Chapter 14

Myofibrillar Myopathies and the Z-Disk Associated Proteins

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Additional information is available at the end of the chapter

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1. Introduction

Myofibrillar myopathies (MFMs) are typically autosomal dominant myopathies with late onset progressive muscle weakness and symptoms initially evident in the distal muscle groups. However, there is a significant variability in the presentation of these diseases, with the age of onset ranging from infantile to late seventies; the involvement of the heart, respiratory muscles, distal or proximal muscle groups; and severity covering the full spectrum from mild muscle weakness to premature lethality. Several myopathies were identified with symptoms within this broad spectrum and the recognition of a common pathology allowed the grouping of these diseases under a single term, MFM [1]. Problems in the classification of these disorders still exist, partially due to the wide spectrum of clinical presentation and the lack of detailed analysis of biopsy samples to identify the defining features of MFM.

The defining features of MFM, identified using histological stains and electron microscopy, are the dissolution of muscle fibres and the formation of protein aggregates. Common pathological features of MFM include presence of amorphous, granular, filamentous or hyaline deposits, interstitial fibrosis, fatty infiltration, centrally located nuclei indicative of regeneration, necrosis and muscle degeneration. Displaced membranous organelles are also evident, either in the cytoplasm or within autophagic vacuoles. Affected areas of the cells are frequently devoid of oxidative enzymatic activity and mitochondria can be abnormally shaped and positioned [2-5]. Characterization of the protein aggregates using immunohistochemistry reveals the presence of a wide range of sarcomeric, extracellular, and ubiquitously expressed proteins including Myotilin, Desmin, αB-Crystallin, Filamin C, BAG3, ZASP, Actin, Titin, Myosin, Xin, Dystrophin, sarcoglycans, Plectin, Delsolin, Ubiquitin, Neural cell adhesion modulator, Gelsolin, Syncoilin, Synemin, TAR DNA-binding protein 43, Heat-shock protein 27, and DNAJB2 [6]. Interestingly, α-Actinin, which

is the primary Z-disk crosslinker and is associated with many of the Z-disk proteins mutated in MFM, is not detected in these protein aggregates [6,7].

The Z-disk provides an important structural linkage in the transmission of tension and contractile forces along the muscle fibre and has a role in sensing of muscle activity and signal transduction. In line with the identification of the Z-disk as the primary site affected in these myopathies the identification of MFM causing mutations has revealed a very strong association with the Z-disk, with all of the proteins affected being localised to this structure. Mutations have been identified in the intermediate filament (IF) protein Desmin [8], the chaperone αB-Crystallin [9], the structural protein Myotilin [10], the α-Actinin binding protein ZASP [11], the actin binding protein Filamin C [12], and the co-chaperone BAG3 [13]. Based on the Mayo Clinic MFM cohort, 14% of MFMs are due to mutations in ZASP, 13% due to Myotilin mutations, 8% Desmin mutations, 5% αB-Crystallin mutations, 4% BAG3 mutations, and 4% due to mutations in Filamin C, with the genetic basis of more than 50% of MFM cases remaining unknown [14].

Whilst subtle differences in morphology and histochemical staining are found to be associated with certain MFM subtypes [3], they are not reliable in identifying the genetic cause of MFM. Ultrastructural studies on the other hand have been shown to be more informative in identifying the subtype of MFM, although repetition with large sample sizes is required to determine the reliability of ultrastructure studies is directing diagnosis [15].

Mutations in any of the identified MFM genes can also result in other forms of myopathy including dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), distal myopathy, spheroid body myopathy (SBM), and limb-girdle muscular dystrophy (LGMD). Whilst mutations can result in different myopathies, within the cases of MFM there is a remarkable consistency in the phenotype regardless of the gene mutated. This unifying pathological presentation suggests a common mechanism of pathology, although the functions of the MFM proteins and how their mutation results in disease are not fully understood. Determination of the mechanism by which these mutation result in disease will not only be important for the development of therapies for these conditions but will also provide insight into the role of these proteins in the muscle and the many functions of the Z-disk. We present an analysis of the literature surrounding each of these proteins and how their mutations result in disease and discuss the implications for MFM and Z-disk function.

2. Desmin and desminopathies

Desmin, named from the word 'desmos' which means 'link' is a small, 53KDa, IF protein found in skeletal, smooth [16], and cardiac [17] muscle cells. In mature skeletal muscle, Desmin along with other Desmin-binding molecules such as Plectin, links adjacent myofibrils at the Z-disk and binds them to the sarcolemma at the costameric level [18]. Desmin localisation to the intermediate filament, Z-disk, and costamere provides a cytoskeletal network that links the contractile apparatus to the cell membrane and other structural elements of the cell, which is critical for maintaining the integrity of the cell, ensuring force transmission and providing with a pathway for signalling. In order to form a fully functional IF network Desmin connects

with different cell structures from the cell membrane to the nuclear envelope. Therefore Desmin interacts with a range of different muscle, non-muscle, and nuclear proteins. At the Z-disk, it interacts with αB-Crystallin (CRYAB) [19] and Nebulin [20,21]. At the periphery of the Z-disk, costameres, nucleus, and neuromuscular junctions Desmin interacts with Vimentin, Synemin [22], Paranemin [23], Desmulsin [24], Lamin [25], Plectin [26], Nestin [27], spectrins [28], and Ankyrin [29]. Deficiency in Desmin not only results in disturbance to the structure of the sarcomere, but also results in striking changes to the cellular morphology, which may have direct implications for muscle function. Desmin knockout mice show abnormal mitochondrial localization, accompanied by an increase in number and size, a rounded shape and distorted membranes, often showing granules and even mineralised bodies [30].

Structurally, Desmin is made up of three domains; an N-terminal head domain, a highly conserved central α-helical core, and a C-terminal tail domain (Figure 1). The central α-helical core, a region responsible for Desmin assembly into IF, is made up of four consecutive helical segments, 1A, 1B, 2A and 2B, which are linked by short non helical linkers [31,32]. These helical domains are made of tandem repeats of a specific seven amino acid sequence that contains the biochemical properties that allow the proper coiling of the protein. Additionally, the 2B helical domain contains a four amino acid insertion, known as the 'stutter', critical for Desmin assembly and conserved between many IF proteins [33,34]. Of the 50 Desmin mutations reported so far that result in severe skeletal and/or cardiac muscle defects the majority affect the coiled domains, five affect the head domain and eleven affect the tail domain (Figure 1). Interestingly, no mutations in domain 2A have been reported to date and more than 50% of reported Desmin mutations are in the 2B domain [35]. Although a correlation between the domain mutated and the clinical features of the patients/carriers has been suggested (reviewed in [35]), when the clinical features are analysed in more detail the only correlation that appears to be maintained is the predominance of skeletal muscle defects in patients with mutations in the 2B domain (Table 1 and Table 2).

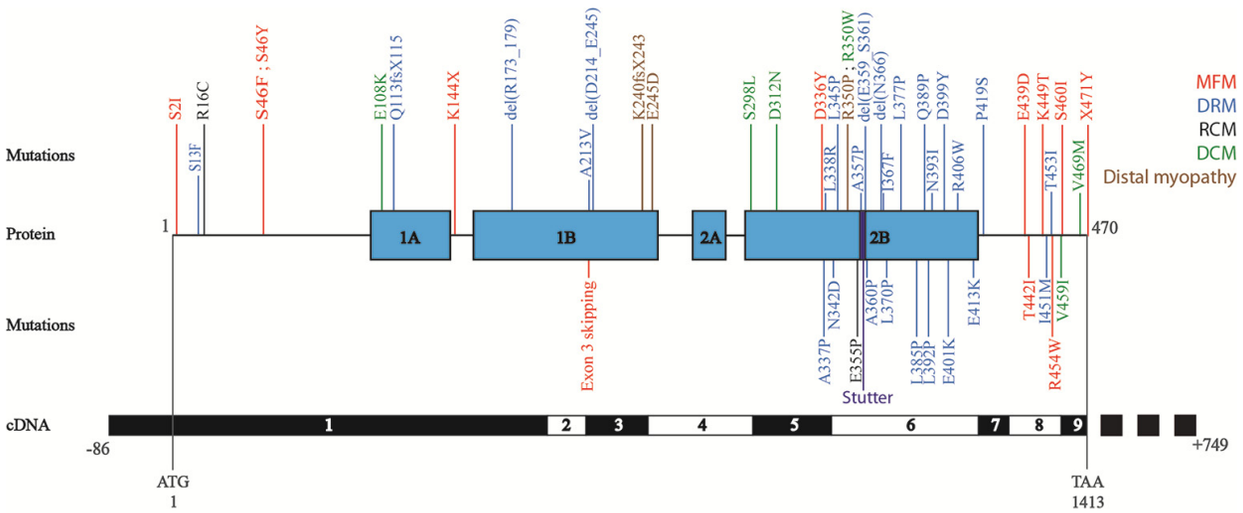


Figure 1. Schematic representation of Desmin domains and mutations.

Mutations are coloured accordingly to the disease classification. Note that 3′UTR is not drawn to scale. Mutations are coloured accordingly to the disease classification. Note that 3′UTR is not drawn to scale.

