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GENE THERAPIES

X-LINKED MYOTUBULAR MYOPATHY

This Disease Education Brochure is for Healthcare Professionals Only

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GENE THERAPIES

X-LINKED
MYOTUBULAR MYOPATHY

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

Life-threatening disease with significant clinical burden

- **XLMTM** is characterized by profound **muscle weakness, leading to life-threatening respiratory and neuromuscular insufficiency**[1–3]
- **Approximately half of patients die by 18 months,** mostly from respiratory failure[1,2]
- Patients with XLMTM require **repeated hospitalizations and procedures**[2–4]

Monogenic disease, caused by mutations in *MTM1*

- XLMTM is a **monogenic disorder caused by mutations** throughout the ***MTM1* gene,** resulting in absent or dysfunctional **myotubularin** protein[1,5]
- **Myotubularin** is a **phosphatase** required for normal development, maturation and **function of skeletal muscle cells**[5]
- May play a role in endosomal recycling required for bile acid export[6]

Most common and severe centronuclear myopathy

- XLMTM is the **most common and severe centronuclear myopathy,** a group of congenital myopathies characterized by **centrally located nuclei**[7]
- **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]

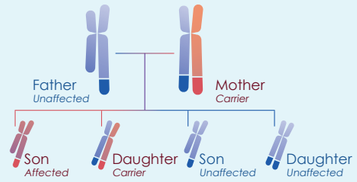
XLMTM is characterized by muscle comorbidities, requiring multidisciplinary care

- **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

Life-threatening	• Affects 1:40,000-50,000 live male births[2,7] • ~50% of patients with XLMTM do not survive past 18 months of age[1]
Respiratory insufficiency	• 90% require respiratory support at birth, most requiring ≥18 hours per day[2,11] • 60% of patients require tracheostomy and show improved survival vs non-tracheostomized patients[2]
Repeated hospitalizations	• Newborns spend an average of 30–50% of their first year of life in the hospital[3] • Morbidity, hospitalization and dependence on ventilation significantly impact quality of life for patients and caregivers[2,11]
Delayed or absent motor milestones	• Little to no muscle strength results in inability to achieve motor milestones, including controlling head, sitting, and standing[3,12]
Hepatobiliary disease	• 24% of patients have history of hepatic disease, including cholestasis and hyperbilirubinemia[13] • Jaundice (18%), hepatomegaly (8%), cholelithiasis (6%)[13]
Feeding difficulties	• >90% require gastrostomy tube[13] • Extensive caregiver support with feeding and secretions management[13]

X-linked, recessive, monogenic disorder



- XLMTM has an X-linked recessive pattern of inheritance[2]
- Over 400 unique mutations in the MTM1 gene have been associated with XLMTM in patients[14,15]
- Loss-of-function mutations have the worst prognosis, with a median survival of 6.2 years[2]

MTM1 encodes myotubularin

Myotubularin is a phosphatase that participates in many cellular processes[16]

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

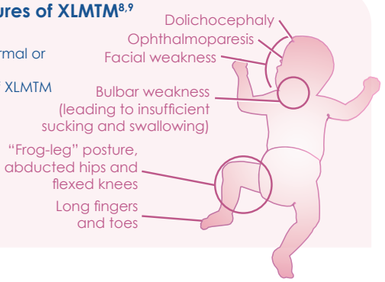
XLMTM has a challenging differential diagnosis; genetic testing is the only definitive diagnostic method

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[9]

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