Factor V Leiden

Bottomline: Factor V Leiden (FVL) is a very common inherited thrombophilia associated with a moderate (3 to 5-fold) increased lifetime risk for venous thromboembolism (VTE), deep vein thrombosis being the most common. Treatment of VTE is not generally affected by FVL status and should follow standard guidelines. Genetic testing is not routinely recommended for the general population, those with unprovoked VTE (as it is unlikely to change management), VTE provoked by a surgical procedure, or for those with a family history of FVL. FVL carrier testing may be considered when the results of testing could affect clinical management:

- An unprovoked VTE involving unusual sites e.g. cerebral
- A VTE provoked by a nonsurgical major transient risk factor e.g. confinement to bed in hospital for at least three days
- A VTE provoked by pregnancy or occurring post-partum
- A VTE associated with the use of combined oral contraceptives
- A VTE at or under age 40 years, either spontaneous or associated with weak environmental risk factors, and at least one first-degree relative with VTE

FVL carrier testing is indicated for those assigned female at birth (AFAB), who are planning a pregnancy, have a family history of VTE and the potential to be homozygous FVL (each parent of the individual is a carrier of FVL). Anticoagulation prophylaxis would be indicated for those with homozygous FVL. FVL carrier testing may also be considered for those AFAB with a family history of VTE or multiple VTE risk factors e.g. obesity, older age, or comorbid medical conditions, as postpartum prophylaxis may be considered.

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What is factor V Leiden?

Factor V is a clotting protein that helps form blood clots by acting as a cofactor for Factor Xa, speeding up the conversion of prothrombin to thrombin during the coagulation cascade.

Factor V Leiden (FVL) is an inherited clotting disorder, a thrombophilia. It is characterized by a poor anticoagulation response to activated protein C (APC). Individuals with this type of APC resistance have a variant (called the Leiden variant) in the factor V gene, resulting in the production of a factor V protein that is very slowly inactivated. Thus more thrombin is generated. For more on the coagulation pathway visit https://calgaryguide.ucalgary.ca/secondary-hemostasis-coagulation-cascade/ [Accessed June 2025]

How common is factor V Leiden?

FVL is the most common inherited thrombophilia. Approximately 5% to 8% of individuals of European descent are carriers (heterozygous, carry one copy of FVL). The incidence is lower in other ethnicities (~0.5-2%).

In an unselected, symptomatic population with venous thromboembolism (VTE), FVL carrier status is observed in ~20%. When there is also a strong family history of VTE, FVL is observed in 40% of individuals.

It is rare (<1%) for an individual to carry two copies of the FVL variant (homozygous).

What are the risks associated with factor V Leiden?

General risk factors for VTE are age, surgery, cancer, pregnancy, recent heart attack, prolonged immobilization (e.g. long air travel), and genetic factors.

Carrying one FVL variant is associated with an increased lifetime risk for VTE, but the absolute risk is small and most individuals with FVL never experience a VTE. People with one FVL variant (heterozygous) have a 3 to 5-fold increased lifetime risk of VTE and incident lifetime VTE risk of 17% (in those older than 45 years). For perspective, a person assigned female at birth (AFAB), of child-bearing age, has about a 1 in 10,000 per year risk of VTE. A person

AFAB of child-bearing age, with one FVL variant, would have a ~3-5 in 10,000 per year risk of VTE. For those with two FVL variants (homozygous) the risk for VTE is about 9-12 in 10,000 per year.

Following a first unprovoked VTE, FVL carrier status has been shown to be associated with a relative recurrence risk of about 1.4, with an absolute risk of 7%-14% per year. Clinical circumstances of the event, adequacy of early treatment, and individual risk factors contribute more to the determination of recurrence risk than genetic status. In other words, recurrence rates for VTE are high following an unprovoked VTE and genetic test results infrequently alter duration of anticoagulation.

FVL carrier status has not been shown to be associated with pregnancy complications, such as severe preeclampsia, fetal growth restriction, placental abruption, stillbirth, or neonatal death. FVL carrier status is not associated with increased risk of mortality.

Who could be considered for genetic testing?

