Test Definition: GNF11

Hemophilia C (Factor XI Deficiency), F11 Gene,
Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating factor XI deficiency (FXID) in patients with a personal or family history suggestive of FXID

Confirming an FXID diagnosis with the identification of known or suspected disease-causing alterations in the *F11* gene

Determining the disease-causing alterations within the *F11* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of FXID

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 FXID

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 *F11* gene associated with factor XI deficiency (FXID), a rare bleeding disorder also known as hemophilia C. 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 FXID.

Testing Algorithm

The clinical workup for factor XI deficiency (FXID) should begin with special coagulation testing for factor XI (FXI) activity.

Genetic testing for FXID is indicated if:

-Factor XI activity is less than 50% of normal (Note: reference ranges may vary depending on the locally established reference range).
-Acquired causes of factor XI have been excluded. Note: FXID appears to be a rare complication of liver transplantation.

Prenatal specimens:
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 (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Special coagulation testing for factor XI (FXI) activity should be performed prior to any genetic testing. For assessment of FXI activity, order F_11 / Coagulation Factor XI Activity Assay, Plasma.

This test should only be considered if clinical and family history, initial coagulation screens, or initial activity tests indicate a diagnosis of FXID (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 mutation testing) is available for the *F11* gene.

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 providers 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 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 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 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 3 to 4 weeks are required to culture fibroblasts 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.

Acceptable:
Specimen Type: Confluent cultured cells
Container/Tube: T-25 flask
Specimen Volume: 2 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/or 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

Whole 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 XI deficiency (FXID) is a rare hereditary bleeding diathesis (also known as hemophilia C) caused by reduced levels of clotting factor XI. It is characterized by a bleeding disorder that is relatively mild, rarely spontaneous, and predominantly occurs in the oral cavity, nasopharynx, and urinary tract. Bleeding frequency and severity are highest when trauma or certain surgical procedures involve tissues in these areas. Menorrhagia and nose bleeds are common.(1-3)

Hereditary FXID is associated with germline variants in the *F11* gene. It is typically inherited in an autosomal recessive manner, although some rare variants in *F11* cause an autosomal dominant form. Both male and female individuals may be affected. The estimated prevalence of severe FXID is 1 per million. However, it is more common in certain ethnic groups. In the Ashkenazi and Iraqi Jewish populations, severe deficiency may be found in 1 in 450 individuals.(1-5)

Plasma FXI activity levels correlate poorly with bleeding severity. This discordance indicates there may be other contributing factors to FXID severity, including differences in clinical criteria for bleeding, variation in genetic backgrounds, the qualities of specific genetic alterations, and coinheritance of other bleeding disorders.(1-3,5)

Acquired (nongenetic) FXID appears to be a rare complication of liver transplantation and should be excluded prior to genetic testing.(6)

The United Kingdom Haemophilia Centre Doctors' Organization provides guidelines regarding diagnosis and management for individuals with inherited bleeding disorders, including FXID.(7)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(8) 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 gene tested may occur. In these instances, only the gene included in the ordered test is provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. Genes not on this ordered test 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 tested gene.

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.(8) 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. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. Blood. 2015;125(13):2052-2061
2. Wheeler AP, Gailani D. Why factor XI deficiency is a clinical concern. Expert Rev Hematol. 2016;9(7):629-637
3. Lewandowska MD, Connors JM. Factor XI deficiency. Hematol Oncol Clin North Am. 2021;35(6):1157-1169
4. Bolton-Maggs PH. Factor XI deficiency--resolving the enigma?. Hematology Am Soc Hematol Educ Program. 2009;97-105
5. Emsley J, McEwan PA, Gailani D. Structure and function of factor XI. Blood. 2010;115(13):2569-2577
6. Yankol Y, Mecit N, Kanmaz T, Acarli K, Kalayoglu M. Acquired factor XI deficiency: a rare complication after liver transplantation. Transplant Proc. 2015;47(1):179-181
7. 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
8. 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 *F11* gene, 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 *F11* gene.

There may be regions of the *F11* gene 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 the *F11* gene is NM_000128.4. 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)

Test Definition: GNF11

Hemophilia C (Factor XI Deficiency), F11 Gene, Next-Generation Sequencing, Varies

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNF11	F11 Gene, Full Gene NGS	94239-1

Result ID	Test Result Name	Result LOINC® Value
619132	Test Description	62364-5
619133	Specimen	31208-2
619134	Source	31208-2
619135	Result Summary	50397-9
619136	Result	82939-0
619137	Interpretation	69047-9
619138	Additional Results	82939-0
619139	Resources	99622-3
619140	Additional Information	48767-8
619141	Method	85069-3
619142	Genes Analyzed	82939-0
619143	Disclaimer	62364-5
619144	Released By	18771-6