



MUSCULAR DYSTROPHY GENETICS AND TESTING

*Information to help you make an informed choice
about testing.*

MUSCULAR DYSTROPHY

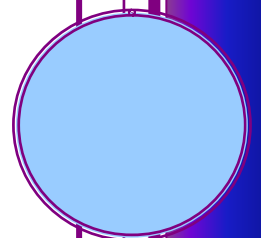
111 BOUNDARY ROAD

NORTH MELBOURNE 3051

AUSTRALIA

+61 3 9320 9555

MDA.ORG.AU



Genetic Counselling



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 control or cure 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 persons in need. 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

TABLE OF CONTENTS:

GENETIC COUNSELLING	3
<ul style="list-style-type: none">- Testing for genetic disorders.- What is genetic counselling and why is it important?- Do I have to have testing?- Can I have my children tested?- What are the likely results of testing?- How do I contact a Genetic Counsellor?- Do you use my information for other family members?	
DEFINITIONS OF COMMONLY USED GENETIC TERMINOLOGY	8
<ul style="list-style-type: none">- Chromosomes- Genes- Gene Change- Bases- Carrier	
TYPES OF INHERITANCE	11
<ul style="list-style-type: none">- Autosomal Dominant inheritance- Autosomal Recessive inheritance- X-linked Recessive inheritance- X-linked Dominant inheritance	
MUSCULAR DYSTROPHIES AND GENETIC TESTING	17
<ul style="list-style-type: none">- Duchenne Muscular Dystrophy- Becker Muscular Dystrophy- Facioscapulohumeral Muscular Dystrophy (FSHD)- Myotonic Dystrophy	
PERIPHERAL NERVE DISORDERS AND GENETIC TESTING	28
<ul style="list-style-type: none">- Charcot-Marie-Tooth Disease	
SPINAL MUSCULAR ATROPHY AND GENETIC TESTING	32
<ul style="list-style-type: none">- Spinal Muscular Atrophy	
ACKNOWLEDGEMENTS	36
GLOSSARY	36

GENETIC COUNSELLING:

TESTING FOR GENETIC DISORDERS:

Genetic testing for a muscular dystrophy 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.



Family attending a genetic counselling

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?

Understanding 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 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 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 not be able to have 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, we ensure the child's right to make their own decision to undergo testing, which is done by allowing them to understand all the information available about the disorder in the family. It is felt that when the child reaches the age of consent, they will be in position to process the information available and then make an informed choice about testing. It also ensures the child's right to privacy.



The only exception to this is 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 in a relationship and is considering having children), may be permitted to undergo testing. However, the testing needs to be approved 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 the child's decision.

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 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. Most of the time, this result will be given to you as a risk (such as 99% chance), rather than as a definite result, as on rare occasions, there are some factors that are not able to be tested for and can not be predicted.

A positive 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 give you information that you can pass on. They 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, the 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 do not have 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 testing is specific for the disorder being tested for, occasionally other sensitive information that may be detected, specifically in genetic testing. 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 the Genetic Health Services Victoria and the genetics 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 Genetic Health Services Victoria provide the genetic counselling service. Website at www.genetichealthvic.net.au.



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 and help you decide if testing is appropriate for you.

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 up the story (us).

Of these 46 chromosomes we get 23 from our mother and 23 chromosomes from our father. Each chromosome from your mother is paired with the same chromosome of the father and these pairs are numbered from 1 – 22, we therefore have 2 copies of the one chromosome. These chromosome pairs are referred to as *Autosomal chromosomes*. There are 2 chromosomes left that are not numbered and determine your gender. These are the X and Y chromosomes. A female has 22 pairs of autosomal chromosomes and two X chromosomes, while a male has 22 autosomal chromosome pairs, one X and one Y chromosome. For example: XX = Female, XY = Male.

In many diagrams, chromosomes will be represented to appear similar to the following:

Fig 1: Diagrammatical representation of a chromosome.

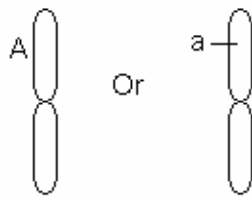


Genes:

Genes are found on the chromosome and are the parts of the chromosome that contain the specific information that is used in the making of an individual. If we use the same book analogy as before, genes are like the words that make up the book that are unique to that chapter (chromosome).

Genes are made up of DNA. The DNA is put together in a way so that the DNA 'spells out' the right sequence so that the genes make sense. It is the genes that together are responsible for who we are. In many diagrams they are represented as a letter next to a part of the chromosome or as a dash on the chromosome similar to the following diagram:

Fig 2: Diagrammatical representation of a gene on a chromosome.



Gene change:

A gene, like words, can either be incorrectly spelt, spelt a number of ways or changed to a completely different word. These are known as a *gene change* (or mutation) and are common. In a book, it depends on which word is changed, that determines if the book is affected. This is the same with genes. Every person has some kind of gene change, examples of this include; different colours of the eyes and different colours of the hair. Often a gene change does not have an affect on the person and they live healthy lives. However, if this change affects a critical gene, for example the dystrophin gene, then the person will develop 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 through 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 a spelling mistake, 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, for example a "normal" statement like 'the fat cat sat on the mat' becomes: 'hef at cats ato nth emat'.

Base:

Bases are the building blocks of DNA. Bases are also known as nucleotides. There are 4 bases: T or thymine, G or Guanine, C or Cytosine and A or Adenine. The genetic code is made up from a sequence of the bases, eg. CCGT GATC TCGT. This base sequence contains all the information needed to make up all the genes in our body, which in turn create who we are. If we think of genes as words in a book, the bases are the letters that spell out the words. When there is a gene change, it means there is an alteration of the bases in that gene in some way (i.e. by deleting, inserting or changing a base or number of bases in a DNA sequence or by increasing or decreasing the number of a base or a sequence of bases in a DNA sequence). This may result in a defective gene.

