

Plasminogen Activator Inhibitor-1, PAI-1 (*SERPINE1*) Genotype

TO ASSESS GENETIC RISK FOR THROMBOSIS-ASSOCIATED PAI-1 ACTIVITY

Disease Overview

- Plasminogen activator inhibitor (PAI-1), or serpin peptidase inhibitor, is an inhibitor of fibrinolysis.
- PAI-1 inhibits tissue-type (t-PA) and urokinase (uPA) plasminogen activator. PAI-1 stimulates interstitial macrophage recruitment and increases transcription of profibrotic genes. PAI-1 is also important for signal transduction, cell adherence, and migration.
- PAI-1 acts as an acute-phase protein in acute inflammation and is important in the pathogenesis of sepsis. Increased levels of PAI-1 are correlated with increased severity of disease, increased levels of various cytokines, acute-phase proteins, and coagulation parameters.
- PAI-1 levels are regulated by metabolic factors, such as triglycerides, cholesterol, and insulin.
- The single guanosine nucleotide deletion/insertion polymorphism (4G/5G) at -675 bp of the *SERPINE1* gene is the major genetic determinant of PAI-1 expression. The PAI-1 promoter 4G allele, compared to 5G allele, is associated with increased PAI-1 transcription activity, higher PAI-1 plasma levels, and reduced fibrinolysis.

Epidemiology

Allele frequency for the 4G allele is 0.52 in Caucasians, 0.38 in Hispanics, and 0.13–0.28 in African-Americans.

Genetics

- Autosomal dominant inheritance.
- The 4G/5G insertion/deletion polymorphism is located in the promoter region of the *SERPINE1* gene, c.-148-672, on chromosome 7q21.3-q22.
- The molecular mechanism for the 4G allele-mediated higher PAI-1 expression is associated with greater binding of upstream stimulatory factor-1 to the E-box adjacent to the 4G site (E-4G) than to the E-5G.
- Individuals with 4G/5G and 4G/4G genotypes, especially those with other thrombophilic risk factors, are at increased risk for venous thromboembolism (VTE).
- Both the 4G/5G and 4G/4G genotypes are also associated with increased risk of myocardial infarction (MI).
- Some studies have associated the 5G/5G genotype with elevated risk of ischemic stroke (IS), along with decreased PAI-1 transcription in brain astrocytes and lower PAI-1 activity levels compared to the 4G/4G genotype.

Indications for Ordering

- To assess genetic susceptibility for VTE or MI in individuals with a personal or family history of thrombotic events.
- Risk-benefit assessment for preventive or therapeutic interventions for VTE or MI.

Contraindication

Fetal testing.

Interpretation

- 5G/5G genotype: Two copies of the *PAI-1* 5G allele were detected.
- 4G/5G genotype: One copy of the 4G allele was detected; this result is associated with an increased risk for VTE and MI.
- 4G/4G genotype: Two copies of the 4G allele were detected; this result is associated with an increased risk for VTE and MI.
- Results of 4G/5G *PAI-1* genotyping should be interpreted in the context of other laboratory tests and clinical information. Thrombotic risk may be altered by other genetic and non-genetic factors not assessed by this assay.

Methodology

- Polymerase chain reaction (PCR) and fluorescence monitoring to detect the *PAI-1* 4G/5G genotype, c.-148-672.
- Analytical sensitivity and specificity are 99 percent.

Limitations

- Variants in the *SERPINE1* gene, other than the 4G/5G, are not evaluated.
- Rare diagnostic errors may occur due to primer-site mutations.

Related Tests

- Thrombotic Risk, DNA Panel ([0056200](#))
- Thrombotic Risk, Inherited Etiologies (Most Common) with Reflex to Factor V Leiden ([0030133](#))
- Thrombotic Risk (Acquired) Reflexive Panel ([0030268](#))
- Prothrombin (F2) G20210A Mutation ([0056060](#))
- Factor V Leiden (F5) R506Q ([0097720](#))
- Plasminogen Activator Inhibitor1, Activity ([0098781](#))
- Methylenetetrahydrofolate Reductase (MTHFR) 2 Mutations ([0055655](#))

References

1. Bentley P, et al. Causal relationship of susceptibility genes to ischemic stroke: comparison to ischemic heart disease and biochemical determinants. *PLoS One* 2010;5:e9136.
2. Boekholdt SM, et al. Genetic variation in coagulation and fibrinolytic proteins and their relation with acute myocardial infarction: a systematic review. *Circulation* 2001;104:3063–8.
3. Gohil R, Peck G, Sharma P. The genetics of venous thromboembolism. A meta-analysis involving ~120,000 cases and 180,000 controls. *Thromb Haemost* 2009;102:360–70.
4. Hultman K, et al. Allele-specific transcription of the PAI-1 gene in human astrocytes. *Thromb Haemost* 2010;104:998–1008.
5. Tsantes AE, et al. Association between the plasminogen activator inhibitor-1 4G/5G polymorphism and venous thrombosis. A meta-analysis. *Thromb Haemost* 2007;97:907–13.
6. Tsantes AE, et al. The effect of the plasminogen activator inhibitor-1 4G/5G polymorphism on the thrombotic risk. *Thrombosis Research* 2008;122:736–42.

Test Information

2004980 Plasminogen Activator Inhibitor -1, PAI-1 (*SERPINE1*) Genotyping

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.