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Factor V Leiden Thrombophilia

Synonym: Hereditary Resistance to Activated Protein C

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Summary

Clinical characteristics

Factor V Leiden thrombophilia is characterized by venous thromboembolism (VTE) manifesting most commonly in adults as deep vein thrombosis (DVT) in the legs or pulmonary embolism. Thrombosis in unusual locations is less common. Factors that predispose to VTE in factor V Leiden thrombophilia include: the number of factor V Leiden variant alleles (homozygotes have a much greater thrombotic risk); family history of VTE; presence of coexisting genetic thrombophilic disorders; acquired thrombophilic disorders (e.g., antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders); and circumstantial risk factors (e.g., pregnancy, malignancy, central venous catheters, travel, combined oral contraceptive use and other combined contraceptives, oral hormone replacement therapy [HRT], obesity, leg injury, and advancing age).

Diagnosis/testing

The diagnosis of factor V Leiden thrombophilia is established in a proband by identification of a heterozygous or homozygous c.1601G>A (p.Arg534Gln) variant in *F5* on molecular genetic testing.

Management

Treatment of manifestations: The first acute venous thrombosis is treated according to current guidelines. The duration of oral anticoagulation therapy should be based on an assessment of the risks for VTE recurrence and anticoagulant-related bleeding.

Prevention of primary manifestations: In the absence of a history of thrombosis, long-term prophylactic anticoagulation is not routinely recommended for asymptomatic factor V Leiden variant heterozygotes. A short course of prophylactic anticoagulation when transient risk factors are present may prevent initial thrombosis in heterozygotes.

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Surveillance: Periodic reevaluation of individuals on long-term anticoagulation to confirm that the benefits of anticoagulation continue to outweigh the risk of bleeding. Factor V Leiden heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy.

Agents/circumstances to avoid: Women with a history of VTE who are heterozygous for the factor V Leiden variant and women homozygous for the factor V Leiden variant with or without prior VTE should avoid estrogen-containing contraception and HRT. Women electing use of oral contraceptives should avoid third-generation and other progestins with a higher thrombotic risk. Women electing use of short-term HRT for severe menopausal symptoms should avoid oral formulations.

Evaluation of relatives at risk: The indications for testing of at-risk family members are unresolved. In the absence of evidence that early identification of the factor V Leiden variant leads to interventions that can reduce morbidity or mortality, decisions regarding testing should be made on an individual basis.

Pregnancy management: Women with thrombophilia should undergo individualized risk assessment. In women heterozygous for the factor V Leiden variant, antepartum prophylactic anticoagulation is not recommended for prevention of the first VTE. In homozygous and double heterozygous women (factor V Leiden and *F2* 20210G>A variants), antepartum and postpartum prophylactic anticoagulation is suggested to prevent a first VTE.

Genetic counseling

Factor V Leiden thrombophilia is inherited in an autosomal dominant manner. Individuals who are heterozygous for the factor V Leiden variant have a slightly increased risk for VTE; individuals who are homozygous for the factor V Leiden variant have a much greater thrombotic risk. Many individuals with the factor V Leiden variant never develop thrombosis. Most individuals with factor V Leiden thrombophilia are heterozygous for the factor V Leiden variant, which they inherited from a parent who is also heterozygous for the factor V Leiden variant. Each child of a heterozygous proband has a 50% chance of inheriting the factor V Leiden variant from the proband; if the proband's reproductive partner is also heterozygous for the factor V Leiden variant, each of their children has a 25% chance of being homozygous for the factor V Leiden variant, a 50% chance of being heterozygous, and a 25% chance of being neither heterozygous nor homozygous for the factor V Leiden variant.

Diagnosis

Suggestive Findings

Factor V Leiden thrombophilia **should be suspected** in individuals with the following clinical, laboratory, and family history findings:

- **Clinical findings.** A history of one or recurrent venous thromboembolism (VTE) manifesting as deep vein thrombosis (DVT) or pulmonary embolism (PE), especially at a young age and in the absence of strong risk factors for VTE
- **Laboratory findings.** Low activated protein C (APC) resistance on APC resistance qualitative and quantitative assays [Amiral et al 2017]

  Note: The assay is (1) cost effective with high sensitivity and specificity; (2) can detect pseudohomozygotes (compound heterozygotes for factor V Leiden variant and another *F5* pathogenic variant that causes factor V deficiency); (3) can suggest other causes for low APC such as other *F5* variants (e.g., *F5* Hong Kong and *F5* Cambridge), protein S deficiency, elevated factor VIII, presence of lupus anticoagulant, exogenous hormone use, and pregnancy or the postpartum period [Douxfils et al 2023].

- **Family history** of first-degree relatives with one or more VTE events consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Molecular genetic testing is recommended in individuals who have [Konstantinides et al 2020, Arachchillage et al 2022, Middeldorp et al 2023]:

- Low APC resistance assay values to confirm the diagnosis and to distinguish factor V Leiden variant heterozygotes from homozygotes and pseudohomozygotes (compound heterozygotes for factor V Leiden variant and another *F5* pathogenic variant that causes factor V deficiency);
- Borderline APC resistance assay values to confirm the diagnosis;
- Received direct thrombin inhibitors or direct factor Xa inhibitors, which may interfere with the results of the APC resistance assay [Kadauke et al 2014];
- Positive lupus anticoagulant and prolonged baseline activated partial thromboplastin time (aPTT);
- VTE provoked by pregnancy or occurring post partum;
- VTE associated with the use of combined oral contraceptives;
- VTE at age ≤40 years, either spontaneous or associated with weak environmental risk factors and family history of at least one first-degree relative with VTE.

The value of factor V Leiden variant testing is not established in:

- Persons with a first unprovoked VTE who are planning to stop anticoagulation;
- Female relatives of persons with VTE or hereditary thrombophilia considering estrogen contraception or hormone replacement therapy (HRT);
- Female relatives of persons with VTE or hereditary thrombophilia contemplating prophylactic anticoagulation during pregnancy.