Carrier:

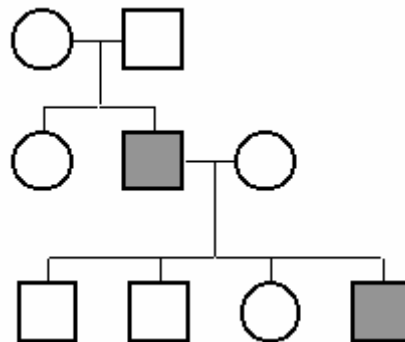
In *recessive* disorders two copies of a gene change are needed for an individual to be affected with the disorder. A carrier is an individual that has one copy of the gene change. Generally, this person is not affected at all and leads a healthy life. If two carriers of the same disorder have a child, 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.

TYPES OF INHERITANCE:

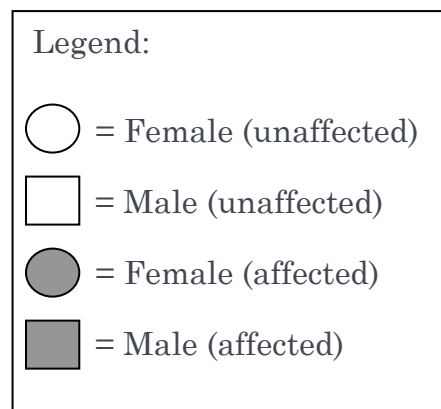
There are a number of ways that genes can be passed on through the generations. Because our chromosomes are paired we each have 2 copies of the one gene. There are a number of ways different disorders can be inherited, however, for the disorders mentioned in this booklet, we only need to understand 4 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 in that gene change to be seen in the person. However, when the change can only be seen when there are 2 changed copies of the gene present on the person, 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 inherited by what is known as autosomal inheritance. Autosomal inheritance can be dominant (i.e. only 1 copy of the gene change needed) or autosomal recessive (both copies of the gene need to have the change). Autosomal inheritance affects both females and males equally.



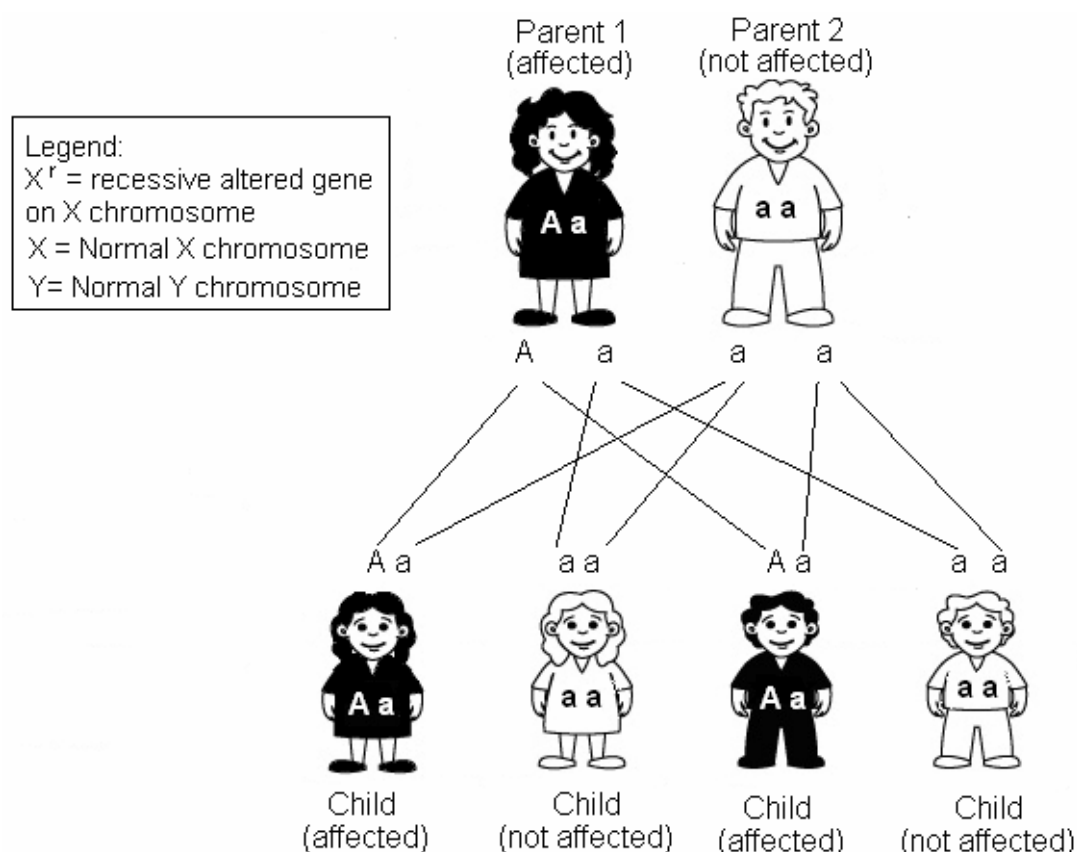
A family tree (or pedigree). These are used to show patterns of inheritance.



Autosomal Dominant Inheritance:

In autosomal dominant inheritance, there is a 50% (or 1 in 2) chance that the gene will be passed onto the next generation. You only need 1 parent to have the gene change. The reason it is said to be dominant is if one of these altered copies is present, it will be seen in that individual. 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. The following diagram shows how parent's chromosomes and genes are passed on through the generations and how only one altered copy of the gene is needed for that individual to have the disorder:

Fig 3: Autosomal Dominant Inheritance:



Anticipation and autosomal dominant inheritance:

In some autosomal dominant disorders, the severity of the disorder gets worse over generations. This is known as Anticipation. This explains why many autosomal dominant disorders are picked up in a child with moderate to severe symptoms and not in their parents who may not have any symptoms.

