SUPPORT | RESEARCH | AWARENESS

Understanding Fabry disease

Information for parents and families

Society for Mucopolysaccharide Diseases
mpssociety.org.uk

In this booklet

This booklet is produced by the **Society for Mucopolysaccharide Diseases (MPS Society)** and is designed to help those affected by Fabry disease – both patients and their families – understand its causes and effects. While there is currently no cure for individuals affected by Fabry disease, this booklet explores how best to understand and manage the disease. It draws on the experiences of patients, carers, families and medical professionals as well as medical literature.

What is Fabry disease?

In the course of normal life, there is a continuous recycling process which consists of building new molecules and breaking down old ones ready for disposal. This activity takes place in a special part of the body's cells called the lysosome, and the process requires a series of biochemical tools called enzymes. Disruption to this process is seen in people with Fabry disease.

What causes Fabry disease?

Fabry disease is caused by a genetic fault in a specific enzyme.

This enzyme is called **alpha-galactosidase A**

Children and adults with Fabry disease are missing, or are deficient in, an enzyme which is essential in breaking down certain waste products in the lysosomes of many different types of cell. When these waste products are not completely broken down, they build up within the cells of the body, causing progressive damage. Babies may show little sign of the disease but as more and more cells become damaged by an accumulation of these waste products, symptoms start to appear.

The main waste product is **ceramide rihexosidase (CTH),** also known as **globotriaosylceramide,** or **Gb3** and **Gl3**

If left untreated, vital organs such as the kidneys, heart and brain eventually start to deteriorate, and severe or life-threatening complications can arise.

Fabry disease is also known as **Anderson-Fabry disease**, and is named after the dermatologist Johannes Fabry and surgeon William Anderson, who independently identified the faulty gene in 1898. It is one of a number of inherited disorders known as lysosomal storage diseases.

How common is Fabry disease?

Fabry is a rare condition, although few specific statistics are available. The disease is seen across all ethnic groups but population-specific incidence rates are unknown. From statistics that are available, it has been estimated that Fabry disease affects between 1 in 40,000 and 1 in 117,000 males in Caucasian populations.

Is Fabry disease inherited?

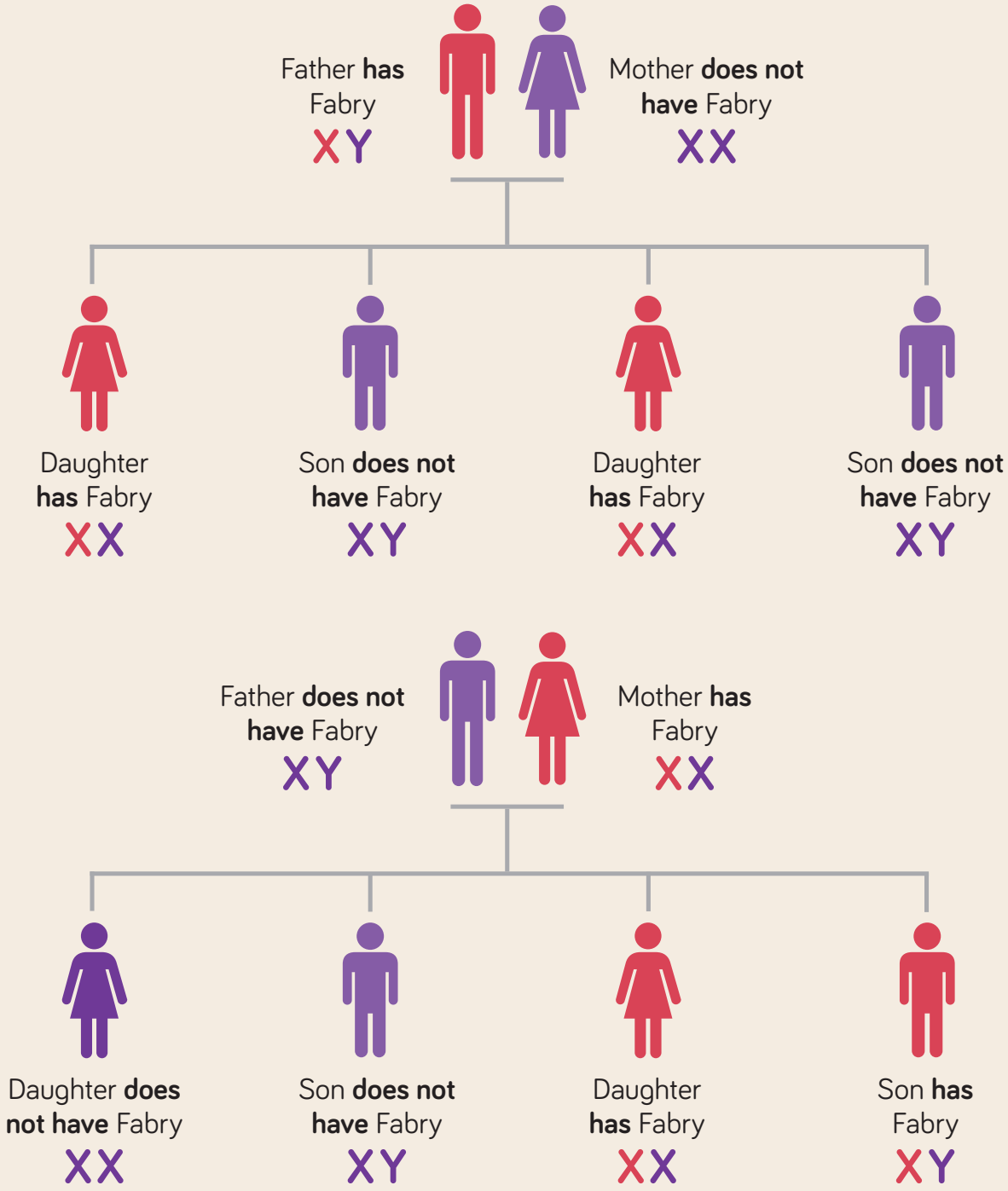
Genes are the unique set of instructions inside our bodies that make each of us who we are. We have thousands of genes and they are the blueprint for our growth and development, as well as controlling how our bodies function. If a particular gene is faulty, or altered, then it will not work efficiently.

