Factor V Leiden (*F5*) R506Q Variant

Indications for Ordering

- Individuals with venous thromboembolism (VTE), especially before age 50
- Individuals with unprovoked VTE at any age
- Women with VTE associated with pregnancy, use of oral contraceptives, or hormone replacement therapy (HRT)
- Women with unexplained recurrent pregnancy loss
- Individuals with activated protein C resistance (APC-R)
  - Usually APC testing is ordered prior to factor V genetic testing
- First-line test when APC-R functional test may be unreliable
- Presymptomatic evaluation of individual with a family history of thrombosis or a family member identified to have Factor V Leiden (FVL)

Test Description

PCR and fluorescent monitoring for *F5* R506Q (c.1691G>A) variant (also known as c.1601G>A or p.Arg534Gln)

Tests to Consider

Typical testing strategy

- Testing should be performed in cases where the results will impact management of the individual or family members
- Testing is based on family and patient history and may include
  - APC-R (with or without reflex to FVL variant; factor V R2 A4070G variant)
- Factor II activity (prothrombin [*F2*] variant G20210A)
- Antithrombin activity (ATIII)
- Protein C activity
- Free protein S antigen
- Antiphospholipid syndrome (beta-2 glycoprotein 1 antibodies, IgG and IgM; anticardiolipin antibodies, IgG and IgM; lupus anticoagulant)

Primary test

Factor V Leiden (*F5*) R506Q Mutation 0097720

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

Related tests

APC Resistance Profile 0030127

- Acceptable initial test to detect activated APC-R due to a 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

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

Factor V, R2 Mutation Detection by PCR 2014248

- Determine thrombotic risk in individuals known to be FVL heterozygotes

Disease Overview

Prevalence

Most common genetic risk factor for thrombosis

- Heterozygosity for R506Q
  - Caucasians – 5%
  - Hispanics – 2%
  - African-Americans and Native Americans – 1%
  - Asians – 0.5%
- Homozygosity for R506Q – 1/5,000

Risk estimates

- Risk of VTE
  - Heterozygotes
    - Nonpregnant adults – 3- to 8-fold lifetime increase
    - Pregnant women – 5- to 52-fold increase
  - Homozygotes – 9- to 80-fold lifetime increase
  - FVL increases risk of deep vein thrombosis (DVT) and recurrent pregnancy loss; may also increase risk for recurrent thrombosis

- Risk of thrombosis among individuals with FVL also impacted by
  - Coexisting genetic thrombophilic disorders (eg, factor II G20210A variant, protein C deficiency, homocystinemia)
  - Acquired thrombophilic disorders (eg, malignancy, hyperhomocysteinemia, high factor VIII levels)
  - Nongenetic risk factors (eg, pregnancy, oral contraceptive use, HRT, selective estrogen-receptor modulators, travel, immobilization, central venous catheters, surgery, transplantation, advanced age)

Genetics

Gene – Factor V (*F5)* R506Q

Inheritance – incomplete autosomal dominant

Penetrance – variable, depends upon genotype

Structure/function

- During normal homeostasis, the factor V protein activates prothrombin to form thrombin
- FVL, a variant of the factor V protein, has prolonged activity due to APC-R
  - Variant accounts for >90% of APC-R
- APC limits clot formation by proteolytic inactivation of the coagulation factors (factors Va and VIIIa)
- The genetic variation (R506Q) responsible for FVL prevents a peptide bond in the molecule from being cleaved

De novo variants – rare

Variant – G>A substitution at nucleotide position 1691

Test Interpretation

Sensitivity/specificity

- Analytical sensitivity/specificity – 99.9%

Limitations

- *F5* gene variants, other than R506Q, are not evaluated by this assay
- Results of *F5* genotyping can be accurately determined for individuals on oral anticoagulant and standard heparin therapy
- Rare diagnostic errors may occur due to primer-site variants
- Not recommended for
  - Population screening and testing of asymptomatic minors for FVL
  - Routine testing for individuals with a personal or family history of arterial thrombotic disorders
  - Exceptions may include young female smokers who have experienced myocardial infarction or individuals <50 years with acute arterial thrombosis in the absence of other risk factors