Myotonic Dystrophy

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Introduction

Neuromuscular disorders and what people commonly call muscular dystrophies are very complex and often devastating conditions. Some strike children, others do not display symptoms until well into adult life. Most are progressively disabling, getting worse over time and some are fatal, often in childhood. Some affect primarily muscles, others can affect a wide spectrum of health, including; personality and intellectual functioning, the eyes, the bones, digestion and diabetes to list just a few. There are over 100 different types of disorders and variations listed under this umbrella. Many disorders have genetic causes but in many cases, just how these genetic mutations cause the symptoms we see is not yet understood. Every day, medicine is making progress in understanding these disorders, but at the present time, there are more theories than facts. Sadly there are no direct treatments yet.

Usually thousands of pages of information can be found on each disorder on the internet. This synopsis is yet another contribution to the public knowledge base. The reader is cautioned that no overview can be comprehensive and cover every question or situation. While a given type of disorder shares the same basic mechanisms and patterns, one of the features of these illnesses is that they are quite variable in how they affect people and no two people will have quite the same symptoms or experiences of the condition. For a given disorder, there is often wide variation between patients concerning how “big” the mutations are and this causes wide differences in how the disorder affects different people. The main aspects that differ are at what age the disorder strikes, how severe the symptoms are in an individual and exactly what is affected.

This is general information and should not be seen as medical advice. The best advice for you and your family is obtained from the doctor and the team of health care specialists who are diagnosing and following your case or that of your child.

The biggest impact of a muscular disorder is on lifestyle. Be it a child who is affected or an adult, the lifestyle of the whole family will be impacted. Yet, ironically, lifestyle is barely covered here. Why? Because the psychological and lifestyle impacts of these disorders are quite unique and evolve over time as the condition emerges, is diagnosed and progresses. It is not practical to offer advice on these complex and individual experiences on a general page like this. There are excellent peer support groups and discussion groups for all disorders on the internet. For even the rarest conditions, there are many others like you and it is usually helpful to discuss your feelings and questions with others who "are in your shoes."

Please feel free to contact Muscular Dystrophy Canada if you have suggestions or questions about this page. Our website is: http://www.muscle.ca/ or e-mail us at info@muscle.ca Thank you.

1). GENERAL OVERVIEW

1-A). What is myotonic dystrophy?

Myotonic dystrophy (DM) is a complex genetic disorder that may affect many different systems in the body, including; muscle, the eye, heart, brain, hormones, the gastrointestinal tract, the uterus and skin. The abbreviation DM comes from its Latin name, *Dystrophia Myotonica*. Sometimes people call it myotonic muscular dystrophy (MMD). First described by Dr. Hans Steinert in 1909, now two types of myotonic dystrophy are recognized (DM1 and DM2). The genetic mutation causing DM1 was discovered in 1992. The genetic cause for DM2 was discovered in 1994 and is less well understood than DM1.

Myotonia causes abnormally long muscle contractions or a slowed relaxation after a muscle contraction as shown by an inability to relax voluntary muscles at will – people cannot let go of the steering wheel of a car after gripping it (A DM1 patient asked to make a forceful handgrip for 5 seconds and then open the hand as quickly as possible may take more than 20 seconds to fully extend the fingers). The core features of myotonic dystrophy are myotonia of the muscles and weakness of the distal muscles – starting in the wrists and fingers, neck and face (eye musculature, tongue and lips) and the lower legs and ankles. Later, weakness spreads to the thighs, hips and shoulders. Chest muscles and the diaphragm may also become involved. Cataracts are common and a wide range of other symptoms may also appear. The symptoms of myotonic dystrophy are extremely variable and symptoms can also vary widely in severity. About 50% of people with the disorder show some visible signs by about age 20, but many do not develop clear symptoms until after 50.

Both major subtypes of myotonic dystrophy display adult onset, with symptoms usually appearing between the twenties and the forties. A rare variant form of DM1, called congenital myotonic dystrophy, involves much more severe symptoms that are present at birth. Generally, the earlier DM begins, the more severe the disorder tends to be.

1-B). Quick Facts about myotonic dystrophy.

What: Myotonic dystrophy (DM or MMD). Three types are recognized: DM1, congenital myotonic dystrophy (a DM1 variant) and DM2.
Who: Anyone.
When: In the most common forms, 50% of people with the disorder show some visible signs by about age 20, but many do not develop clear symptoms until after 50.
Where: Skeletal muscles, mostly in the finger flexors, neck/face, tongue/lips and ankles and eventually, often in other organ systems in the body.
Why: Muscle weakness and other problems are caused by known genetic mutations; however, the exact mechanisms involved are not well understood yet.

1-C). How common is myotonic dystrophy?

Myotonic dystrophy is the second most common muscular dystrophy (MD) overall (behind Duchenne MD) but the most common adult form of muscular dystrophy. Myotonic dystrophy affects about 1 in 8,000 people worldwide but it also occurs in "pockets."

DM1 is disproportionately common in the Saguenay-Lac-Saint-Jean region of Quebec with about 1 in 500 people affected. This high rate has been traced back to one couple who carried DM1 and settled in New France in 1657. This phenomenon is called a "founder effect." Founder effects are largely responsible for differences seen in the frequency and sometimes in the exact nature of genetic characteristics in different populations of people living in different areas. Due to a founder effect, it is possible to see small geographic locations with very high (or very low) rates of a given genetic disorder.

1-D). Are there different types of myotonic dystrophy?

Yes, two types of myotonic dystrophy are currently recognized, DM1 and DM2.

- DM1: Caused be a genetic mutation on Chromosome #19 that affects the dystrophia myotonica protein kinase gene (DMPK gene).
    - Congenital Myotonic Dystrophy (CMD): symptoms appear in the newborn, this is a rarer but far more severe form of the DM1 mutation.
- DM2: Caused by a genetic mutation on chromosome #3 involving the zinc finger protein 9 gene (ZNF9 gene).

DM1 & DM2 have a somewhat different pattern of symptoms and characteristics:

- DM2 was differentiated in 1994 and is less well understood than DM1.

- DM2 may show milder symptoms than those seen in DM1.
- In DM2, no significant correlation between the age of onset and expansion size have been observed.
- In DM2 facial weakness is usually milder than in DM1.
- There are sometimes differences in how DM1 versus DM2 affects the brain, intellectual functioning and personality.
- In DM2, there is usually early involvement of the proximal muscles, rather than the distal, with initial weakness in the thighs and the upper part of the leg.
- Research is contradictory in terms of how common each type is, some studies say that 98 percent of people with myotonic dystrophy have DM1; other sources suggest that the prevalence of DM1 and DM2 is about equal.
- DM2 is found chiefly in Northern Europeans & their children, in Germany, it may be as common as DM1.

