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Dysferlinopathy

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Summary

Clinical characteristics

Dysferlinopathy includes a spectrum of muscle disease characterized by two major phenotypes: Miyoshi muscular dystrophy (MMD) and limb-girdle muscular dystrophy type 2B (LGMD2B); and two minor phenotypes: asymptomatic hyperCKemia and distal myopathy with anterior tibial onset (DMAT).

- **MMD** (median age of onset 19 years) is characterized 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. The forearms may become mildly atrophic with decrease in grip strength; the small muscles of the hands are spared.
- **LGMD2B** is characterized by early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood, with slow progression. Other phenotypes in this spectrum are scapuloperoneal syndrome and congenital muscular dystrophy.
- **Asymptomatic hyperCKemia** is characterized by marked elevation of serum CK concentration only.
- **DMAT** is characterized by early and predominant distal muscle weakness, particularly of the muscles of the anterior compartment of the legs.

Diagnosis/testing

The diagnosis of dysferlinopathy is established in a proband with suggestive findings and biallelic pathogenic variants in *DYSF* identified by molecular genetic testing.

Management

Treatment of manifestations: There is no approved therapy for dysferlinopathy. Treatment is symptomatic only. Management should be tailored to the individual and the specific subtype. Individualized management may include physical therapy, use of mechanical aids, surgical intervention for orthopedic complications, respiratory aids, and social and emotional support.

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Surveillance: Annual monitoring of muscle strength, physical function, activities of daily living, joint range of motion, balance, and respiratory function, and for evidence of cardiomyopathy for individuals with cardiac involvement.

Agents/circumstances to avoid: Weight control to avoid obesity.

Genetic counseling

Dysferlinopathy is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *DYSF* pathogenic variant, each sib of an affected individual has at conception 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 the *DYSF* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

Dysferlinopathy: Included Phenotypes
• Miyoshi muscular dystrophy (Miyoshi myopathy) • Limb-girdle muscular dystrophy type 2B • Asymptomatic hyperCKemia • Distal myopathy with anterior tibial onset

For synonyms and outdated names see Nomenclature.

Diagnosis

No consensus clinical diagnostic criteria for dysferlinopathy have been published.

Suggestive Findings

Dysferlinopathy should be suspected in those with suggestive findings of major phenotypes and considered in those with suggestive findings of minor phenotypes. The diagnosis should be informed by family history.

Major Phenotypes

Dysferlinopathy **should be suspected** in individuals with suggestive findings of the **two major phenotypes**, Miyoshi muscular dystrophy and limb-girdle muscular dystrophy 2B, based on the following findings [Izumi et al 2020].

Miyoshi muscular dystrophy (MMD)

- Mid- to late-childhood or early-adult onset; mean age at onset 19.0 years
- Early and predominant distal muscle weakness affecting the upper and lower limbs, particularly the calf muscles (i.e., gastrocnemius and soleus muscles)
- Slow progression
- Elevation of serum CK concentration, often 10-100 times normal; mean CK: 8,940 IU/L
- Primarily myogenic pattern on EMG

Limb-girdle muscular dystrophy 2B (LGMD2B)

- Predominant early weakness and atrophy of the pelvic and shoulder girdle muscles
- Onset in the proximal lower-limb musculature in the late teens or later
- Slow progression
- Massive elevation of serum CK concentration

- Subclinical involvement of distal muscles, identified by careful examination or ancillary investigations such as muscle CT scan and MRI

Minor Phenotypes

Dysferlinopathy **should be considered** in individuals with suggestive findings of the following **two minor phenotypes**:

- **Asymptomatic hyperCKemia,** characterized by marked elevation of serum CK concentration only
- **Distal myopathy with anterior tibial onset (DMAT),** characterized by early and predominant distal muscle weakness affecting the lower limbs, particularly the muscles of the anterior compartment of the legs.

