Fabry Disease

Overview

Fabry disease is a progressive, genetic disorder caused by a deficiency or absence of lysosomal α-galactosidase A activity due to mutations in the *GLA* gene, located on the X-chromosome.[1,2] Lack of sufficient α-galactosidase A activity leads to progressive accumulation of the glycosphingolipids globotriaosylceramide (denoted GL3 or Gb3) and globotriaosylsphingosine (Lyso-GL3 or Lyso-Gb3) within lysosomes in a variety of cell types, including vascular endothelium, podocytes, arterial smooth muscle cells, and cardiomyocytes.[1,2]

Fabry patients are typically classified as classic or later-onset (non-classic):

	Classic	Non-Classic
	Primarily present in childhood/adolescence with neuropathic pain, angiokeratomas, corneal opacities, hypohidrosis, and GI disturbances that progress to kidney failure, cardiomyopathy, cardiovascular disease, arrhythmias, and stroke/TIA.[1,2]	Most frequently present with cardiovascular symptoms in the 4th to 7th decades of life and may or may not have multi-organ involvement.[1]
	Have a wide spectrum of disease manifestations from asymptomatic to a severe phenotype similar to classic males.[1]	Have a wide spectrum of disease manifestations from asymptomatic to a phenotype similar to non-classic males.[1]

Incidence

- United States incidence estimates based on newborn screening data vary from 1 in 1500 males (Missouri) to 1 in 7800 males (Washington state)[2]
  - Frequency of the classic and late-onset forms is estimated to be up to 1 in 22,570 males and 1 in 1,390 males, respectively[1]

Inheritance

- X-linked inheritance pattern caused by mutations in the *GLA* gene[1]
  - ~70% of all females with a Fabry pathogenic variant exhibit symptoms of varying degrees[5]

Diagnosis

Definitive diagnosis is established by:

Males:[1]
- α-galactosidase A enzyme activity assay: demonstrating deficiency
- *GLA* gene sequencing: demonstrating one pathogenic variant

Females:[1,3]
- *GLA* gene sequencing: demonstrating one pathogenic variant
- Note that females with Fabry disease may have normal-to low-normal α-galactosidase A enzyme levels, and therefore enzyme assay is not recommended as a primary diagnostic test in females.

Measuring lyso-GL-3 levels in plasma may aid in disease classification as well as risk stratification for both males and females.[4]

The following evaluations may support a diagnosis of Fabry disease:

Clinical Findings

- Disease presentation is heterogeneous: neuropathic pain (chronic and acute), gastrointestinal symptoms (postprandial abdominal pain, diarrhea, nausea, vomiting), hypohidrosis or anhidrosis, angiokeratomas, corneal verticillata, chronic fatigue, difficulty gaining weight, hearing loss, tinnitus, depression, anxiety, history of stroke and/or TIA, cardiac or renal event[1]
- Family history of any of the above[1]

Laboratory Testing

- Albuminuria, proteinuria, eGFR decline often more rapid than non-Fabry kidney disease[1]
- Plasma or DBS globotriaosylsphingosine (denoted lyso-GL3 or lyso-Gb3): current evidence suggests lyso-GL3 is significantly increased in classic male patients; elevated but less so in both non-classic males and classic females. May be mildly elevated or normal in non-classic female Fabry patients[1,3]
- Kidney Biopsy Findings: GL3 accumulation ("Zebra" or "myeloid" bodies) in multiple renal cell types, podocyte injury (leading to glomerulosclerosis), tubular atrophy, interstitial fibrosis, arteriolar injury[1]

Other

- Echocardiogram: left ventricular hypertrophy, hypertrophic cardiomyopathy[1]
- ECG: shortened PR interval (in early stages), AV-block, A-fib, bradycardia, T-wave inversion, LBBB/RBBB, NSVT[1]
- Cardiac MRI: late enhancement of posterior inferobasilar wall indicating myocardial fibrosis[1]
- Neuro/Cerebrovascular imaging: small vessel occlusion, dolichoectasia, white matter hyperintensities[1]

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Testing Options for Fabry Disease

Some of the laboratories below offer testing for both α-GAL A enzyme assay and *GLA* sequencing. There may be other testing appropriate for your patient, and this is not an endorsement of any specific laboratory. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. Consult each laboratory for a full range of options. Content is current at time of publication, and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics. Sanofi does not review or control the content of non-Sanofi websites. This listing does not constitute an endorsement by Sanofi of information provided by any other organizations.