Genes are carried on structures called chromosomes. It is usual to have 23 pairs of chromosomes that are numbered in pairs, from pair number 1 to pair number 22, plus one pair of sex chromosomes: XX for a female and XY for a male.
A child will inherit one set of chromosomes from the mother in the egg, and one set from the father in the sperm. One X chromosome is inherited from the mother and one Y or one X chromosome is inherited from the father.

The inheritance pattern is called **X-linked semi-dominant inheritance**

The gene responsible for Fabry disease is carried on the X chromosome, which means both males and females can be affected.

Affected males do not pass the Fabry disease gene to any of their sons as sons can only receive their father's Y chromosome. Every time a female with the Fabry gene has a child she will either pass her affected X chromosome or her non-affected X chromosome to her child meaning there is a 50% chance her son or daughter will have Fabry. In simple terms a father will always pass the Fabry gene to his daughters but never to his sons. A mother will pass the Fabry gene to an average of half her children, boys or girls, but it is a random process so could be all or none or some of her children.


Father **has** Fabry
XY
Mother **does not have** Fabry
XX
Daughter **has** Fabry
XX
Son **does not have** Fabry
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Mother **has** Fabry
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Daughter **does not have** Fabry
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Daughter **has** Fabry
XX
Son **has** Fabry
XY

How is Fabry disease diagnosed?

Fabry disease encompasses a wide spectrum of clinical symptoms, not all of which will appear in all individuals. This, as well as its rarity, can often delay diagnosis. Many individuals may experience some or all of the symptoms that are outlined in this booklet before receiving an actual diagnosis of Fabry.

How is Fabry disease tested?

There is a genetic test that can be used to confirm whether or not a patient has Fabry disease. The doctor will check the level of the enzyme (alpha-galactosidase A) in urine, blood or both, as this tends to be lower in Fabry sufferers.

If the doctor already knows whether the mother or father carry the faulty gene then this can be taken into account. However, with modern diagnostics, it no longer makes any difference to timing whether or not the patient has a diagnosed family member.

There is a genetic test that can be used to confirm whether or not a patient has Fabry disease

What is the value of genetic screening?