Family History

A family history consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity) should inform the consideration of dysferlinopathy in individuals with suggestive findings of the above major and minor phenotypes. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of dysferlinopathy **is established** in a proband with Suggestive Findings and biallelic pathogenic variants in *DYSF* identified by molecular genetic testing (see Table 1).

Note: Identification of biallelic *DYSF* variants of uncertain significance (or identification of one known *DYSF* pathogenic variant and one *DYSF* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of a dysferlinopathy has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *DYSF* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: RNA analysis of *DYSF* in myogenic cells may help identify deeper intronic pathogenic variants and variants affecting splicing (see Molecular Genetics, ***DYSF*-specific laboratory technical considerations**).

A muscular dystrophy multigene panel that includes *DYSF* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options

may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Dysferlinopathy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
DYSF	Sequence analysis [3]	98.6% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	1.4% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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.
4. Izumi et al [2020]
5. Includes pathogenic variants deep within *DYSF* intron 50i [Dominov et al 2019]. See also Molecular Genetics, ***DYSF*-specific laboratory technical considerations**.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Dysferlinopathy includes a spectrum of muscle disease characterized by two major phenotypes (Miyoshi muscular dystrophy [MMD] and limb-girdle muscular dystrophy type 2B [LGMD2B]) and two minor phenotypes (asymptomatic hyperCKemia and distal myopathy with anterior tibial onset [DMAT]) [Ueyama et al 2002]. The major and minor phenotypes can occur within families having the same pathogenic variants [Liu et al 1998, Weiler et al 1999, Illarioshkin et al 2000, Nakagawa et al 2001, Ueyama et al 2001].

The weakness and atrophy may be asymmetric with any of these presentations.

Miyoshi muscular dystrophy. Young adults have muscle weakness and atrophy most marked in the distal part of the legs, especially the gastrocnemius and soleus muscles. Early on, affected individuals are not able to stand on tiptoe, but retain the ability to stand on the heels. Over a period of years, the weakness and atrophy spread to the thighs and gluteal muscles, at which time climbing stairs, standing, and walking become difficult. The forearms may become mildly atrophic with decrease in grip strength; the small muscles of the hands are spared. The weakness may eventually include the shoulder girdle muscles [Mahjneh et al 2001].

Limb-girdle muscular dystrophy type 2B is characterized by early weakness and atrophy of the pelvic and shoulder girdle muscles that begins in adolescence or young adulthood, with slow progression. The spectrum of

muscle involvement can also on occasion manifest as the scapuloperoneal syndrome with initial weakness of the shoulder girdle muscles combined with distal weakness of the legs or congenital muscular dystrophy with early onset – as observed, for example, in two sibs with hypotonia beginning between birth and age two months who had delayed motor development and serum CK concentrations that were normal or slightly elevated before age three years [Paradas et al 2009].

Asymptomatic hyperCKemia. Some individuals have only a marked elevation of serum CK concentration. This is usually considered a presymptomatic presentation of myopathy in an individual who eventually develops muscle weakness and atrophy. Sometimes the calf muscles are enlarged; this presentation may be confused with a dystrophinopathy (i.e., Duchenne or Becker muscular dystrophy).

Distal myopathy with anterior tibial onset is characterized by leg weakness that involves the muscles of the anterior compartment of the leg, causing foot drop [Illa et al 2001].

Table 2. Dysferlinopathy: Comparison of Phenotypes by Select Features

Feature	MMD	LGMD2B	**Asymptomatic hyperCKemia**	**DMAT**
Percent	49.8% [1]	39.2% [1]	6.2% [1]	0.5% [1]
Mean age at onset (range)	22.1 yrs [1] (10-48)	28.2 yrs [1] (10-63)	Asymptomatic	20 yrs [1] (20-20)
Average age when use of a cane is required (yrs after onset)	35.5 yrs [2] (16 yrs)	39.3 yrs [2] (13.6 yrs)	Asymptomatic	Unknown
Age when wheelchair bound (yrs after onset)	42.8 yrs [2] (22.8 yrs)	45.1 yrs [2] (21.4 yrs)	Asymptomatic	Unknown
Median CK level	4,440 [1]	3,481 [1]	7,156 [1]	1,000 [1]
Cardiac complications	3.6% [3]		Asymptomatic	Unknown
Respiratory complications	22.8% [3]		Asymptomatic	Unknown

