



The University of Chicago Genetic Services Laboratories

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Genetic Testing for Centronuclear & X-linked Myotubular Myopathy

Information for Non-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. 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.

X-linked myotubular myopathy is one form of centronuclear myopathy. 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. Intelligence is usually normal. 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. *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.

The majority of patients with **autosomal dominant or later onset CNM** [OMIM#160150] are ambulatory into adulthood. 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. Intelligence is usually normal, 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. NADH staining of patients with *DNM2* mutations often reveals radial arrangement of sarcoplasmic strands, which is highly characteristic of *DNM2*-associated CNM.

Inheritance and Etiology:

CNM can be inherited in an autosomal recessive, X-linked, or autosomal dominant pattern. There is currently no clinical testing available for autosomal recessive CNM. Individuals with mutations in *MTM1* have X-linked CNM, known as **XLMTM**. Approximately 80% of males with a diagnosis of myotubular myopathy by muscle biopsy will have a mutation in *MTM1* identifiable by sequence analysis. Less than 20% of these cases are due to *de novo* or new mutations. 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.

Individuals with mutations in *DNM2* have sporadic or autosomal dominant CNM. *DNM2* mutations account for most, but not all, cases of CNM with autosomal dominant inheritance or later onset. Recurrence risk for affected individuals is 50%. Mutations in *DNM2* have also been associated with dominant intermediate Charcot-Marie-Tooth disease, type B.

Genetic Testing:

The first person to be tested in any family would be the individual with features of CNM. Once a mutation in the *MTM1* or *DNM2* gene is identified in the individual with CNM, testing for other family members, or even prenatal testing, is relatively easy.

Reasons for genetic testing for CNM:

- confirm the diagnosis
- offer reassurance that other family members are not affected
- provide accurate information and counseling resources for future pregnancies
- provide accurate information during a pregnancy regarding possible CNM in the fetus

Test ordering and Billing:

Clinical testing for CNM is now available at The University of Chicago Genetics Services Laboratory. A test requisition form, consent form and clinical data sheet are required for testing. These forms can be found on the lab website (www.genes.uchicago.edu) or by calling the lab. If there are any questions about ordering testing, please contact the lab.

All insurance companies are different, but most of them should cover at least part of the cost of testing. We recommend that a parent or physician's office contact the patient's insurance company with the specific CPT codes (below) to learn more about the specific coverage prior to testing. The University of Chicago will bill the patient's insurance company, hospital or referring laboratory. The patient may receive a bill for any amount not covered by the insurance company. If the patient does not have medical insurance and we cannot bill their institution, we will require payment by check or credit card before beginning testing.

Please send a completed CNM Clinical Checklist and patient consent form with each sample.

MTM1 mutation analysis (sequencing)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$2,025
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:	\$2,025
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

Possible Results of Genetic Testing:

- 1 mutation detected in a patient with possible XLMTM or CNM: finding one mutation will confirm a diagnosis of XLMTM or CNM. This allows for easy testing of other family members, who may choose to be tested.
- No mutation detected: not finding a mutation does not rule out the diagnosis of XLMTM or CNM.
- Variant of unknown significance: A small number of patients will have a change in the *MTM1* or *DNM2* gene, but we are not sure whether that change causes CNM. In this case, we recommend testing parents to give us more information.

Reporting of 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.

Additional Resources:

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

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>

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

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

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

Laboratory Faculty and Staff:

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