Fabry disease is a genetically inherited condition. Therefore if you, or someone in your family, has been diagnosed with Fabry, it is possible that other members of your family may also be at risk of having inherited the condition. You may want to consider discussing the situation with your relatives in order to help your family understand more about the condition, and possibly take further action to see if they may also be affected.

It is vitally important that other family members are encouraged to consider undergoing testing themselves once a diagnosis of Fabry disease has been received within the family. This will ensure that informed decisions can be made over treatment options.

Anyone who suspects that this may be the case should contact their GP straight away. The doctor may find this booklet helpful.

Specialist centres

Alternatively, there are a number of specialist centres in the UK where you can go to be tested and to see a specialist in Fabry disease. Visit **www.mpssociety.org.uk/our-friends** for a comprehensive list of specialist centres.

You should be given the opportunity to see a genetic counsellor. The counsellor will be able to provide non-directive advice on the risks, reproductive choices available and to suggest whether the wider family should be informed.

Is there a test for Fabry disease in pregnancy?

Amniocentesis involves testing a small sample of amniotic fluid

Chorionic villus sampling involves testing a small sample of cells from where the placenta attaches to the uterus

In utero means that the tests are done while the baby is still in the womb

Free foetal DNA is DNA from the foetus that circulates in the mother's blood

In vitro literally means 'in the glass', as the testing is done in a flat glass dish called a petri dish

If you, or your partner, suspect you may have Fabry disease and are planning a family, or are already pregnant, it is important to contact your doctor as soon as possible to discuss the possibility of genetic screening. Both amniocentesis and chorionic villus sampling can be used to diagnose Fabry *in utero* but you should discuss the options in detail with your doctor or genetic counsellor.

In situations where it is the father who is affected, you may choose to have the sex of the foetus determined rather than having an invasive test, as we know that a male foetus will not be affected. This can be done by the female partner having a blood test in pregnancy to look at free foetal DNA and can be done from seven weeks of pregnancy. This test will confirm the sex of the foetus but will not look directly at the Fabry gene.

You can also choose to determine the sex of a foetus in cases where it is the female partner who is affected. However, it is important to note that females can also develop serious symptoms of the condition, even when other females in the family have been minimally affected.

It is important to discuss this option with your metabolic consultant or genetic counsellor.

If the genetic mutations within your family are known, it might also be possible to have pre-implantation genetic diagnosis (PGD). This is an assisted fertility treatment that involves testing embryos *in vitro* before they are implanted, using IVF techniques. This is a complex process and requires referral from your regional genetics service.

What are the symptoms and how are they managed?

Symptoms are known as **clinical presentations**

Fabry disease causes a wide variety of signs and symptoms and is different in everyone. Symptoms can vary from day to day, with some people getting a wide range of symptoms and others only a few. Symptoms can also present at any time, although the following are some of the most commonly reported. There is more information on each one in the following pages.

Early signs

- Pain in the hands and feet, from a sharp, burning pain to pins and needles
- Over time, pain may be experienced in other parts of the body, which can increase depending on the weather; some are affected more by heat and others by cold
- Exercise can also increase pain
- Inability to sweat, causing overheating
- Small, raised, dark red spots on the body
- Changes to the cornea of the eye which do not affect the vision

These small raised, dark spots are called **angiokeratoma**

Minor strokes are known as **transient ischaemic attacks** or **TIAs**

As time progresses, additional symptoms may appear

- Fatigue (extreme tiredness)
- Stomach pain, possibly diarrhoea, constipation or a combination of both
- Nausea and vomiting, which may increase after eating
- Headaches
- Ringing in the ears
- Dizziness
- Intolerance to heat or cold
- Excessive sweating
- Chest pain or palpitations
- Low mood
- Depression
- Poor memory and concentration

Some more serious complications can develop, especially if the condition is not managed or treated

- Kidney disease
- Progressive heart disease
- Stroke and minor strokes

Pain

Pain is one of the most distinctive symptoms of Fabry disease and is often the symptom that sufferers first notice. It may even have gone undiagnosed in childhood. Fabry pain can be broadly divided into two distinct types: constant background pain and short-term severe pain.

Both types of pain are usually a result of certain trigger factors, such as changes in temperature, episodes of stress, physical activity or onset of illness, such as a cold.

