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Review

X-linked myotubular myopathy

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Abstract

X-linked myotubular myopathy (XLMTM) is a severe congenital muscle disease caused by mutation in the *MTM1* gene. *MTM1* encodes myotubularin (MTM1), an endosomal phosphatase that acts to dephosphorylate key second messenger lipids PI3P and PI3,5P2. XLMTM is clinically characterized by profound muscle weakness and associated with multiple disabilities (including ventilator and wheelchair dependence) and early death in most affected individuals. The disease is classically defined by characteristic changes observed on muscle biopsy, including centrally located nuclei, myofiber hypotrophy, and organelle disorganization. In this review, we highlight the clinical and pathologic features of the disease, present concepts related to disease pathomechanisms, and present recent advances in therapy development.

1. Introduction

In 1966, Spiro, Shy and Gonatas described the muscle pathology of an adolescent boy with diffuse muscle weakness that included involvement of the facial and extraocular muscles [1]. The appearance of the muscle was reminiscent of fetal myotubes, and the authors termed the condition "myotubular myopathy". While the precise nature and etiology of the unusual myofibers identified by Spiro remain unclear, the terminology has persisted.

In 1985, Heckmatt, Sewry, Hodes and Dubowitz described 8 additional patients with the broader pathological description of centronuclear myopathy, and further summarized all cases with similar biopsy findings known to that date [2]. They distinguish a severe form of the disorder noted for diffuse early onset weakness, respiratory failure, and premature death, and observed that it conformed to an X-linked inheritance pattern. Based on this, they subdivided centronuclear myopathy into dominant, recessive, and X-linked forms, referring to the X-linked form as X-linked myotubular (centronuclear) myopathy, building on Spiro, Shy, and Gonatas to arrive at the name for the disorder most commonly used to today.

In 1996, using positional cloning followed by single-strand conformation polymorphism (SSCP) and Sanger sequencing analyses, Laporte and colleagues described mutations in the myotubularin (*MTM1*) gene as the cause of X-linked myotubular myopathy (XLMTM) [3]. Subsequently, more than 400 different pathogenic variants in *MTM1* have been identified in XLMTM patients [4]. While initially characterized as a protein tyrosine phosphatase, in 2000 two groups (one lead by Mandel and one lead by Dixon) recognized that MTM1 was, in fact, a lipid phosphatase that dephosphorylates 3-position phosphoinositides [5,6]. The interplay between this enzymatic function, its loss by mutation in XLMTM patients, and disease pathogenesis is still being unraveled.

In 2002, the first animal model of the disease (a knockout mouse made by Buj-Bello and Laporte using homologous recombination) was established [7]. This ushered an era of advancement in terms of model identification

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and development (resulting in establishment of mouse [7,8] and zebrafish models [9,10] of XLMTM and discovery of naturally occurring canine models [11–13]), which in turn fueled rapid discovery with respect to disease pathomechanisms and potential treatments. In 2009, two groups (one using the zebrafish model system, and the other using the mouse) uncovered abnormalities in the skeletal muscle triad and the underlying calcium homeostatic molecular machinery [10,14], shifting the focus of disease pathogenesis away from the nucleus and to the critical process of excitation-contraction coupling. In 2008, the first evidence of the potential effectiveness of AAV mediated gene replacement emerged [15]. After seminal studies in the mouse, and subsequently in a canine model of the disease, gene therapy entered clinical trial for XLMTM in 2018 (ASPIRO, NCT03199469) [16].

At the same time as the establishment of the first pre-clinical models, the natural history of the disease was being established. In 2002, two large studies, one led by Herman and the other by McEntagart and Wallgren-Pettersson, described the clinical characteristics and disease course and established genotype-phenotype correlations [17,18]. Several years later, three dedicated natural history studies were completed [19–21], providing a comprehensive view of the disease and establishing outcome measures for clinical trials. These measures provided the basis for those being studied in the three ongoing interventional trials for XLMTM. Most recently, non-muscle features of the disease have emerged, with liver abnormalities the most potentially concerning [22].

In the remainder of this review, we will present further details on the classical muscle pathology of XLMTM, describe aspects of the clinical disease and the underlying genetics, delve into MTM1 function and disease pathomechanisms, present therapeutic strategies, and conclude with some thoughts related to unanswered questions and future directions (Fig. 1).