Mutation	Age of onset / Initial symptoms	Clinical and pathological features; other studies	Ref
c.5G>T **S2I**	? Skel	**Skel:** MW**. Pathology:** abnormal myofibre size. **Other studies:** *in vitro* assembly assays showed assembly into a wider IF network; SW13 and MEF cells form a normal IF network.	[36,37]
c.137C>T **S46F**	?	**Skel:** MW**. Pathological studies:** abnormal myofibre size. **Other studies:** *in vitro* assembly assays showed IF assembly into wider filaments; SW13 cells form aggregates but MEF cells form a normal IF network.	[36,37]
c.137C>A **S46Y**	?	**Skel:** MW**. Pathology:** abnormal myofibre size. **Other studies:** *in vitro* assembly assays showed assembly into wider IF filaments; SW13 cells show aggregate formation but MEF cells form a normal IF network.	[36,37]
c.430A>T **K144X**	37 Card	**Card:** DCM; AVB.	[38]
c.640-2A>C ? (exon 3 skipping)	26-32 Card	**Card:** AVB that required pacemaker insertion.	[38]
c.1006G>T **D336Y**	37 Card	**Card:** DCM; AVB; pacemaker insertion.	[38]
c.1315G>A **E439D**	51 Card	**Card:** atrial fibrillation.	[38]
c.1325C>T **T442I**	27-35 Skel	**Skel:** MW and wasting leading to wheelchair dependence; MA. **Card:** atrial fibrillation and arrhythmia that required pacemaker insertion; fatal heart failure in some cases. **Pathology:** fibre splitting; internally located nuclei; Desmin-positive aggregates and vacuoles in myofibres. **Other studies:** *in vitro* assembly studies showed normal IF; SW13 and C2C12 cells form normal IF network.	[39]
c.1346A>C **K449Tx**	14 Skel	**Skel:** MW. **Pathology:** abnormal myofibre size. **Other studies:** *in vitro* assembly studies show normal filament formation; SW13 and C2C12 cells form normal IF network.	[36,39]
c.1360C>T **R454W** (+ Myotilin mutation)	15 Card	**Skel:** slowly progressive MW. **Card:** HCM that required Card transplantation. **Pathology:** Desmin-positive aggregates within myofibres. **Other studies:** *in vitro* assembly studies showed formation of short and irregular filamentous structures and aggregates; SW13 cells show aggregate formation and C2C12 form normal IF.	[39,40]
c.1379G>T **S460I**	29 Card	**Skel:** progressive MW and wasting. **Card:** AVB that required pacemaker implantation. **Pathology:** abnormal myofibre size; occasional split and regenerating fibres; vacuoles and Desmin-positive aggregates. **Other studies:** *in vitro* assembly studies showed normal filament formation; SW13 cells show aggregate formation but C2C12 form normal IF.	[39]
c.1413A>C **X471Y**	35 Card	**Card:** AVB that required pacemaker implantation.	[38]

'Other studies' describes results from animal models and *in vitro* systems. Skel: Skeletal muscle; Card: cardiac muscle; MW: muscle weakness; MA: muscle atrophy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; AVB: atrioventricular block; SW13 cells: human carcinoma cells; MEF cells: mouse embryonic fibroblasts; C2C12 cells: mouse myoblast/satellite cells.

Table 1. Description of clinical and pathological features of MFM caused by Desmin mutations.

Mutation		Classification	Ref
c.38C>T	**S13F**	DRM	[37,41-43]
c.46C>T*	**R16C**	RCM	[37,44]
c.322G>A	**E108K**	DCM	[45]
c.338A_339Gdel	**Q113fsX115**	DRM	[46]
c.517_537del*	**del(R173_179)**	DRM	[47,48]
c.638C>T (+α-glucosidase mutation)	**A213V**	DRM	[49,50]
c.639-1G>A + c.735+2A>G	**del(D214_E245)**	DRM	[44,51-53]
c.719dupA	**K240fsX243**	distal myopathy	[54]
c.735G>C/T	**E245D**	distal myopathy	[49,53,55]
c.893C>T	**S298L**	DCM	[45]
c.934G>A	**D312N**	DCM	[45]
c.1009G>C	**A337P**	DCM	[49,50,52,56,57]
c.1013T>G	**L338R**	DRM	[50]
c.1024A>G	**N342D**	DRM	[43,49,52]
c.1034T>C	**L345P**	DRM	[8,49,58,59]
c.1049G>C	**R350P**	distal myopathy and CM	[60]
c.1048C>T	**R350W**	DCM	[45]
c.1064C>G	**E355P**	DRM	[61]
c.1069G>C	**A357P**	DRM	[49,62]
c.1075_1083del	**del(E359_S361)**	DRM	[63]
c.1078G>C*	**A360P**	DRM	[49,52,56]
c.1097_1099del	**del(N366)**	DRM	[63,64]
c.1099A>T	**I367F**	DRM	[65]
c.1109T>C	**L370P**	DRM	[49,62,66]
c.1130T>C	**L377P**	DRM	[67]
c.1154T>C	**L385P**	DRM	[49,68]
c.1166A>C	**Q389P**	DRM	[49,69]
c.1175T>C	**L392P**	DRM	[65]
c.1178A>T*	**N393I**[#]	DRM	[49,50,52,56]
c.1195G>T	**D399Y**	DRM	[49,50]
c.1201G>A	**E401K**	DRM	[50]
c.1216C>T	**R406W**	DRM	[44,49,52,65,69,70]
c.1237G>A	**E413K**	DRM	[39,49,71]
c.1255C>T	**P419S**	DRM	[65]
c.1353C>G	**I451M**	DRM	[52,72-74]
c.1358C>T	**T453I**	DRM	[44]
c.1375G>A	**V459I**	DCM	[45]
c.1405G>A	**V469M**	DCM	[37,41-43]

All disorders are dominantly inherited unless otherwise indicated.*: autosomal recessive inheritance; DRM: Desmin-related myopathy; DCM: dilated cardiomyopathy; CM: cardiomyopathy; RCM restrictive cardiomyopathy.

Table 2. Human myopathies caused by Desmin mutations excluding MFM.

Mutations in Desmin result in many different myopathies (Table 1 and Table 2). Desmin-related myopathies (DRM) is a term that has been used to describe myopathies due to mutations in Desmin and CRYAB including MFMs, here we only use it to refer to those caused by Desmin mutations. In addition to the broad spectrum of DRM, Desmin mutations have also been classified as MFM, distal myopathy, DCM, and RCM (see Table 1 and Table 2). Some of the DRMs may be examples of MFM but without further information it is not

possible to re-classify them as MFMs. There is significant cardiac involvement in many Desmin myopathies and in some cases individuals with the same mutation may initially present with cardiac or skeletal muscle symptoms suggesting there is significant phenotypic variability and the possibility of modifiers of the Desmin myopathies. For example, the I451M mutation has been reported in a case of familial DCM without skeletal muscle phenotypes [72] and in individuals with skeletal myopathy without any evident cardiac defect [74]. Furthermore, the mutation was not fully penetrant in the family with DCM [72]. Potential modifiers include α-Glucosidase, with a single individual identified as a compound heterozygote for α-Glucosidase missense mutations and heterozygous for the Desmin A213V mutation displaying progressive muscle weakness not evident in related individuals carrying A213V alone [50], and Lamin A, as identified in an individual with Emery Dreifuss muscular dystrophy due to heterozygous Lamin A and Desmin V469M mutations [75].

Mutations in Desmin may also affect its capability to interact with its binding partners. Indeed, analysis of mutant protein E245D using solid phase binding assays showed that it binds to Nebulin with increased affinity, reducing Nebulin at the Z-disk, and is more prone to aggregate formation [76]. This interferes with Nebulin's ability to regulate the thin filament and results in disease [76]. Furthermore, the targeted mutation K190A, not yet observed in disease, shows decreased affinity for Nebulin resulting in decreased targeting of Nebulin to the Z-disk, its accumulation in aggregates in both skeletal and cardiac muscle, and narrower Actin bundles. It was therefore hypothesised that the lack of functional Desmin prevents Nebulin from stabilising Actin thin filaments thereby resulting in collapse of the contractile apparatus [21].

To study the role of Desmin in muscle function two independent knockout mice lines were created [77,78]. Both lines develop normally, are viable and fertile, with no defects in myogenesis. However, they present postnatal multisystem disorder, decreased myofibril alignment, defects in nuclear and mitochondrial positioning within the cell, and severe cardiac degeneration [77-81]. Muscle of *Desmin* knockout mice was also found to be more susceptible to damage following contraction [82]. These studies show that the absence of Desmin does not impair muscle formation or animal viability however, it is important for muscle function and integrity. In addition to the abnormal localisation of mitochondria described in the knockout mouse [81], Desmin mutations, such as K240fsX243, R350P, and E413K, can result in abnormal localisation and function of the mitochondria resulting in a deficiency in oxygen metabolism which impairs muscle function and may contribute to muscle degeneration [49,54,71].

It has been extensively suggested that Desmin may be essential in lateral force transmission by connecting adjacent sarcomeres, and even neighbouring myofibres, by costamere-extracellular matrix (ECM) binding. Therefore, Desmin mutations may impair its ability to respond to applied strain. Studies on Desmin with tail domain mutations in which the filament assembly is normal in both *in vitro* cell cultures and in transfected cells showed altered flexibility, with significantly increased stiffness compared to wildtype IF. This altered intrinsic properties of IF is hypothesised to prevent Desmin from responding to

excess strain thereby resulting in muscle pathology [40]. This is also supported by the del(Arg173-Glu179) knock-in mouse. Detailed analysis of the myocardium of these mice revealed the presence of aggregates containing Desmin and other muscle proteins, characteristic of desminopathies, which disturbed overall IF structure and compromised myocardium function both during baseline conditions and during maximal adrenergic stimulation [83].

The analysis of filament formation *in vitro* has identified a clear mechanism by which Desmin mutations may disrupt its assembly into filaments. However, it is still not clear which of the many roles of the IF contribute to pathology in desminopathies. The association of Z-disk proteins with MFM may suggest that it is the role of the IF at the Z-disk that is most relevant to these conditions but mitochondrial organisation and tethering of the myofibrils to the sarcolemma have clear links to muscle function and maintenance. The emerging application of whole genome and exome sequencing to mutation detection may improve identification of modifiers of pathology providing an alternative route to examine Desmin function, explain the phenotypic variations observed, and develop areas of potential therapy.

3. αB-crystallin and αB-crystallinopathies

To date 15 mutations in CRYAB have been reported. CRYAB belongs to the small Heat shock family of proteins (sHSP). It interacts with αA-Crystallin (CRYAA) via non-covalent bonds to form large heterogeneous macromolecular complexes [19]. Both CRYAA and CRYAB are found in high levels in the lens tissue of the eye where they are involved in maintaining lens transparency and refractive index [84]. CRYAB is also found in significant amounts in non-lenticular tissues such as skeletal and cardiac muscle, the kidney, and the brain [85-87]. In skeletal muscle CRYAB expression is highest in the oxidative slow twitch muscle and lowest in the glycolytic fast muscle [85,88]. In skeletal and cardiac muscle CRYAB is localised to the Z-disk [89] where it interacts with the I-band protein Actin [19] and various IF proteins including Desmin [19], Vimentin [90], and Glial fibrillary acidic protein (GFAP) [91].