This table, "**DM 1 vs DM 2 Comparative features"** is from:
http://www.neuro.wustl.edu/neuromuscular/musdist/pe-eom.html#dm2

Feature	**DM 1**	**DM 2**
GENERAL		
Epidemiology	Widespread	European
Onset Age	0 to Adult	8 to 60 years
Anticipation	+	Mild
Cogenital form	+	-
MUSCLE		
Weakness		
Face	+	Mild
Ptosis	+	Mild
Sternomastoid	+	Variable
Proximal legs	Late	Early
Distal	+	Hands
Any location	+	+
Muscle pain	±	+
Myotonia	+	+
Calf hypertrophy	-	+
SYSTEMIC		
Cataracts	+	+
Balding	+	+
Cardiac arrhythmias	+	Variable

Gonadal failure	+	20%
Hypersomnia	+	Variable
Hyperhidrosis	Variable	+
Cognitive disorder	Mild to Severe	Mild
LABORATORY		
Hyperglycemia	+	20%
EMG: Myotonia	+	+
Chromosome	19q13.3	3q21
Mutated gene	DMPK	ZNF9
Mutation type	CTG repeats	CCTG repeats
Repeat size	100 to 4,000	Mean ~5,000

Congenital Myotonic Dystrophy (DM1) can occur in second or third generations and can be fatal for affected infants. It is almost always passed on by a mother who has adult onset DM. Infants with CMD have muscle weakness and poor respiratory function, often leading to death. Motor function gradually improves in surviving children and they are usually able to walk. However, they will develop the clinical signs of classical DM later in life. Cognitive disabilities are present in 50-60% of these individuals.

DM3?
Recently, research has suggested there may be a third form of myotonic dystrophy. Thirty individuals from three generations of a single family displayed symptoms characteristic of myotonic dystrophy but when tested, they did not show the characteristic genetic mutations see in DM1 or DM2. Ten of them had proximal muscle weakness at onset, clinical/electrical myotonia and DM-type cataracts. Dementia was observed later in the course of the disease. Genetic testing suggested a problem on chromosome number 15 and the researchers proposed to designate this disease myotonic dystrophy type 3, DM3. How common this type may be remains to be seen. Suffice to say that research continues (Le Ber, 2004).

It is also common to see a classification of DM based upon severity:

1). “Mild DM” (adult onset): People with “mild DM” often lead active lives and may even be unaware that they have the disorder.

2). “Classical DM” (adult onset): People commonly have muscle weakness and wasting, myotonia, hand and wrist weakness and/or foot drop.

3). “Congenital Myotonic Dystrophy” (CMD): A very severe form of DM1, often fatal in young children (not seen in DM2).

1-E). What other names do people use for myotonic dystrophy?

Myotonic dystrophy is sometimes called Dystrophia Myotonica (DM). Myotonic dystrophy is usually abbreviated as DM.
Many sources also use the term myotonic muscular dystrophy (MMD).

- DM1 – also called myotonic dystrophy 1, myotonic dystrophy of Steinert or Steinert's disease.
  - The rare form is called Congenital Myotonic Dystrophy (CMD or CMyD).
- DM2 – also called myotonic dystrophy 2, Proximal Myotonic Myopathy (PROMM).

1-F). Are there other disorders related to myotonic dystrophy?

There are no disorders directly related to myotonic dystrophy. Myotonia is also seen in a group of genetic disorders called channelopathies (inherited diseases caused by mutations affecting the chloride, sodium or potassium ion transport channels in the muscle membrane). Myotonia congenita (Thomsen's disease) is a type of channelopathy that can be autosomal recessive or dominant and is caused by mutations in the CLCN1 gene encoding the muscle-specific chloride channel, ClC-1. Myotonia is also seen in a condition called potassium-aggravated myotonia (an autosomal dominant disorder caused by mutations in SCN4A, the gene encoding the alpha subunit of the muscle-specific sodium channel).

Disorders of a similar nature: DM is an autosomal dominant muscular dystrophy affecting the skeletal muscles and involving a repeat mutation. Facioscapulohumeral Muscular Dystrophy (FSHD) also falls into this general category. In addition, another disorder, spinocerebellar ataxia (SCA) number 8 (SCA8), shares the same genetic mechanism seen in DM, it is associated with excess RNA accumulation caused by an expanded, noncoding, CTG repeat.

2). SYMPTOMS

2-A). What are the symptoms of myotonic dystrophy?

A wide range of symptoms are seen in myotonic dystrophy. In fact, many research articles caution that the course of myotonic dystrophy varies too widely, even in the same family, to permit a general statement about its effects. At one end of the scale, there are people with the disorder whose symptoms are so mild they hardly know anything is wrong. Whatever muscle weakness they experience is something they take for grated and adapt to, often without ever complaining to a doctor, simply attributing their symptoms to "stiffness" or "arthritis." In some cases, the only symptom may be a cataract. At the other end of the scale, this can be a fatal disorder and in the congenital form, may kill in

childhood. Adding to this complex picture, people in the same family may display widely different symptoms and different degrees of severity. In some cases, symptoms may be severe in one generation and then mild in the next, making it appear that the disorder has "skipped" a generation. In other cases, symptoms get worse with each generation – this is called anticipation, a phenomena that will be explained below.

Myotonic dystrophy causes a typical pattern of general weakness:

- DM1 initially involves the distal muscles of the extremities (finger flexors, ankles) and only later affects the proximal musculature (shoulders, hips, and thighs).
- DM2 usually spares the distal muscles and face and initially strikes the proximal muscles (primarily the upper legs).

As explained above, a person with myotonic dystrophy often displays myotonia and has difficulty relaxing his or her muscles. Once stimulated, the muscle has a difficult time returning to a relaxed state. This especially affects the grip and is more pronounced in the cold. Often, patients cannot remove their hands from the steering wheel of a car. Myotonia can be easily seen using a test of the muscles called an electromyography (EMG).

Myotonic dystrophy may slowly progress to the muscles controlling swallowing and respiration. It also may affect the muscles of the digestive system, causing constipation and other digestive problems. Myotonic dystrophy may also affect a wide variety of other organ systems, may adversely affect intellectual abilities, including memory and concentration, sleep needs often increase and motivation may be low. Other impacts on personality and behavior may also be seen. Hypogonadism (a reduced or absent secretion of sex hormones) is common but it does not cause infertility. Problems with the electrical control of the heart are a common complication.

Synopsis of common symptoms associated with myotonic dystrophy:

Weakness in the Limb muscles:

- Weakness of the distal muscles – those farthest from the center of the body – are usually the first, and sometimes the only, limb muscles affected. The forearms, hands, lower legs and feet have these distal muscles.
- Muscle wasting and weakness in the finger flexors causes the grip to weaken and can make fine finger movements troublesome.
- Muscle wasting and weakness in lower legs and ankles may affect walking leading to frequent tripping and falling. The muscles don't pick up the toe high enough and this causes problems (called foot drop).

