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MTM1-related Myopathy: Molecular pathogenesis, clinical spectrum, diagnostic challenges, and emerging therapeutic strategies

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Abstract
Background: MTM1-related myopathy is an inherited skeletal-muscle disorder caused by pathogenic variants in MTM1, which encodes myotubularin. Although classically associated with severe neonatal disease in males, its clinical spectrum includes milder male phenotypes and symptomatic heterozygous females.
Objective: To review the molecular pathogenesis, clinical spectrum, diagnosis, management, prognosis, and emerging therapies, with emphasis on manifesting females and the possible contribution of skewed X-chromosome inactivation.
Methods: This narrative review synthesizes clinical, genetic, pathological, and translational literature identified through PubMed/MEDLINE, Web of Science, and Google Scholar for January 1995 through October 2026. It is not a systematic review or meta-analysis.
Results: Pathogenic MTM1 variants disrupt myotubularin function, phosphoinositide regulation, membrane organization, and skeletal-muscle architecture. Presentations range from neonatal respiratory failure to childhood- or adult-recognized weakness. Heterozygous females may develop progressive or asymmetric weakness, ocular manifestations, and respiratory dysfunction. Molecular testing is central to diagnosis, with imaging, electrophysiology, and biopsy providing complementary evidence. Supportive multidisciplinary care remains essential while gene replacement and other disease-modifying approaches are investigated.
Conclusion: Recognition of the full clinical spectrum, including affected females, is important for timely diagnosis and appropriate surveillance. Skewed X-chromosome inactivation is a possible contributor to female disease expression but should not be assumed without direct evidence. Further natural-history and therapeutic research is needed.

Keywords: MTM1-related myopathy, X-linked Myotubular Myopathy, Centronuclear Myopathy, manifesting heterozygosity, X-chromosome inactivation, gene therapy

Introduction

MTM1-related myopathy is a rare genetic disorder of skeletal muscle caused by pathogenic variants in MTM1, the gene encoding myotubularin. It is conventionally known as X-linked myotubular myopathy (XLMTM) because the gene is located on chromosome Xq28 and the disorder predominantly affects males. The classical phenotype is characterized by profound congenital hypotonia, generalized muscle weakness, respiratory insufficiency, facial and extraocular muscle involvement, and delayed or absent achievement of independent motor milestones. Nevertheless, the disorder encompasses a substantially broader clinical spectrum, including milder disease in males and clinically significant myopathy in heterozygous females. [1,2]

The identification of MTM1 and subsequent advances in molecular genetics have established the disease as a genetically defined form of centronuclear myopathy. Myotubularin participates in phosphoinositide metabolism and intracellular membrane regulation, processes that are essential for maintaining the specialized architecture of skeletal muscle. Pathogenic variants can impair these functions, producing abnormalities in muscle-fiber organization and contractile performance. Although the characteristic presence of centrally located nuclei provides an important pathological clue, this finding is not unique to MTM1-related disease and may occur in other genetically distinct centronuclear myopathies. Accordingly, molecular confirmation is central to distinguishing MTM1-related myopathy from phenotypically overlapping disorders. [1,2]

The historical understanding of the disease has been shaped largely by its severe neonatal presentation in males. Affected infants may require prolonged respiratory support, enteral feeding, and extensive multidisciplinary care. Respiratory insufficiency is a major determinant of morbidity and mortality, while profound weakness may interfere with swallowing, cough effectiveness, motor development, and independent mobility. However, retrospective natural-history studies have also documented milder phenotypes, demonstrating that the severity of disease cannot be inferred solely from the presence of a pathogenic MTM1 variant. [1,3]

An important development in the clinical understanding of MTM1-related myopathy is the recognition that heterozygous females are not invariably asymptomatic. Although many female carriers have no clinically apparent weakness, published cases and cohort studies have documented women with childhood-onset motor impairment, progressive limb-girdle weakness, asymmetric muscle involvement, respiratory decline, and substantial functional disability. Some affected women have been diagnosed only after years of evaluation for alternative

neuromuscular disorders. These observations challenge the traditional assumption that clinically significant disease expression is restricted almost entirely to hemizygous males. [4-6]

The mechanisms responsible for variable disease expression in females remain incompletely understood. Skewed X-chromosome inactivation is one plausible explanation because it can alter the proportion of cells expressing the normal or pathogenic MTM1 allele. Nevertheless, studies have identified affected females without demonstrable skewing, and measured X-inactivation patterns do not consistently predict clinical severity. Tissue-specific differences in X-inactivation, genetic modifiers, and other biological factors may also contribute to the observed variability. [5-7]

These uncertainties have direct diagnostic implications. Women with chronic proximal weakness, recurrent falls, abnormal gait, respiratory symptoms, or characteristic muscle-biopsy findings may initially be diagnosed with limb-girdle muscular dystrophy, inflammatory myopathy, or peripheral neuropathy. Normal creatine kinase concentrations, the absence of a recognized family history, and a clinical presentation that differs from the classical neonatal phenotype can further delay diagnosis. Comprehensive genetic evaluation is therefore important when the clinical course remains unexplained or when investigations do not substantiate an earlier diagnosis. [4-6]

The development of molecularly targeted treatments has also increased the importance of precise diagnosis. Gene replacement studies have demonstrated the potential for meaningful functional improvement in some severely affected patients, but serious treatment-related toxicity has highlighted the need for careful evaluation of safety, durability, and patient selection. Translational research must therefore address not only the restoration of myotubularin function but also the biological differences between patients with severe congenital disease and those with milder or female-manifesting phenotypes. [8,9]

This review examines MTM1-related myopathy across its clinical, molecular, and therapeutic dimensions. It emphasizes the relationship between pathogenic variants and disease mechanisms, the spectrum of manifestations in males and females, diagnostic challenges in adult patients, current supportive care, and emerging therapeutic strategies. Particular attention is given to the distinction between established molecular findings and proposed mechanisms of female disease expression, with the aim of providing a scientifically rigorous framework for diagnosis, counseling, and future research.

Methods

This narrative review examines the molecular pathogenesis, clinical spectrum, genetic variability, diagnostic evaluation, management, and emerging therapeutic strategies of MTM1-related myopathy. Relevant literature published from January 1995 through October 2026 was considered, using PubMed/MEDLINE, Web of Science, and Google Scholar to identify disease-specific reviews, observational studies, clinical reports, molecular and pathological investigations, and translational research. Priority was given to studies directly addressing pathogenic MTM1 variants, disease mechanisms, clinical phenotypes, and outcomes in affected individuals, including manifesting heterozygous females. Research on other centronuclear myopathies was considered where it informed differential diagnosis or shared molecular mechanisms. Studies of X-chromosome inactivation in other X-linked disorders were included selectively when relevant to interpreting female disease expression. Clinical cohorts and observational studies informed the discussion of phenotype and natural history, while molecular, pathological, and experimental investigations supported the analysis of disease mechanisms. Clinical trial reports and translational studies were considered in evaluating emerging therapeutic approaches.

The core concepts used to organize the search were “MTM1,” “X-linked myotubular myopathy,” “myotubularin,” “manifesting female carrier,” “X-chromosome inactivation,” “centronuclear myopathy,” “respiratory care,” and “gene therapy.” These terms were combined with relevant synonyms and Boolean operators as appropriate. The final search date and exact database-specific strings should reflect the searches actually completed by the authors.

To reduce selection and interpretation bias, the review considered evidence from different study designs and distinguished findings from clinical cohorts, individual case reports, experimental models, and therapeutic studies. Particular attention was given to limitations arising from small sample sizes, referral and publication bias, incomplete follow-up, and the limited generalizability of findings from predominantly male cohorts to affected females. Conflicting findings were considered in the context of study design and methodological limitations rather than treated as evidence of a uniform disease mechanism. The potential contribution of skewed X-chromosome inactivation was evaluated separately from established genetic and clinical findings, and it was not assumed to explain an individual patient's phenotype without direct supporting evidence. Investigational treatments were distinguished from established clinical care. This review provides a narrative synthesis of the relevant literature rather than a formal systematic review or meta-analysis. No formal risk-of-bias scoring or quantitative evidence synthesis is claimed.

Use of generative AI: A generative AI tool was used during manuscript preparation to assist with language editing, reference-format review, and journal-format checks. The authors are responsible for verifying the accuracy, completeness, and interpretation of all scientific claims and references.

Epidemiology and disease burden

MTM1-related myopathy is an uncommon inherited neuromuscular disorder. Historical estimates suggest an incidence of approximately one affected male per 50,000 live male births, although this figure should be interpreted cautiously because large population-based studies with comprehensive case ascertainment have not established the true incidence. Differences in diagnostic access, survival, recognition of milder phenotypes, and identification of symptomatic females may influence estimates of disease frequency. [1]

The epidemiology of MTM1-related myopathy has traditionally been derived from male infants presenting with severe congenital weakness and respiratory insufficiency. This clinical emphasis reflects the visibility and urgency of the neonatal phenotype rather than the complete range of disease expression. Natural-history studies have

demonstrated considerable variability in disease severity, with some males experiencing profound motor and respiratory impairment and others achieving independent ambulation and surviving into adulthood. [1,3]

1. Disease burden in males

Severely affected males may require respiratory assistance from birth, prolonged hospitalization, enteral feeding, and sustained multidisciplinary care. Weakness of the diaphragm and other respiratory muscles may impair ventilation, while reduced cough effectiveness increases the risk of secretion retention and respiratory infection. Bulbar dysfunction can further compromise swallowing and airway protection. These complications may occur alongside profound motor impairment, contractures, scoliosis, and delayed developmental milestones. [1,3]

The burden of disease extends beyond survival. Individuals who live into childhood and adulthood may experience continuing dependence on respiratory equipment, mobility aids, nutritional support, and caregiver assistance. Recurrent respiratory infections, orthopedic complications, and reduced mobility can impose substantial demands on families and healthcare systems.

