Facioscapulohumeral Muscular Dystrophy

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Introduction

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

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

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

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

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

1). GENERAL OVERVIEW

1-A). What is facioscapulohumeral muscular dystrophy?

Facioscapulohumeral [FAYE- she - oh - SCAP - pew - low - humor - ill]

Facio = FAYE- she - oh
scapulo = SCAP - pew - low
humeral = humor - ill

Facioscapulohumeral dystrophy (FSHD) is a genetic disorder affecting the primary skeletal muscles. It is marked by progressive, often asymmetric (unequal from side to side) muscular weakness and usually varies widely with respect to age of onset, severity, and pattern of muscle involvement, both between and within families. Typically symptoms appear in the early teens to twenties and into the thirties, but can occur any time from infancy to later life. It is a genetic disorder inherited in an autosomal dominant manner. In general, the disorder tends to start with weakness in the face and shoulders and later progresses to weakness in the feet and hips.

1-B). Quick Facts about facioscapulohumeral muscular dystrophy.

What: Facioscapulohumeral muscular dystrophies, two types: 1A and 1B
Who: Anyone
When: At any age, but primarily from the late teens to the thirties
Where: Skeletal muscles, initially targeting the face, shoulders, lower legs and torso
Why: Muscle weakness is caused by a poorly understood genetic mutation

1-C). How common is facioscapulohumeral muscular dystrophy?

FSHD is the third most common dystrophy after Duchenne muscular dystrophy (DMD) and Myotonic dystrophy (DM). Facioscapulohumeral muscular dystrophy occurs in the Canadian and world population at an estimated frequency of about one in twenty thousand people.

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

Yes. Currently two distinct types of facioscapulohumeral muscular dystrophy are recognized; 1A and 1B:

- Facioscapulohumeral muscular dystrophy type 1A (FSHD1A) is the more common of the two types, and it is also the better understood of the two at this time. FSHD1A accounts for about 95% of cases of facioscapulohumeral muscular dystrophy.
- In about 5% of FSHD cases there is a different, and less well understood, genetic cause. The disorder related to these cases is referred to as Facioscapulohumeral muscular dystrophy type 1B (FSHD1B).

The name facioscapulohumeral dystrophy (FSHD) was given to this condition by Dr. Walton and Dr. Natrass in the 1950s. It is becoming clear that FSHD might constitute a group of several different conditions with similar causes and symptoms. Thus, the term “FSH syndrome” is being used more frequently (sometimes the term “FSH disease” is seen as well).

Facioscapulohumeral muscular dystrophy is an autosomal dominant muscular dystrophy affecting the skeletal muscles. There are significant differences between different forms of neuromuscular disorders in this category. FSHD whether type 1A or 1B expresses itself differently in different individuals.

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

Facioscapulohumeral muscular dystrophy type 1A has a number of alternate names that are used to identify it.

- Facioscapulohumeral Muscular Dystrophy, FSHD, FSHMD or FMD

Type 1A

- Facioscapulohumeral Muscular Dystrophy, Type 1A; FSHD1A, FSHMD-1A
- Landouzy-Dejerine Muscular Dystrophy
- Facioscapulohumeral Muscular Dystrophy, Infantile,
- Facioscapulohumeral Dystrophy with Sensorineural Hearing Loss and Tortuosity of Retinal Arterioles

Type 1B

Facioscapulohumeral muscular dystrophy type 1B, FSHD1B, FSHMD1B. Facioscapulohumeral muscular dystrophy type 1B is not known by any other name.

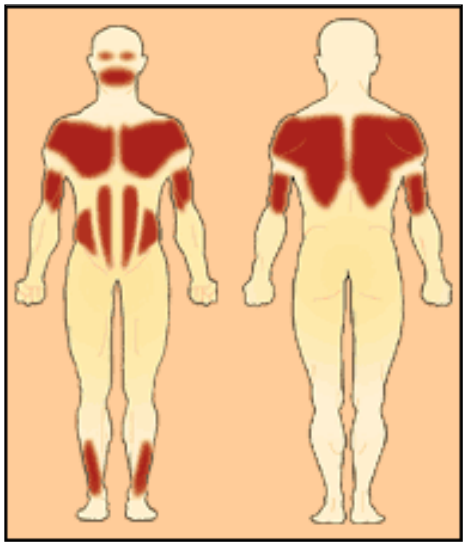
1-F). Are there other disorders related to facioscapulohumeral muscular dystrophy?