Weakness in the muscles of the head, neck and face:

- Muscle wasting and weakness in the head, neck and face.
- Prominent facial weakness gives a tired, sleepy appearance and lack of expression.

- Involvement of the muscles around the eye leads to weakness of eyelid closure, sometimes people can't keep their eyes open and there may be limitation of eye movements.
- Muscle wasting and weakness in the tongue and lips may cause speech disability.
- Muscles that control swallowing may be weakened.

The heart is often involved in adult DM:

- It isn't primarily the muscle of the heart that's affected, but rather the electrical control of the heartbeat.
- It's common to develop what is called a conduction block, a block in the electrical signal that keeps the heart beating at a safe rate.
- Fainting, near fainting or dizzy spells are common symptoms of conduction block and these problems can be fatal.
- Conduction blocks are usually diagnosed by an electrocardiogram (EKG), a test of the electrical control of the heart.
- Conduction blocks can usually be corrected by inserting a pacemaker.

Other muscle weakness and other symptoms include:

- Weakness of the muscles between the ribs and those of the diaphragm, which moves up and down to allow respiration. Sometimes patients have a hard time getting enough oxygen and feel tired much of the time.
- Myotonia of the muscles.
- Cataracts of the lens of the eyes (lens opacities) are extremely common in DM.
- Hypogonadism, a reduced or absent secretion of hormones from the sex glands, may cause a shrinkage of the testes (but does not reduce fertility).
- In DM, many of the involuntary muscles that surround the "hollow organs" can weaken or can have myotonia. These include the muscles of the digestive tract, the gall bladder (gallstones are more common), the uterus (complications in childbirth can be serious for both mother and baby) and the blood vessels (commonly causing low blood pressure).
- The large intestine (colon), rectum and anus can also show weakness and spasm.
- A pattern of early frontal balding is very common in men.
- Cognitive function appears to decline as the age of onset becomes younger and younger and as the size of the repeat expansion section increases (DM1).
- It is commonly reported that in DM1, patients have a difficult time concentrating, applying themselves to a task over time and may not attend to work or family life well.
- In DM1, family members often describe patients using words like; slow, dull, uncaring, unenthusiastic or depressed.
- Adults with DM1 often need much more sleep than other people and may feel tired all the time (never feel rested).
- Diabetes mellitus occurs in 5% of cases.

The severity of symptoms forms the basis for this common classification of DM:

1). “Mild DM” (adult onset): People with “mild DM” often lead active lives and may even be unaware that they have the disorder.

- 50% of people with the disorder show some visible signs by about 20, but many do not develop clear symptoms until after 50.
- If people feel muscle weakness or mild myotonia, they may attribute their stiffness to “arthritis.”
- People are often tested and diagnosed because they have a relative who has been affected and diagnosed with DM.
- Seen in both DM1 and DM2.

2). “Classical DM” (adult onset): People commonly have muscle weakness and wasting, myotonia, hand and wrist weakness and/or foot drop.

- Heart abnormalities are a common concern.
- The individual’s intellect, personality and behaviour may be affected.
- Age of onset is typically in the second or third decade of life, but a mild mask-like appearance of the face (“myotonic facies”) with a “sleepy expression” and myotonia may be observed in childhood.
- Adults may become physically disabled and may have a shortened life span.
- Seen in both DM1 and DM2.

3). “Congenital Myotonic Dystrophy” (CMD): Congenital myotonic dystrophy has the same basic genetic cause as DM1 (not seen in DM2).

- A far more severe but rare form of DM can occur in second or third generations, usually inherited from a mother who has DM (even a mild case) and can be fatal for affected infants.
- Symptoms are present at birth (considered a “childhood onset”) and are different than the adult presentation – there is major muscle weakness but little myotonia is seen at this stage.
- The affected infant is profoundly weak, has a lack of muscle tone (hypotonia), has difficulty with sucking and swallowing, and may have severe respiratory difficulties, often leading to death. Babies with congenital myotonic dystrophy are often described as “floppy.”
- Infants with CMD often exhibit an inverted "V" shaped upper.
- Motor function gradually improves in surviving children and they are usually able to walk. However, they will develop the clinical signs of classical DM later in life.
- CMD babies are often born with clubfeet, a severe curvature of the feet and lower legs that requires surgical correction.
- Major cognitive disabilities are present in 50-60% of these individuals.
- Speech and hearing are often affected.

ANESTHESIA WARNING: An unusually high rate of complications and even deaths are associated with general anesthesia in patients with DM. Even mild myotonic dystrophy

can cause very serious complications. Mild cases may also be even more at risk because patients may not think to tell their surgeons about their diagnosis or a family history of myotonic dystrophy.

2-B). What is the age of onset of myotonic dystrophy?

The genetic defect is present at birth but the onset of visible symptoms is very variable depending upon the severity of the mutation involved and other factors.

Typically, in the most common adult onset forms, symptoms appear in the second or third decade of life although a mild mask-like appearance of the face ("myotonic facies") and myotonia often may be observed in childhood.

Congenital Myotonic Dystrophy symptoms appear in the newborn.

2-C). Are different age-groups affected differently?

Yes, the congenital myotonic dystrophy that affects newborns and children (CMD) has different features and is more severe than the forms that display adult onset. Generally, when DM begins in the teen years or during adulthood, it is often only a moderately disabling condition with slow progression.

2-D). Who can be affected by myotonic dystrophy?

Myotonic dystrophy affects both males and females.

2-E). How does myotonic dystrophy progress and what is the prognosis?

Neuromuscular disorders are usually progressive. That means there keep getting worse and worse over time. The rate of progression in myotonic dystrophy is often quite variable. Typically, muscle weakness and wasting slowly progress to the point of some disability, moving beyond the distal muscles originally involved to those of the shoulders, hips, and thighs. As a rule, disability rarely becomes severe until fifteen to twenty years after the initial onset of symptoms. Adults may become physically disabled and may have a shortened life span, depending upon the severity of the mutation and its impact. The older a person is when muscle weakness is first noticed, the slower is the progression and the less serious the consequences (especially true of DM1).

Prognosis is a prediction of the course of a disorder – how is it going to unfold and develop in the future – what is the outcome going to be? Again, we need to caution that myotonic dystrophy is extremely variable in individuals. Because the condition presents with so many different symptoms and with widely varying degrees of severity, it is not advisable to generalize about prognosis.

2-F). Are there non-neuromuscular problems associated with myotonic dystrophy?

Yes, several other major systems are often affected including the eye, the hormonal system, digestion and the brain.

2-G). How “serious” or disabling is myotonic dystrophy?

Because myotonic dystrophy presents with so many different symptoms and in varying degrees of severity, it is not advisable to generalize. We can say that the more severe the mutation involved, the more severe the impact will be (especially true of DM1). Myotonic dystrophy generally becomes progressively more disabling with time. Also, the impact on other organs and body systems may also increase over time.