2. Muscle biopsy – the classic pathology of myotubular myopathy

XLMTM derives its name from the classic and stereotypic findings on muscle biopsy. While these findings are not solely unique to XLMTM, they form a recognizable picture that is immediately suggestive of the diagnosis. From the light microscopic perspective, muscle biopsies for XLMTM patients most commonly show severe variation in fiber size due to the presence of very small, round fibers, an increased number of fibers with large, internally or centrally placed nuclei, and abnormal central aggregation of mitochondria and other organelles [23,24]. While each of these features has the potential to cause weakness, ultrastructural studies have also identified abnormalities of the triad as a key element of weakness in XLMTM [10,23].

The most uniform pathological change in XLMTM across humans and all animal models is the presence of myofiber smallness in the majority of fibers, often with a second fiber population that may be larger in size or even hypertrophic [23]. The small fibers are characterized by round shapes, consistent with insufficient myofiber growth (*i.e.* hypotrophy), often resulting in fiber sizes of 10 μm or less that do not further grow as affected individuals age. There is often a relationship between fiber smallness and fiber type, as frequently all of the slow fibers are within the small fiber population, and any larger fibers will constitute a portion of the fast fiber population. While muscle tissue at early and middle stages of disease most often shows both large and small fiber populations, a minority of diagnostic biopsies and the vast majority of autopsy/end stage necropsy samples show nearly uniform fiber smallness [25,26]. This suggests that the large fiber population undergoes atrophy at late disease stages as an additional element of pathological progression. At present, it is unknown whether fiber smallness can be used as a prognostic indicator for clinical outcomes, although one study reported that fiber size correlated with patient outcomes [27].

Another key element of XLMTM pathology is the abnormal central localization of nuclei, although the degree to which this is seen is highly variable across biopsies [27]. The nuclear changes in human XLMTM most commonly include a large central nucleus that comprises a large portion of the fiber area within the small fiber population, with more variable internal nuclear placement in the large fiber population. It is currently unclear whether abnormal nuclear placement is a significant driver of disease pathogenesis in XLMTM, as it does not correlate well with function in patients or animal models and nuclear placement remains abnormal in humans following gene therapy despite functional gains in many of the treated subjects (Lawlor et al., manuscript in preparation).

The mislocalization of mitochondria, sarcotubular elements, and other organelles is another characteristic feature of XLMTM, and this is often best viewed on oxidative histochemical stains (NADH, SDH, or COX). Interestingly, there are distinct patterns of organelle mislocalization in different species, with central aggregation of organelles surrounded by a subsarcolemmal area without staining in humans, and conversely variable patterns of subsarcolemmal aggregation in murine and canine XLMTM [23]. The mechanism responsible for this mislocalization is unknown, but it is fairly specific for XLMTM and can be entirely resolved with XLMTM gene therapy [16].

Ultrastructural studies of XLMTM muscle confirm the abnormalities of fiber size, nuclear placement, and organelle placement described above. In addition, several studies have identified that the triad structures (composed of two sarcoplasmic reticula and one T-tubule) are abnormally formed or missing in XLMTM models and patient biopsies [10,14]. The triad is critical for appropriate excitation contraction coupling, and abnormalities in this structure represent an important mechanism of weakness. From a diagnostic perspective, assessment of triad morphology and number is not practical, as small issues during the collection and processing of even normal muscle

