MAYO CLINIC LABORATORIES

Test Definition: APCRR

Activated Protein C Resistance V, with Reflex to Factor V Leiden, Blood and Plasma

Overview

Useful For

Evaluating patients with incident or recurrent venous thromboembolism (VTE)

Evaluating individuals with a family history of VTE

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
APCRV	Activated Protein Resistance V, P	Yes	Yes
SC018	Whole Blood	No	Yes

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
F5DNA	Factor V Leiden (R506Q) Mutation, B	Yes	No
F5DNI	APCRV/F5DNA Summary Interpretation	No	No

Testing Algorithm

If the assay ratio is abnormal, then factor V Leiden variant analysis will be performed at an additional charge.

When the activated protein C resistance V is abnormal or indeterminate and the factor V Leiden variant assay is performed, a summary interpretation will be provided.

Special Instructions

- Coagulation Guidelines for Specimen Handling and Processing
- Informed Consent for Genetic Testing
- Coagulation Patient Information
- Informed Consent for Genetic Testing (Spanish)

Method Name

Optical Clot-Based

NY State Available

Yes

Test Definition: APCRR

Activated Protein C Resistance V, with Reflex to Factor V Leiden, Blood and Plasma

Specimen

Specimen Type

Whole blood
Plasma Na Cit

Ordering Guidance

Although the APC-resistance assay can be performed in the absence of other coagulation tests and clinical information, it is most reliably performed as part of a consultative coagulation test panel with interpretive reporting (including appropriate testing of the same specimen to evaluate for the presence or absence of coagulation abnormalities or conditions that may affect interpretation of the APC-resistance assay); see AATHR / Thrombophilia Profile, Plasma and Whole Blood.

Specimen Required

Blood and plasma are required.

Patient Preparation: Fasting: 8 hours, preferred but not required

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 Type: Platelet-poor plasma
Collection Container/Tube: Light-blue top (3.2% sodium citrate)
Submission Container/Tube: 13-mm x 75-mm, 5-mL, plastic vial (polypropylene preferred)
Specimen Volume: 1 mL Platelet-poor plasma
Collection Instructions:
1. For complete instructions, see Coagulation Guidelines for Specimen Handling and Processing.
2. Within 4 hours of collection, centrifuge, transfer all plasma into a plastic vial, and centrifuge plasma again.
3. Aliquot plasma into separate plastic vial leaving 0.25 mL in the bottom of centrifuged vial.
4. Immediately freeze plasma at -20 degrees C, or ideally, at -40 degrees C or below.
Additional Information:
1. A double-centrifuged specimen is critical for accurate results as platelet contamination may cause spurious results.
2. Each coagulation assay requested should have its own vial.

Forms

1. **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)
2. Coagulation Patient Information (T675)
3. If not ordering electronically, complete, print, and send a Coagulation Test Request (T753) with the specimen.

Specimen Minimum Volume

Platelet-poor plasma: 0.5 mL; Whole blood: 3 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	Reject
Gross icterus	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole blood	Ambient (preferred)	14 days	
	Refrigerated	14 days	
	Frozen	14 days	
Plasma Na Cit	Frozen	14 days	

Clinical & Interpretive

Clinical Information

Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight = 62,000 Da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa. APC proteolyzes and interacts with factors V/Va and VIII/VIIIa at specific APC cleavage and binding sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time fails to prolong significantly after the addition of APC.

The vast majority of individuals with familial APC resistance have a specific alteration in the procoagulant factor V gene (*F5*) encoding for a p.Arg534Gln substitution in the heavy chain of factor V (formerly R506Q). This glutamine to arginine amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden variant varies depending on the population. Approximately 5% of asymptomatic White Americans of non-Hispanic ancestry are heterozygous carriers. In contrast, the carrier frequency among African Americans, Asian Americans, and Native Americans is less than 1%, and the carrier frequency for

Hispanics is intermediate (2.5%). The carrier frequency can be especially high (up to 14%) among White individuals of Northern European or Scandinavian ancestry. Homozygosity for the factor V Leiden variant is much less common but may confer a substantially increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden variant; homozygous individuals have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

Reference Values

ACTIVATED PROTEIN C RESISTANCE V RATIO
> or =2.3
Pediatric reference ranges have neither been established nor are available in scientific literature. The adult reference range likely would be applicable to children older than 6 months.

