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MYOFIBRILLAR MYOPATHIES

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SUMMARY

Myofibrillar myopathies represent a group of muscular dystrophies with a similar morphologic phenotype. They are characterized by a distinct pathologic pattern of myofibrillar dissolution associated with disintegration of the Z-disk, accumulation of myofibrillar degradation products, and ectopic expression of multiple proteins and sometimes congophilic material. The clinical features of myofibrillar myopathies are more variable. These include progressive muscle weakness, that often involves or begins in distal muscles but limb-girdle or scapuloperoneal distributions can also occur. Cardiomyopathy and peripheral neuropathy are frequent associated features. EMG of the affected muscles reveals myopathic motor unit potentials and abnormal irritability often with myotonic discharges. Rarely, neurogenic motor unit potentials or slow nerve conductions are present. The generic diagnosis of myofibrillar myopathies is based on muscle biopsy findings in frozen sections. To date, all myofibrillar myopathy mutations have been traced to Z-disk associated proteins, namely, desmin, αB-crystallin, myotilin, ZASP, filamin C and Bag3. However, in the majority of the myofibrillar myopathy patients the disease gene awaits discovery.

Keywords

Myofibrillar myopathies; Z-disk; desmin; αB-crystallin; myotilin; Zasp; Filamin C; Bag3

1. Introduction

The term myofibrillar myopathies (MFMs) was proposed in 1996 as a noncommittal term for a group of chronic neuromuscular diseases associated with common morphologic features [1,2]. These consist of myofibrillar disorganization beginning at the Z-disk followed by accumulation of myofibrillar degradation products and ectopic expression of multiple proteins in the abnormal fiber regions. The pathologic diagnosis of MFM is established by muscle biopsy. In trichrome stained sections of diseased muscle, 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 (Fig. 1A and D). Many abnormal fiber regions, and especially the hyaline structures, are devoid of, or have diminished, oxidative enzyme activity (Fig. 1B). Some hyaline structures are intensely congophilic (Fig. 1C). Some muscle fibers harbor small vacuoles containing membranous material. Electron microscopy shows that disintegration of the myofibrils begins at 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. The clinical features of MFMs are somewhat more variable. Distal muscles are often involved, and cardiomyopathy and peripheral neuropathy can be associated features.

The myofibrillar myopathies can be viewed as muscular dystrophies. They conform to Erb's definition as diseases caused by the primary degeneration of the muscle fibers [3]. Muscle biopsies from MFM patients show primary degeneration of the muscle fibers, increased fibrosis, as well as necrotic and regenerating fibers. Also, different forms of MFM have the clinical features of muscular dystrophies and some were first reported as such. For example, myotilinopathy was first classified as LGMD1A by the clinical criteria [4,5] and zaspopathy [6,7] was first reported as a distal muscular dystrophy.

2. Pathologic and clinical features

2.1 Morphology

The muscle fibers vary abnormally in size. Some abnormal fibers contain large vesicular nuclei. Groups of small fibers, with 3 or more small fibers per group are a common finding. In most cases, however, the atrophic fibers account for only a small proportion of the total. Some atrophic fibers arise by fiber splitting. Necrotic and regenerating fibers and increased fibrosis can also be present. Sparse perivascular or endomysial mononuclear inflammatory cells were present in about 10 percent of the biopsy specimens in the Mayo Clinic cohort. The pathologic changes are best observed in trichrome stained sections of diseased muscle. The abnormal fibers harbor an admixture of amorphous, granular, or hyaline deposits that vary in shape and size, and are dark blue, blue red or dark green in color (Fig. 1A and D). In a given fiber, these areas are single or multiple, vary in shape and size, are superficial or deep in position, and encompass from a small fraction to nearly the entire extent of the cross-sectional fiber area. Typical cytoplasmic bodies are conspicuous in less than 10% of the patients. Occasional abnormal fibers also contain nemaline rods. Pathologic alterations occur in both atrophic and nonatrophic 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. Many abnormal fiber regions, and especially the hyaline structures, are devoid of, or have diminished, oxidative enzyme activity but the oxidative enzyme activity can be accentuated around the larger inclusions (Fig. 1B). Some muscle fibers harbor small to large vacuoles containing membranous material and some patients have highly enlarged giant fibers. Many hyaline structures are intensely congophilic and congophilia is best observed in Congo red stained sections viewed under rhodamine optics (Fig. 1C). The intensity of the fluorescent signal varies from mild to very intense in different specimens. The congophilic inclusions are not metachromatic with the crystal violet stain (personal communication from Dr. Valerie Askanas confirmed by us) and do not display apple-green birefringence in polarized light. Therefore, they are unlike the small amyloid deposits of inclusion body myositis. The large congophilic deposits are an important diagnostic feature of MFM biopsies. Increases of acid phosphatase appear in some vacuoles and in small foci of many abnormal fibers.

Signs of denervation, consisting of groups of atrophic fibers composed of fibers of either histochemical type and increased reactivity of atrophic fibers for nonspecific esterase are observed in some patients. A few patients show fiber type grouping. Many abnormal fibers contain small lakes of PAS-positive material. The muscle fiber lipid content is normal.

The muscle biopsy findings in MFM patients are generally similar with the following exceptions. With mutations in desmin or αB-crystallin, the pathologic alterations tend to be less severe and more monotonous and the congophilic deposits are less numerous and less intensely fluorescent than in other types of MFM. Preapoptotic and apoptotic nuclei occur at an increased frequency in αB-crystallinopathy and Bag3opathy muscles.

Immunohistochemical studies indicate ectopic accumulation of multiple proteins in the abnormal fiber regions that include desmin, myotilin (Fig. 1F), dystrophin (Fig. 1G), sarcoglycans, neural cell adhesion molecule (NCAM), actin, plectin, gelsolin, ubiquitin, filamin C, syncoilin, Bag3 (Fig. 1H), synemin, Xin, TAR DNA-binding protein 43 (TDP-43), and co-chaperones including αB-crystallin (Fig. 1E), heat shock protein (Hsp) 27 (Fig.1I) and DNAJB2 [8–16]. Additional abnormal accumulation of several other proteins was documented in myotilinopathy and desminopathy. These include phospho-tau, β-amyloid, clusterin, a mutant nonfunctional ubiquitin, the multimeric signal protein p62, glycoxidation and lipoxidation markers, neuronal, inducible and endothelial nitric oxide synthases, superoxide dismutase, neuron-related proteins such as ubiquitin carboxy-terminal hydrolase L1, synaptosomal-associated protein 25, synaptophysin, and α-internexin [11,17–19].

