
For patients with
X-linked myotubular myopathy (XLMTM)
Looking ahead to a brighter future in XLMTM
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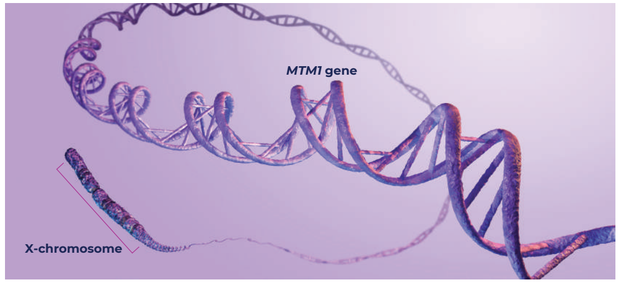
GENE THERAPIES

X-linked myotubular myopathy is a life-threatening, monogenic neuromuscular disorder

X-linked myotubular myopathy (XLMTM) is caused by mutations in the *MTM1* gene[1]



Mutations in the *MTM1* gene can result in profound muscle dysfunction[1,2]

- The *MTM1* gene encodes myotubularin, a protein required for the normal development, organization, and function of skeletal muscle cells
- Mutations in the *MTM1* gene result in the absence of, or dysfunctional, myotubularin protein, and lead to profound muscle weakness and hypotonia, resulting in severe respiratory insufficiency at birth
  - This gene is located on the X chromosome, and XLMTM is inherited in an X-linked recessive manner

Female carriers are frequently asymptomatic, but some exhibit a range of signs and symptoms[3,4]

- Female carriers present from birth to adulthood with symptoms of varying severity that may include:
  - Limb weakness
  - Asymmetric muscle loss
  - Respiratory failure
  - Facial weakness
  - Ptosis
  - Ophthalmoparesis

XLMTM is a rare and life-threatening myopathy requiring early and intensive management

1 in **40,000** to **50,000**
newborn males worldwide[2,5]

- It is a rare congenital myopathy, with an incidence rate estimated at 1 in 40,000 to 50,000 newborn males worldwide[2,5]
- It is the most common and severe form of centronuclear myopathies (CNM), a family of myopathies characterized by muscle fibers with centrally located nuclei[1,5]

Newborn males with XLMTM present with profound muscle weakness, hypotonia, and respiratory distress requiring intensive management[1,2,6]

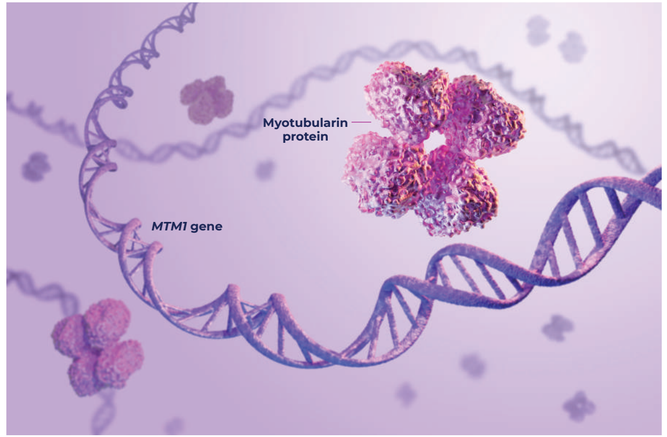
- Approximately 50% of XLMTM patients die in their first 18 months of life due to respiratory failure or related complications[1,6]
- Up to 90% of patients require respiratory support at birth
  - The majority of patients continue to require up to 24 hours of ventilator support thereafter[1,2,6]
- Inability to manage salivary secretions requiring secretion mobilization up to several times hourly[7]
- Feeding difficulties resulting in gastrostomy tube placement in >80% of patients[1,6]
- Comorbidities and complications associated with XLMTM include scoliosis and hepatobiliary disorders[6,8]

~50% of XLMTM patients die in their first 18 months of life[1,6]

References: 1. McEntagart M, et al. *Neuromuscul Disord*. 2002;12(10):939-946. **2.** Graham RJ, et al. *Arch Dis Child*. 2020;105(4):332-338. **3.** Biancalana V, et al. *Acta Neuropathol*. 2017;134(6):889-904. **4.** Cocanougher BT, et al. *Neurology*. 2019;93(16):e1535-e1542. **5.** Vandersmissen I, et al. *Neuromuscul Disord*. 2018;28(9):766-777. **6.** Beggs AH, et al. *Muscle Nerve*. 2018;57(4):550-560. **7.** Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382. **8.** Amburgey K, et al. *Neurology*. 2017;89(13):1355-1364.

