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Myofibrillar Myopathy – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Myofibrillar myopathy is characterized by slowly progressive weakness that can involve both proximal and distal muscles. Distal muscle weakness is present in about 80% of individuals and is more pronounced than proximal weakness in about 25%. A minority of individuals experience sensory symptoms, muscle stiffness, aching, or cramps. Peripheral neuropathy is present in about 20% of affected individuals. Overt cardiomyopathy is present in 15%-30%.

Diagnosis/testing

The diagnosis of myofibrillar myopathy is based on clinical findings, electromyography (EMG), nerve conduction studies, and, most importantly, muscle histology. To date, the genetic basis of myofibrillar myopathy has been elucidated in only about 50% of cases. Pathogenic variants have been identified in *DES*, the gene encoding desmin; *CRYAB*, encoding alpha-crystallin B chain; *MYOT*, encoding myotilin; *LDB3* (*ZASP*), encoding LIM domain-binding protein 3; *FLNC*, encoding filamin-C, and *BAG3*, encoding BAG family molecular chaperone regulator 3. Recently, pathogenic variants in *FHL1,* encoding four and a half LIM domains protein 1, and *DNAJB6*, encoding DnaJ homolog subfamily B member 6 were also identified.

Management

Treatment of manifestations: Consider pacemaker and implantable cardioverter defibrillator (ICD) in individuals with arrhythmia and/or cardiac conduction defects; consider cardiac transplantation in individuals with progressive or life-threatening cardiomyopathy; respiratory support (continuous or bilevel positive airway pressure), initially at night and later in the daytime, in individuals with hypercapnea and other signs of incipient

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respiratory failure; range-of-motion physical therapy and assistive devices for those with advanced muscle weakness.

Other: The role of strengthening exercises has not been defined.

Genetic counseling

Myofibrillar myopathy is most commonly inherited in an autosomal dominant manner. Exceptions include: X-linked inheritance of *FHL1* pathogenic variants and autosomal recessive inheritance of *CRYAB* pathogenic frameshift variants that lead to premature termination of the translational chain resulting in non-transcription of the mutated protein. The inheritance in some families cannot be determined with confidence. When the pathogenic variant(s) in the family are known, carrier testing and prenatal testing for pregnancies at increased risk is possible.

GeneReview Scope

Myofibrillar Myopathy: Included Disorders
• Alpha-B crystallinopathy • *BAG3*-related myofibrillar myopathy • Desminopathy • *DNAJB6*-related myofibrillar myopathy • *FHL1*-related myofibrillar myopathy • Filaminopathy • Myotilinopathy • Zaspopathy

For synonyms and outdated names see Nomenclature.

Diagnosis

Clinical Diagnosis

The term myofibrillar myopathy refers to a group of genetically distinct disorders linked by common morphologic features observed on muscle histology.

The diagnosis of myofibrillar myopathy rests on the following:

- **History of slowly progressive weakness** accompanied in a smaller proportion of individuals by paresthesias, muscle atrophy, stiffness or aching, cramps, dyspnea, and dysphagia. Physical examination reveals proximal and distal weakness in the majority of individuals. In about one third the weakness is greater proximally than distally; in another third it is greater distally than proximally. Facial weakness is uncommon but can occur. Tendon reflexes are normal or diminished.
- **Electromyography** (EMG) that reveals abnormal electrical irritability (fibrillation potentials, positive sharp waves, complex repetitive discharges, and myotonic discharges) in most individuals. The motor unit potentials show either myopathic features or both myopathic and neurogenic features. Abnormal nerve conduction studies are detected in about 20% of individuals.
- **Muscle histology** that reveals the following combination of findings (see Figure 1):
  - Characteristic alterations in trichromatically stained frozen sections consisting of amorphous, hyaline, or granular material in a variable proportion of the muscle fibers;
  - Sharply circumscribed decreases of oxidative enzyme activity in many abnormal fiber regions;
  - Intense congophilia of many hyaline structures, best observed under rhodamine fluorescence optics; and
  - Small vacuoles in a variable number of fibers

