



X-Linked Myotubular Myopathy

Synonyms: Myotubular Myopathy (MTM), XLCNM, X-Linked Centronuclear Myopathy, XLMTM

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Summary

Clinical characteristics

X-linked myotubular myopathy (X-MTM), also known as myotubular myopathy (MTM), is characterized by muscle weakness that ranges from severe to mild.

Approximately 80% of affected males present with severe (classic) X-MTM characterized by polyhydramnios, decreased fetal movement, and neonatal weakness, hypotonia, and respiratory failure. Motor milestones are significantly delayed and most individuals fail to achieve independent ambulation. Weakness is profound and often involves facial and extraocular muscles. Respiratory failure is nearly uniform, with most individuals requiring 24-hour ventilatory assistance. It is estimated that at least 25% of boys with severe X-MTM die in the first year of life, and those who survive rarely live into adulthood.

Males with mild or moderate X-MTM (~20%) achieve motor milestones more quickly than males with the severe form; many ambulate independently, and may live into adulthood. Most require gastrostomy tubes and/or ventilator support. In all subtypes of X-MTM, the muscle disease is not obviously progressive. Female carriers of X-MTM are generally asymptomatic, although manifesting heterozygotes are increasingly being identified. In affected females, symptoms range from severe, generalized weakness presenting in childhood, with infantile onset similar to affected male patients, to mild (often asymmetric) weakness manifesting in adulthood. Affected adult females may experience progressive respiratory decline and ultimately require ventilatory support.

Diagnosis/testing

The diagnosis of X-MTM is established in a proband with suggestive clinical findings and identification of a hemizygous pathogenic variant in *MTM1* by molecular genetic testing.

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Management

Treatment of manifestations: Treatment is supportive. Management optimally involves a team of specialists with expertise in the long-term care of children and/or adults with neuromuscular disorders, often including a pulmonologist, neurologist, physical therapist and/or rehabilitation medicine specialist, and clinical geneticist. Tracheostomy, G-tube feeding, and assistive communication devices are often required. Ophthalmologists, orthopedists, and orthodontists should address specific medical complications related to the underlying myopathy.

Surveillance: Annual pulmonary assessment; polysomnography every one to three years; routine examination for scoliosis; annual ophthalmologic examinations to evaluate for ophthalmoplegia, ptosis, and myopia; routine assessment for dental malocclusion.

Genetic counseling

X-MTM is inherited in an X-linked manner. The risk to sibs of a male proband depends on the carrier status of the mother. If the mother is a carrier, each sib has a 50% chance of inheriting the *MTM1* pathogenic variant. Males who inherit the variant will be affected; females who inherit the variant will be carriers and will generally not be affected. To date, there are no reported males with incomplete penetrance. In simplex cases (i.e., a single occurrence in a family), there is a probability of 80%-90% that a woman is a carrier if her son has a confirmed *MTM1* pathogenic variant. Thus, about 10%-20% of males who represent simplex cases have a *de novo* pathogenic variant in *MTM1* and a mother who is not a carrier. Germline mosaicism has been reported. Carrier testing of at-risk female relatives and prenatal testing for a pregnancy at risk are possible if the *MTM1* pathogenic variant has been identified in an affected male relative.

Diagnosis

Suggestive Findings

The diagnosis of X-linked myotubular myopathy (X-MTM), also known as myotubular myopathy (MTM), **should be suspected in any male** with the following clinical and histopathologic features.

Clinical features

- Neonatal hypotonia
- Neonatal respiratory failure
- Significant and diffuse muscle weakness
- Diminished muscle bulk
- A family history suggestive of X-linked inheritance
- Length and head circumference >90th centile
- Cryptorchidism
- Long fingers and toes
- Involvement of the extraocular muscles (i.e., ophthalmoparesis)

Histopathologic features on muscle biopsy [Lawlor et al 2016]

- Numerous small, rounded myofibers with internally located nuclei that are present at (or very near) the center of a myofiber. The nucleus often appears very large in comparison to the small fiber size.
- Aberrant accumulation of centrally located staining with oxidative stains (SDH and NADH) and glycogen stains (PAS), often in conjunction with a halo-like area of subsarcolemmal clearing on these stains
- Small, predominant type I fibers

- Necklace fibers on hematoxylin-eosin stained sections and with succinate dehydrogenase staining; present in some individuals with sporadic late-onset X-MTM as a basophilic ring-like deposit that follows the contour of the myofiber and aligns with internal myonuclei

The diagnosis of X-MTM **should be considered in females** with the following clinical and histopathologic features:

- Mild to moderate extremity weakness in a limb girdle pattern, often with prominent asymmetry
- Asymmetric muscle growth
- Facial weakness, ptosis, and ophthalmoparesis
- A family history suggestive of X-linked inheritance (affected females may not have a family history of X-MTM)
- Necklace fibers on muscle biopsy, or features of typical centronuclear myopathy

Establishing the Diagnosis

Male proband. The diagnosis of X-MTM **is established** in a male proband with suggestive clinical findings and a hemizygous pathogenic variant in *MTM1* identified by molecular genetic testing (see Table 1).

