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. 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.

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

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

**Disease Overview**

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.

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:

- Males and females with a 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.
- Concentrations of >45 nmol/L are strongly indicative of a classical FD phenotype in men with FD.

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.

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

Plasma globotriaosylsphingosine

Lyso-GL3 levels (median [interquartile range]) were higher in males with Fabry disease. In the combined group of non-classical males and all females, lyso-Gb3 levels were associated with sex, classic phenotype, serum creatinine, renal replacement, left ventricular mass index (LVMI), presence of cardiomyopathy, and stroke/TIA.

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. Higher lyso-GL3 concentration at baseline was associated with sex, classic phenotype, serum creatinine, renal replacement, left ventricular mass index (LVMI), presence of cardiomyopathy, and stroke/TIA.

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. Plasma lyso-GL3 concentrations were available for 351 patients:

- Higher lyso-GL3 concentration at baseline was associated with higher event rate (P<0.001).
- 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/1.73m² 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.

Correlation of Lyso-GL3 with mutation severity and event rate

**Lab** | **Test Name & Code** | **Sample Requirements** | **Kits** | **Mobile Blood Draw** | **Billing** | **Contact**
---|---|---|---|---|---|---
Duke University | α-galactosidase enzyme | WB: 3-5 ml EDTA (lavender) tube; DBS: 5 spots | No | No | Inst | P: 919-613-8400
| GLA Sequencing | WB: 2 ml EDTA (lavender) tube; DBS: 5 spots | 5-7 d | | | W: https://testcatalog.duke.edu
| Lyso-GL3 (LAB9035) | WB: 4 ml EDTA (lavender) tube | 14 d | | | Inst, P: 919-613-8400
Genzyme Clinical Specialty Lab | Plasma Lyso-GL3 | Plasma: 3 x 2 ml plasma; WB: 2 x 6 ml sodium heparin (green) tube | Blood | 30 d | No Charge* | P: 800-745-4447, Option 1
The Lantern Project (performed at PerkinElmer Genomics) | α-galactosidase enzyme | WB: 3-5 ml sodium heparin (green) tube; DBS: 5 spots | Saliva Blood | 3 d | Yes | No Charge* P: 866-354-2910
| GLA Sequencing | WB: 3-5 ml EDTA (lavender) tube; DBS: 5 spots, Saliva: (Oragene) | 3 w | | | E: genomics@perkinelmer.com
| Lyso-GL3 | DBS: 2 spots | 3 d | | | W: www.LanternProjectDx.com
Mayo Clinic Laboratories | α-galactosidase enzyme | WB: 6 ml ACD (yellow) tube; DBS: 2 spots; Serum: 2 ml (red top tube) | DBS (in some cases), Saliva | 8-15 d | Inst (act required), Ins (some cases) | P: 800-533-1710
| GLA Sequencing | WB: 3 ml EDTA (lavender) or ACD (yellow) tube; DBS card: 2-5 spots | 14-20 d | | | E: mcl@mayo.edu
| Globotriaosylsphingosine (LGB3S, LGBWB, or LGBBS) | WB: 3ml EDTA (lavender) tube; DBS: 2 spots; Serum: 0.5-1 ml red top tube | 8-15 d | | | W: www.mayocliniclabs.com
PerkinElmer Genomics | Globotriaosylsphingosine (Lyso-Gb3), B0029 | DBS: 2 spots | DBS | 3 d | No | Inst, Self-Pay P: 866-354-2910

*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.

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

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