

# Facioscapulohumeral muscular dystrophy (FSHD)

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## What are muscular dystrophies?

The muscular dystrophies are a group of muscle diseases which have three features in common: they are hereditary; they are progressive; and each causes a characteristic, selective pattern of weakness.

Please contact Muscular Dystrophy Australia for information about other types of muscular dystrophy and related neuromuscular disorders.

In this factsheet:

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## What is facioscapulohumeral muscular dystrophy (FSHD)?

The term facioscapulohumeral uses three Latin words to describe the muscles most affected by this condition. 'Facio' means face, 'scapulo' means shoulder blade and 'humeral' is Latin for the upper arm. Muscular dystrophy refers to muscle weakness and wasting.

Symptoms may appear at any time from childhood till a person is in their 50's and there is a wide range of severity of the condition. The muscle weakness generally progresses slowly but may affect muscles in other parts of the body such as the legs in the course of the disease. Often only one side of the body is affected. FSHD does not typically affect other body systems and intellectual abilities are not affected.

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FSHD is the third most common neuromuscular condition after Duchenne muscular dystrophy and myotonic dystrophy, affecting approximately 1 in 20,000 people. This is considered an underestimate though and figures of 1 in 14,000 and 1 in 7,500 have been reported recently. FSHD has been previously known as Landouzy-Dejerine muscular dystrophy and facioscapuloperoneal muscular dystrophy.

## What are the symptoms of FSHD?

Symptoms of FSHD can be classified into two groups – adult-onset, which is usually mild and infantile onset which is typically more severe with symptoms appearing in the first two years of life. The infantile onset form is rare, comprising two percent of all FSHD cases.

Symptoms in men are generally more severe and occur at a younger age than in women. In fact, some women do not realise they have the condition until they are genetically tested.

Although the classical symptoms of FSHD involve the muscles of the face, shoulder blade and upper arms, there is variability in which areas are affected. Facial muscle weakness is usually the first symptom and people may notice difficulties in puckering the mouth, as in whistling, or difficulties with the eye muscles causing for example, problems in closing the eyes completely. Facial muscle weakness may also cause difficulty in pronouncing certain words; the person may have pouting mouth or an unusual smile. Another common early sign may be noticed in the shoulder blades (scapula) with weakness preventing movements such as the throwing of balls. The muscle weakness also allows the shoulder blades to wing out.

The muscles of the lower leg may weaken. This may cause difficulties in picking the front part of the foot up during walking – 'foot drop'. Lower leg weakness may also make walking up hills or on uneven surfaces difficult.

An excessive curve in the lower back may develop, due to abdominal muscle weakness. This weakness is called a lordosis and may develop early on in the disorder. Sometimes the muscles surrounding the hip and those of the upper legs also become weak. This can cause problems running, rising from a chair or negotiating stairs.

Muscle shortenings (contractures) may develop as scar tissue replaces normal elastic tissue. This prevents normal joint movement and makes the tissues resistant to stretching. Contractures tend to occur in the ankles and may require surgery to release them.

Damage to the retina of the eye is occasionally associated with FSHD, and in infantile onset FSHD this may progress to an eye condition called 'Coat's disease' which can cause significant loss of sight if not treated. Most individuals with FSHD experience some degree of hearing difficulty and complete hearing loss may occur with severe childhood cases.

Intellectual and cognitive (understanding) difficulties are extremely rare in adults with FSHD and there are many people including those whose symptoms began in childhood, in intellectually demanding occupations. It is important that other symptoms such as deafness and facial immobility are not misdiagnosed as a learning difficulty.

Unlike many of the other muscular dystrophies, cardiac and respiratory problems are rare in FSHD. However, monitoring of cardiac and respiratory function may be recommended for some patients.

Inflammation of the muscles can occur in FSHD which can be a source of pain, as can the altered joint position resulting from muscle weakness.

## What is the prognosis?

The severity of FSHD is widely variable - even among members of the same family. Some report few difficulties throughout life, while others need a wheelchair as walking becomes too difficult or impossible. The condition tends to progress slowly, and there may be long periods where relatively little change in

symptoms occurs. It may take 30 years for serious problems to develop, if at all. Approximately 20 percent of FSH patients require a wheelchair by the age of 50 and this may only be occasionally. With rare exceptions, life expectancy is the same as for the general population.