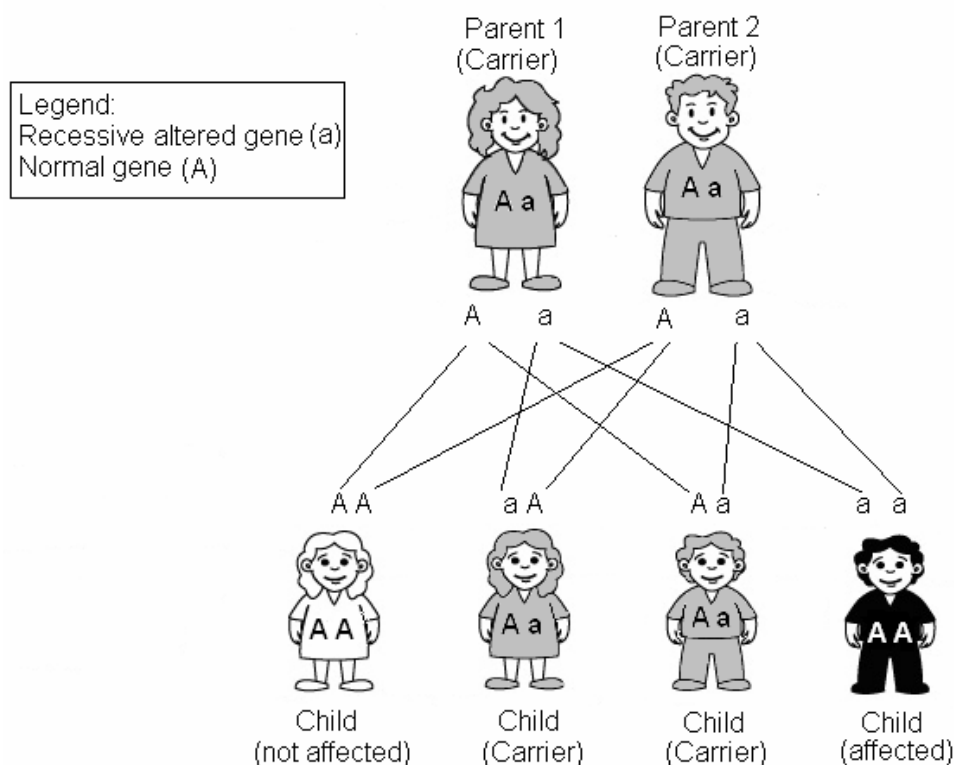
Penetrance and autosomal dominant inheritance:

Another factor that can influence the severity of symptoms is variable penetrance. When there are different severities of symptoms seen randomly in the one family (i.e. parent that is severely affected and has one child that is mildly affected or two sisters who have different severity of symptoms) it is thought that the disorder has variable penetrance. This means that two people may have the same altered gene but one may have no symptoms and the other person does. This does not affect the risk of inheriting the disorder as parents with the altered gene still have a 50% chance of passing this onto their children.

Autosomal Recessive Inheritance:

In autosomal recessive inheritance, both parents need to have an altered copy of the gene for the gene change to be seen in the next generation. It is said to be recessive because the presence of only one altered copy in an individual means that the normal copy of the gene “hides” the altered gene and the manifestation of the disorder is not seen in that individual. So if both parents have the same recessive gene change and decide to have a child, there is a 25% (or 1 in 4) chance that their child will be affected with the disorder. There is also a 50% (or 1 in 2) chance that their child will be a healthy carrier and won't be affected. Autosomal recessive disorders affect both boys and girls equally. The following diagram shows how parent's chromosomes and genes are passed on through the generations and how two altered copies of the gene is needed for that individual to have the disorder:

Fig 4: Autosomal Recessive Inheritance:

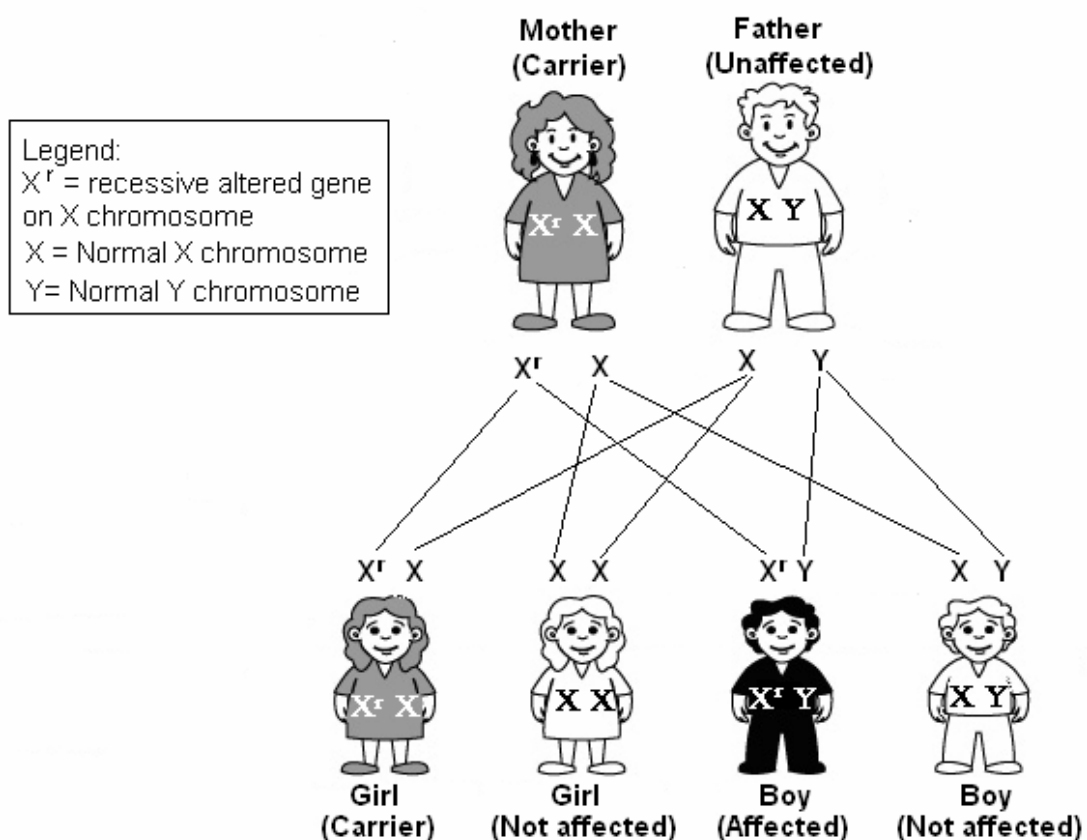


X-Linked recessive inheritance:

The X and Y chromosomes determine gender of a person, they are separate from the autosomal chromosomes. Males have one X and one Y chromosomes, whilst females have two X chromosomes. This means, a mother can only pass on an X chromosome to her child, however the male can pass on either an X or a Y. It is the presence of the Y chromosomes that make a child a boy.

