

Hypercoagulable States - Thrombophilia

Clinical Background

Hereditary thrombophilia is a genetically determined increased risk for thrombosis and thromboembolism. Hypercoagulable states may also be acquired.

Epidemiology

- Prevalence
 - Inherited thrombophilic defects found in 30-50% of venous thromboembolic events in U.S.

Inherited Thrombophilic Disorders			
Disorder	Prevalence in Normals (%)	Frequency in Patients with VTE ⁺ (%)	Relative Risk of First Episode of DVT ⁺⁺
Factor V Leiden (heterozygous)	0.05-4.8*	18.8	7
Factor V Leiden (homozygous)	0.02	1.5	80
Factor V with R2 mutation (heterozygous with FVL)	0.06-0.12	10.0	10
Prothrombin G20210A allele	0.06-2.7*	7.1	2.8
Protein C deficiency	0.2-0.4	3.7	6.5
Protein S deficiency	0.16-0.21	2.3	5.0
Antithrombin deficiency	0.02	1.9	20
Dysfibrinogenemia	<0.01	0.8	Unknown
Hyperhomocysteinemia**	5-7	10	2.95
Elevated factor VIII level	11	25	4.8
Elevated factor IX level	10	20	2.8
Elevated factor XI level	10	19	2.2
Elevated lipoprotein (a) level	7	20	3.2
Elevated thrombin-activatable fibrinolysis inhibitor (TAFI)	9	14	1.7

*Percent lowest in Asian or African descent; highest in Caucasian descent; **>18.5 μmol/L
⁺VTE = venous thromboembolism; ⁺⁺DVT = deep vein thrombosis
 Adapted from Perry, Ortel, and references included within

Whitlatch, NL and Ortel TL. Thrombophilias: When should we test and how does it help? *Seminars in respiratory and critical care medicine*. 2008; 29(1):27.

Etiologies

- Most-common thrombophilias
 - Factor V Leiden
 - Prothrombin G20210A
 - Homocysteinemia (acquired or inherited)

- Less-common thrombophilias
 - Increased clotting factors
 - Elevated factor VIII (FVIII) levels are often found in patients with venous thrombosis, but routine testing is controversial
 - Protein C deficiency
 - Protein S deficiency
 - Antithrombin deficiency
 - Impaired clot lysis (dysfibrinogenemia, abnormal fibrinolysis)
- **Antiphospholipid syndrome** is an acquired thrombophilic state

Select topics are discussed below

Factor V Leiden

- Genetics and pathophysiology
 - The factor V Leiden (FVL) point mutation is the most common inherited thrombophilia
 - Accounts for more than 90% of patients with activated protein C resistance (APC-R)
 - During normal hemostasis, APC limits clot formation by proteolytic inactivation of factors Va and VIIIa
 - FVL prevents inactivation of factor Va by APC at the normal rate, increasing the risk for thrombosis
 - Functional tests for APC-R are generally used as a screening test for FVL
 - DNA tests are used to confirm positive screening tests and to differentiate between heterozygotes and homozygotes
 - Autosomal dominant inheritance
 - Heterozygous carriers have a 5- to 10-fold increased risk
 - Homozygous carriers have a 50- to 100-fold increased risk
- Clinical Presentation
 - Venous thromboembolism (VTE) is the most common type of thrombotic event
 - Recurrent VTE is generally uncommon in heterozygous patients unless additional risk factors are present
 - Risk of recurrent VTE is increased in homozygous carriers
 - Recurrent miscarriage in the second trimester of pregnancy
- Additional risk factors
 - Presence of factor V R2 A4070G mutation in addition to FVL mutation increases risk of thrombotic event 10-fold
 - Many patients with FVL mutation and recurrent episodes of thrombosis have more than one genetic risk factor (eg, concomitant prothrombin [factor II] G20210A mutation, protein C deficiency, homocystinemia)
 - Acquired factors such as pregnancy, oral contraceptives, hormone replacement therapy, and immobilization increase the risk

Prothrombin G20210A

- Genetics and pathophysiology
 - The prothrombin G20210A mutation is the second most common inherited thrombophilia
 - Results in elevated levels of plasma prothrombin which leads to hypercoagulability (gain of function)
 - Detected using DNA tests

- Factor II (prothrombin) activity is not an appropriate test
- Autosomal dominant inheritance
 - A single copy of the G20210A mutation increases the lifetime risk of venous thrombosis by 3-11% while possessing two copies of the mutation leads to even greater risk
- Clinical Presentation
 - VTE
 - Pregnancy complications
- Additional risk factors
 - Combined heterozygosity for the prothrombin G20210A mutation and FVL leads to earlier onset, higher rate of recurrence and more severe thrombotic events than either by itself
 - Risk of thrombosis appears increased during pregnancy and with oral contraceptive use