Disorders of a similar type: FSHD is an autosomal dominant muscular dystrophy affecting the skeletal muscles and involving a repeat mutation. The two forms of myotonic dystrophy (DM1 and DM2) also fall into this general category.

2). SYMPTOMS

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

Major symptom: the progressive weakening and loss of skeletal muscles (atrophy) in the face (facio), shoulder area (scapulo) and upper arms (humeral). Distinctive features are early weakness of the muscles of the eye & mouth (smile, pucker, whistle), with weakness in the shoulder muscles. FSHD symptoms may be so mild that adults may be unaware they have FSHD until a family member with more severe symptoms is diagnosed. About 5% of individuals with the mutation that causes FSHD do not develop any symptoms, but can still pass on the mutation to their offspring.



From: http://www.chb-genomics.org/pat_fam-facio_dyst.php

Weakness around the eyes and mouth are often some of the first symptoms of FSHD. People living with FSHD may be unable to whistle, purse or pucker their lips, or turn up the corners of their mouth when smiling. Eye weakness is also common, and persons with FSHD may not be able to close their eyelids tightly, leading to eye dryness and other eye problems. They may also experience sensitivity to bright light.

The area around the shoulder blades is one of the primary areas of muscle weakness in FSHD (shoulder weakness is the presenting symptom in more than 80% of patients). There is a gradual loss of stability around the shoulders. The shoulder blades, which would otherwise be fixed in place, may not get the leverage necessary to lift or pull causing the scapula bones to lift or "wing" out as they move. Early observable symptoms include the inability to throw objects or lift the arms over the head.

There may be an unequal weakening of the biceps, triceps, deltoids, and lower arm muscles. Muscles of the hands and wrists may also be affected. As well, abdominal and hip muscles can weaken, leading to an exaggerated curvature of the lower spine. Involvement of muscles of the foot, ankle, hips and abdomen are common. These muscle losses frequently result in distorted gait patterns (the way we walk), increased incidence of falls and stress on the remaining functioning **muscles.** This may lead to pain, inflammation and joint and spine problems. Rare symptoms include hearing loss, visual impairment, difficulty swallowing and problems with respiration, in particular, carbon dioxide retention during sleep.

Measured or limited activity is important to maintain range of motion and strength of remaining functioning muscle. Use of orthotic braces as well as an individual physiotherapy routine may help limit stress on healthy muscle. Periods of muscle inactivity can rapidly reduce the ability to use those muscles in the future. Mobility may be affected to the extent that a ‘scooter’ or wheelchair is required.

Research has demonstrated that the extent of the genetic mutation associated with FSHD1A is linked to the severity of the symptoms experienced. There are two major classes: patients with severe mutations who are severely affected while patients with milder mutations show wide variations in onset and clinical presentation.

Most people with FSHD live a normal lifespan. Males tend to be more severely affected than females.

FSHD is a muscular dystrophy of the skeletal muscle and therefore is not directly linked to the type of muscle found in the heart. Still, a few cases (less than 5%) may experience heart problems; atrial arrest, bundle branch block, and dilated cardiomyopathy have been reported.

The esophagus and digestive system are composed of smooth muscles that are not directly affected by FSHD.

All the symptoms listed above describe the classic forms of FSHD. As researchers often note, FSHD can sometimes also appear in ways that are unique or unexpected.

Anesthesia WARNING: A higher rate of complications is generally associated with general anesthesia in patients with neuromuscular disorders. Even mildly affected

patients may have complications. Patients with FSHD or a family history of FSHD need to discuss this with their surgeons.

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

FSHD symptoms can appear in people of any age, but generally, onset of muscle weakness ranges from the teens or early twenties into the thirties. Typically the disorder becomes apparent in the second decade of life. In about five percent of cases, a young child or infant develops symptoms. It follows that teenagers and people in their early twenties are most commonly diagnosed, however in many cases, FSHD may remain undiagnosed for many years because of its unusually slow progression.

