MAYO CLINIC LABORATORIES

Test Definition: PCNGS

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

Overview

Useful For

Ascertaining a pathogenic alteration in the *PROC* gene of patients with congenital protein C deficiency

This test is **not intended for** prenatal diagnosis

Genetics Test Information

This test detects pathogenic alterations in the *PROC* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of protein C deficiency.

The gene target for this test is:
Gene name (transcript): *PROC* (GRCh37 [hg19] NM_000312)
Chromosomal location: 2q14.3

Testing Algorithm

The clinical workup for protein C deficiency includes special coagulation testing for protein C activity.

Genetic testing for protein C deficiency is indicated if:
-Protein C activity is reduced (<75% of normal)
-Acquired causes of protein C deficiency have been excluded (eg, vitamin K deficiency, oral anticoagulation with coumarin compounds, liver disease, intravascular coagulation and fibrinolysis/disseminated intravascular coagulation)

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

For assessment of protein C activity, order CFX / Protein C Activity, Plasma.

If protein C activity is low, consider protein C antigen testing to help distinguish between type I and type II deficiencies. Order PCAG / Protein C Antigen, Plasma.

Shipping Instructions

Ambient and refrigerated specimens must arrive within 7 days of collection, and frozen specimens must arrive within 14 days.

Collect and package specimen as close to shipping time as possible.

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

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA)
Acceptable: Yellow top (ACD) or light-blue top (3.2% sodium citrate)
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: Ambient (preferred)/Refrigerate/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)/Refrigerate/Ambient

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

Blood: 1 mL blood
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

Protein C is a vitamin K-dependent plasma glycoprotein synthesized in the liver. After secretion, protein C circulates in blood mostly in its inactive form until cleaved at residues Arg211-Leu212 to form activated protein C. Activated protein C and its cofactor, protein S, act as a potent anticoagulant by cleaving and inactivating procoagulant factors VIIIa and Va. A deficiency of protein C results in impairment of the ability to control coagulation through the inactivation of procoagulant factors, factor Va and factor VIIIa, leading to an increased risk of venous thrombosis. While protein C deficient individuals are 7 to 10 times more likely to develop venous thromboembolism (VTE), 3% to 9% of these individuals actually develop a VTE, and the annual risk of VTE is between 0.4% and 1.0% per year.(1)

Congenital protein C deficiency is classified into 2 types.
-Type I deficiency is characterized by decreased protein synthesis or increased intracellular protein degradation, which leads to lower levels of protein C in blood. Type I deficiency accounts for about 75% of all cases of congenital protein C deficiency.
-Type II deficiency is characterized by dysfunctional protein C that is produced in normal amounts.
There appears to be no clinical differences between type I and type II phenotypes. Protein C antigen testing (PCAG / Protein C Antigen, Plasma) is helpful to distinguish between type I and type II deficiencies and in cases where genetic testing results yield variants of uncertain significance.

The *PROC* gene encodes for protein C. Pathogenic alterations in the gene can cause congenital protein C deficiency. Congenital protein C deficiency is inherited as an autosomal dominant disorder but with variable penetrance. Both men and women can be affected. The estimated prevalence of protein C deficiency ranges from 200 to 400 per 100,000. Individuals who are heterozygous for a pathogenic *PROC* alteration are at increased risk for VTE and warfarin-induced skin necrosis. The coinheritance of additional thrombotic risk factors (eg, factor V Leiden) can compound this risk, leading to a clinically significant disorder. Homozygosity or compound heterozygosity for pathogenic alterations in the

PROC gene is associated with severe protein C deficiency, which presents in infancy as the development of cerebral vein thrombosis or neonatal purpura fulminans (ie, widespread cutaneous hemorrhage and tissue death due to thrombosis of the microvascular). These infants typically have protein C levels that virtually undetectable. Severe protein C deficient patients with very low but detectable protein C levels typically present with thromboembolic disease during early childhood or adulthood.(2)

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

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 variant that is not identified by the methods performed. The absence of a variant, therefore, does not eliminate the possibility of protein C deficiency. This assay does not distinguish between germline and somatic alterations, particularly with variant allele frequencies 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.

If there is a family history of protein C deficiency, it is often useful to test first-degree family members to help establish the clinical significance of variants of unknown significance.

Technical Limitations:
Next-generation sequencing (NGS) may not detect all types of genetic variants. Additionally, rare variants (ie, polymorphisms) may be present that could lead to false-negative or false-positive results. Therefore, test results should be interpreted in the context of 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/or 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 alterations (ie, 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. Varga EA, Kujovich JL: Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012 Jan;81(1):7-17
2. Heleen van Ommem C, Middeldorp S: Thrombophilia in childhood: to test or not to test. Semin Thromb Hemost. 2011 Oct;37(7):794-801
3. Reitsma PH, Bernardi F, Doig RG, et al: Protein C deficiency: a database of mutations, 1995 update. On behalf of the Subcommittee on Plasma Coagulation Inhibitors of the Scientific and Standardization Committee of the ISTH. Thromb Haemost. 1995 May;73(5):876-879
4. Kottke-Marchant K, Comp P: Laboratory issues in diagnosing abnormalities of protein C, thrombomodulin, and endothelial cell protein C receptor. Arch Pathol Lab Med. 2002 Nov;126(11):1337-1348
5. Cooper PC, Hill M, Maclean RM: The phenotypic and genetic assessment of protein C deficiency. Int J Lab Hematol. 2012 Aug;34(4):336-346
6. Baglin T, Gray E, Greaves M, et al: Clinical guidelines for testing for heritable thrombophilia. Br J Haematol. 2010 Apr;149(2):209-220

Performance

Method Description

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

PDF Report

No

Day(s) Performed

Weekly

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 Regional Manager. 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
PCNGS	PROC Gene, Full Gene NGS	93815-9

Result ID	Test Result Name	Result LOINC® Value
606407	PCNGS Result	50397-9
606408	Alterations Detected	82939-0
606409	Interpretation	69047-9
606410	Additional Information	48767-8
606411	Method	85069-3
606412	Disclaimer	62364-5
606413	Panel Gene List	48018-6
606414	Reviewed By	18771-6