- **Immunocytochemical studies of muscle** that show abnormal ectopic expression of myotilin (90% of abnormal fibers), desmin (75%), α-B crystallin (75%), dystrophin (70%), and β-amyloid precursor protein (70%)
- **Electron microscopy of muscle** showing progressive myofibrillar degeneration commencing at the Z-disk, disintegration of the sarcomeres, accumulation of degraded filamentous material in pleomorphic hyaline inclusions, and dislocation of membranous organelles and their degradation in autophagic vacuoles [Selcen et al 2004]
- **Other tissues**
  - Peripheral nerve biopsies, in a few descriptions, show accumulation of neurofilaments, neurotubules, and formation of axonal spheroids.
  - Myocardial biopsies show desmin-immunoreactive cytoplasmic inclusions, especially near intercalated disks and interstitial fibrosis.
  - Peripheral nerve pathology [Sabatelli et al 1992] and myocardial pathology [Abraham et al 1998, Arbustini et al 1998, Lobrinus et al 1998] have been described briefly in a small number of individuals with myofibrillar myopathy.
- **Serum creatine kinase concentration** can be normal or elevated to no greater than seven times the upper limit of normal.

Molecular Genetic Testing

Genes. To date, the genetic basis of myofibrillar myopathy (MFM) has been elucidated in about 50% of kinships. Pathogenic variants have been identified in the following genes:

- *DES*, encoding desmin [Goldfarb et al 1998, Muñoz-Mármol et al 1998, Dalakas et al 2000]
- *CRYAB*, encoding α-crystallin B chain [Vicart et al 1998, Selcen & Engel 2003]
- *MYOT* (known previously as *TTID*), encoding myotilin [Selcen & Engel 2004]
- *LDB3* (known previously *as ZASP*), encoding LIM domain-binding protein 3 [Selcen & Engel 2005]
- *FLNC*, encoding filamin-C [Vorgerd et al 2005]
- *BAG3*, encoding BAG family molecular chaperone regulator 3 (Bag3) [Selcen et al 2009]
- *FHL1*, encoding four and a half LIM containing protein 1 [Selcen et al 2011]
- *DNAJB6*, encoding DnaJ homolog subfamily B member 6 (heat shock protein 40) [Harms et al 2012; Sarparanta et al 2012; Author, personal observation]

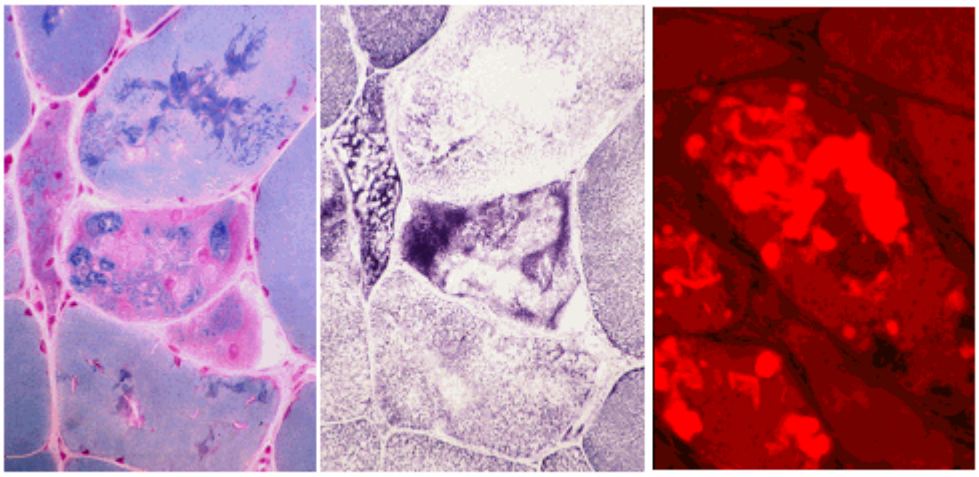

Figure 1. Muscle histology observed in myofibrillar myopathy

Table 1. Molecular Genetic Testing Used in Myofibrillar Myopathy

Gene [1]	Proportion of MFM Attributed to Mutation of This Gene [2]	Test Method	Variants Detected [3]
DES	7%	Sequence analysis [4]	Sequence variants [5]
		Deletion/duplication analysis [6]	Unknown, none reported [7]
CRYAB	3%	Sequence analysis [4]	Sequence variants
		Deletion/duplication analysis [6]	Unknown; none reported [7]
MYOT	9%	Sequence analysis [4]	Sequence variants
		Deletion/duplication analysis [6]	Unknown, none reported [7]
LDB3	11%	Sequence analysis [4]	Sequence variants
		Sequence analysis of select exons	Sequence variants in exon 6 [8]
		Deletion/duplication analysis [6]	Unknown, none reported [7]
FLNC	3%	Sequence analysis [4]	Sequence variants
		Deletion/duplication analysis [6]	Unknown, none reported [7]
BAG3	5%	Sequence analysis [4]	Sequence variants
		Deletion/duplication analysis [6]	Unknown, none reported [7]
FHL1	3%	Sequence analysis [4]	Sequence variants

Table 1. continued from previous page.