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

No. While the symptoms of FSHD are highly variable from person to person, the general progression of the disorder tends to be the same, regardless of the age when symptoms first appear.

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

Facioscapulohumeral muscular dystrophy affects both males and females of any age.

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

FSHD is a progressive disorder, which means the symptoms worsen over time. How rapidly the disability progresses and the extent of muscle loss may differ considerably, even among family members. The degree of severity in a parent cannot predict the extent to which a child may be affected.

The disorder tends to progress from the face downwards. Asymmetry and selective muscle group involvement distinguish FSHD from other muscular dystrophies. Many authors describe stepwise deterioration with prolonged periods of apparent arrest.

Most people with FSHD first experience muscle weakness in their late teens or early twenties. The disorder may gradually limit personal or occupational activities as individuals enter middle age and beyond. Over time, weakness may spread to the entire body as the disorder progresses. As the disorder progresses, involvement of muscles of the foot, ankle and hips frequently results in distorted gait patterns (the way we walk) and about 20% of cases will eventually require a wheelchair.

Prognosis is a prediction of the course of a disorder – how is it going to unfold and develop in the future – what is the outcome going to be? Due to the variable nature of FSHD, predicting the course and outcome of the disorder is difficult. A few general statements may be made about the disorder, but they may not apply to every case:

1) FSHD will likely involve weakness and wasting in the skeletal muscles. Predicting the extent and pace of this wasting and weakening is difficult as it varies greatly from person to person.

2) Most cases of FSHD will not affect or diminish the intellect or directly affect the personality (as some muscular disorders do). Severe cases involving early (childhood) onset may be associated with mental impairment and with epilepsy. The psychological impacts of living with a disorder like FSHD are not easy to define. Each individual's ability to cope is unique. Many factors including friends, family, and personal circumstances may also play a role in successful management of the disorder.

3) The heart and internal muscles (the smooth muscles, such as the diaphragm, esophagus, etc.) will likely not be affected. In most cases, breathing, swallowing, and heart function are not diminished, although problems can arise in some cases.

4) People with FSHD will likely live a normal life span, but one with a certain degree of limitation on personal and occupational activities. The level of limitation to personal and occupation activity varies and can range from very minor mobility problems to disability affecting speech and requiring a wheelchair or other devices to assist with the performance of daily activities.

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

Some people with FSHD experience symptoms that are not directly related to the neuromuscular system. These are usually very mild. These may include (from Tawil, 2004):

- Retinal telangiectasia, a chronic dilation of the capillaries in the retina caused by weakening of the walls of the blood vessels leading to slow loss of vision (Tawil, 2004).
- High frequency hearing loss vision (Tawil, 2004).
- A predisposition to heart problems: atrial arrest, bundle branch block, and dilated cardiomyopathy have been reported vision (Tawil, 2004).
- Premature Ventricular Contractions have also been known to occur.

2-G). How "serious" or disabling is facioscapulohumeral muscular dystrophy?

It is difficult to generalize because FSHD causes a widely varying degree of muscle weakness. However, many people with the disorder are able to live long, productive, and independent lives.

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

Mental impairment and epilepsy are features observed in about 40% of early onset (childhood) FSHD cases and these features are especially associated with larger deletions (Funakoshi, 1998).

3). DIAGNOSIS

3-A). How do I know if I have facioscapulohumeral muscular dystrophy?

Generally, you will notice muscle weakness, especially in the muscles of the face, around the eyes and mouth. You may have weakness in the arms and shoulders. You may notice some speech problems or problems smiling.

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

There are three main diagnostic approaches:

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

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

Clinical diagnosis involves a doctor or neurologist looking for key symptoms to identify the distinctive pattern of muscle involvement. Some symptoms of FSHD might be hard to see in mild cases but in typical cases, clinical diagnosis is usually straightforward.

