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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 a poor anticoagulant response to activated protein C (APC) and an increased risk for venous thromboembolism (VTE). Deep vein thrombosis (DVT) is the most common VTE, with the legs being the most common site. Thrombosis in unusual locations is less common. Evidence suggests that heterozygosity for the Leiden variant has at most a modest effect on risk for recurrent thrombosis after initial treatment of a first VTE. It is unlikely that factor V Leiden thrombophilia (i.e., heterozygosity or homozygosity for the Leiden variant) is a major factor contributing to pregnancy loss and other adverse pregnancy outcomes (preeclampsia, fetal growth restriction, and placental abruption). The clinical expression of factor V Leiden thrombophilia is influenced by the following:

- The number of Leiden variants (heterozygotes have a slightly increased risk for venous thrombosis; homozygotes have a much greater thrombotic risk)
- Coexisting genetic thrombophilic disorders, which have a supra-additive effect on overall thrombotic risk
- Acquired thrombophilic disorders: antiphospholipid antibody (APLA) syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, and increased levels of clotting factors
- Circumstantial risk factors including but not limited to pregnancy, central venous catheters, travel, combined oral contraceptive (COC) use and other combined contraceptives, oral hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), obesity, leg injury, and advancing age

Diagnosis/testing

Factor V Leiden thrombophilia is suspected in individuals with a history of venous thromboembolism (VTE) manifest as deep vein thrombosis (DVT) or pulmonary embolism, especially in women with a history of VTE during pregnancy or in association with use of estrogen-containing contraceptives, and in individuals with a personal or family history of recurrent thrombosis. The diagnosis of factor V Leiden thrombophilia is established in a proband by identification of a heterozygous or homozygous c.1691G>A variant (referred to as

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the factor V Leiden variant in *F5*, the gene encoding factor V) in conjunction with coagulation tests such as the APC resistance assay.

Management

Treatment of manifestations: The first acute thrombosis is treated according to standard 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 Leiden variant heterozygotes. A short course of prophylactic anticoagulation when circumstantial risk factors are present may prevent initial thrombosis in Leiden variant heterozygotes.

Surveillance: Periodic reevaluation of individuals on long-term anticoagulation to assess risks (bleeding) vs benefits.

Agents/circumstances to avoid:

- Women heterozygous for the Leiden variant and a history of VTE should avoid estrogen-containing contraception and HRT.
- Women homozygous for the Leiden variant with or without prior VTE should avoid estrogen-containing contraception and HRT.
- While asymptomatic women heterozygous for the Leiden variant should be counseled to consider alternative forms of contraception and control of menopausal symptoms, those electing use of:
    - Oral contraceptives should avoid third-generation and other progestins with a higher thrombotic risk.
    - Short-term HRT for severe menopausal symptoms should avoid oral formulations.

Evaluation of relatives at risk: Although the genetic status of apparently asymptomatic at-risk family members can be established using molecular genetic testing, the indications for testing of at-risk family members are unresolved. In the absence of evidence that early identification of the Leiden variant leads to interventions that can reduce morbidity or mortality, decisions regarding testing should be made on an individual basis. However, if the results are likely to affect management, clarification of Leiden variant status may be indicated in at-risk female relatives considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age.

Genetic counseling

Factor V Leiden thrombophilia (i.e., predisposition to the development of venous thrombosis) is inherited in an autosomal dominant manner. Homozygosity for the Leiden variant (and a much greater risk for venous thrombosis) are inherited in an autosomal recessive manner. Because of the high prevalence of the factor V Leiden allele in the general population, the genetic status of both parents and/or the reproductive partner of an affected individual needs to be evaluated before information regarding potential risks to sibs or offspring can be provided. Once the Leiden variant has been identified in a family member, prenatal testing for pregnancies at increased risk and preimplantation genetic testing are possible. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis of this genetic change, which is common in the general population and is predisposing to, but not predictive of, thrombosis.