Female proband. The diagnosis of X-MTM **is usually established** in a female proband with suggestive clinical findings and a heterozygous pathogenic variant in *MTM1* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing, exome array) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of X-MTM is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with myopathy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of X-MTM, molecular genetic testing approaches can include a **multigene panel** or **single-gene testing**:

- **A multigene panel** that includes *MTM1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Single-gene testing.** Rarely, single-gene testing can be considered under the appropriate circumstances. These include: (a) a male child with weakness and a positive family history of X-MTM; or (b) a severely

affected male infant with physical features consistent with X-MTM, including diffuse weakness, ophthalmoparesis, and length and head circumference >90th centile. Sequence analysis of *MTM1* is performed first and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by myopathy, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 X-Linked Myotubular Myopathy

Gene ¹	Method	Proportion of Pathogenic Variants ² Detectable by Method
<i>MTM1</i>	Sequence analysis ³	~90% ^{4, 5}
	Gene-targeted deletion/duplication analysis ⁶	~10% ⁷

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. de Gouyon et al [1997], Laporte et al [1997], Herman et al [2002], Tsai et al [2005]

5. The occurrence of deep intronic pathogenic variants has been described [Tosch et al 2010, Al-Hashim et al 2017]; these inform the choice of molecular testing method.

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

7. Laporte et al [2000], Amburgey et al [2013b], Oliveira et al [2013]

Clinical Characteristics

Clinical Description

The clinical characteristics and disease course of X-linked myotubular myopathy (X-MTM) have been described in two retrospective natural history studies including nearly 200 genetically confirmed probands [Amburgey et al 2017, Beggs et al 2018]. One study included a prospective one-year survey in addition to retrospective analysis [Amburgey et al 2017].

Following isolation of *MTM1* in 1996, Herman et al [1999] described a clinical classification for the broader phenotype. Individuals with *MTM1* pathogenic variants were classified as having one of the following:

- **Severe (classic) X-MTM.** Characteristic facies, chronic ventilator dependence, delayed gross motor milestones, inability to independently ambulate, and high incidence of death in infancy. This is by far the most common form of the disease (~80% of all individuals with X-MTM).
- **Moderate X-MTM.** Less severely delayed motor milestones than in the severe form, prolonged periods of decreased ventilatory support

- **Mild X-MTM.** Ambulatory with minimally delayed motor milestones, chronic ventilatory support not required beyond the newborn period, and no/limited impact on life span

Since publication of the phenotypic classification by Herman et al [1999], a rare adult-onset form with slowly progressive myopathy and no clinical manifestations in infancy has been identified [Hoffjan et al 2006]. In addition, manifesting female heterozygotes are increasingly reported [Biancalana et al 2017, Felice et al 2018].

Severe/Classic X-MTM

In males with the severe/classic phenotype, polyhydramnios and decreased fetal movement are frequently reported. Premature delivery is described in approximately one third of males [Beggs et al 2018]. Hypotonia, extremity weakness, and respiratory distress are present during the newborn period. Ventilatory support is required due to respiratory failure [Amburgey et al 2017, Beggs et al 2018]. Hypoxic events may occur, leading to an acquired hypoxic ischemic encephalopathy. Prolonged ventilator dependence leads to an increased risk of respiratory infection, hypoventilation, and hypoxia.

Affected infants often have typical myopathic facies with dolichocephaly, high forehead, long face with midface retrusion, prominent eyes, narrow high-arched palate, and severe malocclusion. Ophthalmoparesis is also frequently observed. Additional features include length greater than the 90th centile with a proportionately lower weight (60% of infants), long fingers and/toes (43%), cryptorchidism and/or undescended testicle (>50%), contractures including clubfeet (30%), and areflexia (60%).

Most infants require lengthy NICU hospitalizations, with approximately 30%-50% of the first year spent in the hospital. Many infants with severe/classic X-MTM succumb to complications of the disorder. The percentage of infants that do not survive the first year of life has been difficult to determine. The reported causes of death are multifactorial, and include removal of ventilatory support. Approximately 25% of male infants die in the first year of life.

Most surviving males are discharged home on 24-hour ventilatory support via tracheostomy and gastrostomy tube feedings. In one study including all forms of X-MTM, 85% of individuals required ventilatory and G-tube support, and nearly all needed wheelchair support for ambulation [Amburgey et al 2017]. The estimated rate of mortality is 10% per year after age one, with few individuals surviving to adulthood. The cause of death is usually related to respiratory failure, though very rarely may be associated with hepatic peliosis.

The muscle disease may not be progressive. A prospective study of the ventilatory support requirements of 33 individuals over one year showed little change. Prospective analysis of muscle function in a small pilot group also detected no large changes over a one-year period [Amburgey et al 2017].

Interestingly, and despite the severe disability and technology dependence of the disease, the annual rate of nonelective hospitalization after the first year of life is not as high as would be expected. In a prospective study of 33 individuals, the rate was 1.1 emergency room visits per year [Amburgey et al 2017]. The rate of hospitalization is higher in very young individuals (age 1-2 years) [Amburgey et al 2017, Beggs et al 2018].

Additional features of the underlying myopathy are ophthalmoplegia, ptosis, and severe myopia. Dental malocclusion (requiring orthodontic care) may occur. Constipation is common. Scoliosis often develops in later childhood (75% of individuals in one study) and may require surgical intervention, though scoliosis surgery is documented in only a minority of individuals ($\leq 10\%$). Scoliosis can exacerbate respiratory insufficiency, in some cases causing ventilator-independent males to become ventilator dependent again as it progresses. Additional orthopedic manifestations include hip dysplasia and long bone fractures [Cahill et al 2007].

