

Factor V Leiden Thrombophilia

Genotyped Variant: Factor V Leiden variant (p.R534Q) in the F5 gene

Clinical Features:

Factor V Leiden thrombophilia is characterized by resistance to activated protein C¹. Individuals who carry the factor V Leiden variant are at increased risk for venous thromboembolism (VTE), with the most common being deep vein thrombosis (DVT) in the lower limbs¹. Factor V Leiden is present in 15-20% of individuals with a first DVT and in up to 50% of individuals with recurrent VTE or estrogen-related thrombosis¹.

Factor V Leiden is the most common cause of inherited thrombophilia and is present among individuals of varying ethnic backgrounds. Approximately 3-7% of the US population is heterozygous for Factor V Leiden, with the highest prevalence occurring in European Americans (5.2%)¹. An estimated 1 in 5,000 persons is homozygous for the factor V Leiden¹ variant.

Individuals who are heterozygous for factor V Leiden have a 4-8 fold increased risk for VTE while the risk is higher (up to 80-fold) for homozygotes. The presence of other inherited or acquired thrombophilia disorders and circumstantial risk factors further increase the risk for thrombosis among individuals with factor V Leiden. Due to reduced penetrance associated with this variant, many individuals with factor V Leiden may never experience a thrombotic event¹.

Individuals with factor V Leiden are also at risk for pulmonary embolism and VTE in unusual sites. Some studies have reported that pregnant women who are heterozygous for the factor V Leiden variant are at slight increased risk for pregnancy loss, while women who are homozygous may be at even higher risk¹. Despite a possible modest increase in relative risk, the absolute risk for fetal loss is low.

Variant Spectrum:

Factor V Leiden accounts for 90-95% of APC-resistance. The p.R534Q variant accounts for all cases of factor V Leiden thrombophilia, and thus can be tested for by targeted DNA analysis^{3,4,5}. Other rare alleles in the factor V gene have been described, which are not detectable by this test. DNA analysis is particularly useful for differentiating factor V Leiden homozygotes from heterozygotes among individuals with a positive functional assay, confirming the diagnosis in individuals with a borderline functional assay, and for carrier testing.

Inheritance Pattern:

Autosomal Semi-Dominant

Test Methods:

Using genomic DNA from the submitted specimen, the relevant portion of the requested gene is PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19 and analyzed for only the requested variant(s). Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Test Sensitivity:

The clinical sensitivity is defined as the proportion of individuals with a venous thrombotic event in whom factor V Leiden is present. Overall, the clinical sensitivity for factor V Leiden ranges from 20-50% for isolated VTE. The analytical sensitivity is defined as the proportion of individuals with a known factor V Leiden variant with a positive test result. The analytical specificity is defined as the proportion of individuals without factor V Leiden with a negative test result. Based on a collection of data from a large number of laboratories, the analytical sensitivity and specificity for factor V Leiden are 99.1% and 99.7%, respectively⁹.

References:

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