Test Definition: GNFIB

Congenital Fibrinogen Disorders, FGA, FGB, and FGG Genes, Next-Generation Sequencing, Varies

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Overview

Useful For

Evaluating congenital fibrinogen disorders (CFD) in patients with a personal or family history suggestive of a fibrinogen disorder

Confirming a CFD diagnosis with the identification of known or suspected disease-causing alterations in the *FGA*, *FGB*, or *FGG* genes

Determining the disease-causing alterations within the *FGA*, *FGB*, or *FGG* genes to delineate the underlying molecular defect in a patient with a laboratory diagnosis of suggestive of CFD

Identifying the causative alterations for genetic counseling purposes

Prognosis and risk assessment based on the genotype-phenotype correlations

Carrier testing for close family members of an individual with autosomal recessive afibrinogenemia/hypofibrinogenemia

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 *FGA*, *FGB*, and *FGG* genes associated with congenital fibrinogen disorders (CFD) including congenital afibrinogenemia/hypofibrinogenemia and dysfibrinogenemia/hypodysfibrinogenemia. See Targeted Genes and Methodology Details for Congenital Fibrinogen Disorders, FGA, FGB, and FGG Genes 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 CFD.

Testing Algorithm

The clinical workup congenital fibrinogen disorders (CFD) should begin with global coagulation screening assays.

In afibrinogenemia, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin clotting time (TT) may be infinitely prolonged.

In hypofibrinogenemia, TT is more sensitive than PT or aPTT for both quantitative and qualitative defects in fibrinogen. Reptilase time (RT) may be performed in addition to, or instead of, TT in specimens known, or suspected, to contain heparin, which artificially prolongs TT.

Further screening and identification of a mild fibrinogen deficiency or dysfibrinogenemia require a clottable fibrinogen assay (typically Clauss-method based) to assess fibrinogen function and an immunologic (antigenic) assay to assess fibrinogen quantity. Hypofibrinogenemia is indicated by a proportional reduction of both antigen and functional plasma fibrinogen concentrations. Dysfibrinogenemia is indicated by the combined presence of normal antigen amounts and reduced functional levels of circulating fibrinogen.(1-3)

Genetic testing for CFD is indicated if:
-Coagulation tests indicate a quantitative or functional defect in fibrinogen
-Acquired causes of fibrinogen disorders have been excluded (eg, liver disease, disseminated intravascular coagulopathy, trauma-induced coagulopathy, medications such as L-asparaginase, multiple myeloma or other malignancy, the use of plasma exchange using albumin as a replacement fluid, rheumatoid arthritis, systemic lupus erythematosus)

For prenatal specimens only:
-If amniotic fluid (nonconfluent cultured cells) is received, amniotic fluid culture/genetic test will be added at an additional charge.
-If chorionic villus specimen (nonconfluent cultured cells) is received, fibroblast culture for genetic test will be added 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
- Targeted Genes and Methodology Details for Congenital Fibrinogen Disorders, FGA, FGB, and FGG Genes

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 single nucleotide and copy number variants in the *FGA*, *FGB*, and *FGG* genes associated with congenital fibrinogen disorders (CFD).

This test should only be considered if coagulation screening tests measuring thrombin clotting time (TT; with or without reptilase time), clottable fibrinogen, and fibrinogen antigen suggest a quantitative or functional defect in fibrinogen, especially if these findings are similar between family members.

For assessment of thrombin clotting time, order TTSC / Thrombin Time (Bovine), Plasma.

For assessment of fibrinogen function, order FIBTP / Fibrinogen, Plasma.

For assessment of fibrinogen quantity, order FIBAG / Fibrinogen Antigen, Plasma.

If genetic testing for CFD using a larger panel is desired, both a 25-gene comprehensive bleeding panel and a 16-gene comprehensive thrombosis panel are available. See GNBLC / Bleeding Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies; and GNTHR / Thrombosis Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies.

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.

Additional Testing Requirements

All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen as this must be a different order number than the prenatal specimen.