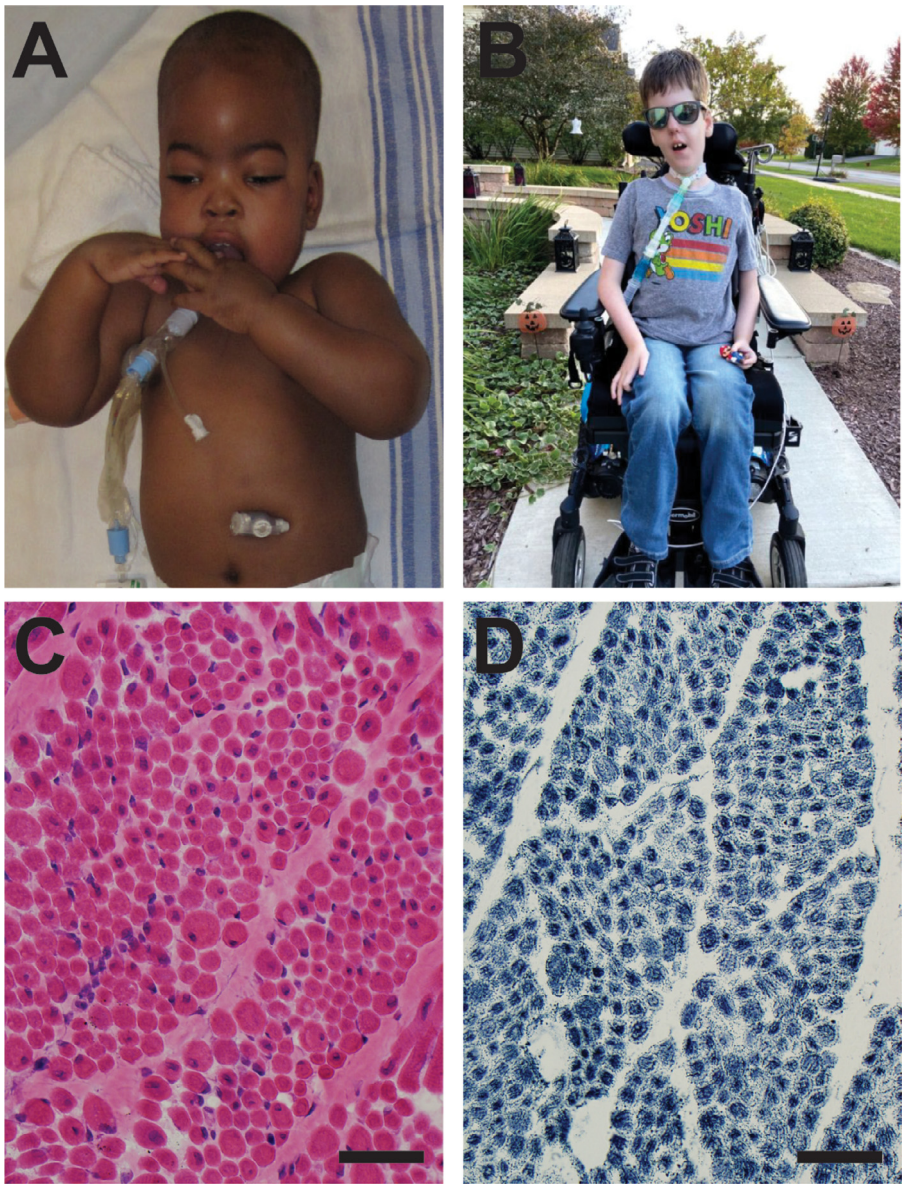

Fig. 1. X-linked myotubular myopathy. (A) 1 year old boy with genetically confirmed XLMTM. Note the long, myopathic facies, bilateral ptosis and extremity muscle hypoplasia. There is evidence of multiple technology dependencies, including invasive ventilator support and G tube for feeding. (B) 8 year old with genetically confirmed XLMTM and typical clinical features of facial weakness, extremity muscle hypoplasia, and wheelchair and ventilator requirements. (C, D) Representative photomicrographs from a muscle biopsy of a boy with confirmed XLMTM. (C) Hematoxylin and eosin stain, showing myofiber hypotrophy and many fibers with prominent, centrally located nuclei, (D) NADH stain showing numerous fibers with accumulated perinuclear organelles. Scale bar = 50 μm.

specimens can produce dramatic artifactual problems in triad morphology.

As mentioned, in their original description, Spiro et al. considered the fibers in XLMTM to be reminiscent of fetal myotubes, and they speculated that XLMTM was caused by an arrest in muscle development. This theory has been the subject of continued debate and discussion, and the true mechanisms underlying the distinctive pathology remain to be fully discovered. In the mouse model, muscle forms normally through the first wave of myogenesis, suggesting fibers are not arrested in the fetal myotube stage. Furthermore, Nishino described the normal appearance of muscle in a 20 week electively terminated fetus, reinforcing that early myogenesis is not impacted [28].

3. Clinical features

While the first published case described an adolescent male who achieved the ability to ambulate and did not require ventilatory support [1], subsequent reports made it clear that this was somewhat exceptional, and that the majority of boys with XLMTM have several weakness that is often fatal in early childhood [2,18]. The typical presentation is one of profound, diffuse weakness and hypotonia manifesting in the

neonatal period, and confounded by persistent respiratory failure and feeding tube dependence [19,20]. One further distinguishing aspect of the clinical phenotype is the presence of ptosis and ophthalmoparesis in the majority of affected individuals [2,19,21].