Congenital myotonic dystrophy tends to be particularly serious, often leading to death in childhood or to severe disability.

2-H). Does myotonic dystrophy affect thinking or behaviour?

Yes, there is evidence that myotonic dystrophy affects the brain and often has a deleterious effect on intelligence as measured by IQ and on memory tasks (Modoni, et al, 2004). Also, certain personality traits have been associated with myotonic dystrophy, including lack of motivation, lack of insight and poor judgment, and avoidant, obsessive-compulsive and passive-aggressive traits (Delaporte, 1998).

3). DIAGNOSIS

3-A). How do I know if I might have myotonic dystrophy?

Generally, you will notice muscle weakness and stiffness, especially in the wrists and hands. Your eyes may be hard to keep open, you may feel tired all the time and you may start to trip from not picking up your toe high enough when walking. You may notice some speech problems or problems swallowing food.

3-B). How is myotonic dystrophy diagnosed and what tests are performed?

There are three main diagnostic approaches:

- Clinical diagnosis: the doctor looks at you and notes your pattern of symptoms.
- Diagnostic tests: These can include blood tests, x-rays and other types of scans, tests of muscle and nerve function and muscle biopsies.
- Molecular and genetic testing: This method looks at genetic material taken from blood samples to see if there is a genetic problem.

Diagnostic approaches for myotonic dystrophy involve clinical diagnosis, diagnostic testing and molecular (genetic) diagnosis.

Clinical diagnosis involves a doctor or neurologist looking for key symptoms to identify the distinctive pattern of muscle involvement. Some symptoms of myotonic dystrophy might be hard to see in mild cases. In typical adult-onset cases, clinical diagnosis is usually straightforward with a presentation of progressive distal weakness in the presence of myotonia, with frontal balding, and cataracts.

Diagnostic testing includes doing studies of the electrical pattern of the muscles using electromyography (EMG). Tiny needles are placed in a muscle and hooked up to a computer to measure the electrical activity of the muscle as it contracts and relaxes. Abnormal myotonia will appear on this test. In addition, the physician will do a blood test called a creatine kinase (CK) level (also known as a phosphocreatine kinase (CPK) level) to test the health of the muscles. If muscles are abnormally breaking down, they release elevated levels of the enzyme creatine kinase into the blood. Other tests may include a Nerve Conduction Velocity (NCV) test to measure how fast electrical signals are moving along the nerves.

Evidence of myotonic dystrophy is provided by demonstration of depressed levels of a chemical in the blood called immunoglobulin (IgG) along with elevated CK levels. Examinations of the eye are also useful in showing early lens opacities. An electrocardiogram (ECG / EKG) an electrical recording of the heart may be done.

A muscle biopsy may be suggested at this stage. A small piece of muscle is surgically removed and examined in the laboratory.

Once a clinical diagnosis has been suggested, the patient and doctor can discuss genetic testing. Molecular (genetic) diagnosis is often used to confirm the clinical diagnosis.

Molecular (genetic) diagnosis involves a much more accurate test than clinical diagnosis and is often used to confirm clinical suspicions. Molecular diagnosis involves a genetic understanding of the disorder and the ability to test the DNA (or RNA) in the blood for specific mutations as compared to a healthy sample.

3-C). Is there a genetic test for it?

Yes, very accurate diagnostic tests of the blood can show the presence and size of the mutation and permit DNA diagnosis in DM (including prenatal diagnosis).

Gene Tests Testing for DM1:
http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=2118&res=&key=hDdAIZDTDh2DY&show_flag=c

Gene Tests Testing for DM2:
http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=113763&res=&key=hDdAIZDTDh2DY&show_flag=c

3-D). Should other members of my family be tested for myotonic dystrophy?

As myotonic dystrophy is a genetic disorder, it is possible that parents, siblings, or children may also carry the mutation responsible for the disorder. It is not uncommon for family members to test positive for the myotonic dystrophy mutation and yet not show any symptoms. This may be important to know in terms of future family planning.

Testing for any genetic disorder is a personal choice and, when done on a seemingly healthy individual, this choice should not be made lightly. Understand the risks of genetic testing and discuss these options with your family and with your doctor.

An excellent site for information on genetic testing is the GeneTests Web site, funded by the National Institutes of Health (USA), see the section on educational materials.
http://www.genetests.org/

3-E). Can I be confident in the diagnosis?

Over the years, neuromuscular disorders have developed a reputation as sometimes being difficult to diagnose. Modern diagnostic procedures are a combination of good clinical judgment and very accurate tests. If you feel unsure about your diagnosis, it is important that you discuss your concerns and options for further testing or a second opinion with your neurologist or doctor.

4). CAUSES and PATHOLOGY

4-A). What causes myotonic dystrophy?

The muscle weakness and other problems seen in DM are caused by known genetic mutations; however, the exact mechanisms involved are not well understood yet.

4-B). How does a person get myotonic dystrophy?

As a genetic disorder, myotonic dystrophy is passed from generation to generation in the genetic code through inheritance. Parents who carry the mutation (and who may or may not know they have the mutation) can pass it on to their children.

Sometimes a new mutation occurs in a family with no previous history of myotonic dystrophy, but in the case of DM, this appears rare.

4-C). Is myotonic dystrophy anyone’s fault? Is it contagious?

No. Myotonic dystrophy is usually passed on from generation to generation by the genetic code or it sometimes arises as a new genetic mutation. Because of the relatively late onset of the disorder, unless there is a clear family history, most patients are not aware that they could pass on the mutation until after they have had children.

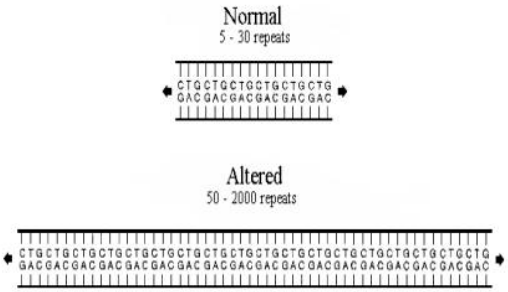
Is it contagious? No, myotonic dystrophy is not contagious. Myotonic dystrophy is a genetic disorder and therefore it cannot be passed from person to person by any sort of physical contact. Genetic disorders can only be passed on through reproduction.

5). GENETICS

5-A). Does genetics play a role in myotonic dystrophy?

It is normal for small sections of the genetic code to be repeated over and over. The number of repeats in a particular section is important and is usually consistent – the number of repeats in children is about the same as the number their parents have. It is now known that mutations can occur that either increase the number of repeats or delete repeats. If there are too many or too few repeats, it may lead to disorders, in the case of DM, the problem is too many repeats in a particular section. An example of a disorder involving too few repeats is FSHD.

