CENTOGENE
THE RARE DISEASE COMPANY

GLA Factsheet

Fabry Disease

CENTOGENE ID	373
Gene(s) name (OMIM®, HGNC)	*GLA*
Gene OMIM®	300644
Disease OMIM®	301500
Gene location	Xq21.3-q22

INHERITANCE PATTERN
X-linked

DISEASE SYNONYMS
Alpha-Galactosidase A Deficiency, Anderson-Fabry Disease, Angiokeratoma Corporis Diffusum, Hereditary Dystopic Lipidosis, Ceramide Trihexosidase Deficiency

MATERIAL

Minimum DNA (µg)	Minimum EDTA Blood (ml)	Minimum Filtercards (pcs)
2	1	1

TURNAROUND TIME
Estimated working days upon sample receipt

Enzymatic (α-GAL A)	Biomarker LYSO-GB3	Full Gene Sequencing	DEL/DUP Analysis
7	7	15	15

We recommend ordering parallel or reflex testing workflows to shorten the total turnaround time.

Clinical Features

Fabry disease (FD) is an X-linked inborn error of glycosphingolipid metabolism caused by absent or significantly reduced levels of a lysosomal enzyme, called α-galactosidase A (α-gal A). The enzyme deficiency leads to the progressive accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3), in numerous organs of the body.[1,2] This deposition causes a range of symptoms, which varies from one person to another, and is characterized by specific neurological, cutaneous, renal, cardiovascular, cochleo-vestibular, and cerebrovascular manifestations. FD affects males and females, and it has two major phenotypes based on % level of α-gal A activity: (1) classic; (2) non-classic. In classic phenotypes, males have less than 1% α-gal A activity and show symptoms in childhood, which include acroparesthesia, angiokeratomas, hypohidrosis, corneal and lenticular opacities, and gastrointestinal complications. With advancing age, they may present with gradual deterioration of renal function to end-stage renal disease (ESRD) and cardiac and/or cerebrovascular disease. Heterozygous females usually have milder symptoms or late age of onset, compared to males, and are barely asymptomatic or might present with a severe phenotype like affected males. In non-classic forms, males with greater than 1% α-gal A activity do not show symptoms in childhood and present with a (1) cardiac; or (2) renal; or (3) cerebrovascular phenotype, between the age of 40 to 80.[3] The estimated prevalence of the classic phenotype is 1 in 40,000-60,000 males and 1 in 20,000 females. The non-classic forms are more prevalent.[4]

FD occurs when a person inherits pathogenic variants in the *GLA* gene. At CENTOGENE, over 500 variants have been detected in the *GLA* gene, which includes missense, frameshift, nonsense, splicing variants, and others.

Enzyme replacement therapy (ERT) and pharmacological chaperone therapy (PCT) for amenable mutations are FD treatment options. ERT can reduce lipid storage, ease pain, and preserve organ function in affected patients.[5]

Differential Diagnosis

The differential diagnosis of Fabry disease and *GLA*-related disorders – depending on the major symptoms in the initial case – includes rheumatoid arthritis, erythromelalgia, neurosis, systemic lupus erythematosus, petechiae, Raynaud syndrome, and early-onset strokes of other origins.

Diagnostic Strategy: Biochemistry & Genetics

FD is diagnosed differently depending on sex. For males, blood samples can be biochemically and genetically tested to confirm the disease. In females, gene analysis should be done, as many affected females might have normal levels of enzyme activity. We offer the following assay for diagnosing Fabry disease:

Biochemistry

Biochemistry analyses are performable via dried blood spot or EDTA blood. In other samples, including DNA, skin biopsies, and amniotic fluid, it is not feasible to perform biomarker or enzymatic quantification.

- The biomarker Lyso-Gb3 is used to identify classic and late-onset affected males FD patients.[6] Additionally, it is able to reflect any potential need of correcting the course of treatment. Tracking biomarkers helps in follow-up of disease progression and estimation of treatment efficacy.[7] We recommend measuring the biomarker at least once every three months.
- Enzymatic quantification (alpha-galactosidase A) in dried blood spot or blood sample.

Genetics

- *GLA* gene sequencing: Single gene or panel testing
- If no pathogenic or likely pathogenic variants are identified, *GLA* deletion / duplication analysis by MLPA is recommended

Referral Reasons

The following individuals are candidates for this particular gene testing:

- Individuals with a known or suspected family history of disease and presentation of the most common symptoms
- Individuals without a positive family history, but with symptoms resembling this disease

Test Utility

Biochemical testing and sequencing should be performed for all individuals. In addition to the above-mentioned testes, detection of deletion/duplication can also be executed in females.Confirmation of a clinicaldiagnosis through genetic testing may direct medical management.
Genetic counseling is recommended and can provide a patient and / or family with the natural history of the condition, identify at-risk family members, provide reproductive risks as well as preconception / prenatal options, and allow for appropriate referral for patient support and / or resources.

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6 Maruyama, H., Miyata, K., Mikame, M. et al. Effectiveness of plasma lyso-Gb3 as a biomarker for selecting high-risk patients with Fabry disease from multispecialty clinics for genetic analysis. Genet Med 21, 44–52 (2019). https://doi.org/10.1038/gim.2018.31
7 Sakuraba, H., Togawa, T., Tsukimura, T. et al. Plasma lyso-Gb3: a biomarker for monitoring fabry patients during enzyme replacement therapy. Clin Exp Nephrol 22, 843–849 (2018). https://doi.org/10.1007/s10157-017-1525-3

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