AN ONGOING COMMITMENT

For more than 25 years, Genzyme has been committed to researching and developing products for people living with lysosomal storage disorders such as Fabry disease. Providing comprehensive and confidential support services that address the unique needs of those living with Fabry disease is part of this ongoing commitment.
It can be scary to think about having a disease, but I think it’s even scarier to have all these symptoms and not know what’s causing them. When you get tested and you find out you have Fabry disease, it puts an end to your uncertainty. You can focus on learning about what Fabry disease is, and what is actually going on in your body. —Kelly
Understanding Fabry Disease

Living with Fabry disease is challenging. Because the disease is rare, many people have not heard of it and don’t understand how it can affect families. People with Fabry disease sometimes say that they have a hard time getting their symptoms taken seriously—by teachers, coworkers, friends, or even healthcare providers. Some say that accurate diagnosis was delayed because of a lack of understanding of Fabry disease and its symptoms.

This booklet explains the signs and symptoms that people with Fabry disease may experience. It provides information for patients to share with family and caregivers. Although the disease is rare, it is important to remember that it touches many lives, and that others are living with similar experiences.

If the signs and symptoms of Fabry disease are recognized early, doctors can help manage them better. That is why it is important for people to be tested if they have concerns (especially when the disease runs in a family), and to be seen by a doctor with a good understanding of the disease.

Please note that the information contained in this brochure cannot replace regular conversations with your doctor or healthcare provider.

*Please see glossary on page 14.*
What Causes Fabry Disease?
What Causes Fabry Disease?

Fabry disease is caused by a defective gene. A person who inherits this gene is unable to produce an enzyme known as alpha-galactosidase A (α-gal) (commonly referred to as alpha-GAL) in amounts needed to do the job it is supposed to do.

What Does the Alpha-GAL Enzyme Normally Do?

Alpha-GAL is one of several enzymes normally present in sac-like structures in our cells called lysosomes. The enzyme’s job is to break down a certain fatty acid, called globotriaosylceramide, (glō-bō-trī-ā-ū-sil-ser-a-mid) or GL-3. Since a person with Fabry disease does not produce enough alpha-GAL, the GL-3 is not broken down, but instead builds up in the cells over time.

What Are the Major Symptoms of Fabry Disease?

As GL-3 builds up in the walls of blood vessels and other tissues, over time it can cause more and more damage. Major organ systems involving the heart, kidney, and brain may not function properly, causing potentially life-threatening problems.

The most serious problems in Fabry disease usually occur in the fourth or fifth decade of life. However, signs and symptoms may appear much earlier. The earlier Fabry disease is recognized, the earlier intervention can begin.

Because of the way Fabry disease is inherited, symptoms vary more in women than they do in men. Most men with Fabry disease will experience the full range of symptoms described here. Women with the disease may experience these symptoms as severely as men, but they may have milder symptoms, or they may have severe symptoms in some organs but not others. For more information about why this occurs, please see the section, “How Is Fabry Disease Passed On?”, beginning on page 8.

Pain and Fatigue

Pain is the most common symptom of Fabry disease and is often the first symptom that brings children and adolescents to their pediatricians. For many, pain is brought on by changes in weather, exposure to hot temperatures, stress, or fatigue. Most people with the disease experience two types of pain, acroparesthesia and “Fabry crises.”

• Acroparesthesia is a burning, tingling pain that mainly affects the palms of the hands and soles of the feet. Some people experience this type of pain every day, while others experience it less often.

• “Fabry crises” are episodes of intense, excruciating, burning pain that start in the hands and feet and spread to other parts of the body. These crises can last from minutes to several days.
We first found out that we had Fabry disease in our family when my mother-in-law went in to see the eye doctor. Two of her sons had had kidney failure and we didn't know why. The eye doctor saw the whorling pattern in her eyes and said, ‘I think I know what caused your sons’ kidney failure.’ The family was tested and we found that, yes, we had Fabry disease in our family.  

—Heather
Many people with Fabry disease find that managing the pain and fatigue associated with the disease means managing every activity they undertake. It can mean avoiding certain activities, being prepared for changing weather conditions, increasing water or liquid consumption, “budgeting” energy or taking frequent naps. Medications may also provide relief.

**Impaired Sweating**

Most people with Fabry disease either perspire very little (hypohidrosis) or not at all (anhidrosis). This can cause frequent fevers, overheating with exercise, and sensitivity to hot weather.

