GLA Gene Sequencing Assay (Fabry Disease): Genetics and Clinical Overview

Test Information:
GLA Gene Sequencing Assay (Fabry Disease) (CMGDL test code 3003)
For sample collection and transport refer to the CMGDL website www.medgen.med.miami.edu/. Also, see the link for additional test ordering information such as CPT codes, test methodology and limitations. (06202012 v1)

Gene and Disease Information
Fabry disease is the result of deficient activity of the enzyme α-galactosidase (α-Gal A) with progressive accumulation of globotriaosylceramide (GL-3) in the lysosomes of cells throughout the body (Metha, 2011). The incidence of Fabry disease is approximately 1:50,000 males (Desnick, 2001). An Italian newborn screening study has indicated an incidence as high as 1:3,100 with a much higher (11:1 ratio) incidence of patients with the later-onset classic phenotypes (Spada, 2006). All ethnic, racial, and demographic groups are affected by Fabry disease.

Molecular Genetics. GLA is the only gene known to be associated with Fabry disease. Fabry disease is inherited in an X-linked manner. GLA is located on Xq22 and spans approximately 13 kb of genomic DNA with seven exons; the cDNA is 1290 bases and encodes a polypeptide of 429 amino acids. More than 300 mutations have been identified and most are family specific, occurring only in single pedigrees (Desnick, 2001; Germain, 2002; Rodriguez-Mari, 2003; Schäfer, 2005).

Clinical Significance
Fabry disease manifestations range from the severe classic phenotype to atypical forms. The classic phenotype is the most common although atypical, late-onset forms of the disease may be missed to diagnosis (Sachdev, 2002; Nakao, 2003). Age of onset is 4-8 years for the classic form whereas renal and cardiac forms onset is in the adulthood.

Classic Fabry Disease, Affected Males. Progressive lysosomal deposition of globotriaosylceramide (GL-3) in the vascular endothelium causes the major clinical manifestations of the classic form in males (Desnick, 2001). Symptoms of the classic form usually occur in childhood or adolescence with periodic episodes of severe pain in the extremities (acroparesthesias), vascular cutaneous lesions (angiokeratomas), hypohidrosis, and characteristic corneal and lenticular opacities. Renal insufficiency usually occurs in the third to fifth decade of life. Complications of renal disease, cardiac involvement, and/or cerebrovascular disease are the main causes of death.

Heterozygous Females (Carriers). Random X-chromosome inactivation is responsible for the variable presentation and penetrance in female carriers (Deegan, 2006), ranging from asymptomatic with normal lifespan to phenotypes as severe as affected males. With age female carriers may develop mild to moderate heart’s left ventricular hypertrophy, valvular disease, myocardial ischemia and infarction. Fatigue, suicidal ideation, and depression may be present in carriers.

Atypical Variants of Fabry Disease. Late-onset of cardiovascular, cerebrovascular, and renal manifestations of Fabry disease are more common than previously suspected. The characteristic skin lesions and acroparesthesias are often not present in the atypical forms, whereas it is present the end-stage renal disease (ESRD), cardiac manifestations, and risk for neurologic complications such as stroke/transient ischemic attack (TIA).

Disease Cardiac variant. Males with atypical Fabry disease cardiac variant are asymptomatic for most of their lives with late disease onset in the sixth to eighth decade of life. Hypertrophic Cardiomyopathy (HCM) is often the clinical presentation that leads to their diagnosis. Screening of males with late onset of HCM has shown that low α-Gal A enzyme activity and GLA mutations were present in 6.3% of patients diagnosed after age 40 and 1.4% of males diagnosed before age 40 (Sachdev, 2002). Thus, cardiac variants may go frequently underdiagnosed among individuals with cardiomyopathies. Fabry disease cardiac variants can also affect women (Cantor, 1998).

Disease Renal variant. Fabry disease manifestations may not be present in individuals with the renal variant and renal insufficiency. In fact, renal variants have been identified in individuals on chronic hemodialysis with no classic Fabry disease signs in whom ESRD was misdiagnosed as chronic glomerulonephritis (Nakao, 2003). Consequently, it is appropriate to test for Fabry disease in patients on renal dialysis or undergoing renal transplantation without a primary or biopsy diagnosis for Fabry disease.
Indications for Testing

- to confirm or establish a Fabry disease diagnosis in male patients, generally after α-galactosidase (α-Gal A) enzyme activity has been determined
- to confirm the carrier state in females with markedly decreased α-Gal A enzyme activity
- to clarify the genetic carrier status in females with an α-Gal A enzyme activity in the normal range
- to rule in an atypical Fabry disease diagnosis in patients with late onset of cardiomyopathies
- to rule in an atypical Fabry disease diagnosis in patients on renal dialysis or undergoing renal transplantation without a primary or biopsy diagnosis for Fabry disease

Note: this test is not designed to identify and detect the deep intronic gene mutations. Please contact us for further information.

Contraindications

- Testing should not be ordered for individuals with previously identified familial GLA mutations. To test for a specific mutation, it is recommended to order Family Testing, Gene Sequencing Targeted Mutation Analysis (CMGDL test code 3000) and provide a copy of the laboratory report stating the familial mutation.
- Prenatal testing is not performed by the CMGDL

Results Interpretation

- Identification of a known pathogenic GLA mutation in a clinically affected individual confirms a diagnosis of Fabry disease
- Failure to identify a GLA mutation in a clinically affected individual does not rule out a clinical and/or biochemical diagnosis of Fabry disease. Patient management should be based on clinical findings and family history
- This test may identify GLA gene variants of unknown clinical significance

Related Tests

- Family Testing, Gene Sequencing Targeted Mutation Analysis (test code 3000)
(visit our website at www.medgen.med.miami.edu)

References

- OMIM. Fabry Disease. # 301500. http://www.omim.org/entry/301500