MUSCULAR Dystrophy Genetics and Testing

Information to help you make an informed choice about testing.
ABOUT THE MDA

The Muscular Dystrophy Association (MDA) is committed to providing **HOPE** for people who are affected by the devastating nerve and muscle disorders. The only way this can be done is an all out offensive to find a treatment for such disorders. MDA supports medical and scientific research to the extent that funds will allow, it runs a comprehensive public education program and provides support and programs to help people with these disorders in their daily lives. The Muscular Dystrophy Association's programs are funded, almost entirely, by voluntary, donations and fundraising initiatives.

You can visit the *Home of MDA* at: [www.mda.org.au](http://www.mda.org.au)
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GENETIC COUNSELLING:

TESTING FOR GENETIC DISORDERS:
Genetic testing for muscular dystrophy and related neuromuscular disorders requires much thought and discussion with both health care workers and your family before deciding to undertake testing. This booklet is designed to help you understand all of the information you may need related to genetic testing, for a number of the most common muscular dystrophies and neuromuscular disorders.

There are many different factors that need to be considered before deciding to undergo genetic testing, including; the implications of a positive, a negative and an uninformative test result on all members of your family and the effect of these results on your relationships. Health and life insurance is another factor that needs to be considered. You should feel comfortable with your insurance before thinking about any testing to ensure you will remain covered after testing. The testing itself also needs to be considered, as a series of many different tests may be required to determine a diagnosis. Often diagnosis requires a process-of-elimination style approach meaning it can be time consuming. However, testing can help give the people affected with a disorder and their families’ information that is not always available without testing, especially for people planning to start a family. Careful consideration needs to be taken into account when deciding upon this course of action.

It is important to remember that the genetic test itself is specific for the disorder being tested; therefore it is unlikely that the genetic testing will uncover any other underlying disorders.
What is Genetic Counselling, and why is it important?

Genetic counselling provides information on the ways that a disorder is passed on through families, the risks to other family members, the risk associated with having another pregnancy, and the likely outcome (or prognosis) of the disorder. The Genetic Counsellors can also explain the tests available to you and other members of your family. This includes:

- Diagnostic testing (determining if you have the disorder)
- IVF and pre implantation genetic diagnosis or PGD (testing the embryo for the disorder before it is used in the IVF procedure)
- Prenatal testing (testing the fetus while in the womb of the mother)
- Predictive testing (tests that can diagnose a disorder that can develop in adulthood)
- Carrier testing (a carrier is someone that carries the disorder and can pass it onto their children but is not affected themselves).

They also will discuss all of your concerns about the disorder, testing and the implications for both you and your family.

The genetic counsellor will go through all of the possible results of the test, what these results mean and provide you with relevant contacts for you to get more information and support. They are also there to support you and your family and to help you find the option that is suitable for you and your family. It is encouraged that people bring someone with them, whom they are comfortable with for support.

Do I have to be tested?

Undertaking genetic testing is absolutely voluntary, however it is encouraged as it provides you with a full picture of your circumstance. You are welcome to speak to a genetic counsellor to get all the available information about both the disorder and testing, before deciding if you wish to undergo testing. It is important to know that if you decide against testing now, that you are free to change your mind to have testing at any stage of your life and if this is the case, you need only to ring your genetic counsellor who will organize an appointment with you.

We advise however, that you do not make any immediate decisions about any testing until you have been informed of all the information that is available and discussed your concerns with a genetic counsellor. This way, any misconceptions and incorrect information you may have received from other sources can be eliminated and you are free to make an educated decision.
**Can I test my other children?**

If a child is not at an immediate risk of having the disorder (i.e. develop the disorder at a young age), children under the age of 18 will be unlikely to have genetic testing such as carrier testing and predictive testing. It can be difficult and frustrating for parents to hear this, especially as every parent wishes to hear their children are healthy, however; the reasons for not testing a child are in that child’s best interests. By not testing children, the child’s right to make their own decision to undergo testing is ensured. It is felt that when the child reaches the age of consent, they will be able to process the information available and then make an informed choice about testing. It also ensures the child’s right to privacy and confidentiality is maintained. It is recommended that when your child starts thinking about having children of their own, they come and speak with a Genetic Counsellor about their own reproductive options and risks.

Of course there are some exceptions to this rule; however, these would need to be discussed with a Genetic Counsellor. An exception may be if the child is showing the symptoms of that same disorder affecting their sibling and testing is thought to be warranted by your doctor. Testing of other family members, such as the parents of an affected child, may need to be undertaken before testing a child, to determine if the child is at risk of developing the disorder and warrant a diagnostic test.

In some special circumstances (i.e. a 17 year old, who is considering having children), a child may be permitted to undergo testing. However, in many cases, testing needs to be passed by an ethics committee and often that younger person may be required to have independent counselling. It is important to understand that it is not the parent’s decision to have their child tested if they believe their child falls into this specific circumstance; it is up to the child to want testing and they are the ones seeking this information.

**Do you use my information with other family members?**

No. Genetic Counsellors do not talk about your information with other members of your family, just as they won’t disclose any information related to other family members to you. This ensures the privacy of both you and your family members. The information you discuss with your genetic counsellor will be sent out to you in a letter after your appointment, which can be used to help you inform family members if you wish. If you are comfortable with a member of your family accessing your information, they may ask you to speak with their genetic counsellor to obtain your permission for this to occur. Only the information that may be relevant to their situation will be discussed.
What are the likely results of testing?

There are 3 types of results that you may receive after genetic testing. These include a positive result, a negative result or an un-informative result.

A result may either confirm a diagnosis or confirm a carrier status, both of which may have implications for other members of the family. The genetic counsellor will be able to explain what this means for you and the risks associated with the positive result to other family members and information can be provided that you can pass on to other family members. Genetic counsellors will also be able to speak to other members of the family who may want more information and/or testing. It is important to remember that hearing the news of a positive result can be upsetting and being prepared for this result is an important factor to consider before deciding if genetic testing is for you. If you don’t feel that you are able to hear the news of a positive result, it may be best to wait until you feel you can deal with the result.

A negative result may either confirm you are not affected by the disorder, are not a carrier, or both. This too can have implications for your family. The genetic counsellor will be able to explain what this means for you and your family. Sometimes a negative result can be just as overwhelming as a positive result, and preparing yourself for this result is equally important as preparing for a positive one. In many cases a negative result can also mean that more testing is required before a diagnosis is confirmed.