A significant proportion (ranging from 25 to 50% depending on country of origin) of XLMTM patients die in the first year of life [17,18,20]. Surviving boys have a high technology dependence, with nearly 80% requiring ventilatory and feeding tube support along with wheelchair assistance for ambulation [19]. There continues to be high risk of premature death (estimated at approximately 10% per year after infancy), usually from respiratory complications [19], and only a small number of individuals with the classic presentation survive to adulthood. There is a less severe form of XLMTM, with symptom onset ranging from birth (with hypotonia and mild-moderate weakness) to later in childhood (with weakness and gait abnormalities) [21,29]. Affected individuals with this milder presentation, which may represent up to 20% of all XLMTM cases, typically can ambulate independently and do not require ventilatory support in childhood (though may ultimately develop nocturnal hypoventilation and the need for BiPAP) [19,21,29]. Feeding assistance may still be required.

While XLMTM is primarily a disorder of the skeletal muscle, it has long been suspected that patients experience non-muscle manifestations. For example, affected individuals often have a unique facial gestalt, and often have large growth parameters and elongated hands and feet. Historically the most feared non-muscle condition was hepatic peliosis [18,30], an ultra-rare hemorrhagic liver disease caused by dilation (and ultimately rupture) of hepatic venules. Recently, a more indolent liver disease has emerged that likely impacts many children with XLMTM [19–21]. It seems to most resemble familial intrahepatic cholestasis, though details related to its associated symptoms and overall clinical impact are just emerging [31]. It is, however, an important consideration, particularly in reference to therapeutic interventions (see below). There may also be an element of central nervous system dysfunction, as highlighted in the natural history studies by the report of abnormal psycho-educational assessments in a subset of affected boys [19].

Of note, female carriers of MTM1 mutations can also manifest symptoms. While many carriers are asymptomatic, there is a growing recognition of important clinical presentations in affected girls and women [32,33]. These include extremity weakness, which is often asymmetric, with associated impairments in motor function. As with XLMTM males, eye musculature can also be impacted. Myalgias and muscle fatigue are common and debilitating symptoms [34]. In its most severe form, manifesting carriers can have a severe motor impairment with wheelchair dependence and the need for respiratory support.

4. XLMTM genetics

Pathogenic variants in the *MTM1* gene are the recognized cause of XLMTM. *MTM1* is on the X chromosome and encodes the myotubularin (MTM1) protein [3]. Single nucleotide variants (SNVs) are the most common mutation type described in the *MTM1* gene, with deletions (both small indels and larger deletions that can include the entire gene) and more complex rearrangements reported but much less common [4,35]. Most pathogenic *MTM1* variants result in loss of MTM protein expression, and include nonsense SNVs, indels that result in frameshift with stop gain, and splice site mutations that alter RNA processing. These loss of expression variants are found throughout the gene, with no specific hotspots [17,19]. Most mutations result in the classic, severe presentation of XLMTM. However, some are associated with less severe presentation. These are mainly missense variants, and the theory is that they partially (but not fully) disrupt protein function or partially impair RNA processing and/or protein stability.

Missense variants are less common but also reported. Most occur within areas encoding the defined functional domains of MTM1, particularly the phosphatase domain, and are thought to result in an expressed protein that has reduced function [36]. Phosphatase domain mutations typically result in a clinical picture similar to that seen with nonsense variants, suggesting they completely eliminate protein function. However, for many variants there is not definitive proof that a stable protein is made, and thus the variants may instead act by altering protein folding and stability. In fact, we have computationally modeled several variants, and our models predict that many missense changes (particularly in the SID domain) promote protein misfolding and would thus be expected not to produce stable MTM1 (van Petegem and Dowling, personal communication).

XLMTM is one subtype of a larger category of myopathies termed centronuclear myopathies [37]. CNMs are unified by muscle biopsy features. Other known genetic causes of CNM include mutations in *BIN1*, *DNM2*, *RYR1*, and *SPEG* [38]. In addition to shared muscle pathology, based on the function of these genes, there are also shared molecular and cellular pathomechanisms [39].