Diagnosis

Suggestive Findings

Factor V Leiden thrombophilia **should be suspected** in individuals with the following

- A history of first and recurrent venous thromboembolism (VTE) manifest as deep vein thrombosis (DVT) or pulmonary embolism (PE), especially in women with a history of VTE during pregnancy or in association with use of estrogen-containing contraceptives
- A family history of recurrent thrombosis

Establishing the Diagnosis

The diagnosis of factor V Leiden thrombophilia **is established** in a proband by identification of a heterozygous or homozygous c.1691G>A variant (referred to as the factor V Leiden variant in *F5*, the gene encoding factor V; see Table 1) in conjunction with coagulation tests such as the APC resistance assay.

APC Resistance Assay

The original APC resistance assay involves performing an aPTT on the individual's plasma in the presence and absence of exogenous APC; the two results are expressed as a ratio (aPTT +APC/aPTT-APC). The APC-resistant phenotype is characterized by a minimal prolongation of the aPTT in response to APC and a correspondingly low ratio.

The modified "second generation" assay involves diluting the patient's plasma in factor V-deficient plasma containing a heparin neutralizer (which increases the specificity and sensitivity of detection of factor V Leiden thrombophilia to almost 100%) [Kadauke et al 2014].

Note: The second generation APC resistance assay: (1) is cost effective, highly accurate, and detects causes of APC resisance other than factor V Leiden thrombophilia and (2) is used to detect "pseudohomozygous" factor V Leiden thrombophilia (defined as heterozygosity for both the factor V Leiden variant and a second *F5* pathogenic variant that causes a factor V deficiency) (see Genotype-Phenotype Correlations) or "pseudo wild-type" factor V Leiden thrombophilia (defined as the combination of a Leiden variant with a normal APC resistance ratio) [Prüller et al 2013, Kadauke et al 2014, Van Cott et al 2016].

Molecular genetic testing is recommended in individuals receiving direct thrombin inhibitors or direct factor Xa inhibitors, which may interfere with results of the APC resistance assay [Kadauke et al 2014], and in individuals with the following laboratory findings:

- Positive APC-resistance assay values: to confirm the diagnosis and to distinguish factor V Leiden variant heterozygotes from homozygotes
- Borderline APC resistance assay values: to confirm the diagnosis
- Very low APC resistance assay values to differentiate:
  - Leiden variant heterozygotes
  - Leiden variant homozygotes
  - "Pseudohomozygotes"
- Strong lupus inhibitors and a markedly prolonged baseline aPTT

Factor V Leiden Variant Testing

The growing consensus is that factor V Leiden variant testing should not be performed on a routine basis and should only be considered when the results will affect clinical management [Chong et al 2012, Canadian Agency for Drugs and Technologies in Health 2015, Stevens et al 2016] for the following reasons:

- No randomized controlled trial has evaluated the effect of thrombophilia testing on the rate of recurrence after a first VTE.
- Analysis of a large cohort of indviduals with VTE suggested that thrombophilia testing at the time of the first VTE did not reduce the risk of recurrence [Coppens et al 2008].
- Not testing patients with VTE for inherited thrombophilia is included in the "Choosing Wisely Campaign" recommended by several professional societies [Hicks et al 2013, Hillis et al 2015].

Factor V Leiden variant testing may be considered in the following individuals when the results of testing would affect clinical management:

- 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
- Female relatives of persons with VTE or hereditary thrombophilia contemplating prophylactic anticoagulation during pregnancy

Factor V Leiden variant testing should not be performed on the following individuals:

- Adults with VTE provoked by major transient risk factors
- Adults with unprovoked VTE while on long-term anticoagulation
- 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 Leiden variant

Factor V Leiden variant testing should not be performed in the following circumstances:

- Routine testing:
  - During pregnancy
  - Prior to the use of oral contraceptives, hormone replacement therapy (HRT), or selective estrogen receptor modulators (SERMs)
  - In asymptomatic children
- Prenatal or newborn testing

Molecular genetic testing approaches can include **targeted analysis for the factor V Leiden variant** (see Table 1) or a **multigene panel** that includes the factor V Leiden variant and other genes of interest (see Differential Diagnosis). Note: The genes included and sensitivity of multigene panels vary by laboratory and are likely to change over time. For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
F5	Targeted analysis for c.1691G>A	100%

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

Clinical Characteristics

Clinical Description

Clinical Manifestations of Factor V Leiden Thrombophilia

Venous thromboembolism (VTE) is the primary clinical manifestation of factor V Leiden thrombophilia. Deep vein thrombosis (DVT) is the most common VTE. The most common site for DVT is the legs, but upper-extremity thrombosis also occurs. Superficial venous thrombosis may also occur.