Men tend to show more weakness and from a slightly earlier age than women. The reason for this is not yet clear. Rarely FSHD affects children under two years of age (5 to 10 percent of FSHD cases). This is known as infantile FSHD and the symptoms are usually more severe and may include hearing and sight loss.

## **How can the symptoms of FSHD be managed?**

There is currently no specific treatment for FSHD but there are many things that can be done to alleviate the symptoms.

### *Diet and exercise*

Exercise is generally considered to be beneficial in FSHD, maintaining muscle strength, flexibility and cardiovascular fitness. If possible, aerobic exercise should be performed at least three times a week for 30 minutes. Swimming is a good way to exercise muscles without straining them and many find the support of water helpful. Moderation is the key with any exercise and it is important to realise that people with FSHD may tire more quickly than others and rest breaks should be taken as needed. If aerobic exercise is not possible a moderate resistance training program (strength training or weight training) is recommended as a substitute. Any new exercise program should be discussed with a doctor or specialist physiotherapist before commencing.

A good balanced diet incorporating plenty of fresh fruit and vegetables is advised. No vitamin or dietary supplements are necessary unless a specific deficiency has been identified. Weight control is important, as excess weight will contribute to tiredness and weakness. Hence calorie intake needs to reflect energy needs, and this is best done at an early stage. Keeping the correct weight will make movement easier and place less strain on the already weakened muscles. It is recommended to consult a dietician for support if necessary.

### *Physiotherapists and other health care professionals*

Physiotherapy can benefit people with FSHD by helping them to maintain their optimum health, prevent and delay secondary complications, maximise functional ability as well as improving and maintaining quality of life. In particular, regular stretching is important to maintain muscle length and to prevent contractures. A detailed physiotherapy brochure for FSHD, commissioned by the FSH Society, can be downloaded: <http://fshsociety.org/pages/patHIExer.html>

Assistive devices, special equipment and aides, home and vehicle alterations are further ways to make life with FSHD easier. These are available through an Occupational Therapist.

Foot-drop due to muscle weakness in the lower legs makes walking difficult for some patients. An orthotist may recommend the use of an ankle-foot orthosis (AFO) to help to maintain the foot in the correct position when walking. Some people develop exaggerated curves in the lumbar spine (lower back). These can be corrected with the use of braces and supports to assist maintaining a more correct spinal posture.

Speech and hearing therapists can help with limitations imposed by hearing loss and improve speech affected by weak facial muscles.

## *Pain and Fatigue*

Many people with FSHD may experience pain, especially around the shoulders, neck, lower back and hips. Often the cause of the pain is difficult to ascertain but it is often due to muscle weakness putting strain on joints or causing poor posture. It has also been suggested that in FSHD muscle inflammation may cause pain. There are no specific treatments for the pain, although physiotherapy and pain medication may help manage it.

Fatigue is also frequently experienced by people with FSHD and other types of muscular dystrophy. Energy conservation strategies can help some patients as can aerobic exercise. It is worth noting that mood disorders such as anxiety and depression can make pain and fatigue worse. These disorders are not more common amongst people with FSHD than the general population but should be appropriately addressed when present.

## *Surgery*

Winged shoulder blades (scapula) can make normal arm movements difficult, so surgically fixing the scapula to the ribs is able to decrease winging and improve arm mobility. An orthopaedic surgeon can recommend whether this surgery may be of assistance. Patients considering surgery should consult an experienced surgeon, have reasonable upper arm strength and should weigh the potential benefits against the possible complications of the procedure.

Surgery may be required by some patients to release contractures (muscle shortenings), usually at the ankle. Surgery on the eyelids may be beneficial where there is incomplete closure of the lids. Incomplete eyelid closure can cause problems with the eye such as inflammation of the cornea (keratitis), so it is important not to ignore the early signs of waking up with dry and red eyes.

