Myotonic Dystrophy:
Making an Informed Choice About Genetic Testing

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http://www.rehabinfo.net

and the author's website:

http://depts.washington.edu/neurogen

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This booklet provides information about myotonic dystrophy (dystrophia myotonica or DM) and genetic testing for DM. Myotonic dystrophy is an inherited disorder of muscle function. It is characterized by muscle weakness and myotonia (slow relaxation of muscles after contraction). DM can also affect other organs of the body such as the eyes, heart and brain. Myotonic dystrophy is one of the most common forms of inherited muscle disease; it is estimated that one person in every 20,000 is affected with DM. Myotonic dystrophy is an extremely variable condition, even within families. Genetic testing is available for DM. The decision to be tested is a personal one, and each person must make his or her own informed choice about testing.

SYMPTOMS OF MYOTONIC DYSTROPHY

The symptoms of myotonic dystrophy vary greatly from person to person. In its most severe form, infants with DM can have extreme muscle weakness and difficulty breathing after birth. In contrast, DM can be so mild in older adults that they may not be aware they are affected until a relative with more severe symptoms comes to medical attention. Almost all affected persons have some

degree of myotonia and muscle weakness due to atrophy or shrinkage of the muscles. Myotonia is most evident in the hands, and results in difficulty releasing grip and a feeling of muscle stiffness (see Figure 1). For example, persons with DM are slow to open their hand after a handshake, or after grasping a doorknob or other object. Myotonia can be diagnosed by an electromyogram (EMG). An EMG is done by inserting fine needles into a muscle and recording electrical activity inside muscle cells. DM is described as being mild, classical or congenital based on the severity and age of onset of symptoms (See Table 1). There is an overlap of symptoms among the three descriptions of myotonic dystrophy. At this time, there is no treatment or cure that can prevent the symptoms of myotonic dystrophy.

In DM, certain muscles are more affected than others. The myotonia and muscle weakness tend to gradually worsen over a period of years (see Figure 2). The muscles of the face are often the first to show weakness, resulting in a lack of facial expression or mask-like appearance of the face (myotonic facies). Persons with DM can have slurred speech (dysarthria) and droopy eyelids (ptosis) because of weak facial muscles. The muscles of the lower leg, ankle, foot, forearm and hand are usually the next group of muscles to show weakness (distal limb muscles). This leads to

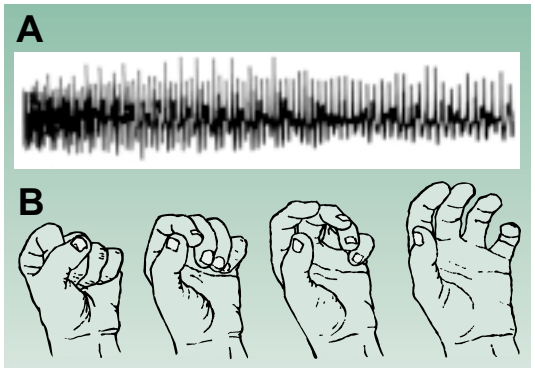

Figure 1. A. Electromyogram (EMG) showing myotonia, the slow relaxation of a muscle after contraction.
B. Grip myotonia manifested as difficulty opening the hand after making a fist

difficulty with walking, and with finger and hand movements. The muscles involved with breathing and swallowing may become weak over time. In rare instances, the muscle weakness in DM can continue to the point where an affected person has difficulty walking and needs a wheelchair. However, the extent to which weakness and myotonia will affect a person's ability to function is variable and unpredictable.