Interpretation

An activated protein C (APC) resistance ratio below 2.3 suggests abnormal resistance to APC of hereditary origin.

If the screening APC resistance test is abnormal, DNA-based testing for the factor V Leiden variant (p.Arg534Gln, formerly R506Q) is performed to confirm or exclude hereditary APC-resistance.

Cautions

This assay is highly sensitive and specific for inherited activated protein C (APC) resistance, most commonly due to the factor V Leiden variant, but it will not detect patients with acquired APC resistance. Persons with acquired APC resistance are at similar risk for venous thromboembolism.

Preanalytical conditions of the patient and the blood specimen are extremely important for reliable performance and interpretation of testing for APC resistance. Plasma specimens that demonstrate prolonged clotting times (prothrombin time, activated partial thromboplastin time) for reasons other than anticoagulant effects (eg, lupus-like anticoagulants or specific coagulation factor inhibitors) generally cannot be reliably tested for the presence or absence of APC resistance. Proper preparation of the plasma specimen is extremely important to help ensure accuracy of results and interpretation.

This assay has greater than 99% sensitivity for detecting the presence of a factor V Leiden variant. Discrepant results of plasma-based activated protein C resistance ratio and DNA-based factor V Leiden testing may occur in recipients of liver or allogeneic hematopoietic stem cell transplants, or due to anticoagulant effects, such as excess heparin; direct thrombin inhibitors argatroban (Acova), bivalirudin (Angiomax) or dabigatran (Pradaxa); or direct factor Xa inhibitors rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa); or a sample mix up. Clinical correlation is suggested. If DNA-based testing for the factor V Leiden variant is clinically indicated, call 800-533-1710.

Clinical Reference

1. Nichols WL, Heit JA. Activated protein C resistance and thrombosis. Mayo Clin Proc. 1996;71(9):897-898
2. Dahlback B. Resistance to activated protein C as risk factor for thrombosis: molecular mechanisms, laboratory investigation, and clinical management. Semin Hematol. 1997;34(3):217-234
3. Rodeghiero F, Tosetto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. Ann Intern Med. 1999;130(8):643-650. doi:10.7326/0003-4819-130-8-199904200-00004
4. Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA; ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V leiden mutation testing. Genet Med. 2001;3(2):139-148.

doi:10.1097/00125817-200103000-00009
5. Press RD, Bauer KA, Kujovich JL, Heit JA. Clinical utility of factor V Leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. Arch Pathol Lab Med. 2002;126(11):1304-1318. doi:10.5858/2002-126-1304-CUOFVL
6. Yohe S, Olson J. Thrombophilia: Assays and interpretation. In: Kottke-Marchant K, Davis B, eds. Laboratory Hematology Practice. Blackwell Publishing; 2012:492-508
7. Favaloro EJ, Lippi G, eds. Hemostasis and Thrombosis: Methods and Protocols. Humana Press; 2017

Performance

Method Description
This assay is performed using the HemosIL Factor V Leiden (APC Resistance V) Kit on the Instrumentation Laboratory ACL TOP instrument. The method uses a modified activated partial thromboplastin time (aPTT) test to detect activated protein C (APC) resistance. The plasma specimen is prediluted in factor V-deficient plasma. Then the aPTT test is performed by incubating patient plasma with a standardized amount of platelet-like phospholipids and activator of the contact factors of the intrinsic coagulation pathway, followed by recalcification of plasma and measurement of clotting time. The ratio of the aPTT test with and without added APC is reported as the APC resistance (or sensitivity) ratio.(Package insert: HemosIL Factor V Leiden [APC Resistance V]. Instrumentation Laboratory Company; Rev 11/2017)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
4 to 7 days

Specimen Retention Time
Plasma: 7 days: Whole blood: 2 weeks

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 Definition: APCRR

Activated Protein C Resistance V, with Reflex to Factor V Leiden, Blood and Plasma

Test Classification

See Individual Test IDs

CPT Code Information

85307

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
APCRR	APCRV, w/Reflex, P	13590-5

Result ID	Test Result Name	Result LOINC® Value
APCR	APCRV Ratio	13590-5
INT55	Interpretation	48591-2
SC018	Whole Blood	No LOINC Needed