

# Factor V Leiden (F5) R506Q Mutation

*TO DETERMINE THE GENETIC CONTRIBUTION TO VENOUS THROMBOSIS IN AFFECTED INDIVIDUALS OR THOSE WITH A SIGNIFICANT FAMILY HISTORY*

## Disease Overview

- During normal homeostasis, the factor V protein activates prothrombin to form thrombin, which is involved in the clotting pathway.
- Factor V Leiden (FVL) is a variant of the factor V protein having prolonged activity due to activated protein C (APC) resistance.
- APC limits clot formation by proteolytic inactivation of the coagulation factors factor Va and VIIIa. The genetic variation (R506Q) responsible for FVL prevents a peptide bond in the molecule from being cleaved.
- Resistance to APC activity increases the risk of deep-vein thrombosis (DVT) and recurrent second- or third-trimester pregnancy loss.
- The FVL mutation is the most common genetic risk factor for thrombosis and accounts for >90 percent of APC resistance.
- The expression of FVL thrombophilia is impacted by:
  - Coexisting genetic thrombophilic disorders (e.g., factor II G20210A mutation, protein C deficiency, or homocystinemia).
  - Acquired thrombophilic disorders (e.g., malignancy, hyperhomocysteinemia, high factor VIII levels).
  - Non-genetic risk factors (e.g., pregnancy, oral contraceptive use, hormone-replacement therapy, selective estrogen-receptor modulators, travel, immobilization, central venous catheters, surgery, transplantation and advanced age).

## Epidemiology

- Approximately 5 percent of Caucasians, 2 percent of Hispanics, 1 percent of African-Americans and Native Americans, and 0.5 percent of Asians are heterozygous.
- Homozygous FVL occurs in about one in 5,000 individuals.

## Genetics

- FVL results from a G>A substitution at nucleotide position 1,691 in the F5 gene.
- FVL is inherited in an autosomal dominant manner, and de novo mutations are rare.
- FVL heterozygotes have a five- to 10-fold increased risk for thrombosis.
- FVL homozygotes have a 50- to 100-fold increased risk for thrombosis.
- The lifetime risk for DVT is 80 percent for FVL homozygotes and 12–20 percent for heterozygotes.

## Indications for Ordering

- Diagnostic testing for individuals with a personal history of thrombosis.
- To determine a genetic cause for recurrent second- or third-trimester pregnancy loss.
- Presymptomatic evaluation of individuals with a family history of thrombosis or a family member identified to have FVL.

## Contraindications for Ordering

- Population screening and testing of asymptomatic minors for FVL.
- Routine testing for patients with a personal or family history of arterial thrombotic disorders (e.g., acute coronary syndromes or stroke). Exceptions may include young female smokers who have experienced myocardial infarction or patients <50 years of age with acute arterial thrombosis in the absence of other risk factors for atherosclerotic arterial occlusive disease.

## Interpretation

- Homozygosity for the F5 R506Q mutation is associated with APC resistance and an increased risk for venous thrombosis.
- Heterozygosity for the F5 R506Q mutation is associated with APC resistance and an increased risk for venous thrombosis.
- Results of F5 genotyping can be accurately determined for patients on oral anti-coagulant and standard heparin therapy.

## Limitations

- F5 gene mutations, other than R506Q, are not evaluated by this assay.
- Rare diagnostic errors may occur due to primer-site mutations.

## Methodology

- Polymerase chain reaction and fluorescent monitoring to detect the F5 R506Q (1691G>A) mutation. Note: Standardized nomenclature for the FVL mutation is c.1601G>A (p.Arg534Gln).
- Analytical sensitivity and specificity are 99.9 percent.

### Related Tests

- 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](#))
- Factor V, R2 Mutation ([2001549](#))

### References

1. Brenner BR, et al. Diagnostic studies for thrombophilia in women on hormonal therapy and during pregnancy, and in children. *Arch Pathol Lab Med* 2002;126(11):1296–1303.
2. 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.
3. Nicolaes GA, Dahlback B. Congenital and acquired activated protein C resistance. *Semin Vasc Med* 2003;3(1):33–46.
4. Tripodi A. A review of the clinical and diagnostic utility of laboratory tests for the detection of congenital thrombophilia. *Semin Thromb Hemost* 2005;31(1):25–32.

### Test Information

**0097720**

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For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).