Gene [1]	Proportion of MFM Attributed to Mutation of This Gene [2]	Test Method	Variants Detected [3]
DNAJB6	2%	Sequence analysis [4]	Sequence variants

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Frequencies based on Mayo Clinic MFM cohort
3. See Molecular Genetics for information on allelic variants.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Expected to identify approximately 99% of pathogenic variants in the coding region.
6. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
7. No large deletions or duplications of *DES*, *MYOT*, *LDB3*, CRYAB, *FLNC*, or *BAG3* have been reported to cause myofibrillar myopathy.
8. Exons sequenced may vary among laboratories.

Testing Strategy

To confirm/establish the diagnosis in a proband

- Generic diagnosis of an MFM can be made on clinical and histologic grounds.
- The diagnosis of a specific MFM is based on molecular genetic testing:
  - If the proband's symptoms suggest a candidate gene (see Genotype-Phenotype Correlations), perform sequence analysis of that gene first.
  - If no pathogenic variant is identified, perform sequence analysis for the remaining genes (Table 1).
  - At present no clear criteria for testing for deletions/duplications exist.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the pathogenic variant(s) in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variant(s) in the family.

Clinical Characteristics

Clinical Description

In the Mayo Clinic series of 80 individuals with myofibrillar myopathy (MFM), the age of onset varied from two to 77 years. The age at diagnosis ranged from 11 to 82 years. *BAG3*-related myofibrillar myopathy (Bag3opathy) characteristically presents in the first or second decade of life and is typically fatal. Desminopathies may also present in the first decade of life, usually with cardiomyopathy. However, the majority of MFM presents after age 40 years.

The predominant presenting symptom in MFM is slowly progressive weakness; a minority of individuals experience sensory symptoms, muscle stiffness, aching, or cramps. The weakness can involve both proximal and distal muscles; however, distal muscle weakness is 25% more common than proximal weakness.

Objective clinical signs or EMG findings of peripheral neuropathy are present in approximately 20% of affected individuals, but muscle biopsy studies suggest an even higher frequency of peripheral nerve involvement.

Overt cardiomyopathy can be a presenting manifestation or can appear during the evolution of myofibrillar myopathy in 15%-30% of affected individuals.

A restrictive ventilatory defect can result from respiratory muscle weakness.

Variable expressivity has been observed in kinships with pathogenic variants in *DES*, with some family members showing signs of cardiomyopathy only, some showing signs of both myopathy and cardiomyopathy, and some with reduced penetrance who have signs of neither myopathy nor cardiomyopathy.

Genotype-Phenotype Correlations

No morphologic features consistently or reliably predict mutation of a given gene.

The only genotype-phenotype correlations detected to date are:

- Cataracts were present in affected members of one of the three reported kinships with pathogenic variants in *CRYAB*, the gene encoding alpha crystallin B chain (also known as α-B crystallin) [Vicart et al 1998].
- Neuropathy and cardiomyopathy were observed in families with pathogenic variants in *MYOT* [Selcen & Engel 2004] and *BAG3* [Selcen et al 2009].
- Rigid spine has been observed in Bag3opathy [Selcen et al 2009] and *FHL1*-related MFM [Selcen et al 2011].
- Neuropathy and cardiomyopathy also occur in individuals in whom the genetic basis of myofibrillar myopathy has not been established.

Penetrance

Data are insufficient to draw conclusions about penetrance.

Anticipation

No convincing evidence of anticipation has been documented.

