Factor II (F2) c.*97G>A (G20210A) Pathogenic 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 second- or third-trimester pregnancy loss

Test Description
Polymerase chain reaction and fluorescence monitoring for F2 c.*97G>A (G20210A) variant

Tests to Consider
Typical testing strategy
• Testing should be performed in situations when results will affect management of the individual or family members
• Testing is based on family and patient history and may include the following
  o Activated protein C resistance (with or without reflex to factor V Leiden (FVL) variant; factor V R2 A4070G variant)
  o Factor II activity (prothrombin)
  o Antithrombin activity (ATIII)
  o Protein C activity
  o Free protein S antigen
  o Antiphospholipid syndrome (beta-2 glycoprotein 1 antibodies, IgG and IgM; antcardiolipin antibodies, IgG and IgM; lupus anticoagulant)

Primary test
Prothrombin (F2) c.*97G>A (G20210A) Pathogenic Variant 0056060
• Order to detect prothrombin c.*97G>A (G20210A) pathogenic variant
• Evaluate for increased genetic risk of VTE in a variety of populations

Risk estimates for thrombophilic events if variant present
• F2 c.*97G>A (G20210A)
  o Second most common genetic defect influencing risk for VTE
  o Most common – FVL
• VTE
  o Adults with first VTE – 6-14% carry the c.*97G>A (G20210A) variant
  o Unclear whether heterozygosity increases the risk of recurrent VTE after a first episode
• Arterial thromboembolism
  o Not a major risk factor
• Myocardial infarction and stroke
  o No convincing association has been demonstrated for heterozygosity or homozygosity

Disease Overview
Prevalence and/or incidence
• Heterozygosity
  o Caucasians – ~2%
  o African Americans – 0.3%
  o Asians and Native Americans – rare
• Homozygosity for G20210A – ~1/10,000

Related tests
Factor II, Activity (Prothrombin) 0030007
• Evaluate for possible factor II deficiency
Factor V Leiden (F5) R506Q Mutation 0097720
• Order to detect FVL variant
• Genetic test for the most common genetic cause of thrombophilia
Risk for prothrombin thrombophilia affected by
- Coexisting genetic thrombophilic disorders (eg, FVL)
  - Coinheritance of F2 c.97G>A (G20210A) and FVL c.1601G>A (R506Q)
  - ~1 in 1,000 individuals
  - 1-5% in individuals with VTE
  - Earlier age of VTE incidence and higher risk of recurrent thrombosis than heterozygotes for either single gene variant
- Acquired thrombotic risk factors (eg, malignancy, hyperhomocysteinemia)
- Nongenetic risk factors (eg, pregnancy, oral contraceptive use, HRT, selective estrogen-receptor modulators, travel, central venous catheters, surgery, and transplantation)
- Prothrombin thrombophilia – mild risk increase for pregnancy loss and preeclampsia

Genetics

Gene – factor II (F2)
Variant – c.97G>A (G20210A)
Inheritance – incomplete autosomal dominant
Penetrance – variable; many adults who are heterozygous or homozygous for c.97G>A (G20210A) do not experience VTE
Structure/function
- The F2 c.97G>A (G20210A) variant is associated with increased prothrombin levels
- Higher levels of prothrombin increase the rate of thrombin generation, resulting in excessive growth of fibrin clots

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity – ~10%
- Analytical sensitivity/specificity – 99%

Results
- Heterozygous – one copy of variant detected
  - Genotype associated with elevated prothrombin levels and an increased risk for VTE
  - Adults have a twofold to fourfold increase in thrombotic risk
- Homozygous – two copies of variant detected
  - Associated with elevated prothrombin levels and an increased risk for VTE
- Rare genotype
  - Greater risk for thrombosis than heterozygous
- Negative – no copies of the variant detected
  - Does not exclude elevated prothrombin levels and hereditary forms of VTE due to other causes

Limitations
- Diagnostic errors can occur due to rare sequence variations
- F2 gene variants, other than c.97G>A (G20210A), will not be detected