MAYO CLINIC LABORATORIES

Test Definition: GNPRC

Protein C Deficiency, PROC Gene, Next-Generation Sequencing, Varies

Overview

Useful For

Evaluating protein C deficiency in patients with a personal or family history suggestive of this hereditary thrombophilia

Confirming a diagnosis of autosomal dominant protein C deficiency with the identification of a known or suspected disease-causing alteration in the *PROC* gene

Confirming a diagnosis of autosomal recessive severe protein C deficiency with the identification of homozygous or compound heterozygous disease-causing alterations in the *PROC* gene

Determining the disease-causing alterations within the *PROC* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of protein C deficiency

Prognosis and risk assessment based on genotype-phenotype correlations

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

Carrier testing for close family members of an individual with a diagnosis of autosomal recessive severe protein C 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 *PROC* gene, associated with protein C deficiency, a rare 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 protein C deficiency.

Testing Algorithm

The clinical workup for protein C deficiency should begin with special coagulation testing for protein C activity.

Genetic testing for protein C deficiency is indicated if:
-Protein C activity is less than 75% of normal (Note: reference range may vary depending on the locally established reference range)
-There is a clinical suspicion of hereditary thrombophilia and possible protein C deficiency due to family history or atypical clinical presentation
-Acquired causes of protein C deficiency have been excluded (eg, vitamin K deficiency, oral anticoagulation with coumarin compounds, liver disease, and intravascular coagulation and fibrinolysis/disseminated intravascular coagulation)

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 initial protein C activity and antigen tests indicate a diagnosis of antithrombin deficiency (see Testing Algorithm). This test does not measure protein C activity or antigen levels.

For assessment of protein C activity, order CFX / Protein C Activity, Plasma. If protein C activity is low, protein C antigen testing could help distinguish between type I and type II deficiencies: order PCAG / Protein C Antigen, Plasma.

For assessment of protein C antigen, order PCAG / Protein C Antigen, 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 variants identified in the *PROC* 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 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. 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

Hereditary protein C deficiency is a rare inherited blood clotting disorder (thrombophilia) associated with germline variants in the *PROC* gene. Protein C is an important component of the body's natural anticoagulant system. A deficiency results in an unchecked clotting cascade and an increased risk of thromboembolism.(1)

Individuals who are heterozygous for a disease-causing variant in *PROC* have mild protein C deficiency, which is inherited in an autosomal dominant manner. Mild protein C deficiency is characterized by an increased risk for venous thromboembolism and warfarin-induced skin necrosis. The coinheritance of additional thrombotic risk factors (eg, factor V Leiden) can compound the clotting risk. The estimated prevalence of mild protein C deficiency is between 1 in 200 to 1 in 500.(1-3)

Homozygosity or compound heterozygosity for disease-causing variants in *PROC* is associated with severe protein C deficiency, which is extremely rare (estimated prevalence of 1 in 500,000 to 1 in 750,000) and is inherited in an autosomal recessive manner. This disorder typically presents with purpura fulminans and disseminated intravascular

coagulation within 72 hours of birth but, occasionally, in later infancy. Infants with severe deficiency typically have protein C levels that are virtually undetectable.(1,2,4)

Several causes of acquired (nongenetic) protein C deficiency should be excluded prior to genetic testing, including vitamin K deficiency, oral anticoagulation with coumarin compounds, liver disease, and intravascular coagulation and fibrinolysis/disseminated intravascular coagulation.(2,5)

The British Society for Haematology provides guidelines regarding diagnosis, management, and laboratory testing for individuals with hereditary thrombophilias, including protein C deficiency.(6)

Reference Values

An interpretive report will be provided.

Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) 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 mutation 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 is performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.(7) 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. Cooper PC, Hill M, Maclean RM. The phenotypic and genetic assessment of protein C deficiency. Int J Lab Hematol. 2012;34(4):336-346
2. Dinarvand P, Moser KA. Protein C Deficiency. Arch Pathol Lab Med. 2019;143(10):1281-1285
3. Mustafa S, Mannhalter C, Rintelen C, et al. Clinical features of thrombophilia in families with gene defects in protein C or protein S combined with factor V Leiden. Blood Coagul Fibrinolysis. 1998;9(1):85-89
4. Minford A, Brandao LR, Othman M, et al. Diagnosis and management of severe congenital protein C deficiency (SCPCD): Communication from the SSC of the ISTH. J Thromb Haemost. 2022;20(7):1735-1743
5. Varga EA, Kujovich JL. Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012;81(1):7-17
6. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P, Laffan M. Thrombophilia testing: A British Society for Haematology guideline. Br J Haematol. 2022;198(3):443-458
7. 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 *PROC* 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), and 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 *PROC* gene.

There may be regions of the *PROC* 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 *PROC* is NM_000312.3. 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

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
GNPRC	PROC Gene, Full Gene NGS	93815-9

Result ID	Test Result Name	Result LOINC® Value
619174	Test Description	62364-5
619175	Specimen	31208-2
619176	Source	31208-2
619177	Result Summary	50397-9
619178	Result	82939-0
619179	Interpretation	69047-9
619180	Additional Results	82939-0
619181	Resources	99622-3
619182	Additional Information	48767-8
619183	Method	85069-3
619184	Genes Analyzed	82939-0
619185	Disclaimer	62364-5
619186	Released By	18771-6