Protein C Deficiency

- Pathophysiology
 - Protein C is a vitamin K-dependent plasma anticoagulant that inactivates factors Va and VIIIa after being activated to APC by thrombin-thrombomodulin
 - Inherited protein C deficiency is uncommon and may be either quantitative (type I) or qualitative (type II)
 - Autosomal dominant inheritance
 - Functional assays (rather than antigenic assays) are preferred for diagnosis
 - Protein C levels vary with age
 - Protein C levels are decreased in acute thrombotic states, disseminated intravascular coagulation (DIC), liver disease, malnutrition (vitamin K deficiency) and with warfarin therapy
 - Elevated FVIII levels (acute phase reactant) may interfere in some functional assays and result in falsely decreased values
 - Increased protein C levels may be seen in diabetes, nephrotic syndrome, during pregnancy, and in patients on oral contraceptives
 - Heparin and direct thrombin inhibitors may interfere in some functional assays, resulting in falsely elevated values
- Clinical Presentation
 - Additional risk factors likely necessary to provoke thrombosis
 - VTE in heterozygotes
 - Neonatal purpura fulminans (DIC) in homozygous infants
 - Warfarin-induced skin necrosis is seen rarely

Protein S Deficiency

- Pathophysiology
 - Protein S is a vitamin K-dependent plasma anticoagulant which acts as a cofactor for activated protein C
 - Protein S exists in 2 forms
 - Free protein S represents 40% of the total and is physiologically active
 - Bound protein S (attached to C4b-binding protein) represents 60% of the total and possesses no anticoagulant activity
 - Inherited protein S deficiency is uncommon and may be either quantitative (type 1) or qualitative (type 2)
 - Autosomal dominant inheritance
 - Antigenic tests for free protein S are preferred for diagnosis

- Free protein S values are higher in males than in females
- Protein S values are decreased in acute thrombotic states, nephrotic syndrome, inflammatory syndromes (due to increased C4b-binding protein), disseminated intravascular coagulation (DIC), liver disease, malnutrition (vitamin K deficiency), pregnancy, estrogen therapy, and with warfarin therapy
 - Elevated FVIII levels may interfere in some functional assays and result in falsely decreased values
 - APC resistance may interfere in some functional assays and result in falsely decreased values
 - Heparin and direct thrombin inhibitors may interfere in some functional assays and result in falsely elevated values
- Clinical Presentation
 - Additional risk factors likely necessary to provoke thrombosis
 - VTE most common, arterial thrombosis may occur
 - Neonatal purpura fulminans (DIC) in homozygous infants
 - Warfarin-induced skin necrosis is seen rarely

Antithrombin Deficiency

- Pathophysiology
 - Antithrombin (AT) is a plasma anticoagulant that inactivates thrombin, factor Xa and other activated clotting factors
 - Antithrombin activity is enhanced by heparin-like glycosaminoglycans on the endothelial surface and by pharmaceutical heparin
 - Inherited antithrombin deficiency may be either quantitative (type 1) or qualitative (type 2)
 - Autosomal dominant inheritance
 - Functional assays are preferred for diagnosis
 - Decreased antithrombin occurs in acute thrombotic states, liver disease, DIC, nephrotic syndrome and heparin therapy; mild decreases may be seen in pregnancy or with oral contraceptive use.
 - Increased AT may occur with long-term warfarin therapy in some patients
- Clinical Presentation
 - VTE
 - Recurrent thrombosis may occur even in the absence of additional risk factors
 - Some deficient patients are resistant to heparin therapy

Hyperhomocysteinemia

- Independent risk factor for thromboembolic events
- Most patients with hyperhomocysteinemia do not have genetic mutations or polymorphisms
- Regardless of the underlying etiology, hyperhomocysteinemia is the result of deranged homocysteine metabolism which may be acquired (deficiency of vitamins B6, B12, or folic acid) or inherited (deficiency of cystathionine β -synthase or expression of a thermolabile form of methylenetetrahydrofolate reductase)
- Thrombotic risk is most closely associated with increased fasting plasma homocysteine levels regardless of the underlying etiology
 - Plasma homocysteine testing is recommended rather than DNA-based tests

