

Factor V Leiden (APC Resistance)

Why is Factor V Leiden an emerging public health issue?

Factor V Leiden (FV) is the most common risk factor identified for thrombosis in the United States. Thrombosis is the formation of blood clots within a blood vessel. Blood clots cut off or limit the supply of blood to tissues. In the United States, half a million people are hospitalized each year and 50-100 thousand deaths occur due to [venous](#) thrombosis. Therefore, the efforts to improve the prevention, diagnosis, and treatment of thrombotic events are well justified.

FV is an important women's health issue as pregnancy, oral contraceptive use and estrogen replacement therapy are all risk factors for thrombosis. Thrombosis is also a leading cause of maternal death. Sixty percent of women who develop thrombosis during pregnancy or the postpartum period have the FV gene change.

The FV [gene](#) change is present in approximately 2-7% of the Caucasian population. FV accounts for 20-40% of cases of deep vein thrombosis (DVT) and up to 75% of cases of recurrent thrombosis.

Testing for FV is of significant benefit for individuals without symptoms who are at-risk and for individuals with a history of thrombosis. This is because anticoagulant therapy can be initiated to reduce the risk of a future thrombosis.

The current debate regarding screening for FV focuses upon the questions: Has the time come for routine testing for FV prior to the prescription of oral contraceptives and should all individuals who have a history of a thrombotic event be tested for FV?

Suggested Reading: Creinin MD, Lisman R, Strickler RC (1999) Screening for factor V Leiden mutation before prescribing combination oral contraceptives. *Fertil Steril* 72:646-51 [[Medline](#)]

What is Factor V Leiden?

The factor V [protein](#) is an important component of blood clotting. When there is a gene change in this protein, a resistance to Protein C (also referred to as APC or activated Protein C) occurs. This change effects the body's natural [anticoagulation](#) system. Presence of the FV gene change increases the risk for thrombosis 3-8 fold in individuals with only one copy of the gene change and 30-140 fold in individuals with two copies.

Most thrombotic events usually do not occur until adulthood. A combination of risk factors appears to be required to provoke thrombosis in children.

What are the symptoms of Factor V Leiden?

Although there are no clinical features specific for FV, diagnosis is suspected in individuals with a history of venous thrombosis. DVT is the most significant symptom of FV. DVT often presents as a painful, swollen area, especially in the leg. Symptoms also include unexplained miscarriage, blood clotting in the lungs, gall bladder dysfunction, stroke or heart attack, preeclampsia, and eclampsia. Individuals who are heterozygous for FV are at an increased risk for pregnancy loss, especially after the first trimester.

What causes Factor V Leiden?

FV gene is [inherited](#) in an [autosomal dominant](#) fashion with incomplete penetrance. Incomplete penetrance means that not all people with the gene for FV will develop the condition. People may have one or two copies of the FV gene. Having one copy of the FV gene in combination (being [heterozygous](#) for FV) with other inherited or acquired clotting disorders, including Protein C, Protein S or antithrombin III, increases the risk for thrombosis dramatically. Having two copies of the FV gene is referred to as being [homozygous](#). Individuals who are homozygous for the FV gene are at a much greater risk for venous thrombosis. Homozygotes have close to a 100% lifetime risk of a thrombotic event.

A small proportion of patients with resistance to activated protein C do not carry the factor V Leiden gene change ([mutation](#)) and are presumably carriers of a change that has yet to be discovered.

How is Factor V Leiden detected?

The diagnosis of FV is made using either a coagulation screening test, such as the APC Resistance assay, or by genetic (DNA) analysis of the FV gene.

Testing should be initiated in individuals with the following indications:

- Venous thrombosis or pulmonary embolism
- Premature stroke
- Peripheral vascular disease, particularly lower extremity [occlusive](#) disease
- Family history of thrombosis or known FV mutation in a relative
- Prior to major surgery, pregnancy, postpartum, oral contraceptive use or estrogen therapy if there is a personal or family history of thrombosis
- Previous finding of activated protein C resistance by laboratory analysis.

APC resistance

The APC Resistance assay measures the anticoagulant response to APC. There are two forms of the APC resistance assay. The modified or second generation assay has a sensitivity and specificity for FV approaching 100% and may be used for patients during pregnancy and those on anticoagulation therapy unlike the original or first generation APC assay. Laboratory testing should be considered even after the identification of FV, since the FV gene often coexists with other disorders associated with thrombosis, such as deficiencies in Protein C, Protein S or antithrombin III.

Although 95% of cases of APC resistance reflect factor V Leiden, 5% of patients have repeatedly abnormal APC resistance tests in the absence of the factor V Leiden allele.

DNA testing

The FV gene is found on [chromosome](#) 1. DNA testing is often used in individuals with the above mentioned indications and very low or borderline second generation APC resistance assay values. Diagnosis of an inherited thrombotic disorder can be made in approximately 50% of all venous thrombosis cases. The FV mutation test is accurate regardless of the clinical condition or medication taken by the individual.

How is Factor V Leiden treated?

It is recommended that homozygotes for FV, with or without a history of thrombosis, receive preventive therapy during at-risk situations such as, surgery, pregnancy, or prolonged immobilization and extended anticoagulant therapy after a thrombotic event. The first thrombotic event is managed routinely with a course heparin, followed by warfarin taken orally for three to six months. Individuals with either persistent risk factors or spontaneous thrombosis with no identifiable provoking factors require longer anticoagulation therapy usually six months or longer.

The optimal duration of anticoagulation for heterozygotes for FV is debated. Heterozygotes who do not have a history of thrombosis and do not have any symptoms should not receive long-term anticoagulation therapy.

There is currently no consensus on the optimal management of women with FV during pregnancy. Until more specific guidelines are defined, the risks and benefits of anticoagulation therapy during pregnancy should be discussed with each patient. Heparin may be considered for women with FV that are pregnant as a possible guard against complications. Preventative anticoagulation is not routinely recommended for women who are not pregnant. Other factors that may influence decisions about indications for or duration of anticoagulation therapy include age, family history, and the severity of the thrombotic episode. Until more specific guidelines are established, decisions regarding long-term anticoagulation therapy as prevention for a possible thrombotic event should be based on a risk/benefit assessment in each case.

Information and Support Resources

- [GeneClinics](#)
- [Genetic Drift](#)
- [NIH: National Center for Biotechnology Information](#)
- [CDC: The Role of Activated Protein C Resistance in the Pathogenesis of Venous Thrombosis](#)