Unfortunately, technology is not able to detect 100% of the causes of all disorders and sometimes, although there are testing options available, and occasionally test may show an uninformative result. This can be very frustrating; therefore it is essential to understand that this is a possibility before undergoing genetic testing. An uninformative result means the cause of the disorder can not be found or there is not enough information to give a conclusive result, however this does not always mean that you don’t have that disorder. Often the causes of a genetic disorder are subtle and extremely difficult to find and today’s technology is unable to detect these subtleties. Some of the time, there are alternate tests that may be undertaken to confirm a result, however this is not always the case. It is important to consider the possibility of an uninformative result and discuss with your doctor or genetic counsellor what other options are available to you if this occurs. When the results are uninformative, it is important to get advice from your doctor and/or genetic counsellor as to where to go from there. It is also important to check back periodically with your doctor to determine if there is any new technology that may have become available.
Will any other information be discovered as a result of testing?

Although genetic testing is specific for the disorder of concern for the family, occasionally other sensitive information may be uncovered. An example of such information may relate to the true biological parents of a child. If you have any concerns about any sensitive information that may be found during the testing process, please discuss these concerns with your doctor and/or your genetic counsellor prior to testing.

How do I contact a genetic counsellor?

You need to get a referral from your doctor. They will contact your local Genetics Service and the clinic co-coordinator will call you and arrange a time for your appointment. The genetic counsellor may call you prior to your appointment and ask you for specific information to ensure the session run as smoothly as possible. It is also important to gather as much information about your family and their health as you can to give the genetic counsellor the best overall picture of your family.

In Victoria, Genetic Counsellors at the Victorian Clinical Genetics Services provide the genetic counselling service (http://www.vcgs.org.au).

The Human Genetics Society of Australia has a list of genetic counselling services in Australia and New Zealand https://www.hgsa.org.au/asgc/find-a-genetic-counsellor
DEFINITIONS OF COMMONLY USED GENETIC TERMINOLOGY:

It is important to understand a few key terms that are related to genetic testing. These terms are commonly used throughout information that you may read and understanding these key concepts will help you read through the information easier.

**Chromosomes:**
Every person is made up of millions of cells. In each of these cells, there are 46 chromosomes that contain all the information needed to make up who we are. If we think of ourselves as a story book, the chromosomes are the chapters that make up the book. Each chapter (or chromosome) is needed to make the story (us).

Of these 46 chromosomes we get 23 from our mother and 23 from our father. Each chromosome from your mother is paired with the same chromosome from your father and these pairs are numbered from 1 – 22 (we have 2 copies of each of these chromosomes). There are two chromosomes left that are not numbered and vary depending on your gender. These are the X and Y chromosomes. A female has 22 pairs of numbered chromosome pairs and two X chromosomes, while a male has 22 numbered chromosome pairs, one X and one Y chromosome. It is the presence of a Y chromosome that determines an individual to be male.

**Genes:**
On average around 500 genes are found on each chromosome. If we use the same book analogy as before, genes are the words that make up each chapter (chromosome) of the book.

Genes are made of a chemical called DNA, which can be thought of as the letters that spell out the words. Each gene carries instructions for the production of a specific protein. Some genes do not produce a protein but are involved in controlling other genes. In some diagrams genes may be represented as a line or a letter on a

**Gene change:**
A gene, like words, can either be incorrectly spelt, spelt a number of ways or changed for a completely different word. In a book, how the story is affected depends on which word is changed and how it is changed. This is the same with genes. Every person has some gene changes, examples of this include; different colours of the eyes and different colours of the hair. Often a gene change does not have an effect on the person and they live healthy lives. However, if this change affects a gene that is responsible for proper
functioning of something like the muscle, that person may develop a disorder, such as a Muscular Dystrophy.

A gene change can also be referred to as a mutation, a faulty gene, an allele or an altered gene. Usually these changes are permanent and can be passed on to the next generations, meaning these gene changes are inherited. Types of gene changes include:

- Deletions (where a section of the gene is missing)
- Insertion (where extra genetic material is accidentally inserted into the gene)
- Amplification (which means a small section of DNA is repeated over more times than it should be)
- Substitution (which are like spelling mistakes, where one letter is changed).

All of these changes can either; make sense allowing the gene to be partially functional (known as a missense mutation), not make any sense, causing the gene to stop functioning (known as a nonsense mutation), or alter the way the gene is read (known as frame shift mutations. This is like putting spaces in the middle of words and trying to read the sentence.)

**Carrier:**

In recessive disorders two copies of a gene change are needed for an individual to be affected with the disorder. A carrier is an individual that has one copy of the gene change. Generally, this person is not affected at all and leads a healthy life. If two carriers of the same disorder have a child, there is a 1 in 4 chance, that their child will be affected. There is also a 1 in 2 chance their child will also be a carrier. (See autosomal recessive inheritance in the following section),
TYPES OF INHERITANCE:

There are a number of ways that genes can be passed on through the generations. Because our chromosomes are paired we each have two copies of the one gene. There are a number of ways different disorders can be inherited, however, for the disorders mentioned in this booklet, we only need to understand four types of inheritance.

When a gene is passed on and is said to be a dominant change, it means only one changed copy needs to be present to affect a person. However, when a person is only affected when there are two changed copies of the gene present, it is said to be recessive.

Depending on the type of chromosomes that are involved, there are different types of inheritance. The chromosome pairs numbered 1 – 22 are known as the autosomes, so if the gene change is on one of these genes it is known as autosomal inheritance. Autosomal inheritance can be dominant or recessive and affects both females and males equally.

The X and Y chromosomes determine gender of a person - males have one X and one Y chromosome, whilst females have two X chromosomes. The sex chromosomes (X&Y) are inherited in what is known as X-Linked, Y-linked or collectively as sex-linked inheritance. This type of inheritance can also be dominant or recessive but can affect females and males differently.

X-Linked recessive inheritance:

In X-linked recessive inheritance, females who have an altered gene on their X chromosome are not affected because she has a “back up” X chromosome and the gene on the other X chromosome “masks” the effect of the altered gene. She is however a carrier and pass the condition onto her children.