5. MTM1 protein function

MTM1 encodes the myotubularin (MTM1) protein, a phosphatase whose main enzymatic function is to dephosphorylate phosphoinositides, specifically the 3-phosphoinositides PI3P and PI3,5P2 [40]. PIPs are small, low abundance phospholipids that serve primarily as signaling molecules by directing the localization and activity of target binding proteins, such as the small GTPase Rab family [41]. MTM1 deactivates PI3P and PI3,5P2 by converting them

to PIP and PI5P, respectively; it also is the main enzyme responsible for generating PI5P [42].

MTM1 and its substrates PI3P and PI3,5P2 are localized to the endo-lysosomal compartment [41]. MTM1's main cellular function, therefore, is related to regulation of dynamic membrane movements within and between the endolysosome. Haucke and colleagues demonstrated a primary role for MTM1 and PI3P in the trafficking of molecular cargo out of the endosome, and in the regulation of the decision to transit cargo either to the plasma membrane or to the lysosome [43]. PI3,5P2 is localized primarily to the lysosome and is critical for lysosomal function [44]. The role of MTM1 dephosphorylation of PI3,5P2 is less well characterized. Of note, via its regulation of PI3P and/or PI3,5P2, MTM1 also functions (at least in cell culture) as a regulator of the mTOR pathway [45], the AKT pathway [46], integrin trafficking and signaling [47], and of the ubiquitin-proteasome system (UPS) [48].

MTM1 likely has non-enzymatic functions as well. It can bind to BIN1 and SPEG [49,50], two proteins also implicated in centronuclear myopathy. The role of the interplay between MTM1 function and interactions with BIN1 and SPEG are not well clarified. Laporte and colleagues demonstrated that MTM1 can interact with Ubiquilin-2 (UBQLN2), and that this interaction is important for the regulated breakdown of intermediate filaments via the UPS [48]. Furthermore, abnormalities in desmin expression, and more generally in protein ubiquitination, have been identified in pre-clinical models of MTM1 deficiency [51]. Lastly, as discussed below, there is an important relationship between MTM1 and DNM2.

MTM1 is the first identified member of a family of lipid phosphatases called the myotubularin related family (or MTMRs). There are both phosphatase active and phosphatase dead MTMRs. The phosphatase dead MTMRs interact with the active MTMRs to regulate their activity [52]. MTM1 directly binds two phosphatase dead MTMRs – MTMR10 and MTMR12 [53]. The closest phosphatase active homologs to MTM1 in the family are MTMR1 and MTMR2. Both have been shown to compensate, at least partially, for the loss of MTM1 in pre-clinical models [10,54,55]. Both are also expressed in muscle, and MTM1 is conversely expressed in many non-muscle tissues. The reason(s) why MTM1 mutation has such a profound impact on skeletal muscle is not clear. Potential explanations include the fact that MTM1 is more highly expressed in muscle than other MTMRs, and that MTM1 may act on different micro pools of PI3P and/or PI3,5P2 as compared to MTMR1 and MTMR2 [56]. Of note, mutations in MTMR2, MTMR5, and MTMR13 cause a recessive form of Charcot-Marie-Tooth disease (CMT4B) [57].

6. XLMTM pathomechanisms

Perhaps the biggest conundrum in the XLMTM field is linking the cellular functions of MTM1 with the pathologic changes observed in muscle with *MTM1* deficiency. In other words, why does loss of an endosomal lipid phosphatase result in the profound abnormalities seen in XLMTM? MTM1's enzymatic activity is at least partially essential for normal muscle structure. This is best demonstrated by the fact that mutations in the active site result in a similarly severe phenotype as seen with null mutations. In addition, reducing PI3P production (via genetic knockdown of *Pik3c2b*) can reverse the pathologic changes seen in *Mtm1* knockout mice [9]. Conversely, there are likely phosphatase independent aspects of the disease phenotype. For example, re-expression of "phosphatase dead" MTM1 in *Mtm1* knockout mice can partially rescue the murine phenotype [58].

An important consideration is how some of the cellular pathways associated with MTM1, such as AKT signaling, desmin breakdown, and autophagy, impact muscle *in vivo*. Changes in the PI3K/AKT/mTOR pathway have consistently been described in animal models of XLMTM [9,43,45,46], and treatment of XLMTM mice with rapamycin ameliorates some aspects of the phenotype [45]. The data related to autophagy is less consistent. On one hand, markers of autophagy can be found to accumulate in advanced stage *Mtm1* KO mice [46]. Also, interfering with autophagy, such as by targeting PIK3C3 or MTMR14, worsens both the zebrafish and mouse phenotypes [9,59]. On the other hand, MTM1 is a weak modulator of autophagy *in vitro* [60], and changes in autophagy are not seen early in the disease process in animal models of the disease.