Hepatic peliosis. Liver hemorrhage due to hepatic peliosis is perhaps the most serious non-muscle-related complication in X-MTM. Several individuals have died following prolonged liver hemorrhage or hemorrhage

into the peritoneal cavity due to hepatic peliosis, a rare vascular lesion characterized by the presence of multiple blood-filled cysts within the liver [Motoki et al 2013]. This complication may occur in up to 5% of individuals.

Growth and pubertal development. Despite chronic illness and prolonged ventilator dependence, many individuals with X-MTM have linear growth above the 50th centile, with some individuals achieving greater than the 90th centile for height. Advanced bone age and/or premature adrenarche have been documented in several young males. However, endocrinologic studies performed on several individuals have been normal. Puberty has occurred normally in the few males who have reached adulthood.

Cognition. A recent natural history study identified that many children require special education for learning/cognitive impairments [Amburgey et al 2017]. This may be due to comorbid hypoxic ischemic encephalopathy, and there are rare individuals with central nervous system complications [McCrea et al 2009]. However, determination of whether there is a primary cognitive component to the disorder awaits further study.

Other. Several medical problems unrelated to the muscle disorder have been reported at low frequency. It is not entirely clear if these are due to *MTM1* pathogenic variants or unrelated comorbidities. They include pyloric stenosis (~5%), gastroesophageal reflux (10%), cardiac arrhythmias (10%; severity is unclear), gallstones (9%), kidney stones (10%), and elevated liver function tests (20%). Herman et al [1999] also identified some individuals with a mild form of spherocytosis and a vitamin K-responsive bleeding diathesis. These have not been recently reported and their presence in this population is unknown.

Mild and Moderate X-MTM

At least three reports of multigenerational families with *MTM1* pathogenic variants and a much milder phenotype have been described [Barth & Dubowitz 1998, Biancalana et al 2003, Yu et al 2003, Hoffjan et al 2006]. In the recent natural history study, 13% of study subjects could walk independently and were thus considered in the mild/moderate category; 2% required no support for ambulation, ventilation, or feeding.

Males with moderate or even mild disease are at increased risk for respiratory decompensation with intercurrent illness and may require transient or increased ventilatory support. They are also at risk for some of the same medical complications (including peliosis hepatis) as those with severe X-MTM [Herman et al 1999]. Most still require some respiratory support (which may be noninvasive), and typically also require feeding assistance.

There are several case reports describing adult males with mild disease and pathogenic variants in *MTM1*. These include two individuals in their 60s at the time of publication who first manifested limb girdle weakness after childhood (first symptoms age 18 and 52 years, respectively) [Biancalana et al 2003, Hoffjan et al 2006]. At least one of these males had facial weakness and ophthalmoparesis. Yu et al [2003] described two males with a pathogenic variant in *MTM1*, age 55 and 30 years, both of whom live independently. The 30-year-old developed some muscle weakness later in life and had decreased muscle bulk that was improved by diet and weight-lifting exercises.

Heterozygous females are generally asymptomatic, although symptomatic heterozygote females have been described [Savarese et al 2016, Biancalana et al 2017, Felice et al 2018]. Severity is variable, and some present with severe infantile weakness resembling that seen in affected males. More commonly, symptoms include mild/moderate asymmetric limb weakness and asymmetric reduction of muscle bulk in the correspondingly affected limbs. Facial weakness, ptosis, and ophthalmoparesis are often present. Respiratory failure is not uncommon, and can be unrecognized at the time of presentation.

Histopathologic features [Lawlor et al 2016]

- The characteristic muscle biopsy demonstrates numerous small, rounded myofibers with varying percentages of centrally located nuclei. The myofiber size may be uniform throughout the tissue, which may lead to underestimation of the decreased myofiber size (as there may be no appropriately sized fibers

for comparison). No diagnostic threshold of central nuclei has been established, as the percentage may increase over time. In rare instances, centrally located nuclei may be absent [Pierson et al 2007]. The combination of small myofiber size and central nucleation may result in the central nuclei comprising the majority of the cross-sectional area in some myofibers, which is not specific for X-MTM but is characteristic of severe centronuclear myopathies in very young individuals.

- Periodic acid-Schiff (PAS) and nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase histochemical staining often demonstrate an accumulation of staining product in the center of the small myofibers, reflecting (respectively) maldistribution of glycogen and mitochondria/sarcotubular organelles [Romero 2010]. In some cases, a particularly striking subsarcolemmal halo will be seen around these aggregates.
- ATPase histochemical staining may show type 1 myofiber predominance or small type 1 and type 2A fibers alongside relatively larger type 2B fibers [Pierson et al 2005]. All fiber types tend to show some degree of decreased myofiber size in most biopsies, however, and appropriately sized or large fibers may be rare or absent. In some biopsies, ATPase staining demonstrates myofibers with central clearing that results from a focal absence of myofibrils [Romero 2010].
- The histopathologic findings listed are not specific to X-MTM and may be encountered in congenital myotonic dystrophy type 1 (see Differential Diagnosis) and in early-onset autosomal forms of centronuclear myopathy. X-MTM with a low percentage of central nuclei and type 1 fiber predominance can also resemble congenital fiber type disproportion [Pierson et al 2005].