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

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

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

Molecular (genetic) diagnosis involves a much more accurate test than clinical diagnosis and is often used to confirm clinical suspicions. Molecular diagnosis involves a genetic understanding of the disorder and the ability to test the DNA (or RNA) in the blood for specific mutations as compared to a healthy sample. A genetic test is available that can confirm FSHD1A. This precise testing ensures that FSHD1A is not confused with other disorders. The gene for FSHD1B has not yet been located and thus a genetic test is not yet available for this type.

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

Yes, accurate (95%) diagnostic tests of the DNA taken from the blood can show the presence of FSHD1A (Tawil, 2004). Research on the genetics of FSHD and on genetic tests continues.

Gene Tests FSHD testing:
http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=2640&res=nous&res=nointl&key=DZorXDdD3qXNz&show_flag=c

A prenatal test for FSHD1A is also available.

There are two questions that need to be asked when considering genetic testing:
(1) What can I gain by being tested? (2) What are the negative effects of being tested?

Some general reasons you might want genetic testing include:

- To reduce worry about having a genetic disorder.
- To adjust your lifestyle to reduce the impact of your disorder on personal or occupational activities.
- To assist your doctor in monitoring the progression of your disorder.
- To determine the possibility of genetically transferring the disorder to offspring.
- To confirm a clinical diagnosis to enable you to access workplace accommodations.
- To claim disability benefits.

Some reasons you might want to avoid genetic testing include:

- A positive diagnosis may prevent you from obtaining insurance coverage.
- A positive diagnosis could lead to problems with employers.
- A positive diagnosis may increase worry about the future.
- A positive diagnosis may strain your friendships of family relationships.

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

As FSHD is a genetic disorder, it is possible that parents, siblings, or children may also carry the mutation responsible for the disorder but may or may not exhibit the symptoms.

Testing for any genetic disorder is a personal choice and, when done on a seemingly healthy individual, that choice should not be made lightly. This question should be discussed with your family and with your doctor. Parents must weigh the pros and cons of having a child tested very carefully. A positive diagnosis could have significant negative as well as positive implications for the child's future. A simple "need to know" on the part of a parent is not a good enough reason to have a child tested.

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

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

Over the years, neuromuscular disorders have developed a reputation as sometimes being difficult to diagnose. Modern diagnostic procedures are a combination of good clinical judgment and very accurate tests. If you feel unsure about your diagnosis, or if the results come back as 'not conclusive,' it is important that you discuss your concerns and options for further testing or a second opinion with your neurologist or doctor.

4). CAUSES and PATHOLOGY

4-A). What causes facioscapulohumeral muscular dystrophy?

FSHD1A is caused by a genetic mutation involving a deletion – some of our genetic code is erased. Scientists and researchers are still debating how the FSHD1A mutation causes the symptoms we see.

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

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

Many cases of FSHD arise as a new or spontaneous mutation. In these cases, the DNA that is passed on by the parents is healthy. In the development of new cells after conception, the DNA is copied over and over. In this copying process, a mistake can occur and the child's DNA suffers a new mutation. Research studies indicate that at least 30% of FSHD cases appear to be caused by spontaneous (new) mutations (Tawil, 2004).

4-C). Is facioscapulohumeral muscular dystrophy anyone's fault? Is it contagious?

No. The mutations that cause FSHD occur by chance and are passed from generation to generation or arise as a new genetic mutation, again by chance. Because of the relatively late onset of the disorder, many people are not aware that they have a problem until after they have had children and have passed on the mutation. FSHD is not something that is routinely screened for. Today, if FSHD1A is suspected or if there is a family history of the disorder, a prenatal test is available.

Is it contagious? FSHD is not contagious; it is a genetic disorder and therefore cannot be passed from person to person by any sort of physical contact. Genetic disorders can only be passed on through reproduction; it is not possible to "catch" a genetic disorder from someone else.

5). GENETICS

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

Yes. Facioscapulohumeral muscular dystrophy is a genetic disorder caused by a genetic mutation. This mutation is either a new, spontaneous mutation or has been passed down from generation to generation.

The mutation involves a deletion of genetic information (referred to as "D4Z4" repeats) on chromosome number 4. It appears that the effects of the FSHD1A mutation are indirect and do not involve the structure of a gene, but rather, act by disrupting the transcriptional control mechanisms that govern one or more as yet unidentified genes. Without these control mechanisms, the function of these genes becomes abnormal, possibly leading to an overproduction of certain enzymes and proteins. Ultimately these changes somehow lead to the symptoms of FSHD1A.