The N-terminal globular domain and the highly conserved C-terminal 'α-crystallin domain' (ACD; Figure 2) of CRYAB are critical for its chaperone-like function [92-94] and dimerisation [95]. CRYAB prevents stress induced aggregation of various proteins including β- and γ-Crystallins [93,93], Desmin [19], Vimentin [90], and GFAP [91]. Following stressful conditions such as osmotic stress, metal toxicity [96], serum starvation, hypertonic stress, and heat shock [90] CRYAB expression is up-regulated and recruited to the IF to remodel the IF network [90]. Mutations in CRYAB have been shown to interfere with both its dimerisation and chaperone functions. Resolution of the crystal structure of the MFM causing R120G mutant protein showed a disruption to its tertiary structure predicted to interfere with its dimerisation and result in the formation of large soluble oligomers [97]. Moreover, the ACD domain of mutant CRYAB adopts an irregular structure, which decreases its chaperone function, makes it unstable and promotes its aggregation [98-100].

The mutant CRYAB has also been shown to have a higher dissociation constant, which prevents its dissociation from Desmin [101] resulting in Desmin containing aggregates as seen in MFM [100,101]. Therefore, alterations in the structure of CRYAB, its inability to perform its chaperone functions, and disruption of its interaction with its binding partners all contribute to disease pathology. In contrast to other MFM genes there does appear to be some correlation between genotype and phenotype with mutations in exon one resulting in isolated cataracts whilst exon three mutations can result in cataracts [102-107], MFM [108-110], distal myopathy [111], and/or CM [112,113], with two mutations resulting in both cataract formation and muscle failure [114,115] (Table 3).

Following contraction CRYAB is phosphorylated and translocates from the cytoplasm to the Z-disk which is thought to allow CRYAB mediated repair or protection of the Z-disk [125]. Recently, a rare case of infantile onset MFM was identified due to a homozygous frameshift mutation, S115fsX14, resulting in muscle stiffness [110]. The authors suggest the mutation results in a loss of contraction timulated translocation to the Z-disk and consequent reduction in muscle repair. CRYAB has also been implicated in indirectly preventing apoptosis and autophagy, inhibiting Caspase 3 mediated [126], Ras induced[127], and Bcl-2 mediated apoptosis [128]. It is therefore not surprising that CRYAB deficiency results in decreased cell viability and an increase in apoptosis in CRYAB knock-out mouse [129] and in patients suffering with CRYAB mutations [108]. In basal breast cancer CRYAB behaves as an oncoprotein [130] and in highly migratory glioma cells prevents apoptosis [131] making it a potential target in cancer therapy. Up-regulation of CRYAB may be part of a general protective mechanism since CRYAB is up-regulated in various pathological conditions such as cardiac ischemia [132], multiple sclerosis [133], Alzheimer's [134], and other neurodegenerative disorders [84].

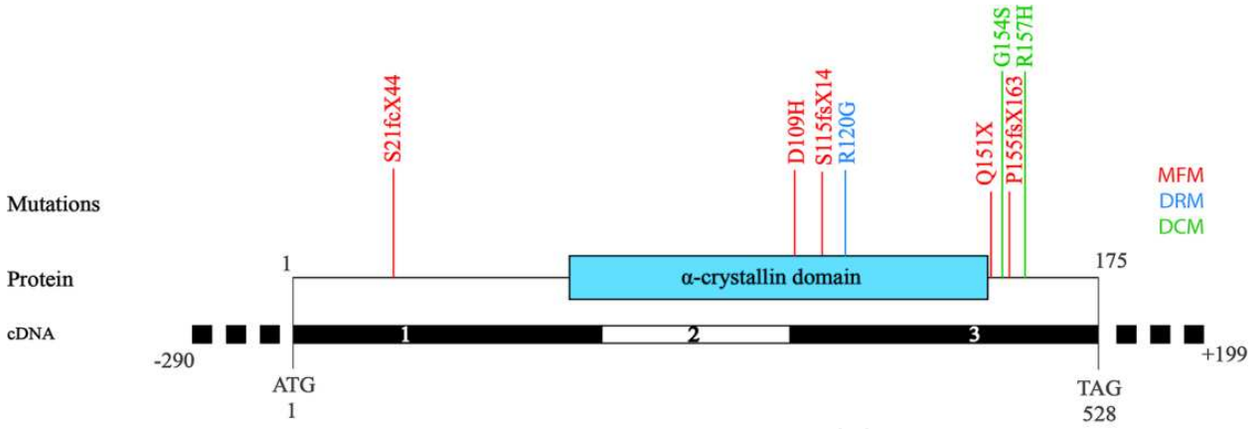
Wildtype CRYAB has the capability to bind to mutant protein to prevent its aggregation. For example, transfection of the MFM causing R120G mutant CRYAB into PtK2 cells results in the formation of aggregates but co-transfection with wildtype CRYAB, or the chaperone molecule Hsp27, results in a significant decrease in the amount of insoluble R120G CRYAB present in the cell and the frequency of aggregate formation [135]. Recently the BAG3 co-chaperone protein has also been shown to co-oligomerise with mutant CRYAB to suppress its aggregation and toxicity [136]. This does highlight that stimulating an increase in wildtype CRYAB, Hsp27, or BAG3 may be sufficient to prevent the formation of protein aggregates.

The observation that there is a 10 fold increase in CRYAB expression in differentiating and proliferating myoblasts [137,138] suggests that CRYAB may play a role in regulating myogenesis. CRYAB has been shown to decrease the synthesis, and increase the degradation, of MyoD, a myogenic regulatory factor that specifies cell lineage, resulting in delayed differentiation. Additionally, up-regulation of CRYAB in muscle cells results in sustained expression of cell cycle markers such as Cyclin D1 indicating cells were more proliferative [139]. Therefore, CRYAB can influence myogenesis by altering MyoD levels and cell cycle exit. Despite the potential for CRYAB to regulate muscle differentiation CRYAB knockout mice have normal muscle at birth but present with severe muscular dystrophy by week 40 suggesting CRYAB is not critical for muscle development but is essential for muscle function [129].

Mutation	Age of onset / Initial symptoms	Clinical and pathological features; other studies	Ref.
c.61delA* **S21fcX44**	Birth-11 weeks Resp	**Skel:** hypertonia. **Pathology:** presence of necrotic and regenerating fibres; atrophic and splitting myofibres and internally located nuclei; Desmin-, Myotilin-, and some Ubiquitin-positive aggregates at the periphery of myofibres, vacuoles and deposits. **Classified as MFM**	[9,109]
c.325G>C **D109H**	35-45 Skel	**Skel:** MW. **Card:** DCM; Cataract formation. **Pathology:** abnormal myofibre size; atrophic and splitting myofibres and internally located nuclei; Desmin-, CRYAB-, and Myotilin-positive aggregates and vacuoles. **Classified as MFM**	[114]
c.343delT* **S115fsX14**	4 months Skel	**Skel:** muscle stiffness. **Pathology:** muscle fibrosis. **Classified as MFM**	[110]
c.358A>G **R120G**	? Skel	**Skel:** MW; **Card:** HCM; Cataract formation. **Pathology:** presence of Desmin and CRYAB aggregates. **Other studies:** altered CRYAB quaternary structure; Partial unfolding exposes hydrophobic regions thus increases susceptibility to proteolysis and aggregation; disrupted protein binding; HeLa cells show hyperphosphorylation mutant CRYAB and accumulation in the cytoplasm; *in vitro* studies show Desmin and CRYAB aggregates in the cytoplasm and around the nuclei; rat cardiomyocytes with perinuclear aggregates containing Ubiquitin, β-Tubulin and Hsp25; cardiomyocytes in culture expressing mutant CRYAB show that the contractile apparatus does not work properly; mutant mice myofibrils alignment are impaired, CRYAB and in some cases Desmin- positive aggregates; cardiac hypertrophy; mitochondrial architecture and alignment are altered in cardiomyocytes; mice die by early adulthood. **Classified as DRM**	[98,99, 115-122]
c.451C>T **Q151X**	43 Skel	**Skel:** slowly progressive MW and MA. **Pathology:** severe abnormal myofibre size; necrotic and regenerating myofibres and internally located nuclei; abnormal Z-disks were detected; Desmin-, CRYAB- and Dystrophin-positive aggregates. **Other studies:** *in vitro* assays show that this mutation prevents oligomerisation, without changing its function, but aggregation is enhanced; *in vitro* assembly assays and COS-7 cells and cardiomyocytes cultures showed an increased tendency to hyperphosphorylation and aggregate formation. **Classified as MFM**	[108,123,124]
c.460G>A **G154S**	48-68 Skel or Card	**Skel:** slowly progressive MW and MA **Card:** DCM; moderate VEFR. **Pathology:** Desmin- and CRYAB-positive aggregates in subsarcolema and in the centre of the myofibres; Z-disk disorganization and smearing, with accumulation of vacuoles and other material. **Classified as DCM**	[111,112]
c.464CTdel **L155fsX163**	52 Resp	**Skel:** MW. **Pathology:** abnormal myofibre size; fibre degeneration; presence of vacuolations and inclusions; disruption of the intermyofibrillar architecture; Desmin-, Myotilin- and CRYAB-positive aggregates. **Classified as MFM**	[108]
c.470G>A **R157H**	40's Card	**Card:** ventricular tachycardia. **Other studies:** rat cardiomyocytes show decreased CRYAB binding to Titin in the cardiac specific domain, without affecting its distribution in the cell. **Classified as DCM**	[113]

'Other studies' describes results from animal models and *in vitro* systems. Mutations involved in isolated cataract formation: R11H; P20S; R56W; D140N; K150fsX184 and A171T are not shown. All disorders are dominantly inherited unless otherwise indicated. *: autosomal recessive inheritance; Skel: skeletal muscle; Card: cardiac muscle; Resp: respiratory system muscles; MW: muscle weakness; MA: muscle atrophy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; VEFR: ventricular ejection fraction reduction; MFM: myofibrillar myopathy; HeLa cells: human cervical cancer immortalised cells; COS-7 cells: African green monkey fibroblast.