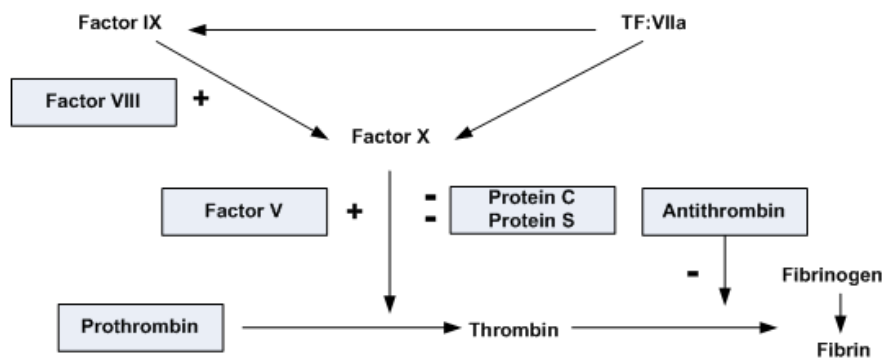
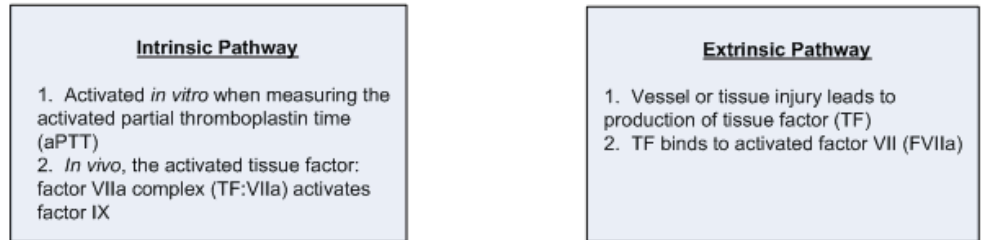
Methylenetetrahydrofolate reductase (MTHFR) mutations

- Genetics
 - Autosomal recessive inheritance

- The most common genetic defects of homocysteine metabolism are the *MTHFR* mutations C677T and A1298C
 - The C677T mutation results in a thermolabile variant of *MTHFR*
- Clinical Presentation
 - Elevated plasma homocysteine levels have been associated with atherosclerotic disease, VTE and arterial thrombosis

[Click here for diagram of Clotting Cascade with an Emphasis on Inherited Thrombophilias](#)

Clotting Cascade with an Emphasis on Inherited Thrombophilias



Overview: Both intrinsic and extrinsic pathways lead to the activation of factor X. Factor X plays a role in converting inactive prothrombin to thrombin. Thrombin converts soluble fibrinogen and fibrin, the major component of blood clots.

The protein C and antithrombin pathways are critical to maintain control of coagulation.

Factor V: Factor V is a procoagulant protein that helps promote the conversion of prothrombin to thrombin. Activated factor V is typically inactivated by a complex that forms between activated protein C and S. When factor V Leiden mutation is present, the protein C/S complex cannot break down activated factor V (Va) as efficiently, leading to a hypercoagulable state.

Prothrombin: The G20210A polymorphism results in increased production of prothrombin. This creates a hypercoagulable state since more thrombin is generated.

Antithrombin: Typically inactivates thrombin, leading to less conversion of fibrinogen to fibrin. Antithrombin deficiency reduces this inhibitory effect, creating a hypercoagulable state. Antithrombin also inactivates factors Xa, IXa and XIa.

Protein C/S: Deficiencies of either protein C or S result in decreased inhibition of activated factor V and increased thrombin generation, leading to a hypercoagulable state.

Activated protein C (ACP) resistance: Leads to a hypercoagulable state since factor Va (normally inactivated by ACP) is not inactivated as quickly. APC also inactivates factor VIIIa.

Reproduced with permission from National Society of Genetic Counselors. Varga E. Inherited thrombophilia: key points for genetic counseling. J Genet Couns. 2007;16(3):263.

Diagnosis

- Laboratory testing
 - Consider acquired disorders such as
 - Antiphospholipid syndrome
 - Homocysteine (cardiovascular disease [non-traditional risk markers])
 - Cancer screening based on age and risk factors

