INHERITED THROMBOPHILIA: FACTOR V LEIDEN

Factor V Leiden (FVL) is the most common genetic risk factor for venous thromboembolism (VTE) and occurs in about 5% of the Caucasian population. It is considered to be a moderate risk factor for VTE, and its clinical expression is influenced by co-existing genetic factors, in addition to acquired and circumstantial risk factors. FVL status seems to have little or no effect on recurrence risk of VTE, does not influence treatment following a VTE event, and is not an indication for primary prophylactic treatment in asymptomatic carriers. There is consensus that in some circumstances genetic testing for FVL has utility, as carriers should be educated about circumstances that might increase the likelihood of VTE, signs and symptoms of VTE, and the potential need for prophylactic anticoagulation in high-risk circumstances.

WHAT IS FACTOR V LEIDEN?

Factor V is a clotting factor with activity regulated by the anti-coagulant activated protein C (APC). A single base substitution in the factor V gene (G>A at position 1691) results in the elimination of one of APC's three cleavage sites. This mutation causes factor V to be inactivated more slowly by APC, generating more thrombin and consequently increasing the potential for clot formation. This specific mutation in the factor V gene is called factor V Leiden (FVL).

FVL is the most common genetic risk factor for VTE. Other co-existing inherited and acquired disorders and circumstantial risk factors affect clinical expression of FVL, for example, also carrying the prothrombin variant 20210G>A, obesity, age, immobility due to injury, surgery or air travel, oral contraceptives, hormone replacement therapy (HRT), selective estrogen receptor modulator (SERMs) or pregnancy. Heart attack, arterial thrombosis and ischemic stroke are not associated with FVL.

This GEC-KO *on the run* will focus exclusively on FVL. FVL is inherited in an autosomal dominant manner. About 5% of the Caucasian population carries the FVL mutation with the prevalence being lower in other ethnicities (about 2% in Hispanic Americans and about 1% in African Americans). Homozygosity for FVL (both copies of the FV gene having the mutation) occurs much less often, in about 1 per 5000 Caucasian individuals. About 20-25% of individuals with VTE, 40-50% of individuals with recurrent VTE or estrogen related thrombosis, and about 50% of individuals with familial thrombophilia are found to have FVL.

RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

Genetic testing for FVL may have clinical utility in certain circumstances (box 1 and 2), however there is no evidence that knowledge of FVL carrier status influences treatment following a VTE event to avoid recurrence. Similarly, there is no evidence that primary prophylactic treatment in asymptomatic carriers improves clinical outcome.

Box 1. When to offer genetic testing for factor V Leiden (FVL).

- A first unprovoked VTE at any age (especially age <50 years)
- A history of recurrent VTE
- Venous thrombosis at unusual sites (e.g., cerebral, mesenteric, hepatic, or portal veins)
- VTE and a strong family history of thrombotic disease
- VTE during pregnancy or the puerperium
- VTE associated with the use of estrogen contraception or hormone replacement therapy (HRT)
- A first VTE and a first-degree family member with VTE < 50 years

Box 2. Other clinical circumstances in which testing **may be appropriate** include the following.

- Female smokers < 50 years with a myocardial infarction or stroke
- Women with recurrent unexplained first-trimester pregnancy losses, or an unexplained fetal loss after 10 weeks gestation, or stillbirth
- Selected women with unexplained severe preeclampsia, placental abruption, or a fetus with severe intrauterine growth restriction
- A first VTE related to the use of tamoxifen or other selective estrogen receptor modulators (SERMs)
- Neonate or child with non-catheter-related idiopathic VTE or stroke
- Asymptomatic adult family members of individuals with a known FVL mutation, especially those with a with a strong family history of VTE at a young age (<50y), when that knowledge may influence pregnancy management, consideration of estrogen contraception use or pregnancy *

*Because thrombosis rarely occurs before young adulthood, asymptomatic relatives younger than 18 years are not usually tested, even relatives of homozygotes.

FVL testing is **not** routinely recommended:

- For the general population
- During routine pregnancy screening
- Before prescribing estrogen contraception, HRT or SERMs
- For prenatal testing or screening of asymptomatic newborns, neonates, and children
- For patients with a personal or family history of arterial thrombosis (acute coronary syndrome or stroke), unless unexplained in an individual under age 50

WHAT DOES THE GENETIC TEST RESULT MEAN?

Population studies suggest that about 10% of FVL carriers develop VTE over their lifetime; the risk is higher for those with a family history of thrombophilia (~25-40%). Carriers of FVL and individuals who are homozygous have an increased risk for VTE, but that absolute risk is very small. FVL carriers do not have an increased risk for mortality.

SURVEILLANCE AND MANAGEMENT

Table 1. Management recommendations for asymptomatic FVL carriers.

Education	Additional testing	During high risk situations
Carriers should be educated about: ✓ Circumstances that might increase the likelihood of VTE (obesity, age, surgery, reduced mobility due to injury or travel, use of oral contraceptives, HRT, or SERMs, and pregnancy) ✓ The signs and symptoms of VTE that require immediate medical attention ✓ The potential need for prophylactic anticoagulation in high-risk circumstances (e.g. postpartum)	FVL is often seen with other inherited and/or acquired disorders. An individual with FVL should be tested for other thrombophilia disorders to better assess the absolute risk of thrombosis. Consider:[1] ✓ Genetic testing for prothrombin 20210G>A variant ✓ Serologic assays for anticardiolipin antibodies and antibeta2glycoprotein 1 antibodies ✓ Multiple phospholipid-dependent coagulation assays for a lupus inhibitor	During high-risk clinical situations (e.g. surgery, pregnancy) prophylactic anticoagulation may prevent some VTE episodes. However, there is no evidence confirming the benefit of primary prophylaxis for asymptomatic FVL heterozygotes. Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment in each individual case. Consultation with a specialist may be considered.

See www.geneticseducation.ca for the full-length GEC-KO Messenger on FVL with additional management recommendations, a point of care tool and how to connect to your local genetics centre.

For a recent review article on FVL see Kujovich JL. Factor V Leiden thrombophilia. *Genet Med* 2011;13(1): 1-13.

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