Nomenclature

"… The light microscopic features of myofibrillar myopathy were described in the 1970s and 1980s under such names as "myopathy with inclusion bodies" [Nakashima et al 1970], "atypical myopathy with myofibrillar aggregates" [Kinoshita et al 1975], "autosomal dominant cardiomyopathy with inclusions" [Clark et al 1978], "cardioskeletal myopathy with intrasarcoplasmic dense granulofilamentous material" [Fardeau et al 1978], "autosomal dominant spheroid body myopathy" [Goebel et al 1978], "myopathy with sarcoplasmic bodies and desmin filaments" [Edström et al 1980], "congenital myopathy with cytoplasmic bodies" [Wolburg et al 1982], "congenital myopathy with Mallory body-like inclusions" [Fidzianska et al 1983], and "familial cardiomyopathy with subsarcolemmal vermiform deposits" [Calderon et al 1987]. Later, however, it became apparent that some authors described the same pathologic reaction under different names; that more than one pathologic alteration thought to be specific for a single disorder could be present in the same muscle specimen, or even in the same muscle fiber; and that in each instance the pathologic changes involve the Z-disks of the myofibril. Edström et al [1980] noted that some inclusions or material around them reacted for desmin. This generated the names of "desmin storage myopathy" [Horowitz & Schmalbruch 1994] and later "desmin-related myopathies" [Goebel 1997]. In 1996 and 1997, detailed immunocytochemical studies revealed that many proteins, not just desmin, accumulate in the abnormal fibers, and prompted the use of the noncommittal term myofibrillar myopathy [De Bleecker et al 1996, Nakano et al 1997]…"

[Selcen et al 2004; republished with permission of Oxford University Press]

Myofibrillar myopathy has also been referred to as desmin storage myopathy, desmin-related myopathy, or protein surplus myopathy. Because myofibrillar myopathy is genetically heterogeneous and the disease-causing protein or involved gene is known only in a minority of cases, because multiple other proteins besides desmin are also overexpressed in muscle, and because myotilin is not related to desmin, the generic term "myofibrillar myopathy" is the preferred designation until the gene(s) in which pathogenic variants occur are determined. When the disease-associated gene or protein is identified, designations such as desminopathy, α-B crystallinopathy, myotilinopathy, zaspopathy (Markesbery-Griggs late-onset distal myopathy), filaminopathy, or *BAG3*-related myofibrillar myopathy are appropriate.

Prevalence

The prevalence of myofibrillar myopathy cannot be estimated at this time.

Genetically Related (Allelic) Disorders

Cardiomyopathy can occur with each genetically defined type of MFM.

Mutation of *CRYAB* can also cause cataracts without causing myofibrillar myopathy.

Mutation of *MYOT* can also cause a limb girdle-like phenotype that has been designated as LGMD1A [Hauser et al 2000] and also as a distal myopathy [Fischer et al 2006, Pénisson-Besnier et al 2006].

Mutation of *FHL1* is associated with several phenotypes: X-linked childhood-onset reducing body myopathy; X-linked early-onset severe reducing body myopathy; *FHL1*-related X-linked Emery-Dreifuss muscular dystrophy; X-linked myopathy with postural muscle atrophy; X-linked dominant scapuloperoneal myopathy.

Mutation of *DBAJB6* is associated with limb-girdle muscular dystrophy type 1E.

Differential Diagnosis

The principle differential diagnoses are late-onset myopathies and especially myopathies with a predominantly distal distribution:

- **Myotonic dystrophy type 1 (DM1)** is a multisystem disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. The clinical findings, which span a continuum from mild to severe, have been categorized into three somewhat overlapping phenotypes: mild, classic, and congenital. Mild DM1 is characterized by cataract and mild myotonia (sustained muscle contraction); life span is normal. Classic DM1 is characterized by muscle weakness and wasting, myotonia, cataract, and often by cardiac conduction abnormalities. Congenital DM1 is characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common. DM1 is caused by expansion of a CTG trinucleotide repeat in *DMPK*. Molecular genetic testing detects pathogenic variants in nearly 100% of affected individuals. DM1 is inherited in an autosomal dominant manner.
- **Myotonic dystrophy type 2 (DM2),** also known as proximal myotonic myopathy (PROMM), is characterized by myotonia and muscle dysfunction (weakness, pain, and stiffness), and less commonly by cardiac conduction defects, iridescent posterior subcapsular cataracts, insulin-insensitive type 2 diabetes mellitus, and testicular failure. Although myotonia has been reported during the first decade, onset is typically in the third decade, most commonly with fluctuating or episodic muscle pain that can be debilitating and weakness of the neck flexors and finger flexors. Subsequently, weakness occurs in the elbow extensors and the hip flexors and extensors. Facial weakness and weakness of the ankle dorsiflexors are less common. Myotonia rarely causes severe symptoms. *CNBP* (*ZNF9*), the only gene known to be associated with DM2, has in intron 1 a complex repeat motif, (TG)n(TCTG)n(CCTG)n, expansion of

