MAYO CLINIC LABORATORIES

Test Definition: FUFXS

Fragile X, Follow-up Analysis (Non-Orderable)

Overview

Useful For

Only orderable as a reflex. For more information see FXS / Fragile X Syndrome, Molecular Analysis, Varies.

Confirming the methylation status of the repeat expansion allele in the *FMR1* gene, to aid the diagnosis of *FMR1*-related disorders

Method Name

Only orderable as a reflex. For more information see FXS / Fragile X Syndrome, Molecular Analysis, Varies.

Methylation Sensitive Polymerase Chain Reaction (PCR) Fragment Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Specimen Required

Only orderable as a reflex. For more information see FXS / Fragile X Syndrome, Molecular Analysis, Varies.

No additional specimen is required. Lab will utilize specimen they already have in the lab for this test.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Note: Where applicable, verbiage refers to sex assigned at birth.

Fragile X syndrome (FXS) is an X-linked disorder with variable expression in male and female patients. In greater than 99% of affected individuals, it is caused by an expansion of the CGG trinucleotide repeat in the 5'UTR (untranslated region) of the *FMR1* gene located on the X chromosome. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 5 to 44. These normal alleles are passed from generation to

generation, with the number of repeats remaining constant. Small expansions, called premutations, range from 55 to 200 CGG repeats. Individuals with a premutation do not exhibit features of FXS but are at risk for other *FMR1*-related disorders, such as fragile X tremor/ataxia syndrome (FXTAS) and primary ovarian insufficiency (POI). Transmission of a premutation by a man to his female child usually results in little or no change in the CGG repeat number. Transmission of a premutation by a woman to her child usually results in further expansion, either to a larger premutation or a full mutation. The risk for a woman with a premutation to have a child affected with FXS by expansion to a full mutation increases with the number of CGG repeats in the premutation. Full mutations are typically greater than 200 repeats long and are generally associated with abnormal methylation of a region adjacent to the *FMR1* gene. This is thought to interfere with normal *FMR1* gene expression, resulting in FXS. There are multiple clinical phenotypes associated with expansion (premutations and full mutations) in the *FMR1* gene.

Fragile X Syndrome:
Approximately 1 in 4000 individuals are affected with FXS. Most affected male patients exhibit moderate intellectual disability with affected female patients having milder, if any, cognitive deficiency. Neuropsychiatric diagnoses, such as autism spectrum and anxiety disorders, are common. Characteristic physical features include a long face with a prominent jaw, protruding ears, connective tissue abnormalities, and large testicles in postpubertal male patients.

Fragile X Tremor/Ataxia Syndrome:
Fragile X tremor/ataxia syndrome is a neurodegenerative disorder that is clinically distinct from FXS. Both male and female patients with a premutation are at risk for FXTAS. However, the disorder is much less common and milder in clinical presentation than FXS and shows a later age of onset in female patients. Clinical hallmarks of the disorder include intention tremor, gait ataxia, dementia, and neuropsychiatric symptoms. The risk for FXTAS increases as the number of CGG repeats increases, and the majority of individuals with FXTAS have CGG repeat expansions of 70 or more. Penetrance of clinical symptoms is associated with increasing age, with the majority of affected male patients showing symptoms between age 70 and 90 years.

Premature Ovarian Insufficiency:
Female patients with a premutation are at risk for increased follicular stimulating hormone levels, early menopause, and POI. Penetrance and early onset of female reproductive symptoms correlate with increasing size of the CGG repeat and reaches its highest penetrance at approximately 80 to 90 repeats. Of note, penetrance remains stable or may even decrease at approximately 100 repeats. There is no risk for increased penetrance of the POI phenotype due to maternal or paternal inheritance of the expanded CGG repeat.

Reference Values

Only orderable as a reflex. For more information see FXS / Fragile X Syndrome, Molecular Analysis, Varies.

Interpretation

The interpretive report includes an overview of the findings as well as the associated clinical significance.

Cautions

For predictive testing, it is important to first document the presence of CGG-repeat amplification in the *FMR1* gene in an affected family member to confirm that molecular expansion is the underlying mechanism of disease in the family.

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

Methylation status will not be assessed on chorionic villus specimens or if the reported sex is female.

Less than 1% of individuals clinically diagnosed with fragile X syndrome do not have the CGG expansion-type mutation. These individuals may have a different type of variant within the *FMR1* gene (eg, deletion or point alteration).

Due to incomplete penetrance and variable expression of the *FMR1* expansion, this test is not reliable for prenatal assessment of disease severity.

The absence of an expansion in the *FMR1* gene does not eliminate the diagnosis of other inherited disorders that have overlapping clinical features with fragile X syndrome, fragile X tremor/ataxia syndrome, or premature ovarian insufficiency.

Clinical Reference

1. Jacquemont S, Hagerman RJ, Hagerman PJ, Leehey MA. Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of *FMR1*. Lancet Neurol. 2007;6(1):45-55
2. Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for *FMR1* gene mutations: practice guidelines of the National Society of Genetic Counselors. J Genet Couns. 2012;21(6):752-60
3. Spector E, Behlmann A, Kronquist K, Rose NC, Lyon E, Reddi HV. Laboratory testing for fragile X, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(5):799-812
4. Hunter JE, Berry-Kravis E, Hipp H, et al. *FMR1* Disorders. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated May 16, 2024. Accessed January 6, 2025. Available at www.ncbi.nlm.nih.gov/books/NBK1384/

Performance

Method Description

Methylation for premutation and full mutation alleles is determined by capillary electrophoresis analysis of a polymerase chain reaction (PCR)-amplified product from DNA that is treated with a methylation-sensitive restriction enzyme.(Grasso M, Boon EM, Filipovic-Sadic S, et al. A novel methylation PCR that offers standardized determination of *FMR1* methylation and CGG repeat length without southern blot analysis. J Mol Diagn. 2014;16(1):23-31; Snow K, Doud LK, Hagerman R, et al. Analysis of a CGG sequence at the FMR-1 locus in fragile X families and in the general population. Am J Hum Genet. 1993;53(6):1217-1228)

PDF Report

No

Day(s) Performed

Varies

Report Available

8 to 10 days

Specimen Retention Time

For retention time information, see FXS / Fragile X Syndrome, Molecular Analysis, Varies.

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

81244

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
FUFXS	Fragile X, Follow up Analysis	No LOINC Needed

Result ID	Test Result Name	Result LOINC® Value
52421	Comment	48767-8
52422	Specimen	31208-2
52423	Source	31208-2
52424	Released By	18771-6