Dear Family,

You are receiving this letter because a family member has been diagnosed with Myotonic Dystrophy type 1 (DM1). This letter will describe the condition, how it is inherited, risks associated with the condition, and how to get testing if desired. Even if you choose not to get testing, you should provide a copy of this letter to your physician so they can be aware of the diagnosis in the family and that you may be at risk to develop symptoms.

General information about Myotonic Dystrophy

DM1 is a genetic condition that affects the muscles and many other parts of the body, such as the eyes and the heart. The symptoms of DM1 vary from person to person and not all people will be affected with the same severity. Some people may have severe symptoms while others may have such mild symptoms that they do not even know that they have DM1. Different people will develop symptoms at different ages. Some people have symptoms beginning at birth while others may not have symptoms until they are teenagers or even adults. Generally, the earlier a person develops symptoms the more severe the disease. Variability of symptoms is seen even among affected members of the same family.

The word “myotonic” refers to the inability to relax muscles, which is a symptom of DM1. Myotonia often causes an affected person to have problems with their hands. For example, they may have trouble with writing, grasping a doorknob, or using tools. The word “dystrophy” refers to progressive muscle weakness and wasting, which is also a symptom of DM1. The muscles of the arms, hands, legs, and feet are often affected. Muscle weakness in the feet and legs may lead to difficulty walking. The muscles of the face and neck may also weaken, which leads to a characteristic appearance of people with DM1. Muscle weakness can also cause difficulty with breathing and swallowing in some people. Men with DM1 often have early, frontal balding, and can also have low levels of testosterone and/or infertility. Women with DM1 often have complications during childbirth. People who experience symptoms of DM1 from birth often have learning problems or intellectual disabilities. DM1 can also cause heart problems, cataracts, sleep apnea, digestive problems (such as irritable bowel), gallstones, diabetes, and can increase the risk of complications from anesthesia or surgery.

The Genetics of Myotonic Dystrophy

DM1 occurs when there is a change (or ***mutation***) in the body’s blueprints. These blueprints, called ***genes***, control not only the way a body is made, but also what it looks like, and how it works. Most genes come in pairs. One gene of each pair comes from the mother and the other from the father. In the thousands of gene pairs, sometimes one will be changed. Sometimes a mutated gene will not cause problems. Other times a gene with a mutation will cause some part of the body not to work correctly, and that person will have a genetic condition such as DM1. A gene mutation is usually inherited from one of the parents and may have been in the family for many generations.

Genes are carried on ***chromosomes***. There are 46 chromosomes in each cell of the body. The chromosomes come in 23 pairs with the first 22 pairs being identical in males and in females. The last pair is the sex chromosomes; typically, females have two X chromosomes, while males have

one X and one Y chromosome. ***DNA*** is the building block of the gene and is made up of four chemical bases represented by the letters C, T, G and A. Three DNA "letters" together form one "word." Each "word" encodes one amino acid. Amino acids are the building blocks of proteins and proteins are the building blocks for different tissues in our bodies, such as our bones, organs, and muscles.

Genetic conditions, such as DM1, occur when there has been a mutation in a gene. The gene that is mutated in a person with DM1 is the *DMPK* gene, which carries instructions for a protein called myotonin-protein kinase. Every person has 2 copies of the *DMPK* gene, located on chromosome 19. DM1 is caused when a person has a mutation in one of their *DMPK* genes. This mutation involves a part of the *DMPK* gene in which a certain 3 letter genetic word, CTG, is repeated several times in a row. This is called a triplet repeat. People normally have this CTG word repeated several times within their *DMPK* genes. However, it is the number of times that this repeat is found in the *DMPK* gene that determines if a person will have DM1. DM1 is caused when this CTG word is repeated too many times within the *DMPK* gene.

People with 35 or fewer CTG repeats in both copies of their *DMPK* gene will not develop DM1 and they cannot pass it on to their children. People with 50 or more repeats in one of their two copies will have DM1 and thus will be expected to eventually develop symptoms of DM1 at some future point. People with a CTG repeat between 36-49 repeats will not develop symptoms of DM1. However, it is possible for a CTG repeat size of 36 or greater to get larger when passed down from a parent to their child, which could explain how a person could develop DM1 with no family history of the disease. This is called *expansion* and it occurs most often when this type of "intermediate" length CTG repeat is passed down from a mother to her child and rarely when passed down from a father to his child. Genetic testing for DM1 is performed by counting the number of CTG repeats a person has in each of their two copies of the *DMPK* gene. This test requires only a blood sample.

The number of CTG repeats an affected person has in their *DMPK* gene is correlated with age of onset and severity of symptoms. The greater the number of repeats, the earlier the age of onset and the more severe the symptoms may be. Because the repeat number can get larger when passed down from a parent to their child, children are often more severely affected than their parents. That being said, for a specific person it is not possible to reliably predict when symptoms will begin or how severe symptoms will be based on their specific *DMPK* repeat size.

Inheritance

DM1 is inherited in an ***autosomal dominant*** pattern. Autosomal means that males and females are equally likely to inherit this condition. Dominant means that only one copy of the *DMPK* gene must be mutated for a person to get DM1.