Note: (1) The clinical and histopathologic features of *MTM1*-associated myopathies are broad, requiring that a distinction be made between central and internal nuclei [Romero 2010]. The former occur at (or very near) the exact center of a myofiber and are typical of (although not specific for) X-MTM, whereas the latter are usually eccentrically situated within the myofiber and may alternatively be associated with other centronuclear myopathies or with chronic myofiber regeneration. (2) Necklace fibers are a distinctive feature that has been described in males with sporadic late-onset X-MTM as well as in manifesting heterozygous females [Biancalana et al 2017]. Necklace fibers appear on hematoxylin-eosin-stained sections as a basophilic ring-like deposit that follows the contour of the myofiber and aligns with internal myonuclei. They can also be visualized with succinate dehydrogenase histochemical staining [Bevilacqua et al 2009]. Necklace fibers may be accompanied by muscle hypotrophy and type 1 fiber predominance. The percentage of myofibers with internal nuclei frequently exceeds the percentage of fibers with central nuclei and both tend to increase with age. (3) Biopsies from older individuals may feature increased connective and adipose tissues.

Immunohistochemical stains on most (not all) muscle samples from individuals with X-MTM demonstrate persistence of fetal-specific muscle proteins or isoforms such as desmin, vimentin, and fetal myosin [Sarnat 1990, Sewry 1998]. Variation in the immunohistochemical expression of NCAM, utrophin, laminin, alpha 5, and HLA1 antigen has also been described [Helliwell et al 1998]. The clinical utility of these immunostains has not been systematically studied.

T-tubule disorganization visualized through immunohistochemistry has been described in X-MTM [Al-Qusairi et al 2009, Dowling et al 2009]. DHPRA1, a T-tubule protein, and RyR1, a sarcoplasmic reticulum protein, are abnormally distributed in myofibers with increased immunoreactivity appearing in the center of small fibers [Dowling et al 2009]. Levels of both proteins are also diminished, as demonstrated by western blot analysis [Bachmann et al 2017]. Since other centronuclear myopathies also have T-tubule defects, the specific diagnostic utility of this finding may be limited [Toussaint et al 2011].

Electron microscopy. Ultrastructurally, X-MTM is characterized by the disorganization or decreased number of triads (interfaces between the sarcotubular reticulum and T-tubules) in longitudinal sections. This has been well demonstrated in human patients and animal models of disease [Al-Qusairi et al 2009, Dowling et al 2009, Childers et al 2014], and quantitative studies have been performed in some animal treatment studies to assist in

the evaluation of therapeutic efficacy [Lawlor et al 2013, Lawlor et al 2016, Mack et al 2017]. These quantitative studies have been highly controlled in the collection and processing of the tissue, however, and quantification of triads or sarcotubular elements in the clinical diagnostic setting is not feasible.

Immunologic testing using antibodies specific for myotubularin, the protein encoded by *MTM1* [Laporte et al 2001b], can detect the presence or absence of myotubularin in cell lines from affected individuals. In 21/24 males with known pathogenic variants, including some missense variants, no myotubularin was detected on western blot. One out of five boys with suspected X-MTM in whom no pathogenic variant was identified also had no detectable protein by western analysis. Tosch et al [2010] demonstrated the absence of detectable protein in eight affected individuals with severe to intermediate phenotypes and a decreased amount of protein in an individual with a mild phenotype. Eight of nine individuals had confirmed *MTM1* pathogenic variants; one individual had no detectable protein and an intermediate phenotype, but no *MTM1* pathogenic variant was detected. While immunologic testing may be helpful in some individuals with suspected X-MTM in whom no pathogenic variant is found, such analysis is not routine, and adequate antibodies to myotubularin are not widely available.

Genotype-Phenotype Correlations

X-MTM is most frequently caused by nonsense, frameshift, and splice site variants that predict loss of function. Pathogenic variants are found throughout the gene with no concentration in any specific domain.

- Nonsense and frameshift variants nearly always result in the severe/classic X-MTM phenotype.
- Splice site and intronic variants may cause the severe presentation or can be associated with the milder phenotype.
- Missense variants can be associated with both severe and mild/moderate phenotypes.
- Variants associated with the phosphatase domain and the SET-interacting domain nearly always cause a severe phenotype. Pathogenic variants outside of these two domains are more likely to be associated with milder phenotypes [Amburgey et al 2017, Beggs et al 2018].
- A large number of pathogenic variants occur in hypermutable CpG dinucleotides; the most common is variant c.1261-10A>G in intron 11, which activates a cryptic splice site and produces an in-frame insertion of three amino acids in the core of the protein tyrosine phosphatase (PTP) site. This pathogenic variant is associated with a severe phenotype in males.

Penetrance

Penetrance is thought to be 100% in males with a pathogenic variant in *MTM1*, as all have shown findings of the disease. However, disease severity can range from mild to severe.

Carrier females are generally asymptomatic, though an increasing number of manifesting heterozygotes are being identified [Savarese et al 2016, Biancalana et al 2017, Felice et al 2018].

Nomenclature

X-MTM (or myotubular myopathy or X-linked centronuclear myopathy [X-CNM]) is considered a subtype of centronuclear myopathy based on the centrally located nuclei of muscle fibers on histologic examination, and based on shared pathogenic mechanisms. Autosomal dominant and autosomal recessive centronuclear myopathy should not be referred to as myotubular myopathy.

Males with X-MTM with identifiable pathogenic variants in *MTM1* are said to have X-linked myotubular myopathy or simply myotubular myopathy (MTM). This term should only be used to refer to individuals with documented or presumed *MTM1* pathogenic variants.

Prevalence

It has been estimated that X-MTM affects approximately one in 50,000 newborn males [Laporte et al 2001a]; careful, large studies attempting complete ascertainment have not been published.

