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
  - Activated protein C resistance (with or without reflex to factor V Leiden (FVL) variant; factor V R2 A4070G variant)
  - Factor II activity (prothrombin)
  - 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

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

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

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 and/or incidence

- Heterozygosity
  - Caucasians – ~2%
  - African Americans – 0.3%
  - Asians and Native Americans – rare
- Homozygosity for G20210A – ~1/10,000

Risk estimates for thrombophilic events if variant present

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

- 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