In X-linked recessive inheritance, when a mother who carries an altered gene passes on that X chromosome to her daughter, she is not affected because she has a “back up” X chromosome and the gene on the other X chromosome “masks” that effects of the altered gene. However, if the mother has a son, he will always have the disorder because they only have one X chromosome with no “back up” meaning the altered gene can’t be masked by the unaltered gene. It is for this reason we generally only see males affected when the disorder is X-linked recessive.

Fig 5: X-Linked recessive inheritance:

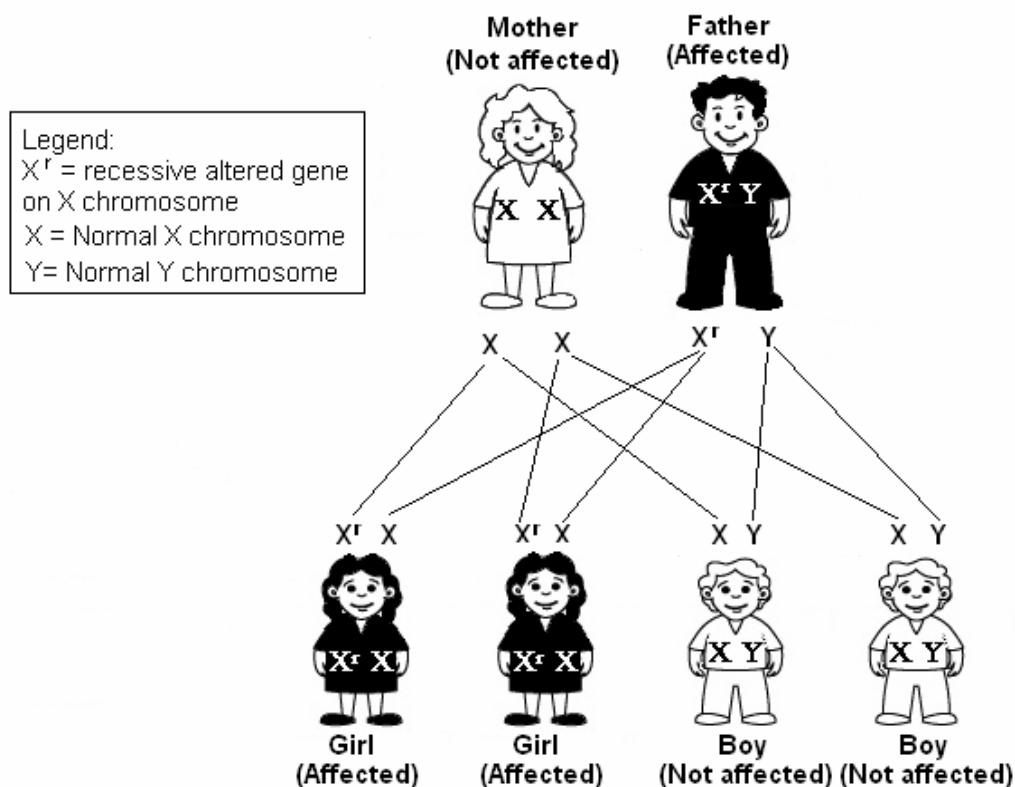


X-linked dominant inheritance:

As previously mentioned, a male has one X chromosome and one Y chromosome, whilst females have two X chromosomes. The reason for this is because females get one X chromosome from their mother randomly (who has two X chromosomes) and the other X chromosome from her father (who will always pass on his one X chromosome). Males however, will inherit one of his mother's X chromosomes at random, but will always get his father's only Y chromosome.

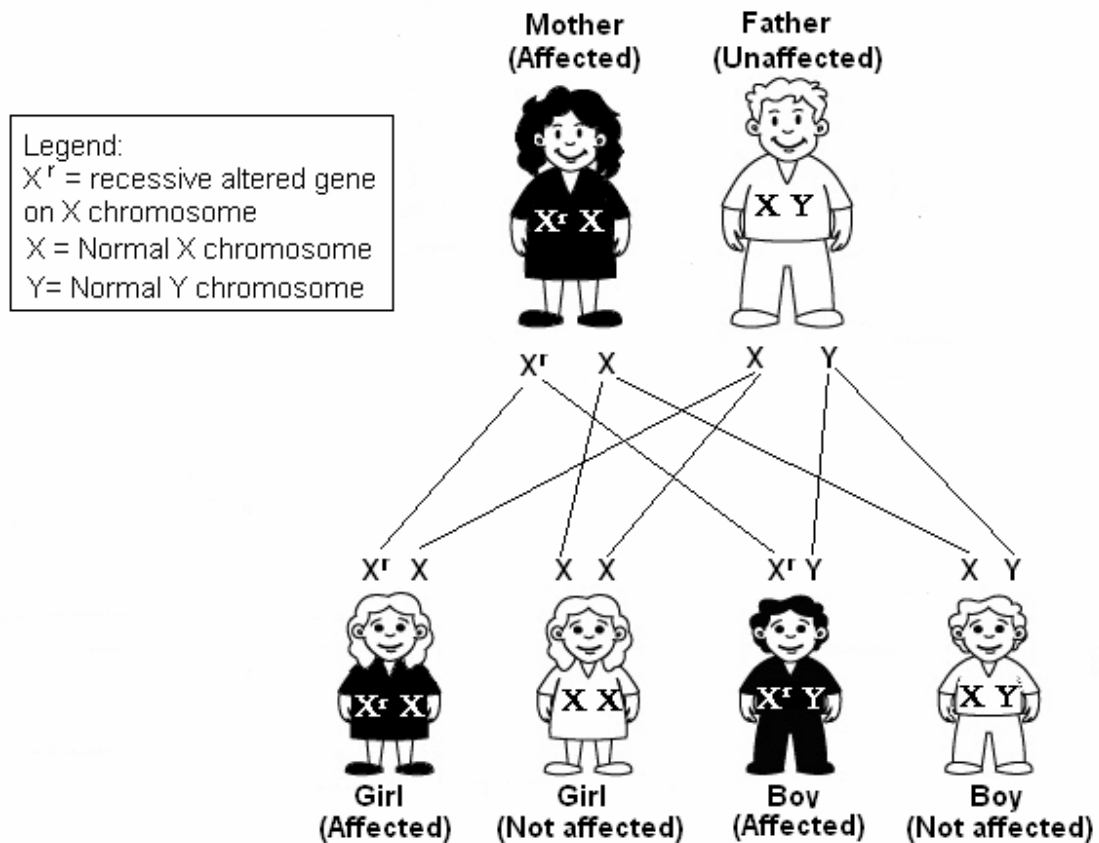
In X-linked dominant inheritance, if a father who is affected with a dominant X-linked disorder passes on his altered X chromosome to his daughter, she will always be affected; however, his boy will inherit his Y chromosome and will therefore be unaffected.