DMAT = distal myopathy with anterior tibial onset; LGMD2B = limb-girdle muscular dystrophy type 2B; MMD = Miyoshi muscular dystrophy

1. Izumi et al [2020]

2. Takahashi et al [2003b]

3. Harris et al [2016]. Note that the authors did not distinguish between phenotypes.

Histology. Muscle biopsy shows evidence of a dystrophy with random variation in fiber size and evidence of degeneration and regeneration. Type I fibers may predominate. There is often evidence of inflammation, sometimes leading to a misdiagnosis of polymyositis.

Genotype-Phenotype Correlations

Studies have reported genotype-phenotype correlates with the following two pathogenic variants [Takahashi et al 2003a, Takahashi et al 2013, Izumi et al 2020]:

- c.2997G>T was associated with a milder form of Miyoshi muscular dystrophy and LGMD2B
- c.3373delG was associated with Miyoshi muscular dystrophy.

Nomenclature

Dysferlinopathy was originally called LGMD2B because at the time that it was mapped to 2p13 it was the second form (2) of autosomal recessive (B) limb-girdle muscular dystrophy (LGMD) to be mapped. The gene for Miyoshi muscular dystrophy and the gene for LGMD2B were mapped to the same genetic interval at chromosome 2p13. Two groups independently identified a novel human skeletal muscle gene, *DYSF*, at this locus and documented that *DYSF* pathogenic variants cause both Miyoshi muscular dystrophy and LGMD2B.

Prevalence

The prevalence is not known. In the initial (1967) description of Miyoshi muscular dystrophy, four affected individuals in two families were from Japan.

Subsequently, Tagawa et al [2003] examined 107 unrelated Japanese individuals, including 53 with unclassified LGMD, 28 with Miyoshi muscular dystrophy, and 26 with other neuromuscular disorders. Using expression of dysferlin protein by immunohistochemistry (IHC) and mini-multiplex western blotting, they found deficiency of dysferlin protein by both methods in 19% of individuals with LGMD and 75% of individuals with Miyoshi muscular dystrophy.

In Libyan Jews, the prevalence of dysferlinopathy is at least 1:1,300, with a carrier rate of approximately 10% for the variant c.4872delG [Argov et al 2000].

A founder variant, c.2779delG, has been identified in Jews of the Caucasus [Leshinsky-Silver et al 2007].

A founder variant, c.5713C>T, has been identified in individuals from Spain [Vilchez et al 2005].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DYSF*.

Differential Diagnosis

Limb-girdle muscular dystrophies. Dysferlinopathy needs to be distinguished from other autosomal recessive limb-girdle muscular dystrophies (see OMIM Phenotypic Series: LGMD, autosomal recessive). Individuals with LGMD generally show weakness and wasting restricted to the limb musculature, proximal greater than distal. Most individuals with LGMD show relative sparing of the heart and bulbar muscles, although exceptions occur depending on the genetic subtype. Onset, progression, and distribution of the weakness and wasting vary considerably among individuals and genetic subtypes.

Multigene panels are increasingly used to identify pathogenic variants and confirm a diagnosis of a specific form of LGMD.

Dystrophinopathies. The dystrophinopathies cover a spectrum of X-linked muscle disease (associated with pathogenic variants in *DMD*) ranging from mild to severe that includes Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and *DMD*-associated dilated cardiomyopathy. DMD usually presents in early childhood with delayed motor milestones including delays in walking independently and standing up from a supine position. BMD is characterized by later-onset skeletal muscle weakness.

Distal myopathies. See Table 3.