Table 3. Description of clinical and pathological features of αB-crystallinopathies.



Mutations are coloured according to the disease classification. Dashed segments in cDNA represent the UTRs that are not drawn to scale.

Figure 2. Schematic representation of CRYAB protein structure and myopathy mutations.

4. Myotilin and myotilinopathies

The first description of myotilinopathy was a missense mutation in a family with LGMD1A [10]. Since this initial discovery, nine additional mutations in Myotilin (myofibrillar protein with Titin-like immunoglobulin domains) have been implicated in LGMD1A [10,140-142], MFM [143], SBM [144] or late onset distal myopathy [145] with all mutations described to date displaying an autosomal dominant pattern of inheritance. One of the mutations identified, S55F, has been found as a cause of both LGMD [141] and MFM [143] suggesting there may be modifiers of the disease that determine the symptoms produced or that there is an overlap in the classification of these conditions that needs to be resolved. Distinctions between these conditions are not clear, since the presence of protein aggregates is associated with MFM and SBM with weakness of distal muscle groups thought to be associated with MFM [143] and proximal muscle groups with LGMD (Table 4).

Myotilin belongs to the immunoglobulin domain containing Actin binding protein family that also contains the Actin organizing proteins Palladin and Myopalladin [146,147]. Myotilin is predominantly expressed in skeletal and cardiac muscle, with the highest levels present in the skeletal muscle. Expression is also detectable at low levels in the peripheral nerves, bone marrow, liver, thyroid gland and lung [153,154]. In skeletal muscle Myotilin is present in both slow type I and fast type II fibers [151] and is localised to the Z-disk [153], although some reports have suggested Myotilin may also be found at the sarcolemma [10,153,155]. A role at the sarcolemma is also supported by the inclusion of Dystrophin in the protein aggregates found in MFM and LGMD1A [10,143]. Like many other Z-disk proteins Myotilin is very dynamic as demonstrated by fluorescent recovery after photobleaching (FRAP) experiments in quail skeletal muscle that showed that 80% of Myotilin in the Z-disk is replaced within five minutes of bleaching [156].

Myotilin contains two identified domains, both essential for its function; a serine rich N-terminal domain, that shares no homology with any known protein, and a C-terminal domain consisting of two Ig-like domains that share high homology to two Z-disk associated Ig-like

domains of the giant protein Titin [153] (Figure 3). Seven of the eight identified Myotilin mutations, including the three MFM mutations [143], are in the serine rich domain with one mutation in the second Ig domain [142]. The serine rich domain consists of a stretch of hydrophobic residues that are believed to direct the localisation of Myotilin to the sarcolemma [10]. The serine rich domain is also responsible for the interaction of Myotilin with a range of proteins including the primary Z-disk crosslinker α-Actinin [153], Filamin- Actin- and Telethonin-binding protein of the Z-disk (FATZ, Myozenin, Calsarcin) [157], ZASP/Cypher [158], Filamin C [157,159] and the ubiquitin ligases MURF-1 and MURF-2 [160]. Interaction of Myotilin with FATZ directly or indirectly directs the localisation of FATZ to the Z-disk [157]. Myotilin also links Filamin C, found at the periphery of the Z-disk, to α-Actinin and anchors the Actin containing thin filaments to the Z-disk thereby providing stability to the sarcomere

Mutation	Age of onset / Initial symptoms	Clinical and pathological features; other studies	Ref
c.17G>A **R6H**	40 Skel	**Skel:** progressive MW, culminated in wheelchair dependence. **Pathology:** abnormal myofibre size and fibrosis; necrotic fibres with macrophage invasion; internally located nuclei; mitochondria aggregation. **Classified as LGMD1A**	[140]
c.116C>T **S39F**	Childhood-60s Skel	**Skel:** progressive MW, in some cases wheelchair dependence. **Pathology:** spheroid bodies with Myotilin immunoreactivity at the periphery. **Classified as spheroid body myopathy**	[144]
c.164C>T **S55F**	48-53 Skel	**Skel:** slowly progressive to severe MW and wasting. **Pathology:** abnormal myofibre size with deposits and vacuoles; atrophic and necrotic myofibres; Myotilin-, CRYAB-, Dystrophin-, Desmin-. and Ubiquitin-positive aggregates; clusters of mitochondria. **Classified as LGMD1A and MFM**	[141,143,148-150]
c.170C>T **T57I**	27 Skel	**Skel:** progressive MW**. Pathology:** abnormal myofibre size; myofibre degeneration and splitting; centrally located nuclei; vacuoles; Z-disc streaming. **Other studies:** mice reproduce human MFM pathology: Myotilin-, Desmin-, Ubiquitin-, and Actin-positive aggregates; fibrosis; Z-disk streaming and sarcomere disorganisation; some centrally located nuclei. **Classified as LGMD1A**	[10,151]
c.179C>G **S60C**	50-77 Skel	**Skel:** severe MW and wasting. **Card:** some asymptomic cases; DCM; VEFR; sometimes fatal**. Pathology:** abnormal and atrophic myofibres with deposits and vacuoles; Myotilin-, CRYAB-, Dystrophin-, Desmin- and Ubiquitin-positive aggregates. **Classified as MFM**	[143,148,152]
c.179C>T **S60F**	40-76 Skel	**Skel:** difficulty in walking and climbing stairs; MW**. Classified as distal myopathy**	[145]
c.284G>T **S95I** ?	?	**Pathology:** abnormal and atrophic myofibres with deposits and vacuoles; Myotilin-, CRYAB-, Dystrophin-, Desmin- and Ubiquitin- positive aggregates **Classified as MFM**	[143]
c.1214G>A **R405K**	41 Skel	**Skel:** impossibility to walk long distances; MW**. Pathology:** abnormal myofibre size; scattered fibres with internally located nuclei; vacuoles and Myotilin-, ZASP-, Desmin- and Actin-positive aggregates. **Classified as LGMD1A**	[142]
c.1214G>A **R405K**	41 Skel	**Skel:** impossibility to walk long distances; MW**. Pathology:** abnormal myofibre size; scattered fibres with internally located nuclei; vacuoles and Myotilin-, ZASP-, Desmin- and Actin-positive aggregates. **Classified as LGMD1A**	[140]

K36E and Q74K mutations are not shown since no information is available (shown in [142]). 'Other studies' describes results from animal models and *in vitro* systems. Skel: Skeletal muscle; Card: cardiac muscle; MW: muscle weakness; DCM: dilated cardiomyopathy; VEFR: ventricular ejection fraction reduction; MFM: myofibrillar myopathy.

Table 4. Description of clinical and pathological features of myotilinopathies.

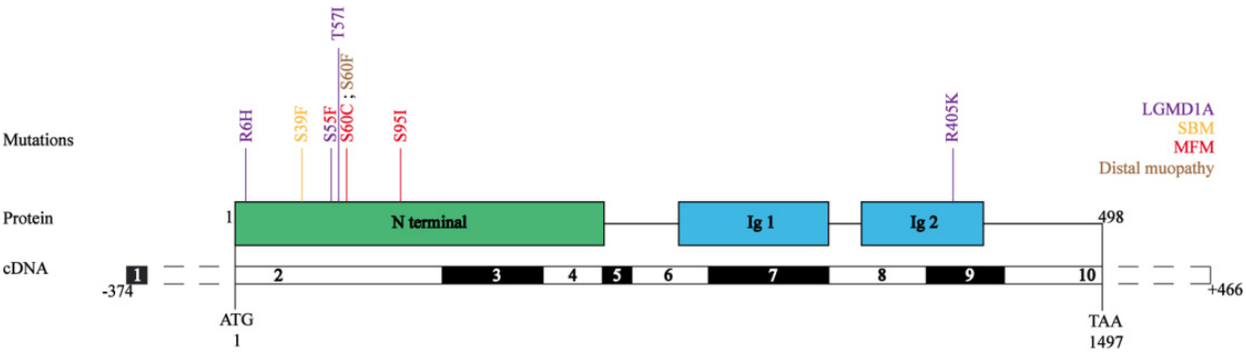
[159,161]. The Ig domain containing C-terminus on the other hand is responsible for antiparallel dimerization of Myotilin, which is essential for its function [153,161]. The Myotilin C-terminus also interacts directly with Actin, despite the lack of a conventional Actin binding site [162], and is thought to prevent the depolymerisation of Actin filaments and enhance the binding of α-Actinin to Actin. Overexpression of Myotilin in CHO cells results in formation of Actin bundles and the delayed expression of Myotilin relative to other Z-disk proteins is thought to be required to avoid premature bundling of Actin fibres [161,162].

Despite the loss of muscle integrity in myotilinopathies Myotilin knockout mice display no muscle defects. Their Z-disk structure and sarcolemma integrity is maintained with no effect on muscle strength and the heart appears normal [163,164]. This suggests that other closely related proteins, such as Palladin and Myopalladin, may have overlapping functions to that of Myotilin and are able to compensate for its loss. Interestingly, mice deficient in Myotilin have a two fold increase in the expression of the muscle stretch sensor Telethonin, which may be responsible for sensing the lack of Myotilin and triggering appropriate signals to prevent muscle failure [163]. However, this hypothesis needs to be validated.

Analysis of Myotilin levels in patients compared to control individuals failed to identify a reduction in protein level [10,142] with other studies reporting an increase in Myotilin in some patients [142,165]. This observation leads to the hypothesis that mutations in Myotilin affect its dimerisation or interaction with binding partners, resulting in pathology. This is certainly true in the case of the identified missense mutation affecting the second Ig domain of Myotilin (R405K) resulting in LGMD [142]. The R405K mutation prevents dimerisation disrupting α-Actinin binding and Actin tethering to the Z-disk. As a result, filament stability is lost, the Z-disk is destabilised, and protein aggregates are formed [142]. However, this is not true for the majority of Myotilin mutations, which are found in the serine rich N-terminal domain. *In vitro* experiments have shown that the S55F, T57I, S60C, and S95I, mutations have no effect on Actin bundling [162], and T57I also has no effect on the interaction with α-Actinin [10]. It has since been hypothesised that mutated Myotilin promotes intermolecular aggregation with other similar Ig domain containing sarcomeric proteins such as Palladin and Titin. The mutant Myotilin expressing transgenic mouse (T57I) that contains aggregates rich in Ig domain containing proteins [151] supports this hypothesis. Interestingly, although in humans the T57I mutation results in LGMD1A in which aggregates are absent, expression in mice results in formation of aggregates that are typical of MFM and SBM. This led to the authors suggesting that the variation in symptoms between MFM, SBM, and LGMD1A, such as protein aggregates, are due to modifying loci [151].

