Screening, Technology, and Research in Genetics is a multi-state project to improve information about the financial, ethical, legal, and social issues surrounding expanded newborn screening and genetic testing – http:// www.newbornscreening.info

Disorder name: Fabry disease

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:

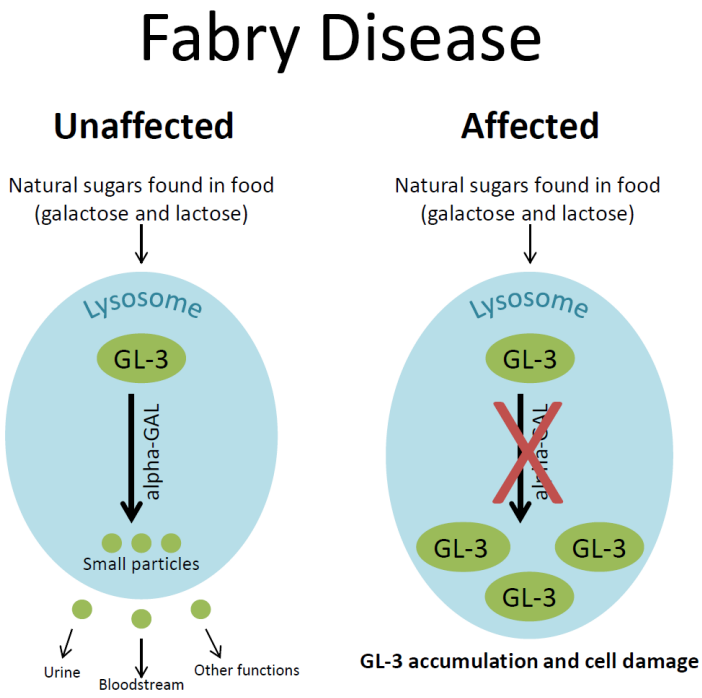
Lysosomal storage disorders (LSDs) are a group of inherited disorders. They are caused by enzymes that do not work properly.

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 is caused by problems with the enzyme called alpha-galactosidase A (alpha-GAL). In people with Fabry disease, alpha-GAL is missing or not working properly. Normally, alpha-GAL helps cells break down a substance called 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.



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
- High blood pressure (hypertension)
- Heart disease like cardiomyopathy
- Heart attack
- Cerebrovascular disease (disease from abnormal blood flow to the brain), like a 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 a 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) replace or increase the function of alpha-GAL, and 2) alleviate symptoms and prevent future complications.

Enzyme therapies

1. **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. ERT is a lifelong treatment and is administered by intravenous infusion every other week. Some experts have recommended that ERT be started as early as possible in all males with Fabry disease and in female carriers that have serious symptoms. ERT may reduce the long-term risk for cardiac, cerebrovascular, and kidney complications. It may also help pain episodes.

2. **Chaperone Therapy**

A new type of medication called a chaperone therapy can be used to restore alpha-GAL in patients with specific genetic variants causing their Fabry disease. This medication does not work for all patients with Fabry disease. Chaperones are small molecules that

help enzymes become functional by correcting their shape and increasing their stability. The chaperone therapy medication attaches to certain unstable forms of alpha-GAL and stabilizes this enzyme which improves how it works in the body. This improvement in enzyme function helps stabilize kidney function and help with a specific heart issue. This therapy is approved for individuals that are 16 years of age or older.

Symptom management

1. **Pain Management**

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

2. **Kidney Support**

Kidney problems and high blood pressure may be treated with ACE inhibitors. If kidney damage becomes extensive, a kidney transplant may be necessary.

3. **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 heart and blood vessel disease (cardiovascular disease). Individuals with Fabry disease should have their kidney function, heart (cardiac) 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. Males have one copy of the GLA gene and females have two copies of the GLA gene. In males with Fabry disease, the 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 GAL 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.

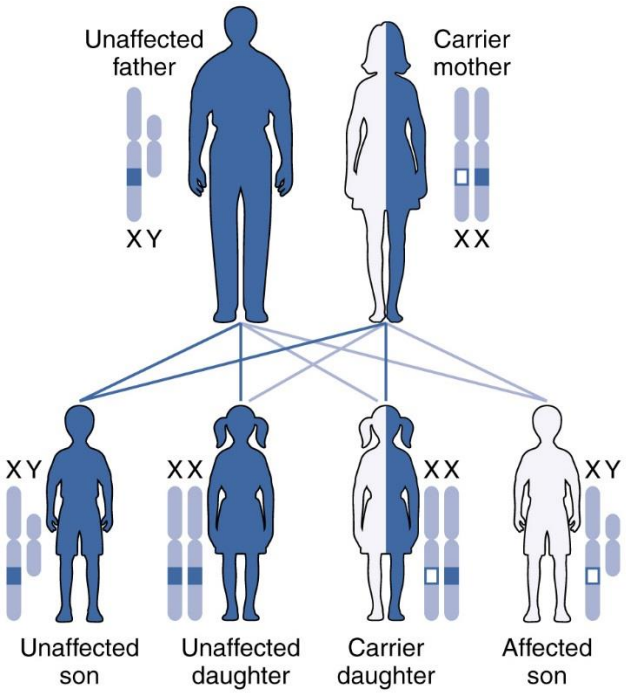
A male inherits one X chromosome from his mother, and one Y chromosome from his father. A female inherits two X chromosomes, one from each parent.

A male with a non-working copy of the gene for Fabry disease on his X chromosome will have Fabry disease. This is because males do not have a second X chromosome with a working copy of the gene. Because of this, 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 GLA 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.



Source: OpenStax CNX

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 (variants) in the GLA 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. Genetic testing can also be used to determine if certain medications can be helpful to treat Fabry disease.

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 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 newborn screen, it **does not** always mean that he or she has Fabry disease. Low alpha-GAL enzyme activity levels 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, DNA 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 a future 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. Parents may also choose to use assisted reproductive techniques to decrease the chance that their future children would have Fabry disease.

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 to determine if they also have Fabry disease. 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/

National Kidney Foundation
https://www.kidney.org/atoz/content/fabry

National Institute of Neurological Disorders
https://www.ninds.nih.gov/Disorders/All-Disorders/Fabry-Disease-Information-Page

MedlinePlus
https://medlineplus.gov/genetics/condition/fabry-disease/

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