Table 3. Distal Myopathies

Gene	Disorders	MOI	Mean Age at Onset (Yrs)	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Muscle Biopsy
GNE	*GNE* myopathy (Nonaka distal myopathy)	AR	20-40	Anterior compartment in legs	Normal or ↑; typically ≤4x normal	Rimmed vacuoles
LDB3 (*ZASP*)	Myofibrillar myopathy 4 (OMIM 609452)	AD	>40	Anterior compartment in legs	Normal or slightly ↑	Vacuolar & myofibrillar myopathy

Table 3. continued from previous page.

Gene	Disorders	MOI	Mean Age at Onset (Yrs)	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Muscle Biopsy
MATR3	Amyotrophic lateral sclerosis 21 (formerly MPD2) (See ALS Overview.)	AD	35-60	Asymmetric lower leg & hands; dysphonia	1-8x normal	Rimmed vacuoles
MYH7	Laing distal myopathy	AD	<5	Ankle & great toe extensors	Usually normal; rarely 8x normal	Type I fiber atrophy in tibial anterior muscles; disproportion in proximal muscles
MYOT	Myofibrillar myopathy 3 (OMIM 609200)	AD	>40	Posterior > anterior in legs	Slightly ↑	Vacuolar & myofibrillar myopathy
TIA1	Welander distal myopathy (OMIM 604454)	AD AR	>40	Intrinsic muscles of hand & extensor pollicus longus	Normal	Rimmed vacuoles
TTN	Udd distal myopathy – tibial muscular dystrophy	AD	>30	Anterior compartment in legs	Normal or slightly ↑	± Rimmed vacuoles

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

Distal myopathies of unknown genetic cause:

- Distal myopathy with *pes cavus* and areflexia (OMIM 601846) is associated with onset between ages 15 and 50 years; the anterior and posterior lower legs are involved initially, serum creatine kinase concentration is elevated to two to six times normal, and muscle biopsy is dystrophic with rimmed vacuoles. This disorder is also associated with dysphonia and dysphagia.
- New Finnish distal myopathy (MPD3; OMIM 610099) is associated with mean onset after age 30 years; the hands or anterior lower legs are involved initially, serum creatine kinase concentration ranges from normal to approximately three times normal, and muscle biopsy is dystrophic with rimmed vacuole and eosinophilic inclusions.

Management

No clinical practice guidelines for dysferlinopathy have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with dysferlinopathy, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Dysferlinopathy

System/Concern	Evaluation	Comment
Musculoskeletal	Neuromuscular, physical medicine & rehab / PT/OT eval	To evaluate extent of disease as determined by: • Muscle strength & function in arms, hands, legs (esp calves), & feet • Balance • Function • Fine motor skills • Impact on activities of daily living • Need for ongoing PT & OT • Need for AFOs & assistive ambulatory devices • Need for adaptive devices • Need for handicapped parking
Respiratory	PFTs incl supine & sitting spirometry, MIP, MEP	To evaluate for effects of muscle weakness on respiratory function, esp in nonambulatory persons
Cardiac	Baseline echocardiogram	To evaluate for evidence of cardiac involvement (cardiomegaly, cardiomyopathy, arrhythmia)
Genetic counseling	By a genetics professional [1]	To review results of genetic testing & to inform patients & families re nature, MOI & implications of dysferlinopathy in order to facilitate medical & personal decision making
Family support/ resources		Assess: • Use of community or online resources, incl patient advocacy organizations; • Need for social work involvement for caregiver support.

AFOs = ankle-foot orthoses; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; MOI = mode of inheritance; OT = occupational therapy; PFTs = pulmonary function tests; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no approved therapy for dysferlinopathy. Treatment is symptomatic only.

Management should be tailored to the individual and the specific subtype. A general approach to appropriate management can prolong survival and improve quality of life.