**Skin Rash**

A reddish-purplish skin rash known as angiokeratomas is the most visible sign of Fabry disease. Angiokeratomas (“angio” refers to blood vessels, and “keratoma” refers to callous or hardened) are often found in the area from the bellybutton to the knees and sometimes in areas where the skin stretches (like elbows or knees). They usually appear during adolescence. Angiokeratomas range in size from pinpoint to several millimeters. Like all symptoms of Fabry disease, they are the result of GL-3 accumulation.

**Corneal Pattern**

A starburst pattern on the cornea is only detectable with a special eye exam. (Used with permission, from R.J. Desnick, PhD, MD)

A starburst pattern on the cornea of the eye is often seen in people with Fabry disease. This pattern can only be seen with a medical instrument called a slit-lamp ophthalmoscope, which most eye care professionals use. The pattern, also known as corneal whorling, is the result of GL-3 deposits in the blood vessels of the eye. It is sometimes the first sign that causes doctors to suspect Fabry disease. The corneal pattern typically does not affect vision.

**Gastrointestinal Problems**

Many people with Fabry disease experience abdominal pains. This may include pain after eating a meal, diarrhea, and nausea. Some doctors recommend a low-fat diet to relieve these symptoms.
Major Organ System Damage

The accumulation of GL-3 causes the blood vessels to become narrowed over time. This means the kidneys, heart, and brain do not get the blood flow they need to function properly. As a result, people with Fabry disease can experience very serious and life-threatening damage to major organ systems. Common problems include:

**Kidney Problems**
- Reduction in kidney function (shown by excessive protein in the urine)
- Kidney failure

Mild reduction in kidney function can be managed in part by a low sodium, low protein diet. Severe kidney problems can be treated with chronic dialysis, or with transplantation in people with kidney failure.

**Heart Problems**
- Enlarged heart
- Malfunctioning heart valves
- Irregular heartbeat
- Heart attack
- Heart failure

Some heart problems can be treated with a pacemaker or bypass surgery.

**Cerebrovascular/Central Nervous System Problems**
- Dizziness or vertigo
- Head pain
- Premature stroke

Anticoagulants (blood thinners) may be prescribed for those at risk of stroke.

Emotional Issues

Many people with Fabry disease experience feelings of depression, hopelessness, alienation, and denial of their symptoms. It may be helpful to talk with someone else from the Fabry community — someone in a similar situation with similar concerns and fears. A medical genetic counselor can help deal with these issues, as well as issues relating to passing the disease on to children.

How Early Do Symptoms Appear?

GL-3 accumulation can begin before birth, and many people experience symptoms of Fabry disease early in childhood — perhaps as early as four years old. However, these early signs and symptoms are sometimes misunderstood, or even ignored, by parents, teachers, and other caregivers.
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To understand how Fabry disease is inherited, it helps to know a little about genetics.

We each inherit an X chromosome from our mother and an X or Y chromosome from our father. If we inherit an X chromosome from our father we are female (XX), and if we inherit a Y chromosome from our father we are male (XY).

The gene for alpha-GAL is located on the X chromosome. If a man’s X chromosome contains the defective 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 defective gene, she will have a 50% chance with each pregnancy of passing it on to both her sons and daughters.

A male who inherits a non-working gene is called “hemizygous” for Fabry disease. This term is used in males, as they have only one copy of the X chromosome, and therefore one copy of the Fabry-causing gene. A female, with two copies of the X chromosome, is called “heterozygous” for Fabry disease if she inherits a Fabry gene, as her other copy of the gene is working properly.

A medical genetic counselor can help you map out the inheritance pattern in your family with a medical family tree. This can help you make informed decisions about family planning and the likelihood of passing on the disease. A medical family tree can also help you understand how Fabry disease has affected relatives, both living and deceased. Use the family tree in the back of this brochure to get started or visit www.fabrycommunity.com.
Telling teachers and coaches that my son has Fabry disease is a challenge. I think they want to sympathize but may not know how because they’ve never heard about it before. I tell them what to look for. He might get a headache and he overheats fast. Make sure he has water. I do that with everybody—the coaches, the teachers, everybody. —Jessica
My wife didn’t know about Fabry disease. She didn’t always realize how much pain I was going through. A lot of our social activities got interrupted because I couldn’t do something. We worked through it, but it was plenty hard. I know it was hard on her, too, seeing what I was going through. —Chuck
Does Fabry Disease Affect Males and Females Differently?