which causes DM2. The number of CCTG repeats in expanded alleles ranges from approximately 75 to more than 11,000 (mean: ~5,000 repeats). The detection frequency of a *CNBP* CCTG expansion is more than 99%. DM2 is inherited in an autosomal dominant manner.

- **Motor and sensory neuropathies**
- **Inclusion body myopathy type 2 (IBM2)** is characterized by adult-onset, slowly progressive distal muscle weakness that begins with gait disturbance and foot drop secondary to anterior tibialis muscle weakness. Weakness eventually includes the hand and thigh muscles, but commonly spares the quadriceps muscles, even in advanced disease. Affected individuals are usually wheelchair bound about 20 years after onset. Muscle histopathology typically shows rimmed vacuoles and characteristic filamentous inclusions. *GNE*, which encodes the bifunctional enzyme UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase, is the only gene known to be associated with IBM2. IBM2 is inherited in an autosomal recessive manner.
- **Inclusion body myositis,** a slowly progressive and typically sporadic vacuolar myopathy, is associated with an autoaggressive inflammatory exudate and small congophilic inclusions.
- **Dysferlinopathy,** caused by pathogenic variants in *DYSF*, includes a spectrum of muscle disease characterized mainly by two phenotypes: Miyoshi myopathy, with primarily distal weakness; and limb-girdle muscular dystrophy type 2B (LGMD2B), with primarily proximal weakness. Miyoshi myopathy is characterized in young adults by muscle weakness and atrophy, most marked in the distal parts of the legs, especially the gastrocnemius and soleus muscles. Over a period of years, the weakness and atrophy spread to the thighs and gluteal muscles. LGMD2B is characterized by early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood, with slow progression. Dysferlinopathy is inherited in an autosomal recessive manner.
- **Other muscular dystrophies** that can predominantly affect distal muscles include tibial muscular dystrophy (Udd distal myopathy), telethoninopathy, Laing distal myopathy caused by *MYH7* pathogenic variants, Welander's distal dystrophy, facioscapulohumeral dystrophy, anoctamin-5 related muscular dystrophy, and other sporadically occurring or dominantly inherited muscular dystrophies.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with myofibrillar myopathy (MFM), the following evaluations are recommended:

- EMG
- Routine ECG to identify arrhythmias and cardiac conduction defects; Holter monitoring if symptoms suggest an intermittent arrhythmia; echocardiogram if cardiac symptoms are present
- Respiratory function tests if respiratory symptoms are present
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Pacemaker and implantable cardioverter defibrillator (ICD) should be considered in individuals with arrhythmia and/or cardiac conduction defects. Individuals with progressive or life-threatening cardiomyopathy are candidates for cardiac transplantation.

Respiratory support, consisting of continuous or bilevel positive airway pressure (CPAP or BIPAP), initially at night and later in the daytime, is indicated in individuals with hypercapnea and other signs of incipient ventilatory failure.

Range of motion physical therapy and assistive devices are appropriate for those with advanced muscle weakness. Treatment of scoliosis by spinal fusion is appropriate. Orthoses are indicated for treatment of foot drop.

Prevention of Secondary Complications

Pacemaker or implantable cardioverter defibrillator placement for individuals with arrhythmogenic cardiomyopathy.

Surveillance

The following are appropriate:

- Physical examination to monitor disease progression yearly or less often depending on rate of progression
- Electrocardiogram and/or echocardiogram yearly for early detection of cardiomyopathy
- Pulmonary function tests for individuals with exertional or nocturnal dyspnea.

