Disorder name: Fabry disease

- What is Fabry disease?
- What causes Fabry disease?
- What are the symptoms of Fabry disease?
- What is the treatment for Fabry disease?
- What happens when Fabry disease is treated?
- What causes the alpha-galactosidase A enzyme to be absent or not working correctly?
- How is Fabry disease inherited?
- Is genetic testing available?
- What other testing is available?
- Can you test for Fabry disease during pregnancy?
- Can other members of the family have Fabry disease or be carriers?
- Can other family members be tested?
- How many people have Fabry disease?
- Does Fabry disease happen more often in a certain ethnic group?
- Does Fabry disease go by any other names?
- Where can I find more information?

This fact sheet contains general information about Fabry disease. Every child is different and some of this information may not apply to your child specifically. Certain treatments may be recommended for some children but not others. If you have specific questions about Fabry disease and available treatments, you should contact your doctor.

What is Fabry disease?

Fabry disease is an inherited disorder that can affect many parts of the body, especially the heart and kidneys. People with Fabry disease have problems breaking down a substance in the body called globotriaosylceramide (GL-3). Fabry disease belongs to a group of disorders known as lysosomal storage disorders.
Lysosomal Storage Disorders

Lysosomal storage disorders (LSDs) are a group of inherited disorders. They are caused by enzymes that do not work properly.

Lysosomes are like recycling centers for cells. They are small sacs filled with enzymes. These enzymes help break down large molecules into smaller molecules that the body can re-use. People with LSDs are missing enzymes or have non-working enzymes. As a result, these people have problems breaking down certain large molecules into usable forms. This leads to a buildup of these molecules, which causes a variety of problems.

The symptoms and treatment vary between LSDs. They can also vary from person to person with the same LSD.

What causes Fabry disease?

Fabry disease occurs when an enzyme called alpha-galactosidase A (alpha-GAL) is missing or not working properly. Normally, alpha-GAL helps cells break down GL-3 into smaller particles that can enter the bloodstream and eventually be discarded or reused. When alpha-GAL doesn’t function properly, GL-3 accumulates in cell lysosomes, eventually causing cell damage.

![Diagram of Fabry Disease](image)
What are the symptoms of Fabry disease?

Fabry disease can cause problems in many systems of the body. The disease is commonly characterized by:

- Episodes of pain in the hands and feet (acroparesthesias)
- Clusters of small, dark red spots on the skin (angiokeratomas)
- Decreased ability to sweat (hypohidrosis)
- Cloudiness of the front part of the eye (corneal opacity)
- Hearing loss

Over time, people with Fabry disease can develop more severe complications such as:

- Kidney damage and kidney failure
- Hypertension
- Heart disease like cardiomyopathy
- Heart attack
- Cerebrovascular disease (disease from abnormal blood flow to the brain) like stroke

What is the treatment for Fabry disease?

People with Fabry disease should be treated by a team of specialists who are familiar with the disorder. Which specialists are needed will depend on the person’s symptoms. All people with Fabry disease should be seen by a biochemical genetics doctor (or metabolic genetics specialist). Their team may also include a cardiologist (heart doctor), audiologist (hearing doctor), neurologist (brain doctor), nephrologist (kidney doctor), and genetic counselor. This team can support the family and help manage the symptoms of Fabry disease. Treatment for Fabry disease has two main goals: 1) to alleviate symptoms and 2) to prevent future complications.

1. **Pain Management**
   Medications including diphenylhydantoin, carbamazepine, or gabapentin may be used to treat pain in the hands and feet.

2. **Enzyme Replacement Therapy (ERT)**
   Fabry disease is caused by not having enough of an enzyme called alpha-GAL. Enzyme replacement therapy gives people a replacement form of that enzyme. This is a long term treatment option, but it is not considered a cure. Some experts have recommended that ERT be started as early as possible in all males with Fabry disease and in female carriers that are significantly affected. ERT may reduce the long term risk for cardiac, cerebrovascular, and kidney complications.

3. **Kidney Support**
   Kidney insufficiency and hypertension may be treated with ACE inhibitors. If kidney damage becomes extensive, kidney transplantation may be necessary.
4. **Psychosocial Support**
   Individual and family counseling, disease education, and participation in patient organizations, advocacy groups, and support groups are important for managing the emotional and psychological impact of Fabry disease.

**What happens when Fabry disease is treated?**

While treatment can help alleviate symptoms and avoid some complications, Fabry disease tends to be progressive, meaning symptoms and problems get worse over time. The most common cause of death in individuals with Fabry disease is cardiovascular disease (heart and blood vessel disease). Individuals with Fabry disease should have their kidney function, cardiac (heart) function and hearing monitored yearly, and consider having brain imaging (MRI) every 2 years.

**What causes the alpha-galactosidase A enzyme to be absent or not working correctly?**

*Genes* tell the body to make different enzymes. The *GLA* gene provides the instructions to make alpha-GAL. In males with Fabry disease, one copy of their *GLA* gene does not work correctly. Females may have either one or two nonfunctioning *GLA* genes. Because of the changes in the *GLA* gene, the alpha-GAL enzyme either does not work properly or is not made at all.

