

Factor V R2 A4070G Mutation

TO ASSESS ADDITIONAL GENETIC CONTRIBUTION TO VENOUS THROMBOSIS RISK IN FACTOR V LEIDEN (FVL) HETEROZYGOTES

Disease Overview

- During normal homeostasis of the clotting pathway, factor V acts as a pro-coagulant by aiding the conversion of prothrombin to thrombin, which leads to generation of fibrin.
- Activated protein C (APC) limits clot formation by proteolytic inactivation of the coagulation factors Va and VIIIa.
- FVL is a variant factor V protein with a missense mutation (R506Q) that resists cleavage by APC, leading to prolonged factor V activity.
- Resistance to APC activity increases the risk of deep-vein thrombosis (DVT) and recurrent second- or third-trimester pregnancy loss.
- R2 (A4070G) is a mild factor V mutation believed to confer additional APC resistance when it is present in individuals who are heterozygous for FVL (R506Q).
- By itself, the R2 mutation does not significantly contribute to venous thrombosis risk.
- Many patients with recurrent episodes of thrombosis have more than one genetic risk factor, such as the presence of FVL with R2, factor II (prothrombin) G20210A mutation, protein C deficiency, or hyperhomocysteinemia.
- Non-genetic risk factors for DVT include pregnancy, oral contraceptive use, major surgery, malignancy, immobilization, and other life-style factors.

Epidemiology

Approximately 12 percent of United States Caucasians, Asians, and Hispanics have one copy of the FV R2 mutation, while 6 percent of African-Americans have the same.

Genetics

- Although the factor V R2 mutation is inherited in autosomal dominant fashion, it is only penetrant when co-inherited with the FVL mutation on the opposite allele.
- Since the R2 mutation is not found on the same chromosomal background as R506Q (FVL), R2 testing is not helpful in individuals homozygous for FVL.
- FVL heterozygotes have a seven-fold increased risk for thrombosis compared to the general population. The average overall lifetime risk for venous thrombosis in individuals with factor V Leiden is 10 percent. This risk is increased when the individual also has factor V R2.FVL/ R2 compound heterozygotes. These individuals appear to have an approximately 10-fold increased risk for venous thrombosis compared to the general population. For FVL/R2 heterozygotes who experience venous thrombosis, the first event occurs, on average, six years earlier than for FVL heterozygotes.

Indications for Ordering

To further clarify thrombotic risk for individuals who are known FVL heterozygotes.

Contraindications for Ordering

- Testing of any individual not already known to be heterozygous for FVL.
- Testing of FVL homozygotes.

Interpretation

- Heterozygosity or homozygosity for the factor V R2 mutation, without the presence of FVL, does not appear to be associated with a significantly increased risk for venous thrombosis.
- Compound heterozygosity for R2/FVL is associated with APC resistance and an increased risk for venous thrombosis above that seen in FVL heterozygotes.
- Individuals heterozygous for FVL, who are not found to have the factor V R2 mutation, still have an increased risk for thrombosis based on their FVL status and other genetic or non-genetic risk factors.
- Results of R2 mutation testing can be accurately determined for patients on oral anti-coagulant and standard heparin therapy.

Limitations

FVL mutations other than R2 (A4070G) are not evaluated by this assay.

Methodology

- Polymerase chain reaction and restriction enzyme digestion followed by gel electrophoresis to detect the factor V R2 (A4070G) mutation.
- Analytical sensitivity and specificity are 99.9 percent.

Related Tests

- Factor V Leiden (F5) R506Q Mutation ([0097720](#))
- APC Resistance Profile ([0030127](#))
- APC Resistance Profile with Reflex to Factor V Leiden ([0030192](#))
- Thrombotic Risk, DNA Panel ([0056200](#))
- Thrombotic Risk, Inherited Etiologies (Most Common) with Reflex to Factor V Leiden ([0030133](#))

References

1. Faion EM, et al. Coinheritance of the HR2 haplotype in the factor V gene confers an increased risk of venous Thromboembolism to carriers of factor V R506Q (factor V Leiden). *Blood* 1999;94(9):3062–6.
2. Benson JM, et al. Factor V Leiden and factor V R2 allele: high-throughput analysis and association with venous thromboembolism. *Thromb Haemost* 2001;86(5):1188–92.
3. Nicolaes GA, Dahlback B. Activated protein C resistance (FV(Leiden)) and thrombosis: factor V mutations causing hypercoagulable states. *Hematol Oncol Clin North Am* 2003;17(1):37–61, vi.
4. Nicolaes GA, Dahlback B. Congenital and acquired activated protein C resistance. *Semin Vasc Med* 2003;3(1):33–46.

Test Information

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

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