The formation of protein aggregates is a defining feature of MFM and SBM. Aggregate containing muscle from myotilinopathy patients contains increased levels of oxidative stress markers including glycation end products, nitric oxide synthase, superoxide dismutase, and mutant Ubiquitin [166,167]. Protein oxidation promotes protein aggregation and reduces proteolytic degradation. Another factor that may promote protein aggregation in myotilinopathies and other MFMs is the inability of cells to degrade misfolded proteins via

the non-lysosomal ubiquitin proteasome system (UPS) responsible for the degradation of 80-90% of myofibrillar proteins [168]. UPS mediated degradation of mutant Myotilin is significantly slower than wildtype Myotilin and inhibition of Myotilin turnover results in aggregates similar to those seen in MFM [169].



Mutations are coloured according to the disease classification. Dashed segments in cDNA represent the UTRs that are not drawn to scale.

Figure 3. Schematic representation of Myotilin domains and myopathy mutations.

5. ZASP and zaspopathies

Z band alternatively spliced PDZ-containing protein (ZASP) [170], also known as LIM Domain Binding 3 (LDB3), Cypher [171], or Oracle [172] belongs to the PDZ-LIM family of proteins and similar to other members of the family, Enigma [173] and α-Actinin associated LIM protein (ALP) [174], localises to the Z-disk. More than 15 mutations in ZASP have been reported resulting in a range of myopathies including DCM [11,175], HCM [176], MFM [177], inclusion body myositis [178], and LVNCC [11,175,177] (Table 5). ZASP contains a PDZ domain, located at the N-terminus, and an internal ZASP/cypher-like motif (ZM) both capable of interacting with α-Actinin-2 [179-181]. Additionally, the PDZ domain interacts with Myotilin [158] and FATZ [182], which provides structural stability to the Z-disk. The C-terminus contains three LIM domains, which act to recruit signalling proteins to the Z-disk.

As its name suggests the ZASP mRNA is extensively spliced to result in multiple ZASP isoforms, a feature conserved in all species examined with four isoforms in worms [183], 12 isoforms in flies [184-186], 13 in zebrafish [187], and six in mice and humans [11,188] (Figure 4). In mice and humans the isoforms have been characterised according to their length and their expression in the heart or skeletal muscle. So far two short isoforms, (2c, 2s) that lack the LIM domains, and four long isoforms (1c, 1s, 3c and 3s), that contain all three LIM domains, have been characterised [11,170]. Isoforms containing exon four (1s, 2s and 3s) are restricted to cardiac muscle whereas isoforms lacking exon four are found in both cardiac and skeletal muscle [11]. Loss and gain of function experiments have highlighted specific roles for the short and long isoforms. Selective deletion of the short isoforms does not lead to any muscle defects however, loss of the long isoforms results in neonatal lethality in 28% of mice [189]. Surviving knockout mice display growth retardation and Z-disk abnormalities in cardiomyocytes leading to DCM in adulthood, demonstrating the requirement for the

Mutation	Age of onset / Initial symptoms	Clinical and pathological features; other studies	Ref
c.163G>A* **V55I**	? Card	**Card:** LVNCC. **Classified as LVNCC**	[175,191]
c.349G>A **D117N**	30-41 Card	**Card:** DCM; AVB; EFR; premature death in some cases. **Other studies:** C2C12 show ZASP aggregates formation and abnormal Actin staining. **Classified as LVNCC**	[11]
c.407C>T **K136M**	16 Card	**Card:** DCM; VEFR. **Classified as LVNCC**	[11]
c.464G>A (mRNA) **A147T**	44-59 Skel	**Skel:** progressive MW and MA. **Card:** some cases of VEFR. **Pathology:** atrophic, necrotic, and regenerating myofibres; fibre splitting and internally located nuclei; small vacuoles and Desmin-, Myotilin-, CRYAB-, and Dystrophin-positive aggregates; streaming and disintegration of the Z-disk; organelles in clusters. **Classified as MFM**	[177]
c.519C>T (mRNA) **A165V**	39-59 Skel	**Skel:** progressive MW and MA. **Pathology:** atrophic, necrotic, and regenerating myofibres; fibre splitting and internally located nuclei; small vacuoles and Desmin-, Myotilin-, CRYAB- and Dystrophin-positive aggregates; streaming and disintegration of the Z-disk; organelles in clusters. **Classified as LVNCC**	[177,192]
c.587C>T **S196L**	7-73 (not accurate) Card	**Card:** DCM or HCM; VEFR. **Other studies:** mice show left ventricular dilation; HCM, VEFR; mild focal fibrosis; sarcomere and Z-disk disorganisation. **Classified as DCM**	[11,176,193]
c.638C>T **T213I**	15 months Card	**Card:** AVB; VEFR. **Other studies:** Reduced binding to PGM1 **Classified as DCM and LVNCC**	[11]
c.827C>T (mRNA) **R268C**	73 Skel	**Skel:** progressive MW. **Pathology:** atrophic, necrotic, and regenerating myofibres; fibre splitting and internally located nuclei; small vacuoles and Desmin-, Myotilin-, CRYAB-, and Dystrophin-positive aggregates; streaming and disintegration of the Z-disk; organelles in clusters. **Classified as MFM**	[177]
c.1056C>G **I352M**	<15-35 Card	**Card:** DCM; VEFR. **Other studies:** Reduced binding to PGM1. **Classified as DCM**	[11]
? **D366N**	68 Card	**Card:** HCM. **Classified as HCM**	[176]
? **Y468S** (+CRSP3 mutation)	46 Card	**Card:** HCM. **Classified as MFM**	[176,191]
? **Q519P**	21 Card	**Card:** HCM. **Classified as HCM**	[176,191]
c.1719G>A **V566M**	40 Skel	**Skel:** slowly progressive MW; MA. **Pathology:** abnormal myofibre size; vacuoles and Desmin-, Myotilin-, CRYAB- and Ubiquitin-positive aggregates	[178]
? **P615L**	28 Card	**Card:** HCM. **Classified as HCM**	[176]
c.1876G>A **D626N**	after birth-69 Card	**Card:** DCM; LVNC. **Other studies:** mice show that mutant ZASP has higher affinity to PKC, which may cause the heart failure. **Classified as LVNCC and DCM**	[175,191]

All conditions are dominantly inherited unless otherwise indicated. 'Other studies' describes results from animal models and *in vitro* systems. *: autosomal recessive inheritance; Skel: Skeletal muscle; Card: cardiac muscle; LVNCC: left ventricular non compaction cardiomyopathy; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; AVB: atrioventricular block; VEFR: ventricular ejection fraction reduction; MW: muscle weakness; MA: muscle atrophy; MFM: myofibrillar myopathy; C2C12 cells: mouse myoblast/satellite cells

Table 5. Description of clinical and pathological features of zaspopathies.

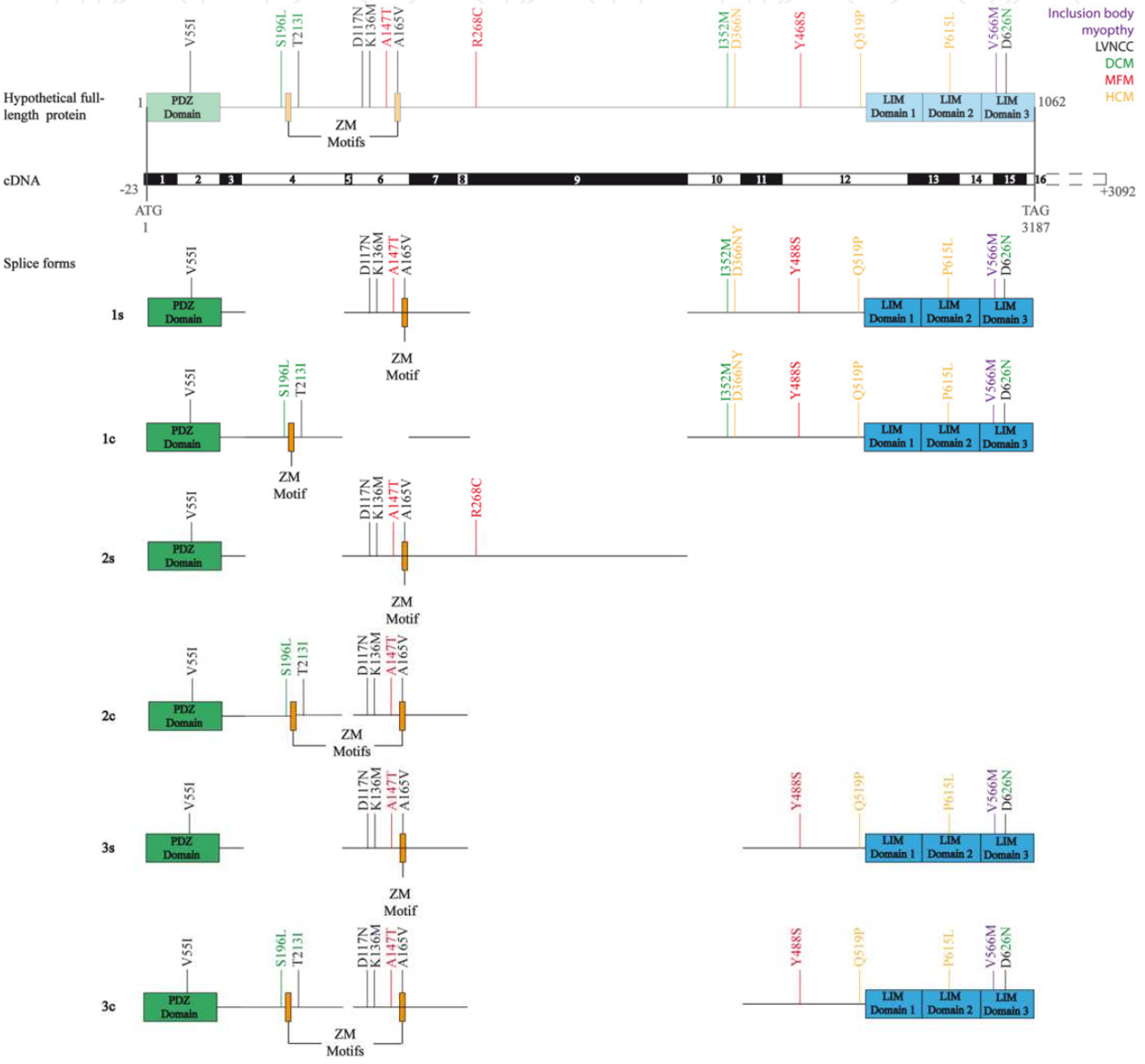
long, but not the short, isoforms in maintaining Z-disk integrity [189]. Loss of both short and long isoforms however, results in death within the first five days [190] suggesting that there is some

