







X-LINKED MYOTUBULAR MYOPATHY

References: 1. McEntagart M, et al. *Neuromuscul Disord* 2002;12(10):939-46; 2. Graham RJ, et al. *Arch Dis Child* 2020;105(4):332-8; 3. Beggs AH, et al. *Muscle Nerve* 2018;57(4):550-60; 4. Herman GE, et al. *J Pediatr* 1999;134(2):206-14; 5. Lawlor MW, et al. *J Neuropathol Exp Neurol* 2016;75:102-10; 6. Molera C, et al. *J Neuromus Dis*, in press; 7. Vandersmissen I, et al. *Neuromuscul Disord* 2018;28:766-77; 8. North KN, et al. *Neuromuscul Disord* 2014;24(2):97-116; 9. Dowling JJ, et al. In: Adam MP, et al, eds. *GeneReviews*. University of Washington, Seattle; 1993-2020; 10. Wang CH, et al. *J Child Neurol* 2012;27:363-82; 11. Servais L, et al. World Muscle Society 2019, Poster P.105; 12. Amburgey K, et al. *Neurology* 2017;89(13):1-10; 13. Dowling JJ et al. *J Neuromuscul Dis*. 2022;9(4):503-516; 14. Biancalana V, et al. *Eur J Hum Genet* 2012;20:1-5; 15. Hnia K, et al. *Trends Mol Med* 2012;18(6):317-27.







This Brochure is for Healthcare Professionals Only



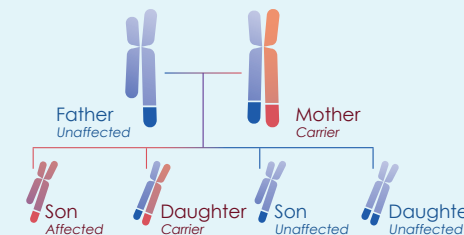
XLMTM is a rare, life-threatening, congenital myopathy caused by mutations in the *MTM1* gene

 Life-threatening disease with significant clinical burden	 Monogenic disease, caused by mutations in <i>MTM1</i>	 Most common and severe centronuclear myopathy	 XLMTM is characterized by muscle comorbidities, requiring multidisciplinary care
<ul style="list-style-type: none"> XLMTM is characterized by profound muscle weakness, leading to life-threatening respiratory and neuromuscular insufficiency¹⁻³ Approximately half of patients die by 18 months, mostly from respiratory failure^{1,2} Patients with XLMTM require repeated hospitalizations and procedures¹⁻⁴ 	<ul style="list-style-type: none"> XLMTM is a monogenic disorder caused by mutations throughout the <i>MTM1</i> gene, resulting in absent or dysfunctional myotubularin protein^{1,5} Myotubularin is a phosphatase required for normal development, maturation and function of skeletal muscle cells⁵ May play a role in endosomal recycling required for bile acid export⁶ 	<ul style="list-style-type: none"> XLMTM is the most common and severe centronuclear myopathy, a group of congenital myopathies characterized by centrally located nuclei⁷ 1 in 40,000 to 50,000 newborn males worldwide are born with XLMTM^{2,7} Clinical suspicion of XLMTM can create a challenging differential diagnosis, as other clinical myopathies present with similar clinical features^{8,9} 	<ul style="list-style-type: none"> XLMTM affects multiple organ systems, and patients experience significant issues with respiratory function, ambulation, gastrointestinal, feeding and liver issues, scoliosis and bone fractures^{1-4,9} Multidisciplinary care teams should include pediatric neurologists, pulmonologists, physical therapists, gastroenterologists, and speech therapists^{9,10}

XLMTM is a life-threatening disease with wide-ranging comorbidities and extensive requirements for medical care

