

# FABRY DISEASE

Fabry disease results from the build-up of fatty substances in the walls of blood vessels, particularly the small vessels in the skin, kidneys, heart, and nervous system. Symptoms associated with Fabry disease include an inability to sweat, fever attacks, atrophy of the cornea, and purple skin lesions called angiokeratomas. As the disease progresses, kidney, heart and neurological complications may develop. The fatty substances, called glycosphingolipids, accumulate because patients are unable to produce  $\alpha$ -galactosidase A, an enzyme needed to break down these fats. The enzyme is lacking due to mutations in the  $\alpha$ -galactosidase A (*GLA*) gene on the X chromosome (Xq22.1).

## GENETICS

Males typically have one X chromosome and one Y chromosome, whereas females have two X chromosomes. If a male has a mutation in the *GLA* gene, they will develop Fabry disease. If a female carries a mutation in the *GLA* gene on one of her X chromosomes she will be a carrier of Fabry disease. In rare cases a female carrier will show some symptoms of the disease, such as left ventricular cardiomyopathy. Most female carriers will not develop symptoms. If a female is a carrier, her sons have a 50% chance of inheriting the mutation and being affected with Fabry disease. Her daughters are unlikely to be affected by Fabry disease but have a 50% chance of inheriting the mutation and being carriers themselves.

An accurate biochemical test is available for the diagnosis of Fabry disease consisting of the analysis of  $\alpha$ -galactosidase A activity in plasma, leukocytes or cultured cells. This test should be considered before molecular analysis is undertaken. Molecular identification of the mutation in individuals with a confirmed diagnosis can be used for carrier testing and prenatal diagnosis in the family. The biochemical test is not reliable for identifying female carriers.

## POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

Sex of Patient	<i>GLA</i> Gene Mutation	Explanation
Male	None detected	This result does not support a diagnosis of Fabry disease
Male	Mutation detected	This result confirms a diagnosis of Fabry disease
Female	None detected	This individual is unlikely to be affected with, or a carrier of Fabry disease
Female	Mutation detected	This individual is a carrier of Fabry disease and may transmit a mutation to offspring

## TEST METHODS

- Complete sequencing of the coding region and flanking exon/intron boundaries of the *GLA* gene to identify point mutations or small insertions/deletions.
- Quantitative testing of the *GLA* gene to detect larger deletions or duplications, using MLPA (Multiplex Ligation-dependent Probe Amplification).
- RNA analysis may also be used for affected clinically suspected males who are negative by sequencing and MLPA upon request.

## WHO SHOULD BE TESTED?

- Individuals clinically and/or biochemically suspected of being affected with Fabry disease.
- Women with a family history of Fabry disease, to determine carrier status.
- Pregnancies at risk due to a family history of Fabry disease.

## For More Information

Online Mendelian Inheritance in Man <http://www.ncbi.nlm.nih.gov/omim/> Item # 301500

GeneReviews online clinical information resource <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=fabry>

International Center for Fabry Disease <http://www.mssm.edu/genetics/fabry/>

To locate a genetics centre near you, please visit the Canadian Association of Genetic Counsellors website at [www.cagc-accg.ca](http://www.cagc-accg.ca) or the National Society of Genetic Counsellors website at [www.nsgc.org](http://www.nsgc.org)



1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of Fabry disease, or the possibility the individual is a carrier.

2. It is often helpful to first identify the mutation(s) in an affected family member or parent of the affected family member. If the familial mutation can be identified, only the familial mutation will be tested for.

3. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

4. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

5. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory in the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.