Prothrombin (Factor II) Thrombophilia

Genotyped Variant: c.*97G>A variant (also known as 20210G>A and G20210A due to alternate nomenclature) in the F2 gene

Clinical Features:

The c.*97G>A variant in the F2 gene is associated with elevated plasma levels of prothrombin and an increased risk for prothrombin-related thrombophilia[1,2]. Prothrombin-related thrombophilia is the second most common inherited thrombophilia after factor V Leiden. Approximately 1-3% of individuals in the general US and European population are heterozygous for the c.*97 G>A variant, and it is found in approximately 6% of patients with a first venous thrombotic event[1,3].

Individuals heterozygous for the c.*97G>A variant have a 2-4 fold increased risk for venous thrombosis[2,4], and this risk is likely greater in individuals who are homozygous for c.*97G>A or carry another variant associated with increased risk for thrombosis, such as factor V Leiden[2,5]. Due to reduced penetrance associated with this variant, many individuals heterozygous or homozygous for the c.*97G>A variant may never experience a thrombotic event[2,6].

While the primary clinical manifestation is deep vein thrombosis and pulmonary embolism, individuals may also be at increased risk for cerebral vein thrombosis, hepatic thrombosis, and possibly pregnancy complications[5,7,8]. Despite a possible modest increase in relative risk for fetal loss, the absolute risk is low.

Variant Spectrum

The c.*97G>A variant (also known as 20210G>A and G20210A due to alternate nomenclature) in the F2 gene accounts for the majority of reported alleles in this gene in patients with venous thrombosis.

As plasma concentrations of prothrombin in heterozygotes overlap with the normal range, molecular analysis of F2 to identify the common c.*97G>A variant is required for a diagnosis of prothrombin-related thrombophilia[1,2].

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 II c.*97G>A is present. Overall, the clinical sensitivity for factor II c.*97G>A is approximately 6% for isolated VTE. The analytical sensitivity is defined as the proportion of individuals with factor II c.*97G>A and a positive test result. The analytical specificity is defined as the proportion of individuals without the variant with a negative test result. Based on a collection of data from a large number of laboratories, the analytical sensitivity and specificity for factor II c.*97G>A are 98.8% and 99.8%, respectively[6].

References:

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