	<p>Life-threatening</p> <ul style="list-style-type: none"> Affects 1:40,000-50,000 live male births⁷ ~50% of patients with XLMTM do not survive past 18 months of age¹
	<p>Respiratory insufficiency</p> <ul style="list-style-type: none"> 90% require respiratory support at birth, most requiring ≥18 hours per day^{2,11} 60% of patients require tracheostomy¹¹ and show improved survival vs non-tracheostomized patients²
	<p>Repeated hospitalizations</p> <ul style="list-style-type: none"> Newborns spend an average of 30–50% of their first year of life in the hospital¹ Morbidity, hospitalization and dependence on ventilation significantly impact quality of life for patients and caregivers^{1,11}
	<p>Delayed or absent motor milestones</p> <ul style="list-style-type: none"> Little to no muscle strength results in inability to achieve motor milestones, including controlling head, sitting, and standing^{3,12}
	<p>Hepatobiliary disease</p> <ul style="list-style-type: none"> 24% of patients have history of hepatic disease, including cholestasis and hyperbilirubinemia¹² Jaundice (18%), hepatomegaly (8%), cholelithiasis (6%)¹³
	<p>Feeding difficulties</p> <ul style="list-style-type: none"> >90% require gastrostomy tube¹² Extensive caregiver support with feeding and secretions management¹²

X-linked, recessive, monogenic disorder



- XLMTM has an X-linked recessive pattern of inheritance^{2,3}
- Over 400 unique mutations in the *MTM1* gene have been associated with XLMTM in patients^{4,15}
- Loss-of-function mutations have the worst prognosis, with a median survival of 6.2 years²

MTM1 encodes myotubularin

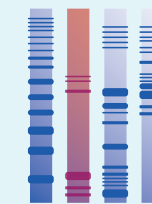


Myotubularin is a phosphatase that participates in many cellular processes^{1,16}

- Excitation–contraction coupling
- Cytoskeletal organization and structure
- Neuromuscular junction structure (triad)
- Satellite cell proliferation and survival
- Endosome recycling and autophagy

XLMTM has a challenging differential diagnosis; genetic testing is the only definitive diagnostic method

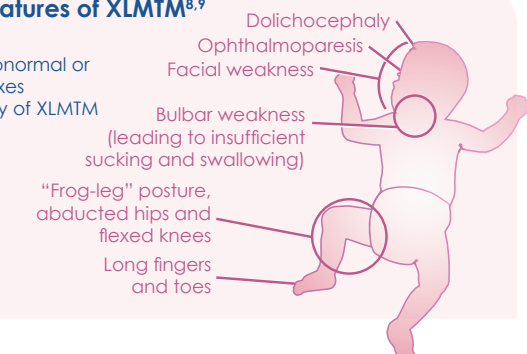
Genetic testing confirms XLMTM diagnosis



Genetic testing is required to confirm clinical suspicion of XLMTM and provide definitive diagnosis^{8,9}

Hallmark features of XLMTM^{8,9}

- Areflexia, abnormal or absent reflexes
- Family history of XLMTM



Optimal care should be provided by an integrated, multidisciplinary team led by a neuromuscular specialist^{3,9,10}

Surgery/anesthesia

- Intensive monitoring during anesthesia
- Avoidance of intubation if possible
- Avoidance of succinylcholine and inhalational agents

Respiratory therapist

- Assessment of pulmonary function for long-term ventilatory management
- Tracheostomy
- Polysomnography every 1–3 years
- Secretion management

Orthopedics

- Evaluation for orthopedic complications
- Scoliosis and contracture examinations
- Prevention and treatment of bone fractures and hip dysplasia

Gastroenterologist

- Investigations and treatment for pyloric stenosis, reflux, gallstones and kidney stones
- Feeding tube placement
- Constipation management

Pediatric neurologist

Patient and family support and point of contact responsible for informing and educating medical team on specific care needs and prognosis

General practitioner

- Maintenance of healthy body weight, good nutrition
- Routine immunizations, pneumococcal and influenza vaccines
- Prophylactic antibiotics

Ophthalmologist

- Examinations for ophthalmoplegia, ptosis and myopia
- Protective assessment of effect of impaired eyelid closure

Physical/occupational therapist

- Feeding, swallowing assessment, speech therapy
- Promotion of physical activity and assisted ambulation and mobility
- Management of pain and fatigue

Hepatologist

- Routine liver function tests and abdominal ultrasound to address risk of hepatic peliosis and hepatobiliary disease