Fabry disease, also called alpha-galactosidase-A deficiency, is classified as a lipid storage disorder. This means that people with Fabry disease are unable to metabolize (breakdown) lipids (fats) properly. Because this process occurs within the lysosomes of our cells (which remove waste from the cell), it is also called a lysosomal storage disorder. This leads to a build-up of lipids in the body, which can cause pain in the hands and feet, areas of small dark red spots called angiokeratomas, not being able to sweat properly (hypohydrosis), a clouding of the cornea (front part of the eye), and hearing loss. In addition, the lipid accumulation can lead to an increased risk of a heart attack or stroke, an enlarged heart (cardiomyopathy), and/or kidney disease (renal insufficiency or renal failure or end stage renal disease).

There are two more mild types of Fabry disease, called the 'cardiac variant' and the 'renal variant'. For both, individuals often will not show symptoms or have significant health issues until later in life. People with the cardiac variant may have hypertrophic cardiomyopathy, cardiac arrhythmia, heart failure, or other heart problems. People with the renal variant of Fabry disease may have varying degrees of kidney disease, and may or may not have issues with other organs in the body.

Causes

We have over 20,000 different genes in the body. These genes are like instruction manuals for how to build a protein, and each protein has an important function that helps to keep our body working how it should. The *GLA* gene makes a protein called alpha-galactosidase-A (GLA). The GLA protein helps to break down a fatty substance in our cells called globotriaosylceramide (GTS). By breaking down GTS in the cells, the GLA protein prevents it from building up. If someone has a harmful change (called a pathogenic variant) in their *GLA* gene, then their body is not going to make as much GLA protein as it should. If the body does not have enough GLA protein, then the cells can not break down the GTS fats like they should, which leads to it building up in the cells. This is what leads to the signs and symptoms we associate with Fabry disease.

The *GLA* gene is located on the X chromosome, so Fabry disease is inherited in an X-linked pattern. Males only have one copy of their X chromosome, and therefore only one copy of all the genes that are on the X chromosome. Females have two X chromosomes, so they have two copies of all the genes on the X chromosome. This means that males with Fabry disease will produce little to no GLA protein, while females may produce some due to their second working copy of the gene. Because of this difference, males are often more severely affected and will often develop health issues at younger ages in comparison to females.

It is estimated that approximately 1 in 40,000 to 1 in 60,000 males have Fabry disease. Women can also be affected with Fabry disease but because the symptoms are generally much less severe, it is unknown how common Fabry disease is in women.

Genetic Testing for Fabry disease

Genetic testing for pathogenic variants in *GLA* is available. There are several different ways to approach to testing depending on the medical and family history, and any prior testing that may have been done. Different approaches include:

- *Single site analysis*: Testing specific to a known pathogenic variant in the family
- *Full gene sequencing and rearrangement analysis*: Comprehensive testing to search for all currently detectable pathogenic variants in the *GLA* gene.
- *Gene panels*: Newer, more broadly based gene tests that would include not only the *GLA* gene, but other genes known or suspected to be associated with the patient's medical concerns

Diagnosing Fabry disease

Fabry disease can be diagnosed either through genetic testing, or through a blood test that can measure the amount of GLA protein. There are also some red flags that could increase the chance for Fabry disease in a family:

- Periods of severe pain in the arms and/or legs
- Areas of small dark red spots called angiokeratomas
- Differences in the ability to sweat (most commonly not sweating enough or at all)
- Clouding in the front part of the eye (cornea)
- An incident of stroke or a specific type of heart disease called left ventricular hypertrophy that is seemingly unexplained
- Reduced kidney functioning with no known cause

Medical Management for Fabry disease

Once the diagnosis of Fabry disease is confirmed, screening may be recommended to evaluate for related health issues. This may include heart, kidney, hearing, eye, neurological, vascular, and other evaluations. To keep an eye on the progression of disease, people with Fabry disease will also need to have routine screening of their kidneys, heart, and hearing (and possibly other screening depending on their personal health concerns).

Fabry disease can also be treated by the use of enzyme replacement therapy (ERT), which involves replacing the missing GLA protein (an enzyme is a specific type of protein). This is done through intravenous (IV) infusion. In the United States there are two approved forms of ERT available, called Replagal® and Fabrazyme®.

These are generalized recommendations for Fabry disease. It is important for affected individuals to work with a medical provider who is familiar with Fabry disease to come up with a medical management plan that is best for them.

Click here to learn more about scheduling a genetic counseling appointment for pregnancy-related questions.

Click here to learn more about scheduling a genetic counseling appointment for infertility or preconception questions.

Click here to learn more about scheduling a genetic counseling appointment for questions about pediatric or adult genetic conditions.

Additional Resources

National Fabry Disease Foundation

Fabry Support and Information Groupe (FSIG)