Electron microscopy (EM) demonstrates disintegration of myofibrils that begins at or in immediate proximity of the Z-disk (Fig. 2A–F). The earliest changes consist of Z-disk streaming (Fig. 2A, D–F) or accumulation of material of Z-disk density intermingled with pleomorphic dappled dense bodies in close proximity to the Z-disk (Fig. 2C). In patients with desminopathy, αB-crystallinopathy and Bag3opathy, small pleomorphic dense structures or granulofilamentous material accumulate between the myofibrils (Fig. 2B and F). In more advanced stages, when the Z-disks have disintegrated, the sarcomeres fall apart and the myofibrils are no longer recognizable (Fig. 3A–F and Supplementary Figs. 1–3). Dislocated membranous organelles and glycogen accumulate in spaces vacated by disintegrating myofibrils (Fig. 3D and Supplementary Figs. 1 and 2). Other fiber regions harbor fragmented filaments or Z-disk remnants that aggregate into globoid inclusions (Fig. 3A). Some dislocated organelles are trapped in autophagic vacuoles (Fig. 3B) and some vacuoles undergo exocytosis. Preapoptotic [20,21] and apoptotic (Fig. 3F) nuclei [15] are present in some cases of MFM.

Claeys and coworkers [21] report distinct EM patterns in different subtypes of MFMs and recommend EM to be included in the diagnostic workup of MFMs. They noted the following specific features: electron dense granulofilamentous material under the sarcolemma in desminopathy and αB-crystallinopathy; filamentous bundles and floccular thin filamentous accumulations in Zaspopathy; and filamentous bundles and tubulofilamentous inclusions in myotilinopathy. However, in our experience these morphologic features are not uniquely specific for the mutated protein and the ultrastructural features in desminopathy and αB-crystallinopathy are more diverse than stated (see Fig 3A–C and Supplementary Figs. 3 and 4).

2.2 Clinical features

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 mostly myopathic motor unit potentials and abnormal electrical irritability often with myotonic discharges.

Some patients have a combination of myopathic and neurogenic motor unit potentials or slow nerve conduction velocities.

2.2.1. Desminopathy—In skeletal muscle, desmin is detected at the periphery of Z-disks, under the sarcolemma, and at the myotendinous and neuromuscular junctions. In cardiac muscle, it is abundant at intercalated disks and Purkinje fibers. Desmin is a type III intermediate filament (IF) protein primarily expressed in skeletal, cardiac and smooth muscle cells. IFs are 10-nm in diameter, intermediate in size between thick (15 nm) and thin (5 to 6 nm) filaments. They serve to maintain structural integrity and resist externally applied mechanical stress [22]. Desmin with other associated IFs form a heteropolymeric lattice that organizes the myofibrils and links them to nuclei, mitochondria, and the sarcolemma [22,23] [24]

Since the first description of desminopathy by Goldfarb *et al.* [25] and Munoz-Marmol *et al.* [26], more than 40 mutations have been reported (Fig. 4). 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 carrying a homozygous in-frame deletion of 7 amino acids (p.Arg173_Glu179del) in *DES* exon 6 presented with syncopal episodes in infancy [27]. An unusual presentation was observed in two brothers with childhood onset progressive axial and proximal muscle weakness, calf hypertrophy, severe joint contractures and dilated cardiomyopathy resembling the Emery-Dreifuss muscular dystrophy phenotype but the disease was caused by a homozygous deletion of 22 bp in *DES* exon 6. Interestingly, the muscle biopsy did not show the typical MFM changes but the pathologic changes were not detailed [28].

2.2.2. αB-Crystallinopathy—The α-crystallins are small heat-shock proteins that associate into 15–20 nm high-molecular-weight soluble aggregates to become functional. At 3.6 nm resolution, the aggregates appear as asymmetric globules with a central cavity [29,30]. The aggregates represent homooligomers, or even hetero-oligomeric complexes between αB-crystallin and another small heat heat-shock protein [31]. The primary role of α-crystallins is to bind to unfolded and denatured proteins to suppress their non-specific aggregation. Like other members of small heat shock protein family, αB-crystallin monomers contain an N-terminal domain (residues 1–63), an α-crystallin domain (residues 64–105), and a C-terminal extension (residues 106–175) [30].

The A and B forms of α-crystallin are encoded by different genes but have highly homologous amino acid sequences [30]. Both forms are abundant in the lens where they prevent cataract formation. αB-crystallin is also found in nonlenticular tissues, with highest levels in cardiac and skeletal muscle. In these tissues, αB-crystallin is immunolocalized to the Z-disk and its expression is enhanced after stress [32] and exercise [33]. αB-crystallin chaperons actin and desmin filaments [34], tubulin subunits of microtubules [35] and a variety of soluble enzymes [36,37], protecting them from stress-induced damage.

In 1998, Vicart *et al.* [38] identified a heterozygous missense mutation in *CRYAB* in a large kinship (Fig. 5). Subsequently, two heterozygous truncating mutations were observed in 2 patients in the Mayo MFM cohort [20]. The affected patients present in adult life, have symmetric proximal and distal muscle weakness and atrophy, and respiratory involvement. Some patients also have hypertrophic cardiomyopathy, palato-pharyngeal weakness, and cataracts. In 2010, another patient with *CRYAB* mutation (Gly145Ser) was reported [39]. The patient presented at age 68 years with slowly progressive distal leg weakness and intermittent atrial fibrillation. The muscle biopsy was typical of MFM.

Recently, a homozygous c.60delC in *CRYAB* was identified as the genetic basis of the fatal infantile hypertonic muscular dystrophy of Canadian Aboriginals [40]. The affected infants present with progressive limb and axial muscle stiffness, develop severe respiratory insufficiency, and most die in the first year of life. MFMs are typically transmitted by dominant inheritance but in this disease the parental phenotype is rescued by limited expression of the highly truncated nonfunctional mutant gene product.

2.2.3. Myotilinopathy—Myotilin is a 57 kDa Z-disk-associated protein expressed strongly in skeletal and weakly in cardiac muscle [41]. It contains a serine-rich amino-terminal region that also comprises a hydrophobic stretch, two immunoglobulin (Ig)-like domains and a carboxy terminal tail. The Ig-like repeats are required for the formation of antiparallel myotilin dimers [41,42]. Myotilin binds to α-actinin, the main component of Z disk that cross link actin filaments at the Z-disk, and to filamin C, a peripheral Z-disk protein. The α-actinin binding site resides between myotilin residues 79–150 [5]; and the filamin C binding site is located in the second Ig-like domain [43]. (Fig. 6) In addition, myotilin cross links actin filaments and plays a role in the alignment of myofibrils during the later stages of myofibrillogenesis [42].