DM1 is caused by a repeat expansion mutation in the DMPK gene located on Chromosome #19 – triplets of CTG code are increased in number. People normally have about 5 to 30 CTG repeats in this section of code. Mild DM1 is seen when there are from 50 to 80 repeats present and severe cases may show more than 2000 repeats. Congenital DM1 may involve more than 4000 repeats.



From: http://www.myotonicdystrophy.org/Genetic%20Information.htm

DM2 is caused by an expansion in the ZNF9 gene, found on chromosome #3 involving CCTG repeats. DM2 involves an expansion with from 75 to 11,000 CCTG repeats and a mean of about 5,000 repeats.

Typically, genetic disorders involve mutations of a specific gene. Genes are used by the cell to make proteins and a mutation usually disrupts a specific protein and this directly causes the disorder. The mutation in myotonic dystrophy is different in that it does not occur in the part of a gene that directly makes protein. In DM, the impact is apparently

more indirect and scientists and researchers are still debating how the myotonic dystrophy mutation causes the diverse and variable symptoms we see. It is believed that the mutation causes secondary effects – an accumulation of defective RNA within the center of the cell – that in turn impairs the proper functioning of one or more genes vital to healthy function.

With each new generation, the number of extra repeats may increase, decrease or stay the same. Because the number of repeats varies over generations, this is called an "unstable mutation."

When the number of extra repeats increases, it leads to a phenomenon called genetic anticipation – as the size of the repeated section increases, successive generations commonly show symptoms at an earlier age and show more severe symptoms. Anticipation is seen in some cases of DM (more common in DM1). Contractions of the enlarged section during transmission from one generation to the next can also lead to reduced symptoms.

5-B). What genes are related to myotonic dystrophy?

In DM1, a CTG repeat is expanded in an untranslated (intron) region of the dystrophia myotonica protein kinase gene (DMPK) located on Chromosome #19.

DM2 is caused by an expansion found in an untranslated (intron) section of the zinc finger protein 9 gene (ZNF9), found on chromosome #3.

5-C). Is myotonic dystrophy inherited and if so, how?

Yes, myotonic dystrophy is inherited – it is passed from generation to generation, in an autosomal dominant fashion.

Certain genes are usually found on certain chromosomes, in our case, the ZNF9 gene on chromosome #3 and the DMPK gene on chromosome #19. These are called autosomes; autosomes carry one pair of each of their genes, one copy is inherited from mom and one version is inherited from dad. Because myotonic dystrophy is genetically dominant, only one copy of the gene with the genetic mutation (inherited from either mom or dad) is necessary for DM to occur in a person (the other copy of code is usually healthy but it is overridden by the dominant version and thus it can't help out).

In autosomal dominant disorders, for each pregnancy, a parent with a mutation has a 50% chance of transmitting the abnormal gene (allele) version and a 50% chance of passing on their other, normal version of the gene to each child born. Each child has a 50% chance of inheriting the defect from a parent with the mutation and a 50% chance of getting the healthy gene version. Because it is dominant, if the child does inherit the defective copy, he or she will display the disorder. These figures are statistical averages – a given family of four might have four children with DM, two with and two without, four children without or some other combination.

It is the mother who usually transmits the disorder in cases of congenital myotonic dystrophy. Mothers with DM can also pass on the adult-onset form. Generally, DM patients born of affected mothers are more severely affected than those born of affected fathers. When a child inherits myotonic dystrophy from the father, it's almost always the adult onset form. These unusual features are not often seen in other genetic disorders.

The wide range of symptoms seen in myotonic dystrophy is due to a greatly variable penetrance of the disorder. Penetrance refers to how many people who have a given genetic trait (the genotype), in this case, the repeat expansion mutation, will actually show signs of it (phenotype – the symptoms seen). In some disorders, penetrance is high and everyone with a particular mutation will display symptoms at some point, other conditions display a low penetrance and some people will never show symptoms of the trait. In myotonic dystrophy, some people with the mutation have a high penetrance (and have early and serious symptoms) some people with the mutation have a low penetrance (and may show very mild symptoms).

Somatic and Germline (gonadal) mosaicism:

This next section is complicated but we need to be aware of it, as it impacts many people with myotonic dystrophy.

The above description of inheritance assumes that if there is a mutation that all of the cells will have it. This does not always happen, sometimes some cells will have the mutation and other cells will be healthy. This complicated scenario is called mosaicism and the individual is referred to as a mosaic. Think of the crisscross pattern of tiles on a black and white mosaic floor – the white tiles are healthy and the black ones are mutated – this is the type of pattern seen in the cells, some are healthy and some carry the mutation.

How does this happen? As described above, genetic mutations are not always inherited from a parent (through an egg or sperm cell), some may occur spontaneously as a new mutation after conception and during the early days of embryonic development.

Very early in the development of an embryo, ancestor cells that are the child's future sperm or egg cells separate from the rest of the developing cells. This batch of cells, called the germline, is set aside – eggs in a female and sperm in a male. Germline cells divide and multiply in the embryo and this division continues after the child's birth. For males, sperm cells don't complete their development until the child becomes an adolescent. A female's egg cells complete part of their development during fetal life and

part at puberty. New mutations can occur in the genes of these cells at any stage during this process. If mutations occur early in development, they often affect many of the subsequent sperm or egg daughter cells. If they occur later, mutations may affect very few cells, or maybe even just one cell.

[We should mention here that new mutations are not uncommon and geneticists estimate that about 30 negative mutations occur during an average lifetime. These mutations accumulate as we age and increase in frequency as we age, this is one of the reasons why birth defects become much more common when the parents are 35 and older.]

The person with a new mutation may display the disorder and will be the first in the family to show it. Other relatives in the family will not be at risk as this was a new mutation and it has not had a chance to be passed on yet.

Whether or not a condition will affect the individual depends in part on the inheritance pattern of the disorder. If the new mutation involves an autosome and a dominant disorder, as is the case with DM, the affected person will be the first in the family to display the condition and may subsequently pass on the mutation if they have children.

[If a new mutation involves a gene on the X chromosome, a male will be affected, while a female will usually not show symptoms, however, she may pass this mutation on to any children – a common scenario in Duchenne and Becker muscular dystrophy. If the disorder is autosomal and is recessive, the person will not be affected by the new mutation because he or she still has another correct copy of the gene to provide the information for the cell to work normally. In these cases, the mutation may be passed on.]

When mutations occur after the germline has separated, there's a good chance they'll affect many sperm or egg cells but not the other cells in the body, such as blood or skin cells – these are the cells commonly used in genetic testing. A genetic test of these cells will not suggest any problems. Even if a sample of sperm or egg cells is tested and shows no mutations, other egg or sperm cells could still carry the mutation. Just one mutated cell is all it takes. Once a mutation has been inherited by a child, it becomes part of his or her DNA and can be passed on to future generations if he or she subsequently has children – the children would have the mutation in every cell.

