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 variants in GLA., located on the X chromosome.[1,2] Lack of sufficient α-galactosidase A activity leads to progressive accumulation of 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]

Patients with Fabry disease 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]

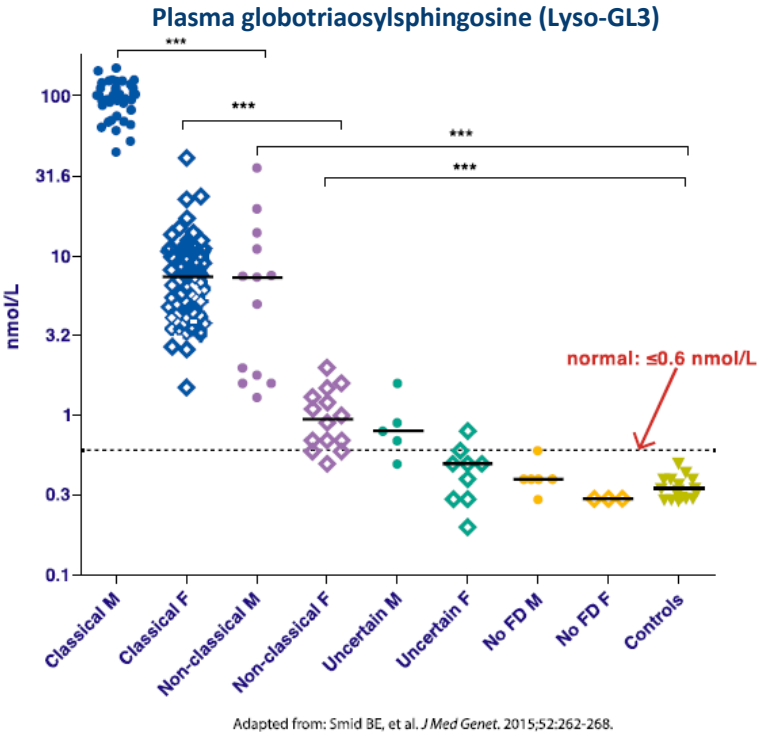
Phenotypic heterogeneity and overlap with more common conditions can make predicting genotype-phenotype correlations challenging.

Biomarker: Globotriaosylsphingosine (Lyso-GL3, Lyso-Gb3)

Distinguishing phenotypes:

First reported in 2008 by Aerts et al, 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. One hundred fifty-four subjects were classified into four groups: classical FD, non-classical FD, uncertain, and no FD.[4]



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

Males (M)=dots, Females (F)=diamonds, horizontal line per group=median, Uncertain FD: Biopsies unavailable to confirm diagnosis, No FD: Negative biopsy or D313Y variant, ***P<0.01

- 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 versus 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 nonclassical phenotype had higher plasma lyso-GL3 values than controls. Lyso-GL3 values in non-classical female subjects showed some overlap with control values: three out of fourteen 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 classical FD phenotype in men with FD.[4]

  Classical FD was defined as α-GalA enzyme activity in leukocytes <5% of the mean reference value (men) and GLA variant and either one or both of the following criteria: ≥1 of the described characteristic features of FD (neuropathic pain, corneal verticillata, clustered angiokeratoma) or family member with definite diagnosis of classical FD. Eighty percent of the women in the classical group had ≥1 characteristic sign or symptom, while 20% was grouped as such because of a family member with a classical FD phenotype.[4]

Did You Know?

Case reports have demonstrated that lyso-GL3 can be elevated in asymptomatic children. Further research is warranted.[5,6]

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Lyso-GL3 is a Bioactive Molecule

Cardiac:

- Stimulates proliferation of vascular smooth muscle cells and cardiomyocytes *in vitro*.[7]
- May be instrumental to development of intra-media thickness and left ventricular hypertrophy[3]
- Correlated with left ventricular mass in females[3]

Renal (all studies performed *in vitro*):

