

## GLA ( $\alpha$ -Galactosidase A) Gene Testing in Fabry Disease

**Disorder also known as:**

Anderson-Fabry Disease, Hereditary dystopic lipodosis,  $\alpha$ -Galactosidase A deficiency

**Clinical Features:**

Males with Fabry disease have attacks of abdominal pain and arthralgia. Vascular skin lesions (angiokeratoma) are frequent, and vascular lesions may also occur elsewhere, including ocular fundi and kidney. Whorl-like corneal dystrophy is not uncommon. Neurological symptoms include autonomic dysfunction, orthostatic hypotension, and acroparesthesia. Angina, exercise intolerance and EKG changes occur, often with normal coronary arteries, heart size and hemodynamics, although left ventricular wall and septal hypertrophy are not infrequent. Respiratory complications include chronic airflow obstruction. Ultimately, renal failure may cause death. Females who harbor a variant in the GLA gene may have manifestations of the disorder, including renal, cardiac and cerebrovascular involvement, angiokeratomas and corneal epitheliopathy. Fabry disease is due to inactivating variants in the X-linked GLA gene resulting in deficiency of the enzyme alpha-galactosidase A.

**Inheritance Pattern/Genetics:**

X-linked recessive

**Test Methods:**

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice junctions of the GLA gene is analyzed as well as an additional region in intron 4 encompassing the IVS4-801 variant. In addition, if no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available for females to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

**Test Sensitivity:**

Nearly 98% of male patients with a clinical diagnosis of Fabry disease have an identifiable variant. This test is less efficient when testing a female relative without prior testing of an affected male in the family, because partial or whole gene deletions, which account for approximately 2% of GLA variants, may not be detectable by sequencing. In females, if no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of the GLA gene.

A variety of variants occur in Fabry disease, including missense, nonsense, splice-site, partial gene rearrangements, and small and large deletions and insertions. Most variants are “private”, occurring only in a single family.

**References:**

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3. Bennett RL et al., J of Genetic Counseling, 11(2):121-146 (2002)
4. Schafer et al., Hum Mutat 25(4):412 (2005)
5. Gupta et al., Medicine 84(5):261-268 (2005)