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### Genetic Testing for Centronuclear & Myotubular Myopathy

#### Information for Patients and Families

#### What do I need to know about testing myself or my child for centronuclear or myotubular myopathy?

Centronuclear myopathy (CNM) is a rare muscle condition caused by a change in someone's genes. People with CNM have mild to severe muscle weakness. X-linked myotubular myopathy is one type of CNM. This blood test may confirm that you or your child has CNM, but a negative result will not rule out CNM. This test may also tell you how CNM runs in your family and your chance of having another child with CNM. The test may find something that we do not understand. We may need to test the individual's parents to learn more. This sheet will provide more details about CNM and this testing. If you have more questions, please talk to a genetic counselor.

#### What is CNM and what causes it?

CNM is a rare muscle disease with muscle weakness that usually does not get worse over time or gets worse very slowly. A muscle biopsy may show that a person has CNM. CNM is caused by changes (mutations) in several different genes, including the *MTM1*, *DNM2*, *BIN1* and *RYR1* genes. Genes are instructions to make proteins. When there is a change (mutation) in the instructions, the protein may not be made or may not work properly, resulting in muscle weakness.

X-linked myotubular myopathy is one type of CNM. Babies with [X-linked myotubular myopathy \(XLMTM\)](#) generally have low muscle tone, feeding and breathing problems, and developmental delay. XLMTM is usually only seen in boys. Females may carry a mutation in the gene for XLMTM, but they usually do not have many symptoms. XLMTM is caused by a change (mutation) in the *MTM1* gene. The *MTM1* gene is located on the X chromosome. Chromosomes contain all of our genes. Females have two copies of the X chromosome, and males have one. If a male has a change in his one copy of the *MTM1* gene, he will not be able to make normal protein and will have XLMTM. If a female has a change in one copy of the *MTM1* gene, she will still be able to make normal protein from her second copy of the *MTM1* gene and usually will not have XLMTM.

Patients with CNM caused by a change (mutation) in the *DNM2* gene usually have muscle weakness in childhood or adulthood, although some may have problems earlier. The *DNM2* gene is located on chromosome 19. Everyone has two copies of the *DNM2* gene. If a person has a change in one copy of the *DNM2* gene, he or she will not be able to make as much normal protein and will have CNM.

Patients with CNM caused by changes (mutations) in the *BIN1* gene usually develop muscle weakness in infancy or childhood. The *BIN1* gene is located on chromosome 2. Everyone has 2 copies of the *BIN1* gene. In order to inherit *BIN1*-associated CNM, a person must have a change in both copies of his or her *BIN1* gene.

Patients with CNM caused by changes (mutations) in *RYR1* usually have muscle weakness which is noted at birth or in early infancy. Everyone has 2 copies of the *RYR1* gene, which is located on chromosome 19. Usually, in order to inherit *RYR1*-associated CNM, a person must have a change in both copies of his or her *RYR1* gene.

#### How does CNM run in families?

XLMTM is X-linked. This means that males only have one copy of the *MTM1* gene while females have two. Most (over 80%) women with a son with XLMTM are carriers, meaning that they have one normal copy and one copy with a change that causes the protein not to work properly. Carriers have a 50% (1 in 2) chance that each of their sons will have XLMTM and a 50% (1 in 2) chance that each of their daughters will be carriers. Women with a son with XLMTM who are not carriers have a much lower chance of having a second child with XLMTM. Males with XLMTM will not pass the condition to any sons but all of their daughters will be carriers.

*DNM2*-associated CNM is autosomal dominant. People with this condition have one normal copy of the *DNM2* gene and one copy with a change that causes the protein not to work properly. Thus, people with *DNM2*-associated CNM have a 50% (1 in 2) chance of passing it down to each child.

*BIN1* and *RYR1*-associated CNM are autosomal recessive conditions. People with either of these conditions have changes in both copies of either their *BIN1* or *RYR1* gene, causing them not to produce a protein that works properly. Thus, parents of a child with *BIN1* or *RYR1*-associated CNM each have a mutation in one copy of either their *BIN1* or *RYR1* gene, and together they have a 25% (1 in 4) chance of having another child with the same condition.

### **Can my child be tested? Can I be tested? Can my family members be tested?**

The first person to be tested should be the person with CNM. Testing for mutations in *MTM1*, *DNM2*, *BIN1* and *RYR1* is complex. It is like reading several books and looking for spelling mistakes. You may read all the books and miss an important “typo”. Or there may be a “typo” that causes the disease in another book that you did not read. However, when you do find the typos, then it is easy to test other family members (i.e. you know that the change is on page 200 of book two in the second paragraph). When changes in *MTM1*, *DNM2*, *BIN1* or *RYR1* are found in the person with CNM, testing other family members, even during a pregnancy, is easy and fast.

### **Reasons for genetic testing for CNM:**

- confirm the diagnosis
- check if other family members are carriers
- provide information and resources for future pregnancies
- provide information during a pregnancy regarding possible CNM in the baby

### **If my son has a mutation in *MTM1*, can my daughter(s) be tested to see if they are carriers?**

Yes, she can be tested. However, the American College of Medical Genetics (ACMG) and the National Society of Genetic Counselors (NSGC) do not recommend carrier testing on children before they are 18 years of age.