Males who inherit the altered gene on their X chromosome will have the disorder because they only have one X chromosome with no “back up”. It is for this reason we generally only see males affected when a disorder is X-linked recessive.

A woman who is a carrier of an X-linked recessive disorder has a one in four chance of having a son who is affected by the condition. Or to put it another way, if she has a son, there is a fifty-fifty chance that he will have the condition. There is also a fifty-fifty chance that if she has a daughter, she will be a carrier of the condition.
Fig 5: X-Linked recessive inheritance:

Legend:
$X^r$ = recessive altered gene on X chromosome
$X$ = Normal X chromosome
$Y$ = Normal Y chromosome

If man affected by an X-linked recessive condition has children, all of his daughters will be carriers and his sons will be unaffected.
**X-linked dominant inheritance:**

In X-linked dominant inheritance, if a father who is affected by a dominant X-linked disorder passes on his altered X chromosome to his daughter, she will always be affected; however, his sons will inherit his Y chromosome and will therefore be unaffected.

*Fig 6: X-linked dominant inheritance when the father is affected by an X-linked dominant disorder.*

If a mother is affected with an X-linked dominant disorder, there is a 50% (or 1 in 2) chance that she will pass on the X chromosome to her child (boy or girl) and they will be affected with the disorder.

*Fig 7: X-linked dominant inheritance when the mother is affected by an X-linked dominant disorder.*
**Autosomal Dominant Inheritance:**

In autosomal dominant inheritance, there is a 50% (or 1 in 2) chance that the altered gene will be passed onto the next generation. You only need 1 parent to have the gene change for the condition to be passed on. The genes are passed on to the next generation randomly (like the flip of a coin). Autosomal dominant disorders affect both boys and girls equally. Only one altered copy of the gene is needed for that individual to have the disorder:

*Fig 3: Autosomal Dominant Inheritance:*

![Diagram showing autosomal dominant inheritance](image-url)
**Autosomal Recessive Inheritance:**

In autosomal recessive inheritance, both parents need to have an altered copy of the same gene for the condition to be seen in the next generation. The parents are known as “carriers” of the genetic condition and they are generally unaffected by the condition because their other “healthy” copy of the gene “hides” the altered gene.

Two altered copies of the altered gene are needed for that individual to have the disorder. If both parents are carriers of the same recessive gene change and have a child, there is a 25% (or 1 in 4) chance that their child will inherit two copies of the altered gene and be affected by the disorder. There is also a 50% (or 1 in 2) chance that their child will inherit one copy of the altered gene and be a carrier like their parents. Autosomal recessive disorders affect boys and girls equally.

**Fig 4: Autosomal Recessive Inheritance:**

![Diagram](Legend:  
Recessive altered gene (a)  
Normal gene (A))
MUSCULAR DYSTROPHIES AND GENETIC TESTING:

Duchenne and Becker muscular dystrophies:

Overview:
Duchenne muscular dystrophy (DMD) is one of the most common muscular dystrophies and is characterised by the progressive break-down of muscle, due to the lack of a protein known as dystrophin. This leads to progressive difficulty walking and loss of general mobility. Other problems that can be associated with the lack of the dystrophin protein include heart problems and eventually muscle weakness leads to difficulty breathing requiring the use of a ventilator. Mild learning difficulties occur in approximately 35% of boys with DMD.

Becker muscular dystrophy (BMD) is very similar to DMD; however, the symptoms are less severe and are generally not seen until later in life. Like DMD, BMD is caused by a change in the dystrophin gene. The age of onset of BMD can range between 12 years old to much later in life. BMD results in muscle degeneration and weakness with the progression of the disorder usually being slow.

Unlike many other recessive genetic disorders, carriers of the DMD gene change may experience some muscle weakness or have a cardiac disorder, known as cardiomyopathy. This means it is important to determine if female members of the family carry the gene change.

Inheritance:
DMD and BMD are inherited in an X-linked recessive pattern (see X-linked recessive inheritance in the “types of inheritance” section for more detail). Only two thirds of cases are inherited, with the other one third of cases resulting spontaneously without the parents carrying the genetic mutation. If there is no family history, genetic testing may be required to determine if a case is spontaneous or inherited. This helps to provide information that may affect other members of the family.

DMD results from an alteration in the dystrophin gene that leads to little or no dystrophin protein being produced. The most common types of mutation are large deletions and duplications which affect 80% of people with DMD.

In BMD the dystrophin protein is less abundant than normal or is a different size but is still able to work to some extent. About 80% of people with BMD
have deletion mutations, but unlike in DMD, the part of the gene that is deleted is not essential to the function of the protein and the rest of the gene is able to be read. This results in the production of a protein that is partially functional.

DMD and BMD are X-linked disorders so only boys are affected (with extremely rare exceptions).

**Testing:**
Your genetic counsellor or doctor may organise some or all of the following testing for the person who is thought to have DMD after you have had an appointment with them:

1) **CK testing:** tests for an enzyme known as Creatine Phosphokinase (also referred to as CK) which leaks into the blood when muscles are damaged. Individuals with DMD have 50 – 100 times the normal CK levels in their blood. This same blood test can be done to determine if the boy’s mother is a carrier, with 70% of carriers having a slightly raised CK level. However, this is not a conclusive test for carriers and further genetic testing may be needed. CK levels are generally only slightly raised in those with BMD.

Three CK blood tests are usually done to get an accurate average CK level measurement over a period of time. The reason for this is because normal day-to-day activities and exercise can also cause muscle cells to become damaged temporarily, resulting in an increase in CK levels.

2) **Electromyography testing (EMG):** Electromyography testing (also known as an EMG) may be performed to rule out some other conditions and involves two parts. The first part involves the use of a small needle that is gently inserted into the arm or thigh that shows electrical patterns of those muscles, which are recorded by a specialist. The second part involves a small electrical pulse that stimulates the nerves of either the arm or the leg to determine how fast the messages are being sent from the brain to the nerves.

3) **Genetic Testing:** If the CK test shows an increase in the CK levels that are expected in a person with DMD, BMD or a carrier of DMD, a genetic test can be undertaken to specifically find the gene alteration in the dystrophin gene. Your genetic counsellor or doctor will organize the testing after an appointment with them. This is done most commonly by taking a simple blood sample that is tested by the laboratory. Testing can confirm the type of alteration that has occurred in the gene, therefore confirming a diagnosis of DMD or BMD. Carriers in the family can then also be more easily identified as they are able to search for the same alteration.