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 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, as they both receive an X chromosome from their mother.

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



MUSCULAR DYSTROPHIES AND GENETIC TESTING:

Duchenne Muscular Dystrophy (DMD):

Overview:

Duchenne muscular dystrophy is one of the most common muscular dystrophies and is characterised by the progressive break-down and deterioration 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 cardiac and cognitive impairment in a small percentage of people.

Unlike many other genetic disorders, carriers of the DMD 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 is 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 DMD cases are inherited, with the other one third of cases resulting spontaneously without a genetic link. Genetic testing may be required to determine if a case of DMD is sporadic or genetic if there is no family history to provide information that may affect other members of the family. DMD results from an alteration in the dystrophin gene that leads to the gene producing a malformed dystrophin protein. This means an individual that is affected with DMD produces dystrophin that is changed or mutated. The types of gene alterations include a large deletion or duplication that affects 65% of people with DMD or a small deletion or other mutation that affects between 30 – 35% of people with DMD. Because DMD is an X-linked disorder, only boys will be affected (with extremely rare exceptions).

Testing:

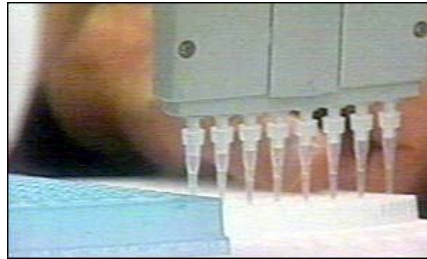
1) CK testing: Your genetic counselor or doctor will organize testing for the boy suspected to have DMD after you have had an appointment with them. To confirm the diagnosis of DMD, they will do 3 simple blood tests, over a period of time, which tests for an enzyme known as Creatine Phosphokinase (also referred to as CK). This is because individuals with DMD lack the protein dystrophin, the muscle cells in their bodies become damaged. This allows for the CK to leak out of the cells and is found in large amounts in the blood. 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, as it only tells us that there is muscle weakness, not what is causing it. Therefore, further genetic testing may be needed.

The 3 CK blood tests get an accurate average CK level measurement over a period of time. The reason that this is needed is because normal day-to-day activities and exercise can also cause muscle cells to become damaged temporarily, resulting in an increase in that individual's CK levels. This means if you work your body too hard in the days before the test, an inaccurate CK level will be recorded. The average ensures that the results seen are what truly represent your normal CK level. If one of the 3 results is extremely different to the other two, a fourth test may be required just to confirm that it is an incorrect result. Your doctor or genetic counselor will advise that the week before the test you do as little physical work as possible and 48 hrs before the test you stop all physical activity. This is an important factor to consider when deciding on genetic testing, as it can have an impact on your professional and personal life.

2) Genetic Testing: If the CK test shows an increase in the CK levels that are expected in a person with DMD or a carrier of DMD, a genetic test can be undertaken to specifically find the gene alteration in the dystrophin gene. Your genetic counselor or doctor will organize the testing after an appointment with them. This is done most commonly by taking a simple blood test (occasionally by tissue 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, making it easier for carriers in the family to be identified as they are able to search for the same alteration. Occasionally, after DNA testing, a person who is suspected to have DMD, 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.

3) Muscle Biopsy: There is a final test that can be performed if the DNA test does not show any gene changes in the person suspected with DMD. This is a muscle biopsy. 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 microscopically. If there is no dystrophin present, then the boy is diagnosed with DMD. If there is a small amount of Dystrophin present, then it is likely that the boy has a related disorder Becker Muscular Dystrophy, which affects the same gene as DMD.

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 DMD. No carrier testing on females will ever be performed on girls under the age of 18.



Becker Muscular Dystrophy (BMD)

Overview:

Becker Muscular Dystrophy is very similar to the Duchenne Muscular Dystrophy (DMD); however, the symptoms are much less severe and are generally not seen until later in life. Like DMD, Becker muscular dystrophy is caused by a change in the dystrophin gene; however symptoms do not usually develop until much later in life. 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 being either slow and progressive or static (not getting any worse). Other problems that can be associated with the lack of the dystrophin protein include cardiac and cognitive (thought process) impairment.

Inheritance:

BMD is inherited in an X-linked recessive pattern (*see X-linked recessive inheritance in the “types of inheritance” section for more detail*). Genetic testing may be required to determine if a case of BMD is sporadic or genetic if there is no family history to provide information that may affect other members of the family. Unlike DMD, the change in the dystrophin gene didn't stop the dystrophin protein being developed. Instead, an incomplete, altered version of the dystrophin protein is able to be produced, resulting in less severe symptoms than those seen in DMD. Because DMD is an X-linked disorder, only boys will be affected (with extremely rare exceptions).