Table 1. Range of symptoms in myotonic dystrophy

Description	Symptoms	Age of Onset or Recognition	Lifespan
"Mild"	• Cataracts • Mild myotonia • Balding • May have diabetes	Adulthood	Normal
"Classical"	• Weakness • Myotonia • Cataracts • Balding • Irregular heartbeat • May have diabetes	Childhood to early adulthood	May be shortened
"Congenital"	• Severe weakness • Myotonia • Breathing difficulties • Often mild to moderate mental retardation	Birth - childhood	Shortened

The majority of persons with myotonic dystrophy will eventually develop cataracts (cloudiness of the lens of the eye) that cause vision to become blurry. Cataracts are often the first recognized sign of DM. They can occur in persons without DM, especially in the elderly. In DM however, cataracts develop at a younger age, usually in the forties or fifties. Cataracts are treatable through surgery.

Abnormalities of heart rhythm, called arrhythmia, are common in persons with DM. Usually this is not serious. In some cases, arrhythmia can be life threatening and cause early death. For this

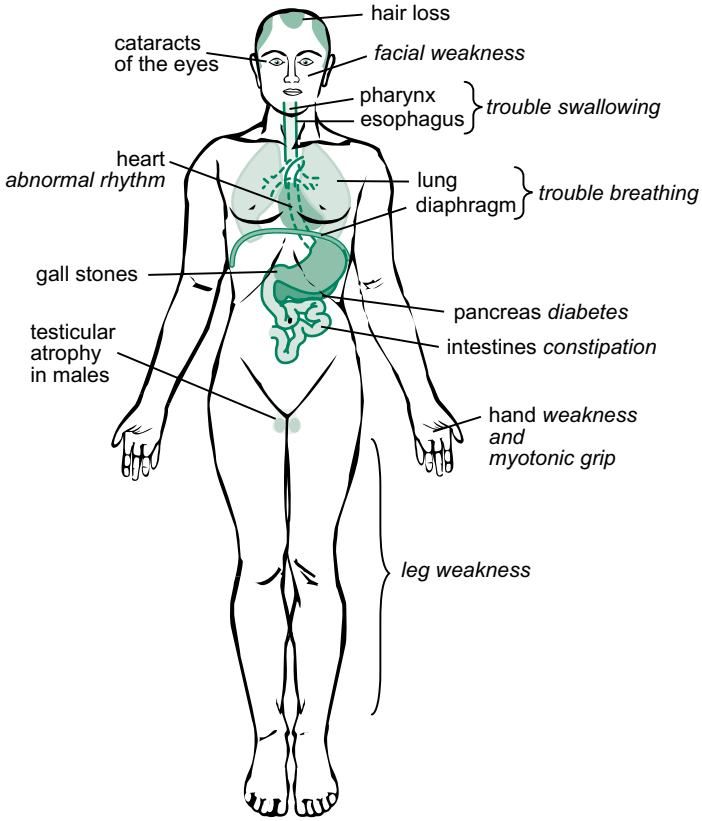

Figure 2. Manifestations of myotonic dystrophy

reason, persons with DM need regular monitoring of their heart rhythm through a simple test called an electrocardiogram (EKG or ECG). Some persons require medication or a pacemaker to treat an arrhythmia.

Other symptoms seen in some but not all persons with DM include diabetes mellitus, gallstones, intestinal irregularity and early frontal balding. These conditions are common in people without DM as well. However, they are more frequent in myotonic dystrophy. Men with DM can have a decrease in the size of the testes over time, but this does not usually cause infertility.

Congenital Myotonic Dystrophy

Congenital DM is the most severe form of myotonic dystrophy. Congenital means “present at birth”. Symptoms may actually be detected prior to birth, and include excess amniotic fluid (polyhydramnios) and decreased movement of the unborn child. After birth, infants with congenital DM often have extreme muscle weakness (hypotonia) and difficulty breathing, and they may not survive past infancy. Those children that do survive can show an improvement in muscle strength. About half of all children with congenital DM have some degree of mental retardation. For reasons that are not completely understood, congenital DM almost always occurs in the child of an affected mother. Both sons and daughters of a woman with DM can be affected with congenital DM.