Pulmonary embolism (PE). Some evidence suggests that PE is less common than DVT in individuals with the Leiden variant. Multiple studies and a meta-analysis consistently found a higher risk of DVT than PE in individuals with a Leiden variant [Dentali et al 2012, van Langevelde et al 2012]. The different effect on the risk of DVT and PE is referred to as "the factor V Leiden paradox"; the mechanism is still not well understood.

Thrombosis in unusual locations such as cerebral veins and splanchnic veins may also occur, but less commonly.

Risk for VTE in adults. The clinical expression of the Leiden variant varies [Campello et al 2016]: many individuals with the Leiden variant never develop thrombosis [Heit et al 2005] and those who do typically experience their first thrombotic event as adults; however, some have recurrent thromboembolism before age 30 years.

Heterozygosity for the 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 [Hille et al 1997, Heijmans et al 1998, Pabinger et al 2012].

While individuals homozygous for the Leiden variant have a higher risk for thrombosis than heterozygotes, the clinical course of an acute thrombotic episode is not more severe or more resistant to anticoagulation in homozygotes than in heterozygotes.

Heterozygotes. The relative risk for venous thrombosis is increased approximately three- to eightfold in Leiden variant heterozygotes. Lower relative risks are reported in heterozygotes identified from general population screening [Juul et al 2004, Heit et al 2005].

The risk for VTE is increased in Leiden variant heterozygotes:

- Three- to eightfold [Rosendaal & Reitsma 2009]
- Four- to fivefold 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].

A heterozygous Leiden variant was associated with the following:

- A sixfold increased risk for primary upper-extremity thrombosis (not related to malignancy or a venous catheter) [Martinelli et al 2004]
- A sixfold increased risk of superficial vein thrombosis not associated with varicose veins, malignancy, or autoimmune disorders [Martinelli et al 1999]
- Increased risk of venous thrombosis at unusual sites [Martinelli et al 2014]
- A fourfold increased risk of cerebral venous thrombosis [Dentali et al 2006]

A Leiden variant:

- May increase the risk of splanchic vein thrombosis;

- Was associated with an 11-fold increased risk of Budd-Chiari syndrome in case-control studies [Janssen et al 2000];
- Confers a threefold increased risk of portal vein thrombosis (meta-analysis by Dentali et al [2008]).

Homozygotes. Compared to heterozygotes, homozygotes have a higher thrombotic risk and tend to develop thrombosis at a younger age.

The risk for VTE is increased in Leiden variant homozygotes:

- Nine- to 80-fold [Rosendaal & Reitsma 2009]
- Nine- to 12-fold [Gohil et al 2009, Simone et al 2013]

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 Leiden variant was associated with CVC-related VTE in some [Neshat-Vahid et al 2016] but not all studies [Thom et al 2014].

A Leiden variant significantly increased the risk of cerebral venous thrombosis in children (odds ratio 2.74); see meta-analysis by Kenet et al [2010].

A Leiden variant was also reported to increase the risk of neonatal cerebral vein thrombosis [Kenet et al 2010, Laugesaar et al 2010].

In a prospective study, asymptomatic children – family members of symptomatic probands with the Leiden variant who were themselves heterozygous or homozygous for the Leiden variant – had no thrombotic complications during follow up that averaged five years [Tormene et al 2002]. Thus, the available data suggest that asymptomatic children with a Leiden variant are at low risk for thrombosis except in the setting of strong circumstantial risk factors (see Table 2).

Risk for VTE in pregnancy. Normal pregnancy is associated with a five- to tenfold increased risk of developing VTE.

Women heterozygous for the Leiden variant have a five to eight times 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 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 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].

In women homozygous for the Leiden variant the relative risk 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].

