
Overview

Useful For

Ascertaining a causative alteration in *SERPINC1* and the affected region of antithrombin (AT) protein in an individual clinically diagnosed with antithrombin deficiency

Genetic confirmation of a clinical AT deficiency diagnosis, particularly in patients with borderline low AT activity levels

Prognosis and risk assessment based on the genotype-phenotype correlations

Ascertaining alteration status of family members related to an individual with a confirmed *SERPINC1* alteration 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 detects pathogenic alterations in the *SERPINC1* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of antithrombin (AT) deficiency based on a reduced AT activity or antigen.

The gene target for this test is:

Gene name (transcript): *SERPINC1* (GRCh37 [hg19] NM_000488)

Chromosomal location: 1q25.1

Testing Algorithm

The clinical workup for antithrombin deficiency begins with an antithrombin (AT) activity assay (see ATTF / Antithrombin Activity, Plasma). An abnormal result is considered less than 80% of normal activity.

Genetic testing for AT deficiency is indicated if:

- AT activity assay is less than 80%
- There is a clinical suspicion for hereditary deficiency of antithrombin due to family history or atypical clinical presentation

If AT activity results are abnormal, an antithrombin antigen assay is usually performed to determine the quantity of antithrombin present (ATTI / Antithrombin Antigen, Plasma). This is done to distinguish between type I AT deficiency (characterized by reduced AT activity and antigen) and type II AT deficiency (low activity and normal antigen).

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 clinical and family history, initial coagulation screens, initial antithrombin activity and antigen tests indicate a diagnosis of antithrombin deficiency.

Shipping Instructions

1. Ambient and refrigerated specimens must arrive within 7 days, and frozen specimens must arrive within 14 days of collection.
2. Collect and package specimen as close to shipping time as possible.

Necessary Information

[Rare Coagulation Disorder Patient Information](#) is required, see Special Instructions. 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: EDTA (lavender top)

Acceptable: ACD (yellow top) or sodium citrate

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send specimen in original tube.

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, see Special Instructions. 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 in Special Instructions:
 -[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.

Specimen Minimum Volume

Blood: 1 mL

Extracted DNA: 100 mcL at 50 ng/mcL concentration

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)	7 days	
	Frozen	14 days	
	Refrigerated	7 days	

Clinical & Interpretive

Clinical Information

Antithrombin (AT) deficiency is a rare hereditary thrombophilia that puts patients at a significantly increased risk of venous thromboembolism. In selected cases, patients manifest heparin resistance. Individuals with AT deficiency are at increased risk for venous thromboembolism (VTE) and late (2nd or 3rd trimester) pregnancy loss.(1,2) It has been estimated that individuals with inherited AT deficiency have a 16-fold increase in risk of VTE compared to individuals without AT deficiency.(4) Women with AT deficiency are at particularly high risk for developing clots during pregnancy and after delivery.(5)

Hereditary AT deficiency is uncommon, with prevalence in the general population of 1 in 2000 to 5000.(1, 2) Hereditary AT deficiency is inherited in an autosomal dominant manner with variable penetrance. Both men and women may be

affected.

AT deficiency is a result of defects in the concentration or function of AT, a natural anticoagulant in blood plasma. AT is the major inhibitor of blood coagulation by inactivating thrombin and factor Xa. The *SERPINC1* gene encodes for antithrombin. Genetic testing of *SERPINC1* is indicated if plasma AT activity assay is abnormally low (ie, typically less than 80% of normal or lower than the reference range established in the local laboratory). AT activity testing should not be performed during acute thrombosis or illness as these could cause a temporary reduction in AT levels. Likewise, it should not be performed while the patient is taking an anticoagulant such as heparin (which may falsely lower levels) or an oral direct factor Xa inhibitor (eg, rivaroxaban, apixaban or edoxaban), which may falsely elevate AT levels.

Additionally, causes of acquired (non-genetic) AT deficiency are much more common than inherited AT deficiency and should be excluded prior to genetic testing. These causes of acquired AT deficiency include liver disease, acute thrombosis, heparin therapy, nephrotic syndrome, disseminated intravascular coagulation, and effects of chemotherapeutic agents such as L-asparaginase. These and other acquired causes of AT deficiency should be excluded prior to genetic testing.

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, and 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 mutation that is not identified by the methods performed. The absence of a mutation, therefore, does not eliminate the possibility of antithrombin (AT) deficiency. This assay does not distinguish between germline and somatic alterations, particularly with variant allele frequencies (VAF) 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 polymorphisms may be present that could lead to false negative or positive results. Therefore test results should be interpreted in the context of antithrombin 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 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. Patnaik MM, Moll S: Inherited Antithrombin deficiency: a review. *Haemophilia* 2008;14(6):1229-1239
2. Blajchamn MA, Austin RC, Fernandez-Rachubinski F, et al: *Blood* 1992;80(9):2159-2171
3. Patnaik MM, Guenther J, Pruthi RK, et al: The Potential Role of Molecular Analysis in Hereditary Antithrombin (AT) Deficiency Diagnosis and Management. *Blood* 2009;114:2976 (Abstract)
4. Di Minno MN, Ambrosino P, Ageno W, et al: Natural anticoagulants deficiency and the risk of venous thromboembolism: a meta-analysis of observational studies. *Thromb Haemost* 2015;135(5):923-932
5. 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
6. Luxembourg B, Delev D, Geisen C, et al: Molecular basis of antithrombin deficiency. *Thromb Haemost* 2011;105(4):635-646

Performance**Method Description**

Next-generation sequencing 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 next-generation sequencing 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 next-generation sequencing when appropriate. (Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Varies

Report Available

21 to 28 days

Specimen Retention Time

Whole Blood: 2 weeks; DNA: Indefinitely

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

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
ATNGS	SERPINC1 Gene, Full Gene NGS	93814-2

Result ID	Test Result Name	Result LOINC® Value
606391	ATNGS Result	50397-9
606392	Alterations Detected	82939-0
606393	Interpretation	69047-9
606394	Additional Information	48767-8
606395	Method	85069-3
606396	Disclaimer	62364-5
606397	Panel Gene List	48018-6
606398	Reviewed By	18771-6