

The University of Chicago Genetic Services



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MTM1 analysis for Myotubular Myopathy

Clinical Features:

X-linked myotubular myopathy (XLMTM) is a non-progressive muscle disease associated with hypotonia, respiratory distress, and delayed motor milestones. Death in infancy is common in males with the classic form of this condition. Milder forms of this condition have been identified, and are characterized by fewer respiratory complications and longer life expectancy than observed in the severe cases [1]. Female carriers of XLMTM are generally asymptomatic, although there have been several cases of symptomatic carriers with skewed X-inactivation [2].

Patients have a typical muscle histopathology that is similar to fetal myotubes, with small rounded muscle fibers and no surrounding contractile elements. In the presence of a family history consistent with X-linked inheritance, this is suggestive of XLMTM. However, other congenital myopathies can have similar findings on muscle biopsy, so it is not diagnostic for XLMTM. Muscle biopsies are generally not used to identify carrier females, as only 50-70% of carriers will have an abnormal biopsy [1].

Inheritance:

XLMTM is an X-linked condition that occurs in 1 in 50,000 male live births [1]. Less than 20% of these cases are due to *de novo* mutations [3]. Recurrence risk for a carrier female is 50%. All daughters of affected males are obligate carriers and at risk for having affected sons. Germline mosaicism has been observed [1].

Molecular Genetics:

XLMTM is caused by mutations in the *MTM1* gene located at Xq28 [4, 6]. *MTM1* codes for the myotubularin protein, a highly conserved phosphatase thought to be involved in cellular transport and trafficking [1]. Over 190 disease-associated mutations have been identified to date in the *MTM1* gene. Truncating and splice site mutations are more likely to be associated with the severe neonatal form, whereas the milder phenotypes are often caused by missense mutations outside of the functional domains [1]. Missense mutations may result in a mild or severe phenotype based on their position in the *MTM1* gene [5].

Approximately 80% of males with a diagnosis of myotubular myopathy by muscle biopsy will have a mutation in *MTM1* identifiable by sequence analysis. About 7% of mutations in *MTM1* are deletions [3].

Additional Resources:

Myotubular Myopathy Resource Group
Phone: (409) 945-8569
Email: info@mtmrg.org
www.mtmrg.org

Test methods:

We offer mutation analysis of all 14 coding exons of *MTM1* by sequencing, which will detect mutations and deletions in males. In addition, deletion analysis of the 5'-UTR (exon 1) is also performed. If a deletion is detected in the *MTM1* gene in an affected male, carrier testing may be performed on females in the family by real-time quantitative PCR. However, if carrier testing is offered prior to identifying the familial mutation, deletions may not be detected in females.

Mutation analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2025
CPT codes:	83891, 83898 x 4, 83904 x 9, 83912
Turn-around time:	4-6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$540
CPT codes:	83891, 83898 x 2, 83894, 83912, 88235-52
Turn-around time:	1-2 weeks

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

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References:

1. Das S, Herman GE (2004) X-linked Myotubular Myopathy. www.genetests.org
2. Kristiansen M, et al. (2003) X-inactivation patterns in carriers of X-linked myotubular myopathy. *Neuromuscul Disord* 13:468-71.
3. Laporte J, et al. (2000) *MTM1* mutations in X-linked myotubular myopathy. *Hum Mut* 15:393-409.
4. Laporte J, et al. (1997) Mutations in the *MTM1* gene implicated in X-linked myotubular myopathy. *Hum Molec Genet* 6:1505-11.
5. McEntagart M, et al. (2002) Genotype-phenotype correlations in X-linked myotubular myopathy. *Neuromuscul Disord* 12:939-46.
6. de Gouyon BM, et al. (1997) Characterization of mutations in the myotubularin gene in twenty-six patients with X-linked myotubular myopathy. *Hum Mol Genet* 6(9): 1499-1504.