Evaluation of Relatives at Risk

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Pregnancy Management

Affected pregnant women may need assistance during delivery if they have significant weakness of their abdominal muscles.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

The role of strengthening exercises has not been defined.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Myofibrillar myopathy (MFM) is most commonly inherited in an autosomal dominant manner. Exceptions include:

- Autosomal recessive inheritance of *CRYAB* pathogenic frameshift variants that predict premature termination of the protein (see Molecular Genetics).
- X-linked inheritance of *FHL1* pathogenic variants

Risk to Family Members – Autosomal Dominant Inheritance

Parents of a proband

- Approximately 25% of individuals diagnosed with autosomal dominant (AD) myofibrillar myopathy have an affected parent.
- A proband with AD myofibrillar myopathy may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include clinical examination looking for weakness, EMG, and possible muscle biopsy. Molecular genetic testing may also be appropriate if a pathogenic variant has been identified in the proband.

Note: Twenty-five percent of individuals diagnosed with myofibrillar myopathy have an affected parent; in other individuals, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband cannot be determined with confidence.
- Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with AD myofibrillar myopathy has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has a pathogenic variant, his or her family members are at risk.

Risk to Family Members – Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one mutated allele).
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Unless an individual with MFM has children with an affected individual or a carrier of a *CRYAB* pathogenic variant, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic frameshift variant in *CRYAB*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier (Heterozygote) Detection

Carrier testing for at-risk family members is possible if the *CRYAB* pathogenic variants in the family have been identified.

Risk to Family Members – X-Linked Inheritance

Parents of a proband

- The father of an affected male will not have MFM nor will he be a carrier of the *FHL1* pathogenic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.

  Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a carrier or the affected male may have a *de novo* pathogenic variant and, thus, the mother is not a carrier. The percent of simplex cases representing *de novo* pathogenic variants is not known.

Sibs of a proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband has a *FHL1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and may be severely affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males pass the *FHL1* pathogenic variant to all of their daughters and none of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their gender, may be at risk of being carriers or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote (Carrier) Detection

Carrier testing for at-risk female relatives is possible if the *FHL1* pathogenic variant in the family has been identified.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder and/or the pathogenic variant, the proband likely has a *de novo* pathogenic variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being affected or carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Muscular Dystrophy Association - USA (MDA)**
  222 South Riverside Plaza
  Suite 1500
  Chicago IL 60606
  Phone: 800-572-1717
  Email: mda@mdausa.org
  www.mda.org
- **Muscular Dystrophy UK**
  61A Great Suffolk Street
  London SE1 0BU
  United Kingdom
  Phone: 0800 652 6352 (toll-free); 020 7803 4800
  Email: info@musculardystrophyuk.org
  www.musculardystrophyuk.org
- **Sudden Arrhythmia Death Syndromes (SADS) Foundation**
  508 East South Temple
  Suite #202
  Salt Lake City UT 84102
  Phone: 800-786-7723 (toll-free); 801-531-0937
  Email: sads@sads.org
  www.sads.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Myofibrillar Myopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
BAG3	10q26.11	BAG family molecular chaperone regulator 3	BAG3 homepage - Leiden Muscular Dystrophy pages	BAG3	BAG3
CRYAB	11q23.1	Alpha-crystallin B chain	CRYAB homepage - Leiden Muscular Dystrophy pages	CRYAB	CRYAB

Table A. continued from previous page.

DES	2q35	Desmin	Human Intermediate Filament Database DES ARVD/C Genetic Variants Database (DES) DES homepage - Leiden Muscular Dystrophy pages	DES	DES
DNAJB6	7q36.3	DnaJ homolog subfamily B member 6	DNAJB6 homepage - Leiden Muscular Dystrophy pages	DNAJB6	DNAJB6
FHL1	Xq26.3	Four and a half LIM domains protein 1	FHL1 homepage - Leiden Muscular Dystrophy pages	FHL1	FHL1
FLNC	7q32.1	Filamin-C	FLNC homepage - Leiden Muscular Dystrophy pages	FLNC	FLNC
LDB3	10q23.2	LIM domain-binding protein 3	LDB3 homepage - Leiden Muscular Dystrophy pages	LDB3	LDB3
MYOT	5q31.2	Myotilin	MYOT homepage - Leiden Muscular Dystrophy pages	MYOT	MYOT

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Myofibrillar Myopathy (View All in OMIM)