In 2000, Hauser *et al.* [5] 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 [44]. One of the reports [44], however, did not assess the pathology of the disease, and the other report [5] showed only Z-disk alteration in some muscle fibers. That myotilin is a Z-disk component, prompted a search for myotilin mutations in the Mayo cohort of MFM patients and resulted in discovery of six mutations in 8 unrelated patients [8]. In the identified patients, the mean age of onset was 60 years. In 3 patients the weakness was more prominent distally than proximally. Cardiac involvement without signs of coronary artery disease was evident in 3 patients. Peripheral neuropathy, reflected by clinical, EMG, and histologic criteria, or by a combination of these, was apparent in all patients. Subsequent studies by other investigators identified additional patients with mutations in *MYOT*, including the kinship originally described under the rubric of “spheroid body myopathy” [11,45–47]. Some kinships show intrafamily phenotypic variability. The majority of the *MYOT* mutations are heterozygous missense amino acid changes in exon 2 [5,8,11,44–46] (Fig. 6) 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 [48]. Expression studies demonstrated decreased homodimerization and decreased binding of myotilin to α-actinin, the backbone of the Z-disk.

2.2.4. Zaspopathy—ZASP (Z-band alternatively spliced PDZ motif-containing protein) is expressed predominantly in cardiac and skeletal muscle [49]. It binds to α-actinin [50], the structural component of the Z-filaments that cross link thin filaments of adjacent sarcomeres. Sixteen *ZASP*-associated exons have been detected in genomic DNA and splice variants of these exist in cardiac and skeletal muscle. Skeletal muscle harbors three isoforms (see Fig. 7). The longest isoform lacks exons 4 and 9; another long isoform lacks exons 4, 9 and 10; and a short isoform lacks exon 4 and carries a stop codon in exon 9. In the mouse and human, three cardiac isoforms resemble those in skeletal muscle but contain exon 4 instead of exon 6 [51]. Recently, however, exon 6 was also detected in the human heart [52]. All ZASP isoforms have an N-terminal PDZ domain important for protein-protein interactions [53] and a 26 residue ZM motif in exons 4 and 6 needed specifically for interaction with α-actinin [54]. The long isoforms have three C-terminal LIM domains that interact with protein kinase-C subtypes [55]. Targeted deletion of *ZASP* in the mouse

(referred to as Cypher [50] or Oracle [56] in the mouse) causes skeletal and cardiac myopathy with fragmented Z-disks [57].

Zaspopathy causing MFM was first described in 2005 by Selcen and Engel [10] in 11 MFM patients who carried heterozygous missense mutations in *ZASP*. The mean age of onset was in sixth decade. Most patients presented with muscle weakness but one patient presented with palpitations and mild hyperCKemia. Seven of 11 patients had family histories consistent with autosomal dominant inheritance. The patients had proximal and/or distal muscle weakness. Three patients had cardiac involvement without signs of coronary artery disease and in one of these the cardiac symptoms antedated the muscle weakness by 10 years. Peripheral nerve involvement by clinical, EMG, or histologic criteria was detected in 5 patients. The mutations detected in these patients were Ala147Thr and Ala165Val in exon 6, and Arg268Cys in exon 9 (Fig. 7). The Ala165Val mutation is within, and the Ala147Thr mutation is immediately before, the ZM motif needed for interaction with α-actinin [54]. Subsequently, the large kinship, described by Markesbery et al in 1974 [6], and 5 other kinships with distal myopathy and MFM pathology were shown to carry the Ala165Val mutation. These 6 kinships and the 3 of the Zaspopathy kinships observed at the Mayo Clinic harboring this mutation may have a common founder [7].

2.2.5. Filaminopathy—The filamins are a family of high MW cytoskeletal homodimeric proteins containing an N-terminal actin-binding domain followed by 24 Ig-like repeats [58]. While the expression of filamins A and B is ubiquitous, filamin-C is largely restricted to skeletal and cardiac muscle. The filamins are involved in multiple processes, such as the organization of actin filaments, membrane stabilization, and they serve as a scaffold for signaling proteins. Filamin C also interacts with several Z-disc proteins and with γ- and δ-sarcoglycan at the sarcolemma [58–60].

In 2005, Vorgerd *et al*. [12] identified a dominant Trp2710X mutation in the last exon of filamin C in 17 affected individuals of a large German kinship (see Fig. 8). Subsequently, the same nonsense mutation was observed in two other German families [61] and three MFM kinships 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, further *FLNC* mutations were detected: an in frame deletion (Val903_Thr933del) [62]; and a complex deletion-insertion mutation (Lys899_Val904del and Val899_Cys900ins) [63], both in the seventh Ig-like repeat in exon 18. Interestingly, three patients in a large Chinese family had chronic diarrhea before the onset of muscle weakness [63].

2.2.6. Bag3opathy—Bag3 (Bcl-2 associated athanogene 3), also referred to as CAIR-1 or Bis, is a multidomain co-chaperone protein interacting with many other polypeptides. Bag3 is strongly expressed in skeletal and cardiac muscle and at a lower level in other tissues. Like other members of the Bag family, it harbors a C-terminal BAG domain that mediates interaction with Hsp 70 and the antiapoptotic protein Bcl-2. It also has a proline rich region that interacts with WW-domain proteins implicated in signal transduction, and with Src-3 homology (SH3)-domain proteins implicated in antiapoptotic pathways (see Fig 9). Bag3 also has a unique N-terminal WW domain that binds proline-rich sequences. Bag3 forms a stable complex with the small Hsp 8 and thereby participates in the degradation of misfolded or aggregated proteins [64–66]. Its targeted deletion in mice results in a fulminant myopathy with early lethality [67].

In 2009, Selcen *et al.* [15] described Bag3opathy in 3 MFM patients who were heterozygous for Pro209Leu in exon 3 (Fig. 9). All three presented in childhood with severe progressive muscle weakness. All had cardiomyopathy and developed respiratory insufficiency with diaphragm paralysis by the second decade, and two also had a rigid spine. The muscle weakness was only proximal in one patient, 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. The EMG of one patient showed both axonal and demyelinating polyneuropathy. The light microscopy findings were typical of MFM (Fig. 1). The affected 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 [65,68,69] and indicates that Pro209 contributes to this effect.