Typically, genetic disorders involve mutations of a specific gene. Genes are used by the cell to make proteins and a mutation usually disrupts a specific protein and this directly causes a disorder. The mutation in FSHD1A is different in that it does not occur in the part of a gene that directly makes protein.

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

In FSHD1A, the more severe the mutation, the more repeats that are deleted and the fewer the number of repeats left in the D4Z4 zone. The fewer the number of repeats left

in the D4Z4 zone, the earlier the onset of symptoms and the more severe the disorder tends to be. It is normal to have from 15 to more than 100 copies of these repeats in the D4Z4 zone. If a mutation reduces the repeats to from 12 to 15 copies, some symptoms are possible (a borderline repeat range). If there are fewer than 12 repeats left in the section, the individual will definitely display symptoms of FSHD1A. If only two or three are left, childhood onset and severe symptoms are usually seen. The genetic test for FSHD1A measures the size of the D4Z4 section and thus can estimate the number of remaining repeats.

In summary, in FSHD1A a mutated section of genetic code on chromosome number 4 called D4Z4 has fewer than normal repeats. Without the proper number of repeats, it is believed other genes near the D4Z4 section produce normal proteins (mainly enzymes) but are overactive and make too much. The excess somehow causes problems, leading to the symptoms. The more severe the mutation and the fewer repeats that are left, the more severe the protein disruptions and the more severe the FSHD1A symptoms will be (Gabellini, 2002).

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

The section of DNA code where the FSHD1A mutation occurs is part of chromosome number 4 but it is not part of a gene (no specific gene(s) linked to FSHD have been identified). It appears that the mutation acts by subsequently affecting the normal operation of one or more genes. Researchers are trying to discover these genes and understand how they operate and how the FSHD1A mutation disrupts them. The search has begun in the area of DNA in the neighborhood of the FSHD1A mutation – the D4Z4 section of repeats on chromosome 4.

The genetic problem causing FSHD1B has not been discovered yet.

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

Yes, FSHD is inherited – it is passed from generation to generation, usually in an autosomal dominant manner.

Certain genes are usually found on certain chromosomes, in our case, we are interested in the D4Z4 section of repeats found on chromosome 4. This is an autosome; autosomes carry two copies of their genetic code, one copy inherited from mom and one version inherited from dad. Because FSHD is genetically dominant, only one copy of the code with the genetic mutation (inherited from either mom or dad) is necessary for FSHD to occur in a person (the other copy of code is usually healthy but it is overridden by the dominant version and thus it can’t help out).

In autosomal dominant disorders, for each pregnancy, a parent with a mutation has a 50% chance of transmitting the abnormal gene (allele) version (or in this case, the mutated section of code) and a 50% chance of passing on their other, normal version of the gene (code) to each child born. Each child has a 50% chance of inheriting the defect from a

parent with the mutation and a 50% chance of getting the healthy version of code. Because it is dominant, if the child does inherit the defective copy, he or she will display the disorder. These figures are statistical averages – a given family of four might have four children with FSHD, two with and two without, four children without or some other combination.

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

When the number of extra repeats changes, it often leads to a phenomenon called genetic anticipation – if the size of the repeated section further decreases with each generation, each successive generation will commonly show symptoms at an earlier age and will show more severe symptoms. Anticipation is seen in some cases of FSHD.

Somatic and Germline (gonadal) mosaicism:

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

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

How does this happen? As described above, genetic mutations are not always inherited from a parent (through an egg or sperm cell), some may occur spontaneously as a new mutation after conception and during the early days of embryonic development – in the case of FSHD, spontaneous mutations appear in up to 30 percent of cases.

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

this process. If mutations occur early in development, they often affect many of the subsequent sperm or egg daughter cells. If they occur later, mutations may affect very few cells, or maybe even just one cell. Kohler (1996) estimates that germline mosaicism appears in 19% of all FSHD cases.

