Fabry Disease: GLA Gene Sequencing

Condition Description

Fabry disease is an X-linked condition caused by a deficiency of alpha-galactosidase A enzyme activity. Affected individuals are unable to metabolize globotriaosylceramide (GL-3) in their lysosomes. The progressive accumulation of GL-3 results in symptoms that include: characteristic lysosomal disease skin rashes (angiokeratomas), decreased sweating (hypohidrosis), chronic fatigue, depression, neuropathic pain in the hands and feet (acroparesthesia), gastrointestinal issues, strokes, cardiac disease (including left ventricular hypertrophy), and renal disease (proteinuria to end stage renal disease). The diagnosis of Fabry disease has increased in importance since treatment with enzyme replacement therapy is now available.

Fabry disease affects both men (hemizygotes) and women (heterozygotes), however, the testing strategy varies based on gender. Alpha galactosidase A enzyme analysis alone will detect nearly all affected males and approximately 60% of heterozygous females with Fabry disease. Combining enzyme analysis with sequencing of the alpha galactosidase A gene increases the speed and reliability of testing females for Fabry disease. Alpha galactosidase A enzyme analysis can be performed on samples concurrently with gene sequencing. Sequencing is available for males with a biochemical diagnosis of Fabry. The Fabry Testing Roadmap is available to help choose the correct tests for diagnosis of Fabry disease in males or females.

Mutations to the GLA gene, located at Xq22, result in a deficiency of the enzyme alpha-galactosidase A. Most mutations are familial, however, a few de novo mutations have been reported.

For further information about lysosomal storage diseases, please call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524. For general questions, call the Emory Genetics Laboratory at (404) 778-8500.

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array KX.

Click here for the GeneReviews summary on this condition.


Genes

GLA

Indications

This test is indicated for:

- Patients with a confirmed or suspected diagnosis of Fabry disease
- Family members of a person diagnosed with Fabry disease

Methodology

The 7 exons and flanking regions of the GLA gene are amplified by PCR and sequenced in both the forward and reverse directions. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as previously described mutations, novel mutations, or variations of unknown significance. This analysis may detect novel variants of unclear effect, which may require further studies.

Detection

This assay will detect over 99% of the sequence variants in the coding region and splice junctions. Mutations in the promoter region, some mutations in the introns, and other regulatory elements cannot be detected by this analysis. Large deletion and insertion mutations will not be detected by this assay. It is possible that some patients with a typical presentation may not carry a mutation detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype. Results of molecular analysis must interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml
Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

**Related Tests**

- Alpha-Galactosidase A Enzyme Activity (LB)
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by sequencing.
- A deletion/duplication assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available to couples who are carriers of GLA gene mutations. Please contact the laboratory genetic counselor to arrange prior to collecting a prenatal specimen.

Sequencing is not appropriate for prenatal samples in which familial mutations have not been identified.