When a male inherits an X chromosome with the defective gene, he produces little or no alpha-GAL, and he develops the symptoms of Fabry disease. A female has two X chromosomes, so even if she has one Fabry gene, she has a second gene that could produce alpha-GAL. However, she may still experience symptoms because of a process called X-inactivation.

What is X-Inactivation?

Each cell in a female’s body contains two X chromosomes, but one is turned off, or inactivated, while she is developing in her mother’s womb. Statistically, half her cells should have one X chromosome working, and half should have the other working. But, like flipping a coin, 50-50 odds do not always result in a perfect 50-50 split.

Each organ in a female’s body has its own X-inactivation pattern. In a female who has Fabry disease, one organ may have 60% of her healthy X chromosome working, while another organ may have only 30% working. A female’s specific X-inactivation pattern can cause her to have some Fabry symptoms, but not others. It can also determine how severe those symptoms will be.

How are People with Fabry Disease Diagnosed?

In males, a lack of alpha-GAL shows that they inherited the gene. Males can be diagnosed through a blood test that measures alpha-GAL enzyme activity.

Females, however, can have low-normal levels of alpha-GAL and still carry the defective gene. Since the X-inactivation pattern may be different in different organs, females may have one or more severely affected organs but still have nearly normal alpha-GAL in the blood. For this reason, a genetic test may be needed for an accurate diagnosis in females.

Who is at Risk for Inheriting Fabry Disease?

Fabry disease can affect people from any ethnic group. It is inherited, so if one person in a family has the disease, others likely will as well. That is why it is important to develop a medical family tree. Use the family tree in the back of this brochure to get started, or visit www.fabrycommunity.com.

For people with Fabry disease, it is important to be seen by a doctor with a good understanding of the disease.
Resources

What Kind of Support is Available for Patients with Fabry Disease?

Genzyme is committed to helping meet the needs of people who are living with Fabry disease. As part of this commitment, we provide services for those who have Fabry disease and their families, and for healthcare professionals. We offer resources and information to help patients advocate for their care.
Please contact Genzyme for:
- Patient resources and advocacy groups to help connect patients and their families to others living with Fabry disease
- Resources regarding diagnostic testing and genetic counseling
- Fabry disease information and educational resources
- Information on the Fabry Registry, a resource to help increase the understanding of Fabry disease

For more information:
- Genzyme Medical Information, 800-745-4447 (option 2) or 617-768-9000 (option 2) Monday – Friday 8am to 6pm US Eastern Time
- fabry@genzyme.com
- www.genzyme.com

Additional Resources
In addition to the information contained in this brochure, a number of organizations are dedicated to providing information and support to the Fabry community and those living with other genetic disorders. Note that the opinions expressed by the organizations below do not necessarily reflect the views of Genzyme. Genzyme does not maintain and is not responsible for the content of communications for the listed organizations or their websites, with the exception of www.fabrycommunity.com and www.fabryregistry.com, which are websites developed and maintained by Genzyme.

Fabry Community
www.fabrycommunity.com

Fabry Registry
www.fabryregistry.com

FSIG – Fabry Support & Information Group
www.fabry.org

National Fabry Disease Foundation
www.theNFDF.org

Genetic Alliance
www.geneticalliance.org

National Institute of Neurological Disorders and Stroke (NINDS)
www.ninds.nih.gov

National Organization for Rare Disorders (NORD)
www.rarediseases.org

Well Spouse Association
www.wellsposue.org

Clinical Trials
www.clinicaltrials.gov
alpha-galactosidase A (alpha-GAL)
(al’a-gä-lak-tö-sid’äs ä)
An enzyme that is missing, ineffective, or present in inadequate amounts in people with Fabry disease. It is normally found in the lysosomes.

Acroparesthesia
An abnormal sensation, such as pain, burning, pricking, tickling or tingling in the hands and feet.

Angiokeratomas
Dark-red to blue skin lesions, which may be flat or slightly raised, that are usually found in the area below the waist and above the knees in patients with Fabry disease.

Anhidrosis
An inability to sweat.

Arrhythmia
An irregularity in the rhythm of the heartbeat.