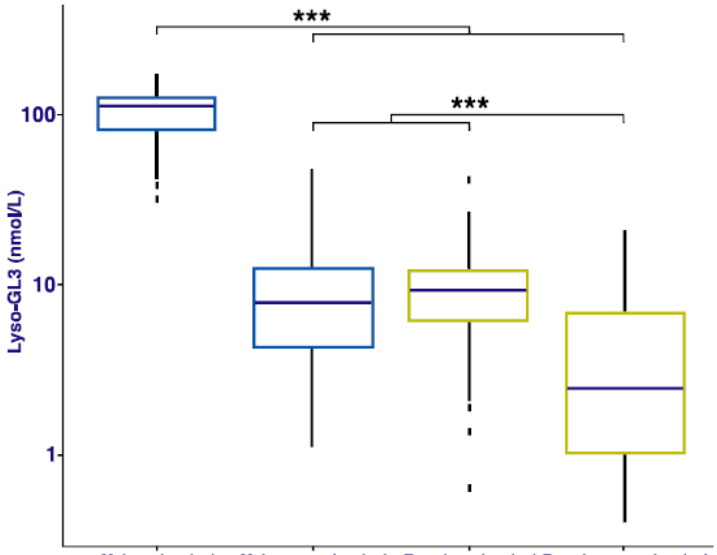
- Induces mechanisms of renal interstitial fibrosis[8]
- Increases RIPK3 expression resulting in increases in albuminuria, podocyte loss, and foot process effacement[9]
- Lyso-GL3 increases TGF-β1 and CD74 mRNA levels in cultured podocytes in a time and dose-dependent manner. TGF-β1 and CD74 are critical mediators of glomerulosclerosis and interstitial fibrosis in diabetic nephropathy.[10]
- Lyso-Gb3 promotes Notch1-mediated inflammatory and fibrogenic responses in podocytes that may contribute to Fabry nephropathy.[11]

Correlation of Lyso-GL3 with Variant Severity and Event Rate

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 three international centers of excellence.[12] Plasma lyso-GL3 concentrations were available for 351 patients:

- Taking all patients together, higher lyso-GL3 concentration at baseline was associated with higher event rate in the past (P<0.001).[12]
- In the analyses of subgroups, an association with event rate was found in men and women with nonclassical FD, whereas no relation was found in men and women with classical FD.[12]
- 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, 14.6to 27.1; P<0.001) on echocardiography in this cohort. LysoGb3 was not associated with eGFR or LVM in men with classical FD phenotype.[12]

Figure Note: The horizontal line inside the box from the 25th to 75th percentile depicts the median, the whiskers extend to the most extreme data point that is no more than 1.5 times the interquartile range. Outliers are indicated by squares. ***P<0.001.



Lyso-GL3 stratified for sex and phenotype. ***P<0.0001.

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

Lyso-GL3 Testing Options

Sanofi does not review or control the content of non-Sanofi websites. These listings do not constitute an endorsement by Sanofi of information provided by any other organizations. The following is a selection of laboratories whose Fabry testing programs include 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.gov/gtr. Content is current at time of printing and tests may not be available in all states; please call the laboratory to confirm test availability, sample shipping information, and all other logistics.

Lab	Test Name and 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	15 d	No	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	28 d	No	Inst	P: 919-613-8400 W: https://testcatalog.duke.edu
The Lantern Project (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	Globotriaosylspingosine (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	Globotriaosylspingosine (Lyso-Gb3), 80029	DBS: 2 spots	DBS	3 d	No	Inst, Self-Pay	P: 866-354-2910 W: www.perkinelmergenomics.com
Sanofi Rare Disease Specialty Testing Program (Labcorp)	Lyso-GL-3	Plasma: 1mL sodium heparin (green) tube	Blood[+]	14 d	No	No Charge* (account required)	P: 888-681-1701 E: RareDiseaseProgram@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. Schiffman R, et al. *Kidney Int*. 2017;91: 284-293. 3. Aerts JM, et al. *Proc Natl Acad Sci* U S A. 2008;105(8):2812-2817. 4. Smid BE, et al. *J Med Genet* 2015;52:262–268. 5. Kritzer A, et al. Mol Genet Metab Rep. 2019;21:100530. 6. Spada M, et al. *Italian J Pediatr* 2017;43:1. 7. Barbey F, et al. *Arterioscler Thromb Vasc Biol*. 2006;26(4):839-844. 8. Jeon YJ, et al. *PLoS One*. 2015;10(8):e0136442. 9. Kim SY, et al. *Cells*. 2021;10(2):245. 10. Sanchez-Niño et al. *NDT*. 2011. 11. Sanchez-Niño et al. *Hum Mol Genet*. 2015. 12. Arends M, et al. *J Am Soc Nephrol*. 2017;28: 1631–1641.

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