**Condition Description**

X-linked myotubular myopathy (XLMTM) is a non-progressive muscle disease associated with hypotonia, respiratory distress, and delayed motor milestones. Four forms of the disease have been described.

- **Severe (classic) XLMTM** presents prenatally with polyhydramnios and decreased fetal movement and in newborns with hypotonia and respiratory distress. Affected males have chronic ventilator dependence and grossly delayed motor milestones; they often fail to walk. Infants with severe XLMTM often have typical myopathic facies with dolicocephaly, high forehead, long face with midface hypoplasia, and narrow high-arched palate with subsequent severe malocclusion. Additional features can include length greater than the 90th centile with a proportionately lower weight, long fingers and toes, cryptorchidism, contractures including clubfeet, areflexia, ptosis, severe myopia, dental malocclusion, and scoliosis. In the absence of significant hypoxic episodes, cognitive development is normal in the majority of individuals. Death in infancy is common.

- **Males with moderate XLMTM** achieve motor milestones more quickly than males with the severe form; about 40% require no ventilator support or intermittent support. Males with moderate or even mild disease are at increased risk for respiratory decompensation with intercurrent illness and may require transient or increased ventilatory support. They are also at risk for some of the same medical complications as those with severe XLMTM.

- **Males with mild XLMTM** may require ventilatory support only in the newborn period; they have minimally delayed motor milestones, are able to walk, and lack myopathic facies.

- **Adult-onset XLMTM** is very rare; affected males do not have clinical manifestations in infancy but develop slowly progressive myopathy in adulthood. They may require respiratory support at night.

The muscle disease of XLMTM is not progressive; muscle strength improves slowly over time. Phenotype can vary within a family. Female carriers of XLMTM are generally asymptomatic, although rare manifesting heterozygotes have been described, usually due to skewed X-inactivation.

The diagnosis of XLMTM has traditionally relied upon identification of characteristic histopathologic changes in muscle samples from males with neonatal hypotonia and a family history consistent with X-linked inheritance. These histopathologic changes, however, are not found in all affected individuals, and are not specific to XLMTM. An abnormal muscle biopsy is found in only 50%-70% of obligate carrier females; thus, muscle biopsy studies are not sensitive enough for carrier testing.

**MTM1** (Xq28) is the only gene associated with XLMTM; its protein product, myotubulin, is required for muscle cell differentiation. Molecular genetic testing of **MTM1** detects mutations in 60%-98% of affected individuals; in individuals with mild XLMTM, fewer than 20% of mutations are identified. Approximately 7% of mutations are large deletions of one or more exons of **MTM1**. In simplex cases (i.e., a single occurrence in a family), there is a probability of 80%-90% that a woman is a carrier if her son has a confirmed **MTM1** mutation. Thus, about 10%-20% of males who represent simplex cases have a de novo disease-causing mutation in **MTM1** and a mother who is not a carrier. Germline mosaicism has been reported.

For patients with suspected XLMTM, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not detected, analysis of the **MTM1** promoter region may be informative.
are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

Click here for the GeneTests summary on this condition.

### Genes

**MTM1**

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of XLMTM
- Carrier testing in adult females with a family history of XLMTM

### Methodology

PCR amplification of 14 exons contained in the *MTM1* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

### Detection

Clinical Sensitivity: Molecular genetic testing of *MTM1* detects mutations in 60%-98% of affected individuals; in individuals with mild XLMTM, fewer than 20% of mutations are identified. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

### Specimen Requirements

Submit only 1 of the following specimen types

#### Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

#### Type: Saliva

Specimen Requirements:

Please contact the laboratory for a saliva collection kit.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

### Related Tests

- Deletion/duplication analysis of the *MTM1* gene by CGH array is available for those individuals in whom sequence analysis is negative (ZA).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- **Custom diagnostic mutation analysis (KM)** is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.