disorganization commencing at the Z-disk followed by accumulation of myofibrillar degradation products and ectopic expression of multiple proteins that include desmin, dystrophin, myotilin, sarcoglycans, neural cell adhesion molecule (NCAM), plectin, gelsolin, ubiquitin, filamin C, Xin, TAR DNA-binding protein 43 (TDP-43), and co-chaperones including  $\alpha$ B-crystallin (Fig. 1C), heat shock protein (Hsp) 27 and DNAJB2, and congophilic amyloid material [3–10]. The diagnosis of MFM is established by muscle biopsy. The pathologic changes are best illustrated in trichrome stained sections of diseased muscle (Fig. 1A). The abnormal fibers harbor an admixture of amorphous, granular, or hyaline deposits that vary in shape and size, and are dark blue or blue red in color. Many abnormal fiber regions, and especially the hyaline structures, are devoid of, or have diminished, oxidative enzyme activity. Some hyaline structures are intensely congophilic. Some muscle fibers harbor small to large vacuoles containing membranous material and in some cases, some fibers are highly enlarged (giant fibers). The abnormal fibers can be distributed focally so if only a small

muscle specimen is obtained, or if a clinically unaffected muscle is sampled, or if only paraffin embedded tissue is examined, the characteristic changes could be overlooked.

Electron microscopy shows that disintegration of the myofibrils begins at or in immediate proximity of the Z-disk. This is followed by accumulation of degraded filamentous material in various patterns, aggregation of membranous organelles and glycogen in spaces vacated by myofibrils, and degradation of dislocated membranous organelles in autophagic vacuoles.

Most patients with MFM present with progressive muscle weakness but in some patients, the cardiomyopathy may precede the muscle weakness. The disease is usually transmitted by autosomal dominant inheritance but infrequently X-linked or autosomal recessive inheritance is observed. Sporadic cases are frequent either because a mutation arises in the germ line, or because the disease in the parents was unrecognized. Peripheral neuropathy can be an associated feature. EMG studies of affected muscles reveal myopathic motor unit potentials and abnormal electrical irritability which often includes myotonic discharges.

Several MFM disease genes have been identified but in the Mayo MFM cohort of 80 patients, only 35 patients had a genetic diagnosis.

### Desminopathy Subset of MFM

Since the first description of desminopathy by Goldfarb *et al.* [11] and Munoz-Marmol *et al.* [10], more than 40 mutations have been reported. The distribution of weakness can be distal, limb-girdle and scapuloperoneal. Muscle atrophy, mild facial weakness, dysphagia, dysarthria, and respiratory insufficiency can occur. Cardiomyopathy, especially arrhythmogenic type, is a common manifestation. The majority of patients present between 10 to 61 years of age but a patient with syncopal episodes since infancy carries a homozygous in-frame deletion of 7 amino acids (p.Arg173\_Glu179del) in *DES* exon 6 [12]. In two brothers with childhood onset progressive axial and proximal muscle weakness, calf hypertrophy, severe joint contractures and dilated cardiomyopathy resembling “Emery-Dreifuss muscular dystrophy” phenotype, the disease was caused by a homozygous deletion of 22 bp in *DES* exon 6. Interestingly, the muscle biopsy does not show the typical MFM changes but a detailed pathologic description is not yet reported [13].

In a recent expression study, de novo aggregation properties of three GFP tagged-desmin mutants were investigated using confocal single-particle fluorescence spectroscopy. The Arg350Pro and Glu413Lys mutants form aggregates in HEK (human embryonal kidney) 293 cells that lack endogenous desmin, and Arg454Trp-mutant forms a filamentous network like wild-type desmin. Spectroscopy shows that the Arg350Pro mutant inhibits desmin assembly, the Glu413Lys mutant forms hyperstable tetramers, and the Arg454Trp mutant shows only a subtle defect in filament assembly [14]. However, another expression system using MEF Vim  $-/-$  (Vimentin knockout mouse embryo fibroblast) cells shows the Arg454Trp mutant forms abnormally short filamentous structures and only forms a filamentous network when cotransfected with wild-type desmin [15]. This paradox highlights that in vitro models may not yield clear insight into the pathogenic effects of the mutants in vivo, and that care needs to be exercised in the use and interpretation of expression studies.