Asymptomatic individuals

FVL carrier testing, in addition to tests for other thrombophilia conditions e.g. Protein C deficiency, may be considered in the following scenarios **when the results of testing would affect clinical management** (e.g. use or duration of anticoagulation prophylaxis):

- Those assigned female at birth and planning a pregnancy who have:
    - A family history of VTE and the potential to be homozygous FVL (each parent of the individual is a carrier of FVL)
        - *Testing for FVL **is indicated** in this scenario.* Anticoagulation prophylaxis would be indicated for homozygous FVL.
    - A family history of VTE
        - *Consider FVL testing if anticoagulation prophylaxis is being considered*
    - Multiple VTE risk factors e.g. obesity, older age, comorbid medical conditions
        - *Consider FVL testing if test results would affect clinical management*

Individuals with symptomatic VTE

FVL carrier testing, in addition to other thrombophilia testing, may be considered for individuals with:

- An unprovoked VTE involving unusual sites e.g. cerebral, when management would be affected. If indefinite anticoagulation is already planned, then testing is not indicated.
- A VTE provoked by a nonsurgical major transient risk factor e.g. confinement to bed in hospital for at least three days
- A VTE provoked by pregnancy or occurring post-partum
- A VTE associated with the use of combined oral contraceptives
- A VTE at or under age 40 years, either spontaneous or associated with weak environmental risk factors, and at least one first-degree relative with VTE

Most clinical management recommendations are not affected by FVL status.

Note: For those seeking gender affirming hormone therapy, the World Professional Association for Transgender Health makes intervention recommendations (e.g. estrogen-sparing intervention, transdermal estrogen) for transgender or non-binary people who are at higher risk of developing VTE. (Coleman Int J Transgend Health 2022; Bouck Res Pract Thromb Haemost. 2023)

How do I order genetic testing for factor V Leiden?

Genetic testing is available through molecular genetic laboratories across Canada. Testing may be listed under thrombophilia panels or hematology testing. Testing involves a blood sample and analysis of the factor V gene for

the presence or absence of the Leiden variant. Contact your local genetics clinic or use eConsult for more on how to order FVL in your province. See links below for FVL testing resources in your province.

- British Columbia
- Alberta
- Saskatchewan
    - Contact the Genetic Resource Centre Tel: 306-655-6450 Email: grc@saskhealthauthority.ca
- Manitoba
- Ontario
- Quebec
- Newfoundland and Labrador
- New Brunswick
- Nova Scotia
- Prince Edward Island

Who should not be considered for genetic testing?

General **population screening is not recommended.** There are potential harms to carrier testing in asymptomatic individuals, such as unnecessary exposure to thromboprophylaxis, or modifications to plans for birth control, surgery, or travel, and improper labelling as an individual with a disease.

FVL carrier testing is **not** recommended for asymptomatic individuals with family members known to have FVL (i.e. cascade screening is not recommended in asymptomatic relatives), unless the individual is assigned female at birth, planning a pregnancy, and there is the possibility for that individual to be homozygous for FVL (i.e. both of their parents are carriers of FVL).

For those considering oral contraception (OC) or hormone replacement therapy (HRT), FVL testing is **not** recommended**.** The incidence of thrombosis is low. Those with a family history of VTE are at a 2-fold increased risk (2 per 10,000 per year) and cautious use of OC and HRT is recommended. For context, the presence of one FVL variant and the use of combined OC increases the risk of thrombosis to 35–40/10,000 per year, approximately <1 in 200 risk of VTE per year.

FVL carrier testing is **not** recommended following:

- Unexplained early pregnancy loss
    - No clear association with FVL status
- Unprovoked VTE, unless at an unusual site e.g. cerebral
    - Anticoagulation duration rarely impacted by FVL status as recurrence rate is high
- Provoked VTE following surgery
    - Recurrence rate is low

How is venous thromboembolism managed in factor V Leiden carriers?

VTE management depends on the clinical circumstances. Treatment of VTE is not generally affected by FVL status.

The first acute thrombosis should be treated according to standard guidelines. (see Thrombosis Canada, Middledorp et al 2023). There is no evidence to support improved health outcomes or changes to clinical management that would be guided by FVL testing.

FVL carrier status alone is not an indication for long term anticoagulation therapy. The decision should be made based on an assessment of the risks for VTE recurrence and anticoagulant-related bleeding.

What should carriers of factor V Leiden know?

Carriers should be informed about:

- Circumstances that might increase the likelihood of VTE i.e. obesity, age, surgery, reduced mobility due to injury or travel, use of oral contraceptives, hormone replacement therapy, and pregnancy
- The signs and symptoms of VTE that require immediate medical attention
- The potential need for prophylactic anticoagulation in high-risk circumstances
- The impact on other family members. First degree relatives have a 50% chance to also carry the FVL. Carrier testing is not generally recommended, only in specific circumstances where results would impact clinical management e.g. thromboprophylaxis.

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Patient Information sheet from Thrombosis Canada

https://thrombosiscanada.ca/uploads/patients%20&%20caregivers/Patient_Materials/11.%20Inherited%20Thrombophilia_10April2024.pdf