Factor V Leiden variant testing should not routinely be performed in:

- Adults with VTE provoked by major transient risk factors;
- Persons with arterial thrombosis;
- Women with unexplained pregnancy loss;
- Neonates and children with asymptomatic central venous catheter-related thrombosis;
- Asymptomatic adult family members of individuals known to have a factor V Leiden variant;
- Routine testing in unaffected individuals (e.g., during pregnancy or prior to use of oral contraceptives, HRT, or selective estrogen receptor modulators), in asymptomatic children, prenatal testing of the fetus, or newborn testing.

Establishing the Diagnosis

The diagnosis of factor V Leiden thrombophilia **is established** in a proband by identification of a heterozygous or homozygous c.1601G>A (p.Arg534Gln) variant in *F5* (factor V Leiden variant; see Table 1) on molecular genetic testing.

Molecular genetic testing approaches can include **targeted analysis** for the factor V Leiden variant or a **multigene panel**.

- **Targeted analysis** for *F5* pathogenic variant c.1601G>A (p.Arg534Gln) can be performed first.
- **A multigene panel** that includes *F5* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not

associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

Table 1. Molecular Genetic Testing Used in Factor V Leiden Thrombophilia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
F5	Targeted analysis for c.1601G>A (p.Arg534Gln)	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.

Clinical Characteristics

Clinical Description

Heterozygosity for the Factor V Leiden Variant

Venous thromboembolism (VTE) is the primary clinical manifestation of factor V Leiden thrombophilia [Pastori et al 2023]. The most common site for VTE is the legs, but upper-extremity, cerebral, and superficial venous thrombosis may also occur.

The relative risk for VTE is increased approximately three- to eightfold in factor V Leiden variant heterozygotes [Rosendaal & Reitsma 2009]. Lower relative risks (four- to fivefold) were reported in two large meta-analyses [Gohil et al 2009, Simone et al 2013]. Despite the increase in relative risk, the overall annual incidence of a first VTE is low in heterozygotes, approximately 0.5% [Middeldorp 2011]. The reported adjusted hazard ratio (HR) for VTE in heterozygotes compared with controls was 2.7 (95% confidence interval [CI] 1.8-3.8) [Juul et al 2004].

Individuals heterozygous for the factor V Leiden variant have a sixfold increased risk for primary upper-extremity thrombosis (not related to malignancy or a venous catheter) [Martinelli et al 2004]. They also have a sixfold increased risk of superficial vein thrombosis not associated with varicose veins, malignancy, or autoimmune disorders [Martinelli et al 1999].

There is an increased risk of VTE at unusual sites. Increased prevalence of the factor V Leiden variant was reported in individuals with cerebral venous thrombosis in a meta-analysis including 1,822 affected individuals and 7,795 controls (odds ratio [OR] 2.70, 95% CI 2.16-3.38) [Li et al 2018]. A meta-analysis including 1,748 affected individuals and 2,716 controls also showed an increased prevalence of the factor V Leiden variant in individuals with retinal vein obstruction (OR 1.66, 95% CI 1.19-2.32) [Rehak et al 2008]. A higher prevalence of the factor V Leiden variant was also found in a cohort of individuals with splanchnic vein thrombosis, with a prevalence from 4%-26% in individuals with Budd-Chiari syndrome [De Stefano & Martinelli 2010].

Recurrent thrombosis. Prospective cohort studies of unselected individuals with a first VTE showed no increased recurrence risk in factor V Leiden variant heterozygotes [Christiansen et al 2005, Lijfering et al 2010]. Several meta-analyses showed a modest, approximately 1.5-fold increased risk of VTE recurrence [Marchiori et al 2007, Segal et al 2009].

The VTE recurrence risk may be higher in individuals from families prone to thrombosis than in unselected individuals. In a prospective study of families with a strong history of thrombosis, the incidence of recurrent VTE was 3.5 in 100 person-years in persons with the factor V Leiden variant [Vossen et al 2005]; however, a large family study found the rate of recurrent VTE in relatives with a factor V Leiden variant to be similar to those reported in the general population (7% after two years, 11% after five years, and 25% after ten years) [Lijfering et al 2009].

Risk for VTE in children. The cause of VTE in children is multifactorial and results from the interaction between acquired clinical risk factors (see Table 2), one or more underlying medical conditions, and an inherited predisposition to thrombophilia [Klaassen et al 2015, van Ommen & Nowak-Göttl 2017].

The most important clinical risk factor for thrombosis in children is a central venous catheter (CVC). A factor V Leiden variant was associated with CVC-related VTE in some [Neshat-Vahid et al 2016] but not all studies [Thom et al 2014].

A factor V Leiden variant was reported to increase the risk of neonatal cerebral vein thrombosis [Kenet et al 2010, Laugesaar et al 2010], and significantly increased the risk of cerebral venous thrombosis in children (OR 2.74) [Kenet et al 2010].

In a prospective study, asymptomatic children heterozygous for a factor V Leiden variant had no thrombotic complications during follow up that averaged five years [Tormene et al 2002]. Thus, asymptomatic heterozygous children appear to be at low risk for thrombosis except in the setting of strong circumstantial risk factors (see Table 2).

Risk for maternal VTE in pregnancy. Normal pregnancy is associated with a five- to tenfold increased risk of developing VTE. Women heterozygous for the factor V Leiden variant have a five- to eightfold greater risk of pregnancy-related VTE than women without the variant [Robertson et al 2006, Bleker et al 2014, Gerhardt et al 2016]. The risk is higher in women from families with a history of thrombosis and in women older than age 34 years. The highest risk of VTE occurs during the first six weeks post partum.

While heterozygosity for the factor V Leiden variant increases the relative risk for pregnancy-associated VTE, the absolute risk is low in the absence of other predisposing factors. VTE is estimated to occur in 1% of pregnancies in women who are factor V Leiden variant heterozygotes. The absolute risk increases to 3% in those with a positive family history of VTE [Bleker et al 2014, Campello et al 2016].

Women with a prior unprovoked VTE and factor V Leiden thrombophilia had the highest recurrence rate during pregnancy (20% of pregnancies). A factor V Leiden variant was associated with an increased risk of antepartum recurrence (OR 10) [Brill-Edwards et al 2000].