Testing:

1) CK testing: Your genetic counselor or doctor will organize testing for the boy suspected to have BMD after you have had an appointment with them. To confirm a diagnosis to have BMD, they will do 3 simple blood tests, over several months, which tests for an enzyme known as Creatine Phosphokinase test (also referred to as CK). Because individuals with BMD have less of the protein dystrophin, the muscle cells in their bodies become damaged. This allows for the CK to leak out of the cells and an increase of CK levels is found in the blood.

The 3 CK blood tests get an accurate average CK level measurement over a period of time. The reason that this is needed is because normal day-to-day activities and exercise can also cause muscle cells to become damaged temporarily, resulting in an increase in that individuals CK levels. This means if you work your body too hard in the days before the test, an inaccurate CK level will be recorded. The average ensures that the results seen are what truly represent your normal CK level. Your doctor or genetic counselor will advise that the week before the test you do as little physical work as possible and 48 hrs before the test you stop all physical activity. This is an important factor to consider when deciding on genetic testing, as it can have an impact of your professional and personal life.

2) Genetic Testing: If the CK test shows an increase of the CK levels that are expected in a person with BMD or a positive carrier result a genetic test can be undertaken to specifically find the gene alteration in the dystrophin gene. Your genetic counselor or doctor will organize the testing after an appointment with them. This is done most commonly by taking a simple blood test (occasionally by tissue 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 BMD, making it easier for carriers in the family to be identified as they are able to search for the same alteration. Occasionally, after DNA testing, a person who is suspected to have BMD, 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 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.



3) Muscle Biopsy: There is a final test that can be performed if the DNA test does not show any gene changes in the person suspected with BMD. This is a muscle biopsy. This involves taking a small piece of muscle tissue, usually from the leg, by using a needle. This sample is then taken to the laboratory where it is stained to look for the presence of dystrophin microscopically. If there are small amounts of dystrophin present, then the male is diagnosed with BMD.

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 young boys will undergo genetic testing only if they show signs of having DMD. No carrier testing on females will ever 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 weakness 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 inherited in an autosomal dominant pattern (*see autosomal dominant inheritance in the “types of inheritance” section for more detail*). FSHD mostly results from either an alteration or deletion of a specific gene on chromosome 4 causing the gene to not function properly. About 30% of FSHD cases arise spontaneously in a person with no previous family history, whilst the other 70% of FSHD cases are inherited. However, if a spontaneous case of FSHD arises in an individual, it can be passed on through the family. About 95% of people that are diagnosed with FSHD are found to have a deletion, which has been detected by genetic testing. There are a small number of people who do not have the deletion, but still have FSHD suggesting that there are other factors, such as other genes, that may play a role in developing the disorder that are yet to be discovered.

FSHD is a disorder that has high penetrance, which means that most people, who have a FSHD deletion, will have at least mild symptoms of FSHD (*see “penetrance and autosomal inheritance” for more information about penetrance*).

Most cases of FSHD have been linked to Chromosome 4, meaning genetic testing will be looking at the 2 copies you have of chromosome 4.

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 counselor or doctor will organize 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) or a tissue sample that is sent to a lab for testing. 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 counselor 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:

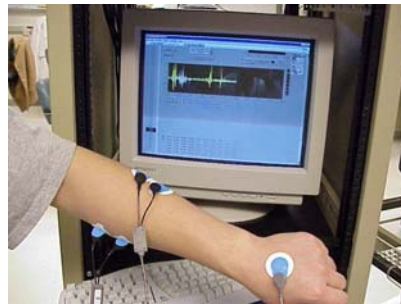
1) CK testing: Your genetic counselor or doctor will organize testing for the person suspected to have FSHD after you have had an appointment with them. To confirm a diagnosis to have FSHD, they will do 3 simple blood tests, over a period of time, which tests for an enzyme known as Creatine Phosphokinase (also referred to as CK).

The 3 CK blood tests get an accurate average CK level measurement over a period of time. The reason this is needed is because normal day-to-day activities and exercise can also cause muscle cells to become damaged temporarily, resulting in an increase in that individuals CK levels. This means if you work your body to hard in the days before the test, an inaccurate CK level will be recorded. The average ensures that the results seen are what truly represent your normal CK level. If one of the 3 results is extremely different to the other two, a fourth test may be required just to confirm that it is an incorrect result. Your doctor or genetic counselor will advise that the week before the test you do as little physical work as possible and 48 hrs before the test you stop all physical activity. This is an important factor to consider when deciding on genetic testing, as it can have an impact of your professional and personal life.

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: 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. 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. The age of onset and characteristic symptoms are combined with this result to determine a diagnosis.



4) Muscle Biopsy: A muscle biopsy is also used to confirm a diagnosis of FSHD. This involves the removal of a small section of muscle tissue using a '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 anesthesia. Even though a muscle biopsy can easily determine a clear diagnosis of FSHD it is generally used as a final test to determine a diagnosis when genetic testing or EMG results are not conclusive.

Myotonic Dystrophy (MytD) (also known as Steinert's Disease)

Overview:

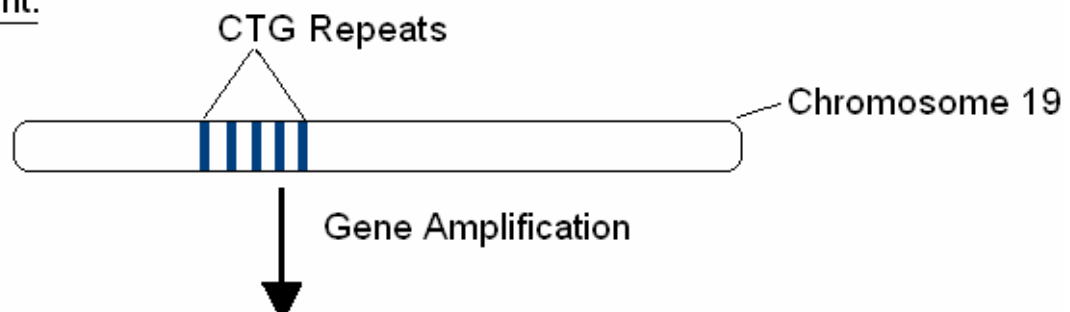
Myotonic Dystrophy is a neurological disorder that is characterized by muscle weakness and myotonia (*delayed muscle relaxation following contraction*). Other areas of the body that can also be affected include the eyes, the heart and the brain. The severity of the disorder can vary greatly, even in families. The age of onset of MytD can also vary widely with diagnosis occurring from just after birth to adulthood. 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.