Recently three other kinships were reported to have the same Pro209Leu mutation in *BAG3*. All patients show the same severe phenotype. One asymptomatic parent was a somatic mosaic for the mutation. Nerve biopsies showed axonal neuropathy with loss of myelinated axons and scattered giant axons [70].

3. Conclusion

MFMs are muscular dystrophies with distinguishing but not always identical morphologic features. That the initial pathologic change in MFMs is centered on the Z-disk accounts for the nearly stereotypic pathology and implicates Z-disk related proteins as culprits. The phenotypes include limb-girdle muscular dystrophy, distal myopathy, scapuloperoneal syndrome or rigid spine syndrome. Distal muscle involvement, cardiomyopathy and peripheral neuropathy are important clinical clues but they are not present in all patients. A major unsolved issue is deciphering the signaling mechanism between the Z-disk and the nucleus that results in abnormal transcription, translation, or both, of multiple genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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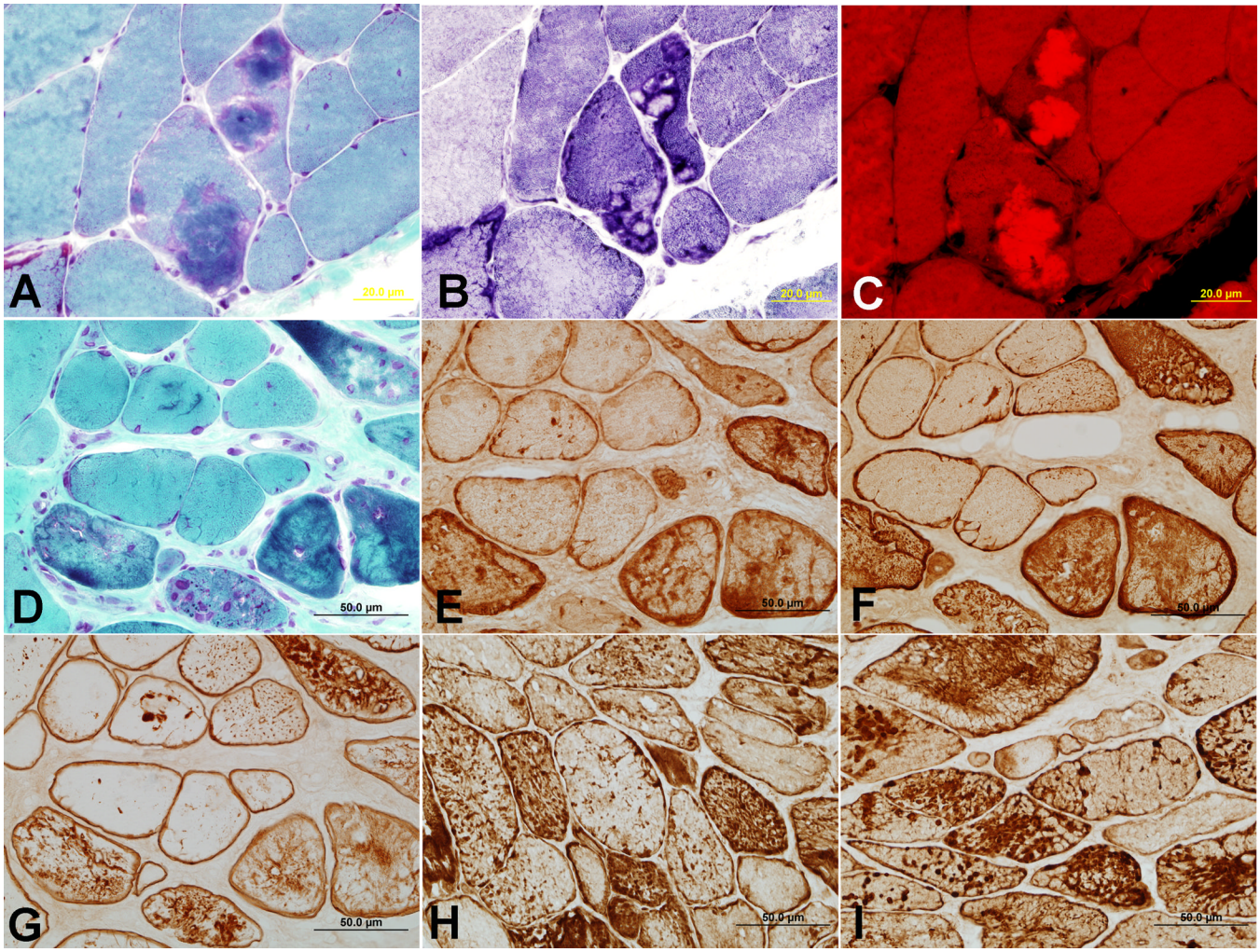

Fig. 1.

(A–C): Characteristic histologic findings of a patient with myotilinopathy in trichrome (A), NADH dehydrogenase (B) and Congo red (C) stained sections. (D–G): Nonconsecutive sections from a patient with desminopathy in the same series stained trichromatically (D), and immunoreacted for αB-crystallin (E), myotilin (F), and dystrophin (G). (H, I) Sections from a patient with Bag3opathy immunoreacted for Bag3 (H), and heat shock protein 27 (I). Note abnormal accumulation of each protein in the structurally abnormal fibers.