Autosomal dominant also means that an affected person has a 50% (1 in 2) chance of passing the mutated *DMPK* gene to <u>each</u> of their children. In this case the children who inherit the mutated *DMPK* gene would eventually develop DM1. An affected person also has a 50% (1 in 2) chance of passing the normal copy of the gene to their children. In this case the children would not develop DM1 and could not pass it on to future generations. These chances are the same for each child born to an affected person.

Testing for Myotonic Dystrophy

The test for DM1 measures the number of CTG repeats in the *DMPK* gene. If the number of repeats is less than 35 in both copies of the gene, the test reveals that a person is unaffected with DM1. If the repeat size is greater than or equal to 50 repeats on either chromosome, the person is considered to be affected with DM1 if that person is showing symptoms. If a person tested positive for the DM1 mutation but is not showing symptoms, he or she is considered to be pre-

symptomatic. By pre-symptomatic we assume that a person with the gene mutation will eventually show symptoms of DM1 if he or she lives to the age that symptoms would normally appear.

In our clinic, individuals first have an appointment in the neurology department with a genetic counselor and a neurologist. The genetics of DM1 are explained and issues regarding testing and the person's reasons for wanting the testing are discussed. The person is given a comprehensive neurological examination and will be told at that time if they are showing any symptoms of DM1. Genetic testing can then be performed if the person chooses to pursue testing. A blood draw is then performed, and the results of this test will be discussed at a future appointment. Results will only be given in person.

You can contact us at the number below if you are interested in pursuing this testing.

Recommended medical surveillance
Until it is proven that you did not inherit an expanded *DMPK* gene, it is strongly recommended for your primary care doctor to order an annual EKG to monitor for risk of cardiac conduction abnormalities. It will also be important for your doctor to monitor your glucose levels and thyroid function.

If testing reveals you have DM1 or are at risk to develop symptoms in the future, we provide specialty care in our MDA myotonic dystrophy clinic. While there is no cure for DM1, treatment is aimed at managing the symptoms of the condition and minimizing disability.

Anesthesia risks for individuals with DM1
Individuals with DM1 are at increased risk for complications from general anesthesia. It is very important your physicians are informed of the diagnosis in the family, particularly prior to any surgeries. Even people with very mild symptoms are at risk for these complications but they can be minimized with a pre-anesthetic assessment and close monitoring during and after sedation.

Pregnancy risks for women with DM1
Pregnant women with myotonic dystrophy need a referral for high risk OB care. There is increased risk for labor and delivery problems, particularly ineffective labor and increased bleeding. Evaluation of cardiac and respiratory status is important; an EKG and echocardiogram should be completed. Respiratory status can occasionally become compromised with increasing size of the fetus. Overall, there is increased risk for diabetes in individuals with myotonic dystrophy. Prenatal diagnosis is often considered via amniocentesis to help with planning for delivery and care of an affected fetus. If prenatal diagnosis is declined, it is important to be prepared for the birth of an infant at risk for congenital myotonic dystrophy who may need resuscitation or neonatal intensive care support.

Congenital Myotonic Dystrophy
As mentioned above, it is possible for a CTG repeat size of 36 or greater to get larger when passed down from a parent to their child. This occurs most often when the CTG repeat expansion is passed down from a mother to her child and rarely when passed down from a father to his child. When the number of CTG repeats expands to more than 1000 repeats, there is a risk for the child to be born with congenital myotonic dystrophy, which is a particularly severe form of DM1. Symptoms of congenital DM1 may present during the pregnancy with decreased fetal movements. The child is at risk for low muscle tone, respiratory problems, and intellectual disabilities from birth.

Family Planning Options
Once someone is identified to carry the *DMPK* gene expansion, family planning options become available which can help to ensure that any future children would not be affected by DM1.

Currently there are several options available for family planning including testing that can be done during and before a pregnancy. Testing performed during a pregnancy can be done as early as 10 weeks (CVS) and later with an amniocentesis (14-15 weeks). This allows the parents to determine if the pregnancy inherited the expanded gene and they can make decisions about the pregnancy based on this information. Alternatively, preimplantation genetic diagnosis (PGD) can be done prior to a pregnancy using the same technology involved with in vitro fertilization (IVF). By genetically testing embryos for DM1 before implantation, parents can select for embryos which did not inherit the gene expansion.

Some individuals decide to pursue these testing options prior to having children so they can ensure that their child will not have DM1. Other individuals decide that they will have children without having this type of testing and hope for the best. Other options include adoption or egg/sperm donation. We encourage anyone in the family who is considering these options or who has questions about genetic testing to speak with a genetic counselor in order to review what is available.

Resources
We recognize that living with DM1 can be very stressful and emotionally difficult. Some people find that talking with other people who are living with the same condition helpful. The Muscular Dystrophy Association (MDA) and the Myotonic Dystrophy Foundation (MDF) are useful resources.

https://www.myotonic.org/

https://www.mda.org/disease/myotonic-dystrophy

To find a genetic counselor in your area search by zip code at:
https://www.nsgc.org/page/find-a-genetic-counselor

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