However, severe neonatal disease should not be regarded as the only clinically relevant presentation. Milder phenotypes may remain unrecognized until childhood or adulthood, particularly when respiratory symptoms are limited or the individual retains independent mobility. The variable natural history reinforces the need for longitudinal assessment rather than prognostic assumptions based exclusively on the initial presentation. [1,3]

2. Disease burden in females

The epidemiology of symptomatic heterozygous females is less clearly defined than that of affected males. Most available evidence comes from clinical case reports, family investigations, and selected cohorts rather than population-based studies.

Biancalana and colleagues characterized 43 affected females and demonstrated a broad spectrum of clinical and pathological involvement, ranging from severe generalized weakness to milder adult presentations. Their observations included asymmetric weakness and respiratory decline, establishing that female manifestations can be clinically significant and may resemble other inherited myopathies. [4]

Earlier work by Savarese and colleagues also identified symptomatic females among individuals evaluated for unexplained myopathy, supporting the possibility that female disease expression is underrecognized in routine neuromuscular practice. [5] Nevertheless, these studies do not establish the proportion of all heterozygous women who will develop symptoms, because affected individuals are more likely than asymptomatic carriers to undergo extensive investigation and appear in published cohorts.

Under recognition may result from the historical classification of female carriers as unaffected, the gradual onset of weakness, normal or mildly elevated muscle enzymes, an absent family history, and diagnostic anchoring on more common neuromuscular disorders. Mild symptoms may be attributed to deconditioning or musculoskeletal problems, while progressive disability may lead to investigations for limb-girdle muscular dystrophy, inflammatory myopathy, or peripheral neuropathy.

The epidemiological implications are important. A disease model based exclusively on severely affected males may underestimate the range of clinical needs associated with MTM1 pathogenic variants. At the same time, the frequency of symptomatic female carriers should not be inferred from referral-based cohorts, and additional population-based research is required to establish reliable estimates.

3. Age at onset and clinical ascertainment

The age at which MTM1-related myopathy is diagnosed does not necessarily correspond to the age at which symptoms begin. Severe disease is generally recognized in the neonatal period, whereas milder male phenotypes and female-manifesting disease may remain undiagnosed for years.

In women, childhood motor difficulties may precede substantial functional decline in adulthood. A history of recurrent falls, waddling gait, impaired running, difficulty climbing stairs, or reduced exercise tolerance may become clinically meaningful only after weakness progresses or additional manifestations emerge. Retrospective reconstruction of the clinical history is therefore important when evaluating adults with suspected inherited myopathy. [4-6]

4. Implications for public health and clinical services

The rarity of MTM1-related myopathy creates challenges for timely diagnosis, specialist access, and the development of adequately powered clinical studies. Patients may require coordinated services across neuromuscular medicine, pulmonology, rehabilitation, nutrition, genetics, and orthopedics. Access to molecular testing and disease-specific expertise may vary substantially across healthcare settings.

The establishment of longitudinal registries standardized clinical assessments, and international collaborations would improve the characterization of disease frequency, natural history, functional outcomes, and treatment response. Such initiatives are particularly important for symptomatic females, whose clinical trajectories remain less well characterized than those of severely affected males.

Genetic basis and inheritance

1. The MTM1 gene and its biological significance

The MTM1 gene is located on chromosome Xq28 and encodes myotubularin, a protein involved in phosphoinositide metabolism and the regulation of intracellular membrane-associated processes. These functions are essential to the organization and maintenance of skeletal muscle. Pathogenic variants in MTM1 cause the disorder conventionally known as X-linked myotubular myopathy. [1,2] (see Figure 9 for an integrated summary of gene structure, variants, and clinical implications).

The gene comprises multiple coding exons, and disease-causing variants have been identified throughout its sequence. The absence of a single predominant pathogenic variant across all populations means that genetic evaluation must accommodate substantial molecular heterogeneity. Large deletions and other structural variants are particularly important because they may not be identified by conventional sequence analysis alone. [1,5,10-15]

The molecular diagnosis must distinguish pathogenic or likely pathogenic variants from variants of uncertain significance. The presence of an uncommon MTM1 variant

does not, by itself, establish that the variant causes the patient's clinical phenotype. Interpretation should incorporate the molecular consequence, population frequency, segregation evidence, functional data when available, and compatibility with the clinical presentation. This is described in the figure 1 below;

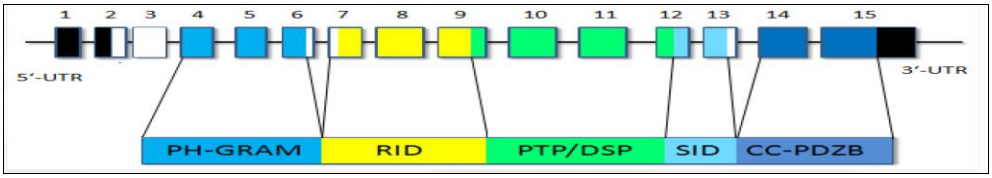


Fig 1: Schematic organization of myotubularin protein domains and functional regions.

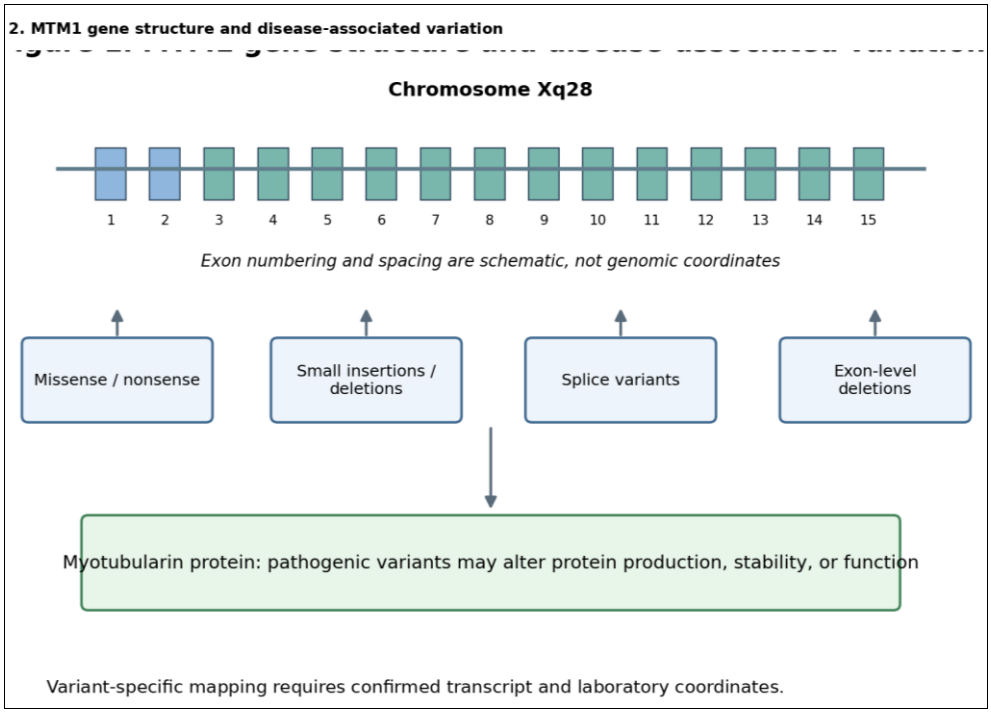


Fig 2: MTM1 gene structure and disease-associated variation. [1,2,10-15].

Schematic overview of the Xq28 location, exon organization, and classes of pathogenic MTM1 variants. Exon spacing is illustrative and is not to scale. The schematic does not represent a patient-specific variant.

2. Spectrum of pathogenic variants

Pathogenic MTM1 variants include nonsense variants, frameshift variants, missense substitutions, splice-site alterations, small insertions or deletions, and larger intragenic deletions. These variants may disrupt protein production, alter transcript processing, impair protein stability, or interfere with myotubularin function. [1,2]

Nonsense and frameshift variants frequently predict substantial loss of protein function and are often associated with severe disease in males. However, the relationship between variant class and phenotype is not absolute. Some splice-site and missense variants are associated with milder presentations, while variants with similar predicted molecular consequences may produce different degrees of clinical severity. [1]

Exon-level deletions are particularly relevant to genetic diagnosis. Their consequences depend on the affected exons, the transcript used for interpretation, the reading frame, and whether essential functional regions are removed. A large deletion may cause major disruption of the protein, but the precise interpretation requires laboratory-level characterization rather than inference from the number of deleted exons alone.

3. Genotype–phenotype relationships

The relationship between MTM1 genotype and clinical severity remains incompletely understood. Although some associations have been described, genetic findings do not provide sufficiently precise predictions of respiratory dependence, ambulatory status, survival, or progression in every patient. [1,3]

Several factors may contribute to this variability. The amount of residual myotubularin function may differ among variants, while differences in transcript processing, protein stability, cellular localization, and downstream biological pathways may influence disease expression. The clinical course is also affected by age at onset, secondary complications, respiratory care, and the availability of multidisciplinary support.

In heterozygous females, interpretation is more complex because the normal and pathogenic alleles are distributed across a mosaic population of cells. X-chromosome inactivation, tissue-specific expression, and other biological modifiers may influence the phenotype. The same pathogenic variant may therefore be associated with very different clinical manifestations in a hemizygous male and a heterozygous female.