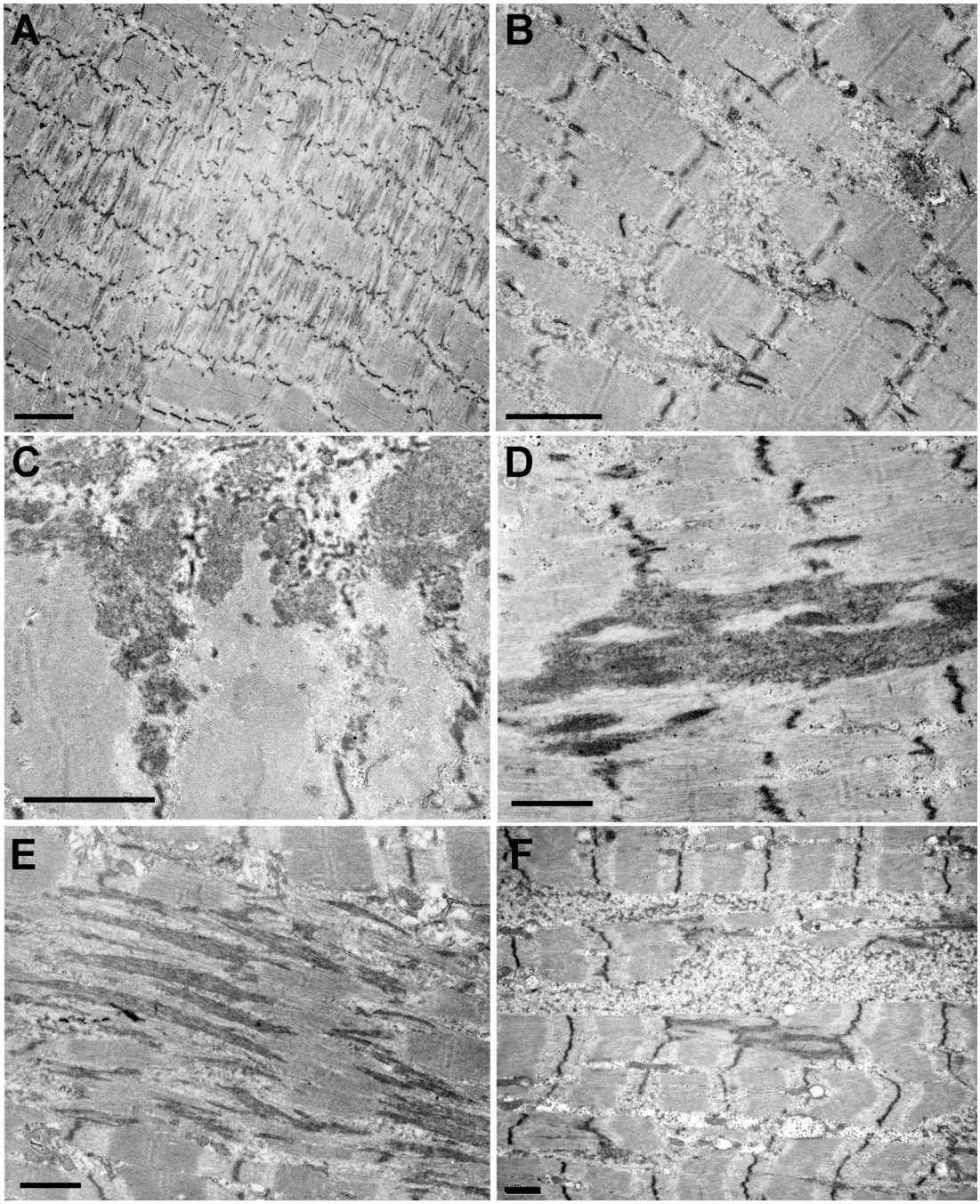

Fig. 2.

Early ultrastructural findings in desminopathy (A and B), αB-crystallinopathy (C), myotilinopathy (D), Zaspopathy (E), and Bag3opathy (F). Z-disk streaming (A, D–F) and accumulation of small pleomorphic structures between the myofibrils (B and F). In (C), normal Z-disks give rise to abnormal expanses of material of Z-disk density intermingled with pleomorphic dappled dense bodies. Bar = 2 μm for (A) and 1 μm for (B–F). (Fig. 2C is reproduced from Ref. [3] by permission)

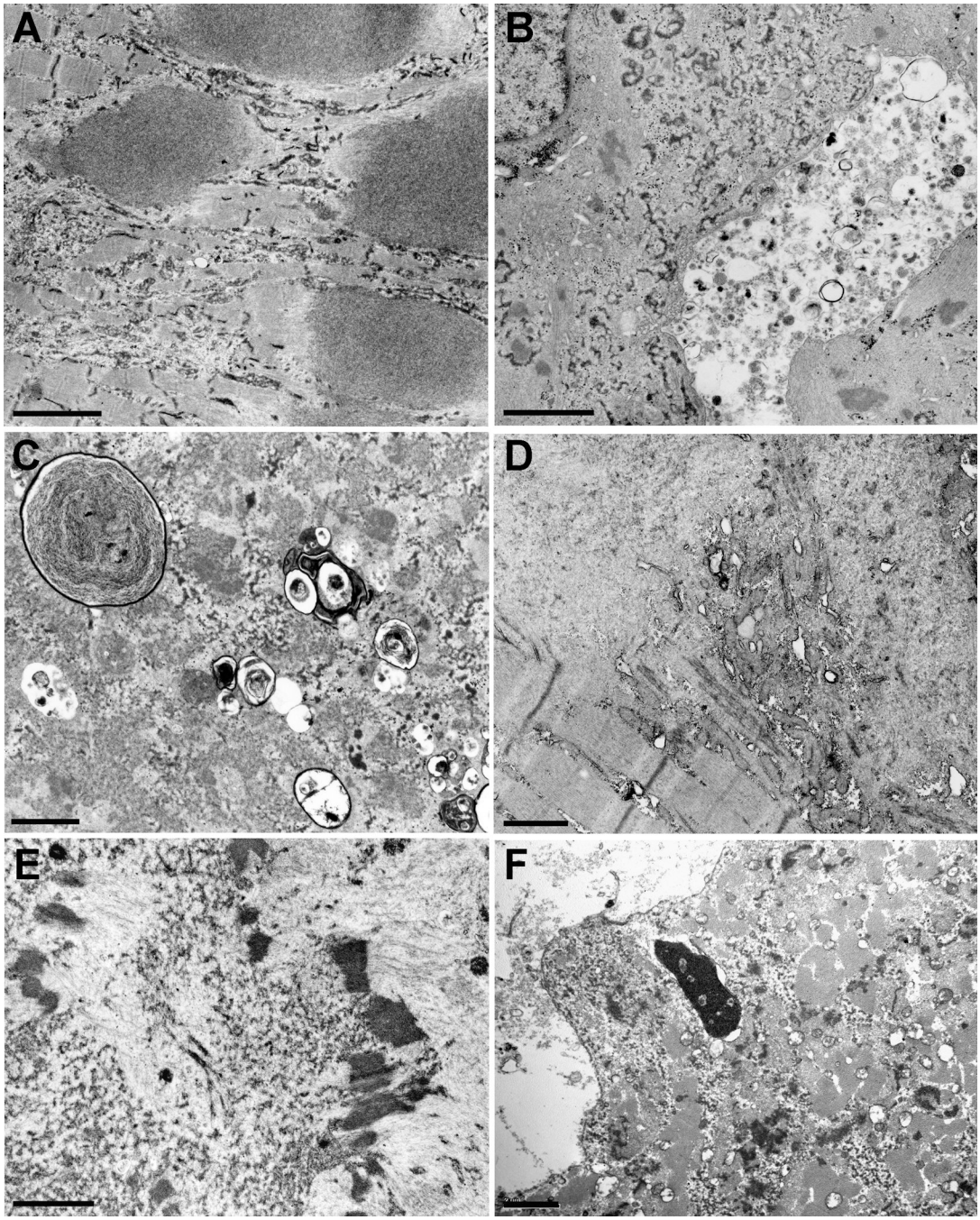

Fig. 3.