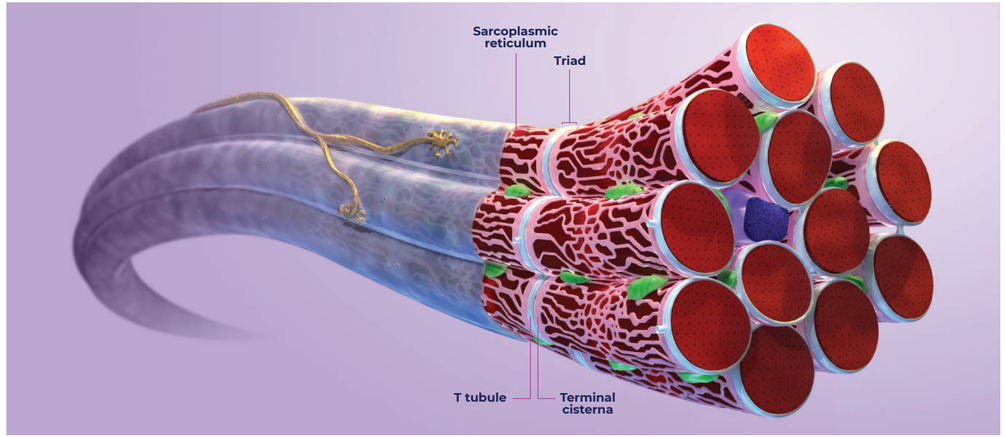
Skeletal muscle impairment due to myotubularin deficiency causes XLMTM

Mutations in the *MTM1* gene result in profound muscle weakness[1,2]



- The *MTM1* gene encodes myotubularin, a protein required for the normal development, organization, and function of skeletal muscle cells[2,3]
- Mutations in the *MTM1* gene result in the absence of, or dysfunctional, myotubularin protein[1,2]

Impaired excitation-contraction coupling causes severe muscle dysfunction in X-linked myotubular myopathy (XLMTM)[4]

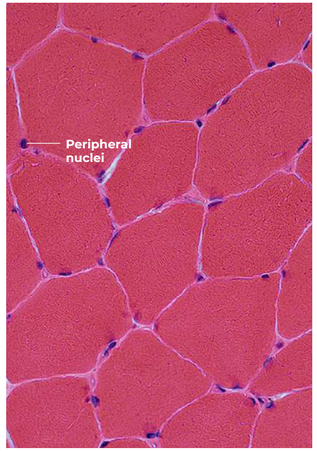


- Dysfunctional or absent myotubularin in skeletal muscle cells results in impaired excitation-contraction (EC) coupling and mislocalization of cellular organelles[4]
- Impaired EC coupling leads to profound muscle weakness, impacting respiratory and neuromuscular function[4]

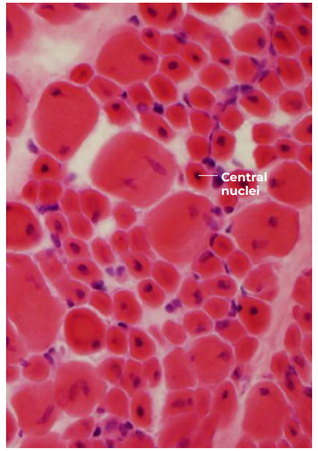
References: 1. Dowling JJ, et al. In: Adam MP, et al., eds. *GeneReviews®*. Published February 25, 2002. Updated August 23, 2018. https://www.ncbi.nlm.nih.gov/books/NBK1432/ **2.** McEntagart M, et al. *Neuromuscul Disord*. 2002;12(10):939-946. **3.** Graham RJ, et al. *Arch Dis Child*. 2020;105(4):332-338. **4.** Zanoteli E. *Expert Opin Orphan Drugs*. 2018;6(6):375-384.