Chronic pain

Constant, chronic pain takes the form of a burning, tingling sensation (normally in the hands and feet), which results in constant discomfort. This is known as acroparasthesia.

Severe pain

Short-term, severe pain is often known as a Fabry crisis and may last for anything from a few minutes to several days. It is often described as an intense burning which starts at the extremities – the palms and the soles of the feet – and spreads throughout the rest of the body.

Pain management

Speak to your specialist centre about the pain you experience. They may advise pain medication or refer you to a pain clinic, where you will be given specific advice on how to manage your pain.

There are other things you can try.

- Distract yourself by doing something you enjoy
- Try to be with friends and family rather than on your own
- Watch a film, try art therapy, puzzles, yoga, music, or other hobbies or activities
- Meet other people (you can use the MPS Society's befriending service to speak to other people with Fabry disease)

Identifying pain triggers can help you manage your pain

However you experience Fabry pain, it can be debilitating and affect your everyday activities. However, if you can try to work out what triggers your pain episodes – like the common triggers listed below – you may be able to manage them more effectively.

Extreme temperatures – either hot or cold

- Wear several thin layers of clothing so that you can easily take layers on and off
- If you are too hot, drink plenty of fluids, especially after exercise
- In cold weather, try not to let yourself get cold, especially your hands and feet
- Avoid holding hot or cold drinks or food containers

Hormone changes

- Be aware of hormone changes, particularly during menstruation, pregnancy and menopause; speak to your specialist doctor if you need help managing this

Alcohol

- Keep consumption to a minimum

Exercise

- Keep to gentle exercise, which is beneficial, and avoid intense physical exertion

Fatigue

- Don't set yourself too punishing a schedule, and allow rest breaks when you can

Stress

- As much as possible, try to avoid highly emotional situations or circumstances that you find stressful
- If you do find yourself become stressed, try to take yourself away from the trigger into a more relaxing environment.

Health

- Look after your general health and ensure that your vaccinations are up to date, such as your flu jabs

Kidney problems

Due to the accumulation of waste products in kidney cells and in the wall of blood vessels supplying the kidney, kidney function may become impaired over time. Kidney disease affects both males and females but it is more common in males. People affected by Fabry disease may have symptoms of reduced kidney function early in life, even during childhood.

Symptoms of kidney problems

You may experience some of the following symptoms:

- High blood pressure
- Muscle cramps
- Weight loss
- Dry, itchy skin
- Poor concentration
- Swollen hands and feet
- Blood or protein in your urine
- Increased need to empty your bladder
- Poor appetite

Testing

Kidney disease can be detected by raised protein levels in the urine, therefore regular screening will be done to monitor kidney function. Other tests sometimes used include ultrasound and biopsy.

A biopsy is when the doctor takes a sample of cells for testing

The heart

Heart problems commonly affect both men and women with Fabry disease. They are due to the build up of waste products in the vessels and tissues of the heart.

Heart problems are known as **cardiac manifestations**

There are a number of ways that Fabry disease can affect the heart. Initial symptoms may be an irregular or fast heartbeat and thickening of the heart wall, but over time, this can develop into more serious complications leading to an enlarged heart, chest pain, increased risk of heart attack and heart failure.

Symptoms of heart problems

- Feeling out of breath
- More tired than usual
- Chest pain or discomfort
- Feeling faint

Testing

Individuals with Fabry disease will be regularly monitored for cardiac changes and may have to undergo regular tests such as an electrocardiogram.

Heart problem terminology:
arrhythmia = irregular heartbeat
palpitations = fast heartbeat
hypertrophy = thickening of the heart wall
angina = chest pain

The digestive system

Individuals with Fabry disease may experience problems with their digestive system due to the accumulation of waste products within the cells of the intestine or the blood vessels and nerves supplying the intestine. Symptoms experienced have sometimes been mistaken for irritable bowel syndrome (IBS).

Symptoms of digestive problems

- Feeling sick, bloated or vomiting after a meal
- Stomach cramps
- Constipation, diarrhoea or both
- Weight loss

You can manage these symptoms in various ways.

