Test Definition: F13NG

F13A1 and B Genes, Full Gene NGS

Overview

Useful For

Detecting the pathogenic alterations within the *F13A1* and *F13B* genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of factor XIII deficiency

Genetic confirmation of hereditary factor XIII deficiency with the identification of an alteration in either the *F13A1* or *F13B* gene known or suspected to cause the condition

Testing for close family members of an individual with a factor XIII deficiency diagnosis

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

Genetics Test Information

This test detects pathogenic alterations within the *F13A1* and *F13B* genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of factor XIII deficiency.

The gene targets for this test are:

Gene name (transcript): *F13A1* (GRCh37 [hg19] NM_000129)

Chromosomal location: 6p24-p25

Gene name (transcript): *F13B* (GRCh37 [hg19] NM_001994)

Chromosomal location: 1q31-q32.1

Testing Algorithm

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

Genetic testing for FXIIID is indicated if:

-Factor XIII activity (FXIII) is reduced on a qualitative functional FXIII activity test

-Acquired causes of factor XIII deficiency 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

Genetic testing should only be considered if reduced factor XIII activity is documented and acquired cases of low factor XIII are excluded.

Shipping Instructions

Ambient and refrigerated specimens must arrive within 7 days of collection, and frozen specimens must arrive within 14 days.

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 volume and concentration of the DNA.

Specimen Stability: Frozen (preferred)/Refrigerated/Ambient

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 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 FXIII deficiency (FXIIID) is a bleeding diathesis of variable severity. The prevalence of factor FXIII deficiency is currently estimated to be 1 in 2 million but the exact prevalence is unknown. The disorder is inherited in an autosomal recessive manner.

Factor XIII is a transglutaminase cross-linking enzyme critical to fibrin clot stabilization. It serves to crosslink alpha and gamma fibrin chains, leading to greater clot strength and resistance to fibrinolysis. Deficiency in FXIII leads to defective crosslinking of fibrin and the formation of a weak, unstable clot. Clots may form properly but break down 24 to 48 hours later, leading to abnormal bleeding. Factor XIII is formed from 2 subunits: catalytic protein FXIII-A, encoded by the *F13A1* gene and synthesized by megakaryocytes and certain white blood cells in bone marrow; and stabilizing protein FXIII-B, encoded by the *F13B* gene and synthesized in the liver. Together, 2 FXIII-A subunits and 2 FXIII-B subunits circulate in plasma as heterotetramer.

Patients with FXIII caused by alteration in *F13A1* (ie, FXIII-A deficiency) typically have a severe bleeding tendency. Onset of life-threatening symptoms is early and may present as umbilical cord and central nervous system bleeding. Eighty percent to 90% of patients have umbilical bleeding in neonatal period. Forty percent to 60% of patients have spontaneous intracranial haemorrhage within first 2 decades of life, making early diagnosis critical. In women, miscarriage, menorrhagia, and intraperitoneal bleeding are common without prophylaxis. Delayed wound healing is sometimes seen. Subjects with heterozygous alterations may be at risk for bleeding complications following surgery, dental extraction, or trauma. Patients with FXIII caused by alterations in *F13B* (FXIII-B deficiency) typically have a relatively milder bleeding tendency relative to individuals with FXIII-A deficiency.

The unpredictable nature of symptoms in FXIII deficiency, its apparent rarity, and limitations in the development of laboratory tests for its detection, especially when activity levels are very low, have made genotype-phenotype correlation difficult.(2) Additionally, any correlation may be impractical given the high risk of intracranial bleeding among all affected patients and the recommendation of a general prophylactic strategy at the time of diagnosis.(2) However, in general, individuals with virtually undetectable functional activity typically have a severe bleeding tendency. FXIII levels between 1 and 4 IU/dL produce moderate to severe bleeding episodes. It is difficult to predict bleeding pattern in patients with alterations that cause activity level to be greater than 5%.(3) Heterozygotes (ie, individuals with only 1 pathogenic alteration in either *F13A1* or *F13B*) have 50% to 70% factor activity and are typically asymptomatic, although serious bleeding episodes have been reported.(4)

Causes of acquired (nongenetic) factor XIII deficiency that should be excluded prior to genetic testing include several medical conditions, such as major surgery, leukemia, liver disease, Henoch-Schonlein purpura (HSP), pulmonary embolism, stroke, inflammatory bowel diseases, sepsis, and disseminated intravascular coagulation. In these acquired FXIII-deficient states, FXIIIA levels drop into the 30% to 70% range. Valproate induces a decrease in FXIII level. FXIII antibodies may develop spontaneously in patients long treated with drugs such as isoniazid, penicillin, phenytoin, practolol, and amiodarone. Development of antibodies are also reported in some cases of severe FXIII deficiency, monoclonal gammopathy of undetermined significance, rheumatoid arthritis, and systemic lupus erythematosus. Factor XIII may also develop spontaneously in older adult patients.

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 XIII 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 and 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. Kohler HP, Ichinose A, Seitz R, et al: Diagnosis and classification of factor XIII deficiencies. J Thromb Haemost. 2011 Jul;9(7):1404-1406

2. Karimi M, Bereczky Z, Cohan N, Muszbek L: Factor XIII deficiency. Semin Thromb Hemost. 2009 Jun;35(4):426-438

3. de Moerloose P, Schved JF, Nugent D: Rare coagulation disorders: fibrinogen, factor VII and factor XIII. Haemophilia. 2016 Jul;22(Suppl 5):61-65

4. Dorgalaleh A, Rashidpanah J: Blood coagulation factor XIII and factor XIII deficiency. Blood Rev. 2016 Nov;30(6):461-475

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 Definition: F13NG

F13A1 and B Genes, Full Gene NGS

Test ID	Test Order Name	Order LOINC Value
F13NG	F13A1 and B Genes, Full Gene NGS	92991-9

Result ID	Reporting Name	LOINC®
113076	F13NG Result	50397-9
113070	Alterations Detected	82939-0
113069	Interpretation	69047-9
113071	Additional Information	48767-8
113072	Method	85069-3
113073	Disclaimer	62364-5
113074	Panel Gene List	48018-6
113075	Reviewed By	18771-6