redundancy in their roles. This hypothesis is supported by rescue experiments showing that expression of either the short or long skeletal isoform in ZASP deficient mice is sufficient for survival in 19% and 49% of carriers respectively [188]. The different phenotypes observed following loss of long or short isoforms raises the question whether mutations in specific isoforms result in specific myopathies. This is clearly true in the case of mutations in the cardiac specific exon four however, why mutations in exons expressed in both skeletal and cardiac muscle results in only one tissue getting affected is not clear. For example the D117N [11], A147W, and A165V [177] mutations in exon six affect both skeletal and cardiac muscle isoforms. However, D117N preferentially affects the cardiomyocytes whereas A165V preferentially affects the skeletal muscle, and A147W results in both tissues being affected. Therefore, there appears to be no clear correlation between the exon affected and the phenotype presented by the patient.

Examination of the diaphragm muscles, which are not active before birth, in ZASP knockout mice identified little or no difference in the sarcomere structure at E17.5 when compared with wildtype mice, but severe disruption of the Z-disk the day after birth [190], suggesting that ZASP is not required for sarcomere assembly but is critical for maintenance of Z-disk integrity. Examination of cardiac muscle in these mice, which becomes active at E8, at E17.5 identified severely disrupted Z- disks which were completely lost by one day after birth [190]. A role for ZASP in Z-disk maintenance is supported by experiments demonstrating that deletion of ZASP in postnatal hearts results in gradual disruption of the Z-disk and severe DCM resulting in premature death within five months [194]. Targeted deletion of ZASP homologues in *Drosophila* results in defects in muscle development suggesting a role for ZASP is in *Drosophila* sarcomerogenesis [184,185]. However, *Drosophila* has only a single protein equivalent to the mammalian ZASP, ALP, and Enigma proteins. It is therefore possible that in mammals, ZASP, ALP, and Enigma have redundant roles and loss of all three proteins in mammals would result in a phenotype similar to that seen in *Drosophila*. In *Drosophila* ZASP was identified as a regulator of cell matrix adhesion localising to integrin adhesion sites in S2 and S2R+ cell lines co-localising with α-Actinin at the Z-disks and integrins at the myotendinous junctions in embryos [184]. ZASP deficient flies display a muscle detachment phenotype and lack α-Actinin at the Z-disk, suggesting that the interaction of ZASP with Integrin is critical in connecting the muscle fibre to the ECM and in directing α–Actinin to the Z-disk [184]. However, localisation of ZASP to myotendinous junctions or costameres has not been reported in any other animal model.

In cardiomyocytes ZASP interacts with Protein Kinase C (PKC) [175], a known modulator of cardiomyocyte growth and contractility. PKC-ε has been shown to interact with RACK-2 and protect cardiomyocytes from ischemic stress [195,196]. Disruption of the PKC-ε - RACK-2 complex results in inhibition of cell contraction [197] and accelerated cell death [198]. *In vivo* studies have revealed increased levels of PKC in hypertrophy, DCM, and heart failure [199-201], suggesting a role for PKC in stress response, potentially modulated by ZASP. Biochemical analysis of ZASP revealed that the D626N LIM domain mutation increases the binding affinity of ZASP for PKC. The authors suggest that this may reduce the amount of PKC-ε available to bind downstream proteins such as RACK-2 therefore resulting in DCM due to altered distribution of PKC [175]. ZASP also interacts with the metabolic protein Phosphoglucomutase 1 (PGM1), an enzyme involved in glycolysis and gluconeogenesis,

through the proline rich regions encoded by exons four, six and, ten and recruits it to the Z-disk [202]. DCM causing mutations in exon four (S196L and T213I) and exon ten (I352M) have been shown to have reduced binding affinity for PGM1 [202]. The binding of ZASP to PGM1 and ZASP mediated targeting of PGM1 to the Z-disk are both increased under stress condition further supporting a role of ZASP in protection and repair of the Z-disk, although the role of PGM1 at the Z-disk is not clear [202].



ZASP contains 16 exons, although no ZASP protein is coded by the hypothetical full-length cDNA. The hypothetical full-length protein is a representation of all protein domains and all mutations described in humans so far. Six splice forms have been described (1s, 1c, 2s, 2c, 3s, 3c) and named accordingly to the presence specific exons, such as the cardiac specific exon 4 (c for cardiac and s for skeletal). Each splice form is shown with all mutations present on the exons it contains accordingly to the amino acid change described when published. Therefore, numbering incongruences are detected depending on the splice form analysed. Mutations are coloured according to the disease classification. Note that the 3'UTR is not drawn to scale.

Figure 4. Schematic representation of *ZASP* domains, human splice variants, and mutations.

6. Filamin and filaminopathies

Filamin C (FLNC) was first implicated in MFM in 2005 with the identification of a missense mutation in a German family that presented with weakness of the proximal muscle groups and respiratory insufficiency [12]. Since this initial discovery five additional FLNC mutations have been identified of which two result in MFM [203,204] and three cause distal myopathies in which protein aggregates are not evident [205,206] (Table 6).

Mutation	Age of onset / Initial symptoms	Clinical and pathological features; other studies	Ref
c.577G>A **A193T**	30's Skel	**Skel:** MW. **Pathology:** residual fibre size variation; focal increase in fibrosis and internal nuclei. **Other studies:** C2C12 show increased number of stress fibres and cell projections; FLNC- and Actin-positive aggregates were detected. **Classified as distal myopathy**	[205]
c.752T>C **M251T**	30's Skel	**Skel:** slowly progressive MW. **Card:** some developed CM. **Pathology:** abnormal myofibre size; internally located nuclei. **Classified as distal myopathy**	[205]
c.2695_2712del + GTTTGTins **del(K899_V904) + ins(V899_C900)**	35-40 Skel	**Skel:** progressive MW. **Card:** AVB. **Pathology:** variation in myofibre size and increased numbers of internal nuclei; vacuoles and deposits positive for Desmin, Dysferlin, Dystrophin and Ubiquitin; necrotic and regenerating myofibres; nemaline bodies. **Classified as MFM**	[204]
c.2788_2799del **del(V930_T933)**	34-60 Skel	**Skel:** difficulty to stand or walk; progressive MW. **Pathology:** abnormal myofibre size; atrophic myofibres and internally located nuclei; aggregates positive for FLNC, Ubiquitin, Desmin, Myotilin and CRYAB; nemaline bodies and mitochondria aggregates. **Classified as MFM**	[203]
c.5160delC **F1720fsX633**	20-57 Skel	**Skel:** MW and MA. **Card:** few cases of CM and VEFR. **Pathology:** from slight myofibre size variation and rare fibre splitting and internally located nuclei to myofibrillar disorganisation, Z-disk streaming, presence of small rods and other deposits. **Classified as distal myopathy**	[206]
c.8130G>A **W2710X**	24-49 Skel	**Skel:** slowly progressive MW; wheelchair dependence in some patients. **Card:** some patients with HCM, AVB and VEFR. **Pathology:** splitting and necrotic fibres; internally located nuclei; aggregates positive for FLNC, Desmin, Myotilin and Dystrophin and vacuoles; Z-disk streaming and nemaline-rod formation. **Other studies:** protein studies showed a decreased stability and dimerisation capacity of the mutant FLNC; PtK2 cells form aggregates. **Classified as MFM**	[4,12,207]

'Other studies' describes results from animal models and *in vitro* systems. Skel: Skeletal muscle; Card: cardiac muscle; MW: muscle weakness; MA: muscle atrophy; CM: cardiomyopathy; HCM: hypertrophic cardiomyopathy; AVB: atrioventricular block; VEFR: ventricular ejection fraction reduction; MFM: myofibrillar myopathy; C2C12 cells: mouse myoblast/satellite cells; PtK2 cells: Potorous tridactylis kidney cells.

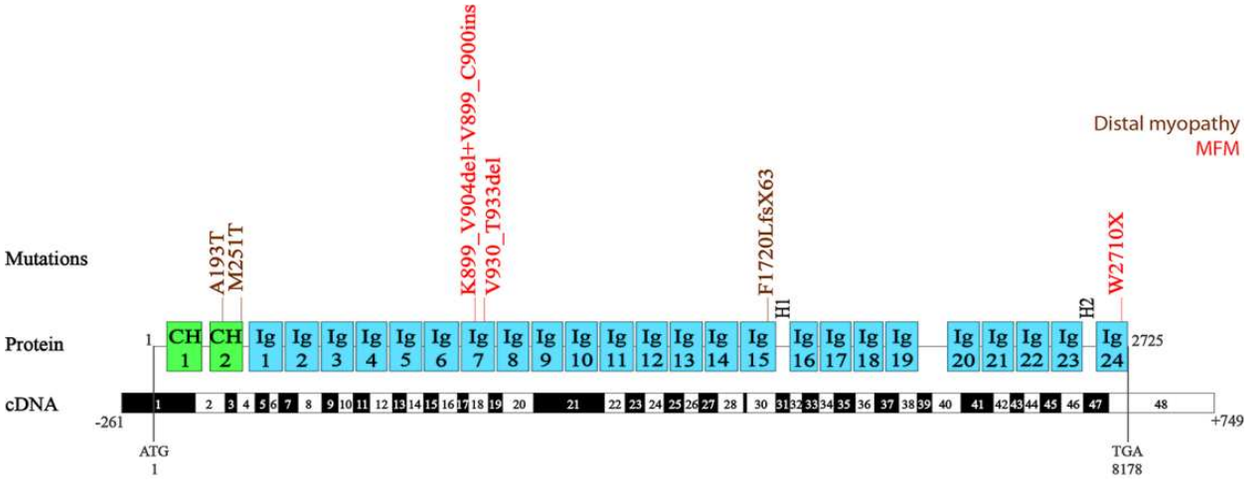
Table 6. Description of clinical and pathological features of filaminopathies.