Occasionally, after DNA testing, a person may get an uninformative result. This means that they were unable to find an alteration in the gene. Although the technology is improving all the time, at the moment, some very small
alterations can be missed. Very rarely, the mother of an affected boy can have a DNA test that comes back to show that she is negative for carrying the gene alteration, however is a carrier. This is because the mother has what is called *germline mosaicism*. This means, the mother has an unaltered copy of the dystrophin gene throughout her body except in her germline, or her eggs. Although it is very rare, it is something that needs to be considered especially if the mother is planning to have another child. This can be discussed at a genetic counselling appointment.

4) Muscle Biopsy: A muscle biopsy can be performed if the DNA test does not show any gene changes in the person suspected with BMD or DMD. This involves taking a small piece of muscle tissue, usually from the leg, by using a needle. The sample is then taken to the laboratory where it is stained to look for the presence of dystrophin protein under the microscope. If there is no dystrophin present, then the boy is diagnosed with DMD. If there is a reduced amount of dystrophin present, then it is likely that the boy has Becker muscular dystrophy.

After each test, you will be contacted by either your genetic counsellor and/or your doctor who will go through the results and the implications for both you and your family. It is important to remember that genetic testing will not be carried out on young boys unless they show signs of having MD. Carrier testing on females will usually not be performed on girls under the age of 18.
Facioscapulohumeral Muscular Dystrophy (or FSH or FSHD)

Overview:
FSHD is characterized by symptoms such as weakness of specific muscle groups in the lower leg, hip, upper arm, shoulder and face. It is very difficult to predict the severity of symptoms for a person with FSHD as it varies greatly, even in families. The age of onset also varies greatly with age of diagnosis ranging from young infants with extreme muscle weakness to adults with very mild symptoms. Generally however, the progression of the disorder is slow, with patients experiencing a gradual loss of strength over a period of years. Only a small number of people require the use of a wheelchair, however the degree to which their muscle weakness will affect the individual’s ability to function varies and can not be predicted. At this current time, there is no treatment or cure for FSHD.

Inheritance:
FSHD is a genetic condition, caused by a change in the DNA (which is often referred to as a ‘mutation’). The mutation may either be inherited from a parent or arise spontaneously. Between 70 and 90 percent of people with FSHD inherit the condition from one of their parents in what is called an 'autosomal dominant' manner. This means that only one copy of the genetic mutation (from either parent) is required for the disease to develop. There is a 50 percent chance of a child of an affected parent to inherit the condition.

It is possible for a parent to have the gene change, yet be unaware of it. One third of people with the mutation experience no symptoms. This is more common in women; 95 percent of males with the DNA change experiencing symptoms by the age of 30.

In 10 to 30 percent of cases, the condition isn't inherited from a parent with FSHD. Instead the genetic mutation may arise spontaneously. In this case a random DNA error occurs in the sperm or the egg from which the child grows. Another possibility is that the condition is inherited from a seemingly unaffected parent who is a 'mosaic'. This means that a proportion of the mother or father’s cells carry the genetic mutation but the rest of the cells in his or her body do not. When a parent is a mosaic they may appear unaffected because the proportion of cells in their body with the mutation is too low to cause symptoms. However, their children are at risk because they could be conceived from a sperm or egg with the mutation and consequently the child will have the mutation in every cell of his or her body.

Most patients with FSHD are missing a small part of chromosome number four. This contains a region of DNA called 'D4Z4'. In a healthy person, D4Z4 contains between 11 and 150 copies of a gene called DUX4. Most patients with FSHD, however, only have between one and ten copies.
Less than 5% of FSHD patients have a different genetic mutation located on chromosome number 18. These patients are given a diagnosis of FSHD2, but the symptoms are very similar to the more common FSHD1.

**Testing:**
Before any testing occurs, a physical examination by a doctor will be performed. Facial and shoulder muscle weakness are often signs of FSHD. An eye exam may also be performed to look for changes in the back of the eye’s blood vessels.

Testing may involve a number of different steps and is often a process of elimination. To confirm a diagnosis of FSHD, a genetic test is required. Your genetic counsellor or doctor will organise the testing for you after you have had an appointment with them. The genetic test available for FSHD involves either a simple blood sample (most common). The testing generally takes between 2 – 6 weeks to complete. A positive result can confirm a diagnosis of FSHD; however it is important to note that a negative result can not rule out a diagnosis of FSHD.

The genetic counsellor will either call or make an appointment with you once they have received the results and will discuss the implications of these results for you and your family.

However, because FSHD can be similar to other muscular dystrophies, you may be asked to undergo other testing to eliminate other disorders. Other tests you may undergo include:

1) **CK testing:** tests for an enzyme known as Creatine Phosphokinase (also referred to as CK) which leaks into the blood when muscles are damaged. CK levels are normal to slightly elevated in individuals with FSHD and usually does not exceed three to five times the upper limit of the normal range.

Three CK blood tests are usually done to get an accurate average CK level measurement over a period of time. The reason for this is because normal day-to-day activities and exercise can also cause muscle cells to become damaged temporarily, resulting in an increase in CK levels.

2) **Nerve Conduction Velocity test (NCV):** This test is used to measure the strength and speed of electrical signals moving down the peripheral nerves. It is done by stimulating a nerve using a electrode with a mild electrical current, whilst a second electrode records the electrical signal “down stream” (or further away from the spine). Surface electrodes are used on the skins surface meaning it is not invasive; however, mild discomfort may be experienced as a result of the electric currents. The speed of the signal is used to determine if there is a problem with the nerve.
3) Electromyography testing (EMG): After a physical examination has been completed and other disorders have been ruled out, Electromyography testing (also known as an EMG) may be performed and involves 2 parts. The first part involves a small needle that is gently inserted into the arm or thigh that shows electrical patterns of those muscles, which are recorded by a specialist. The second part involves a small electrical pulse that stimulates the nerves of either the arm or the leg to determine how fast the messages are being sent from the brain to the nerves.

4) Muscle Biopsy: A muscle biopsy is also sometimes used to confirm a diagnosis of FSHD. This involves the removal of a small section of muscle tissue using a needle and examining it under a microscope. Muscle biopsy is now performed only in those individuals in whom FSHD is suspected but not confirmed by genetic testing.