Myotonic Dystrophy Type 2

Recently, it has been discovered that there is another type of myotonic dystrophy, called myotonic dystrophy type 2 (DM2). DM2 has also been called proximal myotonic myopathy (PROMM). The symptoms of DM2 are very similar to those of DM, and both conditions are inherited in the same way. The main difference between them is at the genetic level. The genetic change that causes DM2 is different from DM. At this time there is no genetic test for DM2.

INHERITANCE OF DM

Myotonic dystrophy is inherited in an autosomal dominant pattern (See Figures 3 and 4). This means each son or daughter of a person with DM has a 1 in 2, or 50% chance of inheriting the condition. Myotonic dystrophy affects males and females equally. DM is caused by a change or mutation in a specific gene, called the myotonic dystrophy protein kinase (DMPK) gene, which is essential for normal muscle and body function.

Genes are the basic units of heredity, and contain the set of instructions that determine how the body grows and develops. Genes are composed of DNA (deoxyribonucleic acid). It is estimated that every cell in a person’s body contains between 50,000 to 100,000 genes. Genes are packaged on chromosomes - the thread-like structures within cells that are visible under a microscope (genes cannot be seen under a microscope). Each person inherits half of their chromosomes from their father, and half from their

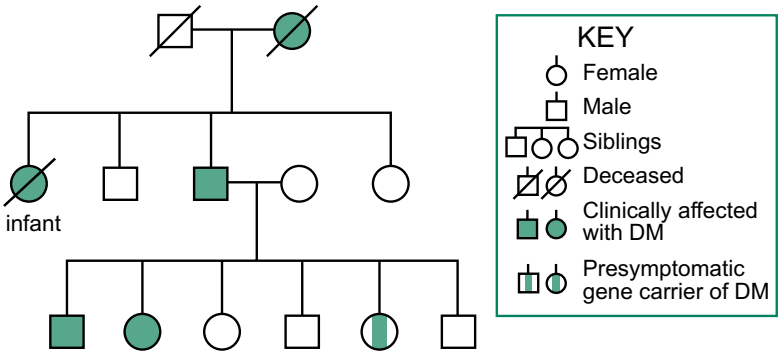

Figure 3. Family tree (pedigree) of a family with myotonic dystrophy showing autosomal dominant inheritance, congenital DM and a female who has tested positive for the DM gene.

mother. Every person has 23 pairs of chromosomes, which contain two copies of each gene. The DMPK gene is located on chromosome number 19.

DM2 is also inherited in an autosomal dominant pattern. The gene for DM2 has not yet been found, but has been localized to chromosome number 3.

The genetic change that causes DM is called a CTG repeat expansion (See Figure 4). CTG represents a specific pattern of DNA. It is normal to have between 5 to 37 CTG repeats in both copies of the DMPK gene. However, in myotonic dystrophy, the CTG pattern is repeated too many times in one copy of the DMPK gene, and disrupts the normal function of the protein made by the gene. If a person has between 38-49 repeats he or she will not

Table 2. Repeat size and severity of symptoms in DM

Description	CTG Repeat Size
Normal range	5 to 37
No symptoms (children at risk)	38 to 49
Mild	50 to about 150
Classical	about 100 to 1000-1500
Congenital	about 1000 and greater

develop symptoms, but his or her children are at risk to inherit myotonic dystrophy. With few exceptions, individuals with 50 or more CTG repeats will develop at least mild symptoms of DM at some point in their lifetime.

Genetic testing is available for DM. The genetic test measures the size of the CTG repeat in both copies of the DMPK gene. In myotonic dystrophy, there is an association between repeat size, age of symptom onset and the severity of symptoms. In general, the larger the repeat size, the younger the age at which a person will develop symptoms of DM and the more severe the symptoms will be. On the other hand, the repeat size cannot be used to predict the age when a person will develop symptoms, or the rate of symptom progression (See Table 2). The largest repeat expansions are seen in congenital DM.