Women doubly heterozygous for the Leiden variant and the 20210G>A *F2* 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 doubly heterozygous women younger than age 35 years than in older women (8.2%) [Gerhardt et al 2016].

Recurrent Thrombosis

In adults heterozygous for a Leiden variant alone. Evidence suggests that a heterozygous Leiden variant has at most a modest effect on risk for recurrent thrombosis after initial treatment of a first VTE.

A modest, approximately 1.5-fold increased risk of VTE recurrence was identified in several meta-analyses [Marchiori et al 2007, Segal et al 2009]; however, in several prospective cohort studies of unselected individuals with a first VTE the recurrence risk was not increased in Leiden variant heterozygotes [Christiansen et al 2005, Lijfering et al 2010].

The reported risk may be higher in studies of 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 per 100 person-years in persons with the Leiden variant (heterozygotes and homozygotes) [Vossen et al 2005]; however, a large family study found the rate of recurrent VTE in relatives with a Leiden variant to be similar to those reported in the general population (7% after 2 years, 11% after 5 years, and 25% after 10 years) [Lijfering et al 2009].

In Leiden variant homozygotes and heterozygotes with other risk factors. Risks for recurrent VTE in Leiden variant homozygotes and double heterozygotes for the Leiden variant and the *F2* 20210G>A variant vary widely between studies.

Similar rates of VTE recurrence for both 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 Leiden variant conferred a 2.6-fold increased risk of recurrent VTE [Segal et al 2009].

Not all studies found a high risk for recurrence in Leiden variant homozygotes and double heterozygotes even when the analysis was restricted to those with a first unprovoked VTE [Lijfering et al 2010].

The risk of VTE is unknown in individuals with the rare combination of Leiden variant and prothrombin 20210G>A variants (i.e., homozygous Leiden variant / heterozygous 20210G>A, homozygous Leiden variant / homozygous 20210G>A). In a retrospective study, the risk of recurrence was 13% at one year and 22% at five years, similar to that expected in individuals with an unprovoked VTE without thrombophilia. However, the recurrence risk in this group was significantly higher than expected after a first VTE provoked by a transient risk factor (6% at 1 year and 26% at 5 years) [Lim et al 2016].

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

In pregnant women. During pregnancy women with a prior history of VTE have an increased recurrence risk, ranging from 0% to 15% in published studies. The risk is higher in women with a prior unprovoked episode or an estrogen-related VTE, and in those with coexisting genetic or acquired risk factors (Table 2). No studies have specifically evaluated the risk for recurrent VTE in pregnant women who have the Leiden variant.

In subgroup analysis of a prospective study of the safety of withholding anticoagulation during pregnancy in 125 women with a history of VTE, Brill-Edwards et al [2000] found the following:

- Women with a prior unprovoked VTE and thrombophilia (especially factor V Leiden thrombophilia) had the highest recurrence rate during pregnancy (20% of pregnancies).
- A Leiden variant was associated with an increased risk of antepartum recurrence (odds ratio 10).
- Women with either thrombophilia or a prior unprovoked VTE (but not both) had recurrence rates of 13% and 7.7%, respectively.

Obstetric Complications

It is unlikely that a factor V Leiden thrombophilia (i.e., heterozygosity or homozygosity for the Leiden variant) is a major factor contributing to pregnancy loss and other adverse pregnancy outcomes (preeclampsia, fetal growth restriction, and placental abruption). At most, factor V Leiden thrombophilia is one of multiple largely unknown genetic and environmental predisposing factors contributing to these complications.

Pregnancy loss. Available data suggest that 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 Leiden variant (4.2%) compared to those without the variant (3.2%) (odds ratio 1.52) [Rodger et al 2010]. A meta-analysis found that heterozygosity for the 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]. Although maternal homozygosity for the Leiden variant was associated with stillbirth, presence of the Leiden variant was not associated with stillbirths in the subset of stillbirths resulting from placental insufficiency [Silver et al 2016].

