Fabry Disease Biomarker: Lyso-GL3 (Lyso-Gb3)

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 microvascular endothelium, podocytes, arterial smooth muscle cells, and cardiomyocytes.[1,2]

Fabry disease patients are typically classified as classical or late-onset (non-classical):

- Classical 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]
- Late-onset patients present with variable age of onset and manifestations, and may not have multiple organ involvement.[1]
- Female Fabry patients have a wide spectrum of disease manifestations from asymptomatic to severe phenotype similar to classical.[1]

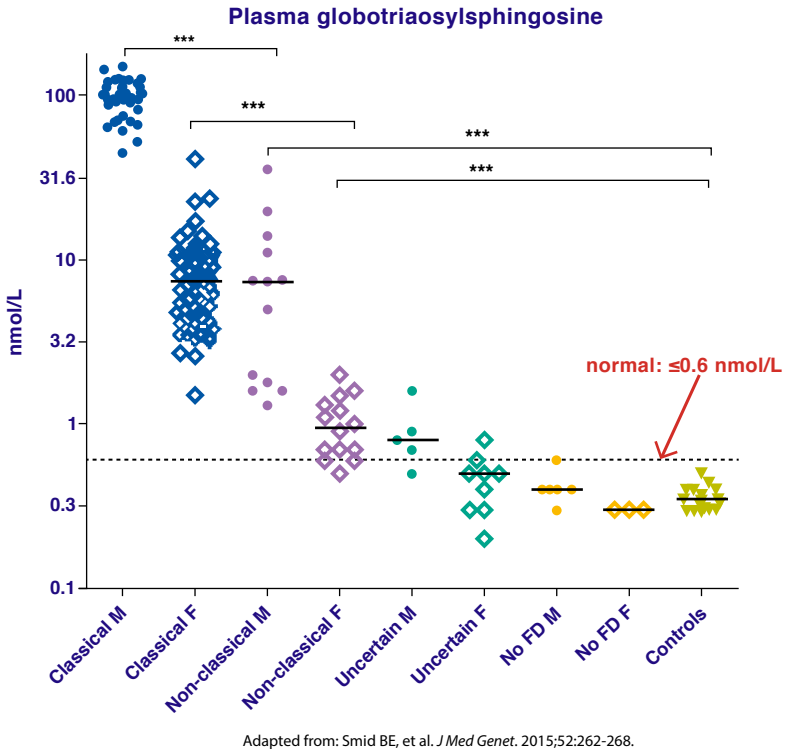
Phenotypic heterogeneity and overlap with more common conditions can make predicting genotype:phenotype correlations challenging.

Biomarker: Globotriaosylsphingosine (Lyso-GL3, Lyso-GB3)

Distinguishing phenotypes:

First reported in 2008 by Aerts et al,[3] globotriaosylsphingosine or lyso-GL3 (also referred to as lyso-Gb3) is a pathogenic, vasoactive metabolite, which may be a useful biomarker for diagnosing Fabry, monitoring disease progression, and differentiating between clinical phenotypes.[3,4]

Plasma lyso-GL3 was measured in a retrospective Dutch adult Fabry Disease (FD) cohort comprising individuals with classical and non-classical FD phenotype. 154 subjects were classified into four groups: classical FD, non-classical FD, uncertain, or no FD[4]:

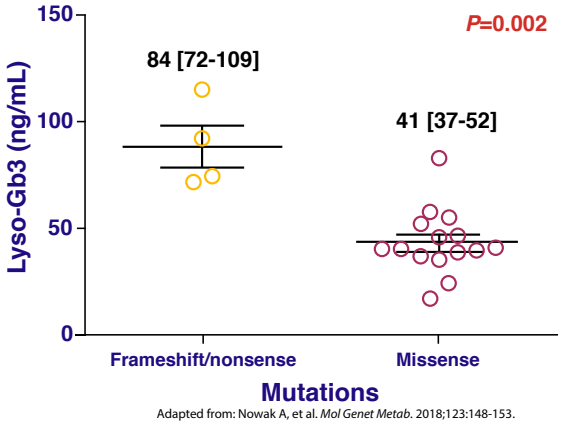


Adapted from: Smid BE, et al. *J Med Genet*. 2015;52:262-268.

- Plasma lyso-GL3 values differ between FD subjects (both male and female subjects with the classical and non-classical phenotype) and controls (P<0.01 for all separate groups vs controls). There was no overlap in lyso-GL3 value between men and women with a classical phenotype or between men with a classical and a non-classical phenotype.[4]
- All men and women with a classical phenotype and men with a non-classical phenotype had higher plasma lyso-GL3 values than controls. Lyso-GL3 values of non-classical female subjects showed some overlap with control values: three out of 14 women with a non-classical phenotype had normal lyso-GL3 values although they were close to the upper limit of the normal range.[4]
- Concentrations of >45 nmol/L are strongly indicative of a classical FD phenotype in men with FD.[4]

Males (M)=dots, Females (F)=diamonds, horizontal lines=median, ***P<0.01.
Classical FD was defined as αGalA enzyme activity in leukocytes <5% of the mean reference value (men) and a *GLA* variant and either one or both of the following criteria: ≥1 of the described characteristic features of FD (neuropathic pain, cornea verticillata, clustered angiokeratoma) or a family member with a definite diagnosis of classical FD.

