MAYO CLINIC LABORATORIES

Test Definition: FABRZ

Fabry Disease, Full Gene Analysis, Varies

Overview

Useful For

Confirmation of a diagnosis of classic or variant Fabry disease in affected males with reduced alpha- galactosidase A enzyme activity

Carrier or diagnostic testing for asymptomatic or symptomatic females, respectively

Testing Algorithm

The following algorithms are available:

-Fabry Disease: Newborn Screen-Positive Follow-up

-Fabry Disease Diagnostic Testing Algorithm

If the patient has abnormal newborn screening results for Fabry disease, refer to the appropriate American College of Genetics and Genomics Newborn Screening ACT Sheet.(1)

Special Instructions

- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Fabry Disease Diagnostic Testing Algorithm
- Fabry Disease: Newborn Screen-Positive Follow-up
- Hereditary Peripheral Neuropathy Diagnostic Algorithm
- Blood Spot Collection Card-Spanish Instructions
- Blood Spot Collection Card-Chinese Instructions
- Informed Consent for Genetic Testing (Spanish)
- Blood Spot Collection Instructions

Method Name

Polymerase Chain Reaction (PCR) followed by DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

The recommended first-tier test for males with suspected Fabry disease is alpha-galactosidase A enzyme activity in blood or serum. Order either AGAW / Alpha-galactosidase, Leukocytes or AGAS / Alpha-galactosidase, Serum.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. For instructions for testing patients who have received a bone marrow transplant, call 800-533-1710.

Submit only 1 of the following specimens:

Preferred:
Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) tube or yellow top (ACD) tube
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate

Acceptable:
Specimen Type: Blood spot
Supplies: Card - Blood Spot Collection (Filter Paper) (T493)
Container/Tube:
Preferred: Collection card (Whatman Protein Saver 903 Paper)
Acceptable: Ahlstrom 226 filter paper, or Blood Spot Collection Card
Specimen Volume: 2 to 5 Blood spots on collection card
Collection Instructions:
1. An alternative blood collection option for a patient older than 1 year of age is finger stick.
2. Let blood dry on the filter paper at ambient temperature in a horizontal position for 3 hours.
3. Do not expose specimen to heat or direct sunlight.
4. Do not stack wet specimens.
5. Keep specimen dry.
Specimen Stability Information: Ambient (preferred)/Refrigerated
Additional Information:
1. Due to lower concentrations of DNA yielded from blood spots, some aspects of the test may not perform as well as DNA extracted from a whole blood sample. When applicable, specific gene regions that were unable to be interrogated will be noted in the report. Alternatively, additional specimen may be needed to complete testing.
2. For collection instructions, see Blood Spot Collection Instructions
3. For collection instructions in Spanish, see Blood Spot Collection Card-Spanish Instructions (T777)
4. For collection instructions in Chinese, see Blood Spot Collection Card-Chinese Instructions (T800)

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:

-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. Molecular Genetics: Biochemical Disorders Patient Information (T527).
3. If not ordering electronically, complete, print, and send a Biochemical Genetics Test Request (T798) with the specimen.

Specimen Minimum Volume
See Specimen Required

Reject Due To
All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information
Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced alpha-Gal A activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues.

Severity and onset of symptoms are dependent on the residual alpha-Gal A activity. Males with less than 1% alpha-Gal A activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. By middle age, most patients develop renal insufficiency leading to end-stage kidney disease, as well as cardiac and cerebrovascular disease. Males with greater than 1% alpha-Gal A activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage kidney disease. Individuals with the renal variant may or may not have other symptoms of classic Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency later in life. The cardiac variant is not associated with renal failure.

Female carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severe. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A.

Variants in the *GLA* gene result in deficiency of alpha-Gal A. Most of the disease causing variants identified to date are family specific. Full sequencing of the *GLA* gene identifies over 98% of the sequence variants in the coding region and splice junctions. In addition, this assay detects the intron 4 alteration common in the Taiwanese population.(1)

The recommended first-tier test for males with suspected Fabry disease is biochemical testing that measures alpha-galactosidase enzyme activity in blood or serum: AGAW / Alpha-galactosidase, Leukocytes or AGAS /

Alpha-galactosidase, Serum. Additionally, testing for the glycosphingolipid, globotriaosylsphingosine (LGb3) may aid in further clarifying disease status in both males and females with suspected Fabry disease (LGB3S / Globotriaosylsphingosine, Serum). Individuals with decreased or absent enzyme activity and elevated LGb3 are more likely to have an identifiable disease-causing variants in the *GLA* gene by molecular genetic testing. However, enzymatic testing alone is not reliable to detect female carriers.

The following algorithms are available:
-Fabry Disease: Newborn Screen-Positive Follow-up algorithm
-Fabry Disease Diagnostic Testing Algorithm

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics recommendations.(2) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of Fabry disease may have a variant that is not identified by this method (eg, large genomic deletions, promoter alterations). The absence of a variant, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of Fabry disease. For carrier testing, it is important to first document the presence of a *GLA* gene variant in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical and biochemical findings, additional testing should be considered.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Clinical Reference

1. ACMG Newborn Screening ACT Sheets. Accessed September 25, 2024. Available at www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx?hkey=9d6bce5a-182e-42a6-84a5-b2d88240c508
2. Hwu WL, Chien YH, Lee NC, et al. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A). Hum Mutat. 2009:30(10):1397-1405
3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-424
4. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30
5 Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007;9(1):34-35
6. Henderson N, Berry L, Laney DA. Fabry Disease practice resource: Focused revision. J Genet Couns. 2020;29(5):715-717

Performance

Method Description
Bidirectional sequence analysis is performed to test for the presence of a sequence variant in all coding regions and intron/exon boundaries of the *GLA* gene.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Varies

Report Available
14 to 20 days

Specimen Retention Time
Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81405-GLA (galactosidase, alpha) (eg, Fabry disease), full gene sequence

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
FABRZ	Fabry Disease Full Gene Analysis	76036-3

Result ID	Test Result Name	Result LOINC® Value
53894	Result Summary	50397-9

53895	Result	76036-3
53896	Interpretation	69047-9
53897	Additional Information	48767-8
53898	Specimen	31208-2
53899	Source	31208-2
53900	Released By	18771-6