Test Definition: F11NG

F11 Gene, Full Gene NGS

Overview

Useful For

Genetic confirmation of a factor XI deficiency diagnosis with the identification of known or suspected pathogenic alterations in the *F11* gene

Carrier testing for close family members of an individual with a factor XI deficiency diagnosis

This test is **not intended for** prenatal diagnosis

Genetics Test Information

This test detects pathogenic alterations within the *F11* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of factor XI deficiency, a bleeding disorder also known as Hemophilia C.

The gene target for this test is:

Gene name (transcript): *F11* (GRCh37 [hg19] NM_000128)

Chromosomal location: 4q35

Testing Algorithm

Genetic testing for factor XI deficiency should only be considered after coagulation screening is performed and if factor XI activity is less than 50% of normal (note: reference ranges may vary depending on the locally established reference range).

Genetic testing for factor XI deficiency is indicated if:

-Factor XI activity is reduced (less than 50% of normal)

-Acquired causes of factor XI have been excluded

Special Instructions

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

Method Name
Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing when appropriate

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
The clinical workup for factor XI deficiency begins with special coagulation testing for factor XI. Order F_11 / Coagulation Factor XI Activity Assay, Plasma.

Shipping Instructions
Ambient and refrigerated specimens **must** arrive within 7 days (168 hours of draw), and frozen specimens must arrive within 14 days (336 hours of draw).

Collect and package specimen as close to shipping time as possible.

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
Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA)

Acceptable: Yellow top (ACD) or light-blue top (3.2% sodium citrate)

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: Ambient (preferred)/Refrigerated/Frozen

Specimen Type: Extracted DNA

Container/Tube: 1.5- to 2-mL tube

Specimen Volume: Entire specimen

Collection Instructions:

1. Label specimen as extracted DNA and source of specimen.

2. Provide indication of volume and concentration of the DNA.

Specimen Stability: Frozen (preferred)/Refrigerated/Ambient

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. If not ordering electronically, complete, print, and send a Coagulation Test Request (T753) with the specimen.

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK

Specimen Minimum Volume

Blood: 1 mL

Extracted DNA: 100 mcL at 50 ng/mcL concentration

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)	7 days	
	Frozen	14 days	
	Refrigerated	7 days	

Clinical & Interpretive

Clinical Information

Factor XI deficiency (FXID) is a bleeding diathesis that is also known as hemophilia C. FXID produces a bleeding disorder that is relatively mild, rarely spontaneous, and associated with certain sites of the body, namely 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.

Overall, in the general population, the prevalence of severe FXID is 1 per million. However, FXID is common in certain ethnic groups. In Ashkenazi Jews, severe deficiency is found in 1 in 450 people. Founder mutations are also found among French Basques and French individuals from Nantes. Hereditary FXID is typically inherited in an autosomal recessive manner. However, some rare alterations exert a dominant-negative effect or interfere with the functioning of normal factor XI (FXI), causing an autosomal dominant bleeding disorder.

FXID is a result of defects in the concentration or function of coagulation FXI, which is synthesized in the liver and circulates in blood plasma as an inactive zymogen. The role of activated FXI includes sustained activation of factor IX, leading to fibrin formation and clot stability, especially in tissues with high fibrinolytic activity, such as oral cavity, nasopharynx, and urinary tract. A significant deficiency in the amount of functional FXI can cause excessive bleeding in these tissues after trauma or certain surgical procedures.

FXID is defined as severe when FXI activity is less than 15% (15 U/dL). It is considered moderate when it is between 15% and 50% (15 to 50 U/dL). However, plasma FXI activity levels to do not correlate well with bleeding phenotype, in part activity levels appear unable to reflect true physiological activity of FXI (eg, p.Ser266Asn is associated with bleeding and defective FXI binding to platelets but is reported not affect aPTT). Some patients with 15% to 50% FXI activity present similarly to severely deficient patients, indicating contributing factors to disease severity, eg, the qualities of the specific alteration(s) underlying the disorder or the co-inheritance of other bleeding disorders. Of note, normal, full-term newborn infants or healthy premature infants may have decreased levels (greater than or equal to 10%) that may not reach adult levels for greater than or equal to 180 days after birth.

The *F11* gene encodes FXI. Genetic testing for pathogenic alterations in *F11* is indicated if FXI activity is below 50% of normal. Patients lacking FXI will also typically have very long activated partial thromboplastin times.

Acquired FXID appears to be a rare complication of liver disease. Liver disease should be excluded prior to genetic testing.

Reference Values

An interpretive report will be provided

Interpretation

An interpretive report will be provided.

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory, or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

Cautions

Clinical:

Some individuals may have a variant that is not identified by the methods performed. The absence of a variant, therefore, does not eliminate the possibility of factor XI deficiency. This assay does not distinguish between germline and somatic alterations, particularly with variant allele frequencies significantly lower than 50%. Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Technical Limitations:

Next-generation sequencing (NGS) may not detect all types of genetic variants. Additionally, rare variants (ie, polymorphisms) may be present that could lead to false-negative or false-positive results. Therefore, test results should be interpreted in the context of activity and antigen measurements, clinical findings, family history, and other laboratory data. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If multiple alterations are identified, NGS is not able to distinguish between alterations that are found in the same allele ("in cis") and alterations found on different alleles ("in trans"). This limitation may complicate diagnosis or classification and has implications for inheritance and genetic counseling. To resolve these cases, molecular results must be correlated with clinical history, activity and antigen measurements, and family studies.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common alterations (ie, polymorphisms) identified for this patient are available upon request.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Clinical Reference

1. Palla R, Peyvandi F, Shapiro AD: Rare bleeding disorders: diagnosis and treatment. Blood. 2015 Mar;125(13):2052-2061

2. Wheeler A, Gailani D: Why factor XI deficiency is a clinical concern. Expert Review of Hematology. 2016 Jul;9(7):629-637

3. Bolton-Maggs, P: Factor XI deficiency-resolving the enigma? Hematology Am Soc Hematol Educ Program. 2009;97-105

4. Emsley J, McEwan PA, Gailani D: Structure and function of factor XI. Blood. 2010 Apr;115(13):2569-2577

5. Gailani D, Geng Y, Verhamme I, et al: The mechanism underlying activation of factor IX by factor XIa. Thromb Res. 2014 May;133 Suppl 1:S48-51

6. Berber E: Molecular characterization of FXI deficiency. Clin Appl Thromb Hemost. 2011 Feb;17(1):27-32

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed.

Regions of homology, high guanine-cytosine (GC)-rich content, and repetitive sequences may not provide accurate

sequence. Therefore, all reported alterations detected by NGS in these regions are confirmed by an independent reference method. However, this does not rule out the possibility of a false-negative result in these regions.

Sanger sequencing is used to confirm alterations detected by NGS when appropriate.(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

Whole Blood: 2 weeks; DNA: Indefinitely

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

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

CPT Code Information

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
F11NG	F11 Gene, Full Gene NGS	94239-1

Result ID	Reporting Name	LOINC®
113060	F11NG Result	50397-9
113054	Alterations Detected	82939-0
113053	Interpretation	69047-9
113055	Additional Information	48767-8
113056	Method	85069-3
113057	Disclaimer	62364-5
113058	Panel Gene List	48018-6
113059	Reviewed By	18771-6