The expanded repeats seen in DM are unstable and prone toward further expansion in a process that is continuous throughout the life of an individual (Martorell, 2004). Research in animals has shown that this instability differs between tissues in the body, the cells in some tissues show higher rates of repeat expansion than others during the lifetime of the organism. For example, expansion instability is more pronounced in the liver, kidney, pancreas and brain and less so in the muscles, heart and lung tissues (Lia, 1998). This progressive

somatic mosaicism has important implications for interpreting genetic testing and evaluating the transmission from generation to generation (which are typically based on the analysis of average section sizes in the DNA in the blood of parents and offspring). The increasing expansions with age need to be taken into account; otherwise it is possible that the measured repeat sizes will not reflect the true germline changes.

[During a person's lifetime, new mutations are also occurring in the somatic (body) cells. These mutations cannot be passed on to future children (because they are not in sperm or egg cells), but they can cause illness in the person's lifetime. Common examples are mutations in skin cells causing skin cancer or in breast cells causing breast cancer.]

In summary, these mutations may affect only some cells, leaving others healthy and leading to mosaicism in the individual.

Mosaicism greatly complicates making predictions about inheritance or the severity of a disorder in children of mosaic parents. Mosaic patients often have less severe symptoms than non-mosaic patients. A mosaic parent who has the mutation in only some of his or her cells may have very mild DM symptoms. But that person's child would inherit the mutation through an egg or a sperm and thus have it present in all cells starting at conception (non-mosaic). Such a child would be more severely affected than his mosaic, partially affected parent. In summary, if a parent has DM diagnosed but his or her mosaic status isn't recognized, by assuming the severity of the disorder will be like that of the parent, the severity in the offspring may be underestimated.

If all germline cells have the mutation, the risk of passing on a dominant disease like FSHD is 50 percent. In mosaics, only some of the cells carry the mutation and the risk of passing on the disorder falls below 50 percent. The actual percentage of risk would reflect the ratio of the number of mutated cells to healthy cells – a ratio we cannot estimate. In a mosaic parent with a mixture of mutated and healthy germ cells (eggs or sperm), there are two possible scenarios: If a mutated egg or sperm cell from the mosaic parent becomes part of the fertilization, the child will have DM (because it is a dominant disorder). In the second scenario, a healthy egg or sperm from the mosaic parent combines with a healthy egg or sperm from the other parent and the child will be DM free. In summary, if a parent has DM diagnosed but his or her mosaic status isn't recognized, the chances of passing on the DM mutation to a child may be overestimated.

In patients who display mild DM symptoms but whose genetic testing suggests a more severe type of mutation, mosaicism should be suspected. In these cases, special genetic testing can be done to reveal the mosaicism.

6). TREATMENT and MANAGEMENT

6-A). How can we cope with this diagnosis?

A diagnosis of myotonic dystrophy comes as a shock, and brings challenges and difficult adjustments for an individual, their family, and their friends. At first, you may experience many mixed emotions, especially grief, anger, and fear. Giving yourself time to adjust, talking to family, friends and professionals, and reading about myotonic dystrophy may help as you deal with this diagnosis. Talking to other people living with myotonic dystrophy, parents of children with myotonic dystrophy, or health professionals may also be helpful.

Many adults with myotonic dystrophy will lead full and almost normal lives. Sadly, many will also experience degrees of disability and medical issues.

Children with congenital myotonic dystrophy will experience major physical challenges and limitations and sadly, may succumb to the disorder. Surviving children will face changing physical challenges and limitations as they grow.

6-B). How can I best manage my life with my symptoms?

You need to manage your symptoms, or those of your child, in close liaison with your medical team. You need to keep on top of things as they change or as new symptoms develop and discuss options with your medical team, family and others who have myotonic dystrophy. The overall condition needs to be kept in mind as each symptom emerges and is managed as the need arises.

6-C). How can doctors and specialists (like neurologists) help?

Neurologists are doctors who specialize in disorders affecting the nervous system and are often consulted for patients who may have myotonic dystrophy. If your family doctor cannot offer specialized advice about myotonic dystrophy, he or she should be able to recommend you to a neurologist. A neuromuscular clinic is best equipped to diagnose your disorder and answer questions about possible management options. There are neuromuscular clinics and hospitals across Canada that are equipped to do the necessary diagnostic testing and to offer advice and support regarding the ongoing management of myotonic dystrophy.

6-D). Are there treatments or medications for myotonic dystrophy?

There are currently no treatments for myotonic dystrophy that can halt or reverse the symptoms and muscle weakness. Each symptom displayed reflects an underlying issue and each needs to have a treatment plan developed to best address the concern on an individual basis.

There are any different treatments and devices that can help ease the pain and discomfort associated with myotonic dystrophy. For example, muscle weakness in the ankles and hands may be addressed with a plastic brace called an orthosis. These are made for the person to try to add strength to their joints and make daily activities easier.

Heart problems can usually be treated with a cardiac pacemaker, an electronic device used to regulate the heartbeat that is surgically inserted near the heart.

Medications may be prescribed to help address many of the possible secondary issues that arise. For example, sleepiness can sometimes be helped with medication. There are drugs that will help the symptoms of myotonia. Also, there are often drugs prescribed to address problems in the digestive tract or with diabetes.

The best advice is to discuss medications for your particular symptoms with your doctor or neurologist.

6-E). Can surgery help?

In myotonic dystrophy, the eyelids may droop – a condition known as ptosis [TOE-sis]. Severe ptosis can be troubling as it may be hard to keep the eyes open for reading, watching television or driving. Special glasses with “eyelid supports” can hold the eyes open. You can usually get these from an optician who will make a pair for you. Surgery can be done to help, but weakness often comes back, making it necessary to repeat the operation.

Surgery may also be indicated to address the problems with the lens of the eye or with possible gallstones.

6-F). Can physiotherapy help?

Once a diagnosis is confirmed, a person living with myotonic dystrophy may be assessed by a physiotherapist in order to evaluate his or her joint mobility, test the ability to move from one position to another, test the ability to walk, and to evaluate other capacities in activities involving gross motor skills (jumping, running, or climbing stairs). Depending upon each person’s needs, a regular monitoring program may be proposed along with a program of activities to practice at home. This program is aimed at strengthening or maintaining range of motion, coordination, and balance. A program may involve moderate exercise, especially swimming, often direct under supervision.

6-G). How can occupational therapy help?

The role of the occupational therapist is to foster fine motor skill development and lessen the impact of the disorder on lifestyle. Accessible transportation is often a requirement. Physical education (for children) or ongoing physical activities need to be adjusted to each person’s capacities as soon as possible.

An occupational therapist can also recommend orthosis, braces, or other special belts to help compensate for weakened muscles. Muscular Dystrophy Canada's equipment loan program relies on the expertise of occupational therapists to recommend equipment required by people living with disorders such as myotonic dystrophy.

In the work environment, it is the responsibility adults living with myotonic dystrophy to negotiate appropriate employment conditions with their superiors and co-workers.

