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 males** 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]
- **Non-classic/Later-onset patients** most frequently present with cardiovascular symptoms in the 4th to 7th decades of life and may not have multi-organ involvement.[1]
- **Female Fabry patients** have a wide spectrum of disease manifestations from asymptomatic to a severe phenotype similar to 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 1390 males, respectively[1]

Inheritance

- X-linked inheritance pattern caused by mutations in the *GLA* gene[1]
  - ~70% of all females with a Fabry mutation exhibit symptoms of varying degrees[4]

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. Lyso-GL3 levels may be informative if gene sequencing results are inconclusive.

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

Sanofi Genzyme does not review or control the content of non-Sanofi Genzyme websites. These listings do not constitute an endorsement by Sanofi Genzyme of information provided by any other organizations. The following is a selection of laboratories offering both α-GAL A enzyme assay and *GLA* sequencing. This is not an exhaustive list of labs that offer one or the other or an endorsement of any one lab Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. To test individuals with a family history of Fabry for a known familial mutation, please contact your lab of choice to discuss. Content is current at time of printing and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics.

Lab	Available Testing	Sample Requirements	Kits	Avg TAT	Mobile Blood Draw	Billing	Contact
Centogene	Enzyme	WB: 1ml EDTA (lavender) tube; DBS card: 10 circles	Blood, DBS, Saliva	7 d	Yes	Inst, Self-pay, Ins	**P:** 617-580-2102 **E:** customer.support-US@centogene.com **W:** https://www.centogene.com
	Sequencing	WB: 1ml EDTA (lavender) tube; DBS card: 10 circles; Saliva; Buccal swab		15-25 d			
	Del/Dup	WB: 1ml EDTA (lavender) tube; DBS card: 10 circles; Saliva; Buccal swab		15 d			
Duke University	Enzyme	WB: 3-5 ml EDTA (lavender) tube; DBS card: 5 circles	No	15 d	No	Inst	**P:** 919-613-8400 **E:** clientservices@dm.duke.edu **W:** https://testcatalog.duke.edu
	Sequencing	WB: 2 ml EDTA (lavender) tube; DBS card: 5 circles		28 d			
	Lyso-GL3	WB: 4 ml EDTA (lavender) tube		28 d			
The Fabry Diagnostic Project (performed at EGL)	Enzyme	WB: 5-10 ml heparin (green) tube	Blood, Saliva	7-10 d	No	No charge*	**P:** 800-200-1524 or 404-778-8518 **E:** fabry.testing@emory.edu **W:** www.genetics.emory.edu/patient-care/lysosomal-storage-disease-center
	Sequencing	WB: 5-10 ml EDTA (lavender) or ACD (yellow) tube		4 wks			
	Del/Dup	WB: 5-10 ml EDTA (lavender) or ACD (yellow) tube		4 wks			
Greenwood Genetic Center	Enzyme	WB: 5-10 ml heparin (green) tube; DBS card: 3 circles	Blood, DBS, Saliva	2 wks	No	Inst, Self-pay, Ins (SC residents only)	**P:** 800-473-9411 **E:** labgc@ggc.org **W:** www.ggc.org
	Sequencing	WB: 5-6 ml EDTA (lavender) tube; DBS card: 3 circles; Saliva		2 wks			
	Del/Dup	WB: 5-7 ml EDTA (lavender) tube		26 d			
LabCorp/ Integrated Genetics	Enzyme	WB: 5-10 ml ACD (yellow) tube	Blood	7-10 d	Yes	Inst, Ins, Self-pay	**LabCorp Customers:** **P:** 800-345-4363 **W:** www.labcorp.com **Integrated Customers:** **P:** 800-848-4436 **E:** asklGclientservices@integratedgenetics.com **W:** www.integratedgenetics.com
	Sequencing	WB: 7 ml EDTA (lavender) tube or ACD (yellow) tube		18-21 d			
The Lantern Project (performed at PerkinElmer Genomics)	Enzyme	WB: 2-10 ml EDTA (lavender) tube (volume varies with age); DBS card: 3 circles	Blood, DBS, Saliva	3 d	Yes	No charge*	**P:** 866-354-2910 **E:** genomics@perkinelmer.com **W:** www.LanternProjectDx.com
	Sequencing (including Del/Dup)	WB: 2-10 ml EDTA (lavender) tube (volume varies with age); DBS card: 3 circles, Saliva: (Oragene)		3 wks			
	Lyso-GL3	DBS: 2 circles		3 d			
Mayo Clinic Laboratories	Enzyme	WB: 6 ml ACD (yellow) tube; DBS card: 2 spots; Serum: 2 ml (red top tube)	DBS (in some cases), Saliva	8-15 d	Yes	Inst (ins can be billed in some cases, Inst acct required)	**P:** 800-533-1710 **E:** mcl@mayo.edu **W:** www.mayocliniclabs.com
	Sequencing	WB: 3 ml EDTA (lavender) or ACD (yellow) tube; DBS card: 2-5 spots		14-20 d			
	Lyso-GL3 (LGB3S, LGBWB, LGBBS)	WB: 1 ml EDTA (lavender); Serum: 1 ml (red top tube); DBS: 2 circles		8-15 d			
Mount Sinai International Center for Fabry Disease	Enzyme	WB: 20 ml sodium heparin (green) tube	Blood, Buccal	7-10 d	No	No charge*	**P:** 866-322-7963 **E:** fabry.disease@mssm.edu **W:** https://icahn.mssm.edu/research/fabry
	Sequencing	WB: 20 ml sodium heparin (green) tube; 2 buccal brushes		10-14 d			
Sema4	Enzyme	WB: 2 x 5-10 ml sodium heparin (green)	Blood, Saliva	7-10 d	Yes	Inst, Ins, Self-pay	**P:** 800-298-6470 **E:** clientservices@sema4.com **W:** www.sema4.com
	Sequencing	WB: 5-10 ml ACD (yellow) AND 2 x 5-10 ml EDTA (lavender); Saliva		2-3 wks			

***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.** Wilcox WR, et al. *Mol Genet Metab.* 2008 Feb;93(2):112- 28

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