Here are some reasons for this:

- The goal of genetic testing is to help the child. Genetic testing has no health benefits for a young girl that does not have any symptoms of XLMTM. However, this testing could change her self-image, change your view of her, or cause her stress, as she grows older.
- Genetic testing is very complicated and a very personal decision. We believe that each individual must consent to genetic testing. A child cannot provide his/her own consent. It would be better, if she waited until she is old enough to discuss the issues about testing and decide whether she would like to be tested.

We suggest meeting with a genetic counselor to make the best decision for your family.

### **What does it mean if they find one mutation?**

- Finding only one change in the *MTM1* gene in a male with possible XLMTM confirms the diagnosis of XLMTM.
- Finding only one change in the *DNM2* gene in a patient with possible CNM confirms the diagnosis of CNM.
- Finding only one change in the *BIN1* or *RYR1* gene in a patient with possible CNM means that the individual most likely has a second change in her/his other copy of the *BIN1* or *RYR1* gene that was unable to be identified.

### **What does it mean if they don't find a mutation?**

If someone does not have any changes in *MTM1*, *DNM2*, *BIN1* or *RYR1*, then his/her CNM is most likely not caused by problems in the gene that was tested. There are probably changes in other genes that cause CNM that we do not yet know about, so negative *MTM1*, *DNM2*, *BIN1* and/or *RYR1* testing does not rule out a diagnosis of CNM.

### **What does it mean for my child if they find a variant of unknown significance?**

A small number of patients will have a change in the *MTM1*, *DNM2*, *BIN1* or *RYR1* gene, but we are not sure whether that change causes CNM or not. In this case, we may recommend testing parents to give us more information.

### **How do I get myself or my child tested?**

We recommend that a neuromuscular specialist, geneticist or genetic counselor help you order the test for you or your child. If you think that you or your child has CNM, you should see a genetic or neuromuscular specialist. Your doctor or hospital can help you set this up. This specialist can order the testing. If there are any questions about ordering the testing, please ask the physician or genetic counselor to contact The University of Chicago Genetics Services Laboratory. A blood sample is required for testing.

### **How much does the testing cost and will my child's health insurance cover it?**

The cost for sequencing *MTM1* is \$1200 per gene, the cost for sequencing *BIN1* is \$1440 per gene, the cost for sequencing *DNM2* is \$1560 per gene, and the cost for sequencing *RYR1* is \$2200. The cost for deletion/duplication testing is \$1000 per gene. All insurance companies are different, but most of them should cover at least part of the cost of testing. We recommend that you contact your insurance company to learn more about your coverage prior to testing. If you are interested in testing either *MTM1*, *BIN1* or *DNM2* you should ask your insurance company what your coverage is for the following CPT (Current Procedural Terminology) codes: 81406 for sequencing, and 81405 for deletion/duplication testing. If you are interested in testing *RYR1* you should ask your insurance company what your coverage is for the following CPT (Current Procedural Terminology) codes: 81408 for sequencing, and 81407 for deletion/duplication testing. Insurance companies use these codes to define the method of testing. The University of Chicago or your hospital or lab will bill your child's insurance company. You may receive a bill for any amount not covered by your insurance company, i.e. copayment, deductible, etc. If you do not have medical insurance, you will need to pay by check or credit card before the lab will start testing.

If a mutation is found in your child, testing of other family members is \$390. The CPT code for a family member test is 81403. Testing during a pregnancy is \$540. The CPT code for prenatal testing is 81403.

### **When/how will I get the results?**

Testing of *MTM1*, *BIN1*, *DNM2* or *RYR1* takes approximately 4 weeks. The test results will be faxed to your doctor.

### **What happens to the information from this test?**

Your doctor will send a form about you/your child's symptoms with the blood sample. This will help the lab understand the test result. The symptoms and test results will be put into a public database after removing the name and all personal information. Information from people with CNM will increase what we know about these disorders and the genetic test.

### **How can I meet or talk to other families?**

Support groups are a great way to talk to other families that have gone through similar experiences. The [Myotubular Myopathy Yahoo Support Group](http://health.groups.yahoo.com/group/Myotubular_Myopathy) ([health.groups.yahoo.com/group/Myotubular\\_Myopathy](http://health.groups.yahoo.com/group/Myotubular_Myopathy)) is an online group for families to chat about their lives with CNM. Please remember that all people with CNM are not the same, so their symptoms may be different from yours (your child's). Also, remember that the information given on this type of website is not written by an expert in CNM, so you should discuss it with your doctor before using it to make management or treatment decisions. Support groups, however, are a great place to share ideas, experiences, and feelings.

### **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: [lswanson@enders.tch.harvard.edu](mailto:lswanson@enders.tch.harvard.edu)  
<http://www.childrenshospital.org/research/beggs>

**Myotubular Myopathy Resource Group**  
Phone: (409) 945-8569  
[www.mtmrg.org](http://www.mtmrg.org)

**Muscular Dystrophy Association (MDA)**  
Phone: (800)572-1717  
[www.mda.org](http://www.mda.org)

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