6-H). How can a nurse help?

The nurse may provide additional information about myotonic dystrophy and available services and resources in your community. A nurse may offer support to help the individual and family members cope with the disorder, provide guidance with the administrative processes when required, and liaise with the various health care professionals from the clinic and other external services.

6-I). How can a genetic counselor help?

Molecular geneticists and genetic counselors are employed in major hospitals across Canada and are available to patients and their families for the purpose of genetic diagnosis and counselling. Genetic specialists can inform the patient and their family members about the specific inheritance mechanisms involved in myotonic dystrophy, the genetic testing available to patients, as well as family planning alternatives they may wish to consider. The information provided by a genetic counselor can be specifically tailored to an individual's family history and this knowledge might be very useful in understanding why and how the disorder has affected them.

6-J). How can a dietician help?

A balanced, nutritional diet is essential to achieve the maximum function of muscles. It is often a challenge for the average person to keep fit and keep their weight from rising as the years go by. This is especially true in patients who have muscle disorders because their ability to exercise and burn off calories is usually greatly impaired. Excessive weight gain by people living with myotonic dystrophy is not recommended. The extra work that weakened muscles must do to lift excess weight adds to the challenge.

A dietician can offer advice in building a balanced diet for anyone living with a neuromuscular disorder. Some specific advantages to working with a dietician may include weight control and finding a proper balance of food that will keep the body as healthy as possible. Parents may need to provide their child with support and information about healthy nutrition based on work with a dietician. Where nutrition is concerned, the ongoing support and understanding of family is very important.

6-K). What is ventilation and will I need it?

In some types of neuromuscular disorders the muscles that control breathing are weakened. In these cases, machines may be needed to help air move in and out of the lungs.

People living with myotonic dystrophy may experience respiratory problems. Often these issues can be addressed with a small, portable ventilator that helps move air into the lungs during the night. In more severe cases and especially in congenital myotonic dystrophy, more complex and more aggressive artificial ventilation may be required.

7). LIFESTYLE IMPACTS

7-A). How will myotonic dystrophy affect my lifestyle?

It is very difficult to answer this question due to the wide range of severity seen in myotonic dystrophy. Perhaps the most honest answer is “it depends.” Lifestyle impacts will depend upon the type and severity of symptoms you, or your child, experience. When symptoms emerge will also be a big factor.

Neuromuscular disorders may have wide impacts on many different aspects of our lifestyle. These may include physical aspects like impacts on breathing, swallowing, bathroom habits, one’s sex-life and other day-to-day activities. In addition, there are major psychological impacts on the patient and on the rest of the family as the disorder progresses and adaptations have to be made. Progressive disorders involve progressive changes and progressive impacts. As you adjust to things, things often change again. Lifestyle impacts and psychological adaptations are therefore an unfolding process that mirrors the progression of the disorder.

8). RESEARCH

8-A). What research is being done on myotonic dystrophy?

One of the keys to treating myotonic dystrophy will be to better understand the mechanisms of myotonic dystrophy and how it causes the wide variety of symptoms seen. Currently, in Canada and in the rest of the world, researchers are seeking to understand the basic mechanisms of myotonic dystrophy and potential ways to block or correct them. This kind of understanding may lead to future strategies to help people living with myotonic dystrophy.

Muscular Dystrophy Canada funds an active and broad research agenda. You can find out more information about recent myotonic dystrophy research funded by Muscular Dystrophy Canada at: http://www.muscle.ca/content/index.php?id=90

8-B). Are there clinical trials for myotonic dystrophy?

Several clinical trials are planned or underway in North America for myotonic dystrophy, including (as of October 2005):
1. Myotonic Dystrophy Registry. Status: Recruiting.
2. RAMYD Study - Evaluation of Arrhythmic Risk in Myotonic Dystrophy. Status: Recruiting.
3. Efficacy and Safety of DHEA for Myotonic Dystrophy. Status: Recruiting.
4. Effects of SomatoKine (rhIGF-I/rhIGFBP-3) in Myotonic Dystrophy Type 1. Status: Not yet recruiting.

You can search for the latest clinical trials by entering the term "Myotonic" at: http://clinicaltrials.gov/

9). MUSCULAR DYSTROPHY CANADA SUPPORTS

9-A). How can organizations like MDC help?

Muscular Dystrophy Canada provides a number of services to people registered with the organization, including: Information and Education, Equipment, Peer Support, Chapter Support, Referral, Social Action.

9-B). What kind of information is available?

Muscular Dystrophy Canada provides information to registered clients, their families, community professionals, and the general public about neuromuscular disorders and related issues. Information is available in the form of disorder specific information sheets, research updates, brochures, videos, and books. An extensive and dynamic website (www.muscle.ca) provides access to electronic copies of all our publications, plus links to news and in depth coverage of our research funding. Muscular Dystrophy Canada publishes a national newsmagazine, Connections, available in both French and English. The magazine features information on a variety of neuromuscular disorders as well as related topics such as research, genetics, parenting, and quality of life. Regional offices may also keep people registered in their area up to date through regional newsletters. Services staff in our regional offices will respond to any request for information that you may have, or they will help you find the information that you need.

9-C). What kind of assistance is available for medical equipment?

The Muscular Dystrophy Canada equipment loan program provides basic medical equipment, on loan, from a stock of recycled devices such as scooters, manual and electric wheelchairs, and hospital beds. Some funding assistance may be available for the purchase of new equipment. If a request is made for a device that MDC does not cover, or only partially covers, MDC staff may be able to suggest other sources of funding. For more information about equipment funding, call the regional office nearest you.

9-D). What is peer support and how can it help?

Peer support means getting help or advice from, or just plain talking to, other people who have experience with myotonic dystrophy. Often, others who have the same disorder are good people to ask questions and to get advice from, especially in terms of how to manage the small day-to-day frustrations that come up. There are groups on the internet where you can join in discussions with other myotonic dystrophy patients, see: http://www.myotonicdystrophy.org/support.htm

Support comes in many forms and needs to be tailored to individual needs. Some people already have strong support systems in place through family, community, and church and their needs are minimal. Other people are facing stresses such as financial difficulties or family problems, in addition to the day-to-day reality of life with a neuromuscular disorder.

The Muscular Dystrophy Canada Peer Support Program offers those facing challenges the chance to talk to someone who has gone through similar experiences. People registered with MDC, family members, and close friends – trained by Muscular Dystrophy Canada staff – offer information about resources, tips on coping, and an "understanding ear" to people who are looking for support.

For people registered with Muscular Dystrophy Canada who might prefer support in a group setting, MDC staff can refer you to a local network or support, or even help you to create a new one.

Also see: http://muscle.ca/content/index.php?id=145

9-E). How can Chapters help?

Muscular Dystrophy Canada Chapters form a nationwide network of people registered with us, their families, and volunteers. They actively help Muscular Dystrophy Canada to achieve our common objectives, especially at a local level. Chapter activities can include support, social events, and fund raising.