Other obstetric complications. Available data suggest that factor V Leiden variant heterozygosity is at most a weak contributor to recurrent or late pregnancy loss. A meta-analysis evaluating only prospective cohort studies reported a slightly increased risk of pregnancy loss in women with the factor V Leiden variant (4.2%) compared to those without the variant (3.2%) (OR 1.52) [Rodger et al 2010]. A meta-analysis found that heterozygosity for the factor V Leiden variant is associated with a twofold increased risk for a late unexplained fetal loss and a fourfold higher risk for loss in the second trimester compared to the first trimester [Robertson et al 2006]. Presence of the factor V Leiden variant was not associated with stillbirths in the subset of stillbirths resulting from placental insufficiency [Silver et al 2016].

A systematic review focused on prospective cohort studies found no significant association of preeclampsia or placental abruption with factor V Leiden thrombophilia [Rodger et al 2010]. A Danish case-cohort study found that heterozygosity for the factor V Leiden variant increased the risk of severe preeclampsia (OR 1.6), severe fetal growth restriction (OR 1.5), and symptomatic placental abruption (OR 1.7) [Lykke et al 2012]. Such conflicting results may reflect the varying diagnostic and selection criteria, different ethnic groups, and small number of individuals included. However, given that preeclampsia and placental abruption are heterogeneous disorders, it is unlikely that a single thrombophilic variant (such as the factor V Leiden variant) plays a major causal role.

Prognosis. Heterozygosity for the factor V Leiden variant is not associated with an increase in mortality or reduction in normal life expectancy even in the presence of a history of VTE [Pabinger et al 2012].

Homozygosity for the Factor V Leiden Variant

VTE. Compared to heterozygotes, homozygotes have a higher thrombotic risk and tend to develop thrombosis at a younger age. The risk for VTE in homozygotes is reported to be nine- to 80-fold [Rosendaal & Reitsma 2009] or nine- to 12-fold [Gohil et al 2009, Simone et al 2013]. The reported adjusted HR for VTE in homozygous individuals compared with controls was 18 (95% CI 4.1-41) [Juul et al 2004].

Recurrent thrombosis. Similar rates of VTE recurrence for both factor V Leiden variant homozygotes and heterozygotes were found in a recent study [Perez Botero et al 2016], whereas an earlier systematic review found that homozygosity for the factor V Leiden variant conferred a 2.6-fold increased risk of recurrent VTE [Segal et al 2009].

Risk for VTE in pregnancy. In women homozygous for the factor V Leiden variant, the relative risk of VTE during pregnancy is increased 17- to 34-fold [Robertson et al 2006, Gerhardt et al 2016]. The absolute risk of developing pregnancy-related VTE is estimated at 2.2%-4.8% of pregnancies. The risk is higher (14%) in homozygotes with a positive family history and in those older than age 34 years [Bleker et al 2014, Gerhardt et al 2016].

Obstetric complications. Maternal homozygosity for the factor V Leiden variant was associated with an increased risk of stillbirth (OR 87.44, 95% CI 7.88-970.92) in a Stillbirth Collaborative Research Network study [Silver et al 2016] but not in a Stockholm regional study [Björk et al 2019].

Additional Factors that Predispose to Thrombosis

In addition to the number of factor V Leiden variant alleles, the clinical expression of factor V Leiden thrombophilia is influenced by family history, coexisting genetic abnormalities, acquired thrombophilic disorders, and circumstantial risk factors.

Positive family history. Individuals with a factor V Leiden variant who have a first-degree relative with a history of thrombosis had a threefold increased risk for VTE compared to those with a factor V Leiden variant with a negative family history [Bezemer et al 2009]. In the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis, a population-based case-control study including 1,605 individuals with a first venous thrombosis and 2,159 controls, a total of 505 affected individuals (31.5%) and 373 controls (17.3%) reported having one or more first-degree relatives with a history of venous thrombosis. A positive family history increased the risk of venous thrombosis more than twofold (OR 2.2, 95% CI 1.9-2.6) and up to fourfold (OR 3.9, 95% CI 2.7-5.7) when more than one relative was affected. Family history corresponded poorly with known genetic risk factors [Bezemer et al 2009].

The risk was increased to fivefold in those with a relative with a VTE before age 50 years and to 18-fold with two or more affected relatives. The family history had additional value in predicting risk even in those with a factor V Leiden variant, suggesting the presence of unknown genetic risk factors.

Prothrombin thrombophilia due to heterozygosity for *F2* variant c.*97G>A (commonly known as 20210G>A). Individuals with the factor V Leiden variant and the *F2* 20210G>A variant (double heterozygotes) had a three- to ninefold higher risk of recurrent VTE compared to those with neither variant, and a threefold higher risk compared to individuals heterozygous for the factor V Leiden alone [De Stefano et al 1999, Meinardi et al 2002, Segal et al 2009]. The annual incidence of recurrent VTE was 12% per year in double heterozygotes, compared to 2.8% in those with neither thrombophilia-related variant [González-Porras et al 2006]. Women with the factor V Leiden variant and the *F2* 20210G>A variant are reported to have an eight- to 47-fold increased relative risk of pregnancy-related VTE [Jacobsen et al 2010, Gerhardt et al 2016]. The probability of VTE during pregnancy and the puerperium is lower (5.5%) in double heterozygous women younger than age 35 years than in older women (8.2%) [Gerhardt et al 2016]. In children with the factor V Leiden variant,

prothrombin thrombophilia appears to have at most a modest effect on the risk of recurrence, similar to findings in adults [Klaassen et al 2015].

Acquired thrombophilic disorders include antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, and increased levels of clotting factors. Despite the following observations, the effect of these acquired disorders on factor V Leiden variant-associated thrombotic risk is not well defined.

- Factor V Leiden variant heterozygotes with factor VIII levels greater than 150% of normal had a two- to threefold increased incidence of VTE than factor V Leiden variant heterozygotes alone [Lensen et al 2001]. The reason for the association of high factor VIII levels with VTE is unknown.
- A factor V Leiden variant was reported to contribute to increased risk for thrombotic complications in persons with polycythemia vera and essential thrombocytosis [Trifa et al 2014].

Additional Acquired Risk Factors for VTE

Additional acquired risk factors for VTE in factor V Leiden variant heterozygotes or homozygotes are summarized in Table 2.

