Factor V, R2 Variant

Indications for Ordering

• To further clarify thrombotic risk for individuals who are known factor V Leiden (FVL) heterozygotes
• Individual may be taking anticoagulants (no interference with test results)

Test Description

Polymerase chain reaction (PCR)

Tests to Consider

Primary test

**Factor V, R2 Mutation Detection by PCR 2014248**

• Determine thrombotic risk in individuals known to be FVL heterozygotes
• Testing performed by Esoterix Coagulation

Related tests

**APC Resistance Profile 0030127**

• Acceptable initial test to detect activated protein C resistance (APC-R) due to an FVL variant
  o In the following conditions, Factor V Leiden (F5) R506Q Mutation (0097720) is the preferred initial test
    ▪ Supratherapeutic concentrations of heparin
    ▪ Direct thrombin inhibitors
    ▪ Extreme factor V deficiency
    ▪ Lupus anticoagulants with markedly prolonged baseline clotting times
  o Test is not affected by therapeutic concentrations of warfarin or heparin

**APC Resistance Profile with Reflex to Factor V Leiden 0030192**

• Recommended test to detect APC-R and confirm presence of an FVL variant

**Factor V Leiden (F5) R506Q Mutation 0097720**

• Order to detect FVL variant
• Genetic test for the most common genetic cause of thrombophilia

**Thrombotic Risk, DNA Panel 0056200**

• Acceptable panel to detect the two most common inherited thrombophilies (prothrombin related and FVL related)

**Thrombotic Risk, Inherited Etiologies (Most Common) with Reflex to Factor V Leiden 0030133**

• Acceptable screening panel for common inherited thrombophilies

Disease Overview

Prevalence

U.S. prevalence for the factor V R2 variant (one copy)

• Caucasians, Asian, Hispanics – 12%
• African Americans – 6%

Risk estimates for venous thrombosis

• FVL heterozygotes
  o Sevenfold increased risk
  o Average overall lifetime risk – 10%
• FVL/R2 compound heterozygotes
  o ~10-fold increased risk
  o First thrombotic event occurs, on average, six years earlier than for FVL heterozygotes
• In absence of the FVL variant, factor V R2 heterozygosity or homozygosity is not associated with increased risk
• Individuals with recurrent episodes of thrombosis may have >1 genetic risk factor (eg, FVL with R2, factor II [prothrombin] G20210A variant, protein C deficiency, or hyperhomocysteinemia)
• Thrombotic risk also impacted by nongenetic factors (eg, pregnancy, oral contraceptive use, major surgery, malignancy, immobilization, and other lifestyle factors)

Genetics

**Gene** – factor V (F5) R2 (A4070G)

**Inheritance** – autosomal dominant

**Penetration** – only when coinherited with the FVL variant on the opposite chromosome
Structure/function

- The FVL variant and factor V R2 variant are never located on the same chromosome
- During normal homeostasis, the factor V protein activates prothrombin to form thrombin which generates fibrin
- APC limits clot formation by proteolytic inactivation of the coagulation factors Va and VIIIa
- FVL, a variant factor V protein with a missense variant (R506Q), resists cleavage by APC, leading to prolonged factor V activity
- Resistance to APC activity increases risk for
  o Deep vein thrombosis (DVT)
  o Recurrent second- or third-trimester pregnancy loss
- R2 (A4070G) is a mild factor V variant
  o Confers additional APC resistance in individuals who are heterozygous for FVL (R506Q)
  o Histidine to arginine substitution at amino acid residue 1299 in factor V protein

Test Interpretation

Sensitivity/specificity

- Analytical sensitivity/specificity – 99.9%

Results

- Positive
  o Homozygosity for factor V R2 variant (implies FVL variant is not present) confers no increased risk of thrombosis
  o Compound heterozygosity for FVL/R2
    ▪ Associated with APC resistance and an increased risk for venous thrombosis above that seen in FVL heterozygotes
  o Negative – absence of the factor V R2 polymorphism

Limitations

- F5 variants other than R2 (A4070G) are not evaluated
- Test is not for individuals who are known to be negative or homozygous for FVL