GENE MESSENGER

☆ Topic: Factor V Leiden

☆ **Summary:** Factor V Leiden is the most common inherited risk factor associated with thrombophilia. Risk of venous thromboembolism (VTE) is moderated by complex gene-gene and gene-environment interactions.

☆ **Bottom line:** Genetic testing for factor V Leiden can identify those at an increased risk for VTE and allow for individualized risk assessment and risk avoidance. Testing is recommended for those with VTE before age 50, recurrent VTE, venous thrombosis at an unusual site, VTE in a pregnant woman or woman taking oral contraceptives, first VTE with strong family history of VTE, asymptomatic relatives of individuals with a factor V Leiden mutation considering oral contraceptive use or pregnancy, among others. General population screening is not recommended given the low absolute thrombotic risk in heterozygotes.

✓ The Disease

- Factor V Leiden thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk of venous thromboembolism (VTE).
- VTE includes deep vein thrombosis (most commonly in the leg) and pulmonary embolism; more rarely, VTE can be superficial or occur in the central retinal vein, hepatic vein or cerebral sinus.
- Factor V Leiden refers to a specific mutation (R506Q) that causes the factor V coagulation factor to persist longer in the circulation. The abnormal protein is inactivated at a rate approximately ten times slower than normal factor V, resulting in increased thrombin generation and a mild hypercoagulable state.
- Individuals with one copy of factor V Leiden (heterozygotes) have a slightly increased risk for venous thrombosis; individuals with two copies of the factor V Leiden mutation (homozygotes) have a much greater thrombotic risk.
- Prevalence of factor V Leiden mutation
  - 3-8% of the US and European populations are heterozygous (www.genetests.org).[1]
  - Rare in Asian and African populations.
  - Present in ~ 20% of individuals with idiopathic venous thrombosis.[2]

✓ The Gene

- FV gene on chromosome 1 makes the "coagulation factor V" protein.
- Normal FV gene stimulates clot formation in response to injury.
- Abnormal FV gene slows APC ability to inactivate coagulation factor V which results in abnormal clotting due to excess conversion of prothrombin to thrombin.

✓ Consequences of having a faulty gene

- Relative risk of VTE:
  - Heterozygotes= 5-fold[3]
    - ► Lijfering et al. looked at relatives of individuals with thrombosis and FV Leiden and reported a 0.49% annual incidence of VTE among relatives who carried FVL compared to 0.05% in relatives who did not.[4]
    - ► Not associated with an increase in mortality or reduction in normal life expectancy.
  - Homozygotes= 10-fold[3]

- Clinical expression is extremely variable – many individuals with the factor V Leiden allele never develop thrombosis: of those who do, some will not experience their first thrombotic event until adulthood, while others have recurrent thromboembolism before age 30 years.
- Women with factor V Leiden have a small (1%) increased risk for pregnancy loss but do not appear to have an increased risk for placenta-mediated pregnancy complications.[5]
- Other risk factors for VTE:
  - Genetic risk factors: number of factor V alleles, other coexisting genetic abnormalities (protein C or S deficiency, antithrombin III deficiency, prothrombin mutation, hyperhomocystinemia).
  - Circumstantial risk factors: age, surgery, pregnancy, post-partum period, oral contraceptive (OC) use, hormone replacement therapy use, dehydration, prolonged immobilization (e.g. lengthy travel, cancer, inflammation).
- Moderating risk factors can have multiplicative effect on thrombotic risk.
  - e.g. The combination of oral contraceptive use and factor V Leiden produces an increase in relative risk for thrombosis that is greater than that conferred by either factor alone.[6]

✓ Who should be considered for testing?

- Based on 2001 American College of Medical Genetics Consensus Statement (reaffirmed in 2006)[7], testing should be offered for:
  - First VTE before age 50
  - Recurrent VTE
  - Venous thrombosis at unusual sites (cerebral, mesenteric, portal, and hepatic veins)
  - VTE in pregnant women or in women taking oral contraceptives or hormone replacement therapy
  - A first VTE and a strong family history of VTE
  - Relatives of individuals with VTE under age 50
  - Myocardial infarction in female smokers under age 50
- Testing may also be considered in individuals with a first unprovoked VTE at any age, asymptomatic members of a family with a known factor V Leiden mutation, especially for women considering pregnancy or oral contraceptive use, for women with recurrent unexplained pregnancy losses.
- Note that routine heterozygote testing of relatives of a person with factor V Leiden is controversial given the low absolute thrombotic risk.[8]
- Testing is NOT recommended as a general population screen, or as a routine initial test during pregnancy or prior to the use of hormone medications. Testing is not generally recommended in children.

✓ Testing

- The diagnosis of factor V Leiden thrombophilia is made either using DNA analysis of the FV gene or by coagulation screening test.
- If the coagulation screening test is abnormal, DNA testing is needed for confirmation and to distinguish heterozygotes from homozygotes.
- "DNA testing for factor V Leiden" can be ordered using a regular blood test requisition.
- Some labs may have a "thrombophilia panel" (factor V Leiden plus others such as Prothrombin 20210A mutation).

✓ Benefits of genetic testing

- Testing in affected families can identify individuals who might benefit from thromboprophylaxis during risk periods such as surgery, pregnancy, or prolonged immobilization.
- Decisions regarding prophylactic anticoagulation should be based on the personal and family history and a risk/benefit assessment in each individual case.
- Advice can be given on ways to modify environmental risks (e.g., immobility on long flights, oral contraceptives, dehydration) and the signs or symptoms of thrombosis.

✓ Harms/limitations of testing

- Other inherited or acquired coagulation risk factors (e.g., deficiency of protein C, protein S, antithrombin III) will not be detected by the factor V Leiden test.
- Although the presence of the factor V Leiden allele is an established risk factor, it does not predict thrombosis with certainty, penetrance is variable even within the same family.

Web Resources: www.genetests.org

References:

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