Test Definition: GNADM

Hereditary Thrombotic Thrombocytopenic Purpura, ADAMTS13 Gene, Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating hereditary thrombotic thrombocytopenic purpura (TTP) in patients with a personal or family history suggestive of thrombotic microangiopathy

Confirming a hereditary TTP diagnosis with the identification of known or suspected disease-causing alteration(s) in the *ADAMTS13* gene

Determining the disease-causing alterations within the *ADAMTS13* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of hereditary TTP

Identifying the causative alterations for genetic counseling purposes

Prognosis and risk assessment based on genotype-phenotype correlations

Carrier testing for close family members of an individual with a diagnosis of hereditary TTP

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 *ADAMTS13* gene associated with hereditary thrombotic thrombocytopenic purpura (TTP). 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 hereditary TTP.

Testing Algorithm

The clinical workup for hereditary thrombotic thrombocytopenic purpura (TTP) should begin with a plasma ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats) activity assay performed on a specimen collected before initiation of plasma therapy.

Clinical scoring systems, such as the PLASMIC score, may assist in providing guidance for the necessity of ADAMTS-13 activity testing.(1)

Genetic testing for hereditary TTP is indicated if:
-ADAMTS-13 activity is less than 10% and a functional inhibitor screen as measured by the Bethesda assay is negative (defined as less than 0.4 Bethesda units)
-Non-TTP medical conditions that may be associated with severe ADAMTS-13 deficiency (< or =10%) have been excluded, eg, hemolytic uremic syndrome, hematopoietic stem cell and solid-organ transplantation, liver disease,

disseminated intravascular coagulation, malignancy, viral infection (eg, HIV), sepsis, pregnancy (preeclampsia/eclampsia or HELLP [hemolysis, elevated liver enzymes and low platelets] syndrome), and medications, such as antiplatelet agents, calcineurin inhibitors, and certain chemotherapeutics

International expert groups have provided recommendations on best practices for ADAMTS-13 assays in clinical laboratories and established testing algorithms for the identification of TTP.(2,3)

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 is designed to detect disease-causing variants in the *ADAMTS13* gene and to be utilized for genetic confirmation of a clinical diagnosis of hereditary thrombotic thrombocytopenic purpura (TTP). Genetic testing for hereditary TTP should only be considered if a patient's clinical presentation and initial ADAMTS-13 activity and functional inhibitor screens indicate a diagnosis.

This test does not measure ADAMTS-13 activity or the presence/absence of inhibitors. For assessment of ADAMTS-13 activity and inhibitor status, order ADM13 / ADAMTS13 Activity and Inhibitor Profile, Plasma.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for the *ADAMTS13* 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 it 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 a 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 thrombotic thrombocytopenic purpura (TTP), also known as Upshaw-Schulman syndrome or congenital TTP (cTTP), is a rare blood condition associated with germline variants in the *ADAMTS13* gene. It is inherited in an autosomal recesssive manner with variable expressivity.(4)

Hereditary TTP is characterized by a severe deficiency of the ADAMTS-13 (a disintegrin and metalloproteinase with

thrombospondin type 1 motif 13) protease resulting in the abnormal accumulation of ultra-large von Willebrand factor multimers, which are thought to aggregate with platelets to form occlusive microvascular platelet-rich thrombi.(3-5)

Systemic platelet thrombi lead to the classic pentad of TTP findings: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), fever, neurologic symptoms (ischemic attack and stroke), and kidney dysfunction. While some individuals with hereditary TTP may have symptoms that present at birth, others can remain asymptomatic for decades. Although patients are at significant risk for complications of microvascular thrombosis throughout their lives, two periods appear to be associated with particularly severe risk: the first days of life and pregnancy.(5,6)

Acquired, immune-mediated TTP (caused by the presence of autoantibodies to ADAMTS-13) is more common than hereditary TTP and can be distinguished through ADAMTS-13 antibody or inhibitor assays.(3)

Several other non-TTP causes of thrombotic microangiopathy and severe ADAMTS-13 deficiency should be excluded prior to genetic testing, including hemolytic uremic syndrome, hematopoietic stem cell and solid-organ transplantation, liver disease, disseminated intravascular coagulation, malignancy, viral infection (eg, HIV), sepsis, pregnancy (preeclampsia/eclampsia or HELLP [hemolysis, elevated liver enzymes and low platelets] syndrome), and medications, such as antiplatelet agents, calcineurin inhibitors, and certain chemotherapeutics.(3,7,8)

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. Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol. 2017;4(4):e157-e164
2. Scully M, Cataland S, Coppo P, et al. International Working Group for Thrombotic Thrombocytopenic Purpura: Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017;15(2):312-322
3. Mackie I, Mancini I, Muia J, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of ADAMTS13. Int J Lab Hematol. 2020;42(6):685-696
4. Alwan F Vendramin C, Liesner R, et al. Characterization and treatment of congenital thrombotic thrombocytopenic purpura. Blood. 2019 Apr;133(15):1644-1651
5. Smock KJ. ADAMTS13 testing update: Focus on laboratory aspects of difficult thrombotic thrombocytopenic purpura diagnoses and effects of new therapies. Int J Lab Hematol. 2021;43 Suppl 1:103-108
6. Hovinga JAK, George JN. Hereditary thrombotic thrombocytopenic purpura. N Engl J Med. 2019;381(17):1653-1662
7. Saha M, McDaniel JK, Zheng XL. Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. J Thromb Haemost. 2017;15(10):1889-1900
8. Zuno JAN. Thrombotic thrombocytopenic purpura evaluation and management. In: Khaddour K, ed. StatPearls [Internet]. StatPearls Publishing; 2021. Updated September 27, 2023. Accessed March 2, 2026. Available at www.statpearls.com/articlelibrary/viewarticle/30113
9. George JN. Thrombotic thrombocytopenic purpura: From 1972 to 2022 and beyond. Semin Thromb Hemost. 2022;48(8):926-936
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 *ADAMTS13* 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 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 *ADAMTS13* gene.

There may be regions of the *ADAMTS13* 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 *ADAMTS13* is NM_139025.4. 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

Test Definition: GNADM

Hereditary Thrombotic Thrombocytopenic Purpura, ADAMTS13 Gene, Next-Generation Sequencing, Varies

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GNADM	ADAMTS13 Gene, Full Gene NGS	99960-7

Result ID	Test Result Name	Result LOINC® Value
619230	Test Description	62364-5
619231	Specimen	31208-2
619232	Source	31208-2
619233	Result Summary	50397-9
619234	Result	82939-0
619235	Interpretation	69047-9
619236	Additional Results	82939-0
619237	Resources	99622-3
619238	Additional Information	48767-8
619239	Method	85069-3
619240	Genes Analyzed	82939-0
619241	Disclaimer	62364-5
619242	Released By	18771-6