Genetically Related (Allelic) Disorders

No other phenotype is known to be associated with pathogenic variants in *MTM1*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of X-Linked Myotubular Myopathy

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/X-MTM	Distinguishing from X-MTM
Congenital myotonic dystrophy type 1	<i>DMPK</i>	AD	<ul style="list-style-type: none"> • Polyhydramnios • ↓ fetal movements • Hypotonia • Myopathic facies • Respiratory distress • ID • Muscle biopsy possibly indistinguishable 	<ul style="list-style-type: none"> • Absence of ophthalmoparesis • AD family history
<i>DNM2</i> -related CNM (OMIM 160150)	<i>DNM2</i>	AD	<ul style="list-style-type: none"> • Hypotonia • Diffuse muscle weakness • Ptosis • Ophthalmoparesis • Myopathic facies • Muscle biopsy w/central nuclei 	<ul style="list-style-type: none"> • Clinical features possibly less severe • Normal/reduced growth parameters • "Spoke on wheel" changes w/ oxidative stains on muscle biopsy
<i>RYR1</i> -related CNM ¹	<i>RYR1</i>	AR	<ul style="list-style-type: none"> • Neonatal hypotonia • Weakness • Ophthalmoparesis • Ptosis • Myopathic facies • Severe respiratory compromise • Muscle biopsy w/central nuclei 	<ul style="list-style-type: none"> • Clinical features possibly less severe • Normal/reduced growth parameters • May have other non-MTM features on biopsy (cores, dystrophic changes)
<i>BIN1</i> -related CNM (OMIM 255200)	<i>BIN1</i>	AR	<ul style="list-style-type: none"> • Onset in infancy possible • Muscle biopsy w/central nuclei 	<ul style="list-style-type: none"> • Clinical features less severe • Normal growth parameters
<i>SPEG</i> -related CNM (OMIM 615959)	<i>SPEG1</i>	AR	<ul style="list-style-type: none"> • Onset in infancy • Diffuse weakness • Respiratory failure • Ophthalmoparesis • Muscle biopsy w/central nuclei 	<ul style="list-style-type: none"> • Can have prominent cardiac involvement • Biopsies may lack central nuclei.
Nemaline myopathy (OMIM PS161800)	>10 genes	AD AR	<ul style="list-style-type: none"> • Can present w/diffuse weakness starting in infancy, often w/ prominent facial weakness • Biopsies can feature myofiber hypotrophy & type I fiber predominance. 	<ul style="list-style-type: none"> • Ophthalmoparesis is rare (except in <i>LMOD3</i>-related nemaline myopathy). • Muscle biopsy showing nemaline rod aggregates (essentially never seen in X-MTM) • Central nuclei usually not ↑

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/X-MTM	Distinguishing from X-MTM
Multiminicore disease (OMIM 606210, 180901)	<i>SEPN1</i> <i>RYR1</i>	AR 2	<ul style="list-style-type: none"> • May present w/diffuse weakness starting from birth • Ophthalmoparesis in a subset of persons 	<ul style="list-style-type: none"> • Weakness usually less than in X-MTM • Muscle biopsy showing characteristic disruptions of mitochondrial & sarcotubular organization on oxidative stains (i.e., cores) • Central nuclei usually not ↑
Congenital myasthenic syndromes	>25 genes	AD AR	<ul style="list-style-type: none"> • Can present w/similar symptoms in early childhood, w/facial & extremity weakness & involvement of extraocular muscles • Both conditions may respond to mestinon. • Electrodiagnostic features of CMS (abnormal repetitive stimulation & jitter on single-fiber EMG) may be seen in X-MTM. 	<ul style="list-style-type: none"> • Fluctuating weakness variably present in CMS (not typical of X-MTM) • Biopsies are either normal or show nonspecific changes; features of X-MTM are not seen on biopsy in CMS.

AD = autosomal dominant; AR = autosomal recessive; CNM = centronuclear myopathy; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; MTM = myotubular myopathy

1. Wilmshurst et al [2010], Amburgey et al [2013a]

2. The occurrence of minicore myopathy in two generations in a few families – suggestive of autosomal dominant inheritance – has been reported.

See [Myopathy, centronuclear: OMIM Phenotypic Series](#) to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked myotubular myopathy (X-MTM), the following evaluations are recommended if they have not already been completed:

- Assessment of pulmonary function for long-term ventilatory management, either during initial hospitalization (if presentation at birth) or after the diagnosis has been established.
- Feeding/swallowing assessment, as performed by a qualified occupational therapist or equivalent allied health professional
- Ophthalmologic evaluation, either during initial hospitalization (if presentation at birth) or after the diagnosis has been established
- In individuals with hemolysis or unexplained anemia, osmotic fragility test to detect spherocytosis
- In the presence of infantile vomiting, investigation for pyloric stenosis
- Consultation with a clinical geneticist and/or genetic counselor
- In older children, evaluation for orthopedic complications, including examination for scoliosis

Treatment of Manifestations

Management of individuals with X-MTM is based on supportive care measures and in large part is similar to that for other congenital myopathies [Wang et al 2012]. Management optimally involves a team of specialists with expertise in the long-term care of individuals with neuromuscular disorders. Such teams often include a pulmonologist, neurologist, physical therapist and/or rehabilitation medicine specialist, and clinical geneticist.

Once the specific diagnosis of X-MTM is confirmed, management may be guided by family decisions regarding continued ventilatory support for the affected family member. Families may benefit from the involvement of professionals familiar with the data concerning the overall prognosis for X-MTM. Talking with other families who have children with the disorder can be extremely helpful, as can discussion with members of an MTM family foundation (see Resources). There is also a patient-/family-oriented guide for care for X-MTM.