4) Genetic Testing: Your genetic counsellor or doctor may organise genetic testing after an appointment with them. This is done most commonly by taking a simple blood test that is tested by the laboratory. Occasionally, after DNA testing, a person who is suspected to have FSH, may get an uninformative result. This means that they were unable to find an alteration in the gene. Although the technology is improving all the time, at the moment, some very small alterations can be missed.
Myotonic Dystrophy (DM) (also known as Steinert’s Disease)

Overview:
Myotonic Dystrophy is a neurological disorder that is characterized by muscle weakness and myotonia (delayed muscle relaxation following contraction). Other areas of the body that can also be affected include the eyes, the heart and the brain. The severity of the disorder can vary greatly, even in families. Occasionally, the symptoms are so mild that an adult is not diagnosed until another relative with a severe form of the disorder is diagnosed. Mild forms of the disorder can be as subtle as difficulty releasing grip after a hand shake or grasping a door handle and a feeling of muscle stiffness.

There are two types of DM caused by different genetic mutations. Type 1 (DM1) is the most common and symptoms may appear at any time from birth to old age. Type 2 myotonic dystrophy (DM2), also sometimes called ‘PROMM’ (proximal myotonic myopathy), is only found in adults, with an age of onset generally between 30 and 60 years. People with DM2 do not usually have the same kind of facial muscle weakness or swallowing problems that are often seen in DM1. In common with DM1 patients, DM2 patients may experience cataracts, heart problems and diabetes.

Inheritance:
DM is inherited in an autosomal dominant pattern (see autosomal dominant inheritance in the “types of inheritance” section for more detail). DM results from gene alteration known as an amplification, which means a small sequence of DNA is repeated more than it should be (See diagram below). This only needs to occur on one of the two copies of the gene.

Figure 8: Gene amplification

Parent:

Child:
In DM1 the segment of DNA that is amplified is a small repeat sequence of DNA that is called a CTG repeat. Most people have between 5 and 37 CTG repeats, whilst people who have more than 50 CTG repeats have DM. People who fall between these two groups generally have no symptoms but fall into a group that is known as a promutation group. This means that there is a chance that the number of repeats may change in the next generation, which may result in their child having DM1. The inheritance of DM1 is further complicated by what is known as “anticipation”. Anticipation is when the disorder gets worse over generations. Often there are only very subtle symptoms in the parent and the cause is not recognized until they have a child that is diagnosed with the disorder and they become more aware of their own symptoms. We are just beginning to understand why anticipation occurs and in the case of DM1, it has been found that the size of the repeat can increase over the generations that result in more severe symptoms being seen in the next generation. The severity of the disorder is directly linked to the number of CTG repeats. The following table shows the number of CTG repeats and how that affects the severity of symptoms:

**Table 1: Repeat size and severity of symptoms in DM:**

<table>
<thead>
<tr>
<th>Description of severity</th>
<th>CTG repeat size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>5 to 37</td>
</tr>
<tr>
<td>No symptoms (children at risk)</td>
<td>38 to 49</td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>50 to about 150</td>
</tr>
<tr>
<td>Classical</td>
<td>About 100 to 1000-1500</td>
</tr>
<tr>
<td>Congenital (diagnosed at birth, most severe)</td>
<td>About 1000 and greater.</td>
</tr>
</tbody>
</table>

Genetic testing is available to determine if a person is affected with DM and the size of the CTG repeat, which will assist in giving some idea of a prognosis.

In DM2 a four letter DNA code is repeated many hundreds of times instead of the usual number which is 26 or fewer. Unlike DM1, it appears that ‘anticipation’ (repeat count increasing with each successive generation) is not a feature of DM2

**Testing:**
Your genetic counsellor or doctor may organise some or all of the following testing for the person who is thought to have DM after you have had an appointment with them.
1) CK testing: tests for an enzyme known as Creatine Phosphokinase (also referred to as CK) which leaks into the blood when muscles are damaged. Serum CK concentration may be mildly elevated in individuals with DM1 with muscle weakness.

Three CK blood tests are usually done to get an accurate average CK level measurement over a period of time. The reason for this is because normal day-to-day activities and exercise can also cause muscle cells to become damaged temporarily, resulting in an increase in CK levels.

2) Nerve Conduction Velocity test (NCV): This test is used to measure the strength and speed of electrical signals moving down the peripheral nerves. It is done by stimulating a nerve using a electrode with a mild electrical current, whilst a second electrode records the electrical signal “down stream” (or further away from the spine). Surface electrodes are used on the skins surface meaning it is not invasive; however, mild discomfort may be experienced as a result of the electric currents. The speed of the signal is used to determine if there is a problem with the nerve.

3) Electromyography testing (EMG): After a physical examination has been completed and other disorders have been ruled out, electromyography testing (also known as an EMG) may be performed and involves 2 parts. The first part involves a small needle that is gently inserted into the arm or thigh that shows electrical patterns of those muscles, which are recorded by a specialist. The second part involves a small electrical pulse that stimulates the nerves of either the arm or the leg to determine how fast the messages are being sent from the brain to the nerves.

4) Muscle Biopsy: A muscle biopsy can also be used to confirm a diagnosis of DM. This involves the removal of a small section of muscle tissue using a needle and examining the sample under a microscope. Muscle biopsy is now performed only in those individuals in whom DM is suspected but not confirmed by genetic testing.

4) Genetic Testing: Genetic testing is available to determine if a person has inherited the gene amplification. This is done most commonly by taking a simple blood test that is tested by the laboratory. Testing usually takes between 2 and 4 weeks and either your doctor or genetic counsellor will call you or arrange an appointment with you to discuss the results.
Myotonic dystrophy type 1, the most common type of myotonic dystrophy, is caused by the inheritance of extra DNA code at the end of a gene called ‘DMPK’. DM2 is caused by the inheritance of extra pieces of repeated DNA in the ‘CNBP’ gene (also known as ‘ZNF9’). Very few cases of myotonic dystrophy occur ‘out of the blue’. Almost always, one parent proves to be affected, often very mildly.
PERIPHERAL NERVE DISORDERS:

Charcot–Marie–Tooth Disease (CMT)

Overview:
Charcot-Marie-Tooth disease is the most commonly inherited disease that affects the peripheral nervous system. The peripheral nervous system controls our ability to move and feel parts of our bodies, such as the hands and feet. Initial symptoms of CMT include weakness of the hands and feet, muscle atrophy (decrease in size), sensory loss and foot irregularities (see picture to the left).