Laboratory	Available Testing	Sample Requirements	Avg TAT
Centogene	Enzyme	WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles	7 d
	Sequencing (incl Del/Dup)	WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles; Saliva; Buccal swab	15-25 d
	Lyso-GL3	WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles	7 d
Duke University	Enzyme	WB: 4 ml EDTA (lavender) tube; DBS card: 5 circles	15 d
	Sequencing	WB: 2-3 ml EDTA (lavender) tube; DBS card: 5 circles	28 d
	Lyso-GL3	WB: 4 ml EDTA (lavender) tube	28 d
The Fabry Diagnostic Project (run by Emory University)	Enzyme	WB: 5-10 ml heparin (green) tube	7-10 d
	Sequencing (incl Del/Dup)	WB: 5-10 ml EDTA (lavender) or ACD (yellow) tube	4 wks
Greenwood Genetic Center	Enzyme	WB: 5-10 ml sodium heparin (green) tube; Plasma; DBS card: 3 circles	2 wks
	Sequencing	WB: 5-6 mL EDTA (lavender) tube; DBS card: 3 circles; Saliva	3 wks
Labcorp	Enzyme	WB: 5-10 ml ACD (yellow) tube	7-10 d
	Sequencing	WB: 7 ml EDTA (lavender) tube or ACD (yellow) tube	18-21 d
Mayo Clinic Laboratories	Enzyme	WB: 6 ml ACD (yellow) tube; DBS card: 2 circles; Serum: 2 ml (red top tube)	8-15 d
	Sequencing	WB: 3 ml EDTA (lavender) or ACD (yellow) tube; DBS card: 2-5 circles	14-20 d
	Lyso-GL3 (LGB3S, LGBWB, LGBBS)	WB: 1ml EDTA (lavender) tube; Serum: 1 ml (red top tube); DBS card: 2 circles	8-15 d
Revvity Omics (including The Lantern Project*)	Enzyme	WB: 2-10 ml EDTA (lavender) tube (volume varies with age); DBS card: 3 circles	3 d
	Sequencing (incl Del/Dup)	WB: 2-10 ml EDTA (lavender) tube (volume varies with age); DBS card: 3 circles; Saliva: (per Oragene kit)	3 wks
	Lyso-GL3	WB: 2-10 ml EDTA (lavender) tube (volume varies with age); DBS card: 3 circles	3 d

Laboratory	Kits	Mobile Phlebotomy	Billing	Contact
Centogene	Blood, DBS, Saliva	Yes	Inst, Self-pay, Ins	P: 617-580-2102 E: customer.support-US@centogene.com W: www.centogene.com
Duke University	No	No	Inst	P: 919-613-8400 E: clientservices@dm.duke.edu W: https://testcatalog.duke.edu
The Fabry Diagnostic Project (run by Emory University)	Blood, Saliva	No	No charge*	P: 800-200-1524 or 404-778-8518 E: fabry.testing@emory.edu W: https://med.emory.edu/departments/human-genetics/clinical-trials/research/aakp-emory-fabry-testing-project.html
Greenwood Genetic Center	Blood, DBS, Saliva	No	Inst, Self-pay, Ins (SC residents only)	P: 800-473-9411 E: labgc@ggc.org W: www.ggc.org
LabCorp	Blood	Yes	Inst, Ins, Self-pay	P: 800-345-4363 W: www.labcorp.com
Mayo Clinic Laboratories	DBS (in some cases)	Yes	Inst (ins can be billed in some cases, Inst account required)	P: 800-533-1710 E: mcl@mayo.edu W: www.mayocliniclabs.com
Revvity Omics (including The Lantern Project*)	Blood, DBS, Saliva	No	Inst, Self-pay, No charge*	P: 866-354-2910 E: genomics@revvity.com W: www.revvity.com W: www.LanternProjectDx.com

***Testing is performed at no charge; local charges may apply for sample collection, processing, or shipping.**

acct = account; avg TAT = average turnaround time; d = days; DBS = dried blood spot; del = deletion; dup = duplication; Ins = insurance; Inst = institution; lyso-GL3 = globotriaosylsphingosine; WB = whole blood; wks = weeks.

References: **1.** Ortiz A, et al. *Mol Genet Metab.* 2018;123:416–427. **2.** Schiffmann R, et al. *Kidney Int.* 2017;91:284–293. **3.** Smid BE, et al. *J Med Genet.* 2015;52:262–268. **4.** van der Veen SJ, et al. *Clin J Am Soc Nephrol.* 2023 Oct 1;18(10):1272-1282. **5.** Wilcox WR, et al. *Mol Genet Metab.* 2008 Feb;93(2):112–128.

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