Table 5. Treatment of Manifestations in Individuals with Dysferlinopathy

Manifestation/ Concern	Treatment	Considerations/Other
Musculoskeletal	PT, rehabilitation medicine	Ambulatory assistive devices, balanced physical activity [1], stretching exercises to promote mobility & prevent contractures; regular exercise as tolerated
	Orthopedic surgery	As needed for complications incl foot deformity & scoliosis
Activities of daily living	PT	• Transfers (e.g., from bed to wheelchair, wheelchair to car) • Medical alert system for those unable to stand after a fall
	OT	• Techniques & devices to accomplish tasks incl mobility, washing, dressing, eating, cooking, grooming • To assist w/household modifications to meet special needs
Respiratory	Respiratory function	Per treating pulmonologist; a concern mostly in nonambulatory persons

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family support/ resources	Social & emotional support & stimulation	To maximize sense of social involvement & productivity & ↓ sense of social isolation common in these disorders

OT = occupational therapy; PT = physical therapy
1. All affected persons should consult their physician before beginning an exercise program.

Surveillance

Routine follow up with the multidisciplinary team (annually or more frequently as determined by managing physician) is recommended. See Table 6.

Table 6. Recommended Multidisciplinary Team Surveillance for Individuals with Dysferlinopathy

System/Concern	Evaluation	Frequency
Neuromuscular	Evaluate disease progression & coordinate care.	At least annually
Rehabilitation medicine	Eval & monitoring of: • Muscle strength testing using a quantitative scale (e.g., MMT, hand-held dynamometry, QMA [1]) to evaluate progressive muscle involvement • Physical function (e.g., 6-min walk test, AMAT [2]) • Activities of daily living	At least annually
PT	Eval & mgmt for balance & need for AFOs, cane, walker, wheelchair. & powerchair	At least annually, or more frequently based on needs
OT	Eval & mgmt of fine motor skills & hand function, such as Jebsen Hand Function Test [3]	At least annually
Respiratory	PFTs incl supine & sitting spirometry, MIP, MEP on affected persons at advanced stages of disease	As needed, if symptomatic or abnormal PFTs
Cardiac		Follow up not needed unless symptomatic or findings on initial eval were abnormal
Family support/ resources	Assess social & emotional support & stimulation.	At least annually

AFOs = ankle-foot orthoses; AMAT = Adult Myopathy Assessment Tool; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; MMT = manual muscle testing; OT = occupational therapy; PFTs = pulmonary function tests; PT = physical therapy; QMA = Quantitative Muscle Assessment
1. Visser et al [2003]
2. Harris-Love et al [2015]
3. Jebsen et al [1969]

Agents/Circumstances to Avoid

Control weight to avoid obesity; avoid use of steroids [Walter et al 2013].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Comparison of the effect of prednisolone with vamorolone on dysferlin-deficient myofiber repair showed that vamorolone stabilized dysferlin-deficient muscle cell membrane and improved repair of dysferlin-deficient mouse myofibers [Sreetama et al 2018].

Exon skipping is a therapeutic approach that is feasible for various genetic disorders [Rodrigues & Yokota 2018]. Dominov et al [2019] designed antisense oligonucleotides (AONs) to bypass the effect of the affected individual's pathogenic variant on RNA splicing. AON-mediated exon skipping corrected the aberrant pseudoexon splicing events in vitro, which increased normal mRNA production and significantly restored dysferlin protein expression [Dominov et al 2019].

Ono et al [2020] recently demonstrated that AMP-activated protein kinase (AMPK)γ1 was bound to a region of dysferlin, and AMPK complex was vital for the sarcolemmal damage repair of skeletal muscle fibers. Treatment with an AMPK activator rescued the membrane-repair impairment observed in immortalized human myotubes with reduced expression of dysferlin and dysferlin-null mouse fibers [Ono et al 2020].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register 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.

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

Dysferlinopathy is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *DYSF* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *DYSF* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *DYSF* pathogenic variant, each sib of an affected individual has at conception 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.