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

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

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

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

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

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

In summary, these mutations may affect only some cells, leaving others healthy and leading to mosaicism in the individual. In about 20% of FSHD cases, we find that only some of the person’s egg or sperm cells (the germline cells) actually have the FSHD mutation.

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

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

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

6). TREATMENT and MEDICAL MANAGEMENT

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

A diagnosis of FSHD comes as a shock, and brings challenges and difficult adjustments for an individual, their family, and their friends. At first you may experience many mixed emotions, especially grief, anger, and fear. Giving yourself time to adjust, talking to family, friends and professionals, and reading about FSHD, may help as you deal with this diagnosis. Talking to other people living with FSHD, parents of children with FSHD, or health professionals may also be helpful. There are several FSHD Peer Support and Network groups in Canada and around the world. People belonging to these organizations frequently have a wealth of information as well as resources and knowledge through personal experience.

Children with FSHD will experience physical limitations as they grow and their body changes. Even so, like other children, they need to have as normal a life as possible. Developing self-esteem, having fun, participating in recreational activities, living a normal life with family and friends at home, at school and in the community are all very important aspects in coping with a chronic disorder.

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

You need to manage your symptoms in close liaison with your medical team. You need to keep on top of things as they change or as new symptoms develop and discuss options with your medical team, family and others who have FSHD. The overall condition needs to be kept in mind as each symptom emerges and is managed as the need arises. Most clinicians agree it is important to maintain activity and exercise for as long as possible but it is critical to balance activity with rest.

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

Neurologists are doctors who specialize in disorders affecting the nervous system and the muscles. They are often consulted for patients who may have facioscapulohumeral muscular dystrophy. Where your family doctor may not be able to offer specialized advice about FSHD, they should be able to recommend you to a neurologist in a neuromuscular clinic who is better equipped to diagnose your disorder and answer questions about possible management options. There are neuromuscular clinics and hospitals across Canada that are equipped to do the necessary diagnostic testing and to offer advice and support regarding the ongoing management of FSHD.

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

There is no “cure” for FSHD. There are currently no treatments for FSHD that can halt or reverse the symptoms and muscle weakness. Each symptom displayed reflects an underlying issue and each needs to have a treatment plan developed to best address the concern on an individual basis. Please see the sections on medication, surgery, and physical therapy for more information.

Examples of management of individual symptoms may include:

- Ankle-foot orthosis are useful early on to manage foot-drop (Tawil, 2004).
- Surgically fixing the scapula in place may help arm mobility in a focused group of individuals (Tawil, 2004).
- Certain medications may be given to help address some symptoms.
- Canes, walkers, scooters, electric wheelchairs and other ‘appliances’ can be used as needed to maintain independence for as long as possible.
- Home renovations can also help to reduce fatigue and maintain independence by making the home more accessible.

There are no drugs that will help FSHD directly. However, certain drugs have been tested and studied and show some potential beneficial effects on the symptoms of the disorder. Medications appear to be more helpful if used early. Anti-inflammatory drugs may be

prescribed to reduce inflammation associated with FSHD. The best advice is to discuss medications with you doctor or neurologist.

6-E). Can surgery help?

People living with FSHD might be recommended for certain surgical procedures to stabilize the shoulder blades. Surgery may "produce significant benefits, though these have to be balanced against postoperative immobilization, need for physiotherapy and potential complications" (Mummery CJ, 2003).

The decision to proceed with surgery should be taken with a full understanding of the nature of the operation and after discussion about the experience and success the individual surgeon has had with this operation. As FSHD progresses, there may be a loss of muscle in the upper arm that will result in difficulty in raising the arms (with or without the scapular fixation). There are a number of methods of using surgery to secure the scapula. Usually the remaining muscles over the scapula are removed. In the case of wiring of the scapula some patients have complained of discomfort due to a lack of muscle padding. Occasionally wires need repositioning and a second operation is required. A fairly long recuperation is often involved. A reduction of mobility during this time may well result in further progression of the FSHD.

Persons with Neuromuscular Disorders also need to be aware of added precautions that must be taken before and after any procedures involving the use of anesthetic.

6-F). Can physiotherapy help?