Table 2. Increased Risk of Thrombosis in Persons with the Factor V Leiden Variant and Additional Acquired Risk Factors

Risk Factor	Risk for VTE	Comment	Citation
Malignancy [1]	HR 1.64 (95% CI 1.48-1.80)	Risk varies according to type of cancer; incl persons w/factor V Leiden &/or *F2* G20210A variant	Shi et al [2023]
CVC use	RR 2.7 (95% CI 1.9-3.8)	Incl persons w/factor V Leiden or *F2* G20210A variant	Van Rooden et al [2004]
	OR 4.6 (95% CI 2.6-8.1)	Meta-analysis involving 1,000 affected persons	Dentali et al [2008]
Travel	OR 8.1 (95% CI 2.7-24.7)	Risk ↑ w/travel duration; travel by car, bus, or train led to high RR of thrombosis.	Cannegieter et al [2006]
	Normal weight w/: • O blood group: OR 5.6 (95% CI 2.4-12.9) • Non-O blood group: OR 16.3 (95% CI 7.5-35.4)	Overweight/obese persons w/factor V Leiden & non-O blood had highest risk of thrombosis when travel coexisted as risk factor.	Ribeiro et al [2016]
	Overweight w/: • O blood group: OR 13.6 (95% CI 3.1-60.9) • Non-O blood group: OR 21.7 (95% CI 10.0-47.1)		

Table 2. continued from previous page.

Risk Factor	Risk for VTE	Comment	Citation
	Obesity w/: • O blood group: OR 9.2 (95% CI 2.0-42.2) • Non-O blood group: OR 37.5 (95% CI 10.5-133)		
COCs [1]	OR 20.6 (95% CI 8.9-58)	COCs are assoc w/higher risk of VTE than progestin-only contraception in those w/ factor V Leiden variant	Bergendal et al [2014]
	RR 6.14 (95% CI 2.58-14.46)		van Vlijmen et al [2016]
	• ≤1 yr COC use: OR 62.2 (95% CI 29.8-129.6) • >1 yr COC use: OR 25.4 (95% CI 16.5-39.2)	After 1st year of COC use RR ↓ but remained high (data incl those w/factor V Leiden or *F2* 20210G>A variant)	Martinelli et al [2016]
	OR 19.3 (95% CI 13.9-26.8)	Risk by progestogen type in COC: • Gestodene: OR 22.1 (95% CI 11.3-43.3) • Desogestrel: OR 26.3 (95% CI 15.2-45.5) • Levonorgestrel: OR 17.4 (95% CI 11.4-26.6) • Cyproterone: OR 31.8 (95% CI 17.2-59.0)	Khialani et al [2020]
	• ≤2 yrs COC use: HR 5.73 (95% CI 5.31-6.17) • >2 yrs COC use: HR 2 (95% CI 1.86-2.16)	Highest risk of VTE in 1st 2 yrs of use; from study of 240,000 women in UK Biobank	Lo Faro et al [2024]
Progestogen-only contraception	OR 5.4 (95% CI 2.5-13)		Bergendal et al [2014]
Oral HRT [1]	OR 16.4 (95% CI 4.3-62.2)	Postmenopausal women	Straczek et al [2005]
	OR 17.1 (95% CI 3.7-78)	Estrogen-progestin HRT	Douketis et al [2011]
	OR 6.69 (95% CI 3.09-14.49)		Cushman et al [2004]
Transdermal HRT [1]	OR 4.6 (95% CI 1.6-13.8)	Transdermal estrogen	Straczek et al [2005]

Table 2. continued from previous page.

Risk Factor	Risk for VTE	Comment	Citation
Obesity (BMI >30 kg/m^2)	HR 5.27 (95% CI 2.74-10.14)	Risk ↑ w/BMI	Severinsen et al [2010]
	• O blood group: OR 5.6 (95% CI 3.0-10.4) • Non-O blood group: OR 15.7 (95% CI 9.4-25.9)	Greater risk in those w/non-O blood	Ribeiro et al [2016]
Overweight (BMI >25 to <30 kg/m^2)	HR 3.60 (95% CI 2.31-5.63)	Risk ↑ w/BMI	Severinsen et al [2010]
	• O blood group: OR 4.4 (95% CI 2.9-6.6) • Non-O blood group: OR 10.7 (95% CI 7.7-14.8)	Greater risk in those w/non-O blood	Ribeiro et al [2016]
Organ transplantation	No significant association	↑ risk of hepatic arterial thrombosis in liver transplantation has been reported.	Ghisdal et al [2010], Pereboom et al [2011], Parajuli et al [2016]
Minor leg injury	OR 49.7 (95% CI 6.8-362.7)	Minor injury in previous 3 mos	van Stralen et al [2008]
	OR 11.0 (95% CI 2.5-48.0)	Below-knee cast immobilization	van Adrichem et al [2014]
Surgery	Likely ↑ risk	Major orthopedic surgery	Joseph et al [2005], Charen et al [2015]
	>15-fold ↑	Arthroscopy of knee	van Adrichem et al [2015]
Age	17.1% (95% CI 11.4%-21.4%)	Lifetime risk in heterozygotes & homozygotes for factor V Leiden variant	Bell et al [2016]
Age >70 yrs	OR 2.2 (95% CI 1.2-3.9)		Karasu et al [2016]
Age <40 years + nonsmoker + BMI <25 kg/m^2	0.7% in heterozygotes (95% CI 0.5%-1%)	Lowest 10-yr absolute risk of VTE is in those of younger age, nonsmokers, & lower BMI	Juul et al [2004]
	3% in homozygotes (95% CI 1%-8%)		
Age >60 years + smoker + BMI >30 kg/m^2	10% in heterozygotes (95% CI 7%-14%)	Highest 10-yr absolute risk of VTE is in those of older age, smokers, & ↑ BMI	
	51% in homozygotes (95% CI 13%-100%)		

BMI = body mass index; COCs = combined oral contraceptives; CVC = central venous catheter; HR = hazard ratio; HRT = hormone replacement therapy; OR = odds ratio; RR = relative risk; VTE = venous thromboembolism
1. See text that follows table for more details.