XLMTM pathology has the potential to be improved

Skeletal muscle contractile force in X-linked myotubular myopathy (XLMTM) has the potential to be improved



Normal muscle fibers



Abnormal muscle fibers, XLMTM*

Future therapies can potentially improve the pathology of XLMTM

- Like other centronuclear myopathies (CNMs), XLMTM is characterized by central nuclei in >25% of muscle fibers without obvious evidence of dystrophy[1-3]
- Although absence of or lack of myotubularin causes disorganization of muscle fibers, necrosis is usually absent[1,2]
- Skeletal muscle function in XLMTM is unique in its potential to be improved by repairing function of the triad and recovering contractile force[4-8]

*Courtesy of Michael Lawlor, MD/PhD, Director, Congenital Muscle Disease Tissue Repository, Medical College of Wisconsin.

Unlike in other neuromuscular disorders, muscle fiber necrosis is usually absent in XLMTM[1,2]

Neuromuscular disorder	Clinical findings	Muscle fiber status
X-linked myotubular myopathy (XLMTM) Caused by mutations in *MTM1*[3]	**Profound hypotonia** and **respiratory insufficiency at birth**.[9] Frequently accompanied by[2,9]: • Facial weakness • Dolichocephaly • Bulbar weakness • Ophthalmoparesis, often with ptosis • Long fingers and toes • Frog leg posture • Areflexia	Central nuclei. **Muscle fiber atrophy and necrosis usually absent**[1]
Spinal muscular atrophy, Type 1 (SMA, Type 1) Caused by biallelic mutations in *SMN1*[10]	Progressive muscle weakness, **lack/regression of motor development** and poor muscle tone before 6 months of age.[11] Frequently accompanied by: • **Expressive face** • Respiratory insufficiency • Bulbar weakness	**Muscle fiber atrophy and muscle wasting** due to motor neuron degeneration and loss[11]
Myotonic dystrophy, Type 1 (DM1) Caused by trinucleotide repeat expansion in *DMPK*[12]	Combination of[12,13]: • Hypotonia • Respiratory insufficiency • Difficulty feeding • Facial weakness • Generalized weakness affecting skeletal, smooth muscle, eye, cardiac • **Inverted V upper lip** • Positional malformations, including club foot	Central nuclei. **Muscle fiber atrophy** (particularly of Type 1 fibers), no necrosis[14]
Prader-Willi syndrome (PWS) Caused by loss of expression of multiple genes in chromosome 15 (imprinting disorder, not mutation)[15]	Early infancy: profound hypotonia, bulbar weakness.[15] Followed in later infancy/early childhood by: • Delayed motor milestones and language development • **Cognitive impairment** • Areflexia • **Almond-shaped eyes** • Excessive eating • Hypogonadism	Normal[15]

Muscle fiber degeneration and necrosis are usually absent in XLMTM

References: 1. Lawlor MW, et al. *J Neuropathol Exp Neurol*. 2016;75(2):102-110. **2.** North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116. **3.** McEntagart M, et al. *Neuromuscul Disord*. 2002;12(10):939-946. **4.** Buj-Bello A, et al. *Hum Mol Genet*. 2008;17(14):2132-2143. **5.** Childers MK, et al. *Sci Transl Med*. 2014;6(220):220ra10. **6.** Elverman M, et al. *Muscle Nerve*. 2017;56(5):943-953. **7.** Mack DL, et al. *Mol Ther*. 2017;25(4):839-854. **8.** Maani N, et al. *Nat Commun*. 2018;9(1):4849. **9.** Dowling JJ, et al. In: Adam MP, et al., eds. *GeneReviews®*. Published February 25, 2002. Updated August 23, 2018. https://www.ncbi.nlm.nih.gov/books/NBK1432/ **10.** Arnold WD, et al. *Muscle Nerve*. 2015;51(2):157-167. **11.** Darras BT, et al. Spinal muscular atrophies. In: Darras BT, et al., eds. *Neuromuscular Disorders of Infancy, Childhood, and Adolescence*. 2nd ed. Academic Press; 2015:117-145. **12.** Moxley RT, et al. Myotonic dystrophy. In: Darras BT, et al., eds. *Neuromuscular Disorders of Infancy, Childhood, and Adolescence*. 2nd ed. Academic Press; 2015:697-718. **13.** Bird TD. In: Adam MP, et al., eds. *GeneReviews®*. Published September 17, 1999. Updated October 29, 2020. https://www.ncbi.nlm.nih.gov/books/NBK1165/ **14.** Thornton CA. *Neurol Clin*. 2014;32(3):705-719. **15.** Driscoll DJ, et al. In: Adam MP, et al., eds. *GeneReviews®*. Published October 6, 1998. Updated December 14, 2017. https://www.ncbi.nlm.nih.gov/books/NBK1330/