Once a diagnosis is confirmed, a person living with FSHD may be assessed in physiotherapy in order to evaluate their joint mobility, test their facility to move from one position to another, test their ability to walk, and to evaluate their capacities in activities involving gross motor skills (jumping, running, or climbing stairs). A regular or control monitoring may be suggested and depending on each person’s needs, completed with a program of activities to practice at home. These programs are aimed at strengthening or maintaining range of motion (ROM), coordination, and balance.

It is helpful if you can choose health care practitioners who are familiar with FSHD or who have experience dealing with patients with FSHD.

A physiotherapist may also prescribe a program of moderate exercise, especially swimming, under their supervision.

6-G). How can occupational therapy help?

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

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

In the work environment, it is the responsibility of adults living with FSHD to negotiate employment conditions with their superiors and co-workers. In the work environment it is often possible to negotiate employment conditions with employers. Before doing this it is a good idea to be familiar with provincial legislation requirements with respect to an employers legal "duty to accommodate" persons with disabilities. Speaking with other individuals who have been through the accommodation process or with the provincial Human Rights Commissions may also be beneficial. There are financial incentives, retraining programs and government legislation protecting the rights of individuals with disabilities. Navigating 'the system' to access the assistance needed to continue to be gainfully employed can be extremely difficult. Fatigue associated with FSHD can be very debilitating making it difficult to work while accessing the needed information. An advocate or access to an FSHD Peer Support Network can be helpful. Many work places have Employee Assistance Programs that may provide counseling and the required information. Obtaining appropriate accommodations at work can be difficult and time consuming. Serious financial mistakes and premature retirement can result without access to comprehensive information and support.

6-H). How can a nurse help?

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

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

Geneticists, doctors who specialize in medical genetics, molecular geneticists, and genetic counselors are employed in major hospitals across Canada and are available to people and their families for the purpose of diagnosis and counselling. Genetic specialists can inform the person living with FSHD and their family members about the specific inheritance processes involved, the genetic testing available, as well as family planning alternatives they may wish to consider. The information provided by a genetic counselor can be specifically tailored to an individual's family history and this knowledge might be very useful in further understanding how the disorder has affected him or her and his or her family.

6-J). How can a dietician help?

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

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

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

In some types of neuromuscular disorders the muscles that control breathing are weakened. In these cases bi-level ventilators may be used, these are machines that force air into the lungs, then reduce pressure as you breathe out to allow you to expel the carbon dioxide in your lungs.

People living with FSHD are not usually affected by respiratory weakness. Respiratory impairment is seen in fewer than 10% of patients. Weakness resulting in poor breathing function leading to retention of carbon dioxide and poor oxygenation has been reported in FSHD. As trunk muscles weaken to the degree that the body can not be continually held fully erect while sitting the upper trunk will compress against the diaphragm resulting in respiratory insufficiency. If left untreated this respiratory insufficiency may be life threatening. High night time levels of carbon dioxide are associated with several symptoms. Daily overall aching muscle, ‘foggy brain,’ sleeping deeply for long periods of time but feeling tired when awaking, difficulty waking up, lethargy, difficulty breathing and shortness of breath, and frequent headaches especially upon awakening may indicate a problem. If the above symptoms are experienced an overnight evaluation in a sleep lab with continuous recording of carbon dioxide and oxygen levels can be arranged by your doctor.

Be aware there is some variation from night to night in breathing. This may result in a false negative result. This variation may be related to the depth and length of sleep as well as body position. Often the use of a bi-level (BiPap) ventilator while sleeping is sufficient to provide adequate ventilation.

Chronic respiratory insufficiency leads to poor quality of life and may cause a more rapid progression of FSHD.

7). LIFESTYLE IMPACTS

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

It is very difficult to answer this question due to the wide range of symptoms seen in FSHD. Perhaps the most honest answer is "it depends." Lifestyle impacts will depend upon the type and severity of symptoms you experience. When you experience them (at what stage in your life) may also be a big factor.