Malignancy. To what extent inherited thrombophilia increases the risk of VTE in persons with cancer remains controversial [Decousus et al 2007, Pabinger et al 2015]. Because malignancy is such a strong thrombotic risk factor, it may obscure the effect of mild thrombophilic disorders including factor V Leiden thrombophilia.

Thrombophilia status was not considered in guidelines for prophylaxis and treatment of VTE in individuals with cancer [Farge et al 2013].

Combined oral contraceptive (COC) use substantially increases the relative risk for VTE in women heterozygous for the factor V Leiden variant [LaVasseur et al 2022]. The incidence of VTE in COC users with either the factor V Leiden variant or the *F2* 20210G>A variant ranged from 0.49 to 0.86/100 pill-years in heterozygotes or double heterozygotes, respectively [van Vlijmen et al 2011].

The supra-additive effect of both a factor V Leiden variant and use of COCs was confirmed in multiple studies in which the OR for VTE ranged from 11 to 41 [Wu et al 2005, Dayan et al 2011, Bergendal et al 2014, van Vlijmen et al 2016]. For women who are either homozygous for the factor V Leiden variant or double heterozygous for the factor V Leiden variant and the *F2* 20210G>A variant, the OR for VTE ranged from 17 to 110 [Mohllajee et al 2006, van Vlijmen et al 2016].

The thrombotic risk in COC users with the factor V Leiden variant is at least as high in women older than age 50 years as in younger users [Roach et al 2013]. However, since the incidence of VTE increases with age, the absolute risk for VTE in women older than age 50 years is much higher than in younger COC users.

Oral hormone replacement therapy (HRT) is associated with a two- to fourfold increased relative risk for VTE in healthy postmenopausal users of HRT compared to nonusers [Renoux et al 2010, Eisenberger & Westhoff 2014]. The risk increases with higher estrogen doses and may differ with the particular estrogen and progestin components [Renoux et al 2010, Canonico et al 2011, Smith et al 2014]. The risk of VTE is increased threefold in postmenopausal women with a factor V Leiden or *F2* 20210G>A variant than in HRT users without thrombophilia [Roach et al 2013].

Transdermal HRT. Multiple observational studies consistently found that transdermal HRT did not increase the risk of VTE [Canonico et al 2010, Sweetland et al 2012, ACOG 2013a]. There is also evidence that transdermal estrogen is associated with a lower thrombotic risk (HR 1.1, 95% CI 0.8-1.8) than oral estrogen (HR 1.7, 95% CI 1.1-2.8) in women with the factor V Leiden variant [Canonico et al 2010]. The risk for women with a prothrombotic variant (including the factor V Leiden variant) using transdermal estrogen was similar to that of women with a prothrombotic variant who were not using transdermal estrogen (OR 4.4, 95% CI 2.0 to 9.9 and OR 4.1, 95% CI 2.3 to 7.4, respectively) [Straczek et al 2005]. However, no prospective randomized trials have confirmed the safety of transdermal HRT in women with inherited thrombophilia. Among women with the factor V Leiden variant, the use of oral estrogen was associated with a fourfold increased risk for VTE over transdermal estrogen [Straczek et al 2005].

Arterial Thrombosis

Recent evidence from a large meta-analysis suggested a role for factor V thrombophilia in arterial thrombotic disease [Agosti et al 2023, Valeriani et al 2023]. The OR for cerebrovascular disease was 2.76 (95% CI 1.83-4.18) in individuals homozygous for the factor V Leiden variant, and 1.48 (95% CI 1.29-1.71) for individuals heterozygous for the factor V Leiden variant [Valeriani et al 2023]. The OR for coronary heart disease was 1.68 (95% CI 1.02-2.77) in individuals homozygous for the factor V Leiden variant, and 1.39 (95% CI 1.19-1.61) for individuals heterozygous for the factor V Leiden variant [Valeriani et al 2023].

Prevalence

Factor V Leiden thrombophilia is the most common inherited form of thrombophilia. The prevalence varies by population.

Heterozygosity for the factor V Leiden variant occurs in 3%-8% of the general United States and European populations. The highest heterozygosity rate is found in Europe. Within Europe, prevalence varies from 10%-15% in southern Sweden and Greece to 2%-3% in Italy and Spain [Kujovich 2011]. The factor V Leiden

variant is extremely rare in Asian, African, and indigenous Australian populations [Kujovich 2011]. In the US, prevalence reflects the world distribution of the factor V Leiden variant [Ridker et al 1997, Kujovich 2011], which is present in 5.2% of Americans of European origin, 2.2% of Hispanic Americans, 1.2% of African Americans, 0.45% of Asian Americans, and 1.25% of Native Americans.

The frequency of homozygosity for the factor V Leiden variant is approximately 1:5,000.

The factor V Leiden variant is present in approximately 15%-20% of individuals with a first deep vein thrombosis and up to 50% of individuals with recurrent VTE or an estrogen-related thrombosis.

Differential Diagnosis

The differential diagnosis of venous thromboembolism (VTE) includes several other inherited thrombophilic disorders, including those caused by other variants in *F5* (see Molecular Genetics), and acquired thrombophilic disorders (outside of the scope of this *GeneReview*).

Prothrombin thrombophilia is characterized by VTE manifesting most commonly in adults as deep vein thrombosis (DVT) in the legs or pulmonary embolism. The clinical expression of prothrombin thrombophilia is variable; many individuals heterozygous or homozygous for the 20210G>A *F2* variant never develop thrombosis, and while most heterozygotes who develop thrombotic complications remain asymptomatic until adulthood, some have recurrent thromboembolism before age 30 years. The relative risk for DVT in adults heterozygous for the *F2* 20210G>A variant is two- to fivefold increased; in children, the relative risk for thrombosis is three- to fourfold increased. Factors that predispose to thrombosis in prothrombin thrombophilia include: the number of *F2* 20210G>A variant alleles; presence of coexisting genetic abnormalities, including the factor V Leiden variant; and acquired thrombophilic disorders (e.g., antiphospholipid antibodies). Circumstantial risk factors for thrombosis include pregnancy and oral contraceptive use.

Inherited abnormalities or deficiencies of the natural anticoagulant proteins C, S, and antithrombin are approximately tenfold less common than the factor V Leiden variant, with a combined prevalence of less than 1%-2% of the population. Anticoagulant protein deficiencies are found in 1%-3% of individuals with a first VTE.