## *Hearing and sight*

Children with infantile onset FSHD are at risk of profound hearing loss that if not detected can lead to delayed language development. Consequently, hearing should be tested routinely in infants and preschool children diagnosed with FSHD. Children and adults diagnosed with FSHD at a later age do not require extra hearing tests unless there are signs of hearing difficulty.

An eye condition called 'retinal vasculopathy' is relatively common in people with FSHD but it is usually so mild that it doesn't require treatment. If severe though, Coat's syndrome develops and this can result in significant loss of sight. Children diagnosed at an early age are at the highest risk of Coat's syndrome; however it is treatable with lasers. It is recommended that all patients with FSHD be referred to an ophthalmologist. If no significant retinal vascular disease is detected in adult patients, no further follow-up is needed unless visual symptoms develop. In young children, yearly follow-up is recommended until the child is old enough to report visual symptoms.

## *Breathing and heart problems*

It is estimated that less than one percent of patients with FSHD experience breathing problems. Nevertheless, it is recommended that patients with moderate to severe FSHD have their breathing monitored routinely. If a breathing problem develops non-invasive ventilator support devices can be used.

About 5 percent of patients may have some mild changes to heart function but this usually doesn't require treatment.

## Is FSHD inherited?

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

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

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

Genetic testing gives families information on whether a genetic mutation is in the family or whether the disorder is the result of a spontaneous mutation. This is done with the support of a genetic counselling service. Genetic counselling provides information on the inheritance pattern, risks to other family members, and the 'prognosis' (likely outcome of the disorder). Family members that are found to be carriers of the condition can discuss with a genetic counsellor family planning options to reduce the risk of passing the condition on to future children. Prenatal testing for the genetic mutation is possible but couples considering this should consult with their local genetic service, preferably prior to becoming pregnant. Genetic counseling services are available across Australia. You may contact these services directly, or be referred by your doctor or other health professional. This website can be used to find a genetic counsellor (<http://www.hgsa.org.au/asgc/find-a-genetic-counsellor>).

## What causes FSHD?

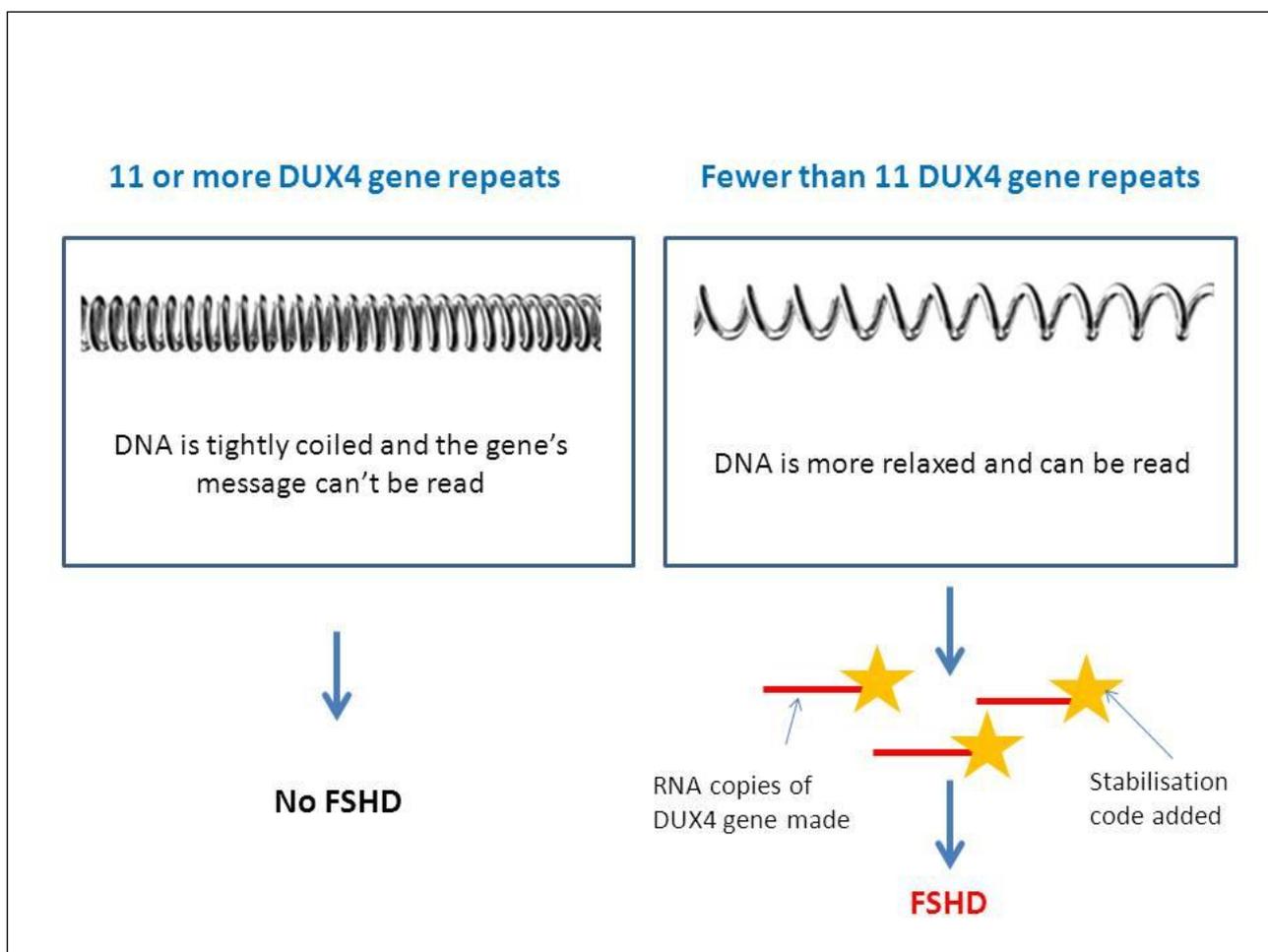
Our DNA is packaged into thread-like structures called chromosomes. We have 23 pairs of chromosomes and in 1990 it was discovered that most patients with FSHD are missing a small part of chromosome number four. This contains a region of DNA called 'D4Z4'. In a healthy person, D4Z4 contains between 11 and 150 copies of a gene called DUX4. Most patients with FSHD, however, only have between one and ten copies.