## $\alpha$ B-Crystallinopathy Subset of MFM

In 1998, Vicart *et al.* [16] identified a heterozygous missense mutation in *CRYAB* in a large kinship. Subsequently, two heterozygous truncating mutations were observed in this gene in 2 patients in the Mayo MFM cohort [17]. The affected patients presented in adult life, had symmetric proximal and distal muscle weakness and atrophy as well as respiratory involvement. Some patients also had hypertrophic cardiomyopathy, palato-pharyngeal weakness, and cataracts [16]. In 2010, another patient with *CRYAB* mutation (Gly145Ser) was reported [18]. The patient presented at age 68 years with slowly progressive distal leg weakness and intermittent atrial fibrillation. The muscle biopsy was typical of MFM.

## Myotilinopathy Subset of MFM

In 2000, Hauser *et al.* [19] detected a missense mutation in *MYOT* in a large kinship that had previously been linked to the myotilin locus at 5q31. The disease was identified as limb-girdle muscular dystrophy 1A (LGMD1A). Two years later, a second kinship with a similar phenotype was found to have a missense mutation in myotilin [20]. Because myotilin is a Z-disk component, we searched for myotilin mutations in the Mayo cohort of MFM patients and identified six mutations in 8 unrelated patients [3]. Therefore, the morphologic substrate of LGMD1A is MFM pathology. Moreover, we found that distal myopathy, cardiomyopathy and peripheral neuropathy can be facets of myotilinopathy. Subsequent studies by other investigators identified additional patients with mutations in *MYOT*, including the kinship originally described under the rubric of “spheroid body myopathy” [6,21–23]. Some kinships also show intrafamily phenotypic variability. The majority of the *MYOT* mutations are heterozygous missense amino acid changes in exon 2 [3,6,19–22] but recently an Arg405Lys mutation was discovered in exon 9, in the second immunoglobulin-like domain of myotilin which is important for homodimer formation and protein-protein interaction [24\*]. Expression studies demonstrated decreased homodimerization and decreased binding of myotilin to  $\alpha$ -actinin, the backbone of the Z-disk.

## Zaspopathy Subset of MFM

Zaspopathy was first described in 2005 by Selcen and Engel [5] in 11 MFM patients who carried heterozygous missense mutations (Ala147Thr and Ala165Val) in *ZASP*. The mean age of onset was in 6th decade. The patients had proximal and/or distal muscle weakness. Three patients had cardiac involvement without signs of coronary artery disease and in one patient the cardiac symptoms antedated the muscle weakness by 10 years. Peripheral nerve involvement by clinical, EMG, or histologic criteria was detected in 5 patients. Subsequently, a large kinship, originally described by Markesbery *et al.* [25], and 5 other kinships with distal myopathy and MFM pathology were shown to carry the Ala165Val in *ZASP* [26].

Recent knockdown experiments of the *Drosophila* ortholog of human *ZASP* demonstrated the importance of Zasp in muscle structure. Knockdown flies cannot fly and do not form Z-disks or recruit  $\alpha$ -actinin to the Z-disk [27,28].

## Filaminopathy Subset of MFM

In 2005, Vorgerd *et al.* [7] identified a dominant Trp2710X mutation in the last exon of *FLNC* in a large German kinship. Then, two additional German families were reported with the same nonsense mutation in filamin C. These families may have a common founder [29]. Subsequently, 3 MFM kinships carrying the same mutation were identified in the Mayo MFM cohort. The age of onset is between 24 and 60 years. All patients have progressive muscle weakness. The serum CK level is normal to 10-fold elevated above the upper limit of normal. Cardiomyopathy, respiratory insufficiency and peripheral neuropathy are associated features.

Recently, two other kinships were reported to have an in frame deletion (Val903\_Thr933del) [30] and a complex deletion-insertion mutation (Lys899\_Val904del and Val899\_Cys900ins) [31] in the seventh Ig-like repeat of *FLNC* at exon 18. Interestingly, three patients in a large Chinese family had chronic diarrhea before the onset of muscle weakness [31].

## Bag3opathy Subset of MFM

Bag3 is a multidomain co-chaperone protein interacting with many other polypeptides. Like other members of the Bag family, it harbors a C-terminal BAG domain that mediates interaction with Hsp 70, antiapoptotic protein Bcl-2, and a proline-rich region that interacts with WW-domain proteins implicated in signal transduction and with Src-3 homology (SH3)-domain proteins such as phospholipase C $\gamma$ -1 that also participates in antiapoptotic pathways. Bag3 itself has a unique N-terminal WW domain that binds proline-rich sequences. Bag3 forms a stable complex with the small Hsp 8 and participates in the degradation of misfolded or aggregated proteins [32–34]. Bag3 is strongly expressed in skeletal and cardiac muscle and at a lower level in other tissues. Its targeted deletion in mice results in a fulminant myopathy with early lethality [35].