- Intrafamilial clinical variability may be observed between sibs who inherit biallelic *DYSF* pathogenic variants; for example, Miyoshi muscular dystrophy, limb-girdle muscular dystrophy type 2B, and distal myopathy with anterior tibial onset have been reported in the same family [Saito et al 2007].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with dysferlinopathy are obligate heterozygotes (carriers) for a pathogenic variant in *DYSF*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *DYSF* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal and preimplantation genetic 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 carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DYSF* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **Jain Foundation Inc.**

  The Jain Foundation is a non-profit foundation whose mission is to diagnose and cure limb girdle muscular dystrophies caused by dysferlin protein deficiency (LGMD2B/Miyoshi Myopathy).

  2310 130th Avenue Northeast

  Suite B101

  Bellevue WA 98005

  Phone: 425-882-1440

  Email: ehwang@jain-foundation.org

  www.jain-foundation.org

- **Muscular Dystrophy Association (MDA) - USA**

  Phone: 833-275-6321

Email: ResourceCenter@mdausa.org

mda.org

- **Muscular Dystrophy UK**

  United Kingdom

  Phone: 0800 652 6352

  musculardystrophyuk.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. Dysferlinopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DYSF	2p13.2	Dysferlin	DYSF homepage - Leiden Muscular Dystrophy pages	DYSF	DYSF

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 Dysferlinopathy (View All in OMIM)

253601	MUSCULAR DYSTROPHY, LIMB-GIRDLE, AUTOSOMAL RECESSIVE 2; LGMDR2
254130	MIYOSHI MUSCULAR DYSTROPHY 1; MMD1
603009	DYSFERLIN; DYSF

Molecular Pathogenesis

Dysferlin is expressed in the plasma membrane of skeletal muscles and is involved in calcium-mediated membrane fusion events and plasma membrane repair [Bansal et al 2003, Lennon et al 2003].

Mechanism of disease causation. Loss-of-function variants result in very low levels of dysferlin expression in skeletal muscle membranes.

***DYSF*-specific laboratory technical considerations**

- *DYSF* RNA analysis from muscle cells or myogenic cells transduced from skin fibroblasts can be useful in identifying variants affecting splicing [Dominov et al 2019].
- Dysferlin immunohistochemical and immunoblot analyses on muscle tissue that identify dysferlin protein deficiency can assist in interpretation of variants of uncertain significance. However, dysferlin expression can also be reduced in other muscular dystrophies: dystrophinopathy [Piccolo et al 2000], sarcoglycanopathy [Piccolo et al 2000], caveolinopathy [Matsuda et al 2001], and calpainopathy [Tagawa et al 2003].

Table 7. Notable *DYSF* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_003494.4 NP_003485.1	c.2779delG	p.Ala927LeufsTer21	Founder variant in Jews of the Caucasus [Leshinsky-Silver et al 2007]
	c.2997G>T	p.Trp999Cys	Common variant assoc w/milder form [Izumi et al 2020]
	c.3373delG	p.Glu1125LysfsTer9	Common variant assoc w/MMD [Izumi et al 2020]
	c.4872delG (1624delG)	p.Glu1624AspfsTer10	Founder variant in Libyan Jewish population [Argov et al 2000]
	c.5713C>T (6086C>T)	p.Arg1905Ter	Founder variant in Spain [Vilchez et al 2005]
NG_008694.1	c.5668-824C>T	p.Lys1889_Asp1890insTer47	Common variant that results in inclusion of pseudoexon 50.1 [Dominov et al 2019]

MMD = Miyoshi muscular dystrophy
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Revision History

- 27 May 2021 (bp) Comprehensive update posted live
- 5 March 2015 (me) Comprehensive update posted live
- 22 April 2010 (me) Comprehensive update posted live
- 19 April 2006 (me) Comprehensive update posted live
- 5 February 2004 (me) Review posted live
- 24 September 2003 (ma) Original submission

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