Although there are many different forms of CMT, all of which have different severity and symptoms, generally all individuals affected with CMT have muscle weakness and wasting as a result of the loss of stimulation from the affected nerves. Many people also experience some loss of sensory nerve function, which means the sensation of touch is reduced.

There are many different types of CMT, all of which initially present similar symptoms. They are;

Type 1: Our nerves are covered by what is known as a Myelin Sheath, it helps to speed up the delivery of messages from our brain to parts of the body. If the myelin sheath is damaged or absent, the messages sent from the brain travel much slower to the part of the body we wish to move. This is known as demyelination and results in CMT type 1. This type is further broken down into subtype including; 1A, 1B, 1C, 1D, 1E, 1F, 1X (also known as X-linked CMT) and Hereditary Neuropathy with Liability to Pressure Palsies (HNPP).

Type 2: If the nerve itself is damaged or if there are a reduced number of nerves to the muscle, the brain has trouble trying to send a message to the muscles. This reduction of nerves is said to be an axonal form of CMT. This means the muscle is not able to get as strong a signal as it should. This type is further broken down also into subtypes, which include; 2A, 2B, 2C, 2D and 2E.

Type 3: The most severe form of CMT is type 3 with most individuals being diagnosed very early in life. These individuals are found to have severe demyelination or severe reduction in the number of nerves. There are two subtypes of CMT type 3, they being; Dejerine-Sottas Syndrome (or DSS) and Congenital hypomyelination (CH).

Type 4: CMT type 4 is considered to be very rare. Depending on their subtype, they may be either demyelinating or axonal. Once again, this type is further broken down into sub types, they being; 4A, 4B, 4C 4D and 4F.
**Inheritance:**

*Autosomal dominant*

CMT is most commonly inherited in a pattern known as “autosomal dominant”. We all generally have two copies of each gene - one inherited from each parent. The inheritance of one altered copy of the gene from either parent is sufficient for a person to be affected by an autosomal dominant disorder. This altered gene over-rides the healthy copy inherited from the other parent. Each affected person usually has one affected parent. The chance of a child inheriting the condition from a parent with the condition is 50 percent, or 1 in 2.

*X-linked*

The second most common type of CMT – CMT 1X is inherited in an “X-linked recessive” pattern. This is because the causative gene (GJB1) is located on the X-chromosome. Females have two X chromosomes — one inherited from each parent — so in most cases females who inherit a faulty GJB1 gene will show no symptoms or only mild symptoms of the disorder because the normal gene on her other X chromosome will compensate. Females with one faulty GJB1 gene are known as carriers and they can pass the condition on to their sons.

Males have one X chromosome which they inherit from their mother and one Y chromosome which they inherit from their father. If a boy’s mother is a carrier of a faulty GJB1 gene there is a 50:50 chance that he will inherit this gene and will have CMT because, unlike females, he doesn't have another X chromosome to make up for the faulty one. The daughters of carriers each have a 50:50 chance of being carriers.

If a male with CMT 1X has children with a non-carrier female, their sons would not inherit the condition and their daughters would all be carriers.

*Autosomal recessive*

More rarely, CMT is inherited in an “autosomal recessive” pattern which means that for an individual to develop the condition they need to inherit two altered genes - one from each parent. The parents of an individual with this type of CMT each carry one copy of the altered gene, and are known as ‘carriers’, but they typically do not have symptoms of the condition. Their other ‘good’ copy of the gene is enough to prevent the condition developing. If both parents are carriers the likelihood of a child inheriting the condition is 25 percent, or 1 in 4. Autosomal recessive inheritance is more common in cultures where marriage within families occurs.

Occasionally, a person can also develop CMT sporadically without any family history. If this is confirmed to be the case (by genetic testing), then it is very likely that no one else in the family is affected. This sporadic gene change can however, be passed onto the affected individuals children.
Testing:
There is a process by which a diagnosis of CMT is determined. Genetic testing is just one step in this process.

1) Physical examination: If the signs of CMT are noticed by a doctor, they will be referred to a neurologist. Examples of these signs include the legs don't have stretch reflexes (especially ankle jerks), and the person may have trouble lifting their feet (dorsiflexion) and bringing the thumb upwards (thumb abduction). A physical examination by a neurologist will be needed prior to testing to look for signs of distal weakness and sensory loss.

2) Nerve Conduction Velocity test (NCV): This test is used to measure the strength and speed of electrical signals moving down the peripheral nerves. It is done by stimulating a nerve using an electrode with a mild electrical current, whilst a second electrode records the electrical signal “down stream” (or further away from the spine). Surface electrodes are used on the skin surface meaning it is not invasive; however, mild discomfort may be experienced as a result of the electric currents. The speed of the signal is used to determine if there is a problem with the nerve. The results of the NCV can be used to separate type 1 and type 2 CMT. Axonal CMT (i.e. type 1) is confirmed if the speed of nerve transmission is slightly slowed, whilst CMT resulting from demyelination (type 2) shows dramatically slowed signals.

3) Electromyography testing: After a physical examination has been completed and other disorders have been ruled out, electromyography testing (also known as an EMG) may be performed and involves 2 parts. The first part involves a small needle that is gently inserted into the arm or thigh that shows electrical patterns of those muscles, which are recorded by a specialist. The second part involves a small electrical pulse that stimulates the nerves of either the arm or the leg to determine how fast the messages are being sent from the brain to the nerves..

4) Genetic tests: Genetic testing is also an option to confirm a diagnosis of CMT. This may be important in distinguishing the disorder's sub type (i.e. CMT type 1A, etc). Because there are different genes responsible for each subtype, it is important to narrow the possible type of CMT as much as possible using the previously mentioned tests. If the gene change can been found and confirmed, this information can then be used to help in testing other family members to determine if they are carriers of the disease.