Chapter members are often people registered with MDC and their families. However, anyone who is interested in furthering the aims and objectives of Muscular Dystrophy Canada is welcome to join. In communities across Canada, dedicated Chapter members provide valuable time, energy, and experience that ultimately benefit people with neuromuscular disorders and the communities they live in. For the location of the Chapter nearest you, please see: http://muscle.ca/content/index.php?id=45

9-F). What kinds of referrals are made?

MDC staff can provide referrals and contact information to neuromuscular clinics, agencies, and other community resources, to help people find solutions to problems they face in their daily lives.

9-G). What is Muscular Dystrophy Canada's Social Action Plan?

Muscular Dystrophy Canada engages in social action to ensure that people with neuromuscular disorders can participate fully in all aspects of daily living. It aims to do this by working with other organizations to bring about policy changes in provincial and federal governments and providing volunteers in local Chapters and communities with tools they need to participate in local and community advocacy efforts.

9-H). How can I receive Muscular Dystrophy Canada services?

If you wish to receive more information about one or more of the neuromuscular disorders under the Muscular Dystrophy Canada service umbrella, or about the organization itself, please contact the regional office nearest you. Services staff can provide you with general information in response to your needs, or help you in registering with Muscular Dystrophy Canada to receive direct services.

9-I). What is the mission of Muscular Dystrophy Canada?

Muscular Dystrophy Canada supports the independence and full participation of Canadians with neuromuscular disorders. We assist individuals to participate in the decisions that affect them and collaborate with others for social change. We fund research to improve the quality of life of people with neuromuscular disorders and to find a cure.

9-J). How can I help?

Muscular Dystrophy Canada conducts year-round fund raising campaigns to support our diverse programs. Your gift will help MDC provide the dollars necessary to assist individuals living with neuromuscular disorders, and fund much-needed medical research and educational information. Please make a gift through our National office or any Regional or Community Muscular Dystrophy Canada office.

9-K). How can family and friends help?

Family support is a critical part of any illness, especially a chronic and progressive one like myotonic dystrophy. Sometimes family will also need to go through a period of adjustment and "getting used to" a new diagnosis. Over time, family members can learn about myotonic dystrophy and how they can best help you meet your particular challenges. Family can also play an important role in looking out for symptoms and in helping deal with the health care system.

Friendships are important to everyone. Regular interaction with friends and social groups can encourage positive attitudes and a positive sense of worth for both children and adults. Regular interaction and playtime with siblings and children in the neighborhood and at school help a child learn necessary social and problem-solving skills. Adults also benefit from a social network that is satisfying to them and that understands their needs.

Friends play an integral role in the emotional well-being of those living with any neuromuscular disorder.

Family and friends also play a critical role in helping the person liaise with Muscular Dystrophy Canada and with other persons with disorders. Muscular Dystrophy Canada also thanks family and friends for their tremendous efforts in fund raising and the many other activities they become involved with, including raising awareness and in advocacy of persons with muscular dystrophy.

10). OTHER RESOURCES

10-A). What other resources and information are available to people living with myotonic dystrophy?

There are literally thousands of web pages on myotonic dystrophy. Readers will discover a wide range of information both in complexity and credibility. Generally, the web pages of National organizations, the Government and of educational facilities are usually credible sources. The best approach is to compare several sources of information with each other to gather a consensus of facts.

Congenital muscular dystrophy: http://www.emedicine.com/neuro/topic549.htm

Facts About Myotonic Muscular Dystrophy from the Muscular Dystrophy Association (USA): http://www.mdausa.org/publications/fa-mmd-qa.html

Gene Tests (National Library of Medicine, University of Washington): http://www.genetests.org/

Gene Tests Review of DM1: http://www.genetests.org/servlet/access?id=8888890&key=X7rcrzxI5gHVk&gry=INSERTGRY&fcn=y&fw=GEUQ&filename=/profiles/myotonic-d/index.html

Gene Tests Testing for DM1: http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=2118&res=&key=hDdAIZDTDh2DY&show_flag=c

Gene Tests Testing for DM2: http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=113763&res=&key=hDdAIZDTDh2DY&show_flag=c

Genetics Home Reference (National Library of Medicine, USA): http://ghr.nlm.nih.gov/condition=myotonicdystrophy

Harper, Peter (2002) *Myotonic Dystrophy: The Facts.* New York: Oxford University Press.

International Myotonic Dystrophy Organization: http://www.myotonicdystrophy.org/

The Muscular Dystrophy Campaign (UK): http://www.muscular-dystrophy.org/information_resources/factsheets/medical_conditions_factsheets/myotonic.html

Neuromuscular Disease Center, Washington University, St. Louis, MO. USA
http://www.neuro.wustl.edu/neuromuscular/musdist/pe-eom.html#myd
On DM2: http://www.neuro.wustl.edu/neuromuscular/mother/activity.html#prom

Online Mendelian Inheritance in Man (OMIM). This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information, National Institutes of Health (NIH):
OMIM Page on myotonic dystrophy (DM1):
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=160900

OMIM Page on myotonic dystrophy (DM2):
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=602668

10-B). References used in this paper.

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Lia, A.S. et al (1998). Somatic instability of the CTG repeat in mice transgenic for the myotonic dystrophy region is age dependent but not correlated to the relative intertissue transcription levels and proliferative capacities. Human Molecular Genetics, 7, 1285-1291.

Martorell, L. et al (2004). Germline mutational dynamics in myotonic dystrophy type 1 males Allele length and age effects. Neurology; 62:269–274.

Modoni, A.; Silvestri, G.; Pomponi, M. G.; Mangiola, F.; Tonali, P. A.; Marra, C. Characterization of the pattern of cognitive impairment in myotonic dystrophy type 1. *Arch. Neurol. 61*: 1943-1947, 2004.

Other recent reviews of myotonic dystrophy:

- Day, J. W. and Ranum, L. P. W.. Genetics and Molecular Pathogenesis of the Myotonic Dystrophies. *Current Neurology and Neuroscience Reports* 2005, *5*:55–59.

- Day, J. W. and Ranum, L. P. W. Review: RNA pathogenesis of the myotonic dystrophies. *Neuromuscular Disorders 15* (2005) 5–16.

- Machuca-Tzili, L., Brook, D., and Hilton-Jones, D. Clinical and molecular aspects of the myotonic dystrophies: A review. *Muscle Nerve 32*: 1–18, 2005.

Please feel free to search for specific terms on the internet. A number of excellent medical and genetic dictionaries are also now online.

For example:
http://www.nlm.nih.gov/medlineplus/mplusdictionary.html

http://cancerweb.ncl.ac.uk/omd/

http://www.stedmans.com/

http://www.dorlands.com/wsearch.jsp

http://www.onelook.com/

END.