



# FABRY DISEASE

## What is Fabry Disease

Fabry (pronounced fabree) disease (called Fabry-Anderson disease in the UK) is a genetic disorder. In this disorder, an enzyme called alpha-galactosidase A (a-gal for short) does not work in the body. Enzymes trigger chemical reactions in the body. In the case of a-gal, this enzyme normally breaks down large fatty molecules from cell membranes into smaller parts in lysosomes. Lysosomes are small bodies inside cells that normally recycle chemical parts. Without this enzyme action, this fatty material called globotriaosylceramide (or Gb3 for short) builds up in lysosomes, makes them much larger and prevents their normal function. This ultimately damages the cell; it may die and be replaced by scar tissue.

### What is the role of Gb3 in Fabry Disease?

Gb3 starts to build up in cells before the affected patient is born. Over time, with more and more build up, it causes damage in many tissues and organs in the body, including blood vessels. Eventually, major organs like the heart and kidneys may fail with life-threatening problems.

Signs and symptoms usually appear in childhood or early adolescence.

### How does Fabry Disease affect kidneys?

Fabry kidney disease starts in childhood with albumin, a blood protein, leaking out into the urine due to injury to the filtering units in the kidneys. Over years, this may worsen with increasing protein in the urine and a gradual decline in kidney function with high blood pressure. This can eventually progress to kidney failure in adulthood. The risk of this is very high in men but is rare in women. People with reduced kidney function can take a number of steps to protect their kidney health like maintaining a healthy lifestyle, controlling their high blood pressure and limiting urine protein. Attention to a low salt diet and blood pressure-lowering medications is critical to these goals. Your healthcare team can help you manage your diet and medications. Some patients will need a kidney biopsy. During a kidney biopsy, a tiny piece of kidney tissue is removed under local anesthetic with a skinny needle. A kidney biopsy is used to confirm the diagnosis of Fabry kidney disease and to help decide treatment. Kidney failure can be treated with dialysis or a kidney transplant. Fortunately, Fabry disease does not recur in transplanted kidneys.

## What are the symptoms of Fabry Disease?

The symptoms of Fabry disease are due to Gb3 build-up with damage to a variety of body tissues. It is important to remember that the symptoms of Fabry disease vary, and not everyone will experience the same symptoms.

### Fatigue

This is the most common symptom of Fabry disease. It is non-specific as it can be found in many chronic illnesses. It may be due to a decrease in how the cell makes energy in Fabry disease.

### Pain

Pain is the next most common symptom of Fabry disease. It is due to damage to the sensory nerves by Gb3 build up in Fabry disease. Patients describe a burning, tingling, prickly pain that affects the hands and feet. This often starts during childhood when it is commonly triggered by a fever from a viral illness. This pain can also be brought on by changes in weather, exposure to hot or cold temperatures, stress, or fatigue. Some people have this type of pain every day, while others have it off and on. Avoiding situations that trigger the nerve pain will help. Many patients will benefit from use of medications that specifically target this type of nerve pain. Some patients will experience Fabry pain crises with severe pain that can be all over; they may require admission to hospital for several days for intravenous pain medication.

### Impaired sweating

Many people with Fabry disease either sweat very little or not at all. This can cause fever, overheating with exercise, and sensitivity to hot weather. In particular, this may limit children from playing sports where overheating may lead to nerve pain in the hands and feet.

### Skin Rash

Small, reddish-purplish skin spots called angiokeratomas are the most visible sign of Fabry disease. They are often found in clusters in the area from the bellybutton to the knees. They usually appear during childhood and range in size from pinpoint to several millimeters. They typically increase in number as patients get older. Some patients will develop these marks over the finger pads, lips and back of the throat. While some patients have no angiokeratomas, most Fabry patients will have at least a few of these. Some of the men with this condition will have thousands of these spots. The spots may rarely bleed and usually do not cause any pain. Note that angiokeratomas can occur in other conditions other than Fabry disease and so they are not necessarily a sign that a patient has Fabry disease.

### Corneal whorls

A distinct whorl-like pattern on the outer covering or cornea of the eye is seen in most people with Fabry disease starting in early childhood. This pattern is due to build up of Gb3 in the eye tissue. It is seen with a common eye test called a slit-lamp exam carried out by eye doctors or optometrists. Sometimes it is the first sign of Fabry disease. The corneal whorls do not affect vision. Note that the corneal whorls are not specific for Fabry disease as they can be caused by some medications.

## **Gastrointestinal problems**

Many people with Fabry disease get intermittent abdominal pain, nausea, diarrhea and constipation. These symptoms can start in childhood and may be triggered by certain foods. This can disrupt daily life with missed school or work. Medications may help with these symptoms.

## **Hearing problems**

Tinnitus, or ringing in the ears, dizziness and hearing loss are common in Fabry disease. Sudden deafness can be permanent in some patients. Hearing aids may be helpful.

## **Heart Disease**

Thickening of the heart muscle commonly develops in Fabry disease in men in their 40s and women in their 50s with build of Gb3 in heart muscle cells. Patients may have shortness of breath or chest pain, and a slow or irregular heartbeat known as arrhythmia. Patients can develop severe heart valve damage requiring valve surgery. A pacemaker and/or implantable defibrillator are helpful for severe arrhythmias. Heart failure can occur later in life. In some this can be treated with a heart transplant.