These observations argue against using variant class alone as a substitute for clinical assessment. Genotype–phenotype interpretation should integrate molecular findings with the individual's history, neurological examination, respiratory function, functional status, and longitudinal course.

4. X-linked inheritance

MTM1-related myopathy follows an X-linked inheritance pattern. Males typically have one X chromosome, so a pathogenic variant affecting their single MTM1 copy can produce disease. Females generally have two X chromosomes and may be heterozygous for a pathogenic variant, with clinical expression ranging from no overt weakness to substantial myopathy. [1]

When a woman carries a pathogenic MTM1 variant, each pregnancy has a 50% probability of inheriting that variant. Sons who inherit it are expected to be affected, although severity varies. Daughters who inherit it are heterozygous and may be asymptomatic or develop clinically significant manifestations. An affected male transmits his X chromosome to all daughters and to none of his sons.

A negative family history does not excludes the diagnosis. Some affected individuals have a de novo pathogenic variant, and some families may have unrecognized female manifestations or previously undiagnosed affected males. Germline mosaicism can also complicate recurrence-risk assessment in selected families. Genetic counseling should therefore be individualized according to the molecular findings and family history. [1]

5. Genetic counseling and family assessment

Identification of a pathogenic MTM1 variant has implications beyond the individual patient. It may justify targeted testing of at-risk relatives, clarification of reproductive risks, and reassessment of family members with unexplained muscle weakness or a history of neonatal neuromuscular disease.

Counseling should communicate the variable expression of the disorder in females. A heterozygous result should not automatically be described as a clinically irrelevant carrier state, particularly when the individual has symptoms consistent with myopathy. Conversely, a pathogenic variant does not mean that every heterozygous woman will develop substantial weakness.

Where appropriate, reproductive counseling may include discussion of prenatal testing and preimplantation genetic testing. These options should be presented in a nondirective manner and interpreted within the relevant clinical, ethical, and regulatory framework.

6. Interpretation of genetic findings

Genetic findings should be interpreted using the laboratory's variant classification, transcript annotation, predicted molecular consequence, and supporting evidence. A pathogenic or likely pathogenic MTM1 variant, when concordant with the phenotype, can establish the molecular diagnosis. A variant of uncertain significance should not be treated as diagnostic without additional evidence. The presence of a pathogenic MTM1 variant does not, by itself, prove that skewed X-chromosome inactivation explains disease expression in a heterozygous female.

Molecular pathogenesis

1. Myotubularin and phosphoinositide regulation

Myotubularin is a phosphoinositide phosphatase that regulates phosphatidylinositol 3-phosphate and phosphatidylinositol 3,5-bisphosphate. These signaling lipids participate in endosomal trafficking, membrane organization, intracellular protein handling, and other processes essential to cellular homeostasis. Disruption of myotubularin function alters these pathways and contributes to the structural and functional abnormalities observed in MTM1-related myopathy. [2,16]

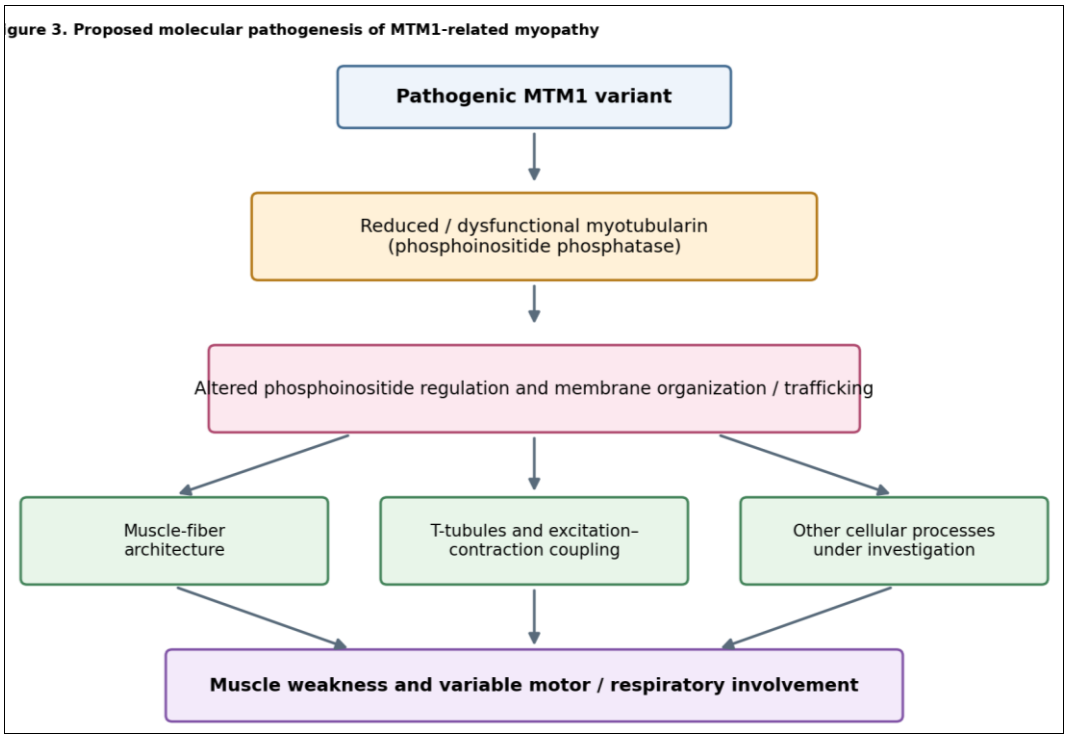


Fig 3: Proposed molecular pathogenesis of MTM1-related myopathy. [17-22]. The mechanistic relationships are a simplified proposed model; individual interactions should be interpreted in light of the cited experimental evidence.

Proposed relationship between pathogenic MTM1 variants, impaired myotubularin function, altered phosphoinositide regulation and membrane organization, and muscle dysfunction. Downstream pathways are presented as interacting mechanisms; the figure does not imply that every step has been demonstrated in every patient.

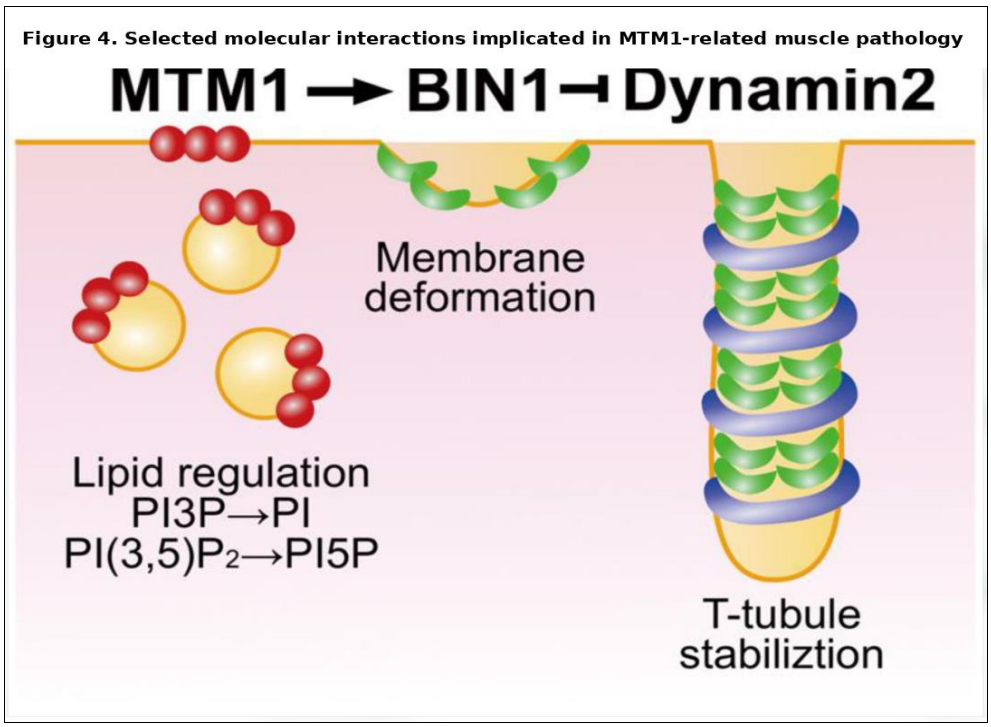


Fig 4: Conceptual depiction of selected molecular interactions relevant to centronuclear myopathy and membrane remodeling. [23,24].

2. Muscle-fiber organization and maturation

MTM1-related myopathy is characterized by structural abnormalities in skeletal muscle, including centrally located nuclei, fiber-size variation, and altered intracellular organization. The historical term myotubular myopathy reflects the resemblance of some affected muscle fibers to immature developmental structures.

The disease is not simply a failure of muscle maturation. Evidence supports abnormalities in the maintenance of mature muscle-fiber architecture and the organization of the cellular components required for contraction. Consequently, the pathological phenotype should be understood as a complex structural and functional disorder rather than as an isolated abnormality of nuclear positioning. [1,2]

3. T-tubules and excitation–contraction coupling

Normal skeletal-muscle contraction requires the transmission of electrical signals from the muscle membrane into the interior of the muscle fiber. Transverse tubules and their associated structures coordinate this process with calcium release from the sarcoplasmic reticulum.

Experimental studies of MTM1 deficiency have demonstrated abnormalities in membrane organization and excitation–contraction coupling. These defects can compromise the efficiency of muscle contraction and contribute to weakness, even in the absence of extensive primary muscle-fiber necrosis. [2,16]

This mechanism is clinically important because it helps explain why the degree of weakness may be disproportionate to routine serum muscle-enzyme abnormalities. The principal dysfunction may involve muscle architecture and contractile performance rather than a destructive process that consistently produces substantial CK elevation.