Early and intensive intervention is frequently required

A majority of X-linked myotubular myopathy (XLMTM) patients die within the first 18 months of life[1]

~50% **Death occurs in ~50% of XLMTM patients in the first 18 months of life[1]**

Death usually occurs due to respiratory failure or related complications such as[1-3]:

- Pneumonia
- Respiratory tract infections
- Ventilator-related accidents

Vast majority of patients experience significant morbidity

90% **Up to 90% of patients require respiratory support at birth[1-3]**

XLMTM patients frequently require early and intensive medical intervention including[1-3]:

- Up to 24 hours of ventilatory support
  - Mechanical ventilation is most common (e.g., transtracheal intubation), with median time to tracheostomy placement at 4.7 months in patients ≤ 5 years old[3]
- Inability to manage salivary secretions requiring secretion mobilization techniques used up to several times hourly[4]

XLMTM morbidity significantly impacts the quality of patient and caregiver lives

Patients experience high rates of hospitalization and procedures

- **1/3 to 1/2 of first year of life:** Average time newborns spend in the hospital[2]
- **2 to 4 surgeries per year:** Required over the next 5 years; gastrostomy and tracheostomy are most common[2]
- **Motor milestones:** 87% of patients are nonambulatory, never achieving normal motor milestones, such as head control, sitting, standing, or walking[2,5]
- **Salivary secretion mobilization:** Inability to manage salivary secretions that require secretion mobilization techniques up to several times hourly[4]
- **Gastrostomy tube placement:** Feeding difficulties result in gastrostomy tube placement in >80% of patients[2,5,6]

Despite the various procedures, patients encounter several complications

- **Scoliosis:** In >70% of patients, which can worsen over time and further impair breathing, requiring surgery[5]
- **Hepatobiliary disorders:** A potentially fatal complication occurring in ~6% of patients[2]

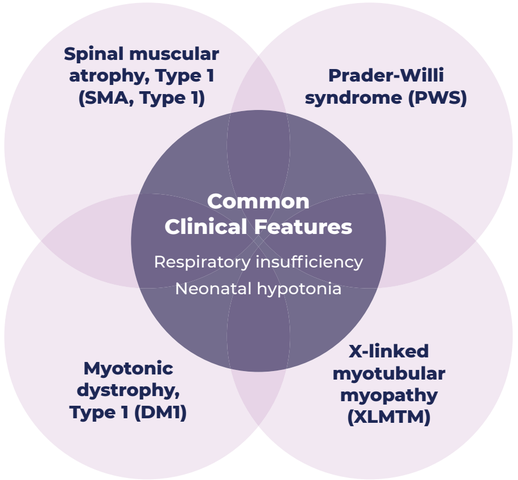
XLMTM is characterized by high rates of morbidity and mortality

References: 1. McEntagart M, et al. *Neuromuscul Disord*. 2002;12(10):939-946. **2.** Beggs AH, et al. *Muscle Nerve*. 2018;57(4):550-560. **3.** Graham RJ, et al. *Arch Dis Child*. 2020;105(4):332-338. **4.** Wang CH, et al. *J Child Neurol*. 2012;27(3):363-382. **5.** Amburgey K, et al. *Neurology*. 2017;89(13):1355-1364. **6.** Annoussamy M, et al. *Neurology*. 2019;92(16):e1852-e1867.

Early and accurate diagnosis of XLMTM is important for effective disease management

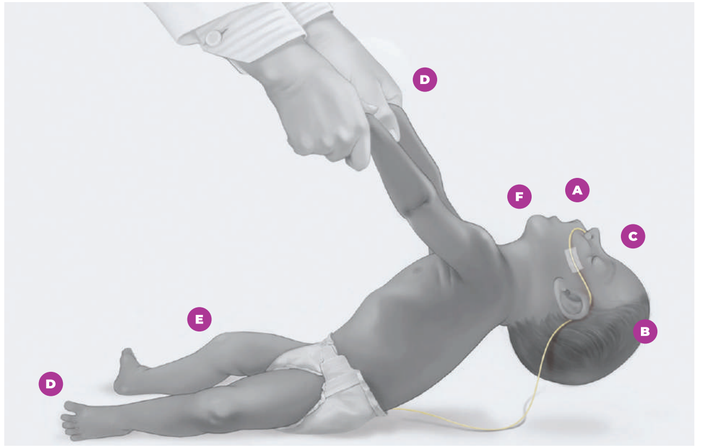
Clinical suspicion of X-linked myotubular myopathy (XLMTM) can create a challenging differential diagnosis

