MAYO CLINIC LABORATORIES

Test Definition: GNANG

Hereditary Angioedema Focused Gene Panel, Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating hereditary angioedema (HAE) with normal C1 inhibitor (C1INH) in patients with a suggestive personal or family history

Confirming a diagnosis of HAE with normal C1INH with the identification of a known or suspected disease-causing alteration in the *F12*, *PLG* or *KNG1* gene

Determining the disease-causing alteration within the *F12, PLG or KNG1* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of HAE with normal C1INH

Evaluating factor XII deficiency in patients with a suggestive personal or family history

Confirming a factor XII deficiency diagnosis with the identification of known or suspected disease-causing alteration(s) in the *F12* gene

Determining the disease-causing alteration(s) within the *F12* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of factor XII deficiency

Identifying the causative alteration(s) for genetic counseling purposes

Prognosis and risk assessment based on the genotype-phenotype correlations

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

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

Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *F12*, *KNG1*, and *PLG* genes associated with hereditary angioedema with normal C1 inhibitor (HAE with normal C1INH). This test also detects variants in the *F12* gene associated with factor XII deficiency. See Targeted Genes and Methodology Details for Hereditary Angioedema Focused Gene Panel and 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 HAE with normal C1INH and factor XII deficiency.

Testing Algorithm

The clinical workup for hereditary angioedema (HAE) with normal C1 inhibitor (C1INH) begins with measurements of serum complement factor 4 (C4), C1 inhibitor (C1-INH) antigen, and C1-INH function.

Genetic testing for HAE with normal C1INH is indicated in patients with:

-A history of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema
-Normal or near-normal C4, C1-INH antigen, and C1-INH function
-Lack of response to high-dose antihistamines

International expert consortia have established testing algorithms and diagnostic guidelines for the identification of HAE with normal C1INH.(1,2)

The clinical workup for factor XII deficiency begins with special coagulation testing for factor XII activity. Order F_12 / Coagulation Factor XII Activity Assay, Plasma.

Genetic testing for factor XII deficiency is indicated if:
-Factor XII activity is less than 55% of normal (Note: reference range may vary depending on the locally established reference range).
-Acquired causes of factor XII deficiency have been excluded (eg, liver disease, nephrotic syndrome, DIC, and hematologic neoplasms)

Special Instructions

- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)
- Rare Coagulation Disorder Patient Information
- Targeted Genes and Methodology Details for Hereditary Angioedema Focused Gene Panel

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

This test is designed to detect disease-causing variants in the *F12, KNG1*, and *PLG* genes and to be utilized for genetic confirmation of a clinical diagnosis of hereditary angioedema with normal C1 inhibitor (HAE with normal C1INH) or factor XII deficiency.

Genetic testing for HAE with normal C1INH should only be considered if there is a documented family history of angioedema that does not respond to chronic, high-dose antihistamine therapy, normal complement studies, normal

C1-INH level and function, and no exposure to medications that could cause angioedema, such as angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs.

Genetic testing for factor XII deficiency should only be considered if clinical and family history, initial coagulation screens, or initial activity tests indicate a diagnosis.

This test does not measure complement 4, C1INH antigen, C1INH functional, or factor XII activity levels.
-For assessment of C4, order C4 / Complement C4, Serum.
-For assessment of C1INH antigen, order C1ES / C1 Esterase Inhibitor Antigen, Serum.
-For assessment of functional C1INH , order C1INF / C1 Esterase Inhibitor, Functional, Serum.
-For assessment of factor XII activity, order F_12 / Coagulation Factor XII Activity Assay, Plasma.

Customization of this panel and single gene analysis for any gene present on this panel are available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

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

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

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

Specimen Type: Whole blood
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.
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

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
1 mL

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
Hereditary angioedema with normal C1 inhibitor (HAE with normal C1INH) is a rare blood and immunologic disorder associated with germline variants in the *F12* gene (F12-HAE), *PLG* gene (PLG-HAE), and *KNG1* gene (KNG1-HAE). It is inherited in an autosomal dominant manner with incomplete penetrance.(3,4)

HAE with normal C1INH is characterized by recurrent episodes of severe skin and submucosal swelling, abdominal pain attacks, and upper airway obstruction that does not respond to high-dose antihistamine therapy. Facial and tongue swelling are common. Affected individuals have normal complement studies, normal C1INH antigen and function, and no exposure to medications that could cause angioedema, such as angiotensin-converting-enzyme inhibitors or non-steroidal anti-inflammatory drugs. Estrogen exposure exacerbates disease severity in many patients.(2-6)

Acquired angioedema is associated with B-cell lymphoproliferative disorders in some patients, the presence of autoantibodies to C1-INH, and the use of renin-angiotensin-aldosterone system-blockers.(4)

In addition to HAE with normal C1INH, germline variants in the *F12* gene are associated with autosomal recessive factor XII deficiency. While this rare blood disorder is characterized by prolonged activated partial thromboplastin time and reduced factor XII activity, it is rarely associated with an excessive bleeding tendency or abnormal bleeding during trauma or surgery. Individuals with factor XII deficiency are generally asymptomatic.(7)

Causes of acquired (nongenetic) factor XII deficiency should be excluded prior to genetic testing, including liver disease, nephrotic syndrome, and chronic granulocytic leukemia.

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.

Deletion/Duplication Analysis:
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.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic 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 providers 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. Bowen T, Cicardi M, Farkas H. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):24
2. Zuraw BL, Bork K, Binkley KE. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. Allergy Asthma Proc. 2012 Nov-Dec;33 Suppl 1:S145-56
3. Santacroce R, D'Andrea G, Bruna Maffione AB, Margaglione M, d'Apolito M: The genetics of hereditary angioedema: A review. J Clin Med. 2021 May 9;10(9):2023
4. Lopes Veronez C, Sevciovic Grumach A: Angioedema without urticaria: novel findings which must be measured in clinical setting. Curr Opin Allergy Clin Immunol. 2020 Jun;20(3):253-260.
5. Busse PJ, Christiansen SC: Hereditary angioedema. N Engl J Med. 2020 Mar 19;382(12):1136-1148
6. Bork K, Gul D, Hardt J, Dewald G: Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course. Am J Med. 2007 Nov;120(11):987-992
7. Naudin C, Burillo E, Blankenberg S, Butler L, Renne T: Factor XII contact activation. Semin Thromb Hemost. 2017 Nov;43(8):814-826
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 May;17(5):405-424. PMID 25741868

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 *F12*, *KNG1*, and *PLG* 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 *F12*, *KNG1*, and *PLG* 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. See Targeted Genes and Methodology Details for Hereditary Angioedema Focused Gene Panel and Methodology Details for details regarding the targeted genes analyzed for each test and specific gene regions not routinely covered.(Unpublished Mayo method)

The reference transcript for *F12* is NM_000505.3, *KNG1* is NM_001102416.3, and *PLG* is NM_000301.3. 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

Supplemental

Day(s) Performed

Varies

Report Available

28 to 42 days

Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location

Rochester

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

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Next-Generation Sequencing, Varies

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

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNANG	Hereditary Angioedema Panel, NGS	105329-7

Result ID	Test Result Name	Result LOINC® Value
619216	Test Description	62364-5
619217	Specimen	31208-2
619218	Source	31208-2
619219	Result Summary	50397-9
619220	Result	82939-0
619221	Interpretation	59465-5
619222	Additional Results	82939-0
619223	Resources	99622-3
619224	Additional Information	48767-8
619225	Method	85069-3
619226	Genes Analyzed	82939-0
619227	Disclaimer	62364-5
619228	Released By	18771-6