

The University of Chicago Genetic Services Laboratories



5841 S. Maryland Ave., Rm. L035, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 834 0556
ucgslabs@genetics.uchicago.edu www.genes.uchicago.edu
CLIA #: 14D0917593 CAP #: 18827-49

MTM1 & DNM2 analysis for Centronuclear & Myotubular Myopathy

Information for Genetics Professionals

Clinical Features:

Centronuclear myopathy (CNM) is a rare muscle disease associated with non-progressive or slowly progressive muscle weakness that can develop from infancy to adulthood [1,2]. On muscle histopathology, patients with CNM have increased frequency of central nuclei, as well as type 1 fiber predominance and hypotrophy, in the absence of other significant abnormalities. Other neuromuscular conditions can have similar findings on muscle biopsy, so these features are not always diagnostic for CNM [1,2].

Patients with [X-linked myotubular myopathy \(XLMTM\)](#) [OMIM#310400] generally present with hypotonia, feeding difficulties, respiratory distress, and delayed motor milestones. Death in infancy is common in males with the classic form of this condition. Milder forms of XLMTM have been identified and are characterized by fewer respiratory complications and longer life expectancy than observed in the severe cases [3]. Intelligence is usually normal [1]. Muscle of patients with XLMTM appears 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, these findings are suggestive of XLMTM. Female carriers generally do not have significant muscle weakness or notable features of XLMTM, although there have been several cases of symptomatic carriers with skewed X-inactivation [4]. *MTM1* testing can be considered in females with a biopsy consistent with CNM. Muscle biopsies are generally not used to identify XLMTM carrier females, as only 50-70% of carriers will have an abnormal biopsy [3].

The majority of patients with [autosomal dominant or later onset CNM](#) [OMIM#160150], including *DNM2*-associated CNM, are ambulatory into adulthood [1,2]. Some patients with *DNM2*-associated CNM have a more severe infantile onset and may have early feeding and respiratory issues, as well as delayed milestones [5]. Intelligence is usually normal [1], but at least one family with a *DNM2* mutation has been reported to have mild cognitive impairment, as well as mild axonal peripheral nerve involvement [6]. NADH staining of patients with *DNM2* mutations often reveals radial arrangement of sarcoplasmic strands, which is highly characteristic of *DNM2*-associated CNM [6].

Inheritance:

[XLMTM](#) is an X-linked condition that occurs in 1 in 50,000 male live births [7]. Less than 20% of these cases are due to *de novo* mutations [7]. 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 [3].

[DNM2-associated CNM](#) is a rare condition and is generally believed to be less common than XLMTM. The majority of cases appear to be autosomal dominant, but *de novo* mutations are not uncommon and several recurrent *de novo* mutations have been identified [8]. Recurrence risk is 50%. Germline mosaicism has not been reported in *DNM2*-associated CNM but remains a possibility.

Molecular Genetics:

CNM can be caused by mutations in at least three genes, including *DNM2* and *MTM1*. [XLMTM](#) is caused by mutations in the *MTM1* [OMIM#300415] gene located at Xq28 [9,10]. *MTM1* codes for the myotubular protein, a highly conserved phosphatase thought to be involved in cellular transport and trafficking [3]. 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 [3]. Missense mutations may result in a mild or severe phenotype based on their position in the *MTM1* gene [11]. 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 [7].

DNM2 [OMIM#602378] is the only gene currently known to be associated with **autosomal dominant CNM**. *DNM2* mutations account for most, but not all, cases of CNM with autosomal dominant inheritance or later onset. The *DNM2* gene, located at 19p13.2, encodes the dynamin 2 protein, a ubiquitously expressed GTPase primarily involved in endocytosis and membrane trafficking [8]. The protein is composed of 5 different domains, including the middle and PH domain. To date, fewer than 10 disease-associated mutations have been identified in the *DNM2* gene. Mutations in the PH domain of the protein are more likely to be associated with severe neonatal onset, whereas the milder phenotypes with later onset are often caused by mutations in the middle domain [5]. The majority of mutations identified thus far are missense mutations, but at least one small deletion has been reported [5,8]. Mutations in *DNM2* have also been associated with dominant intermediate Charcot-Marie-Tooth disease, type B [OMIM#606482].

Additional Resources:

The Information Point for Centronuclear and Myotubular Myopathy
<http://centronuclear.org.uk/>

Joshua Frase Foundation
Phone: (617) 715-1155
<http://www.joshuafrase.org/>

Congenital Myopathy Research Program
Beggs Laboratory, Childrens Hospital Boston
Phone: (617) 919-2169
Email: edechene@enders.tch.harvard.edu
<http://www.childrenshospital.org/research/beggs>

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

Muscular Dystrophy Association (MDA)
Phone: (800)572-1717
www.mda.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.

We also offer mutation analysis of all 22 coding exons of *DNM2* by sequencing, which will detect mutations in males and females.

MTM1 mutation analysis (sequencing)

Sample specifications:	3 to10 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

DNM2 mutation analysis (sequencing)

Sample specifications:	3 to10 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 to10 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:	\$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
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:

Soma Das, Ph.D.
Director, Molecular Genetics Laboratory
ABMG Certified Molecular Geneticist

Stuart Schwartz, Ph.D.
Director, Cytogenetics Laboratory
ABMG Certified Cytogeneticist

William B. Dobyns, M.D. and Darrel J. Waggoner, M.D.
Clinical Advisors
ABMG Certified Clinical Geneticists

Melissa Dempsey, M.S.
Certified Genetic Counselor

References:

1. Pierson CR, *et al* (2005) X-linked myotubular and centronuclear myopathies. *J Neuropathol Exp Neurol* 64(7): 555-64.
2. Fardeau M, Tome F (1994) Congenital Myopathies. In: Engel AG, Franzini-Armstrong C, eds. *Myology*, 2nd ed. New York: McGraw-Hill: 1500-1505.
3. Das S, Herman GE (2004) X-linked Myotubular Myopathy. www.genetests.org
4. Kristiansen M, *et al*. (2003) X-inactivation patterns in carriers of X-linked myotubular myopathy. *Neuromuscul Disord* 13:468-71.
5. Bitoun M, *et al* (2007) Dynamin 2 mutations cause sporadic centronuclear myopathy with neonatal onset. *Ann Neurol* 62(6): 666-70.
6. Echaniz-Laguna A, *et al* (2007) Subtle central and peripheral nervous system abnormalities in a family with centronuclear myopathy and a novel dynamin 2 gene mutation. *Neuromuscul Disord* 17: 95-9.
7. Laporte J, *et al*. (2000) *MTM1* mutations in X-linked myotubular myopathy. *Hum Mut* 15:393-409.
8. Bitoun M, *et al* (2005) Mutations in dynamin 2 cause dominant centronuclear myopathy. *Nat Genet* 37: 1207-9.
9. Laporte J, *et al*. (1997) Mutations in the *MTM1* gene implicated in X-linked myotubular myopathy. *Hum Molec Genet* 6:1505-11.
10. 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.
11. McEntagart M, *et al*. (2002) Genotype-phenotype correlations in X-linked myotubular myopathy. *Neuromuscul Disord* 12:939-46.

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS