

A Guide for Women Living with Fabry Disease



SANOFI GENZYME 

Women often place a greater priority on the health of their family than their own personal health. If you are a woman living with Fabry disease, it is especially important that you care for yourself first so that you are able to care for your family.

You may have been told for years that you are “only a carrier” or you may feel your disease is not as bad as your son’s or your father’s, for example. But as the understanding of Fabry disease improves, the concept of female “carriers” is evolving. We now know that females who inherit the altered gene are affected by Fabry disease and can experience life-threatening symptoms. It is important for

women with a family history of this progressive, potentially life-threatening disease to be tested. If you have Fabry disease and experience symptoms, speak to your doctor about appropriate medical care.

This booklet explains the signs and symptoms that women with Fabry disease may experience, based on recent medical research. It also explains why those signs and symptoms are variable and may not be the same in all women with Fabry disease.

Wang et al. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genet Med* 2007;9:34-45.

“Advocating for oneself is not easy when it comes to Fabry disease. I have had to talk to several employers about it, doctors who don’t know about it. And my softball coach. When we’d get out in the heat, he’d be saying, ‘run laps’. And I’m doing what I can, but I’m overheating because I’m not sweating very much, and my hands and feet are on fire. And he just could not understand that at all. I hated it. But you do what you can to get your point across. And if they don’t believe you, you just move on.” -Jessica

“When we first started going to meetings and listening to different doctors talk about Fabry disease, we were literally written off. I had a doctor tell me, “You’re just a carrier. You don’t have it.” I said, “Baloney, I do have it and I do have symptoms.” Today, it’s not “carrier” anymore. You do have the disease. You have more support. They will listen to you .” -Jody

FEMALES AND FABRY DISEASE

Fabry disease is an inherited disorder that was once thought to affect only males. Females were called “carriers” because it was believed that they carried the gene for the disorder without developing symptoms. According to a study in Australia*, Fabry disease affects an estimated 1 in 117,000 live births, so for many years, little clinical information was available about its effects on the body.

In the past 15 years, research on Fabry disease has increased dramatically. New research is demonstrating that females with Fabry disease do, in fact, have a wide range of symptoms. These symptoms vary from one female to

another, more than they vary among males. They range from mild to severe, may start later in life, and may affect different organ systems in different people. The effects of Fabry disease on an individual female depend on a number of factors.

If you know or suspect that there is a history of Fabry disease in your family, or if you suspect you may have Fabry disease, it is important to talk to your doctor or a genetic specialist and get tested. A genetic test can determine whether you have Fabry disease. Your doctor will provide you the information needed to manage your health.

* Meikle PJ et al. JAMA. 1999;281:249-254

Remember that taking care of your health also means nurturing your emotional well-being. Tap into a support network, or talk to your friends, family, co-workers and loved ones. You are not alone — there are other women like you with Fabry disease, and support is available.

What is Fabry disease?

Fabry disease is an inherited disorder caused by an altered gene. A person who inherits this gene is unable to produce enough of an essential enzyme called alpha-galactosidase A (al'-fă gă-lak'-tō-si-dās ā), or alpha-GAL.

Alpha-GAL breaks down a fatty substance called globotriaosylceramide (glō'-bō-trī-ă-ō-sil-ser-a-mīd), or GL-3, so that it can be removed. Since a person with Fabry disease does not produce enough active alpha-GAL, GL-3 is not removed, but instead builds up in the cells.

Over many years, as GL-3 slowly builds up in the walls of blood vessels and other tissues, it can cause more and more damage. Major organ systems involving the heart, kidney, and brain may eventually 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 disease management can begin.





To understand how Fabry disease affects males and females, it helps to have a basic understanding of chromosomes, genes, and inheritance patterns.

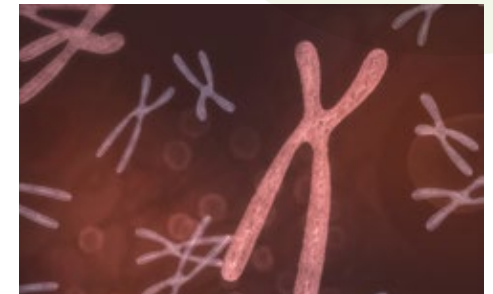
Different diseases are passed down in different ways. Fabry disease is considered an X-linked genetic disease. This means that the altered gene that causes Fabry disease is on the X chromosome, which gets passed down from parent to child. Chromosomes are in our cells and contain our DNA.

If a man with Fabry disease has children, any and all of his daughters will inherit the gene and will have Fabry disease. None of his sons will have the disease.

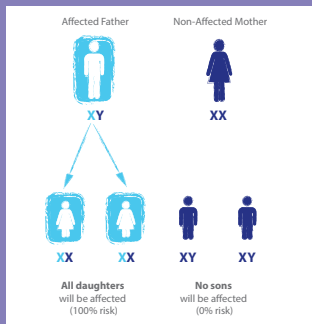
If a woman with Fabry disease has children, she has a 50% risk (with each birth) of passing the altered gene to both sons and daughters. Any sons and daughters who inherit the gene will have Fabry disease.

Men who inherit the altered gene that causes Fabry disease will likely have symptoms of Fabry disease. But it's a little different for women. Women who inherit the altered gene may or may not experience all the symptoms of Fabry disease.

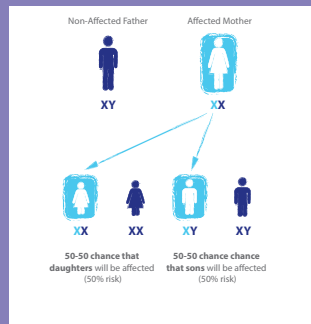
Women (any daughters) may experience only a few or all of the symptoms of Fabry disease. This holds true no matter whether the daughter inherited the disease from the father or the mother.



X Marks the Spot: The altered gene that causes Fabry disease is on the X chromosome.



When the father is affected, all of his daughters will have the altered gene. Daughters may experience only a few symptoms or many symptoms. The affected father will not pass the gene on to any sons, and therefore, no sons will be affected.



When the mother is affected or has the altered gene, she has a 50-50 chance (like the flip of a coin) with each birth of passing the altered gene on to her sons and daughters. Daughters who have inherited the altered gene may experience only a few symptoms or many symptoms.

Inheritance Pattern

When a male inherits an X chromosome with the altered gene, he produces little or no alpha-GAL, and he develops symptoms of Fabry disease. A female has two X chromosomes, so even if she has one altered gene, she has a second gene that can produce alpha-GAL. However, females often will experience symptoms of Fabry disease. This is because the amount of alpha-GAL a female produces depends on a process called X-inactivation.

About X-Inactivation and Why Fabry Disease is Different for Women

Why is it that women experience Fabry disease differently from men? Why is it that each woman with Fabry disease is different and may or may not have all the symptoms of the disease?

The altered gene that causes Fabry disease is on the X chromosome. Women have two X chromosomes, whereas men only have one. For men who have Fabry disease, their only X chromosome is the one that has the altered gene. And that X chromosome is in every one of his cells.

But in women, the altered gene is only in one of the two X chromosomes they have. In every cell only one of the two X chromosomes has been activated – it may or may not be the one with the altered gene. This is a completely random process that occurs before birth. Only cells that have an activated X chromosome with the altered gene will be affected by Fabry disease.

Since women can have symptoms of Fabry disease to different extents, all women with the altered gene should be seen regularly by their doctors. We'll talk more about this in the upcoming pages.

About the Fabry Registry

The Fabry Registry is an international database, sponsored and administered by Sanofi Genzyme, that collects information on Fabry disease patients.

The Fabry Registry has been established in order to better understand the progression and management of Fabry disease, as well as the different ways in which Fabry disease affects men and women.

What Fabry disease symptoms affect females?

Some females with Fabry disease remain healthy throughout their lives, while others experience the full range of disease symptoms. For most, symptoms occur later and are less severe than in males, but this is not always true.