It is important to remember that siblings under the age of 18 will not be tested unless they show symptoms of the disorder. Partners of an individual that carries the gene change will also be able to get genetic testing if the couple is planning to have children. Genetic testing usually involves as simple blood test to determine if a person is affected or a carrier of CMT. A positive result can confirm a diagnosis of CMT; however it is important to note that a negative result can not rule out a diagnosis of CMT.
5) **Nerve and/or Biopsy:** Small samples of tissue are removed and examined in a laboratory. Either nerve or muscle tissue (or both) may be examined. This is not commonly done, and is unnecessary if a genetic abnormality is found, however, it can confirm a diagnosis of CMT if other tests fail to do so.
### Overview:
Spinal muscular atrophy (SMA) is characterised by the degeneration of motor neurons. In the body, motor neurons link the muscle fibres to the brain or spinal cord. A signal telling the muscle to contract is sent from the brain, along the spinal cord, then along the motor neurons and finally to the muscles, which contract. The degeneration of these motor neurons prevents the signals from the brain and nervous system reaching the muscle. Over time, the muscle becomes smaller (atrophy) and weaker.

There are 4 different categories of SMA that are determined by the age of onset and the severity of the disorder. These categories are as follows:

### Table 2: Categories of SMA and there age of onset.

<table>
<thead>
<tr>
<th>Category of SMA</th>
<th>Age of onset</th>
<th>Also known as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 SMA</td>
<td>Infant (Usually see symptoms before 8 months of age)</td>
<td>- Infantile SMA - Werdnig-Hoffman disease</td>
</tr>
<tr>
<td>Type 2 SMA</td>
<td>Infant/Toddler (Symptoms first seen between 6 to 18 months of age)</td>
<td>- Intermediate SMA</td>
</tr>
<tr>
<td>Type 3 SMA</td>
<td>Toddler/child (Symptoms first seen from 18 months up to 10 years or older)</td>
<td>- Juvenile SMA - Kugelberg-Welander disease</td>
</tr>
<tr>
<td>Type 4 SMA</td>
<td>Adult (Symptoms first seen in mid-30’s)</td>
<td>- Adult SMA - Adult onset SMA</td>
</tr>
</tbody>
</table>

### Inheritance:
SMA is inherited in an autosomal recessive pattern (see autosomal recessive inheritance in the “types of inheritance” section for more detail). The gene that has been linked to SMA is known as SMA1 and is located on chromosome 5. A gene change in the SMA1 gene on both chromosomes will result in that individual developing SMA. 95-98% of people who are affected with disorder have a deletion of the SMA1 gene on both chromosomes, whilst the other 2-5% have a deletion of SMA1 on one chromosome and a small change on the SMA1 gene on the other chromosome.

Everybody has another similar gene called SMA2 gene which can reduce the severity of symptoms, if that individual has more than 1 copy on either chromosome.
Type 4 SMA can be more genetically complex as the SMA genes are not always involved. It is believed that there are other genes that may also be involved in the development of Type 4 SMA that are not known at this stage. This means genetic testing for Type 4 SMA are often inconclusive and other forms of diagnosis may be required.

Because you need two copies of the altered SMA1 gene to have SMA, one copy of a faulty gene can be passed down through the generations without ever seeing a person affected with the disorder. Genetic testing can be done to determine if other family members are carriers of the disorder in adulthood.

Testing:
There are a number of ways by which a diagnosis of SMA is determined. Genetic testing is just one step in this process.

Initially, because the symptoms of SMA are similar to many other disorders that affect the muscles, other testing may be asked for such as a creatine phosphokinase (or CK) test to rule out other disorders such as Duchenne muscular dystrophy.

1) Electromyography testing: Once these other disorders have been ruled out, electromyography testing (also known as an EMG) may be performed and involves 2 parts. The first part involves a small needle that is gently inserted into the arm or thigh that shows electrical patterns of those muscles, which are recorded by a specialist. The results of this tests that are associated with a diagnosis of SMA suggest that the muscle has lost its nerve supply as a result of the degeneration of the motor neurons. The second part involves a small electrical pulse that stimulates the nerves of either the arm or the leg to determine how fast the messages are being sent from the brain to the nerves. This procedure usually uses the same needle and equipment used in the first test. The test can be uncomfortable, however, your doctor may be able to suggest ways to minimize the discomfort and an experienced electromyographer can minimize the pain and length of the procedure.

2) Nerve Conduction Velocity test (NCV): This test is used to measure the strength and speed of electrical signals moving down the peripheral nerves. It is done by stimulating a nerve using a electrode with a mild electrical current, whilst a second electrode records the electrical signal “down stream” (or further away from the spine). Surface electrodes are used on the skins surface meaning it is not invasive; however, mild discomfort may be experienced as a result of the electric currents. The speed of the signal is used to determine if there is a problem with the nerve. This is usually performed simultaneously with an EMG.

3) Genetic testing: Genetic testing is also an option to confirm a diagnosis of SMA and to confirm the gene change that has caused the disorder to develop. Once the gene change has been found and confirmed, this information can
then be used to help in testing other family members to determine if they are carriers of the disease. It is important to remember that siblings under the age of 18 will not be tested unless they show symptoms of the disorder. The partner of an individual that carries the gene change will also be able to get genetic testing if the couple is planning to have children. Genetic testing usually involves a simple blood test. A positive result can confirm a diagnosis of SMA; however it is important to note that a negative result can not rule out a diagnosis of SMA.

4) Muscle Biopsy: A muscle biopsy is also used to confirm a diagnosis of SMA. This involves the removal of a small section of muscle by either a surgeon removing a small piece of muscle tissue or by ‘punch’ muscle biopsy. The ‘punch’ muscle biopsy is becoming more popular for testing both infants and children as it is much less invasive and does not require heavy sedation or anaesthesia. A muscle biopsy is generally used as a final test to determine a diagnosis when genetic testing or EMG results are not conclusive.
ACKNOWLEDGEMENTS:

MDA would like to acknowledge Jessica Nagy, for her time and effort to put together this great resource.

GLOSSARY:

**Allele:** one of two or more different variations of a specific gene. We can have 2 of the same alleles (known as homozygous) or 2 different alleles (known as heterozygous). Different alleles are responsible for the differences in each individual, such as hair colour, eye colour etc. Occasionally, an allele has the potential to cause a disorder that is undesirable. Depending on the allele, the presence of either one copy (in a dominant disorder) or two copies (in a recessive disorder) of the allele may cause an undesirable disorder. A change in the gene creates a new allele that can be passed on through the generations.