- Given the risks for aspiration pneumonia and respiratory failure in infants with moderate or severe disease, tracheostomy and G-tube feeding should be seriously considered. Even individuals with mild disease are at risk for significant morbidity and mortality from intercurrent respiratory infection and hypoventilation.
- For ventilator-dependent individuals, communication support incorporates speech with a capped tracheostomy or Passy-Muir valve, sign language, and/or communication devices such as writing boards.
- Affected individuals older than age five years attend school, usually assisted by a dedicated nurse or aide, or have home-based teachers to limit exposure to infectious agents. Based on the emerging natural history study data, neuropsychologic evaluation may help identify learning difficulties and enable optimized educational planning.
- Ophthalmologists, orthopedists specializing in scoliosis management, and orthodontists should address specific medical complications related to the underlying myopathy.
- Children with X-MTM and an unexpected decline in motor skills should be evaluated for a potential abnormality in neuromuscular junction (NMJ) function. Robb et al [2011] identified one individual with mild X-MTM and unexplained decline in motor skills (i.e., lost ambulation) consistent with a disorder of NMJ transmission. On evaluation, this individual was found to have the electrodiagnostic features of NMJ disease (electrodecrement with repetitive stimulation and jitter with single-fiber EMG) but no laboratory evidence to support a co-occurring diagnosis of myasthenia gravis. Subsequent treatment with pyridostigmine resulted in rapid recovery of ambulation.
- In addition, and even without signs of unexplained decline, individuals with X-MTM may have underlying abnormalities in NMJ structure and function and thus may benefit from treatment targeted at improving NMJ signaling. A preclinical study in a mouse model of X-MTM identified structural abnormalities in the NMJ and demonstrated significant improvement in muscle fatigue with pyridostigmine treatment [Dowling et al 2012]. Pyridostigmine has been used "off label" by many individuals with X-MTM, with several anecdotal reports of clinical improvement [Author, personal communication]. The drug, however, has not been systematically studied in individuals with X-MTM; a retrospective study aimed at understanding the potential impact of pyridostigmine on clinical symptoms is ongoing.

Surveillance

Appropriate surveillance includes the following:

- Annual pulmonary assessment, including pulmonary function testing if able to be performed
- Polysomnography every one to three years unless symptoms of sleep-disordered breathing are present on history
- Spinal examination for signs of scoliosis, particularly in late childhood and adolescence
- Annual ophthalmologic exams for ophthalmoplegia, ptosis, myopia, and for protective assessment of the effect of impaired eyelid closure
- Assessment for dental malocclusion, with referral for orthodontia if indicated

Currently, the risk for non-neurologic events including bleeding diatheses and gastrointestinal complications is uncertain. Furthermore, the benefit of screening for such abnormalities has yet to be determined. Potential screening tests may include the following, though these studies have not been found to reliably identify actionable abnormalities:

- Annual blood counts [Herman et al 1999]
 - Annual liver function test and abdominal ultrasound to address the potential risk of peliosis hepatis
- Note: No advanced screening has been found to be useful for detecting hepatic peliosis prior to the development of clinically significant hemorrhage.

Agents/Circumstances to Avoid

It is generally agreed that neuromuscular paralytics such as succinylcholine should be avoided as part of anesthesia for patients with X-MTM. However, it is important to note that individuals with X-MTM are NOT susceptible to malignant hyperthermia [Litman et al 2018].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Gene replacement therapy is a promising treatment strategy for X-MTM. AAV-mediated delivery of *MTM1* is associated with significant improvement in strength, histopathology, and survival in both murine and canine models of the disease [Childers et al 2014]. A Phase I/II clinical trial (ASPIRO) is currently under way testing the safety and efficacy of this treatment in X-MTM in boys under age four years.

Several other strategies have shown promise in preclinical models of X-MTM. Lowering of *DNM2*, a key disease modifier, using either genetic or antisense oligonucleotide-mediated gene knockdown, resulted in increased strength and prolonged survival in a murine model of X-MTM [Cowling et al 2014, Tasfaout et al 2017]. Similarly, genetic knockdown or chemical inhibition of the lipid kinase *PIK3C2B* both prevented and reversed the disease course in an X-MTM murine model [Sabha et al 2016]. Additional development of treatments based on these data is under way, with a goal of translation to the clinical arena.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

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

X-linked myotubular myopathy (X-MTM) is inherited in an X-linked manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives

and if the *MTM1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.

- The carrier risk for a woman whose son has a confirmed *MTM1* pathogenic variant and is the sole affected male in the family is 80%-90% [Laporte et al 2000, Herman et al 2002, author observation]. Thus, an estimated 10%-20% of affected males who are the only affected individual in the family have *de novo* pathogenic variants in *MTM1* and mothers who are not carriers.

Sibs of a proband. The risk to sibs of a male proband depends on the genetic status of the mother:

- If the mother of the proband has an *MTM1* 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 heterozygotes and will generally be asymptomatic, although symptomatic heterozygote females have been described [Savarese et al 2016, Biancalana et al 2017, Felice et al 2018].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *MTM1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism. Several instances of maternal germline mosaicism for *MTM1* pathogenic variants have been described [Vincent et al 1998, Häne et al 1999, Laporte et al 2000].

Note: Postzygotic and germline mosaicism has been reported in the maternal grandfather of a severely affected male proband [Hedberg-Oldfors et al 2017].

