Test Definition: GNANT

Antithrombin Deficiency, SERPINC1 Gene, Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating antithrombin AT deficiency in patients with a personal or family history suggestive of this hereditary thrombophilia

Confirming an AT deficiency diagnosis with the identification of a known or suspected disease-causing alteration in the *SERPINC1* gene, particularly in patients with borderline low AT activity levels

Determining the disease-causing alteration within the *SERPINC1* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of AT deficiency

Prognosis and risk assessment based on genotype-phenotype correlations

Ascertaining the variant status of family members related to an individual with a confirmed *SERPINC1* variant for the purposes of informing clinical management and genetic counseling

Evaluating individuals with apparent heparin resistance

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 *SERPINC1* gene associated with antithrombin (AT) deficiency, a rare hereditary blood clotting disorder. See 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 AT deficiency.

Testing Algorithm

The clinical workup for antithrombin (AT) deficiency should begin with an AT activity assay.

Genetic testing for AT deficiency is indicated if:
-AT activity assay is less than 80% of normal (Note: reference range may vary depending on the locally established reference range)
-There is a clinical suspicion of hereditary thrombophilia and possible AT deficiency due to family history or atypical clinical presentation
-Acquired (nongenetic) causes of AT deficiency have been excluded (eg, liver disease, acute thrombosis, heparin therapy, nephrotic syndrome, disseminated intravascular coagulation, and chemotherapeutic agents such an L-asparaginase)
Note: Low AT levels may be temporarily associated with other conditions such severe trauma, severe burns, or the presence of acute blood clots.

Special Instructions

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

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 should only be considered if clinical and family history, initial coagulation screens, and/or initial antithrombin (AT) activity and antigen testing results suggest a diagnosis of antithrombin deficiency (see Testing Algorithm).

This test does not measure AT activity levels. For assessment of AT activity, order ATTF / Antithrombin Activity, Plasma.

If genetic testing for hereditary blood clotting disorders using a larger panel is desired, a 16-gene comprehensive thrombosis panel is available; order GNTHR / Thrombosis Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the *SERPINC1* gene. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

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 healthcare professionals 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. For information about testing patients who have received a bone marrow transplant, call 800-533-1710.

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 4 days
Additional Information: To ensure minimum volume and concentration of DNA are met, the requested volume must be submitted. Testing may be canceled if DNA requirements are inadequate.

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

Antithrombin (AT) deficiency is a rare hereditary blood clotting disorder (thrombophilia) associated with germline variants in the *SERPINC1* gene. It is inherited in an autosomal dominant manner with variable penetrance; both men and women may be affected. The prevalence varies widely, with estimates between 1 in 500 to 1 in 5000 individuals.(1-3)

AT deficiency is characterized by defects in the concentration or function of AT, a natural anticoagulant in blood plasma. It leads to the highest risk of venous thromboembolism among the known inherited thrombophilias. In some cases, patients have resistance to heparin therapy. Affected women have a particularly elevated risk for pregnancy-related complications, including thromboembolic events during pregnancy and after delivery, as well as fetal loss.(4-7)

Acquired (nongenetic) AT deficiency is more common than inherited AT deficiency and should be excluded prior to genetic testing. Causes of acquired AT deficiency include liver disease, acute thrombosis, heparin therapy, nephrotic syndrome, disseminated intravascular coagulation, and chemotherapeutic agents, such an L-asparaginase.(4,8)

The British Society for Haematology provides guidelines regarding diagnosis, management, and laboratory testing for individuals with hereditary thrombophilias including AT deficiency.(9)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(10) 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.

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.

Deletion/duplication events that extend past the gene tested may occur. In these instances, only the gene included in the ordered test is provided on the report and interpreted, and genomic breakpoints are reported if they are confirmed. Genes not on this ordered test are typically not reported or interpreted for haploinsufficiency/triplosensitivity. CMACB /

Chromosomal Microarray, Congenital, Blood; WESPR / Panel to Whole Exome Sequencing Reflex Test, Varies; or WGSDX / Whole Genome Sequencing for Hereditary Disorders, Varies is recommended for a full interpretation of deletions/duplications predicted to extend past the tested gene.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic mutations 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 professionals 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.(10) 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. Tait RC, Walker ID, Perry DJ, et al. Prevalence of antithrombin deficiency in the healthy population. Br J Haematol. 1994;87(1):106-112
2. Wells PS, Blajchman MA, Henderson P, et al. Prevalence of antithrombin deficiency in healthy blood donors: a cross-sectional study. Am J Hematol. 1994;45(4):321-324
3. Thaler E, Lechner K. Antithrombin III deficiency and thromboembolism. Clin Haematol. 1981;10(2):369-390
4. Patnaik MM, Moll S. Inherited Antithrombin deficiency: a review. Haemophilia. 2008;14(6):1229-1239

5. Blajchamn MA, Austin RC, Fernandez-Rachubinski F, Sheffield WP. Molecular basis of inherited human antithrombin deficiency. Blood. 1992;80(9):2159-2171
6. Bauer KA, Nguyen-Cao TM, Spears JB. Issues in the diagnosis and management of hereditary antithrombin deficiency. Ann Pharmacother. 2016;50(9):758-767
7. Rogenhofer N, Bohlmann MK, Beuter-Winkler P, et al. Prevention, management and extent of adverse pregnancy outcomes in women with hereditary antithrombin deficiency. Ann Hematol. 2014;93(3):385-392
8. Corral J, de la Morena-Barrio ME, Vicente V. The genetics of antithrombin. Thromb Res. 2018;169:23-29
9. Arachchillage DJ, Mackillop L, Chandratheva A, et al. Thrombophilia testing: A British Society for Haematology guideline. Br J Haematol. 2022;198(3):443-458
10. 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;17(5):405-424

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 *SERPINC1* gene, 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 deletion-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 *SERPINC1* gene.

There may be regions of the *SERPINC1* gene 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.(Unpublished Mayo method)

The reference transcript for the *SERPINC1* gene is NM_000488.3. 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

No

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

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

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNANT	SERPINC1 Gene, Full Gene NGS	93814-2

Result ID	Test Result Name	Result LOINC® Value
619006	Test Description	62364-5
619007	Specimen	31208-2
619008	Source	31208-2
619009	Result Summary	50397-9
619011	Interpretation	59465-5
619012	Additional Results	82939-0
619013	Resources	99622-3
619014	Additional Information	48767-8
619015	Method	85069-3
619016	Genes Analyzed	82939-0
619017	Disclaimer	62364-5
619018	Released By	18771-6
619010	Result	82939-0