## **Cerebrovascular/central nervous system problems**

Dizziness or vertigo, headache, and stroke are all symptoms of Fabry disease affecting blood vessels in the brain. Stroke occurring under age 55 years of age is typical of Fabry disease and is due to abnormal blood vessels and clots in this condition. Prevention is aimed at decreasing risk factors for stroke such as high blood cholesterol, smoking and high blood pressure. Blood thinners may be prescribed to lessen the risk of stroke.

## **How is Fabry disease inherited?**

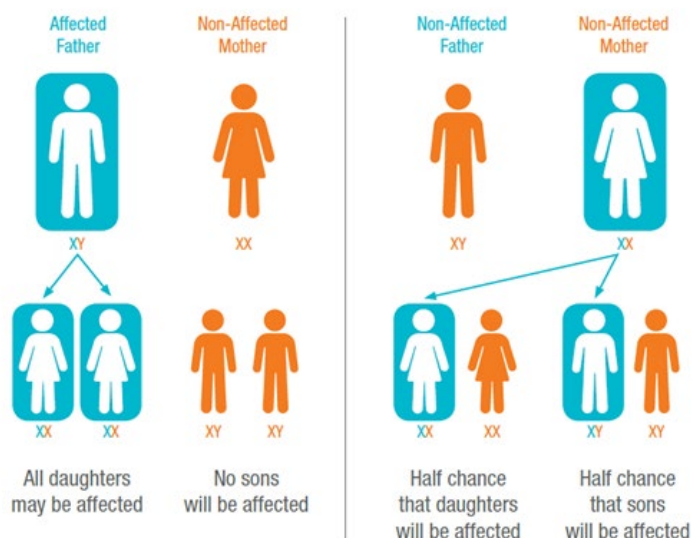
To understand how Fabry disease is inherited, it helps to know something about genetics. All humans have genetic information in large molecules called DNA that is stored in 23 separate chromosome in each cell. Chromosomes are large twisted chains of DNA organized into genes, each of which has instruction for the making of a different protein. All males have an X chromosome and a Y chromosome in every cell in their body. Women have two X chromosomes in every cell. We each inherit an X chromosome from our mother and an X or Y chromosome from our father. See figure. This determines whether we are male (XY) or female (XX).

The X chromosome contains the GLA gene for the a-gal enzyme. This enzyme does not work in Fabry disease due to a change or mutation in the GLA gene instructions about how to make the a-gal enzyme. As a result of the gene mutation, the enzyme is not made correctly in the cell and does not work.

If a man's X chromosome contains an altered GLA gene, he will pass it on to all of his daughters and none of his sons. If one of a woman's X chromosomes contains the altered GLA gene, she will have a 50% chance with each child of passing the abnormal gene on to either her sons or daughters. Any children who inherit the altered GLA gene will have Fabry disease.

Because females have two X chromosomes, they have two copies of the GLA gene. In each female cell, only one copy of the X chromosome is active. As a result, in females, some cells will be healthy with a normal copy of the GLA gene active. Other cells will be affected with the altered copy of the GLA gene active. Females with Fabry disease are then a mixture of healthy and affected cells, a condition known as a mosaic. This is why Fabry disease affects females differently than males, with females having less severe disease.

**Figure: X-linked inheritance of Fabry disease**



## How is Fabry disease diagnosed?

Signs and symptoms of Fabry disease can begin to appear in childhood. These early symptoms may be misunderstood or even dismissed by parents, teachers, and other caregivers. Because the symptoms vary among people, the disease may be difficult for doctors to recognize. Many people with Fabry disease are not diagnosed until adulthood when more advanced symptoms start to appear.

Fabry disease is progressive, which means it gets worse over time. If the signs and symptoms are recognized early, then treatment can be started at a younger age with better results.

In males, the presence of low blood a-gal activity is used to diagnose Fabry disease. A blood test will confirm the mutation in the GLA gene.

Females can have normal or low-normal levels of blood a-gal activity and still have Fabry disease. The diagnosis of Fabry disease can only be made by a blood test to find a mutation in the GLA gene.

Fabry disease is inherited, so if one family member has it, on average a further 7 other family members will be found to have this condition as well. A medical geneticist who is a physician specialist trained in genetic diseases should arrange testing for family members; a genetic counselor can help you understand this condition further.

## Treatment

Many patients with Fabry disease have mild disease that does not need treatment. For those that do need therapy, a variety of treatment options are available. Specific treatment with intravenous enzyme replacement therapy is the most common treatment. Some patients will benefit from oral treatment with a chaperone drug that increases the a-gal activity. Some of the latest treatments, such

as gene therapy, are available through research studies. There are specialized Fabry disease clinics in most major medical centres across the country. Talk to your doctor to learn more.

For further information, or if you wish to help us in our efforts, please contact The Kidney Foundation of Canada office in your area. You can also visit our website at [www.kidney.ca](http://www.kidney.ca).

With acknowledgement to Dr. Michael West, Division of Nephrology, Department of Medicine, Dalhousie University, Halifax NS for his assistance in compiling and reviewing this information, and to the National Programs and Policy Committee of the Kidney Foundation for their input.

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