Anticipation

Myotonic dystrophy is characterized by a phenomenon called anticipation. Anticipation refers to an earlier age of symptom onset and increasing severity of disease from one generation to the next in a family. In other words, an affected child can have more severe symptoms than the affected parent. With the recent discovery of

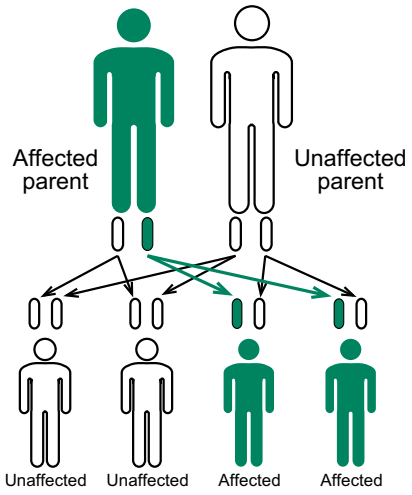

Figure 4. Diagram of autosomal dominant inheritance. Each child has a 50% chance of inheriting DM from an affected parent.

the genetic cause of DM, the biologic basis of anticipation in this condition is beginning to be understood. It has been found that the repeat size can change when passed from parent to child. For example, if a parent has a specific repeat size on genetic testing, a child may have a larger repeat size. Anticipation cannot be predicted and does not always occur.

The most striking example of anticipation is seen with congenital DM. For reasons that are not yet known, women with a CTG repeat expansion are at risk to have a child with congenital DM. In some cases, women have been diagnosed with mild DM during pregnancy because problems are found in an unborn child. The exact risk for a woman with DM to have a child with the severe congenital form of DM is not known. Rarely, children with congenital DM have inherited a repeat expansion from their father.

Penetrance

The term penetrance refers to the proportion of persons with a repeat expansion for DM who will actually develop symptoms of the condition. In DM, penetrance is very high, meaning that almost everyone with a repeat expansion of 50 or larger will develop symptoms of DM at some point in their lifetime. In some cases, a person's symptoms can be so mild (such as cataracts in late middle age or frontal balding) that they are never diagnosed with DM.

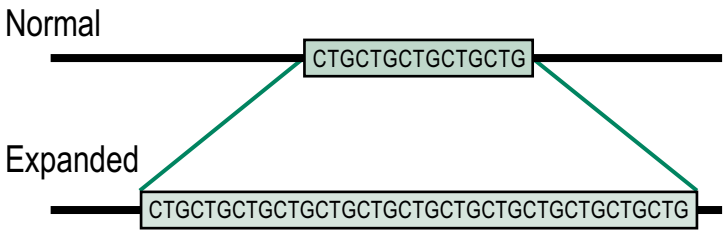

Figure 5. Diagram of CTG repeat expansion.

DNA TESTING

Genetic testing is available to determine whether or not a person has inherited the CTG repeat expansion that causes DM. The testing can be done on a blood or tissue sample. Testing for DM usually takes between 2-4 weeks for results.

There are three possible outcomes from DNA testing:

Negative/Normal

This result means that the person being tested has not inherited DM. The CTG repeat number will fall into the normal range (less than 38 repeats). The accuracy of this result is close to 100%. A person can appear to have DM and still have a negative test result. This can happen if a person has mild non-specific symptoms not actually caused by DM such as cataracts, balding or weakness, or if the person has DM type 2. A negative result is most useful if a parent or other affected relative has been tested and found to have a CTG repeat expansion for DM.

Positive

This result means that a person has inherited the CTG repeat expansion for DM (50 or more repeats). The accuracy of this result is close to 100%. A positive result does not necessarily mean that a person has any physical signs of DM, nor does it indicate at what age a person will begin to show signs of DM. A positive result usually means that at some point in that person's lifetime, he or she will develop at least mild signs of DM. However, there is variability in the severity of symptoms and the rate of symptom progression, as well as the age of disease onset even within the same family. Persons with symptoms of DM should be examined by a neurologist who can confirm the diagnosis and provide continuing medical support and care.