The analysis highlighted in this section includes disease data on 1,132 males, 1,055 females. Depending on her X-inactivation pattern, a female's symptoms may include:

Heart¹

Heart problems are reported to be the most common serious manifestation of Fabry disease in females who participated in the Fabry Registry. Females with Fabry disease reported heart problems almost as often as males with the disease, although they were older when these problems developed.

Heart problems observed included angina (constricting pain in the chest), irregular heartbeat, an enlarged left ventricle, and heart attack. Regular exams, including electrocardiography and echocardiography, are recommended for women with Fabry disease, because heart disease can develop even when there are no obvious symptoms.

Cerebrovascular¹

In the Fabry Registry, stroke was reported by 4.2% of females (n = 44) and 6.7% of males (n = 76), at an average age of 44 and 40, respectively. Transient ischemic attack (TIA, sometimes called a “mini stroke”) was actually more common among females, and was reported by 3.9% of females (n = 41) and 1.7% of males (n = 19).

Kidney¹

Many female patients in the Fabry Registry reported experiencing significant kidney problems, demonstrated by proteinuria (excess protein in the urine) and reduced kidney function. In the Fabry Registry, 19% of females (n = 121) had chronic kidney disease stage 3 or higher, compared to 34% of males (n = 207). In addition, 2% of females (n = 23) and



Angiokeratomas

14% of males (n = 156) had reached end-stage renal disease (ESRD), requiring dialysis or transplantation at an average age of 39 and 38 years, respectively. A lower percentage of female patients than males had kidney problems of any type. However, when females did have kidney problems, they occurred at a similar or only slightly higher age than reported in males.

Skin¹

A painless, purplish skin rash called angiokeratomas were seen in about 18% (n = 200 males; n = 188 females) of both male and female patients in the Fabry Registry.

Gastrointestinal¹

In the Fabry Registry, 21% (n = 226) of females reported abdominal pain and 19% (n = 199) reported diarrhea; 13.4% (n = 152) of males reported abdominal pain and 11.9% (n = 135) reported diarrhea.

Eye²

A distinctive pattern on the cornea that typically does not affect vision, called corneal whorling or corneal verticillata have been reported in almost all males with Fabry disease, and in 70% of females. This pattern can only be seen with a slit lamp, an instrument used by eye doctors.

Quality of Life¹

Both males and females in the Fabry Registry reported lower quality of life than the general population, especially when they are in their mid 30s and older. Quality of life is measured using a widely accepted questionnaire called the SF-36, which has been used to evaluate quality of life in people with a wide range of chronic health conditions.

HOW IS FABRY DISEASE DIAGNOSED?

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

Females, however, can have normal to low-normal levels of alpha-GAL enzyme and still have Fabry disease. Since the X-inactivation pattern may be different in different organs such as the heart or kidney, females may have one or more severely affected organs but still have nearly normal alpha-GAL in their blood. For females with normal to low-normal alpha-GAL, a genetic test is needed for an accurate diagnosis.

Genetic testing can confirm or rule out the presence of Fabry disease. A negative test can relieve uncertainty, while a positive test can allow a person to pursue medical options. Because Fabry disease is progressive, early intervention is important.

How should testing be handled in Fabry families?

When one person in a family is diagnosed as having Fabry disease, it is likely that others are also at risk. If you receive a positive diagnosis, a genetic specialist can help you determine who else in your family might be affected by Fabry disease and who should consider testing.

CareConnectPSS Patient Education Liaisons can help you better understand the testing, genetic counseling, and disease management options available to you and your family. Contact CareConnectPSS at **800-745-4447 (option 3)** or **617-768-9000 (option 3)** for more information.

Where can I find support if I receive a positive diagnosis?

Getting tested for Fabry disease can be emotionally stressful. Many people in families with Fabry disease have already seen close relatives become affected with the disorder. News that they actually carry the altered gene can lead to depression and even despair.

Emotions elicited by test results can produce changes in feelings among family members. Someone who is carrying the altered gene may feel anger, while one who is not may feel guilt for not having a disease that afflicts a close relative. A parent may feel guilty for passing the disease on to a child.