4. Cellular organization and protein homeostasis

Research has also examined the contribution of organelle positioning, sarcomeric organization, and protein quality-control pathways to MTM1-related disease. Disruption of these processes may contribute to abnormal muscle-fiber structure and impaired contractile function. [16]

Although these mechanisms are biologically plausible and supported by experimental findings, their individual contributions to clinical severity remain incompletely defined. They should therefore be presented as components of an interacting pathophysiological network rather than as independently established causes of specific symptoms.

5. Integrated pathophysiological interpretation

The available evidence supports a model in which pathogenic MTM1 variants impair myotubularin function, disrupt phosphoinositide-dependent cellular processes, and alter membrane organization and muscle-fiber architecture. These abnormalities interfere with normal muscle contraction and produce the characteristic phenotype of weakness, hypotonia, and variable respiratory dysfunction.

In females, the model must also account for the distribution of cells expressing the normal and pathogenic alleles. Nevertheless, the precise mechanism underlying disease expression in each heterozygous woman cannot be inferred from the genetic result alone.

Clinical manifestations

MTM1-related myopathy encompasses a broad clinical spectrum, ranging from severe neonatal disease to milder presentations recognized during childhood or adulthood. The major manifestations include generalized or proximal weakness, hypotonia, impaired motor development,

respiratory muscle dysfunction, facial weakness, ocular motor abnormalities, and secondary orthopedic complications. Their severity varies according to the individual's phenotype and disease course. [1,3]

1. Prenatal and neonatal manifestations

Severe disease may be suspected prenatally when reduced fetal movements or polyhydramnios occurs in a compatible clinical context. These findings are nonspecific and cannot establish the diagnosis independently.

Affected newborns commonly present with profound hypotonia, generalized weakness, weak respiratory effort, feeding difficulties, and respiratory failure. Facial weakness and extraocular muscle involvement may also be apparent. Respiratory support may be required immediately after birth, and some infants remain dependent on ventilatory assistance for prolonged periods. [1,3]

The combination of congenital hypotonia, respiratory insufficiency, facial weakness, and a compatible family history should prompt early evaluation for an inherited neuromuscular disorder. Timely molecular diagnosis can clarify the underlying disease, guide respiratory and nutritional management, and facilitate genetic counseling.

2. Childhood manifestations

Children with milder disease may achieve motor milestones later than expected and experience difficulty running, climbing stairs, maintaining balance, or participating in physical activities. Muscle weakness may affect both proximal and distal muscle groups, although the distribution varies.

Persistent weakness can contribute to gait abnormalities, falls, contractures, scoliosis, and reduced endurance. Some children acquire independent ambulation, while others require assistance with mobility and daily activities.

The clinical course should be assessed longitudinally because secondary complications may worsen functional ability even when the underlying myopathy does not demonstrate rapid progression.

3. Adolescent and adult manifestations in males

Milder male phenotypes may remain unrecognized until adolescence or adulthood. Individuals may present with proximal weakness, reduced muscle bulk, difficulty rising from a seated position, limited exercise tolerance, or progressive loss of functional abilities.

Respiratory involvement should not be assumed to be absent merely because the individual remains ambulatory. The degree of limb weakness may not reliably predict respiratory muscle function, and evaluation should be guided by symptoms and objective findings. [1]

4. Manifesting heterozygous females

Females with pathogenic MTM1 variants may develop clinically significant disease despite retaining a second X chromosome. Their manifestations range from subtle weakness and exercise intolerance to severe progressive myopathy with substantial mobility impairment. Published cases include childhood-onset disease, adult-recognized proximal weakness, asymmetric muscle involvement, respiratory decline, and ocular manifestations. [4-6]

The female phenotype is particularly important because it may not resemble the classical neonatal presentation. A woman may have a history of waddling gait, frequent falls, difficulty climbing stairs, or reduced physical endurance long before a neuromuscular diagnosis is established.

Asymmetric weakness is a noteworthy clinical clue. Some affected females have more pronounced weakness or muscle wasting on one side of the body, which can lead clinicians to consider alternative diagnoses. However, asymmetry is not specific to MTM1-related disease and should be interpreted alongside the broader phenotype and genetic findings. [4]

Respiratory symptoms may emerge gradually and should be actively investigated. Orthopnea, morning headaches, nonrestorative sleep, daytime somnolence, weak cough, recurrent chest infections, or disproportionate exertional dyspnea may indicate respiratory muscle dysfunction.

Ocular manifestations, including ptosis and ophthalmoparesis, may provide additional diagnostic clues. New diplopia nevertheless requires appropriate evaluation because it may reflect a concurrent ocular, neuromuscular-junction, cranial-nerve, or central nervous system disorder.

5. Musculoskeletal complications

Chronic weakness and altered muscle balance can contribute to contractures, abnormal foot posture, scoliosis, reduced joint mobility, and impaired gait. Recurrent falls can result in fractures and accelerate functional decline.

Management should address both the primary myopathy and the secondary consequences of reduced mobility. Physiotherapy, orthoses, mobility aids, orthopedic review, and adaptations to daily activities may preserve independence and reduce injury risk.

6. Fatigue, pain, and quality of life

Fatigue, exercise intolerance, muscle discomfort, and reduced endurance may substantially affect quality of life. These symptoms may be underrecognized when clinical assessment focuses narrowly on manual muscle testing or serum CK concentrations

The burden of disease includes difficulties with self-care, employment, education, transportation, and participation in social activities. In more severe cases, dependence on respiratory support or mobility aids can create considerable demands on caregivers.

For these reasons, assessment of MTM1-related myopathy should incorporate functional independence, patient-reported symptoms, and quality of life in addition to conventional neurological examination.

X-chromosome inactivation and female disease expression

X-chromosome inactivation is a physiological process through which one X chromosome becomes transcriptionally inactive in most female somatic cells. Because the process occurs across individual cell lineages, a heterozygous female may have a mosaic population of cells expressing the normal or pathogenic MTM1 allele.

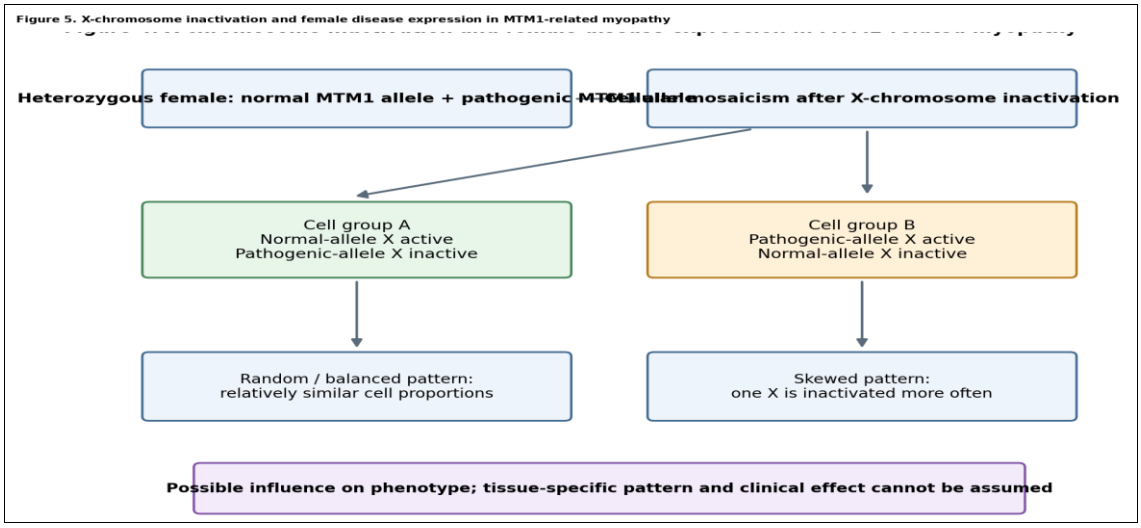


Fig 5: X-chromosome inactivation and female disease expression in MTM1-related myopathy. [4-7,25,26]. XCI is a possible contributor to variable expression and is not established as a universal explanation in affected females.

Conceptual illustration of cellular mosaicism in a heterozygous female. Cells may differ in whether the normal or pathogenic MTM1 bearing X chromosome remains active. Preferential inactivation of the normal allele could contribute to disease expression, but this mechanism is not universal and must not be claimed in an individual without direct evidence.

Subsequent studies have reinforced the complexity of the relationship. Biancalana and colleagues identified a broad spectrum of clinical manifestations in affected females and reported asymmetry and respiratory decline as important features. Other investigations have described symptomatic females without demonstrable skewing or a consistent relationship between the degree of skewing and disease severity. [4,5]

These findings indicate that X-inactivation should be regarded as one potential contributor rather than the sole mechanism of female disease expression. Differences between blood and skeletal muscle, limitations of X-inactivation assays, allele-specific expression, structural abnormalities of the X chromosome, and additional genetic modifiers may contribute to the observed variability.

In clinical practice, the diagnosis should be established through the integration of molecular findings and phenotypes. X-inactivation testing may be informative when technically appropriate, but a blood-based result should not automatically be assumed to represent the pattern in skeletal muscle. Similarly, a pathogenic MTM1 variant does not establish that skewed X-inactivation caused a particular woman's symptoms unless supporting evidence is available.