Uncertain

There is an area of uncertainty or "gray area" in DM genetic testing. If the repeat size falls in between the normal and the expanded range (38 to 49 repeats), that person will not develop symptoms of DM, but is at risk to pass DM on to his or her children. Very few people undergoing testing fall into this range. Children of this person could be at risk to inherit a repeat expansion that increases in size when passed from parent to child (anticipation). As a result, the child could inherit a repeat expansion that is now clearly within the range seen in affected persons.

TESTING PROCESS

Genetic testing for DM involves more than providing a blood sample.

Symptomatic and presymptomatic testing

There is a big difference between genetic testing done to find the cause of myotonia or muscle weakness in an affected person (symptomatic testing) versus a person who is at risk for DM and has no symptoms of the condition (presymptomatic testing). For a person with symptoms, testing for DM is part of a diagnostic evaluation. If the test is positive, it provides a diagnosis for the person, as well as an explanation for the symptoms. Often the most difficult thing for a symptomatic person who has a positive test result is learning that his or her children, siblings and other family members are now at risk for DM. For a person without symptoms, there are many issues to think about prior to having testing. The following information is most applicable to at-risk persons considering presymptomatic testing for DM, but may also be useful for those with symptoms of DM who are undergoing testing.

Genetic counseling

Genetic counseling is an essential part of the presymptomatic testing process. Genetic counseling involves education and counseling about the implications of the testing by someone with expertise in genetic testing such as a genetic counselor or medical geneticist. A neurological exam is done as part of the testing process to find out if a person is showing any signs of DM. Persons with symptoms may discuss testing with a neurologist.

Confirmation of DM in the family

It is very important to confirm the diagnosis of DM in the family. Often medical records on affected family members are requested. It is most useful to perform the DNA blood test on an affected family member to confirm the presence of a repeat expansion for DM. Other diseases may mimic DM, but persons with other diseases will have a normal DNA test for DM. The other diseases include DM2 and a condition called facioscapulohumeral muscular dystrophy, in addition to other causes of weakness and myotonia.

Do you think you have inherited myotonic dystrophy?

Honestly considering your feelings about whether or not you believe you have or will develop DM is important. It can be more difficult to deal with the test results if the results are the opposite of your inner feelings. Sometimes people can have signs of DM without knowing it. Many people with mild DM never come to medical attention.

Support person

The decision of whether or not to have testing for DM can be stressful. Waiting for the results can also be stressful. The results, even "good news," can take time for adjustment. Having a support person (such as a close friend or spouse) who is able to be present at all appointments is helpful. This person can be a second set of ears as well as a sounding board to talk through feelings about testing, and provide support after the test results are given.

Cost

Costs will vary among testing programs. Usually the cost of testing (DNA blood test, pre- and post-test counseling, and neurological examination) is under $1,200. Many insurance companies will cover the cost of this testing.

THE DECISION TO BE TESTED

The decision to be tested is very personal and may be one of the most important decisions you ever face. Members of the same family may have different feelings about testing. It is important to respect each person's feelings. For at-risk persons who do not have symptoms of DM, there can be both medical and psychological benefits to having testing. In persons who test positive, screening for arrhythmia, cataracts and diabetes can be done to prevent or minimize any potential complications from these symptoms of DM. The test results also have important implications for many life decisions. The following are just some of the issues to consider in the decision to have presymptomatic testing:

Timing of testing

The process of being tested for DM and dealing with the results will be stressful and is often disruptive to a person's life. It is best to choose a time to be tested when complicating factors from the

outside are at a minimum. For example, the middle of a divorce or break-up of a relationship, or a stressful time at school or work is not a good time to be tested. Testing at a time of celebration may not be optimal, for example, directly before or after marriage, or in the middle of important holidays.

It is easy to become consumed with thinking about testing for DM. It can be useful to make a decision about whether or not to be tested even if the decision is not a yes or no answer. For example, deciding not to be tested for a certain period of time ("next year", or "after I turn 30"), can help you put this aspect of DM aside for a period of time until you are ready to readdress testing issues in the future.

