X-linked Myotubular Myopathy: \textit{MTM1} Gene Deletion/Duplication

\textbf{Test Code:} ZA  
\textbf{Turnaround time:} 2 weeks  
\textbf{CPT Codes:} 81405 x1

\textbf{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.

\textit{MTM1} (Xq28) is the only gene associated with XLMTM; its protein product, myotubulin, is required for muscle cell differentiation. Molecular genetic testing of \textit{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 \textit{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 \textit{MTM1} mutation. Thus, about 10%-20% of males who represent simplex cases have a \textit{de novo} disease-causing mutation in \textit{MTM1} and a mother who is not a carrier. Germline mosaicism has been reported.

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## Genes

**MTM1**

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of XLMTM in individuals who have tested negative for sequence analysis
- Carrier testing in adult females with a family history of XLMTM who have tested negative for sequence analysis

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### 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

- Sequencing analysis of the MTM1 gene is available (YZ) and is required before deletion/duplication analysis.
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- 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.