Test Definition: GNF13

Factor XIII Deficiency, F13A1 and F13B Genes, Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating factor XIII deficiency (FXIIID) in patients with a personal or family history suggestive of FXIIID

Confirming an FXIIID diagnosis with the identification of known or suspected disease-causing alterations in the *F13A1* or *F13B* genes

Determining the disease-causing alterations within the *F13A1* or *F13B* genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of FXIIID

Identifying the causative alterations for genetic counseling purposes

Prognosis and risk assessment based on genotype-phenotype correlations

Carrier testing for close family members of an individual with a diagnosis of FXIIID

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *F13A1* and *F13B* genes associated with factor XIII deficiency (FXIIID), a rare bleeding disorder. See Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for FXIIID.

Testing Algorithm

The clinical workup for factor FXIII deficiency (FXIIID) should begin with special coagulation testing for factor XIII activity.

A standard testing algorithm for FXIIID has been developed by the Scientific and Standardization Committee of the International Society for Thrombosis and Haemostasis.(1)

Genetic testing for FXIIID is indicated if:
-The clot solubility test, a screening test for possible factor XIII deficiency, is abnormal or FXIII antigen or activity is decreased
-Acquired causes of FXIIID have been excluded (eg, leukemia, liver disease, Henoch-Schonlein purpura, inflammatory bowel diseases, disseminated intravascular coagulation, pulmonary embolism, stroke, and sepsis, exposure to valproate)
Note: Factor XIII may occur spontaneously in older adults.

If an amniotic fluid specimen is received, an amniotic fluid culture will be performed at an additional charge.?
If a chorionic villi specimen or cultured chorionic villi are received, a fibroblast culture will be performed at an additional charge.?
For any prenatal specimen that is received, maternal cell contamination testing will be performed at an additional charge.

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Rare Coagulation Disorder Patient Information

Method Name

Sequence Capture and Targeted Next-Generation Sequencing followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Special coagulation testing for factor XIII (FXIII) activity should be performed prior to any genetic testing. For assessment of FXIII activity, order ALBLD / Bleeding Diathesis Profile, Limited, Plasma, which includes the factor XIII screening assay.

Genetic testing should only be considered if clinical and family history, initial coagulation screens, or initial activity tests indicate a diagnosis of FXIII deficiency (see Testing Algorithm).

If genetic testing for hereditary bleeding disorders using a larger panel is desired, both a 6-gene focused bleeding panel and a 25-gene comprehensive bleeding panel are available. For more information see GNBLF / Bleeding Disorders,

Focused Gene Panel, Next-Generation Sequencing, Varies or GNBLC / Bleeding Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known mutations testing) is available for the *F13A1* and *F13B* genes. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

Additional Testing Requirements

All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on both the prenatal specimen and the maternal specimen as separate order numbers..

Necessary Information

Rare Coagulation Disorder Patient Information is required. Testing may proceed without the patient information, however, the information aids in providing a more thorough interpretation. Ordering healthcare professionals are strongly encouraged to fill out the form and send with the specimen.

Specimen Required

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

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD)
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 (preferred) 4 days/Refrigerated 4 days
Additional Information: To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

Prenatal Specimens
Due to its complexity, consultation with the laboratory is required for all prenatal testing; call 800-533-1710 to speak to a genetic counselor.

Specimen Type: Amniotic fluid
Container/Tube: Amniotic fluid container
Specimen Volume: 20 mL
Specimen Stability Information: Refrigerated (preferred) 24 hours/Ambient 4 hours
Additional information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for

specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid. An additional 2 to 3 weeks are required to culture amniotic fluid before genetic testing can occur.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Chorionic villi
Container/Tube: 15-mL Tube containing 15 mL of transport media
Specimen Volume: 20 mg
Specimen Stability Information: Refrigerated 24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing. An additional 2 to 3 weeks are required to culture amniotic fluid before genetic testing can occur.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Specimen Type: Confluent cultured cells
Container/Tube: T-25 flask
Specimen Volume: 2 Full flasks
Collection Instructions: Submit confluent cultured cells from another laboratory.
Specimen Stability Information: Ambient (preferred) 24 hours/Refrigerated 24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing.
3. **All prenatal specimens must be accompanied by a maternal blood specimen;** order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen.

Forms

1. **Rare Coagulation Disorder Patient Information (T824) is required**
2. **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)
3. If not ordering electronically, complete, print, and send an Coagulation Test Request (T753) with the specimen.