Disclosure of results

If you decide to be tested it is important to plan to whom you will tell your results and when. Will you tell them on the same day that you are given your results? Exactly how and when do you plan to tell them? What if you change your mind and do not want them to know quite yet or at all? Planning what you will do the day you are given the results can be helpful. Will you go directly home, and who will be there? Will you take some time off from work or family responsibilities?

Effect on relationships

Spouse - Is this person supportive of your decision to be tested or do they have a conflict with your decision? Is he or she pushing you to have testing? Have you discussed decisions that affect you as a couple that you might make differently depending on your test results, for example, decisions to have children, retirement and long-term care issues? Many people who are at risk for DM fear abandonment by their spouse or significant other when they develop signs of the condition. Have you discussed this fear or other fears with your partner?

Child - Do your children know about DM? Are they pushing you to have testing or are you involving them in your decision making? Will you tell them your results? If yes, how and when will you tell them?

Extended family - How do you perceive the results of the testing will impact your interactions with your brothers and sisters, your parents and extended family? If the results show you have inherited the DM mutation, will this impact how you feel about your affected relatives, for example, feeling closer or more distant from them? If you do not have the DM mutation you may experience "survivor guilt", meaning that you wonder why you have escaped this disease whereas others in your family have been less fortunate. A person given a normal result may also feel an increased responsibility to take care of affected family members that he or she may not have felt before testing. Who, if anyone, in your family do you plan to tell your results? How would you tell each of them (by phone or letter, at a family meeting)?

Friends - Are there people in your life that you feel you can talk to about DM and your decision regarding testing? Have you been through difficult periods in your life with them before? In what ways were they supportive to you?

Professional support

If you have used professional support services such as a therapist, psychologist, religious professional or psychiatrist during a difficult time in the past, it may be helpful to discuss your decision about testing with this person. This is particularly important if you have had prior problems with depression, anxiety or stress.

Family planning

If you have not yet started a family, or are thinking about having more children, it is important to consider how the test result may impact your family planning decisions. For example, some people feel that if they test positive, they will not have children. Persons who already have children may feel guilty because their children may develop DM.

Career decisions

Will your test results affect your decisions about the type of work you are doing now or plan to do in the future? Do you plan to tell the people you work with about your decision to be tested or your test results?

Insurance issues

You should be comfortable with your insurance coverage (life, health and disability) prior to being tested. Potential problems can include: cancellation of existing benefits (unlikely), exclusions for coverage related to symptoms of DM, extended waiting periods for coverage, and an increase in costs for premiums. Some people may feel locked into a certain job to maintain insurance coverage. Life insurance may be especially difficult to obtain for persons with a positive test result.

COPING WITH RESULTS

You will most likely have strong emotional feelings when the results are given, regardless of the outcome. Many people feel relief at having an answer and disbelief that the answer is accurate. Often people express a feeling of "loss of identity", particularly if the result is different from the one they expected. Frequently people go through a period of regretting past decisions, which they might have made differently if they had known their status with regards to DM. This is particularly true if those decisions were permanent, for example, decisions about whether or not to have children, or career paths. Most people eventually adjust well to their test results. It is important to draw on the support of professionals, family and friends. Some other feelings specific to the test result may be:

Positive or high risk in a person with no symptoms

Many people express a sense of isolation, feeling that there are few other people who can relate to their feelings. Participating in a support group or continued support from a genetics professional can help them feel they are not alone in dealing with the result. Some people will have difficulty with not knowing when they will first develop symptoms of myotonic dystrophy. An appointment with a neurologist or neurogeneticist can help determine if a person is beginning to show signs of DM. Feelings such as depression, anger, loss of hope, despair and severe stress can occur. If these feelings occur, treatment by a psychologist, psychiatrist or counselor can be very helpful. The sense of "riding an emotional roller coaster" with good days and bad days is normal. Most people eventually come to terms with their results and use the information to help them make plans for the future.

