Plasminogen Activator Inhibitor-1 (SERPINE1) Genotyping

Indications for Ordering

• Screen for genetic susceptibility for venous thromboembolism (VTE) or myocardial infarction (MI) in individuals with a personal or family history of thrombotic events
• Aid risk/benefit assessment for preventive or therapeutic interventions for VTE or MI

Test Description

Polymerase chain reaction and fluorescence monitoring

Tests to Consider

Primary test
Plasminogen Activator Inhibitor-1, PAI-1 (SERPINE1) Genotyping 2004980
  • Genotyping of SERPINE1 4G/5G allele

Related tests
Plasminogen Activator Inhibitor 1, Activity 0098781
  • Detect elevated concentrations of plasminogen activator inhibitor 1 (PAI-1)
    o Low concentrations of PAI-1 may not be accurately quantified

Thrombotic Risk, Inherited Etiologies (Most Common) with Reflex to Factor V Leiden 0030133
  • Acceptable screening panel for common inherited thrombophilias

Disease Overview

Frequency: 4G allele (by ethnicity)
  • White: 0.52
  • Hispanic: 0.38
  • African American: 0.13-0.28

Diagnostic issues

• Abnormalities in the fibrinolytic system may be associated with thrombotic events, such as VTE or MI
• SERPINE1 polymorphisms that alter PAI-1 activity are an uncommon genetic cause for increased VTE or MI risk
  o Increased activity of PAI-1 increases the risk of VTE and MI

Pathophysiology

• SERPINE1 gene encodes PAI-1 protein

• PAI-1 inhibits tissue-type plasminogen activator and urokinase-type plasminogen activator
  o Both activate plasminogen into plasmin, which breaks down fibrin clots
• Overexpression of PAI-1 may prevent normal clearance of fibrin and cause thrombosis
• Deficiency or absence of PAI-1 is associated with lifelong tendency to hemorrhage
• PAI-1 levels are regulated by metabolic factors, such as triglycerides, cholesterol, and insulin

Genetics

Gene: SERPINE1

Inheritance: autosomal dominant

Mutations

• 4G/5G insertion/deletion polymorphism is located at c.-817dupG (from start of translation) in the promoter region of the SERPINE1 gene
• PAI-1 promoter 4G allele: associated with
  o Increased PAI-1 transcription activity
  o Higher PAI-1 plasma levels
  o Reduced fibrinolysis
  o Increased risk for VTE, especially in individuals with other thrombophilic risk factors
  o Increased risk for MI

Test Interpretation

Sensitivity/Specificity

• Clinical sensitivity: unknown
• Analytical sensitivity/specificity: 99%

Results

• 5G/5G genotype: two copies of 5G allele detected
  o Not at increased risk of VTE and MI
  o Does not exclude other genetic or nongenetic causes of thrombosis
• 4G/5G genotype: one copy of 4G allele detected
  o Associated with increased risk of VTE and MI
• 4G/4G genotype: two copies of 4G allele detected
  o Associated with increased risk of VTE and MI

Limitations

• Variants other than the 4G/5G polymorphism in the SERPINE1 gene are not evaluated
• Diagnostic errors can occur due to rare sequence variations