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

8). RESEARCH

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

One of the keys to treating FSHD will be to better understand the gene(s) affected by the FSHD mutation and how they work within the cell. Currently, researchers are working to understand what the genes do within the cell and to tie genes into the FSHD mutation or into the FSHD symptoms seen. Someday, perhaps the missing repeat sections can be replenished or the genes involved in FSHD may be manipulated to reverse the symptoms seen.

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

8-B). Are there clinical trials for this disorder?

Only a few treatment trials aimed at slowing the progression of the disorders have been performed to date. These have involved corticosteroids and no significant benefit was found on any of the drugs tested (Tawil, 2004).

As of November 2005, two trials are recruiting patients in North America:

1). Study of Albuterol and Oxandrolone in Patients with Facioscapulohumeral Dystrophy (FSHD)

2). Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Registry

Conditions: Myotonic Dystrophy; Muscular Dystrophy, Facioscapulohumeral; Muscular Dystrophy

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

9). MUSCULAR DYSTROPHY CANADA SUPPORTS

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

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

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

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

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

The Muscular Dystrophy Canada equipment program provides medically-prescribed equipment. Funding assistance may be available for the purchase of new equipment. If a request is made for a device that MDC does not cover, or only partially covers, Muscular Dystrophy Canada staff may be able to suggest other sources of funding. For more information about equipment funding, call the regional office nearest you.

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

Peer support means getting help or advice from, or just plain talking to other people who have experience with FSHD. Often others who have the same disorder are good people to ask questions and to get advice from, especially in terms of how to manage the small day-to-day frustrations that come up.

Support comes in many forms and is dependent on individual needs. Some people already have strong support systems in place through family, community, and church and their needs are minimal. Other people are facing stresses such as financial difficulties or family problems, in addition to the day-to-day reality of life with a neuromuscular disorder. Life can become difficult at particular times, such as when the diagnosis is made or when symptoms seem to get suddenly worse.

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

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

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

9-E). How can Chapters help?

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

Chapter members are often people registered with MDC and their families. However, anyone who is interested in furthering the aims and objectives of Muscular Dystrophy Canada is welcome to join. In communities across Canada, dedicated Chapter members provide valuable time, energy, and experience that ultimately benefit people with neuromuscular disorders and the communities they live in. For the location of the Chapter nearest you, call your regional or community office.

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

Staff can provide referrals and contact information to neuromuscular clinics, agencies, and other community resources, to help people registered with Muscular Dystrophy Canada find solutions to problems they face in their daily lives.

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

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

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

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

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

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

9-J). How can I help?

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

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

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

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

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

10). OTHER RESOURCES

10-A). What other resources are available to people living with facioscapulohumeral muscular dystrophy?

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

An FSHD Peer Support or Contact group enables individuals and families to access a wealth of information and assistance before a need arises in order to better 'manage' their disability.

Internet sources:

Facioscapulohumeral (FSH) Society, Inc.
3 Westwood Road,
Lexington, MA
02420 USA.
Phone: (781) 860-0501, (781) 862-8422.
Fax: (781) 860-0599
www.fshsociety.org

eMedicine article: http://www.emedicine.com/neuro/topic133.htm

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

Gene Tests FSHD testing:
http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888891&fcn=c&qry=2640&res=nous&res=nointl&key=DZorXDdD3qXNz&show_flag=c

Gene Tests FSHD Review:
http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=DZorXDdD3qXNz&gry=&fcn=y&fw=r0F7&filename=/profiles/fsh/index.html

Muscular Dystrophy Association (USA): http://www.mdausa.org/disease/fshd.cfm
and http://www.mdausa.org/publications/fa-fshd.html

Neuromuscular Disease Center, Washington University, St. Louis, MO. (USA):
http://www.neuro.wustl.edu/neuromuscular/musdist/pe-eom.html#fsh

Online Mendelian Inheritance in Man (OMIM). This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information, National Institutes of Health (NIH):
Page on FSHD: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=158900

10-B). References used in this paper.

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Upadhyaya, M & Cooper, D N, Facioscapulohumeral Muscular Dystrophy (FSHD): Clinical Medicine and Molecular Cell Biology, BIOS Scientific Publishers. March 2004: 250pp. ISBN: 1859962440

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

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

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

http://www.stedmans.com/

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

http://www.onelook.com/

END.