Other clinical myopathies and neuromuscular disorders present some of the same clinical features[1]



Family history and clinical features can assist in raising the suspicion of XLMTM[1]

Key hallmarks of XLMTM



- **A** Facial weakness
- **B** Dolichocephaly, length and head circumference greater than 90th percentile
- **C** Ophthalmoparesis, often associated with ptosis
- **D** Long fingers and toes
- **E** "Frog-leg" posture with abducted hips and flexed knees
- **F** Bulbar weakness, leading to insufficient sucking and swallowing

Areflexia, abnormal, or absent reflexes

Family history of XLMTM

In addition to profound hypotonia and respiratory insufficiency at birth, the above **combined** common features can assist in the differential diagnosis.[1]

Recognizing the key hallmarks of XLMTM can assist in the differential diagnosis process

Reference: 1. North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116.

Genetic testing accelerates and confirms XLMTM diagnosis

While clinical suspicion may be indicative of X-linked myotubular myopathy (XLMTM), genetic testing is required to confirm diagnosis[1-3]

Historically, the following tests have been utilized in the differential diagnosis of XLMTM[1]:

Muscle biopsy

Helps identify centronuclear myopathies (CNMs) like XLMTM, characterized by large, central nuclei of the muscle fibers

Electromyography (EMG)

Helps differentiate between myopathic (e.g., XLMTM) and neuropathic disorders (e.g., SMA)

Although muscle biopsies are indicative of XLMTM, these procedures are invasive and time-consuming and can delay reaching a confirmed diagnosis in the critical early period after birth.[4]

Genetic testing offers several advantages[4]

Establishing the confirmatory molecular diagnosis of XLMTM

Less invasive for patients and cost-effective

Enables early initiation of appropriate management

When ordering a genetic test, please keep these factors in mind[1]

- **Order a panel that includes the relevant genes, especially *MTM1***
- **When possible, involve a geneticist/genetic counselor for interpretation of test results and patient/caregiver communication (e.g., future family planning)**

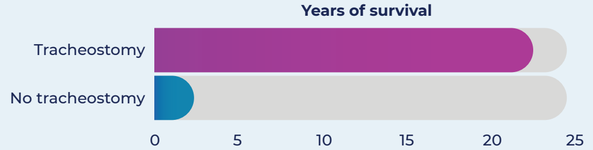
When ordering a genetic test, confirm that *MTM1* is included in the genetic panel

References: 1. Dowling JJ, et al. In: Adam MP, et al., eds. *GeneReviews®*. Published February 25, 2002. Updated August 23, 2018. https://www.ncbi.nlm.nih.gov/books/NBK1432/ **2.** Lawlor MW, et al. *J Neuropathol Exp Neurol*. 2016;75(2):102-110. **3.** North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116. **4.** Harmelink M. *Clin Perinatol*. 2020;47(1):197-209.

Improvements in care are on the horizon

Early and intensive intervention can significantly increase survival

The median time to death for patients with a tracheostomy was 22.8 years compared with 1.8 years for patients without a tracheostomy[1]