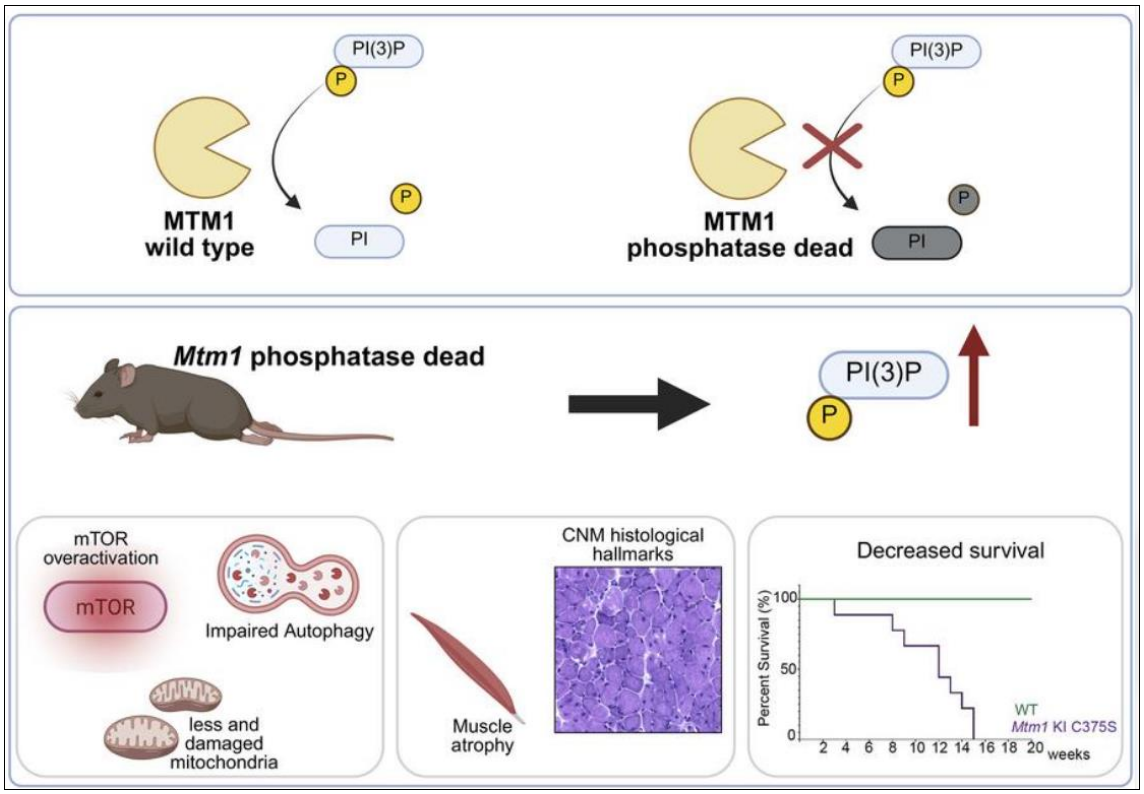


Fig 6: Illustrative pathological and outcome findings reported in MTM1-related myopathy. [19,22,27,28]. Findings from human studies and animal models are distinguished; preclinical outcomes should not be interpreted as established human treatment effects.

Diagnostic evaluation

1. Clinical suspicion

MTM1-related myopathy should be considered in patients with congenital or childhood-onset weakness, unexplained progressive proximal myopathy, characteristic ocular findings, respiratory muscle dysfunction, or a muscle biopsy demonstrating a centronuclear pattern.

In adult women, the history should specifically explore childhood gait abnormalities, recurrent falls, difficulty rising from a chair, impaired running, reduced exercise tolerance, and progressive loss of mobility. A negative family history or normal CK should not prevent genetic investigation when the overall phenotype remains suggestive. [1,4]

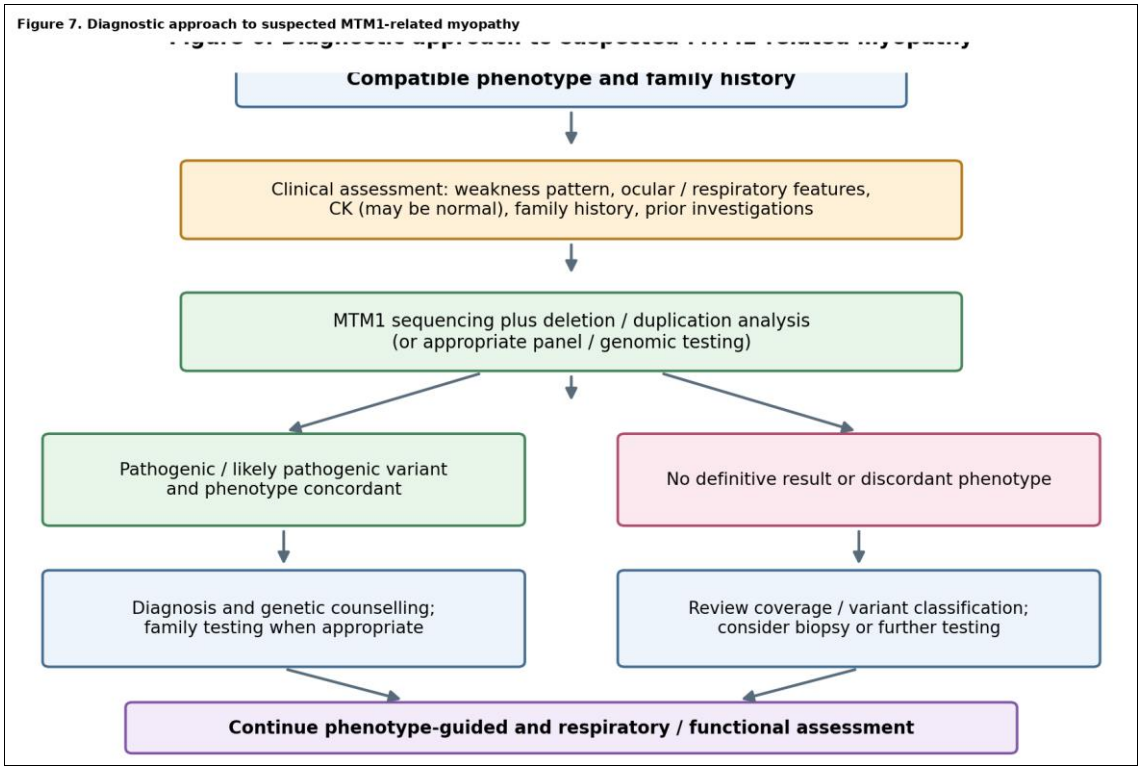


Fig 7: Diagnostic approach to suspected MTM1-related myopathy. [1,4-6,10-15,29-31].

Proposed clinical workflow integrating phenotype and family history with molecular testing, including sequence analysis and deletion/duplication assessment. If results are inconclusive or inconsistent with the phenotype, review variant classification and assay coverage and consider additional investigations, including muscle pathology, when clinically indicated. This schematic is not a formal clinical practice guideline.

2. Laboratory investigations

CK and aldolase may be normal or variably elevated. Their concentrations are not sufficiently sensitive to exclude MTM1-related myopathy.

Additional laboratory investigations should be selected according to the differential diagnosis. Thyroid testing, inflammatory markers, myositis antibodies, and other investigations may be appropriate when alternative causes of weakness are being considered.

3. Electrophysiological evaluation

Electromyography and nerve-conduction studies can help distinguish a primary myopathy from peripheral neuropathy, neuromuscular-junction disorders, or other causes of weakness. However, findings may be nonspecific or nondiagnostic in congenital myopathies.

When an earlier diagnosis of CIDP or another neuropathy is not supported by repeat electrodiagnostic testing, the differential diagnosis should be reconsidered. Persistent weakness alone does not establish an inflammatory or demyelinating disorder.

4. Muscle imaging

Muscle MRI can characterize the distribution of muscle involvement, identify fatty replacement, and assist with biopsy-site selection. It may be particularly useful in patients with asymmetric weakness or a suspected limb-girdle phenotype.

Imaging findings are not sufficiently specific to establish MTM1-related myopathy independently. Their value lies in the integration of anatomical patterns with clinical findings, histopathology, and molecular testing.

5. Muscle biopsy

Muscle biopsy may demonstrate centrally located nuclei, muscle-fiber hypotrophy, type 1 fiber predominance, and abnormalities in intracellular organization. Some patients show necklace fibers or other characteristic histochemical findings. These features can support the diagnosis of centronuclear myopathy, but none is obligatory or entirely specific to MTM1-related disease. [1,4]

Biopsy is particularly useful when molecular findings are uncertain, when the phenotype is atypical, or when additional pathological characterization is needed. It should not replace genetic testing when a molecular diagnosis can be established. [29-31]

6. Molecular genetic testing

Molecular testing is central to diagnosis. Depending on the clinical presentation, an MTM1-focused assay, a congenital-myopathy panel, or broader genomic testing may be appropriate.

The testing strategy should account for sequence variants and exon-level or larger deletions. If initial sequencing is negative despite a strong clinical suspicion, deletion/duplication analysis or broader genomic investigation may be indicated. [1,5]

A pathogenic or likely pathogenic variant should be interpreted alongside the phenotype and relevant laboratory evidence. A variant of uncertain significance should not be treated as equivalent to a confirmed disease-causing variant.

7. Integrated diagnostic approach

The evaluation begins with recognition of a compatible clinical phenotype, followed by targeted neurological and respiratory assessment. Laboratory testing, electrophysiology, and muscle imaging provide complementary evidence. Molecular testing then establishes the genetic basis when a pathogenic MTM1 variant is identified and is consistent with the phenotype. Muscle biopsy and additional genetic studies may be appropriate when the results remain unresolved.

This integrated approach is particularly important in women whose symptoms are atypical or have previously been attributed to other neuromuscular disorders.