Correlation of Lyso-GL3 with mutation severity and event rate



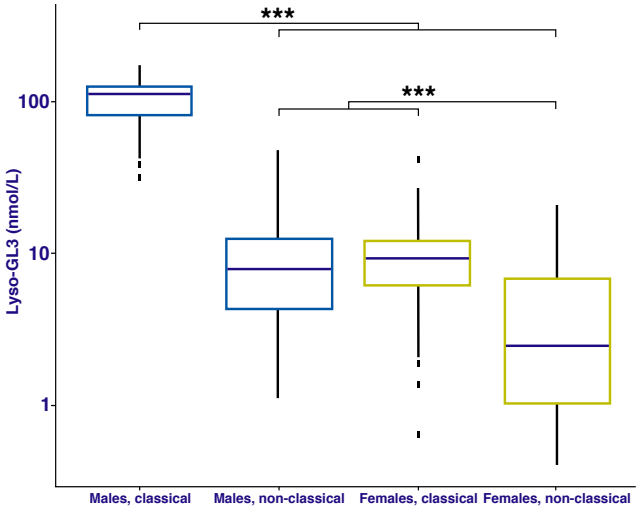
Adapted from: Nowak A, et al. *Mol Genet Metab*. 2018;123:148-153.

Nowak and colleagues explored the potential for lyso-GL3 levels to associate with FD-related comorbidities and genotype severity in 69 consecutive adults (28 males, 41 females) diagnosed with Fabry disease.[5]

- Lyso-GL3 levels (median [interquartile range]) were higher in males with frameshift and nonsense mutations than males with missense mutations. Lyso-Gb3 levels of female patients did not depend on the mutation severity.[5]
- In a univariate linear regression analysis of the same cohort, lyso-Gb3 levels were associated with sex, classic phenotype, serum creatinine, renal replacement, left ventricular mass index (LVMI), presence of cardiomyopathy, and stroke/TIA.[5]

Arends and colleagues retrospectively assessed event-free survival in 499 treatment-naïve adult patients (mean age 43 years old; 41% males, 57% with classic phenotype) from 3 international centers of excellence.[6] Plasma lyso-GL3 concentrations were available for 351 patients:

- Higher lyso-GL3 concentration at baseline was associated with higher event rate (P<0.001).[6]
- In the combined group of non-classical males and all females, a ten-point increase in lyso-GL3 resulted in a more rapid decrease in eGFR (additional decline of-0.34 ml/min/1.73m^2 per year; P<0.01). It was also associated with a 20.7% higher LVMI (95% CI, 14.6 to 27.1; P<0.001) on echocardiography in this cohort.[6]



Adapted from: Arends M, et al. *J Am Soc Nephrol*. 2017;28:1631-1641.

Lyso-GL3 testing options:

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 whose Fabry testing program includes lyso-GL3. 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. 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	Test Name & Code	Sample Requirements	Kits	Avg TAT	Mobile Blood Draw	Billing	Contact
Centogene	Lyso-Gb3	WB: 1ml EDTA (lavender) tube; DBS card: 10 circles	Blood, DBS	7 d	Yes	Inst, Self-Pay, Ins	P: 617-580-2102 W: www.centogene.com
Duke University	Lyso-GL3 (LAB9035)	WB: 4ml EDTA (lavender) tube; Plasma: 1ml	No	5-7 d	No	Inst	P: 919-613-8400 W: https://testcatalog.duke.edu
The Lantern Project (performed at PerkinElmer Genomics)	Lyso-GL3†	DBS: 2 spots	Saliva Blood DBS	3 d	Yes	No Charge*	P: 866-354-2910 E: genomics@perkinelmer.com W: www.LanternProjectDx.com
Mayo Clinic Laboratories	Globotriaosylsphingosine (LGB3S, LGBWB, or LGBBS)	WB: 1ml EDTA (lavender) tube; DBS: 2 spots; Serum: 1ml red top tube	DBS (in some cases), Saliva	8-15 d	Yes	Inst (acct required), Ins (some cases)	P: 800-533-1710 E: mcl@mayo.edu W: www.mayocliniclabs.com
PerkinElmer Genomics	Globotriaosylsphingosine (Lyso-Gb3), B0029	DBS: 2 spots	DBS	3 d	No	Inst, Self-Pay	P: 866-354-2910 E: genomics@perkinelmer.com W: www.perkinelmergenomics.com
Sanofi Genzyme Rare Disease Specialty Testing Program (performed at LabCorp)	Lyso-GL-3	Plasma: 1ml (from sodium heparin/green tube).	Blood⁺	14 d	No~	No Charge* (account required)	P: 888-681-1701 E: RareDiseaseProgram@LabCorp.com W: www.labcorp.com

d=days, DBS=dried blood spots, Ins=Insurance, Inst=Institutional, WB=whole blood, w=weeks.

***Testing is performed at no charge; local charges may apply for sample collection, processing, or shipping. †Lyso-GL3 as part of The Lantern Project is for diagnostic assistance only, not monitoring of existing patients. ⁺Individual testing supplies can be ordered. ~ Phlebotomy is covered if performed at a LabCorp Patient Service Center (PSC).**

1. Ortiz A, et al. *Mol Genet Metab*. 2018;123:416-427. **2.** Schiffmann R, et al. *Kidney Int*. 2017;91:284-293. **3.** Aerts J, et al. *Proc Natl Acad Sci U.S.A*. 2008;105(8):2812-2817. **4.** Smid B, et al. *J Med Genet*. 2015;52(4):262-268. **5.** Nowak A. et al. *Mol Genet Metab*. 2018;123:148-153. **6.** Arends M. et al. *J Am Soc Nephrol*. 2017;28(5):1631-1641.

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