Advanced ultrastructural findings in desminopathy (A and B), αB-crystallinopathy (C), myotilinopathy (D), Zaspopathy (E), and Bag3opathy (F). Note dense globoid inclusions in (A), autophagic vacuoles in (B). Large expanse of degraded material in (C–F), dislocated membranous organelles in (D), nemaline rods abutting on degraded Z-disk material in (E) and an apoptotic nucleus in (F). Bar = 2 μm for (A) and 1 μm for (B–F).

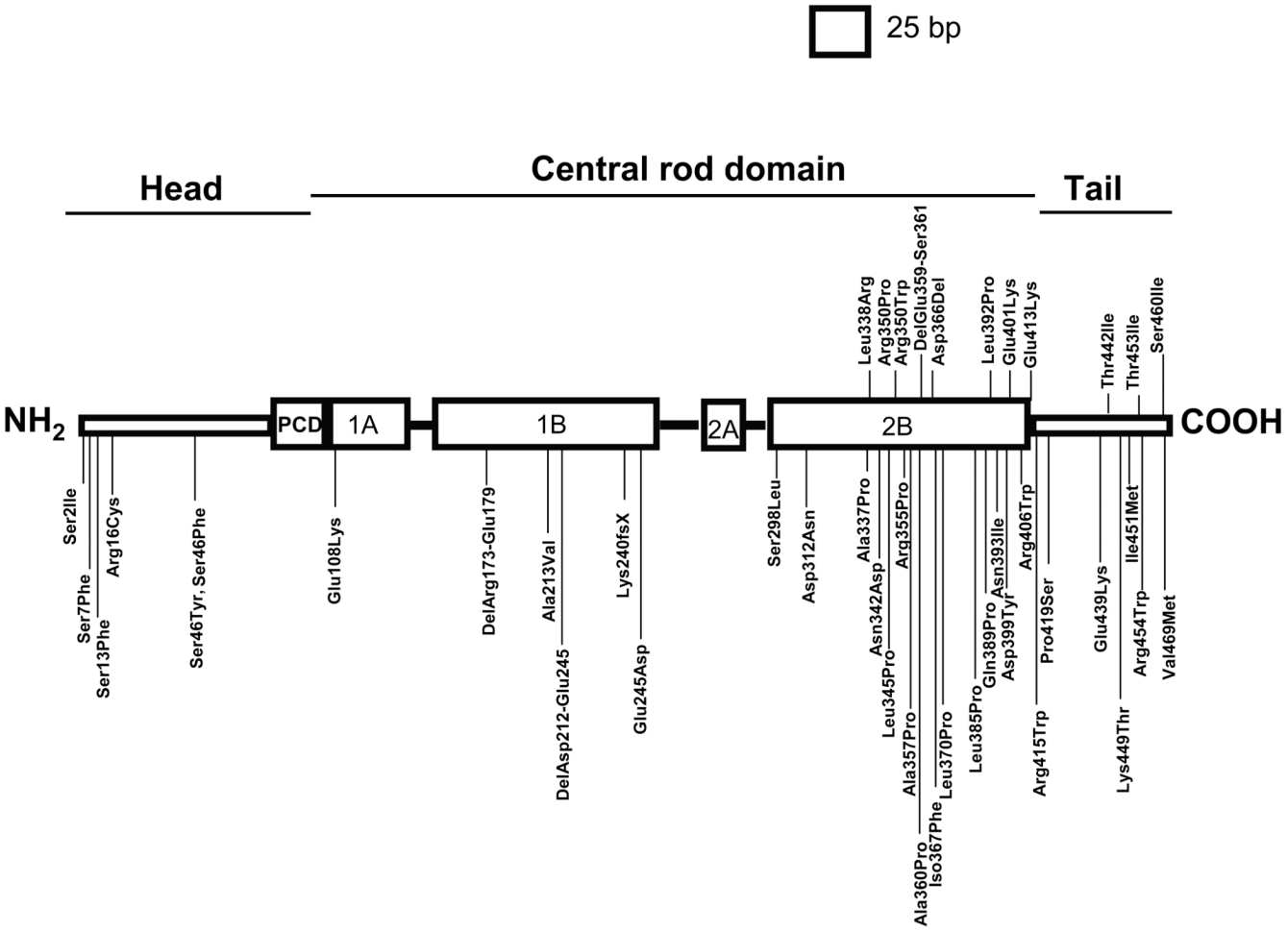

Fig. 4.
Schematic diagram of desmin and the identified mutations to date.

