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)
  - 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

- Caucasians – 0.52
- Hispanics – 0.38
- African Americans – 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
  - 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
  - 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
  - Increased PAI-1 transcription activity
  - Higher PAI-1 plasma levels
  - Reduced fibrinolysis
  - Increased risk for VTE, especially in individuals with other thrombophilic risk factors
  - 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
  - Not at increased risk of VTE and MI
  - Does not exclude other genetic or nongenetic causes of thrombosis
- 4G/5G genotype – one copy of 4G allele detected
  - Associated with increased risk of VTE and MI
- 4G/4G genotype – two copies of 4G allele detected
  - 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