102565	FILAMIN C; FLNC
123590	CRYSTALLIN, ALPHA-B; CRYAB
125660	DESMIN; DES
300163	FOUR-AND-A-HALF LIM DOMAINS 1; FHL1
601419	MYOPATHY, MYOFIBRILLAR, 1; MFM1
603883	BCL2-ASSOCIATED ATHANOGENE 3; BAG3
604103	MYOTILIN; MYOT
605906	LIM DOMAIN-BINDING 3; LDB3
608810	MYOPATHY, MYOFIBRILLAR, 2; MFM2
609200	MYOPATHY, MYOFIBRILLAR, 3; MFM3
609452	MYOPATHY, MYOFIBRILLAR, 4; MFM4
609524	MYOPATHY, MYOFIBRILLAR, 5; MFM5
611332	DNAJ/HSP40 HOMOLOG, SUBFAMILY B, MEMBER 6; DNAJB6

Molecular Genetic Pathogenesis

Because myofibrillar myopathy is caused by pathogenic variants in any of eight different genes and each disease-associated gene may have different types of pathogenic variants, the molecular pathogenesis may vary from case to case. However, in all myofibrillar myopathies, the initial pathologic change involves disintegration of the Z-disk, and all disease proteins identified to date are involved in maintaining the structural integrity of the Z-disk. Because the Z-disks are sites of tension transmission between sarcomeres, the myofibrils fall apart when the Z-disks disintegrate.

Animal models. Desmin knockout mice show normal development of cardiac and skeletal muscle but subsequently show myofiber necrosis and phagocytosis [Capetanaki et al 1997]. This model is not comparable with human cases of desminopathy in which pathogenic missense variants weaken sarcomere structure and are associated with abnormal accumulation of desmin and other proteins. Transgenic mice that produce an inactivated form of human desmin (p.Arg173_Glu179del) show desmin immunoreactive aggregates in myocardium [Muñoz-Mármol et al 1998]. Transgenic mice expressing an α-B crystallin mutated protein (p.Arg120Gly) develop a severe cardiomyopathy with abnormal accumulation of desmin and α-B crystallin in the heart; muscle pathology was not mentioned in this report [Wang et al 2001].

DES

Gene structure. *DES* consists of nine exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than forty pathogenic variants including missense, frameshifting nucleotide insertion, small in-frame deletion, and splice-site variants have been reported [Goldfarb et al 2004]. See Table 2.

Table 2. Selected *DES* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.517_537del	p.Arg173_Glu179del	NM_001927.3 NP_001918.3

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. Desmin, comprising 470 amino acids, is a constituent of intermediate filaments in cardiac and skeletal muscle linking Z-disks with each other and to the subsarcolemmal cytoskeleton.

Abnormal gene product. Expression data suggest abnormal aggregation of mutated desmin molecules in heterologous systems. Pathogenic variants may interfere with desmin assembly and filament formation [Bär et al 2006].

CRYAB

Gene structure. *CRYAB* consists of three exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. A nonsense variant, a missense variant, and a small frameshifting deletion have been reported [Vicart et al 1998, Selcen & Engel 2003]. Recently, autosomal recessive inheritance was shown for the p.Ser115ProfsTer14 [Forrest et al 2011] and Ser21AlafsTer24 [Del Bigio et al 2011] frameshift variants. See Table 3.

Table 3. Selected *CRYAB* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.60delC [1]	p.Ser21AlafsTer24	NM_001885.1 NP_001876.1
c.343delT [2]	p.Ser115ProfsTer14	
c.358A>G	p.Arg120Gly	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Del Bigio et al [2011]
2. Homozygosity in an affected individual for this pathogenic variant in an autosomal recessive form of MFM [Forrest et al 2011]

Normal gene product. Alpha crystallin B chain (α-B crystallin) is a small heat-shock chaperone protein required for maintaining the structural integrity of desmin. It is composed of 175 amino acid residues.

Abnormal gene product. Mutated alpha crystallin B chain molecules form smaller molecular-weight polymers than wild type in human muscle. In heterologous cells that constitutively express desmin, misfolded desmin molecules appear in aggregates.

MYOT (*TTID*)

Gene structure. *MYOT* consists of ten exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Five missense variants have been reported; all are in exon 2 [Hauser et al 2000, Hauser et al 2002, Selcen & Engel 2004]. See Table 4.