In terms of the importance of MTM1's association with desmin and the UPS, changes in ubiquitination are seen in the mouse model and in human muscle [48]. Desmin alterations are observed in the mouse knockout as well [51], but not as a common or consistent aspect of the human pathology. Furthermore, both the mouse knockout and human disease are quite distinct from desminopathies, calling in to question the disease relevance of this interaction.

The interplay between MTM1 deficiency and DNM2 is probably the clearest association in terms of disease pathomechanisms. Loss of *Mtm1* in essentially all models studied results in increased DNM2 levels [61]. In wild type mice, overexpression of DNM2 promotes changes in the muscle that resemble most/all the features of centronuclear myopathy [62]. Dominant, gain of function mutations in *DNM2* also cause centronuclear myopathy [63,64]. In many ways, therefore, the increase of DNM2 in XLMTM may drive most aspects of disease pathogenesis. Furthermore, reduction of DNM2 in the XLMTM mouse model, either genetically or with RNA knockdown-based approaches [61,65], can ameliorate most features of the disease. How exactly DNM2 overexpression and/or overactivity leads to CNM is not completely worked out. It likely involves premature scission by DNM2 of the growing T tubule, and also altered maintenance of the triad after formation. It is not clear how triad structural changes, as instigated by loss of MTM1 and increased DNM2 activity, and the central nucleation and organellar disorganization that are hallmarks of the disease are linked, or if they instead represent parallel processes. It is also not known why *MTM1* mutation leads to increased DNM2 levels. As DNM2 transcript levels are only marginally

changed in XLMTM, it appears to at the post-transcriptional level.

7. Therapy development for XLMTM

Despite the incomplete understanding of MTM1 function and disease pathomechanisms, several therapeutic strategies have been identified for XLMTM, and three treatments are in active clinical trial. Therapy development has been greatly aided by the existence of faithful pre-clinical models, including the mouse and zebrafish models mentioned above, and the identification of a naturally occurring canine model. In addition to the three therapeutic approaches highlighted below, other strategies shown to provide at least some amelioration of pre-clinical disease features include PIK3C2B knockdown [9], mTOR modulation [45], and neuromuscular junction stimulation [66,67]. Neuromuscular junction modulators, particularly the acetylcholinesterase inhibitor pyridostigmine, have been shown in a case series to be effective in some XLMTM patients [67].

The therapy in the most advanced stage of testing is gene replacement therapy. MTM1 is encoded by an 1800 base pair cDNA, and thus easily fits within the size restrictions of AAV based gene therapy. AAV based gene replacement was first tested by intramuscular injection, where it proved effective in ameliorating the pathology of the injected muscle [15]. Subsequently, in seminal studies carried out first in a mouse model and later in a canine model, systemic (through IV infusion) treatment with AAV8 encapsulated MTM1 (driven by the desmin promoter) was tested [16]. This therapy showed remarkable effectiveness in these models, preventing disease when administered pre-symptomatically, and reverse disease when given after the animals develop symptoms. The efficacy was seen at the histopathological level, with resolution of pathologic abnormalities, and at the clinical level, with restoration of muscle force generation to normal and with expansion of survival to ages comparable to wild type animals. Interestingly, some molecular aspects of the disease were not completely reversed, as demonstrated by the fact that changes remain when comparing transcriptomes (via RNAseq) between treated disease models and their wild type counterparts [68,69].

A clinical trial of gene replacement therapy (ASPIRO, sponsored by Astellas, NCT03199469) was initiated in 2018. To date, 24 XLMTM patients (age under 6 and with $>$ 12 h permanent ventilation at the start of treatment) have been treated in the clinical trial. Unpublished data presented at international meetings have suggested that the therapy promotes dramatic clinical improvements, though true understanding of the efficacy of the therapy awaits peer reviewed publication. Of note, as mentioned earlier in this review, important adverse events of fatal liver failure were observed in 3 individuals in the study [22,70], underscoring the need for establishing a safe and effective dose of gene therapy, and highlighting an under-recognized role of liver disease in XLMTM.

