Test Definition: F12NG

F12 Gene, Full Gene NGS

Overview

Useful For

Genetic confirmation of hereditary angioedema (HAE) type III with the identification of an alteration in the *F12* gene known or suspected to cause the condition

Testing for close family members of an individual with an HAE type III diagnosis

Genetic confirmation of factor XII deficiency with the identification of an alteration in the *F12* known or suspected to cause the condition

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

Genetics Test Information

This test detects pathogenic alterations in the *F12* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of factor XII deficiency or hereditary angioedema with normal C1 inhibitor (FXII-HAE).

The gene target for this test is:

Gene name (transcript): *F12* (GRCh37 [hg19] NM_000505)

Chromosomal location: 5q35.3

Testing Algorithm

Factor XII deficiency:

Special coagulation testing for factor XII should be performed prior to any genetic testing.

Genetic testing for factor XII deficiency may be considered if:

-Factor XII activity is reduced (less than 55% of normal)

-Acquired causes of factor XII have been excluded

Hereditary angioedema type III (FXII-HAE):

An international consortium has established a testing and diagnostic algorithm for the identification of hereditary angioedema (HAE) type III.(1)

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 for factor XII deficiency typically has little clinical utility. Caution in ordering is advised.

Prior to any genetic testing, factor XII activity should be assessed. Order F_12 / Coagulation Factor XII Activity Assay, Plasma.

For hereditary angioedema type III, genetic testing should only be considered when there is a documented family history of angioedema that does not respond to chronic, high-dose antihistamine therapy, normal complement studies, normal C1 inhibitor level and function, and no exposure to medications that could cause angioedema, such as angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs.

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: Peripheral 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. **Rare Coagulation Disorder Patient Information (T824) is required**. Fax the completed form to 507-284-1759.

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 XII (FXII) is a serine protease capable of activating factor VII and factor IX to their active forms but does not appear to significantly contribute to hemostasis. Rather, factor XII activity appears directed more toward inflammatory response through activation of the kallikrein-kinin system .Pathogenic alterations in the *F12* gene, which encodes FXII, can cause one of two different phenotypes. Alterations in *F12* that reduce the amount of plasma FXII or disrupt its functional activity result in FXII deficiency. Alterations in *F12* that disrupt glycosylation or lead to increased contact-mediated autoactivation of zymogen FXII are associated with hereditary angioedema (HAE) type III with normal C1 inhibitor (C1INH).

A deficiency of FXII does not cause excessive bleeding tendency or abnormal bleeding even during trauma or surgery despite prolonged partial thromboplastin time (aPTT). Some with severe deficiency experience thrombosis, but a causal connection remains unproven. Individuals with FXII deficiency are generally entirely asymptomatic, making disease state

classifications unnecessary. FXII deficiency is inherited in an autosomal recessive manner. Genetic testing for FXII deficiency is generally unnecessary but may be considered if prolonged aPTT and reduced FXII activity is documented and acquired causes of low FXII are excluded. Causes of acquired (nongenetic) FXII deficiency that should be excluded prior to genetic testing include liver disease, nephrotic syndrome, and chronic granulocytic leukemia. A study of 300 healthy blood donors found that 2.3% had FXII deficiency.(2) Actual prevalence of the condition is unknown. Of note, normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15%-20%) that may not reach adult levels for greater than or equal to 180 days after birth.

Defects in *F12* that increase contact-mediated FXII autoactivation and lead to excess generation of proinflammatory peptide hormone bradykinin cause HAE type III with normal C1INH. HAE type III is characterized by recurrent skin swelling, abdominal pain attacks, and upper airway obstruction. Symptoms occur almost exclusively in women because estrogen exposure appears to exacerbate the condition and attacks are precipitated or worsened by high estrogen levels. However, not all female patients who carry FXII alterations are symptomatic, thus HAE type III is considered an autosomal dominant disorder with incomplete penetrance. Alterations in *F12* are found in 20 to 30% of patient with HAE type III. Genetic testing for HAE type III may be indicated when there is a documented family history of angioedema that does not respond to chronic, high-dose antihistamine therapy, normal complement studies, normal C1INH level and function, and no exposure to medications that could cause angioedema, angiotensin-converting enzyme inhibitors or nonsteroidal antiinflammatory drugs. Of note, acquired causes of angioedema, such as B-cell lymphoproliferative, the presence of autoantibodies to C1 inhibitors, and the use of renin-angiotensin-aldosterone blockers, should be considered and excluded prior to genetic testing of *F12* for HAE type III.

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 XII deficiency or hereditary angioedema type III. 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. Bowen T, Cicardi M, Farkas H, et al: 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):24

2. Halbmayer WM, Haushofer A, Schon R, et al: The prevalence of moderate and severe FXII (Hageman factor) deficiency among the normal population: evaluation of the incidence of FXII deficiency among 300 healthy blood donors. Thromb Haemost.. 1994 Jan;71(1):68-72

3. Schmaier AH: The contact activation and kallikrein/kinin systems: pathophysiologic and physiologic actitivies. J Thromb Haemost. 2016 Jan;14(1):28-39

4. Banerji, A: The burden of illness in patients with hereditary angioedema. Ann Allergy Asthma Immunol. 2013 Nov;111(5):329-336

5. Björkqvist J, de Maat S, Lewandrowski U, et al: Defective glycosylation of coagulation factor XII underlies hereditary angioedema type III. J Clin Invest. 2015 Aug 3;125(8):3132-3146

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
F12NG	F12 Gene, Full Gene NGS	94238-3

Result ID	Reporting Name	LOINC®
113068	F12NG Result	50397-9
113062	Alterations Detected	82939-0
113061	Interpretation	69047-9
113063	Additional Information	48767-8
113064	Method	85069-3
113065	Disclaimer	62364-5
113066	Panel Gene List	58902-8
113067	Reviewed By	18771-6