Hereditary dysfibrinogenemias (OMIM 616004) are rare and infrequently cause thrombophilia and thrombosis.

See OMIM Phenotypic Series: Thrombophilia to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To assess the risk for venous thromboembolism (VTE) in an individual found to have a factor V Leiden variant, the following are recommended:

- DNA analysis for prothrombin thrombophilia (*F2* variant c.*97G>A, commonly known as 20210G>A)
- Multiple phospholipid-dependent coagulation assays for a lupus inhibitor
- Serologic assays for anticardiolipin antibodies and anti-beta-2-glycoprotein 1 antibodies

For high-risk individuals (i.e., those with a history of recurrent VTE, especially at a young age, or those with strong family history of VTE at a young age), evaluation should also include assays of:

- Protein C activity
- Antithrombin activity
- Protein S activity or free protein S antigen

Note: Measurement of the following is NOT recommended:

- Plasma concentration of homocysteine, as no data support a change in duration of anticoagulation or the use of vitamin supplementation in individuals with hyperhomocysteinemia and a history of VTE
- *MTHFR* variants, as no clinical rationale for this testing exists
- Factor VIII and other clotting factor levels [Moll 2015]

Treatment of Manifestations

Treatment of VTE in Adults

The management of individuals with factor V Leiden thrombophilia depends on the clinical circumstances.

The first acute thrombosis should be treated according to current guidelines [Kearon et al 2016, Witt et al 2018, Konstantinides et al 2020]. For initial treatment of VTE, current guidelines suggest a direct oral anticoagulant (dabigatran, edoxaban, rivaroxaban, or apixaban) over warfarin because of a lower bleeding risk and greater convenience [Kearon et al 2016, Witt et al 2018, Konstantinides et al 2020]. Of note, a higher dose is administered for the first three weeks of treatment with rivaroxaban and for the first week of treatment with apixaban. The recommendation for a direct oral anticoagulant may not apply to certain subgroups such as individuals with severe renal insufficiency, antiphospholipid antibody syndrome, or extremes of body weight [Ortel et al 2020].

For individuals not treated with one of the direct oral anticoagulants, administration of warfarin is started concurrently with low-molecular-weight heparin (LMWH) or fondaparinux (except during pregnancy), and monitored with the international normalized ratio (INR). A target INR of 2.5 (therapeutic range 2.0-3.0) provides effective anticoagulation, even in individuals homozygous for the factor V Leiden variant [Kearon et al 2008, Tzoran et al 2017]. LMWH and warfarin therapy should be overlapped for at least five days, and until the INR has been within the therapeutic range for 24 hours, at which time LMWH is stopped [Witt et al 2018].

Note: LMWH and warfarin are both safe in women who are breastfeeding (see Pregnancy Management for issues with anticoagulants).

The duration of oral anticoagulation therapy should be based on an assessment of the risks for VTE recurrence and anticoagulant-related bleeding. Recurrence risk is determined by the clinical circumstances of the first event (provoked or unprovoked), adequacy of early treatment, and individual risk factors.

- Heterozygosity for the factor V Leiden variant alone is not an indication for long-term anticoagulation in the absence of other risk factors, according to the American College of Chest Physicians guidelines on antithrombotic therapy [Stevens et al 2021] and the American Society of Hematology (ASH) guidelines for management of VTE [Witt et al 2018].
- Anticoagulation for at least three months is recommended for persons with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) associated with a transient (reversible) risk factor [Kearon et al 2012, Kearon et al 2016, Konstantinides et al 2020].

Indefinite anticoagulation is recommended for individuals with a first or recurrent unprovoked proximal DVT of the leg and a high risk of recurrence due to risk factors such as cancer, combined thrombophilia, or homozygosity for the factor V Leiden variant [Konstantinides et al 2020]. The decision should be based on an assessment of potential risks and benefits regardless of factor V Leiden variant status [EGAPP Working Group 2011]. Long-term anticoagulation is considered in individuals homozygous for the factor V Leiden variant or with multiple thrombophilic disorders, particularly in the presence of additional risk factors, as the potential benefits from long-term anticoagulation may outweigh the bleeding risks [De Stefano & Rossi 2013].

Several scores were developed to help clinicians estimate the risk of recurrence of DVT or PE after a first episode [Konstantinides et al 2020]. Individuals with two or more episodes of VTE and/or PE need lifelong anticoagulation treatment [Konstantinides et al 2020]. In individuals taking apixaban and rivaroxaban, a long-term prophylaxis dose after a first VTE/PE episode may be an option [Konstantinides et al 2020].

Treatment of VTE in Children

Treatment recommendations for children with VTE were largely adapted from studies in adults, but recently, studies on VTE recurrence and treatment in children have been performed [Limperger et al 2016, Giossi et al 2023].

The treatment of acute VTE is not influenced by identification of a factor V Leiden variant. Children with a first VTE should receive initial treatment with either unfractionated heparin or LMWH for at least five days. ASH guidelines suggest using either LMWH or warfarin in children with symptomatic DVT or PE [Monagle et al 2018]. Recently, use of direct oral anticoagulants were approved for affected children. Clinical trials showed efficacy and safety equal to warfarin/LMWH [Giossi et al 2023]. The decision on anticoagulant should be individualized based on preference of the affected individual, underlying condition, comorbidities, and other medications [Monagle et al 2018]. LMWH is often favored over warfarin for continued therapy, especially in very young children and those with complex medical problems [Monagle & Newall 2018].

In children with a factor V Leiden variant, the duration of anticoagulation following VTE may include indefinite anticoagulation or intermittent anticoagulation in high-risk situations after considering the risk of side effects of anticoagulation (e.g., major bleeding), the risk of recurrent VTE, and the preference of the affected individual. To date, outcomes from these treatment strategies have not been studied in children [van Ommen & Nowak-Göttl 2017]. Recommendations on the duration of antithrombotic therapy are based on the nature of the thrombotic event (e.g., spontaneous or provoked) [Monagle et al 2012]. Anticoagulation is recommended:

- For at least three months following a VTE provoked by a clinical risk factor that has resolved;
- At least three months and until the risk factor has resolved in children with an ongoing but potentially reversible risk factor;
- For six to 12 months after a first unprovoked VTE.