The observation of DNM2 overexpression in XLMTM led to the hypothesis that lowering DNM2 levels would effectively treat the disease. An antisense oligonucleotide (ASO) based RNA knockdown strategy has been successfully tested in XLMTM mice and is now being advanced to the clinic [65]. A clinical study in adult patients has been initiated (UNITE-CNM, NCT04033159, sponsored by Dynacure), with a pediatric study planned in the near future. Of note, DNM2 knockdown has been explored in models of other forms of CNM (due to *DNM2* mutation and *BIN1* mutation), either by using the genetic and/or the ASO approach and shown to be effective [71,72]. The UNITE-CNM trial is planned to test these subtypes of CNM as well.

Two groups serendipitously identified tamoxifen as a disease modifier in the XLMTM mouse model [73,74]. Daily tamoxifen greatly extends the lifespan of *Mtm1* knockout mouse, and ameliorates many aspects of the phenotype, including the changes in triad structure and in muscle contractility. Maani et al. proposed that tamoxifen acts in the setting of XLMTM by lowering DNM2 levels and demonstrated that tamoxifen can reduce DNM2 expression in both *Mtm1* knockout mice and in fibroblasts from XLMTM patients [74]. Based on these data, a multi-national clinical trial has recently launched to test tamoxifen in XLMTM patients aged 2–65 (TAM4MTM, NCT04915846).

The clinical trials for XLMTM have been greatly aided by multi-national natural history studies [19,21,75]. These studies have been instrumental in defining the key clinical features of the disease and the trajectory of the disease through childhood and into adulthood. They have also enabled the identification of robust, disease sensitive outcome measures that have formed the basis for the design of all three of the current trials.

Importantly, the successful initiation of three independent clinical trials for an ultra-rare condition like XLMTM has been remarkable and reflects the coordination of effort from academics and industry partners, and the support of several funding agencies. It also underscores the amazing work of advocacy groups including the Joshua Frase Foundation, the Myotubular Trust, ZNM Stark!, Where's there a Will, there's a Cure, and the CNM/MTM family connection. Perhaps most importantly, it reflects the dedication of parents and care givers, and the energy and perseverance of affected XLMTM individuals.

8. Future directions

With the first potential therapies on the horizon, the future looks very bright for XLMTM. With potential treatments being available, the need to revise diagnostic recommendations for centronuclear myopathies and to update standards of care becomes important. There is also much that remains to be understood regarding MTM1 function and XLMTM disease pathomechanisms, and the field still fundamentally has not defined MTM1's normal function in skeletal muscle and how loss of this function leads to muscle disease. The emergence of non-muscle phenotypes,

particularly liver disease, requires new study in pre-clinical models, and also new considerations in terms of therapeutic strategies.

Declaration of Competing Interest

MWL is, or has recently been, a member of advisory boards for Solid Biosciences, Taysha Therapeutics, Astellas Gene Therapies (formerly Audentes Therapeutics), and Ichorion Therapeutics. MWL is also a consultant for Astellas Gene Therapies (formerly Audentes Therapeutics), Encoded Therapeutics, Modis Therapeutics, Lacerta Therapeutics, Dynacure, AGADA Biosciences, Affinia Therapeutics, and Biomarin. MWL receives research support from Astellas Gene Therapies, Solid Biosciences, Kate Therapeutics, and Prothelia. JJD is a scientific and medical advisor for Kate Therapeutics and Dynacure, is a site PI for the ASPIRO trial, and has received research support from Astellas and Dynacure.

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Disclosures

MWL is, or has recently been, a member of advisory boards for Solid Biosciences, Taysha Therapeutics, Astellas Gene Therapies (formerly Audentes Therapeutics), and Ichorion Therapeutics. MWL is also a consultant for Astellas Gene Therapies (formerly Audentes Therapeutics), Encoded Therapeutics, Modis Therapeutics, Lacerta Therapeutics, Dynacure, AGADA Biosciences, Affinia Therapeutics, and Biomarin. MWL receives research support from Astellas Gene Therapies, Solid Biosciences, Kate Therapeutics, and Prothelia. JJD is a scientific and medical advisor for Kate Therapeutics and Dynacure, is a site PI for the ASPIRO trial, and has received research support from Astellas and Dynacure.

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