**How is Fabry disease inherited?**

Fabry disease is inherited in an X-linked pattern. In this type of inheritance, the gene, *GLA*, is located on the X chromosome, one of the sex chromosomes. Genes usually come in pairs, with each parent giving one copy to their child. The sex chromosomes, however, are different.

A male inherits one X chromosome from his mother, and one Y chromosome from his father. A female inherits two X chromosomes, one from each parent.

A male with a non-working copy of the gene for Fabry disease on his X chromosome will have Fabry disease. This is because he does not have a second X chromosome with a working copy of the gene. Therefore, it is more common for males to have Fabry disease than females.

Females with one non-working copy of the *GLA* gene on one X chromosome are variably affected by Fabry disease. They may experience the same symptoms as affected males, milder symptoms than affected males, or even no symptoms at all.

If a mother has one non-working copy of the gene, she is called a carrier. For carriers, there is a 50% chance that each male pregnancy will have Fabry disease. For carriers, there is a 50% chance that each female pregnancy will be a carrier, like her mother.
A father passes his Y chromosome to his sons and his X chromosome to his daughters. Therefore, if a father has Fabry disease, none of his sons will have the disease and all of his daughters will be carriers.

Genetic counseling is available to families who have children with Fabry disease. Genetic counselors can answer questions about how Fabry disease is inherited, choices during future pregnancies, and how to test other family members. Ask your doctor about a referral to a genetic counselor.

Is genetic testing available?

Genetic testing for Fabry disease can be done on a blood sample. Genetic testing, also called DNA testing, looks for changes in the pair of genes that causes Fabry disease. If a gene change has been found in other family members, testing can find out if your child has the same gene change.

DNA testing is not always necessary to diagnose Fabry disease in boys. However, genetic testing is necessary to determine whether females are carriers.

What other testing is available?

Screening Tests
Newborn Screening
Newborn screening for Fabry disease is done in some states. A blood spot from the baby’s heel is used to screen for many different conditions. Newborn screening detects Fabry Disease.
Fabry disease by looking for alpha-GAL enzyme activity. Alpha-GAL enzymes are active in every healthy newborn’s blood. Since babies with Fabry disease have alpha-GAL enzymes that are either missing or not working properly, they will have reduced alpha-GAL enzyme activity.

If a baby has a positive result on the initial Fabry screen, it does not yet mean that he or she has Fabry disease. Low alpha-GAL enzyme activity level can sometimes be found in people who never develop Fabry disease. A positive screening result means that further testing must be done to confirm or rule out Fabry disease. Rarely, there can also be false positives with additional testing.

**Confirmatory testing**

For males, the amount of alpha-GAL enzyme activity is measured in the blood or in other cells from the body. In females, genetic testing is necessary to confirm the diagnosis as some female carriers have normal alpha-GAL levels in their blood.

Genetic testing of the *GLA* gene may also be performed to help confirm the diagnosis.

**Can you test for Fabry disease during pregnancy?**

If a genetic cause has been identified, DNA from the fetus can be tested. The sample for this testing is obtained by either **CVS** or **amniocentesis**.

Parents may choose to have testing during pregnancy or wait until birth to have the baby tested. A genetic counselor can talk to you about your choices and answer questions about prenatal testing or testing your baby after birth.

**Can other members of the family have Fabry disease or be carriers?**

Only some states offer newborn screening for Fabry disease. It is very important that other family members are told that they could be at risk of having Fabry disease or being carriers.

**Having Fabry disease**

Each full brother (same mother and father) of a baby with Fabry disease has a 50% (1 in 2) chance of also having Fabry disease. Even older siblings who have not shown any symptoms of the disease could have late-onset Fabry disease that has not caused symptoms yet, but will in the future. All siblings of an individual with Fabry disease should be tested to see if they also have Fabry disease because early treatment can prevent more serious health problems.

In addition, the father of a female baby who is found to be a carrier of Fabry disease after newborn screening could also have Fabry disease and not yet noticed or experienced any symptoms. It is important for both parents of a female carrier of Fabry disease to be tested.
Carrier for Fabry disease
Since males cannot be carriers, unaffected brothers cannot be carriers for the disease. Sisters who do not show symptoms of Fabry disease still have a chance of being carriers like their mother. Each sister has a 50% chance of being a carrier.

Can other family members be tested?

Diagnostic testing
Brothers of a child with Fabry disease should be tested, by measuring alpha-GAL enzyme activity or DNA testing. Talk to your doctor or genetic counselor if you have questions about testing for Fabry disease.

Carrier testing
Female family members can have DNA testing to see if they are carriers. If you have questions about carrier testing, ask your genetic counselor or doctor.

How many people have Fabry disease?
It is estimated that 1 in every 50,000 males will be born with Fabry disease, although some recent studies show it may be more common than previously thought. The disease is much less common in females.

Does Fabry disease happen more often in a certain ethnic group?
Fabry disease occurs in people of all ethnic groups around the world.

Does Fabry disease go by any other names?

Fabry disease is also sometimes called:
- Angiokeratoma, diffuse
- Anderson-Fabry disease
- Hereditary dystopic lipidosis

Where can I find more information?

Fabry Support & Information Group
http://www.fabry.org

National Fabry Disease Foundation
http://www.fabrydisease.org/