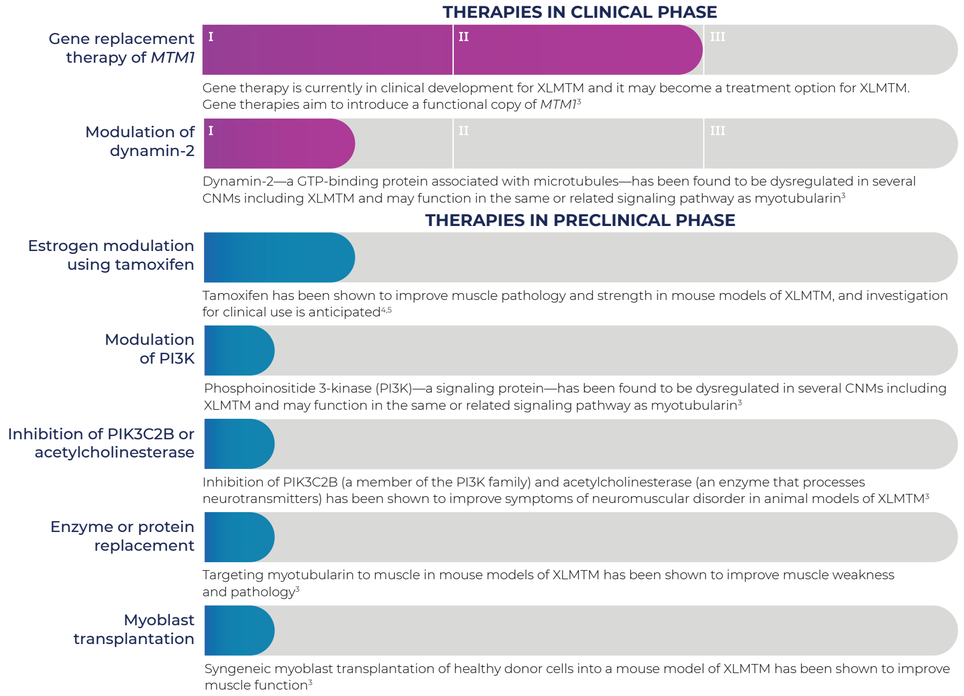


Tracheostomy and gastrostomy tube feeding are often recommended to mitigate risks for aspiration pneumonia and respiratory failure.[2]

Early referral to neuromuscular centers is important for patients to receive optimal care[2]

- Neuromuscular centers are specially equipped to assist X-linked myotubular myopathy (XLMTM) patients in getting an accurate diagnosis and standard of care
- Optimal care of XLMTM patients should be provided by an integrated, multidisciplinary team led by a neuromuscular specialist
- **An XLMTM care team may be composed of specialists in:**
  - Neonatology
  - Pediatric neurology
  - Pulmonology / Respiratory care
  - Genetics and genetic counseling
- Additional support to address specific medical complications related to the underlying myopathy may include specialists in:
  - Gastroenterology
  - Physical therapy
  - Orthodontics
  - Ophthalmology
  - Nutrition
  - Speech therapy
  - Mental health
  - Orthopedics
  - Social services

Several therapies are being investigated for the treatment of XLMTM, some of which target the underlying cause of disease



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Improvements in care are on the horizon

X-linked myotubular myopathy (XLMTM) is a life-threatening, monogenic neuromuscular disorder

It affects approximately 1 in 40,000 to 50,000 newborn males and is caused by mutations in the *MTM1* gene[1,2]

XLMTM pathology has the potential to be improved

Unlike in other neuromuscular disorders, muscle fiber degeneration and necrosis are usually absent in XLMTM[3-5]

XLMTM is associated with high morbidity and mortality

- Death occurs in ~50% of XLMTM patients in the first 18 months of life due to respiratory failure or related complications[6]
- Patients who survive often require intensive medical intervention with up to 24 hours of ventilatory support[1]
- The majority of patients never achieve normal motor milestones, such as head control, sitting, standing, or walking[6]

Genetic testing accelerates and confirms the diagnosis of XLMTM

Recognizing key clinical features of XLMTM and early genetic testing can accelerate diagnosis

XLMTM patients can look forward to improvements in care

Several therapies are being investigated for the treatment of XLMTM, some of which target the underlying cause of the disease[7]

For more information, please visit XLMTM.com

References: 1. Graham RJ, et al. *Arch Dis Child*. 2020;105(4):332-338. **2.** Vandersmissen I, et al. *Neuromuscul Disord*. 2018;28(9):766-777. **3.** Guan X, et al. *Methods*. 2016;99:91-98. **4.** Lawlor MW, et al. *J Neuropathol Exp Neurol*. 2016;75(2):102-110. **5.** North KN, et al. *Neuromuscul Disord*. 2014;24(2):97-116. **6.** McEntagart M, et al. *Neuromuscul Disord*. 2002;12(10):939-946. **7.** Zanoteli E. *Expert Opin Orphan Drugs*. 2018;6(6):375-384.

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