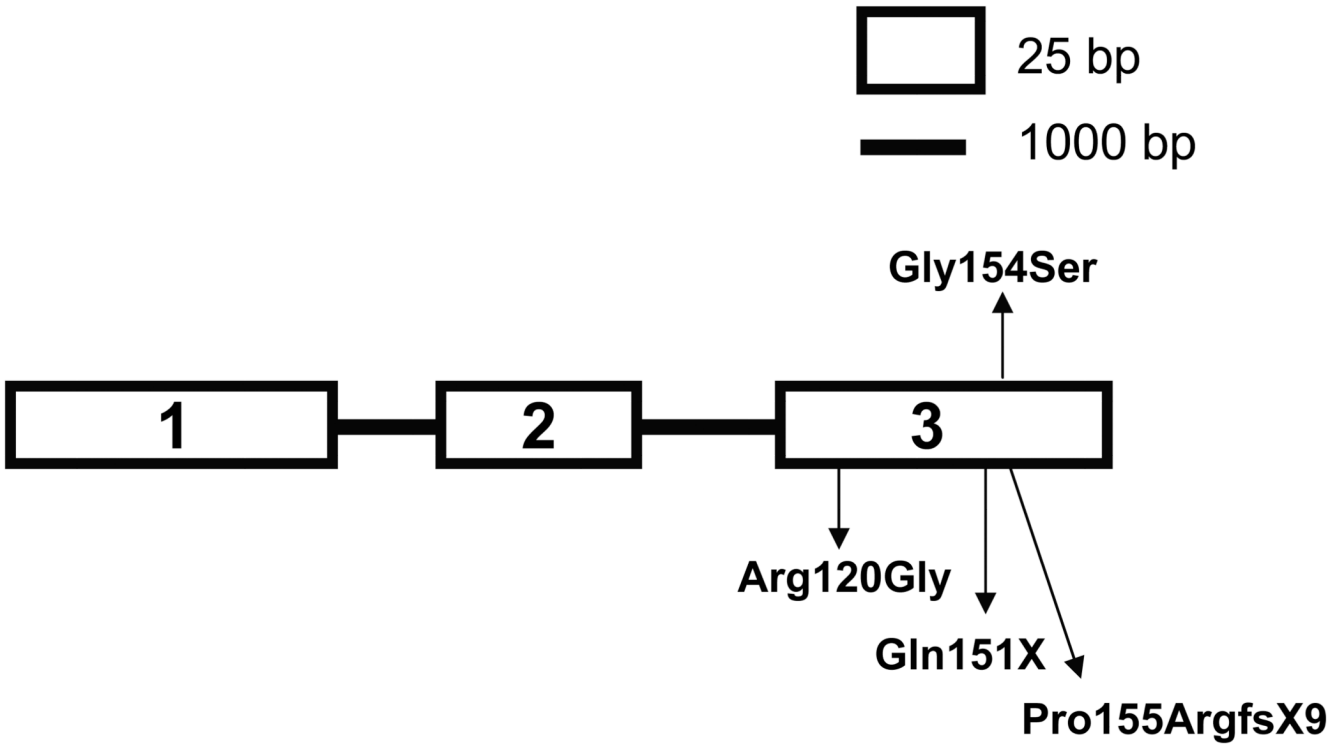

Fig. 5.
Schematic diagram of αB-crystallin and the identified mutations that cause MFM.

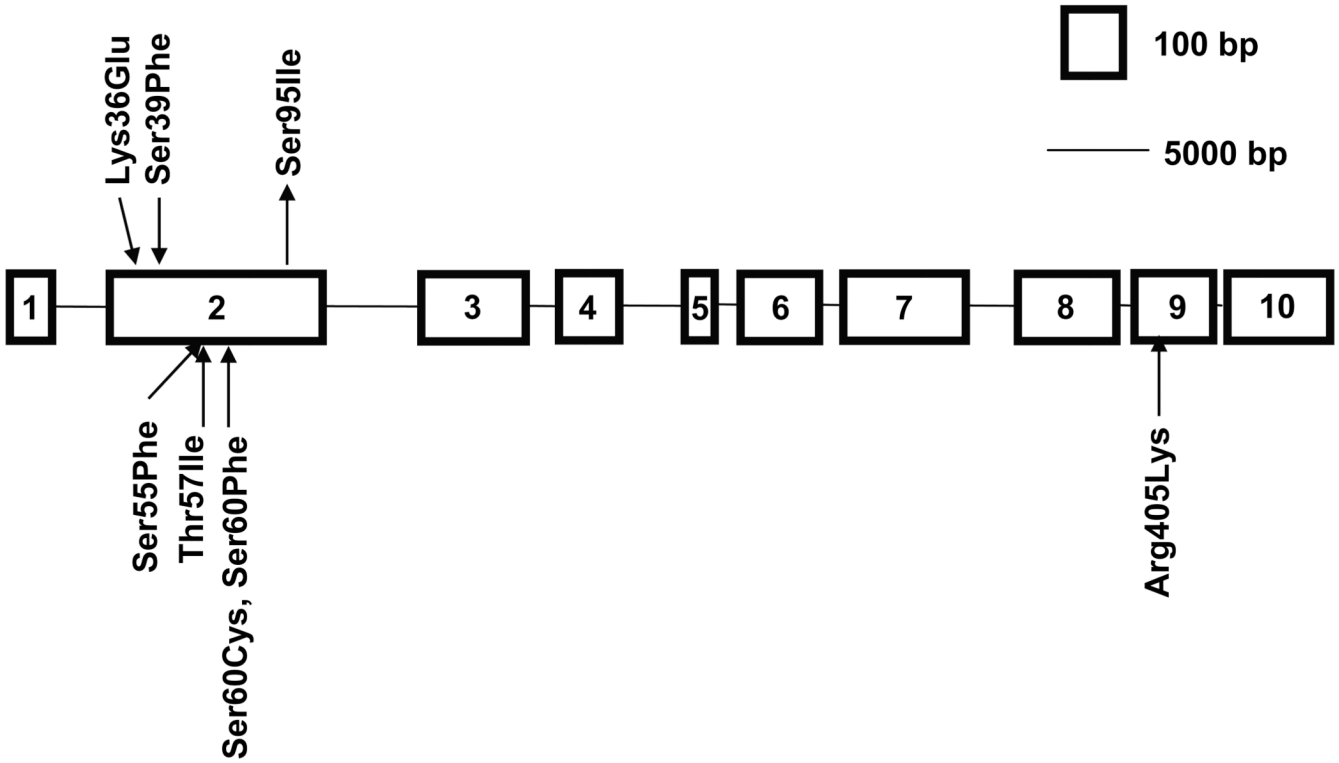

Fig. 6.
Schematic diagram of myotilin and the identified mutations to date.