- Eating smaller meals at more regular intervals
- Sitting up straight while eating and taking small mouthfuls
- Avoiding spicy, high-fat food and acidic food
- Avoiding excesses of alcohol and caffeine
- Taking regular, gentle exercise
- Drinking plenty of water
- Try gradually increasing your fibre intake if you are constipated or eating less if you have diarrhoea

Make one change at a time so you can see what is helping

The brain

There are a number of possible neurological symptoms indicative of Fabry disease, which are caused by incorrect circulation of protective fluid around the brain and spinal cord.

Stroke

Individuals with Fabry disease may develop a stroke. This may be a minor stroke, or TIA, followed by a full recovery, but more severe strokes can occur.

Nervous system

Individuals with Fabry disease may suffer from headaches, vertigo and a ringing sound in the ears.

Ringing in the ears is known as **tinnitus**

The eyes

Changes to the eyes are nearly always present in individuals with Fabry disease. One common symptom is corneal opacity, which occurs when the cornea becomes scarred and stops light from passing through to the retina. The cornea may appear white or clouded. Although it does not generally impair or affect sight, it can be detected by eyecare professionals and provide an early sign that should be investigated before a diagnosis is made.

Changes to the eyes are known as **opthalmological changes**

Individuals with Fabry disease also experience reduced sweating, while some individuals do not sweat at all

The skin

Small, dark red spots frequently appear on the abdomen, groin, buttocks and thighs of individuals with Fabry disease. They often appear during late childhood and could be one of the first signs of Fabry disease.

Individuals with Fabry disease also experience reduced sweating, while some individuals do not sweat at all. As a result, sufferers may experience fevers and find it difficult to exercise or cope with hot temperatures. Some patients may experience increased sweating, which is more common in females.

The spots are called **angiokeratoma**

Terminology associated with sweating:
hypohidrosis = reduced sweating
anhidrosis = no sweating
hyperhidrosis = increased sweating


Welcome to
The

Naomi talks about living with Fabry disease

My name is Naomi, I am 20 years old and I have Fabry disease, which I was diagnosed with when I was 10. Having a chronic health condition is time consuming. There's hospital appointments, with the travel that entails, and the days written off due to poor health.

When I was a child I was treated with an enzyme replacement infusion every two weeks. With the help of a nurse and my mum I was able to undergo treatment in the comfort of my own home. Recently I have been lucky enough to be able to go onto an oral chaperone therapy, which I take every other day.

I enjoy having the opportunity to tell my story and have progressed towards my goals as a writer. Fabry hasn't smothered my sporty side, as I have embraced the fun that is wheelchair tennis. Despite being an irregular school attender, I have still managed to do well in my academic studies. I'm hoping to start as an undergraduate next autumn.

Fabry might cause things to be more awkward, but there's no need to let it consume a life worth living.

Fabry might cause things to be more awkward, but there's no need to let it consume a life worth living.

What kind of treatments and therapies are available?

Although there is currently no cure, many treatments are available for those affected by Fabry disease, depending on the symptoms they experience. Because symptoms are highly individual, treatment will vary from person to person. And because changes and advances in treatment are being made all the time, new treatments are constantly becoming available. We have therefore created a separate detailed factsheet, which covers the most up-to-date therapies, what they involve and how they work.

The most common current treatment is enzyme replacement therapy (ERT). This uses a genetically engineered form of the missing or malfunctioning enzyme administered about every two weeks by intravenous infusion.

Some mutations of the disease respond to chaperone treatment, the aim of which is to find medicines that will stabilise abnormal enzymes and allow them to function well enough to prevent lysosomal storage in the cells.

If you would like more information on treatment options and clinical trials, then please contact your Fabry specialist or the MPS Society.

Because symptoms are highly individual, treatment will vary from person to person

Where can I get more information and support?

The Society for Mucopolysaccharide Diseases (MPS Society) is the only registered UK charity providing professional support to individuals and families affected by MPS and related lysosomal storage diseases throughout the UK.

The MPS Society was established in 1982 by Chief Executive, Christine Lavery MBE, after her son, Simon, passed away following a diagnosis of MPSII, Hunter Disease. Since then, the MPS Society has developed into the leading provider of information and support for MPS and related lysosomal storage diseases, with a mission to transform lives through specialist knowledge, support and advocacy and research.

Society for Mucopolysaccharide Diseases

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