

Fabry Disease via *GLA* Gene Sequencing -- Test #471

Brief Description of Clinical Features: Fabry disease (OMIM 301500) is a lysosomal storage disorder due to deficiency in the lysosomal enzyme glycohydrolase alpha-galactosidase A (α -GAL A) (Brady et al. N Engl J Med 276:1163-1167, 1967). The enzymatic deficiency results in the progressive accumulation of globotriaosylceramide and related glycosphingolipids in the vascular endothelium, causing the disease manifestations. Fabry Disease is inherited as an X-linked recessive trait, and female carrier may develop the disease. It is a clinically heterogeneous disease even among affected members of the same family (Banikazemi et al. <http://emedicine.medscape.com/article/951451-overview>).

In male patients with Fabry Disease, two forms are recognized: the classic and atypical forms. The classic form is characterized by onset during the first two decades of life and features including corneal and lenticular opacities, angiokeratoma (skin lesions), acroparesthesias (excruciating pain in the extremities) and hypohidrosis (decreased ability to sweat). In the atypical form, symptoms begin later in life and include left ventricular hypertrophy, arrhythmias and /or cardiomyopathy. The classical features are not present in cases with the atypical form of the disease.

In female heterozygotes, clinical manifestations are largely determined by random X inactivation (Dobrovolny et al. J Mol Med 83:647-654 Epub, 2005). Female heterozygotes may be asymptomatic throughout a normal life span or affected with variable severity. Fabry Disease occurs in diverse ethnic groups throughout the world, with an estimate incidence of 1 in 60,000 males (Meikle et al. JAMA 281:249-254, 1999). In untreated patients, death results from renal failure, heart failure and/or myocardial infarction. See also the Fabry Support & Information group at (<http://www.fabry.org>).

Genetics: Mutations in the *GLA* gene are responsible for the α -GAL A enzyme deficiency and subsequent development of Fabry Disease (Bernstein et al. J Clin Invest 83:1390-1399, 1989). More than 500 mutations, distributed along the entire coding region of the gene have been detected in patients with Fabry Disease. Most mutations were unique to single families and included missense, nonsense, splicing, and small insertions/deletion mutations. Partial or whole deletions of the *GLA* gene accounted for less than 0.05 % of all Fabry Disease cases, and complex rearrangements have been detected in only three patients.

Description of This Particular Test: The *GLA* gene encodes the alpha-galactosidase A enzyme. This test involves bidirectional DNA sequencing of all 7 coding exons and splice sites of the *GLA* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutation or to confirm previous results.

Reference Sequences: Genomic: **NC_000023.9** mRNA and protein: **CCDS 14484.1**

Indications for Test: Male patients with Fabry Disease and potentially heterozygous females are candidates.

Sensitivity of Test: This test detects *GLA* mutations in nearly 100% of males with Fabry Disease (Mehta and Hughes, GeneReviews, 2008, www.genetests.org). The sensitivity of this test in female heterozygote is currently not known.

Turn Around Time: Maximum of 40 calendar days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the *GLA* Gene: \$ 490

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x7	83898	\$ 120	Sequencing x7	83904	\$ 190
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 70

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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