Offspring of a proband

- **Classic/severe X-MTM.** In general, affected males with the classic/severe form of X-MTM do not survive to reproductive age. Those who do survive may have reproductive limitations related to physical disability. It is not known if males with severe disease are infertile.
- **Mild X-MTM.** Affected males with mild X-MTM will pass the pathogenic variant to all of their daughters and none of their sons. Biancalana et al [2003] reported an affected male with mild disease detected at age 20 who fathered two unaffected daughters, both of whom had affected sons. There are other similar unpublished examples related to males with mild disease.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant, and the aunt's offspring, depending on their sex, 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

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder are generally asymptomatic, although symptomatic heterozygote females have been described [Savarese et al 2016, Biancalana et al 2017, Felice et al 2018]. (2) Identification of female heterozygotes requires either: (a) prior identification of the *MTM1* pathogenic variant in the family; or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/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 heterozygotes (carriers) or are at increased risk of being heterozygotes (carriers).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *MTM1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Several instances of germline mosaicism for *MTM1* pathogenic variants have been described [Vincent et al 1998, Häne et al 1999, Laporte et al 2000]. Thus, it is important to discuss the option of prenatal testing in a male fetus even in instances in which the pathogenic variant is not identified in DNA extracted from the mother's leukocytes.

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](#).

- **Joshua Frase Foundation**
PO Box 2041
Ponte Vedra Beach FL 32004
Phone: 904-607-1358
Fax: 904-273-9818
Email: info@joshuafrase.org
www.joshuafrase.org
- **MTM-CNM Family Connection, Inc**
www.mtm-cnm.org
- **Where There's A Will There's A Cure**
Phone: 630-208-1105
www.will-cure.org
- **Muscular Dystrophy Association (MDA) - USA**
Phone: 833-275-6321
www.mda.org

- **Myotubular Trust**
United Kingdom
Email: melaniespring@myotubulartrust.org
www.myotubulartrust.org
- **ZNM- Zusammen Stark! e. V.**
Germany
www.znm-zusammenstark.org/en/myopathie/author/holger/
- **Congenital Muscle Disease International Registry (CMDIR)**
The CMDIR is a global partnership of patient advocacy organizations, researchers, and clinicians, all working toward the same goal: to find treatments for congenital muscle disease.
CMDIR/Cure CMD
www.cmdir.org
- **International Family Registry for Centronuclear and Myotubular Myopathies**
[Joshua Frase Foundation - Family registry for people with CNM/MTM](#)
- **Myotubular and Centronuclear Myopathy Patient Registry**
www.mtmcnmregistry.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. X-Linked Myotubular Myopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>MTM1</i>	Xq28	Myotubularin	MTM1 homepage - Leiden Muscular Dystrophy pages	MTM1	MTM1

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 X-Linked Myotubular Myopathy ([View All in OMIM](#))

300415	MYOTUBULARIN; MTM1
310400	MYOPATHY, CENTRONUCLEAR, X-LINKED; CNMX

Gene structure. *MTM1* is approximately 90 kb in size and comprises 15 exons ([NM_000252.2](#)). The first exon is noncoding and encompasses the putative promoter region of the gene. The start codon is present in exon 2. The gene is ubiquitously expressed and shows a muscle-specific alternative transcript because of the use of a different polyadenylation signal [Laporte et al 1996]. For a detailed summary of gene, transcript, and protein information, see Table A, **Gene**.

Benign variants. To date, more than 20 benign variants have been identified in *MTM1* [Laporte et al 2000, Herman et al 2002] (see Table A, **ClinVar**). The majority of changes identified represent rare variants, with the exception of c.1260+3G>A, which occurs at a frequency of approximately 50% in the general population [Laporte et al 2000].

Pathogenic variants. More than 250 pathogenic variants that cause X-linked myotubular myopathy have been described [Laporte et al 2000, Herman et al 2002, Biancalana et al 2003, Bertini et al 2004, Tsai et al 2005] (see Table A, **Locus-Specific Databases** and **HGMD**). Pathogenic variants are evenly distributed throughout the gene. While some pathogenic variants appear to be recurrent, no predominant common variant has been identified in any population. Interestingly, *in silico* analyses showed that *MTM1* had significantly fewer single-nucleotide variants than expected, which predicts that it is extremely intolerant of loss-of-function alleles and relatively intolerant of missense variants (see [EXaC database](#)). This echoes the finding that most *MTM1* variants are rare and disease causing [Lek et al 2016].

A large number of pathogenic variants occur in hypermutable CpG dinucleotides and this mechanism may explain the recurrence of some variants. Six recurrent variants account for about 24% of cases in the *MTM1*-LOVD database [Oliveira et al 2013].

Table 3. *MTM1* Variants Discussed in This *GeneReview*

Variant Classification	DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
Benign	c.1260+3G>A ¹	NA	NM_000252.2
Pathogenic	c.1261-10A>G ²	NA	NP_000243.1

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.

NA = not applicable

1. [rs222410](#)

2. See Genotype-Phenotype Correlations.

Contiguous-gene deletions. Contiguous-gene deletions in individuals with clinical features in addition to those of X-MTM have been reported [Dahl et al 1995, Hu et al 1996, Laporte et al 1997, Bartsch et al 1999, Biancalana et al 2003, Tsai et al 2005].