- If factor V Leiden mutation found, consider testing the following (based on recommendation of the American College of Medical Genetics)
 - Prothrombin gene mutation G20210A
 - Factor V gene R2 mutation
 - Measurement of total plasma homocysteine concentration
 - Functional coagulation assays for antithrombin III, protein C and protein S deficiencies
- Indications for testing for inherited disorders
 - Population screening is not recommended
 - Patient with new VTE or recurrent VTE without obvious acquired risk factors (see Differential Diagnosis)
 - Abnormalities may be identified in a significant number of patients; however, identification of an abnormality may not predict risk of recurrence or change therapy
 - Test in cases where the results will impact management of the patient or patient family members
 - Situations where testing should be considered
 - Idiopathic thrombosis in patient ≤ 50 years of age
 - Recurrent thrombosis
 - Unusual sites of thrombosis
 - First-degree relatives with thromboses
 - Thrombotic event during pregnancy
 - Thrombotic event while taking oral contraceptives
 - If testing indicated, consider the following
 - Activated protein C resistance (with or without reflex to FVL mutation); Factor V R2 A4070G mutation
 - Prothrombin mutation
 - Antithrombin activity
 - Protein C activity
 - Free protein S
 - Factor VIII activity (testing other factor activities such as FVIII and FIX is controversial and not currently recommended)
 - Testing for less common disorders is available if results are uninformative and additional testing is indicated
 - Many tests are altered by acute thrombotic states (acute phase response, consumption of factors and anticoagulant factors) and anticoagulant therapy
 - Delay testing 2-3 months after acute event
 - Preferable to discontinue oral anticoagulant therapy at least 2 weeks to 1 month before testing
 - Heparin and direct thrombin inhibitors interfere with many of the tests and should be discontinued prior to testing
 - Heparin interference in tests may be due to therapy with unfractionated or low molecular weight heparin or heparin contamination from a line draw
 - DNA-based tests are not affected by an acute phase response or anticoagulant therapy
 - Consider repeating abnormal functional or antigenic testing before making a definitive diagnosis of an inherited thrombophilia
 - Low results can be obtained due to patient condition//biologic variability, medications, and assay variability or interference
 - Consider patient age and gender when interpreting results; normal ranges vary by age and gender

Differential Diagnosis

- Provoked/acquired causes of thrombophilia are more common than hereditary causes and should be considered when evaluating patients with thrombosis.
- Examples of provoked/acquired causes of thrombophilia include:
 - Antiphospholipid antibodies/lupus anticoagulant
 - Malignancy
 - Long distance travel
 - Trauma
 - Surgery
 - Immobilization
 - Presence of a central venous catheter
 - Pregnancy/postpartum
 - Therapy-related thrombophilia
 - Hormone replacement therapy
 - Oral contraceptives
 - Tamoxifen/raloxifene
 - Chemotherapy
 - Heparin-induced thrombocytopenia

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Thrombotic Risk, Inherited Etiologies (Most Common) with Reflex to Factor V Leiden 0030133 Method: Refer to individual components	Identify common inherited thrombotic risk factors	See individual components	See individual components
Thrombotic Risk, Inherited Etiologies (Uncommon) 0030177 Method: Clotting/Microlatex Particle-Mediated Immunoassay	Identify less common inherited thrombotic risk factors	See individual components	See individual components
Thrombotic Risk (Acquired) Reflexive Panel 0030268 Method: Refer to individual components	Identify acquired thrombotic risk factors, including lupus anticoagulant	See individual components	Interpretation provided in test report

<p>APC Resistance Profile with Reflex to Factor V Leiden 0030192 Method: Clotting/Polymerase Chain Reaction/Fluorescence Monitoring</p>	<p>Refer to laboratory testing Diagnose APC resistance due to factor V Leiden mutation First-line test in the evaluation of thrombophilia</p>	<p>APC resistance profile may be affected by heparin levels above 2 IU/mL, direct thrombin inhibitors, and low factor V activity levels (<50%) Perform PCR testing as first-line test if these are present APC resistance not due to a factor V mutation will not be detected</p>	
<p>Prothrombin (F2) G20210A Mutation 0056060 Method: Polymerase Chain Reaction/Fluorescence Monitoring</p>	<p>Refer to laboratory testing; same as for APC resistance First-line test in the evaluation of thrombophilia</p>	<p>Other mutations within the prothrombin gene or mutations in other genes that cause elevated prothrombin will not be detected Factor II (prothrombin) activity is not an appropriate test to identify the prothrombin mutation</p>	
<p>Antithrombin, Enzymatic (Activity) 0030010 Method: Chromogenic Assay</p>	<p>Refer to laboratory testing Detects both quantitative and qualitative deficiency of antithrombin. First-line test in the evaluation of thrombophilia</p>	<p>Avoid testing during acute thrombosis and in patients receiving heparin Refer to antithrombin deficiency in Clinical Background for additional limitations</p>	
<p>Protein C, Functional 0030113 Method: Clotting</p>	<p>Refer to laboratory testing Detects both quantitative and qualitative deficiency of protein C First-line test in the evaluation of thrombophilia</p>	<p>Avoid testing during acute thrombosis and in patients receiving oral anticoagulants Refer to protein C deficiency in Clinical Background for additional limitations</p>	
<p>Protein C, Functional with Reflex to Protein C, Total Antigen 0030041 Method: Clotting/Enzyme-Linked Immunosorbent Assay</p>	<p>Refer to laboratory testing Detects both quantitative and qualitative deficiency of protein C First-line test in the evaluation of thrombophilia</p>	<p>Avoid testing during pregnancy, acute thrombosis and in patients receiving oral anticoagulants</p>	