Specimen Minimum Volume

Blood: 1 mL; Amniotic fluid: 10 mL; Other specimen types: 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

Factor XIII deficiency (FXIIID) is a rare hereditary bleeding disorder associated with germline variants in the *F13A1* and *F13B* genes. It is inherited in an autosomal recessive manner with variable expressivity; both male and female patients may be affected. The estimated prevalence is 1 in 2 million individuals.(2-4)

Factor XIII deficiency caused by homozygous or compound heterozygous variants in *F13A1* (FXIII-A deficiency) typically presents as a severe bleeding tendency. Onset of life-threatening symptoms often occurs early with umbilical cord and central nervous system bleeding. Additional symptoms include easy bruising, intramuscular and subcutaneous hematomas, oral mucosal bleeding, epistaxis, perioperative bleeding, and impaired wound healing. Among the rare bleeding disorders, FXIIID appears uniquely associated with pregnancy loss. Affected women have an increased risk of miscarriage, postpartum hemorrhage, menorrhagia, and intraperitoneal bleeding.(2-7)

Individuals with FXIIID caused by homozygous or compound heterozygous variants in *F13B* (FXIII-B deficiency) tend to have a milder bleeding tendency, although a severe phenotype can occur.(1,2)

Accurate correlation between genotype and phenotype in FXIIID has proven challenging due to the unpredictable nature and variability of disease symptoms, its rarity, and the limitation of some laboratory assays. Routine coagulation tests are often normal.(2,3,5)

Several causes of acquired (nongenetic) FXIIID should be excluded prior to genetic testing, including leukemia, liver disease, Henoch-Schonlein purpura, inflammatory bowel diseases, disseminated intravascular coagulation, pulmonary embolism, stroke, sepsis, and exposure to valproate. FXIIID also may occur spontaneously in older adults.(1-3)

The United Kingdom Haemophilia Centre Doctors' Organization provides guidelines regarding diagnosis and management for individuals with inherited bleeding disorders, including FXIIID.(8)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(9) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:
Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:
Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

Deletion/duplication events that extend past the genes included on the panel may occur. In these instances, genes included in the ordered test are provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. However, copy number variants for genes not listed in the Method Description are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB / Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the genes included on the panel.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic mutations and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who

have received a bone marrow transplant.

Reclassification of Variants:
Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare professionals to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

Variant Evaluation:
Evaluation and categorization of variants are performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(9) Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

Clinical Reference

1. Kohler HP, Ichinose A, Seitz R, et al. Diagnosis and classification of factor XIII deficiencies. J Thromb Haemost. 2011;9(7):1404-1406
2. Karimi M, Bereczky Z, Cohan N, Muszbek L. Factor XIII deficiency. Semin Thromb Hemost. 2009;35(4):426-438
3. Dorgalaleh A, Rashidpanah J. Blood coagulation factor XIII and factor XIII deficiency. Blood Rev. 2016;30(6):461-475
4. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. Blood. 2015;125(13):2052-2061
5. de Moerloose P, Schved JF, Nugent D. Rare coagulation disorders: fibrinogen, factor VII and factor XIII. Haemophilia. 2016;22 Suppl 5:61-65
6. Pelcovits A, Schiffman F, Niroula R. Factor XIII deficiency: a review of clinical presentation and management. Hematol Oncol Clin North Am. 2021;35(6):1171-1180
7. Sharief LAT, Kadir RA. Congenital factor XIII deficiency in women: a systematic review of literature. Haemophilia. 2013;19(6):e349-e357
8. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2014;167(3):304-326
9. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee: 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

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the *F13A1* and *F13B* genes, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp, and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the *F13A1* and *F13B* genes.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.(Unpublished Mayo method)

The reference transcript for *F13A1* is NM_ 000129.4 and *F13B* is NM_001994.2. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

PDF Report

No

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Amniotic fluid, cultured amniocytes, chorionic villi, cultured chorionic villi: 1 month; 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

81479
88233-Tissue culture, skin, solid tissue biopsy (if appropriate)
88240-Cryopreservation (if appropriate)
88235-Amniotic fluid culture (if appropriate)
81265-Maternal cell contamination (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNF13	F13A1 and B Genes, Full Gene NGS	92991-9

Result ID	Test Result Name	Result LOINC® Value
619146	Test Description	62364-5
619147	Specimen	31208-2
619148	Source	31208-2
619149	Result Summary	50397-9
619150	Result	82939-0
619151	Interpretation	69047-9
619152	Additional Results	82939-0
619153	Resources	99622-3
619154	Additional Information	48767-8
619155	Method	85069-3
619156	Genes Analyzed	82939-0
619157	Disclaimer	62364-5
619158	Released By	18771-6