All-in-one solution for single gene disorders with diverse mutations

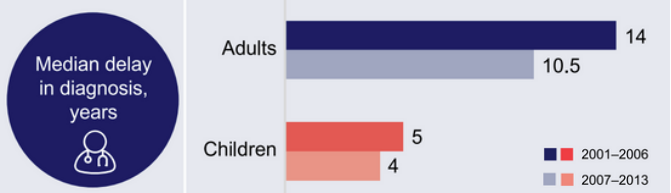
Fabry Disease

Background

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene, resulting in deficient or absent alpha-galactosidase A (α-Gal A) activity. This deficiency leads to the accumulation of globotriaosylceramide (GL-3) and glycosphingolipids (lyso-GL-3) in various cells and tissues. Fabry disease is classified into two forms: classic and late-onset. The clinical manifestations are diverse and typically involve multiple organ systems, most commonly the nervous system, kidneys, heart, skin, gastrointestinal tract, and eyes.

Symptom-based evaluation is always challenging for suspected patients due to the variability in symptom expression. Although enzyme activity analysis is usually effective for diagnosing hemizygous males, it often fails in heterozygous females and late-onset cases. In such instances, genetic testing may be the only tool for a definitive diagnosis.

Fabry disease diagnosis is **often delayed by years**



~25% of patients were initially misdiagnosed
as rheumatological, neuropsy chological, orthopedic, or other diseases

Summary of Fabry Outcome Survey data from reference [1]

Over a thousand *GLA* variants have been reported (HGMD database, 2025) without causative hotspot mutations. Exon analysis with NGS or Sanger sequencing is common for routine practice, but these methods are at risk of missing structural variants and deep intronic variants. This may lead to years of delayed diagnoses due to inconclusive phenotype and absent of genetic findings.

Comprehensive Analysis of Fabry Disease (CAFD)

is your best Fabry disease solution

Comprehensive Analysis of Fabry Disease (CAFD) is a full-length *GLA* gene sequencing assay. Powered by SMRT sequencing technology, it offers an analytical sensitivity of >99.9% while covering all mutation types in a single assay, aligning with the gold standard. CAFD is used to identify the most variants associated with Fabry disease, including deep intronic variants, structural rearrangements, and *cis/trans* configurations.

Disorders (Gene)	Testing Scope
Fabry disease (GLA)	Pathogenic, likely pathogenic, and some VUS SNVs/InDels
	Some large intragenic deletions/duplications classified as pathogenic, likely pathogenic or VUS

Technology: Single molecule real-time (SMRT) sequencing
Platform: PacBio Vega, Sequel II, and Sequel IIe system
Sample type: Blood, DBS, and gDNA
Turnaround time: 17 working days
(starting from the date of sample arrival at the testing laboratory)

Improved diagnostic yield through CAFD's comprehensive variant detection

A total of 48 unrelated suspected probands and 34 relatives were retrospectively tested using Sanger sequencing (*GLA* exons and exon boundaries) and CAFD [2]:

- CAFD identified the *GLA* variant(s) in all probands, whereas Sanger sequencing missed 3 intronic variants in 2 probands
- 16 variants were novel (15 SNVs/InDels and a 1715 bp intronic insertion)
- Nearly all probands (97.92%) can be diagnosed based on the detected variant(s) and clinical indicators, with the exception of a female carrying 2 intronic VUS
- The diagnostic yield can be increased by 2.09% compared to routine Sanger sequencing

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References: [1] Beck M, Ramaswami U, Hernberg-Ståhl E, et al. Twenty years of the Fabry Outcome Survey (FOS): insights, achievements, and lessons learned from a global patient registry. *Orphanet J Rare Dis*. 2022;17(1):238. [2] Yao F, Hao N, Li D, et al. Long-read sequencing enables comprehensive molecular genetic diagnosis of Fabry disease. *Hum Genomics*. 2024;18(1):133.

INT_TGSFDv1.1012026

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