<p>Protein S Free, Antigen 0098894</p> <p>Method: Microlatex Particle-Mediated Immunoassay (LIA)</p>	<p>Refer to laboratory testing</p> <p>Detects quantitative protein S deficiency and most forms of qualitative protein S deficiency</p> <p>First-line test in the evaluation of thrombophilia</p>	<p>Avoid testing during pregnancy, acute thrombosis and in patients receiving oral anticoagulants</p> <p>Refer to protein S deficiency in Clinical Background for additional limitations</p>	
<p>Protein S, Free Antigen with Reflex to Protein S, Total Antigen 2002269</p> <p>Method: Microlatex Particle-Mediated Immunoassay (LIA)</p>	<p>Refer to laboratory testing</p> <p>Detects quantitative protein S deficiency and most forms of qualitative protein S deficiency</p> <p>First-line test in the evaluation of thrombophilia</p>	<p>Avoid testing during acute thrombosis and in patients receiving oral anticoagulants</p>	
<p>Homocysteine, Total 0099869</p> <p>Method: Enzymatic</p>	<p>Refer to laboratory testing</p> <p>First-line test in the evaluation of thrombophilia</p>		
<p>Factor VIII, Activity 0030095</p> <p>Method: Clotting</p>	<p>Refer to laboratory testing</p>	<p>Testing should be performed at least 6 months after an acute thrombotic event when the patient is stable</p>	
<p>Factor V, R2 Mutation 2001549</p> <p>Method: Polymerase Chain Reaction/Restriction Enzyme Digestion/Gel Electrophoresis</p>	<p>Further clarify thrombotic risk for individuals who are known FVL heterozygotes</p>	<p>FVL mutations other than R2 (A4070G) are not evaluated by this assay</p> <p>The factor V, R2 mutation, by itself, does not significantly contribute to venous thrombosis risk</p>	

Additional Tests Available

Test Name and Number	Comments
<p>APC Resistance Profile 0030127</p> <p>Method: Clotting</p>	<p>APC resistance profile may be affected by heparin levels above 2 IU/mL, direct thrombin inhibitors, and low factor V activity levels (<50%)</p> <p>Perform PCR testing as first-line test if these are present</p> <p>APC resistance not due to a factor V mutation will not be detected</p>
<p>Antithrombin, Antigen 0030015</p> <p>Method: Microlatex Particle-Mediated Immunoassay</p>	<p>Functional test should be ordered first</p> <p>Use if necessary to distinguish quantitative from qualitative AT deficiency</p>

Protein S, Functional 0030114 Method: Clotting	Protein S free is the recommended initial test Aid in the diagnosis of suspected protein S deficiency
Protein S, Total Antigen 0030112 Method: Microlatex Particle-Mediated Immunoassay	Protein S free is the recommended initial test Aid in the diagnosis of suspected protein S deficiency
Protein C, Total Antigen 0030111 Method: Enzyme Immunoassay	Functional test should be ordered first Use if necessary to distinguish quantitative from qualitative protein C deficiency
Methylenetetrahydrofolate Reductase (MTHFR) 2 Mutations 0055655 Method: Polymerase Chain Reaction/Fluorescence Monitoring	Not recommended for nonsymptomatic patients <18 years of age. Total homocysteine is the recommended first-line test Analytical sensitivity and specificity – 99%
Thrombotic Risk, DNA Panel 0056200 Method: Polymerase Chain Reaction	
Antithrombin Panel 0030370 Method:	
Protein C & S Panel, Functional 0030182 Method: Clotting	
Protein C & S Panel, Total, Antigen 0030116 Method: Microlatex Particle-Mediated Immunoassay	

Guidelines

Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy. American College of Chest Physicians evidence-based clinical practice guidelines 8th edition. American College of Chest Physicians - Medical Specialty Society. 2001 January (Revised 2008 June).

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