These feelings are understandable. If you are considering testing or have received a positive diagnosis, ask your doctor for help in finding the support you need, or contact your CareConnectPSS Case Manager at **800-745-4447 (option 3)** or **CareConnectPSS.com** for assistance in finding support in your area.



“When I was a teenager, I knew that I could pass Fabry disease on if I had children, but I thought the only symptoms I would experience were that my hands and feet would hurt when I got a fever, along those lines. But women can have more than just the mild symptoms. When my mother passed away, she’d had a stroke. She had some kidney failure, she had multiple heart problems. And, I still think when she passed away they didn’t attribute all that to Fabry disease, but in my mind that’s what caused it.” —Kelly

Recommended Medical Assessments

Because Fabry disease is progressive — meaning it can get worse over time — females with Fabry disease should have regular medical assessments in addition to yearly physical exams, even if they feel fine.

Since some of the symptoms of Fabry disease may only be recognized through specific medical evaluations, it is important for females with Fabry disease to have regular assessments with their doctor — especially to monitor their heart, brain and kidney function. Talk to your doctor and ask your CareConnectPSS Case Manager for a copy of the “Taking Better Control of Fabry Disease” booklet to learn more about these assessments.

“A lot of information on Fabry disease says girls are just carriers, they will not have the disease.

And here I have my daughter with raging fevers, burning hands and feet, not being able to move for four or five days, missing school. It took a long time to find someone who would listen, and it was very frustrating. Her gym teacher thought she was just lazy, you know, and she’s passing out from heat exhaustion.” —Heather

CareConnectPSS is committed to helping meet the needs of women and families who are living with Fabry disease. As part of this commitment, we provide resources and information to help patients advocate for their comprehensive care.

Please contact CareConnectPSS 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
- Personalized support from a CareConnectPSS Case Manager including helping you understand health insurance options and coordinating with your healthcare providers
- For more information contact your CareConnectPSS Case Manager, **800-745-4447 (option 3)** or **CareConnectPSS.com**

CareConnectPSS Patient & Caregiver Portal CareConnectPSS.com

If you or a loved one is living with Fabry disease, managing your time and energy is important. The Patient & Caregiver Portal was developed to provide you with the convenience of 24/7 online access to the personalized support and information you need.



Alpha-galactosidase A

(alpha-GAL) (al'-fă gă-lak'-tō-si-dās ā)
An enzyme that is ineffective, missing or present in inadequate amounts in people with Fabry disease. It is normally found in the lysosomes.

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.

Carrier

A person who carries the gene for a disease without experiencing symptoms.

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.

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.

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-ă-ō-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.

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.

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.

Stroke

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

Whorling

A star burst 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-inactivation

A phenomenon in which one of two X chromosomes in every cell of a female's body is inactivated. The process of X-inactivation is random, which helps account for variation in the symptoms of females who carry the Fabry disease gene on only one X chromosome.

X-linked disease

A genetic disease in which the altered gene is carried on the X chromosome. Fabry disease is an X-linked disease.

1. Wilcox W, Oliveira J, Hopkin R, Ortiz A, Banikazemi M, Feldt-Rasmussen U, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Mol Genet Metab.* 2008;93(2):112-28.

2. Desnick R, Brady R. Fabry disease in childhood. *J Pediatr* 2004;144:S20-6.

PERSONALIZED SUPPORT FOR PEOPLE LIVING WITH FABRY DISEASE AND FAMILIES AFFECTED BY RARE DISEASE

CareConnectPSS represents Sanofi Genzyme's more than 35-year commitment to supporting the rare disease community. Whether you are newly diagnosed or already receiving treatment, your CareConnectPSS team will work closely with you and your health care providers to give you the confidential and personalized support you need.

- In-person education as well as disease-specific resources for newly diagnosed people
- Assistance with insurance verification
- Information on medical family trees, genetic testing, and diagnostic labs
- Insurance support related to changes in employment, marital, or dependency status, or if you now qualify for Medicare, Medicaid, or other insurance options

**Call us today to reach your CareConnectPSS Case Manager:
1-800-745-4447, Option 3**



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