**Amniocentesis:** A testing procedure that may be performed during pregnancy to determine if the fetus has a genetic change that may be suspected. This is usually done at least 14 weeks after conception. The procedure involves a using a needle to take a small amount of amniotic fluid that surrounds the developing baby. This sample is then sent to the lab for analysis.

**Anticipation:** the severity of the disorder gets worse over generations.

**Atrophy:** A decrease in size of a body organ, tissue or part thereof as a result of disease, injury or lack of use.

**Autosomal chromosomes:** Chromosomes that are numbered 1 – 22 and do not have any influence on gender. They are usually paired; one chromosome from our mother and the other from our father.

**Autosomal dominant inheritance:** A pattern of inheritance characteristic of some genetic diseases. "Autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes. "Dominant" means that a single copy of the altered gene inherited from either parent is enough to cause the disease.

**Autosomal recessive inheritance:** A pattern of inheritance characteristic of some genetic diseases. "Autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes. "Recessive" means that two copies of the altered gene must be inherited (one from each parent) for the disease to develop.

**Axon:** An extension of a nerve cell that conducts impulses away from one nerve cell to another nerve cell or a muscle cell. Generally there is only one axon to a cell, and it may extend up to 0.9 m in length.

**Cardiomyopathy:** A type of heart disease in which the heart muscle is abnormally enlarged, thickened and/or stiffened. As a result, the heart muscle’s ability to pump blood is impaired.

**Chromosome:** Thread-like structure containing most of the DNA of a living organism. Humans have 46 chromosomes (23 pairs) in most cells of their bodies. The only exceptions are the unfertilized egg and sperm cells which contain only 23 unpaired chromosomes each. Fertilization of a 23-chromosome egg by a 23-chromosome sperm produces a new 46-chromosome cell which grows into a new individual. In this way one half of each chromosome pair is inherited from each parent.

**Cognitive:** The mental processes of knowing, perceiving, or being aware.
**De novo:** A spontaneous or new gene change.

**Distal:** Located furthest away from the middle of the body (i.e. the spine).

**Embryo:** The earliest stages of development after conception (i.e. the fertilization of a woman’s egg with the male’s sperm). After 8 weeks of development the embryo is becomes known as a fetus.

**Fetus (Foetus):** In humans, it refers to the unborn child, from the end of the 8th week after conception until the birth of the baby.

**Gait:** A particular way or manner of moving on foot, such as walking or running. Medically, difficulties with walking are referred to as “gait difficulties” and are a common first sign of a muscular disorder.

**Gene:** A unit of DNA that is responsible for one or multiple functions of the body. It has a specific location on a chromosome and can be passed on to the next generation.

**Genotype:** The genetic make-up of an individual.

**Heterozygous:** An individual that has two different versions (DNA sequence) of a specific gene.

**Homozygous:** An individual that has the same version (DNA sequence) of a specific gene.

**Hypotonic:** Having less muscle tone than usually seen

**Inherited:** Traits or characteristics that are passed on from the parents to their offspring (children) via their genes

**In vitro fertilization (or IVF):** The process involving the removal of a women’s eggs from her ovaries, fertilizing them with sperm in a laboratory, and then transferring the fertilized egg (known as an embryo) into the womb of the woman.

**Muscle biopsy:** A small muscle sample that is removed and tested in the laboratory for muscular disorders such as muscular dystrophies.

**Muscular dystrophy:** A group of inheritable disorders that cause progressive muscle weakness and wastage due a change in the gene.

**Myelin sheath:** The insulating envelope of myelin that surrounds the core of a nerve fibre or axon and that facilitates the transmission of nerve impulses. Myelin is a white fatty material, composed chiefly of lipids and proteins.

**Myopathy:** A neuromuscular disorder in which the muscle fibres do not function for one reason or another, resulting in muscle weakness. It refers to the muscles being the cause of the weakness and not the nerves.

**Myotonia:** muscles contract, remain tense and are unable to quickly relax after contracting

**Neuropathy:** Disease of the peripheral nerve or nerves.

**Pathogenicity:** The ability to cause disease. Gene changes that result in the development of a disorder are said to be pathogenic.

**Phenotype:** The physical characteristics or traits that are seen on an individual (i.e. hair colour, eye colour etc.). These are either as a result of that individual’s genetic make up or the combination of an individual’s genetic make up and the environment.
**Pre-implantation Genetic Diagnosis (PGD):** The testing of very early embryos for a specific genetic condition before they are implanted into the womb. Couples undergo standard in vitro fertilisation (IVF) during which eggs are fertilised by sperm outside the womb. Only embryos that are not affected by the disorder that runs in the family are transferred into the womb of the mother-to-be.

**Pedigree:** Also known as a family tree diagram. A pedigree chart shows the occurrence of a particular gene or disease from one generation to the next. The pedigree is used by genetic counsellors and other medical professionals to assess families and try to spot patterns which may be helpful in diagnosing a condition that runs in the family.

**Penetrance:** The degree to which a genetic condition can be seen in an affected individual. This means that some people may be mildly affected whilst others with the same genetic change are affected severely. This variation may be due to an environmental factor, other genes that may interact with that gene or another unknown factor.

**Protein:** Large molecules composed of one or more chains of building blocks called ‘amino acids’ in a specific order. The order is determined by the gene that contains the instructions for the construction of the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs. They are the building blocks of our bodies. We have millions of different proteins in our body and each has unique functions. Two examples are the enzymes in our stomach that digests our food and the collagen which holds our skin together.

**Schwann cell:** type of cell found throughout the entire peripheral nervous system (PNS). The PNS includes all nerves going out to muscles as well as sensory nerves coming from the muscles back to the spinal cord. Schwann cells are a type of “support” cell in the PNS and are responsible for insulating (myelinating) nerve fibres (axons), which is necessary for sending appropriate electrical signals throughout the nervous system.

**Scoliosis:** side-to-side curvature of the spine.

**X chromosome:** A gender determining chromosome that can be passed on to the next generation. Females have two X chromosomes and males have one X and one Y chromosome.

**Y chromosome:** A gender determining chromosome that can be passed on to the next generation. Males have one Y chromosome and one X chromosome whereas females have two X chromosomes and no Y chromosome.