In 2009, Selcen *et al.* [9\*\*] described Bag3opathy in 3 MFM patients who were heterozygous for Pro209Leu in exon 3. All three presented in childhood with severe progressive muscle weakness. All had cardiomyopathy and developed respiratory insufficiency with diaphragm paralysis by the second decade. Two also had a rigid spine. The muscle weakness was only proximal in one patient, both proximal and distal in the second patient, and distal more than proximal in the third patient. The serum CK ranged from 3 to 15 times above the upper limit of normal. EMG of one patient showed both axonal and demyelinating polyneuropathy. The light microscopy findings were typical of MFM (Fig. 1). The 3 patients differed from most other MFM patients in early age of onset, rapid evolution of the illness, and presence of the rigid spine. Apoptosis was found in 8% of the nuclei. The enhanced nuclear apoptosis in Bag3opathy is consistent with known antiapoptotic effect of Bag3 [33,36,37] and indicates that Pro209 contributes to this effect.

## FHL1opathy

A wide clinical and pathologic spectrum is associated with FHL1 mutations. This includes late onset X-linked scapulo-axio-peroneal myopathy with bent spine syndrome (XMPMA) [38], reducing body myopathy (RBM) [39,40\*], X-linked dominant scapulo-peroneal

myopathy [41], rigid spine syndrome [42] and Emery-Dreifuss muscular dystrophy like phenotype [43,44]. Although some pathologic features of the FHL1opathies and the MFMs overlap, reducing bodies have not been observed in other forms of MFMs [40\*,45\*].

## Conclusion

MFMs are muscular dystrophies with distinguishing but not always identical morphologic features. The phenotypes include limb-girdle muscular dystrophy, distal myopathy, scapuloperoneal syndrome or rigid spine syndrome. The responsible disease genes in the majority of MFM kinships await discovery.

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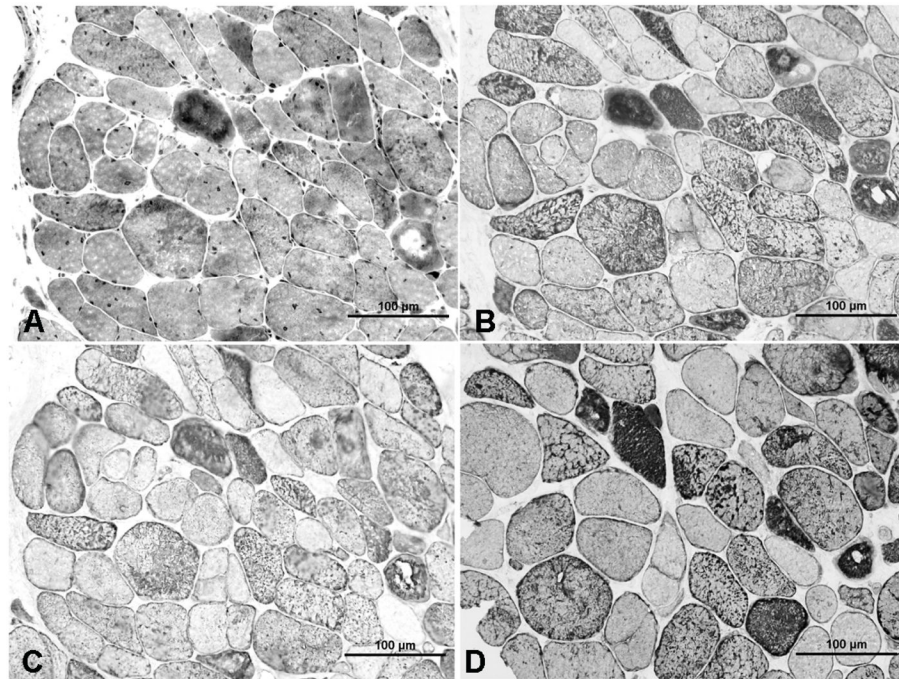
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**Figure 1.** Sections from nonconsecutive sections from a patient with Bag3opathy. Sections (A), (B) and (C) are from the same series. Many abnormal fibers in trichrome section (A) show abnormal accumulation of Bag3 (B),  $\alpha$ B-crystallin (C) and heat shock protein 27 (D).