Positive test result in a person with symptoms

For some people it is a relief to actually have an explanation for some of the problems they may have been experiencing. Sometimes this information can reduce stress in the work environment. The person with DM may be eligible for job reclassification or medical benefits. Stress in the family may also be reduced. As with the diagnosis of any chronic illness, the diagnosis of DM can bring feelings of shock, grief, anger, disbelief, depression, hopelessness and loss of control. Professional support and support from friends and family can help someone with DM continue to lead a productive and satisfying life.

Uncertain results

This can be the most frustrating result since the at risk person chose to be tested in order to have an answer.

Negative or normal result

Most people feel joy and relief with a negative result but may experience a low period following the testing. They may be disappointed that the "good news" did not bring as many positive changes in their life as anticipated. The problems that existed before the DM testing are most likely still there. Myotonic dystrophy is still very much a part of their family life. Often there may be a feeling of increased responsibility for caring for affected family members. They may feel a new pressure to "make something of themselves". They may also feel guilty that they will not develop DM when other close family members will, particularly if they are the only family member who has escaped the disease.

TESTING OF CHILDREN

Testing is not offered to children under the age of legal consent (age 18) except in cases where a child may be having signs of DM. There is no medical reason to test a child without symptoms of DM. When children become adults they may make their own choice about testing. Children who are suspected of having symptoms of DM should be evaluated by a pediatrician or neurologist. In a child with symptoms, DM testing may be an important part of evaluating the child's medical problems.

PRENATAL TESTING

Genetic testing can be done during pregnancy to determine if an unborn baby (fetus) has inherited the repeat expansion for DM. This testing may be done if pregnancy complications develop that are suspicious for congenital DM, or if a parent has tested positive. In a pregnancy with complications, a positive test with a large repeat expansion indicates that the fetus is likely to have the severe congenital form of DM. This information can be very helpful for planning the delivery and care after birth. If a parent has tested positive and the fetus is found to have inherited a repeat expansion for DM, the CTG repeat size cannot be used to predict the severity of DM in the child with 100% accuracy. If a fetus tests positive for DM, the options are to terminate the pregnancy, or carry the pregnancy to term. This type of testing raises difficult ethical questions. For some people, termination of pregnancy or abortion is not an option under any circumstances. Others feel that a child should not be brought into the world if he or she will develop DM. If prenatal testing is done and the parents choose not to terminate an affected pregnancy, then genetic testing will have been done on a child. Whether or not to terminate a pregnancy for DM is a very difficult decision. In the situation where a parent has tested positive, ideally the risks of prenatal diagnosis techniques of amniocentesis and chorionic villi sampling (CVS) should be thoroughly discussed with a genetic counselor prior to pregnancy and before undertaking prenatal diagnosis.

RESEARCH

Direct testing for DM has only been available for a few years. Testing for DM2 is likely to become available in the future. As more people participate in testing for DM, our knowledge of the long-term psychological effects of this testing will improve so that we can better support people through this difficult process. As of yet, the mechanisms that cause DM are not understood. As our understanding is improved through research, hopefully the ability to treat and manage this condition will improve. There is a great deal of research being done on myotonic dystrophy and related neurological conditions. Receiving information from the Muscular Dystrophy Association is an excellent way to stay informed about new advances.

RESOURCES

Muscular Dystrophy Association (MDA)
National Headquarters
3300 E. Sunrise Drive
Tucson, AZ 85718
Phone: (800) 572-1717
Email: mda@mdausa.org
Web: http://www.mdausa.org/home.html

National Society of Genetic Counselors (NSGC)
233 Canterbury Drive
Wallingford, PA 19086-6617
Phone: (610) 872-7608
Fax: (610) 872-1192
Email: nsgc@aol.com
Web: http://www.nsgc.org

National Institute of Neurological Disorders & Stroke (NINDS)
Web: http://www.ninds.nih.gov/

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