There has been a lot of confusion and controversy as to how the genetic mutation causes FSHD and it is only in the past few years that scientists have agreed on a mechanism and it still not completely understood. A simplified version of the very complicated mechanism is described below.

When the D4Z4 DNA region is composed of many DUX4 gene copies the DNA is tightly coiled and can't be read. As a result, the DUX4 gene is switched off. However, if there are only a few DUX4 copies, the DNA 'relaxes' and becomes accessible. This exposes the DNA code to be read by the cell, like opening a book. When this happens, carbon copies of the DUX4 gene are made - called RNA. These contain the instructions to build a DUX4 protein.

A further complicating factor is that an extra piece of DNA code also needs to be present next to the DUX4 gene for the symptoms of the condition to develop. Not everybody has this code in their DNA. This code stabilises the DUX4 RNA – like laminating the pages of the book so they can be read for a long time and not torn. Researchers have also found that different versions of DUX4 RNA are made that have different effects, but we won't go into this here.

Most scientists now believe that the out-of-control RNA messages cause the muscle weakness in FSHD patients, probably because of the DUX4 protein they produce. It is also possible that DUX4 protein and/or RNA could then disrupt the control of other genes, which ultimately causes the symptoms of the condition.



## What about FSHD2?

Less than 5% of FSHD patients have a different genetic mutation located on chromosome number 18. These patients are given a diagnosis of FSHD2, but the symptoms are very similar to the more common FSHD1. In 2012 researchers found an explanation for this similarity which centres around the fact that most FSHD2 patients have changes to a gene on chromosome 18 called 'SMCHD1'. This gene normally ensures that the DNA of the D4Z4 region on chromosome 4 (containing the DUX4 gene) is closed, and thus not read. However, the mutation in SMCHD1 allows the D4Z4 region to open and be read. So the end result in FSHD1 and FSHD2 is the same – the production of harmful DUX4 RNA and protein.