Inheritance:

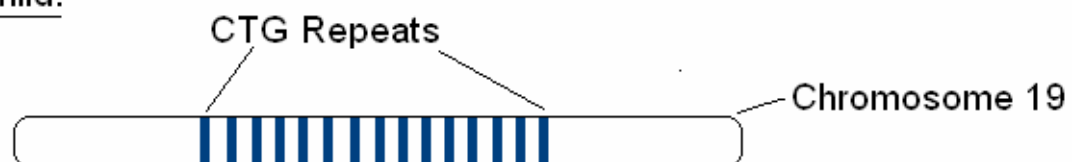
MytD is inherited in an autosomal dominant pattern (*see autosomal dominant inheritance in the "types of inheritance" section for more detail*). DM results from gene alteration known as an amplification, which means a small sequences of DNA is repeated more than it should be (See diagram below). This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

Figure 8: Gene amplification

Parent:



Child:



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 MytD. People who fall between these two groups generally have no symptoms but fall into a group that is known as a permutation 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 MytD. The inheritance of MytD 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 MytD, it has been found that the size of the repeat can increase over the generations that result in a 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 MytD:

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

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

Testing:

Your genetic counselor or doctor will organize the testing for the person who is thought to have MytD after you have had an appointment with them. 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 (occasionally by tissue sample) that is tested by the Laboratory for that CTG repeat expansion. Testing usually takes between 2 and 4 weeks and either your doctor or genetic counselor will call you or arrange an appointment with you to discuss the results.

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 abilities 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).



When we wish to move a part of our body, such as our leg, our brain sends a signal through the spinal cord, to the motor neurons (that connect the spinal cord to the muscle), which pass the message to move onto our muscles in the leg. If this movement is the result of a stimulus, for example, stepping on something hot, the sensory receptors send a message to the brain via the sensory neurons, causing the brain to signal to be sent back to the leg to move. 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:

There are 3 different ways that CMT can be inherited. All cases of CMT type 1 (except the subgroup CMT type 1X), CMT type 2 and HNPP are inherited in an autosomal dominant pattern (see *autosomal dominant inheritance in the “types of inheritance” section for more detail*). Depending on the type and subtype of CMT, the gene and the chromosomes involved in causing the disorder vary. Because they are inherited in an autosomal dominant pattern, it is likely that the parents of an affected child have CMT, but have very mild symptoms that go unnoticed. Spontaneous cases of CMT can also occur in families who have no family history of the disorder.

CMT type 1X has been linked to the X chromosome and therefore is inherited via X-linked dominant (see X-linked dominant inheritance in the “types of inheritance” section for more detail).

CMT type 3 arises by autosomal recessive inheritance (see autosomal recessive inheritance in the “types of inheritance” section for more detail). This means both parents are carriers of the disorder but are not affected. As CMT type 3 results in very severe symptoms in infants, it is very unlikely that either parent would be affected with CMT type 3.

CMT type 4 also arises as a result of autosomal recessive inheritance.

Occasionally, a person can also develop CMT sporadically with out 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's 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. 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. The age of onset and characteristic symptoms are combined with this result to determine a diagnosis.

4) Genetic tests: Genetic testing is also an option to confirm a diagnosis of CMT and to confirm the gene change that has caused the disorder to develop. 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. Currently the subtypes that have a known gene alteration that can be tested for include; CMT types 1A, 1B, 1C, 1D, 1X (X-linked form), 2A, 2E, 2F, 4F and HNPP). If the gene change can be 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 a simple blood test (occasionally can require a tissue sample) 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.

SPINAL MUSCULAR ATROPHY:

Spinal Muscular Atrophy (SMA)

Overview:

Spinal muscular atrophy is characterised by degeneration of motor neurons (also known as a nerve cell) in the body. 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) that results in muscle weakness.

There are 4 different categories of SMA that are determined by the age of onset. They also can determine the severity of the disorder in an affected individual. These categories are as follows:

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

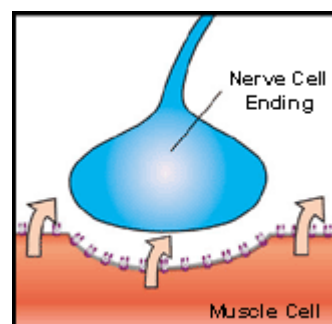
Category of SMA	Age of onset	Also known as:
Type 1 SMA	Infant (Usually see symptoms before 8 months of age)	- Infantile SMA - Werdnig-Hoffman disease
Type 2 SMA	Infant/Toddler (Symptoms first seen between 6 to 18 months of age)	- Intermediate SMA
Type 3 SMA	Toddler/child (Symptoms first seen from 18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

Inheritance:

SMA is inherited in an autosomal recessive pattern (see *autosomal recessive inheritance in the “types of inheritance” section for more detail*). There are two genes that have been linked to SMA known as SMA1 and SMA2 on chromosome 5. A gene change on both chromosomes in the SMA1 gene 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. The SMA2 gene is also important as can actually 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 less commonly conclusive 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 generation 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.



The arrows in this diagram represent signal being sent from the muscle to the nerve. Here, the nerve cell receives the signal that is sent from the muscle. In patients with SMA, the signal is unable to be transmit it along the nerve cell and therefore a reply message to the muscle doesn't get back to the muscle, causing it not to carry out the movement required.

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 Duchene's Muscular Dystrophy and Becker muscular dystrophy (for more information on the testing procedure for these disorders, please refer to the "genetic testing" section of either Duchene Muscular Dystrophy or Becker Muscular Dystrophy pages.).