Cardiovascular
Of or relating to the heart.

Cerebrovascular
Of or relating to the blood vessels that supply the brain.

Chromosome
A threadlike strand of DNA and protein in every plant and animal cell. Chromosomes carry the genes that define a person’s bodily makeup (for example: hair and eye color, disease expression).
Cornea
The thin transparent outer covering of the eyeball.

Corneal
Of or relating to the cornea.

Dialysis
A treatment for patients with severe kidney disease that removes excess substances or waste substances from the blood. Healthy kidneys normally serve this function.

DNA
An abbreviation for deoxyribonucleic acid, the storehouse of all hereditary characteristics. All chromosomes are made up of genes, and genes are made of DNA.

Enzyme
A protein produced by the body that acts to chemically change other substances. Enzymes are involved in breaking down or chemically altering substances so that the body can use or excrete them. Enzymes are typically named by adding an “—ase” to the end of a word that describes the enzyme.

Fabry disease
A genetic disorder caused by a deficiency of the enzyme alpha-galactosidase A.

Fabry crisis
A term used to describe episodes of intense pain in people with Fabry disease.

Gene
A piece of DNA that codes for a particular substance. Each gene occupies a specific location on a chromosome, which defines a person’s bodily makeup and function.

Genetic
Affecting or affected by genes (genetic disorder).

GL-3
An abbreviation for globotriaosylceramide.

Globotriaosylceramide (glō-bō-trī-à-ū-sil-ser-a-mīd)
One type of glycosphingolipid compound which accumulates in the blood vessel walls of people with Fabry disease as a result of a deficiency in alpha-galactosidase A.

Glycosphingolipids
Fatty substances. There are many different types of glycosphingolipids; in the case of Fabry disease, certain glycosphingolipids cannot be broken down, and thus accumulate, due to an enzyme deficiency.

Hypohidrosis
Abnormally decreased ability to sweat.

Lysosome
A small structure in most cells acting as the chemical plant of the cell. Lysosomes contain and make various enzymes that digest or break down substances. In Fabry disease, GL-3 builds up in the lysosomes.
Lysosomal storage disorder
A disease resulting from the storage or accumulation of material in the lysosomes. Fabry disease is a lysosomal storage disorder.

Metabolic disorders
Diseases that may be caused by inherited enzyme defects. These enzyme defects prevent the body from breaking down, or metabolizing, certain substances. Fabry disease is a metabolic disorder.

Mitral valve prolapse
A condition in which the valve between the left atrium and ventricle does not completely close, and therefore does not block the backward flow of blood. Heart valves close when the heart pumps to keep blood flowing in one direction.

Protein
The building blocks of cells involved in all essential life functions (for example: cell growth, energy production, metabolism).

Proteinuria
Excessive protein in the urine.

Renal
Of, relating to, or in the region of the kidneys.

Renal failure
Inability of the kidneys to excrete wastes and to help maintain the electrolyte balance.

Slit lamp ophthalmoscopy
Examination of the eye with an instrument consisting essentially of a mirror that reflects light into the eye and a central hole through which the eye is examined. It is a simple exam that is performed by most eye care professionals. It is useful for visualizing the whorling pattern often seen in the eyes of people with Fabry disease.

Stroke
A sudden loss of brain function caused by a blockage or rupture of a blood vessel to the brain.

Whorling
A starburst pattern commonly found on the cornea of people with Fabry disease.

X chromosome
The sex chromosome associated with female characteristics. All females typically have two X chromosomes while males typically have only one X chromosome.

X-linked disease
A genetic disease whereby the defective gene is carried on the X chromosome. Fabry disease is an X-linked disease.
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The Family Medical Tree

Creating a medical family tree can help you understand the inheritance pattern in your family and your risk of passing on Fabry disease. You can fill out this sample chart to get started. A medical genetic counselor can help you take it from there.

Complete the information about yourself first and then be sure to fill in both sides of your family. Squares represent men and circles represent women. Diamonds can be used for either gender. Wherever you see a diamond, fill in whether the family member is a male (M) or female (F). To show a family member with Fabry disease, fill in the shape. To show family members who are carriers, draw a dot or fill in half of the circle or diamond. Remember, women in your family who are carriers may or may not also be affected by Fabry disease. If they experience the symptoms of the disease, fill in the shape completely.

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