Normal gene product. *MTM1* encodes myotubularin, a protein of 603 amino acids [Laporte et al 1996, Laporte et al 1998]. The *MTM1* protein is composed of the following domains: PH-GRAM (pleckstrin homology-glycosyltransferase / Rab-like GTPase activator / myotubularin) domain, PTP (dual specificity and tyrosine phosphatase) domain, SID (SET protein interacting domain), and a PEST/PDZ domain.

Myotubularin functions primarily as a lipid phosphatase [Taylor et al 2000], specifically acting to remove phosphates from the 3-position of phosphoinositides. Studies using both cell-free biochemical assays and exogenous expression in cell culture have shown that myotubularin converts phosphoinositide-3-phosphate (PI3P) to phosphoinositide phosphate (PIP) and phosphoinositide-3,5-bisphosphate (PI3,5P2) to phosphoinositide-5-phosphate (PI5P) [Taylor et al 2000, Chaussade et al 2003, Robinson & Dixon 2006]. Myotubularin is also predicted to function as a protein phosphatase, though this activity has not been convincingly demonstrated.

Myotubularin's cellular function is inferred in part from the known roles of the phosphoinositides upon which it acts and from the fact that it localizes to endosomes [Laporte et al 2002, Tsujita et al 2004, Cao et al 2007, Dowling et al 2008]. *In vitro*, myotubularin has been demonstrated to regulate the sorting of cargo in and through the endosome through its ability to promote the conversion of phosphoinositides [Ketel et al 2016].

Myotubularin likely has roles in other cellular processes as well. It has been shown to interact with the intermediate filament network and specifically with desmin [Hnia et al 2011]. This interaction may both mediate myotubularin localization and also enable myotubularin to participate as a regulator of mitochondrial dynamics. It also interacts as part of a ubiquitin ligase complex that modulates the breakdown of misfolded cytoskeletal components including the desmin filament network [Gavriilidis et al 2018]. In addition, much of the protein

does not localize to endosomes, but is instead at steady state in a dense cytoplasmic network and can be found transiently at Rac-induced membrane ruffles [Laporte et al 2002]. Importantly, there is still a gap between the defined functions of myotubularin in cell systems and its role in skeletal muscle development and homeostasis.

Myotubularin was the first described member of a large group of homologous, evolutionarily conserved proteins [Raess et al 2017]. To date, 14 myotubularin-related (MTMR) proteins have been characterized [Robinson & Dixon 2006]; eight have dual-specificity phosphatase activity identical to myotubularin. The remaining have nonfunctional phosphatase domains, and are thought to act as coactivators or regulators of the enzymatically active members of the family. Several MTMRs are critical for mammalian development and human neurologic disease (reviewed by Raess et al [2017]).

Abnormal gene product. Pathogenic variants in *MTM1* result in loss of function or absence of the myotubularin protein. Disease is mediated at least in part by loss of myotubularin's phosphatase activity, as missense variants that impair myotubularin's enzymatic activity are associated with the severe/classic phenotype. Pathogenic variants that do not affect the enzymatic domain support the hypothesis that myotubularin has functions in addition to phosphatase activity [Amoasii et al 2012]. This is further supported by the observation that expression of an *MTM1* construct without phosphatase activity in *Mtm1* knockout mice can partially rescue the murine phenotype [Amoasii et al 2012].

The mechanism(s) whereby lack or dysfunction of myotubularin produces the disease phenotype seen in X-MTM have come into focus. Based on data from animal models, the weakness in myotubular myopathy is caused, at least in part, by defective excitation-contraction (E-C) coupling [Al-Qusairi et al 2009, Dowling et al 2009]. E-C coupling is the process by which electrical stimuli at the neuromuscular junction (NMJ) are translated into muscle contraction. It is mediated by the triad, a structure composed of the T-tubule and the terminal sarcoplasmic reticulum; the triad is responsible for regulated calcium release. Loss of myotubularin results in abnormalities in the structure of the triad as well as impaired stimulus-dependent calcium release early in the disease process, and is likely an early pathogenic event in humans with X-MTM. Interestingly, abnormalities in the E-C coupling apparatus have been observed in the genetically determined autosomal forms of myotubular myopathy, thus suggesting a common pathogenic mechanism for all types of MTM [Toussaint et al 2011, Jungbluth et al 2018]. The precise mechanism(s) through which loss of *MTM1* impairs triad structure and function are not fully elucidated. Furthermore, the relationship between *MTM1* function, triad biology, and the presence of the pathognomonic appearance of central nuclei is also unclear. Data suggest that both internal nucleation and triad disorganization may be mediated by altered N-WASP function and its impact on key filamentous networks within the myofiber [Falcone et al 2014, Roman et al 2017].

Loss of myotubularin likely affects other aspects of muscle function as well. In both zebrafish and murine models of X-MTM, disorganization of the NMJ has been reported [Robb et al 2011]. In the murine model and in cells derived from biopsies of affected individuals, abnormal mitochondrial function has been described [Hnia et al 2011]. The specific contribution(s) to the disease phenotype of these changes remain to be determined. Patient muscle cells demonstrate a significant decrease in expression of the ryanodine receptor 1, a decrease in muscle-specific microRNAs, and a considerable upregulation of histone deacetylase-4, which are likely consequent to the primary genetic defect and related to the severe decrease in muscle strength observed in patients [Bachmann et al 2017]. In addition, non-muscle phenotypes have been described in individuals with X-MTM, including unusual growth parameters and the rare occurrence of hepatic peliosis. These features have not been observed in animal models of X-MTM, and thus the mechanisms underlying them have evaded elucidation.

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