FLNC belongs to the Filamin family of proteins characterised by their ability to cross link Actin. Three Filamin isoforms have been identified all of which are encoded by different genes [208,209]: Filamin A (α-Filamin or Filamin 1) and Filamin B (β-Filamin), which are ubiquitously expressed, and FLNC (Filamin 2, γ-Filamin, Actin Binding Protein 280 (ABP-280) or Actin Binding Protein Ligand (ABP-L)) [210-212], which is expressed specifically in striated and cardiac muscle [204,212]. In striated muscle, FLNC localises in two different pools: 97% of FLNC is contained within the Z-disk of the sarcomere and 3% is found in the

sarcolemmal membrane at the level of the costameres and myotendinous junctions [213]. In cardiac muscle FLNC is found in intercalated discs [213,214].

Filamin proteins contain two distinct functional regions (Figure 5). The N-terminal region, which contains two calpain homology domains that are responsible for interacting with Actin and promoting its polymerisation [215]. Two of the three distal myopathy causing FLNC mutations, in which protein aggregates are not evident, are found in this N-terminal region. This suggests that the presence of a functional N-terminal Actin binding domain in MFM causing FLNC mutant protein may be important in the formation of protein aggregates. The other four FLNC mutations are found in the semi-flexible rod domain, which contains 24 homologous Ig-like domains, each about 93 to 103 amino acids long [203]. The Ig-like domains act as an interface for the interaction of FLNC with its binding partners and allow FLNC dimerisation, through domain 24 [216], which is essential for its function.

Disruption of FLNC dimerisation leads to failure of the Z-disk as in the case of W2710X MFM causing FLNC mutation. Truncation of the dimerisation domain results in the loss of secondary structure of the mutant protein hence making it less stable and more susceptible to degradation by proteolytic enzymes [12,207], but is also more prone to aggregation [207] . Although the mutant protein is unable to form dimers, it neither disturbs dimerisation of wildtype FLNC nor affects its interaction with Actin or the sarcoglycans, two key FLNC binding partners [207]. In between FLNC Ig-like domains 15 and 16 (Figure 5), a differentially spliced Hinge 1 (H1) region is present, that provides flexibility to FLNC, but is absent from the predominant form expressed in striated muscle. Additionally, FLNC has a second hinge region (H2, Figure 5) between Ig-like domains 23 and 24, found in both splice variants [210,212], and contains a unique 82 amino acid insert between Ig-like domains 19 and 20 [213], which is thought to recruit FLNC specifically into the Z-disk [157].



Mutations are coloured according to the disease classification.

Figure 5. Schematic representation of FLNC domains and mutations.

FLNC has been proposed to have several functions in the muscle. The interaction of Ig-like domain 20 of FLNC with the Z-disk protein Xin is important in regulating the development

and remodelling of the Actin cytoskeleton [217]. Additionally, the interaction of FLNC Ig-like domains 19, 20, 21, and domain 23 with the Z-disk proteins Myotilin [159] and FATZ [157,182,218,219] maintains the stability of the sarcomere. At the sarcolemma, FLNC interacts with the transmembrane proteins γ- and δ-Sarcoglycans (repeats 20 to 24) [213], Cbl-associated protein (CAP or Ponsin, domain 2) [220], Ankyrin G (repeat 5 and 6) [221], and β1-integrin (domain 20-21) [157]. FLNC therefore connects the Z-disk to the sarcolemma and the ECM providing both a structural linkage and a mechanism for signalling from the sarcolemma to the Z-disk [159,213]. In cardiac muscle FLNC interacts with Nebulette [222], the cardiac specific homologue of the thin filament ruler Nebulin. This interaction has been thought to be important in targeting FLNC to the cytoskeleton therefore ensuring the correct localisation and function of FLNC. FLNC, through Ig-like domains 20, 21, and 23 also interacts with the muscular dystrophy KY protein but the functional importance of this interaction is not known [214]. The identification of a distal myopathy as a result of FLNC haploinsufficiency suggests that the levels of FLNC maybe critical for its function [206]. Additionally, the altered distribution of both sarcomeric and ECM proteins in filaminopathies suggests that the functions of FLNC at the Z-disk and sarcolemma are compromised in filaminopathies. Analysis of the FLNC mouse knockout identified a decrease in the number of primary muscle fibres suggesting a role for FLNC in myogenesis [223]. However, the recent characterisation of a Medaka FLNC mutant showed no difference in the expression of myogenic factors [224]. The role of FLNC in fibre differentiation is therefore still questionable.

The process by which mutations in FLNC result in muscle disease is not understood but the identification of a haploinsufficient form of filaminopathy, and the finding that the W2710X mutant does not disrupt wildtype FLNC dimerisation, together with the severe muscle defects seen in the FLNC knockout mouse suggest that Filamin related MFM manifests as result of direct or indirect loss of functional FLNC. It is therefore hypothesised that the progressive, late-onset, nature of filaminopathies results from a reduction in FLNC function commensurate with the increasing sequestration of wildtype FLNC and FLNC binding partners by mutant FLNC in the cytoplasm.

7. BAG3 and bag3opathies

Bcl2-related athanogene 3 (BAG3, Bis, CAIR) is the most recently identified MFM causing Z-disk protein with the report of a missense mutation (P209L) in exon three resulting in MFM with cardiac complications [13]. Since then 10 additional *Bag3* mutations have been reported of which nine result in DCM [225,226] and one in MFM [227] (Table 7). BAG3 is one of six members of the BAG family of proteins. It is a multidomain co-chaperone expressed at high levels in skeletal and cardiac muscle and found at lower levels in tissues such as neurons, adrenal gland, ovaries and testis [228,229]. In skeletal muscle BAG3 co-localises with Desmin and α-Actinin at the Z-disk [228]. An increase in BAG3 expression is detected following an increase in static strain [230], eccentric contraction [231], or nemaline myopathy [232] which suggests that BAG3 plays a role in repair and regeneration of skeletal muscle injuries caused by mechanical stress and disease.

Mutation	Age of onset / Initial symptoms	Clinical and pathological features; other studies	Ref
c.211C>T **R71W**	41-59 Card	**Card:** DCM; VEFR; heart transplantation required. **Classified as DCM**	[225]
c.268C>T **R90X**	44 Card	**Card:** DCM; VEFR. **Classified as DCM**	[225]
c.326A>G **H109R**	21 Card	**Card:** DCM; VEFR. **Classified as DCM**	[225]
c.367C>T **R123X**	25-36 Card	**Card:** DCM in some cases; some cases with VEFR; some required heart transplantation. **Classified as DCM**	[225]
c.626C>T **P209L**	5-13 Skel and Card	**Skel:** moderate to severe MW and MA; easy fatigability **Card:** Restrictive HCM; heart transplantation needed in some cases; early death in most cases. **Pathology:** abnormal myofibre size which larger fibres showed splitting or breakdown; necrotic and regenerating myofibres and internally located nuclei; abnormal fibres with ectopic staining for BAG3, CRYAB, Desmin, Myotilin, Dystrophin and Ubiquitin; presence of dense structures and aggregates of mitochondria; Z-disk streaming. **Other studies:** neonatal rat cardiomyocytes showed problems in cell fusion; COS-7 cells presented granules in their cytoplasm; C2C12 with reduced BAG3 protein levels show increased apoptosis. **Classified as MFM**	[13,226, 228,240]
c.625C>T + c.772C>T **P209W + R258W**	6 Skel	**Skel:** progressed from clumsy walking into MW and decreased spine movement **Card:** restrictive HCM. **Pathology:** atrophic fibres; focal myofibrillar disorganisation and degeneration; sarcoplasmic accumulation of granulofilamentous material. **Classified as MFM**	[227]
c.652C>T **R218W**	73 Card	**Cardiac muscle:** ventricular wall thickness; severe VEFR; ectopic atrial rhythm**. Other studies:** neonatal rat cariomyocyes presented abnormal Z-disk assembly (seen by Desmin and α-Actinin staining) and increased susceptibility to apoptosis. **Classified as DCM**	[226]
c.652Cdel **R218fsX89**	47 Card	**Card:** DCM; VEFR; early death. **Classified as DCM**	[225]
c.784G>A **A262T**	42-44 Card	**Card:** DCM; AVB; severe VEFR; required heart transplantation. **Classified as DCM**	[225]
c.1385T>C **L462P**	27-34 Card	**Card:** ventricular wall thickness; VEFR; cardiac contraction defects. **Other studies:** neonatal rat cardiomyocytes presented abnormal Z-disk assembly and increased susceptibility to apoptosis. **Classified as DCM**	[226]
c.1430G>A **A477H**	47-50 Card	**Card:** DCM; severe VEFR; pacemaker insertion. **Classified as DCM**	[225]

'Other studies' describes results from animal models and *in vitro* systems. Skel: Skeletal muscle; Card: cardiac muscle; MW: muscle weakness; MA: muscle atrophy; HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; VEFR: ventricular ejection fraction reduction; AVB: atrioventricular block; MFM: myofibrillar myopathy; COS-7 cells: African green monkey fibroblast; C2C12 cells: mouse myoblast/satellite cells.

Table 7. Description of clinical and pathological features of bag3opathies.

BAG3 has three recognisable functional domains (Figure 6); no mutations have been reported in the WW domain containing N-terminal region, which interacts with proline rich motifs of signal transduction proteins, or in the proline rich central region, which interacts with WW domains and Src3 homology (SH3) domains of signal transduction proteins such as Phospholipase C (PLCγ) [233].

