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
  - 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
  - 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 thrombophilias (prothrombin related and FVL related)

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

- Acceptable screening panel for common inherited thrombophilias

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
  - Sevenfold increased risk
  - Average overall lifetime risk – 10%
- FVL/R2 compound heterozygotes
  - ~10-fold increased risk
  - 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

Penetrance – 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
  - Deep vein thrombosis (DVT)
  - Recurrent second- or third-trimester pregnancy loss
- R2 (A4070G) is a mild factor V variant
  - Confers additional APC resistance in individuals who are heterozygous for FVL (R506Q)
  - Histidine to arginine substitution at amino acid residue 1299 in factor V protein

Test Interpretation

Sensitivity/specificity

- Analytical sensitivity/specificity – 99.9%

Results

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