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) 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. 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 (occasionally can require a tissue sample) to determine if a person is affected or a carrier of SMA. 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.

3) 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 anesthesia. Even though a muscle biopsy can easily determine a clear diagnosis of SMA, it 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 recourse.

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 any genetic changes that may be suspected. This is usually done after at least 14 weeks after conception. The procedure involves taking a needle and taking 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. This is generally due to genetic factors; however, environmental factors may also play a role.

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 mothers and the other from our fathers.

Autosomal Dominant Inheritance: A pattern of inheritance in which a trait will be expressed if the altered gene is inherited from either parent

Autosomal Recessive Inheritance: A pattern of genetic inheritance where two altered genes are needed to display the trait or disease

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 usually impaired

Chromosome: An inheritable unit that contains all the genetic information needed for life.

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 (i.e. the spine).

Embryo: An organism, such as a developing human, in its earliest stages of development after conception (i.e. the fertilization of a women's egg with the male's sperm). This stage occurs in the womb before it has reached the stage where it can be identified at around 8 weeks.

Fetus: 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. Different alleles of a gene may alter the characteristics that are associated with that gene.

Genotype: The genetic make up of that individual, which, along with interactions from the environment on some occasions, are responsible for the physical appearance of an individual.

Heterozygous: An individual that has two different alleles for a specific gene.

Homozygous: An individual that has the same allele for a specific gene.

Hypotonic (When referred to in a medical context): Having less tension or tone than usually seen, as of in the muscles or in the arteries.

Inherited: Traits or characteristics that come from a person's ancestry, which are passed on from the parents to their offspring (children) via their genes. This means these genes will be present at birth and is not under the control of the parent.

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

Muscle Biopsy: A small muscle sample that is removed by a surgeon (or by less evasive means) that is tested in the laboratory for muscular disorders such as muscular dystrophies, inflammation and other muscle disorders.

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

Myelin Sheath: Myelin is an electrically insulating layer that surrounds the axons of many neurons.

Myopathy: A neuromuscular disorder in which the muscle fibres do not function for one reason or another, that results 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. It usually presents as weakness or numbness of the muscles as a result of the affected nerves that stimulate it.

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. Dominant traits will hide recessive traits that may be present on a person's genetic make up. An individual needs to be homozygous for a recessive allele before it can be physically seen.

Pre-implantation Genetic Diagnosis (PGD): PGD can be done when a couple is undergoing IVF (in vitro fertilization). It involves taking a few cells from the embryo before it is

implanted into the womb of the mother to determine if it may be affect or carry a genetic disorder known to the family. Only embryos that are not affected by the disorder that runs in the family will be implanted into the womb of the mother-to-be.

Pedigree: Also known as a family tree. These are drawn to see any patterns in a family that may be related to disorder.

Penetrance: The degree to which a disorder can be seen in an affected individual. This means that some people may be mildly affected whilst others with the same disorder will be affected severely. This variation can be seen in families with a parent having very severe symptoms, whilst their child and sibling are only affected mildly (or vice versa). This variation may be due to an environmental factor (which we have no control over), other genes that may interact with that gene or another unknown factor.

Protein: The product produced by a gene or a number of genes that are used in the body, allowing it to function.

Schwann cell: Any of the cells that cover the nerve fibers in the peripheral nervous system and form the myelin sheath.

Scoliosis: side-to-side curvature of the spine that is commonly associated with the rotation of the vertebrae. When looking at the spine from the back, it appears to be straight, when looked at side on, there is a noticeable curve. Depending on the severity of the curve, there may be some pain as a result of curve.

X chromosome: A gender determining chromosome that can be passed on to the next generation. A mother will give one of her two X chromosome to all of her children and a father will only give his X chromosome onto his daughters.

X-linked Dominant Inheritance: The genes that are located on the X chromosome can be passed onto the next generation. A mother will give one of her two X chromosome to all of her children and a father will only give his X chromosome onto his daughters. If there is an altered gene on the X chromosome that is dominant, it will always seen in that individual and can be passed onto the next generation where they will have the same trait.

X-linked Recessive Inheritance: The genes that are located on the X chromosome can be passed onto the next generation. A mother will give one of her two X chromosome to all of her children and a father will only give his X chromosome onto his daughters. If there is an altered gene on the X chromosome that is recessive, males, who only have one X chromosome, will express the recessive characteristic because they do not have a second copy of the gene to mask the recessive characteristic. However, a female must inherit 2 altered copies of the gene before the characteristic is seen in that individual.

Y chromosome: The presence of the Y chromosome determines gender - male. This chromosome is passed down from a father to their son.

Y-linked Inheritance: Because the male has a Y chromosome, genes on the males Y chromosome can only passed onto his sons. This means if the father has an altered gene on the Y chromosome, he will always pass this onto his sons.

DIAGRAMS FROM:

Picture1: http://www.massgeneral.org/livingwithtsc/images/care/popup/i_care_genetic_jacob.jpg

Picture 2:
<http://www.sickkids.ca/cancergeneticsprogram/images/dna.gif>

Picture 3:
<http://www.idph.state.il.us/images/babyfeet669.jpg>

Picture4:
<http://faculty.clintoncc.suny.edu/faculty/michael.gregory/files/Bio%20101/Bio%20101%20Laboratory/Pedigree%20Analysis/PEDIGREE.HTM>

Picture 5:
<http://www.campmda.org/>

Picture 6:
http://news.bbc.co.uk/olmedia/460000/images/462156_testing300.jpg

Picture 7:
<http://pro.corbis.com/images/42-17765989.jpg?size=572&uid=%7BB3BBCAB0-BE45-4E69-B3CC-8F7FADF51982%7D>

Picture 8:
<http://www.shoulderdoc.co.uk/images/uploaded/FSHD2a.jpg>

Picture 9:
<http://www.pitt.edu/~zmli/handlab/2005image/EMG.JPG>

Picture 10:
<http://www.dna-worldwide.com/typo3temp/04a2e6bca2.jpg>

Picture11:
<http://www.mda.org/publications/quest/q73anesthesia.html>