Two mutations have however been reported in the evolutionary conserved C-terminal BAG domain that has a key role in the apoptotic and chaperone functions of BAG3 [234-236]. The BAG domain binds with high affinity to, and regulates, stress inducible Heat shock protein 70 (Hsp70) [233-235,237] and the constitutively expressed Heat shock cognate protein 70 (Hsc70) [237], that ensure

correct protein folding and targeting of misfolded proteins for proteasomal degradation [238]. BAG3 competitively binds to the ATPase domain of these chaperone proteins and alters their chaperone properties thereby targeting chaperone associated proteins for proteasomal degradation [237,239]. In fact, BAG3 has recently been shown to form a stable complex with the small Heat shock protein HspB8 and stimulate macroautophagy [236], a process that is particularly important in Huntington disease where association of BAG3 with HspB8 promotes degradation of mutant Huntingtin [236,241]. In inclusion body myositis, macroautophagy plays a role in removing β-amyloid aggregates [242] and it is possible that BAG3 also plays a role in this cellular response to protein aggregates in MFM. However, as the primary defect in MFM is the dissolution of muscle fibres beginning at the Z-disk preventing the formation of protein aggregates is unlikely to be sufficient to prevent muscle pathology.

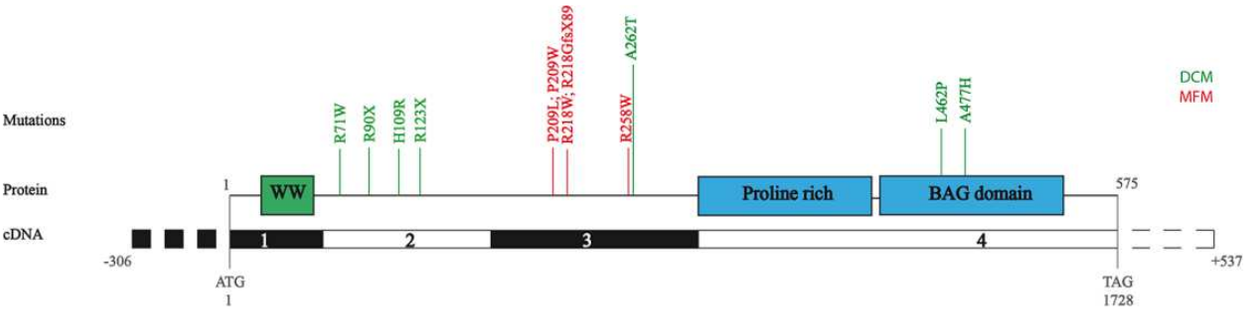
In αB-crystallinopathies BAG3 suppresses protein aggregation and toxicity by preferentially binding mutant CRYAB, reducing its aggregation and increasing its solubility [136]. This demonstrates that BAG3 not only indirectly regulates protein folding and degradation but also has the potential to prevent misfolding and promote degradation of mutant proteins thereby preventing disease pathology. Interestingly, deletion of the BAG domain results in a similar inhibition of aggregation of mutant CRYAB. BAG3 may therefore function through a pathway that is independent of Hsp70/Hsc70 [136]. BAG3 synergistically interacts with Bcl-2, via the BAG domain, to prevent Bax induced and FasL-

Fas mediated apoptosis [239,243]. BAG3 levels are up-regulated in response to oxidative stress [244], heat shock, heavy metal exposure [245,246], or photoinjury in the retina [247] and increased levels of BAG3 in human epithelial cells has been show to result in decreased Bax or Fas mediated apoptosis demonstrating the critical adaptive role of BAG3 in response to cell stress.

Immunohistochemistry on P209L mutant muscle biopsy samples revealed increased immunoreactivity in abnormal fibres for the chaperone molecules Hsp27 and CRYAB and the anti- apoptotic protein Bcl-2. This was accompanied by increased apoptosis suggesting that the P209L mutation interfered with the anti-apoptotic functions of BAG3 [13]. Non-denaturing gel electrophoresis revealed faster migration of the mutant BAG3 complex than wildtype [13], suggesting that the loss of function may be due to reduced interaction with partner proteins, possibly Bcl-2, given that an increase in apoptosis is observed. This is supported by transfection of P209L mutant BAG3 into neonatal cardiomyocytes resulting in increased susceptibility to stress mediated apoptosis [226] and the observation that mice deficient in BAG3 also display increased apoptosis [228]. It has been shown that the down-regulation of BAG3 enhances the apoptotic response to chemotherapy in lymphocytic

leukaemia cells making it a potential target for cancer therapies [248], and further demonstrating its anti-apoptotic role.

Since the primary defect in BAG3opathies is the fragmentation of fibres it can be postulated that perhaps BAG3 has a role in muscle development or maintenance of muscle structure. BAG3 deficient mice are normal at birth but cease to gain weight at day 12. Muscle histology revealed myofibril and Z-disk defects with no sarcolemma damage [228]. Taken together, this data suggests that BAG3 is not necessary for sarcomerogenesis but is critical for maintenance of fibre integrity. By the 25th day BAG3 deficient mice die as a result of intercostal muscle failure or pulmonary oedema that results in cardiac failure [228]. Targeted knockdown of BAG3 in zebrafish has also resulted in severe cardiac defects demonstrating a critical role of BAG3 in maintaining the structural integrity of cardiomyocytes [225]. A recent study has shown that BAG3 regulates myofibril stability by facilitating the interaction of Hsc70 with CapZ, a protein that caps the barbed ends of Actin filaments that extend into Z-disk [230]. Loss of BAG3 makes CapZ more vulnerable to degradation resulting in loss of CapZ and fibre fragmentation following mechanical stress [230].



Mutations are coloured according to the disease classification. Dashed segments in cDNA represent the UTRs that are not drawn to scale.

Figure 6. Schematic representation BAG3 domains and mutations.

In summary, the most recently identified MFM causing gene plays key roles in the localisation of CapZ to the Z-disk through its interaction with Hsc70, protein folding and degradation, and in the regulation of apoptosis. Given the indirect role BAG3 plays in Z-disk and muscle function, its binding partners are excellent candidates for further genes that may be mutated in MFM. However, given the fact that most of the identified disease causing mutations lie outside a recognised domain in BAG3 there may be many more functions for BAG3 that remain to be characterised, perhaps including a direct role in the Z-disk.

8. Conclusion

The many functions of the MFM proteins, which are themselves just a very small subset of the Z-disk associated proteins, highlights the complex and dynamic nature of the Z-disk. Whilst a characteristic feature of MFM is dissolution of the myofibril, originating at the Z-disk, these disorders are not due to simple loss or disruption of structural components in

this tensile load bearing structure. This is exemplified by the identification of BAG3, which localises to the Z-disk but appears to only have indirect association to it, as an MFM protein. Further support comes from analysis of mouse knockouts for the MFM genes, none of which have defects in the formation of myofibrils.

The progressive nature of the disease and the identification of roles for the associated proteins in muscle repair and maintenance is more suggestive of a gradual accumulation of defects in Z-disk organisation eventually leading to structural failure. An interesting finding from mice lacking the long isoforms of ZASP is that they have increased levels of the MFM proteins Myotilin, CRYAB, and FLNC as well as the extracellular matrix proteins β1D Integrin and the sarcoglycans [189]. Up-regulation of Z-disk components is observed in α-Actinin-3 knockout mice in which FLNC, Myotilin, ZASP, and CRYAB are up-regulated [249]. Increased levels of FLNC are also detected in patients with LGMD or Duchenne muscular dystrophy [213]. This data, together with that previously presented, strongly supports the idea that the MFM proteins are up-regulated to protect the sarcomere and ECM from damage, whether that damage is caused by muscle activity, mutation of muscle proteins, or increases in oxidative, metabolic, and other forms of cell stress. Whether this is through a general stress response pathway that up-regulates the expression of Z-disk associated proteins or through a more specific pathway that selectively target proteins based on the nature of the stress remains to be determined.

For more than half of the cases of MFM the causative mutation is not known. As we have described there are many binding partners for the known MFM proteins, mutations in which may account for some of these cases. Additionally there is evidence from experiments with Desmin that mutations in other genes may act as modifiers of disease. Far more mutations have been identified in Desmin than in other MFM genes and it may be that modifiers will be identified in other subtypes of MFM as larger cohorts are analysed. Given the hypothesised role for the MFM proteins in stress response it is possible that any mutations that result in cellular stress may modify the presentation of MFM perhaps accounting for some of the differences in age of onset. Furthermore, differences in stress between cardiac and skeletal tissues may explain the differences in symptoms between these tissues, even in individuals with the same mutation. As the application of whole genome sequencing to mutation detection in myopathy becomes more widespread it may be possible to identify potential modifiers and investigate their role in MFM.

The existing literature on MFM and the MFM associated proteins has identified many exciting avenues for investigation. To investigate these areas further animal models, modelling specific MFM mutations, are required that would allow for better characterisation of pathology and the progression of disease together with a consistent genetic background to allow the analysis of potential genetic modifiers. The development of better tools to investigate the function of the MFM proteins, together with the identification of further MFM genes and modifiers, will allow us to improve our understanding of the many diverse

and complex roles of these Z-disk associated proteins and move closer to the development of effective therapies for these conditions.

9. Abbreviations

ACD domain: α-crystallin domain
AVB: atrioventricular block
BAG3: Bcl2-related athanogene 3
CM: cardiomyopathy
CRYAA: αA-Crystallin
CRYAB: αB-Crystallin
DCM: dilated cardiomyopathy
DRM: Desmin-related myopathy
ECM: extracellular matrix
FLNC: Filamin C
HCM: hypertrophic cardiomyopathy
IF: intermediate filament
Ig: immunoglobulin
LVNCC: left ventricular non-compaction cardiomyopathy
MA: muscle atrophy
MFM: myofibrillar myopathy
MW: muscle weakness
PGM1: Phosphoglucomutase 1
PKC: Protein kinase C
SBM: spheroid body myopathy
ULF: unit length filament
UPS: ubiquitin proteasome system
UTR: untranslated region
VEFR: ventricular ejection fraction reduction
ZASP: Z-band alternatively spliced PDZ-motif protein
WT: wildtype
ZM: ZASP/Cypher-like motif
GFAP: Glial fibrillary acidic protein

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