## What research is being done?

### *Gene silencing*

Now that researchers know that DUX4 is causing the symptoms of FSHD, the race is on to find a way to block its harmful effects. New potential therapies are aiming to switch off the DUX4 gene so that the RNA copy of it is not made. This is called 'RNA interference' or 'gene silencing'. It involves introducing into the cell tiny pieces of genetic material called 'micro RNA' that are designed to specifically switch off a particular gene. Several research groups around the world are testing this approach using a virus to deliver 'micro-RNA' into the muscles of mice and have reported promising results.

However, there are several challenges still to be overcome. The first is that there isn't a good mouse model of FSHD, so it is difficult to reliably test potential gene silencing treatments. Secondly, the mechanism causing FSHD is so complex that it isn't fully understood yet, which makes it difficult to design therapies and assess their success. In particular, it has been proposed that in addition to muscle fibres, muscle stem cells may be involved in the FSHD disease process, so it will be important to determine if treating the muscle stem cells is necessary and find a way to do this. Also it is thought that the production of certain versions of DUX4 is beneficial for muscle so this needs more investigation so that scientists can make sure that the gene silencing is specific only for the toxic DUX4. Finally gene silencing is still new technology and the first clinical trials in humans for other conditions have only just started to produce results. Although these results appear promising so far, caution will have to be exercised to make sure it is safe.

### *Boosting muscle growth*

An approach which could potentially be applicable to a wide range of muscular dystrophies involves a protein naturally produced in the body called 'myostatin'. It is an inhibitor of muscle growth which keeps the size and strength of muscle within the normal range. Researchers have shown in animals that blocking the activity of myostatin causes the muscles to increase in strength and size. This approach is an attractive avenue for developing a therapy because it may be a useful way to 'bulk up' muscles in people with muscle disease, helping to increase their muscle strength. Several different approaches to block myostatin are being researched with some preliminary clinical trials started, but no success has been reported yet.

### *Reducing inflammation*

Research that aims to reduce inflammation in the muscles and improve muscle regeneration, such as the research MDA funds, may also lead to the discovery of a treatment to help reduce the severity of muscle weakness in FSHD. Read more about this research <http://www.nmdrc.org/>.

### *Steroid drugs*

Steroids such as prednisolone are currently the only medications proven to slow down the progression of muscle weakness in Duchenne muscular dystrophy. However, they are not usually prescribed to people with FSHD because it is thought that the benefit will not outweigh the risk of detrimental side effects which can be very serious, including weight gain, mood changes, stunted growth, fragile bones, cataracts, high blood pressure, diabetes and increased chance of infections.

Researchers in the USA have discovered a drug that is similar to prednisolone which does not seem to cause the worrying side effects when tested in mice. Consequently it might be useful to treat more mild forms of muscular dystrophy like FSHD and could replace the steroids currently used to treat Duchenne

MD. In studies in mice the drug – called VBP15 – worked better than prednisolone without the harsh side effects. Clinical trials of VBP15 are being planned with an expected start date in 2014.

You can read more about this steroid research on the MDA website (<http://mda.org.au/research/steroidalt.asp>).

## Further information

- Clinical trials – your questions answered ([www.mda.org.au/trials/index](http://www.mda.org.au/trials/index)).
- Physiotherapy guidelines for FSHD ([www.fshsociety.org/assets/pdf/PhysicalTherapyAndFSHD.pdf](http://www.fshsociety.org/assets/pdf/PhysicalTherapyAndFSHD.pdf)).
- A report on recommended standards of care for people with FSHD is available for download after paying a fee (written in technical language) (<http://www.nmd-journal.com/article/S0960-8966%2810%2900188-4/abstract>).
- OMIM is a continuously updated catalogue of human genes and genetic disorders and traits. It is written in technical language (<http://omim.org/entry/158900>)
- You can get regular updates by becoming a friend of the MDA Facebook page ([www.facebook.com/MDA.MuscularDystrophyAustralia](http://www.facebook.com/MDA.MuscularDystrophyAustralia)) or follow our Scientific Communications Officer on Twitter (@kelvidge).

For further information on any of the areas discussed above, please contact MDA on (03) 9320 9555, email [info@mda.org.au](mailto:info@mda.org.au)

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