Differential diagnosis

The differential diagnosis includes other centronuclear myopathies, limb-girdle muscular dystrophies, congenital myopathies, inflammatory muscle diseases, peripheral neuropathies, and neuromuscular-junction disorders.

DNM2-related and BIN1-related centronuclear myopathies can resemble MTM1-related disease clinically and histologically, but their genetic causes and inheritance patterns differ. RYR1-related myopathy may share congenital weakness and respiratory involvement, while some limb-girdle muscular dystrophies produce progressive proximal weakness and loss of ambulation. [23,24,32]

Inflammatory myopathies may present proximal weakness, but the diagnosis requires integration of the clinical course, laboratory findings, imaging, and pathological evidence.

Similarly, CIDP should be considered when there is appropriate clinical and electrodiagnostic evidence of peripheral nerve involvement, rather than inferred from weakness alone.

Myasthenia gravis and other neuromuscular-junction disorders may produce ptosis, diplopia, and generalized weakness. Fluctuating symptoms and disease-specific investigations can help distinguish them from structural muscle disorders.

The presence of central nuclei on muscle biopsy should therefore prompt consideration of a centronuclear myopathy, not automatic assignment of an MTM1-related diagnosis. Molecular testing remains central to distinguishing these overlapping disorders. [1,2]

Management and supportive care

Management should be individualized according to respiratory function, swallowing ability, mobility, orthopedic complications, and the patient's overall clinical trajectory. A multidisciplinary approach involving neuromuscular medicine, pulmonology, rehabilitation, nutrition, genetics, and other relevant specialties is essential. [33-35]

Respiratory care should include symptom assessment and objective evaluation of respiratory muscle function when indicated. Depending on disease severity, management may involve pulmonary function testing, cough assessment, overnight evaluation for hypoventilation, airway-clearance techniques, and noninvasive or invasive ventilation. Respiratory infections require timely assessment because limited respiratory reserve can increase the risk of deterioration. [1,36]

Nutritional care should address swallowing safety, adequate intake, growth in children, and aspiration risk. Speech and swallowing specialists, dietitians, and gastroenterologists may be involved when clinically appropriate. Enteral feeding may be required when oral intake is unsafe or insufficient.

Physical and occupational therapy can help preserve mobility, reduce contractures, improve positioning, and support independence in daily activities. Exercise programs should be individualized to avoid excessive fatigue and injury while minimizing unnecessary inactivity and deconditioning.

Orthopedic assessment is important when scoliosis, contractures, abnormal foot posture, or recurrent falls occur. Orthoses, mobility aids, seating adaptations, and selected orthopedic interventions may improve function and reduce complications.

Ophthalmological evaluation may be needed for ptosis, ophthalmoparesis, diplopia, or impaired eyelid closure. Psychosocial support and genetic counseling are also important because the disease can affect independence, family planning, employment, and caregiver well-being.

Women with manifesting MTM1-related myopathy should receive the same clinically appropriate attention to respiratory, nutritional, musculoskeletal, and functional complications as other affected individuals. Their surveillance should be guided by symptoms, examination, and objective findings rather than assumptions based on sex or heterozygous status.

Emerging therapies and disease-modifying treatment

1. Therapeutic rationale

The molecular basis of MTM1-related myopathy provides a rationale for therapies intended to restore myotubularin function or modify downstream pathways involved in muscle dysfunction. Research has focused particularly on gene replacement, as well as approaches directed at membrane organization, intracellular trafficking, and other cellular processes.

Supportive management remains essential regardless of therapeutic advances. Experimental or investigational interventions should be distinguished from established care [35,36]. Biological improvement in preclinical models should not be equated with proven clinical benefit [27,28].

2. Gene replacement therapy

Resamirigene bilparvovec, previously known as AT132, is an investigational AAV8-mediated gene replacement approach developed for XLMTM. The ASPIRO clinical trial evaluated intravenous delivery of a functional MTM1 construct in affected boys.

Published results demonstrated meaningful functional improvements in some treated participants, including reduced ventilator dependence and gains in motor function. However, serious hepatobiliary toxicity and fatal adverse outcomes were also reported, raising substantial concerns regarding safety and the overall risk–benefit profile. [8,9]

These findings illustrate both the promise and the complexity of gene replacement therapy. Restoring a functional gene can potentially address the underlying molecular defect, but effective delivery, dose selection, immune responses, organ toxicity, and long-term safety remain major considerations.

The clinical status of resamirigene bilparvovec must be verified against current regulatory and trial records before it is described as an available treatment. It should not be presented as an established routine therapy solely on the basis of early efficacy findings.

3. Other investigational strategies

Research has explored pharmacological approaches and interventions intended to modify pathways downstream of myotubularin deficiency. These strategies seek to improve muscle structure or function without necessarily replacing the defective gene.

Tamoxifen and other experimental approaches have been investigated in the broader therapeutic research landscape, but their clinical role must be determined from the quality of evidence, safety findings, and appropriately designed clinical studies. Investigational treatments should not be recommended as established therapy without sufficient evidence and applicable regulatory approval.

4. Therapeutic implications for females

Most interventional research has focused on severely affected males. The extent to which those findings apply to adult women with heterozygous MTM1 variants remains uncertain.

Manifesting females may differ in age at onset, residual muscle function, disease distribution, and cellular expression of the pathogenic allele. These differences could influence treatment response and safety. Future clinical studies should therefore assess female participants explicitly and avoid assuming that results from male cohorts are fully generalizable to all MTM1-related phenotypes.

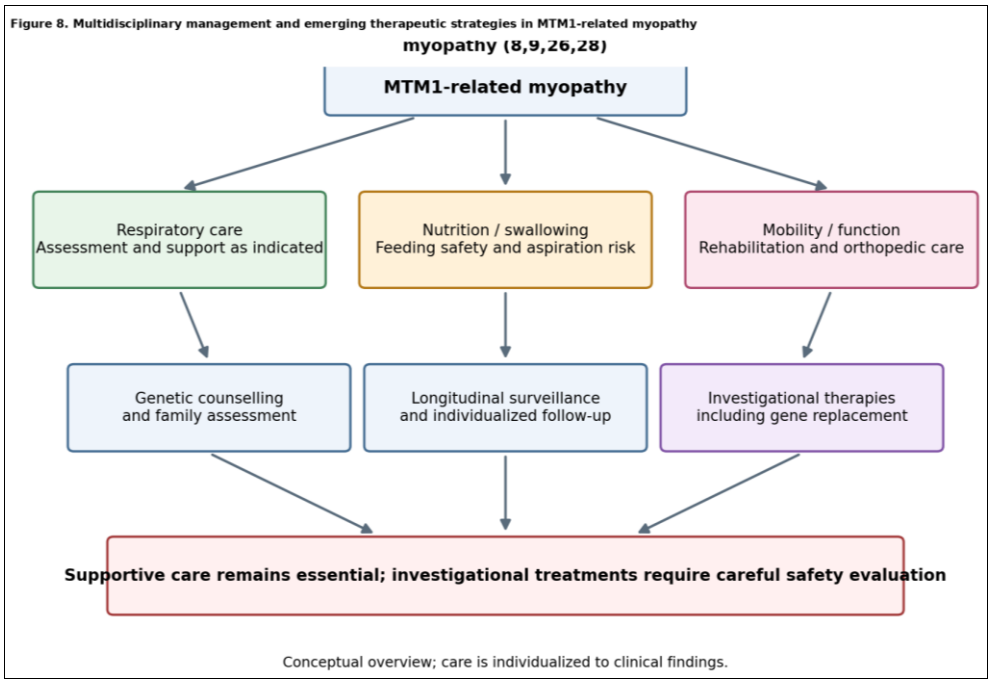


Fig 8: Multidisciplinary management and emerging therapeutic strategies in MTM1-related myopathy [8,9,35,36]. Gene-replacement approaches remain investigational; clinical trial findings should be interpreted with the reported safety limitations.

Overview of supportive care domains, including respiratory assessment, nutrition and swallowing, rehabilitation, orthopedic care, genetic counselling, and longitudinal follow-up, alongside investigational therapeutic approaches. Supportive care remains essential; investigational interventions should not be presented as established routine treatment.

Prognosis and natural history

The prognosis of MTM1-related myopathy varies widely. Severe congenital disease may be associated with substantial respiratory morbidity and early mortality, whereas milder phenotypes can permit prolonged survival and varying degrees of independent function. [1,3]

Among individuals with severe disease, respiratory insufficiency, recurrent infections, ineffective cough, aspiration, and nutritional complications are important determinants of outcome. In milder phenotypes, long-term function may be influenced by progressive weakness, contractures, scoliosis, respiratory impairment, and deconditioning.

The natural history of manifesting females is particularly heterogeneous. Some women experience mild weakness, while others develop substantial functional decline over decades. A diagnosis made in adulthood may follow many years of childhood-onset symptoms, emphasizing that age at diagnosis is not a reliable substitute for age at onset. [4-6]

Longitudinal assessment should therefore focus on motor function, respiratory status, swallowing, mobility, and quality of life. A pathogenic MTM1 variant confirms the molecular basis of disease when appropriately interpreted, but it does not establish an individual's precise rate of progression or future respiratory requirements.

Genetic counseling and reproductive considerations

Genetic counseling should address X-linked inheritance, the variable expression of heterozygous females, testing of at-risk relatives, and reproductive options. When a pathogenic familial variant is known, targeted testing can clarify the genetic status of relatives and inform appropriate clinical assessment.