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

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. For instructions for 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

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)/Ambient
Additional information:
1. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid.
2. **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
Additional Information:
1. A separate culture charge will be assessed under CULFB / Fibroblast Culture for Biochemical or Molecular Testing.
2. **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)/Refrigerated
Additional Information:
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

Blood: 1 mL; Amniotic fluid: 10 mL; Other specimen types: see Specimen Required

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

Congenital fibrinogen disorders (CFD) are rare bleeding abnormalities associated with germline variants in the *FGA*, *FGB*, and *FGG* genes. They manifest as one of 2 broad subtypes: autosomal recessive afibrinogenemia/hypofibrinogenemia (also known as a type I fibrinogen defect) or autosomal dominant dysfibrinogenemia (also known as a type II defect).

Afibrinogenemia and hypofibrinogenemia are considered quantitative defects characterized by undetectable or low levels of fibrinogen, respectively. Afibrinogenemia often presents in the neonatal period as umbilical cord bleeding. However, a later age of onset is not unusual and bleeding in the skin, oral cavity, gastrointestinal tract, genitourinary tract, and the central nervous system can occur. Individuals with hypofibrinogenemia are typically asymptomatic due to fibrinogen levels that, while lower than normal, are adequate to protect against spontaneous bleeding.

Dysfibrinogenemia is considered a qualitative defect. It is caused by structural changes in fibrinogen that modify its function, resulting in impaired clotting ability. Individuals with dysfibrinogenemia are commonly asymptomatic or have episodic symptoms. Cases are frequently discovered incidentally during routine coagulation testing or because of a positive family history.

Patients with CFD can also present with thrombotic events. Affected women are at increased risk of obstetric complications, including pregnancy loss, placental abruption, and postpartum hemorrhage.(3-6)

Causes of acquired (nongenetic) fibrinogen disorders should be excluded prior to genetic testing, including liver disease, consumptive coagulopathy (eg, disseminated intravascular coagulopathy, trauma-induced coagulopathy, medications (eg, L-asparaginase), malignancy (eg, multiple myeloma), the use of plasma exchange using albumin as a replacement fluid, and autoimmune conditions resulting in antifibrinogen antibodies (e.g., rheumatoid arthritis and systemic lupus erythematosus).(3,4)

The United Kingdom Haemophilia Centre Doctors' Organization provides guidelines regarding diagnosis and management for individuals with inherited bleeding disorders including fibrinogen deficiency.(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.

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. Mackie IJ, Kitchen S, Machin SJ, Lowe GDO: Guidelines on fibrinogen assays. Br J Haematol. 2003 May;121(3):396-404
2. Boender J, Kruip MJHA, Leebeek FWG: A diagnostic approach to mild bleeding disorders. J Thromb Haemost. 2016 Aug;14(8):1507-1516
3. May JE, Wolberg AS, Lim MY: Disorders of fibrinogen and fibrinolysis. Hematol Oncol Clin North Am. 2021 Dec;35(6):1197-1217
4. Tiscia GL, Margaglione M: Human fibrinogen: Molecular and genetic aspects of congenital disorders. Int J Mol Sci. 2018 May 29;19(6):1597
5. Palla R, Peyvandi F, Shapiro AD: Rare bleeding disorders: diagnosis and treatment. Blood. 2015 Mar 26;125(13):2052-2061
6. de Moerloose P, Casini A, Neerman-Arbez M: Congenital fibrinogen disorders: an update. Semin Thromb Hemost. 2013 Sep;39(6):585-595
7. Mumford AD, Ackroyd S, Alikhan R: 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 Nov;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 May;17(5):405-424

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence of variants in coding regions and intron/exon boundaries of the *FGA*, *FGB*, and *FGG* 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 *FGA*, *FGB*, and *FGG* 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 Congenital Fibrinogen Disorders, FGA, FGB, and FGG Genes 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 *FGA* is NM_000508.5, *FGB* is NM_005141.4, and *FGG* is NM_000509.5 and NM_021870.3.

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; Amniotic fluid, cultured amniocytes, chorionic villi, cultured chorionic villi: 1 month

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)

81265-Maternal cell contamination (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNFIB	FGA/B/G Genes, Full Gene NGS	92992-7

Result ID	Test Result Name	Result LOINC® Value
619160	Test Description	62364-5
619161	Specimen	31208-2
619162	Source	31208-2
619163	Result Summary	50397-9
619164	Result	82939-0
619165	Interpretation	59465-5
619166	Additional Results	82939-0
619167	Resources	99622-3
619168	Additional Information	48767-8
619169	Method	85069-3
619170	Genes Analyzed	82939-0
619171	Disclaimer	62364-5
619172	Released By	18771-6