Table 4. Selected *MYOT* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.170C>T	p.Thr57Ile	NM_006790.2 NP_006781.1

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. Myotilin is a key Z-disk protein that interacts with α-actinin, filamin-C, and actin. It has 498 amino acid residues.

Abnormal gene product. Mutated myotilin is predicted to weaken the linkage of Z-disk filaments to thin filaments. Transgenic mice with the p.Thr57Ile pathogenic variant and muscle disease similar to LGMD1A have been described [Garvey et al 2006].

LDB3 (*ZASP*)

Gene structure. *LDB3* consists of 16 exons. It is alternatively spliced. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Three missense variants have been reported [Selcen & Engel 2005]. See Table 5.

Table 5. Selected *LDB3* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.440C>T [1]	p.Ala147Val	NM_001080116.1 NP_001073585.1

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Presents as a distal myopathy (see Genotype-Phenotype Correlations)

Normal gene product. LIM domain-binding protein 3 (Zasp) is a key Z-disk protein that interacts with α-actinin and protein kinase C. It has 283 amino acid residues.

Abnormal gene product. Mutated LIM domain-binding protein 3 (Zasp) is predicted to weaken the linkage of Z-disk filaments to thin filaments.

FLNC

Gene structure. Two *FLNC* transcript variants encoding different isoforms have been found for this gene (see Table A, **Gene**). The longer isoform, NM_001458.4, consists of 48 exons.

Pathogenic variants. One nonsense variant and in-frame deletions have been reported [Vorgerd et al 2005, Shatunov et al 2009, Luan et al 2010].

Normal gene product. Filamin-C is a Z-disk protein that interacts with actin and myotilin. The protein NP_001449.3 has 2725 amino acid residues.

Abnormal gene product. Mutated filamin-C has a disturbed secondary structure that prevents normal dimerization.

BAG3

Gene structure. *BAG3* consists of four exons. No splice variants have been identified. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The variant p.Pro209Leu has been reported [Selcen et al 2009]. See Table 6.

Table 6. Selected *BAG3* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.626C>T	p.Pro209Leu	NM_004281.3 NP_004272.2

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. BAG family molecular chaperone regulator 3 (Bag3) is a co-chaperone for the Z-disk and has anti-apoptotic properties. It has 575 amino acid residues.

Abnormal gene product. Mutated Bag3 may alter the folding of Bag3 or may allosterically affect the binding properties of the canonical Bag3 domains.

FHL1

Gene structure. *FHL1* has three alternatively spliced transcript variants that encode different protein isoforms with different tissue localizations and protein interactions. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Selected reports of pathogenic variants include Quinzii et al [2008], Schessl et al [2008], Windpassinger et al [2008], Selcen et al [2011].

Normal gene product. FHL1 is a Z-disk related protein and some of its isoforms shuttle between cytoplasm and nucleus.

Abnormal gene product. Not known; likely dominant-negative effect.

DNAJB6

Gene structure. *DNAJB6* has published two alternatively spliced transcript variants that encode different protein isoforms. The longer transcript variant, NM_058246.3, has ten exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants have been reported [Harms et al 2012, Sarparanta et al 2012].

Normal gene product. The transcript NM_005494.2 encodes a protein isoform with 241 amino acid residues (NP_005485.1). DnaJ homolog subfamily B member 6 (DNAJB6) is a member of heat shock protein family with molecular chaperone function.

Abnormal gene product. In vitro studies demonstrated that the pathogenic missense variants increase the half-life of DNAJB6 and reduce its anti-aggregation effect [Sarparanta et al 2012].

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Chapter Notes

Revision History

- 9 May 2019 (ma) Chapter retired: histologic diagnosis without strong genetic correlation
- 29 October 2012 (me) Comprehensive update posted live
- 27 July 2010 (cd) Revision: sequence analysis for *BAG3* mutations available clinically
- 2 February 2010 (me) Comprehensive update posted live
- 10 March 2008 (cd) Revision: sequence analysis and prenatal diagnosis available clinically for zaspopathy (*LDB3* mutations)
- 1 March 2007 (me) Comprehensive update posted live

- 9 January 2006 (ds) Revision: included disorders added (zaspopathy, filaminopathy)
- 1 July 2005 (ds) Revision: *DES* testing clinically available
- 28 January 2005 (me) Review posted live
- 2 August 2004 (ds) Original submission

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