Counseling should avoid presenting heterozygous females as invariably unaffected. Conversely, a heterozygous result does not establish that every woman will develop clinically significant weakness. The potential contribution of X-chromosome inactivation should be explained as a mechanism that may influence disease expression but does not reliably predict an individual's phenotype.

Prenatal and preimplantation genetic testing may be discussed when relevant to the family's circumstances, preferences, and applicable clinical and regulatory requirements. A diagnosis in an affected woman may also prompt reassessment of relatives with unexplained weakness, gait abnormalities, or a history of neonatal neuromuscular disease.

Discussion

MTM1-related myopathy provides an important example of how a pathogenic variant in a single gene can produce markedly different clinical outcomes across individuals. The disease is conventionally associated with severe congenital weakness in males, yet the available clinical and molecular evidence demonstrates a broader spectrum that includes milder male phenotypes, prolonged survival, and clinically significant disease in heterozygous females. A comprehensive understanding of MTM1-related myopathy must therefore extend beyond its classical neonatal presentation and integrate molecular pathogenesis, developmental biology, respiratory complications, genetic variability, and the mechanisms underlying female disease expression. [1,3,4]

1. Reconsidering the classical disease model

The historical description of MTM1-related myopathy has been dominated by severely affected male infants who present with profound hypotonia and respiratory failure. This phenotype remains central to clinical recognition and reflects the substantial morbidity associated with loss of normal myotubularin function. However, it does not represent the full spectrum of disease.

Clinical natural-history studies have documented variability in motor development, respiratory dependence, and survival, while reports of symptomatic females have challenged the assumption that clinically meaningful disease is restricted to males. [1,3-5] The expanded phenotype has implications for diagnosis, genetic counseling, and the design of clinical studies.

A diagnosis based exclusively on the classical neonatal presentation risks missing individuals with milder disease. This is especially consequential when symptoms develop gradually, respiratory involvement is not initially apparent, or the patient has no recognized family history. Clinicians should therefore consider MTM1-related myopathy in a broader range of unexplained congenital and progressive muscle disorders.

2. The diagnostic significance of female manifestations

The recognition of affected females is among the most clinically important developments in the understanding of MTM1-related disease. Women may present with progressive proximal weakness, gait abnormalities, falls, ocular manifestations, asymmetric muscle involvement, and respiratory dysfunction. Some remain undiagnosed until adulthood, when functional decline prompts a more extensive neuromuscular evaluation. [4-6]

These presentations may be misclassified because they do not resemble the severe neonatal phenotype typically associated with the disorder. A woman with childhood-onset waddling gait and slowly progressive limb-girdle weakness may initially be evaluated for a muscular dystrophy, while a patient with persistent weakness and inconclusive nerve-conduction studies may be investigated for an acquired peripheral neuropathy.

Such diagnostic pathways are understandable because the clinical features overlap with several common and uncommon neuromuscular conditions. Nevertheless, repeated failure to substantiate an earlier diagnosis should prompt reconsideration of the differential rather than automatic continuation of the original diagnostic framework.

Normal CK concentrations, preserved reflexes, or the absence of a recognized family history should not independently exclude a primary genetic myopathy. When these findings coexist with childhood-onset weakness, progressive functional impairment, and compatible pathological or genetic evidence, MTM1-related disease warrants consideration.

3. The role and limitations of skewed X-chromosome inactivation

Skewed X-chromosome inactivation offers a biologically plausible explanation for why some heterozygous females develop clinically significant disease. The mechanism is consistent with the mosaic expression of X-linked genes and is supported by reports in which affected women demonstrate preferential activity of the X chromosome carrying the pathogenic variant. [7]

However, the literature does not support treating skewed XCI as a universal explanation for symptomatic female MTM1-related myopathy. Affected women have been reported without demonstrable skewing, and the relationship between measured X-inactivation ratios and clinical severity is not consistent. [4-7,25,26]

Several methodological issues complicate interpretation. First, XCI patterns in blood may differ from those in skeletal muscle. Second, an assay that measures the degree

of skewing may not establish which allele remains active. Third, XCI is only one potential determinant of phenotype and may interact with other genetic or cellular factors.

Consequently, the most scientifically defensible approach is to distinguish the established genetic diagnosis from the proposed mechanism of female disease expression. A pathogenic MTM1 variant, interpreted in the context of a compatible phenotype, may establish MTM1-related myopathy without proving that skewed XCI caused the clinical manifestations.

This distinction is important in reviews of female disease expression. Mechanistic hypotheses should be distinguished from established findings and should not be presented as directly demonstrated without appropriate evidence.

4. Diagnostic implications of female manifestations

Published reports and clinical series show that MTM1-related myopathy in heterozygous females can remain unrecognized for years because symptoms may begin in childhood, progress gradually, and differ from the classical severe neonatal presentation in males. Reported features include gait abnormalities, recurrent falls, proximal weakness, asymmetric involvement, ocular manifestations, and respiratory dysfunction. [4-6]

These presentations may be mistaken for limb-girdle muscular dystrophy, inflammatory myopathy, or peripheral neuropathy. When the clinical course and investigations do not support an earlier diagnosis, clinicians should reconsider the differential diagnosis and evaluate whether a genetic myopathy could explain the findings. [4-6]

Molecular findings should be interpreted alongside the phenotype and the quality of the supporting evidence. A variant of uncertain significance should not be assumed to cause disease or establish a second diagnosis without additional evidence.

The literature supports the clinical relevance of female MTM1-related disease but does not establish skewed X-chromosome inactivation as a universal mechanism. Unless X-inactivation has been directly investigated, its contribution in an individual should be described as a hypothesis rather than a demonstrated finding. [4-7,25,26]

Figure 10 provides a composite visual summary of the proposed mechanisms and clinical spectrum; mechanistic relationships are conceptual and should not be interpreted as proven in every affected individual.

5. Molecular diagnosis and the interpretation of muscle pathology

Muscle biopsy remains valuable when a structural myopathy is suspected, particularly when the clinical phenotype overlaps with other neuromuscular conditions. Central nuclei and type 1 fiber predominance can support a centronuclear myopathy diagnosis, but they do not uniquely identify the underlying gene.

Molecular testing has therefore become central to disease classification. It enables clinicians to distinguish MTM1-related myopathy from other centronuclear myopathies and supports accurate genetic counseling. Copy-number analysis is particularly relevant when large deletions are suspected or when conventional sequencing does not explain the phenotype. [1,5]

The strongest diagnostic interpretation emerges when clinical history, examination, molecular findings, and pathology are concordant. When they are not, the appropriate response is to investigate the discrepancy rather than allow any single finding to determine the diagnosis automatically.

6. Respiratory surveillance as a continuing priority

Respiratory complications remain a major source of morbidity in MTM1-related disease. Severe neonatal presentations clearly demonstrate the importance of respiratory muscle function, but respiratory impairment should not be regarded as exclusive to severely affected infants.

Milder phenotypes and manifesting females may also experience respiratory dysfunction, potentially without dramatic limb weakness. The absence of obvious daytime respiratory symptoms does not necessarily exclude nocturnal hypoventilation or impaired cough effectiveness.

Clinical care should therefore incorporate appropriate respiratory assessment according to symptoms, disease severity, and functional trajectory. Early recognition of respiratory deterioration may facilitate timely intervention and reduce the risk of avoidable complications.

7. Implications for therapeutic development

The development of gene replacement therapy represents a major advance in translational research for MTM1-related myopathy. Clinical studies have demonstrated that restoring a functional copy of MTM1 can be associated with meaningful functional improvement in some patients. However, serious hepatobiliary toxicity has also shown that therapeutic efficacy cannot be considered independently of safety. [8,9]

Future studies must determine how to optimize delivery, dose, tissue targeting, immune management, and long-term monitoring. They must also establish which patients are most likely to benefit and how treatment effects should be measured across different degrees of baseline disability.

The inclusion of manifesting females is particularly important. Their clinical phenotype and cellular expression of the pathogenic allele may differ from those of severely affected males, and the relevance of existing therapeutic evidence to this population remains uncertain.

Therapeutic research should therefore avoid treating all MTM1-related phenotypes as biologically or clinically identical. Stratification by age, sex, respiratory status, functional ability, and molecular characteristics may improve the interpretability of future trials.

8. Priorities for future research

The most important research priorities include prospective characterization of the natural history of symptomatic females, improved methods for evaluating tissue-specific XCI and allele-specific expression, comprehensive investigation of genotype–phenotype relationships, and development of safer targeted therapies.

International registries and standardized clinical outcome measures could improve the quality of observational evidence and facilitate the recruitment of adequately

characterized participants into clinical studies. Particular attention should be directed toward individuals whose disease remains underrecognized because their presentation is mild, atypical, or first diagnosed in adulthood.
Research should also investigate the relationship between molecular mechanisms and clinically meaningful outcomes. Demonstrating an abnormal cellular pathway is important, but its ultimate clinical value depends on whether it improves diagnostic accuracy, prognostic assessment, or treatment development.

Limitations of the evidence
The literature on MTM1-related myopathy is limited by the rarity of the disorder, the predominance of small cohorts and case reports, and differences in clinical assessment across studies. Published reports may disproportionately represent severely affected individuals or unusual female presentations, while milder cases remain undiagnosed.
The relationship between genotype and phenotype is incompletely defined, and the mechanisms underlying disease expression in heterozygous females remain uncertain. Studies of X-chromosome inactivation have used different methods and tissues, limiting direct comparisons and complicating conclusions about the relationship between skewing and clinical severity.
Therapeutic evidence is also constrained by small study populations, evolving clinical trial designs, and significant safety concerns. Early functional improvement does not establish long-term efficacy or an acceptable risk–benefit profile.
As a narrative review, this article does not claim exhaustive literature retrieval or quantitative synthesis. Its conclusions should be interpreted in light of the rarity of MTM1-related myopathy and the predominance of small cohorts, case reports, and preclinical studies.