Consensus guidelines and expert opinion emphasize the importance of a careful risk vs benefit assessment in each individual.

Prevention of Primary Manifestations

In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended for asymptomatic individuals who are heterozygous for the factor V Leiden variant because the 1%-3% per year risk for major bleeding from warfarin is greater than the estimated less than 1% per year risk for thrombosis.

Because the initial thrombosis in 50% of factor V Leiden variant heterozygotes occurs in association with other circumstantial risk factors (see Table 2), a short course of prophylactic anticoagulation during exposure to hemostatic stresses may prevent some of these episodes. However, currently no evidence confirms the benefit of primary prophylaxis for asymptomatic factor V Leiden variant heterozygotes. Factors that may influence decisions about the indication for and duration of anticoagulation include age, family history, and other coexisting risk factors.

Selected factor V Leiden variant heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy. Recommendations for prophylaxis at the time of surgery and other high-risk situations are available in consensus guidelines [Kearon et al 2016, Kakkos et al 2021].

Surveillance

Individuals receiving long-term anticoagulation require periodic reevaluation of their clinical course to confirm that the benefits of anticoagulation continue to outweigh the risk of bleeding.

Factor V Leiden heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy.

Agents/Circumstances to Avoid

Women with a history of VTE who are heterozygous for the factor V Leiden variant should avoid estrogen-containing contraception and hormone replacement therapy (HRT).

Women homozygous for the factor V Leiden variant with or without prior VTE should avoid estrogen-containing contraception and HRT.

Asymptomatic women heterozygous for the factor V Leiden variant:

- Should be counseled on the risks of estrogen-containing contraception and HRT use and should be encouraged to consider alternative forms of contraception and control of menopausal symptoms;
- Electing to use oral contraceptives should avoid third-generation and other progestins with a higher thrombotic risk;
- Electing short-term HRT for severe menopausal symptoms should use a low-dose transdermal preparation, which has a lower thrombotic risk than oral formulations and is not associated with higher thrombotic risk in healthy women [Morris & Talaulikar 2023].

Evaluation of Relatives at Risk

The genetic status of apparently asymptomatic at-risk family members can be established using molecular genetic testing for the *F5* pathogenic variant c.1601G>A (p.Arg534Gln).

Note: The indications for family testing are sustained by low clinical evidence.

In the absence of evidence that early identification of the factor V Leiden variant leads to interventions that can reduce morbidity or mortality, decisions regarding testing should be made on an individual basis. In particular, individuals with a first-degree relative with a factor V Leiden variant, no (or only minor) risk factors, and no history of VTE should not tested [Middeldorp et al 2023].

At-risk females (family history of recurrent VTE at a young age and/or known factor V Leiden thrombophilia) should avoid estrogen-containing contraception and HRT [Middeldorp et al 2023].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Prevention of Thrombosis During Pregnancy

Guidelines from ASH state all women with inherited thrombophilia should undergo individualized risk assessment [Bates et al 2018]. Decisions about anticoagulation should be based on the number and type of thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

For pregnant women with a prior VTE, including those heterozygous for the factor V Leiden variant, who are not already receiving anticoagulation for a prior VTE:

- Provoked by a hormonal risk factor or unprovoked, antepartum prophylactic anticoagulation is recommended [Bates et al 2018];
- Provoked by a transient risk factor not related either to pregnancy or to the use of estrogen, antepartum prophylactic anticoagulation is not suggested [Bates et al 2018] and clinical vigilance during pregnancy is suggested [Bates et al 2012].

In women heterozygous for the factor V Leiden variant, antepartum prophylactic anticoagulation is not suggested for first VTE prevention, regardless of family history of VTE [Bates et al 2018].

In women homozygous for the factor V Leiden variant, antepartum prophylactic anticoagulation is suggested to prevent a first VTE, regardless of family history of VTE [Bates et al 2018].

In double heterozygous women for the factor V Leiden and *F2* 20210G>A variants, antepartum prophylactic anticoagulation is suggested to prevent a first VTE, regardless of family history of VTE [Bates et al 2018].

Standard-dose LMWH is suggested for antepartum prophylaxis, while standard- or intermediate-dose LMWH is suggested for postpartum prophylaxis [Bates et al 2018].

The oral direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) are not recommended during pregnancy and breastfeeding because of (1) absence of data on fetal and neonatal safety and (2) animal studies that showed reproductive toxicity [Ageno et al 2012, Bates et al 2018].

Prevention of Thrombosis During the Postpartum Period

For pregnant women with a prior VTE, including those heterozygous for the factor V Leiden variant, not already receiving anticoagulation, postpartum prophylactic anticoagulation is recommended [Bates et al 2018].

In **women heterozygous** for the factor V Leiden variant [Bates et al 2018]:

- With a family history of VTE, postpartum prophylactic anticoagulation is not suggested to prevent a first VTE;
- Without a family history of VTE, postpartum prophylactic anticoagulation is not suggested to prevent a first VTE.

In **women homozygous** for the factor V Leiden variant, postpartum prophylactic anticoagulation is suggested to prevent a first VTE, regardless of family history of VTE [Bates et al 2018].

In **women double heterozygous** for the factor V Leiden and *F2* 20210G>A variant, postpartum prophylactic anticoagulation is suggested to prevent a first VTE, regardless of family history of VTE [Bates et al 2018].

In breastfeeding women using unfractionated heparin, LMWH, fondaparinux, or danaparoid are recommended for prophylaxis [Bates et al 2018].

Although an increased risk of VTE may persist for 12 weeks post partum [Kamel et al 2014], women are much more likely to develop VTE during the first six weeks after delivery [Kamel et al 2014, Kourlaba et al 2016]. Therefore, extending prophylaxis between six and 12 weeks post partum is unlikely to be of significant benefit [Bates et al 2018].

Other

Unexplained pregnancy loss. Current consensus guidelines and expert opinion recommend against the use of antithrombotic therapy outside of clinical trials in women with inherited thrombophilia and unexplained pregnancy loss because of the absence of high-quality evidence confirming benefit [Bates et al 2012, ACOG 2013b, Middeldorp 2013, Skeith et al 2016].