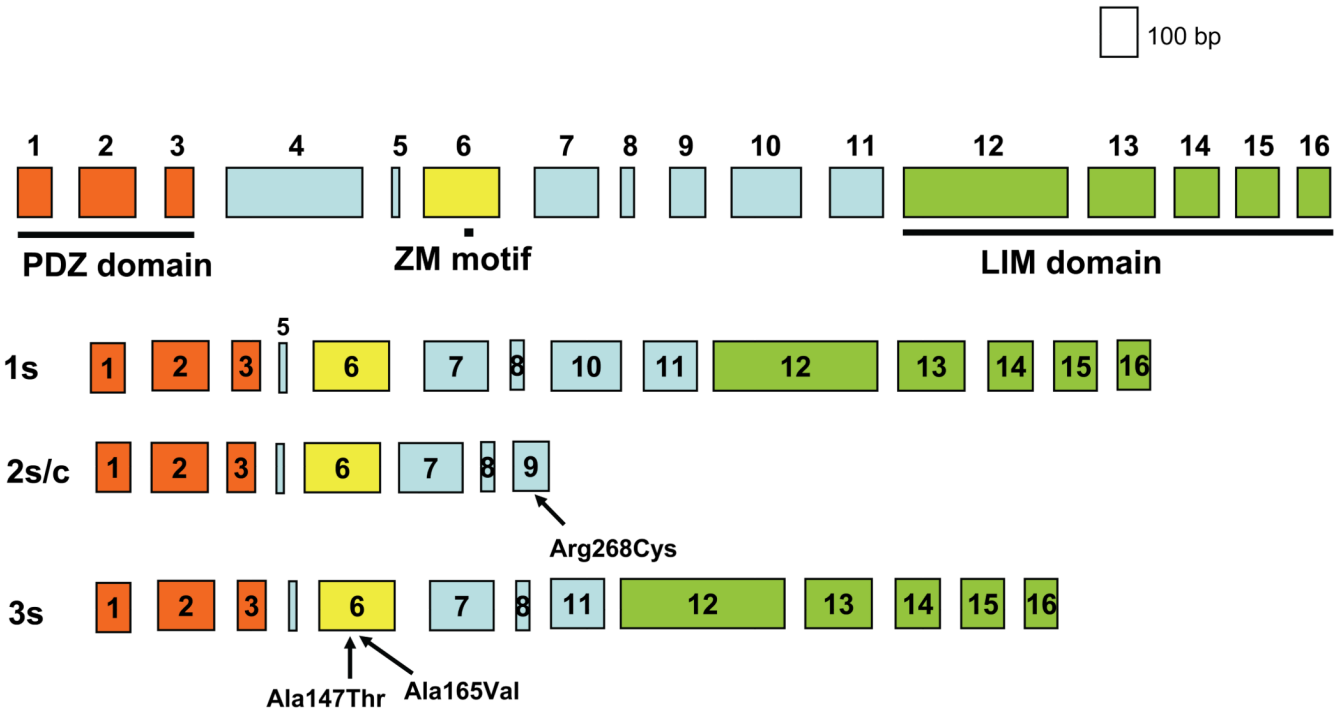

Fig. 7.

Scheme of the genomic structure of *ZASP* and the identified mutations to date. Top row shows the 16 ZASP exons. Not all exons are transcribed in cardiac and skeletal muscle. 1s, 2s and 3s are expressed in skeletal muscle. The PDZ domain and the ZM motif appear in all three transcripts; the three LIM domains are present only in the two long transcripts. The Ala147Thr and Ala165Val mutations are predicted to appear in all three ZASP isoforms whereas the Arg268Cys mutation is predicted to appear only in the short isoform.

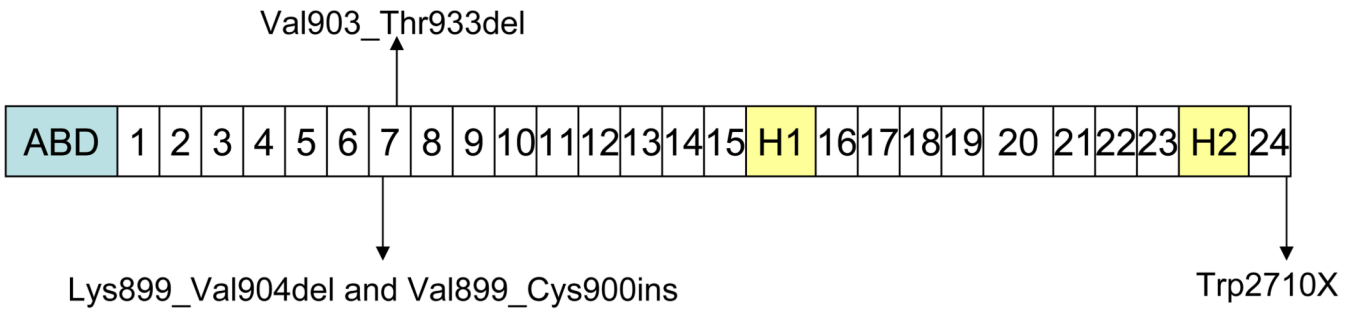

Fig. 8.
Scheme of the domains of *FLNC* and the identified mutations.

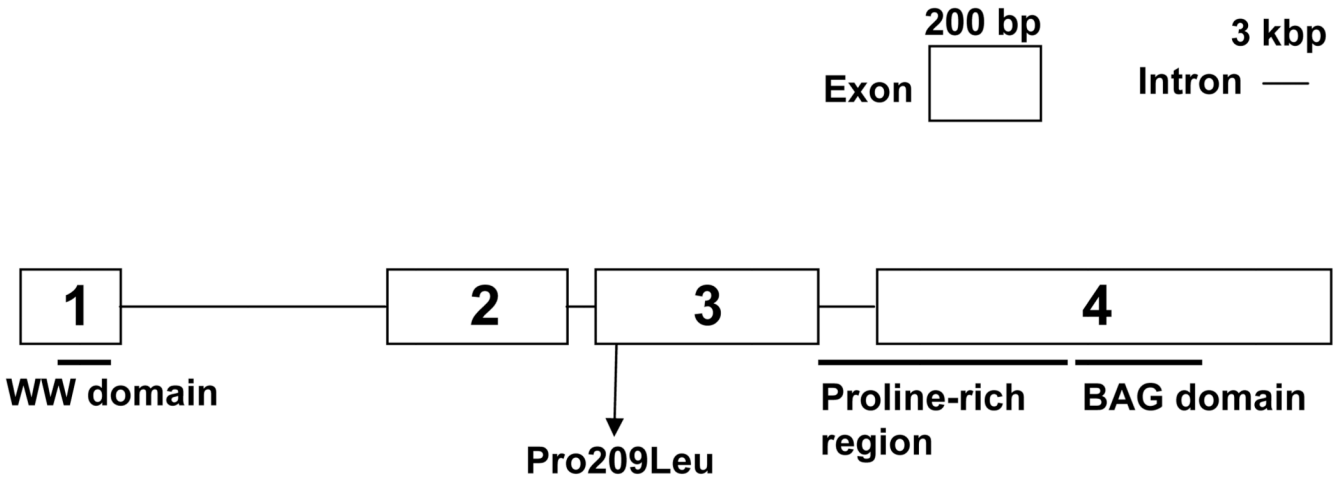

Fig. 9.
Scheme of the genomic structure of *BAG3* and the identified mutation.