Future directions
Future research should establish the natural history of MTM1-related myopathy across the full clinical spectrum, with particular attention to manifesting females and individuals diagnosed in adulthood. Prospective studies should evaluate changes in strength, mobility, respiratory function, swallowing, and quality of life using standardized outcome measures. [3-5,35,37]
Improved methods for characterizing XCI and allele-specific expression are needed to determine when these mechanisms meaningfully explain female disease expression. Studies should also investigate additional genetic modifiers and tissue-specific biological factors that may contribute to phenotypic variability. [6,25,26]
Advances in genomic sequencing and copy-number analysis may improve the identification of pathogenic variants in individuals whose initial genetic investigations are nondiagnostic. Functional studies remain important for clarifying uncertain variants and establishing more reliable genotype–phenotype relationships. [10-15,38]
Therapeutic research should prioritize durable clinical benefit and safety. Studies of gene replacement and other disease-modifying approaches should incorporate careful evaluation of organ toxicity, immune responses, dose selection, and patient-specific factors. The inclusion of women with manifesting disease is essential to determine whether therapeutic approaches developed predominantly in males are applicable to other MTM1-related phenotypes. [8,9,27,28]
International registries, collaborative natural-history studies, and standardized reporting would strengthen the evidence base, improve counseling, and support future clinical trials.

Conclusion
MTM1-related myopathy is a genetically defined skeletal-muscle disorder with a broader clinical spectrum than its traditional characterization as a severe neonatal disease in males suggests. Pathogenic MTM1 variants disrupt myotubularin function and interfere with cellular processes essential for normal muscle-fiber organization and contractile performance.
The recognition of manifesting heterozygous females is particularly important because these women may develop childhood-onset or adult-recognized progressive weakness, asymmetric muscle involvement, ocular manifestations, respiratory dysfunction, and substantial functional disability. Normal muscle enzymes, an absent family history, or a previous diagnosis of another neuromuscular disorder should not automatically exclude the possibility of MTM1-related disease.
Molecular genetic testing is central to diagnosis, while muscle pathology, imaging, and electrophysiological studies provide complementary evidence. Skewed X-chromosome inactivation is a plausible contributor to female disease expression, but its role must be distinguished from the established genetic diagnosis and should not be assumed without supporting evidence.
Management remains multidisciplinary, with respiratory surveillance, rehabilitation, nutritional support, orthopedic care, and genetic counseling forming essential components of clinical practice. Emerging disease-modifying therapies offer potential opportunities, but their long-term efficacy and safety require continued investigation.
Finally, earlier recognition of the full clinical spectrum, more precise molecular characterization, and inclusion of affected females in natural-history and therapeutic research are necessary to improve diagnosis, counseling, and care.

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Consent for publication: Not applicable. This manuscript contains no individual patient data, images, or videos.

Availability of data and materials: Not applicable. No datasets were generated or analyzed for this narrative review.

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Integrated visual summaries

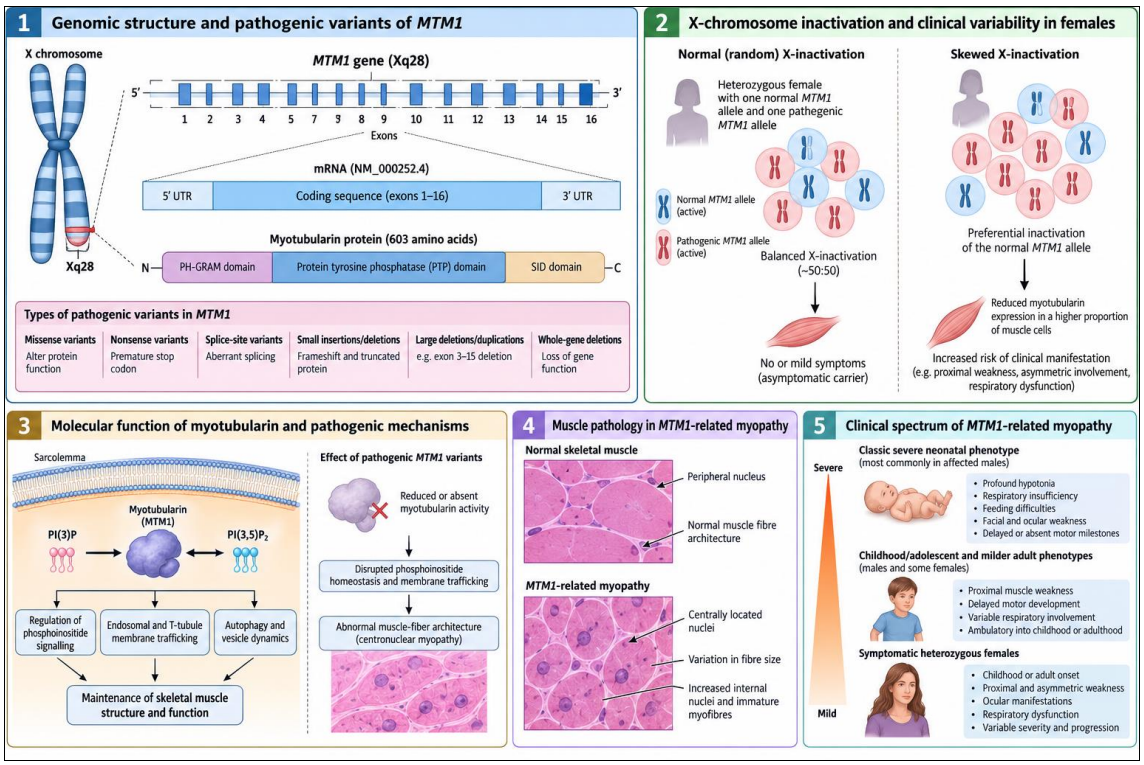


Fig 9: Integrated overview of MTM1 gene structure and pathogenic variants, X-chromosome inactivation, molecular mechanisms, clinical spectrum, and management. Confirm before submission that this composite was created by the authors; if adapted or reproduced, cite the original source and obtain any required permission.

List of abbreviations

AAV, adeno-associated virus; CK, creatine kinase; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNM, centronuclear myopathy; MTM1, myotubularin 1 gene; PLEC, plectin gene; XCI, X-chromosome inactivation; XLMTM, X-linked myotubular myopathy

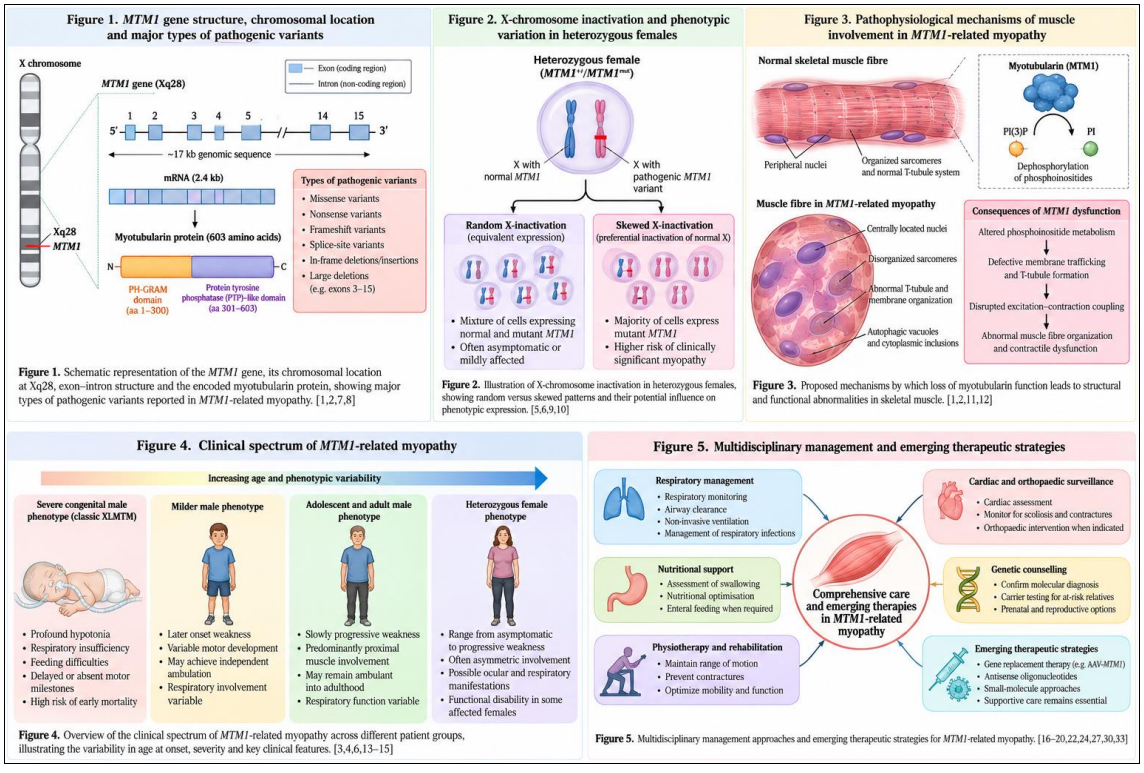


Fig 10: Composite overview of MTM1 genomic structure, female X-chromosome inactivation, molecular pathogenesis, muscle pathology, and clinical phenotypes. Confirm before submission that this composite was created by the authors; if adapted or reproduced, cite the original source and obtain any required permission.

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