Pregnancy complications. Current guidelines recommend against antithrombotic prophylaxis for women with inherited thrombophilia and a history of other pregnancy complications such as preeclampsia or placental abruption [Bates et al 2012, ACOG 2013b].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Factor V Leiden thrombophilia (i.e., predisposition to the development of venous thrombosis) is inherited in an autosomal dominant manner.

Individuals who are heterozygous for the factor V Leiden variant (*F5* variant c.1601G>A [p.Arg534Gln]) have a slightly increased risk for venous thrombosis; individuals who are homozygous for the factor V Leiden variant have a much greater thrombotic risk (see Clinical Description, Homozygosity for the Factor V Leiden Variant). Many individuals with the factor V Leiden variant never develop thrombosis (see Clinical Description).

Risk to Family Members

Parents of a proband

- Most individuals with factor V Leiden thrombophilia are heterozygous for the factor V Leiden variant, which they inherited from a parent who is also heterozygous for the factor V Leiden variant.
- More rarely, individuals with factor V Leiden thrombophilia are homozygous for the factor V Leiden variant, having inherited one factor V Leiden variant from each parent.
- Occasionally – because of the relatively high frequency of the factor V Leiden variant in the general population – one parent is homozygous for the factor V Leiden variant or both parents are heterozygous for the factor V Leiden variant.
- The family history of some individuals diagnosed with factor V Leiden thrombophilia may appear to be negative because no other family members developed thrombosis or because of failure to recognize factor V Leiden thrombophilia in affected family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous (or homozygous) for the factor V Leiden variant.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents.

- If one parent is heterozygous for the factor V Leiden variant, each sib of the proband is at a 50% risk of being heterozygous for the factor V Leiden variant.
- If one parent is homozygous for the factor V Leiden variant, each sib of the proband has a 100% chance of being heterozygous for the factor V Leiden variant.

- If both parents are heterozygous for the factor V Leiden variant, each sib of the proband has a 25% chance of being homozygous for the factor V Leiden variant, a 50% chance of being heterozygous, and a 25% chance of being neither heterozygous nor homozygous for the factor V Leiden variant.

Offspring of a proband

- Each child of a heterozygous proband has a 50% chance of inheriting the factor V Leiden variant from the proband. If the proband's reproductive partner is also heterozygous for the factor V Leiden variant, each of their children has a 25% chance of being homozygous for the factor V Leiden variant, a 50% chance of being heterozygous, and a 25% chance of being neither heterozygous nor homozygous for the factor V Leiden variant.
- All children of an individual who is homozygous for the factor V Leiden variant will inherit the factor V Leiden variant from the proband. If the proband's reproductive partner is heterozygous for the factor V Leiden variant, each of their children has a 50% chance of being homozygous and a 50% chance of being heterozygous for the factor V Leiden variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: the family members of an individual who is heterozygous or homozygous for the factor V Leiden variant are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults with factor V Leiden thrombophilia.
- See Pregnancy Management for review of prevention of thrombosis during pregnancy and the postpartum period.

Prenatal Testing and Preimplantation Genetic Testing

Once the factor V Leiden variant has been identified in a family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly in regard to testing for the factor V Leiden variant, which is common in the general population and is predisposing to, but not predictive of, thrombosis.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Factor V Leiden thrombophilia
- **National Blood Clot Alliance**

Phone: 703-935-8845
Email: info@stoptheclot.org
www.stoptheclot.org

- **Thrombosis UK**
  United Kingdom
  Phone: 0300 772 9603
  Email: admin@thrombosisuk.org
  www.thrombosisuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Factor V Leiden Thrombophilia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
F5	1q24.2	Coagulation factor V	F5 database	F5	F5

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Factor V Leiden Thrombophilia (View All in OMIM)

188055	THROMBOPHILIA DUE TO ACTIVATED PROTEIN C RESISTANCE; THPH2
612309	COAGULATION FACTOR V; F5

Molecular Pathogenesis

Factor V Leiden variant refers to missense variant c.1601G>A in *F5*, which encodes coagulation factor V, a key regulator in the coagulation cascade. Once activated, factor V functions as a cofactor that accelerates clot formation. Factor V is inactivated when cleaved by activated protein C (APC). The factor V Leiden variant, c.1601G>A (p.Arg534Gln), causes the substitution of glutamine for arginine at the Arg534 APC cleavage site, which is required for factor V inactivation by APC [Kujovich 2011].

Factor V with the Leiden variant is inactivated at an approximately tenfold slower rate than normal due to this amino acid change, resulting in less efficient APC cleavage. Factor V with the Leiden variant persists longer in the circulation, resulting in increased thrombin generation and a mild hypercoagulable state, reflected by elevated levels of D-dimer, prothrombin fragment F1+2, and other activated coagulation markers [Martinelli et al 1996, Zöller et al 1996, Dahlbäck 2008, Kujovich 2011].

The factor V Leiden variant is frequent in the population (see Prevalence), leading to speculation of a survival advantage associated with the heterozygous state [Kujovich 2011].

Other *F5* variants at APC cleavage sites, p.Arg334Thr (*F5* Cambridge) and p.Arg334Gly, are not major risk factors for thrombosis, but may contribute when combined with other genetic or acquired risk factors.

Mechanism of disease causation. The lower inactivation rate of factor V with the Leiden variant results in increased thrombin generation [Kujovich 2011].

***F5*-specific laboratory technical considerations.** Using legacy nomenclature, amino acid numbering begins 28 amino acids after the ATG transcription start site.

Table 3. Notable *F5* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_000130.5 NP_000121.2	c.1000A>G	p.Arg334Gly (Arg306Gly)	Additional variant in factor V APC cleavage site (See Molecular Pathogenesis.)
	c.1001G>C	p.Arg334Thr (Arg306Thr)	*F5* Cambridge (See Molecular Pathogenesis.)
	c.1601G>A (1691G>A)	p.Arg534Gln (Arg506Gln)	Factor V Leiden variant

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions. Using legacy nomenclature amino acid numbering begins 28 amino acids after the ATG transcription start site.

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Contact Prof Daniele Pastori to inquire about review of *F5* variants of uncertain significance.

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