Preeclampsia, fetal growth restriction, and placental abruption may also involve impaired placental perfusion; however, their association with inherited thrombophilia is more controversial [Greer et al 2014]. For example:

- 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 Leiden variant increased the risk of severe preeclampsia (odds ratio 1.6), severe fetal growth restriction (odds ratio 1.5), and symptomatic placental abruption (odds ratio 1.7) [Lykke et al 2012].

Such conflicting results may reflect the varying diagnostic and selection criteria, different ethnic groups, and small number of cases included. However, given that preeclampsia and placental abruption are heterogeneous disorders, it is unlikely that a single thrombophilic variant (such as the Leiden variant) plays a major causal role.

Arterial Thrombosis NOT Convincingly Associated with the Leiden Variant

The available evidence indicates that presence of a Leiden variant is not a major risk factor for arterial thrombosis of any sort, including myocardial infarction and stroke in fetuses, children, and adults, the majority of which occur in the presence of established cardiovascular risk factors (including hypertension, hyperlipidemia, diabetes mellitus, and smoking). For more information click here (pdf).

Clinical Expression of Factor V Leiden Thrombophilia

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

A positive family history. Individuals with a 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 Leiden variant with a negative family history [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 Leiden variant, suggesting the presence of unknown genetic risk factors.

Coexisting genetic abnormalities. The combination of Leiden variant heterozygosity and most other thrombophilic disorders (including protein C deficiency, protein S deficiency, antithrombin deficiency, and the *F2* thrombophilia variant [c.*97G>A, commonly known as 20210G>A]) has a supra-additive effect on overall thrombotic risk [Ridker et al 1997a] (see Differential Diagnosis). For example:

- Individuals heterozygous for either the Leiden variant or the *F2* thrombophilia variant had a four- to fivefold increased thrombotic risk, compared to double heterozygotes, who had a 20-fold increased thrombotic risk [Emmerich et al 2001].
- The *F2* thrombophilia variant was four- to fivefold more common in Leiden variant homozygotes with VTE than in controls without a Leiden variant and with no thrombotic history [Ehrenforth et al 2004].

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

- Leiden variant heterozygotes with factor VIII levels greater than150% of normal had a two- to threefold increased incidence of VTE than heterozygotes for a Leiden variant alone [Lensen et al 2001]. The reason for the association of high FVIII levels with VTE is unknown; factor VIII, an acute phase reactant, is high in the presence of inflammation and estrogen. Although suspected, a genetic basis has not been identified.
- A Leiden variant was reported to contribute to increased risk for thrombotic complications in persons with polycythemia vera and essential thrombocytosis [Trifa et al 2014].

Circumstantial Risk Factors for VTE

Circumstantial risk factors for VTE in Leiden variant heterozygotes or homozygotes are summarized in Table 2. Other risk factors that to date have not been studied in Leiden variant heterozygotes are the newer forms of combined hormonal contraception, transdermal and vaginal ring contraception, for which the risk of VTE is at least as great as the risk associated with combined oral contraceptives (COCs) [Dore et al 2010, Lidegaard et al 2012].

Table 2. Circumstantial Risk Factors: Increased Risk for Thrombophilia in Persons with the Factor V Leiden Variant (heterozygosity and homozygosity not specified)

Circumstance	Relative Risk for VTE	Comment	Citation
Malignancy [1]	Unknown: probably modest	In persons w/cancer, no indication for: • Testing for the Leiden variant; • Prophylaxis	Farge et al [2013], Kovac et al [2015], Pabinger et al [2015]
Central venous catheter use	2x-3x ↑ relative risk		Van Rooden et al [2004]
	5x ↑ relative risk in those w/cancer		Dentali et al [2008]
Travel	2x ↑ relative risk	Risk ↑: • W/travel duration; • In those w/thrombophilia	Chandra et al [2009]
	8x ↑ relative risk when traveling ≥4 uninterrupted hrs		Cannegieter et al [2006]
COCs [1]	Much ↑ during 1st yr of use than subsequent yrs		Martinelli et al [2016]
	↑ in COC w/desogestrel or drospirenone than COC w/ levonorgestrel		Bergendal et al [2014]

Table 2. continued from previous page.

Circumstance	Relative Risk for VTE	Comment	Citation
Unopposed progesterone contraception	Injectable medroxyprogesterone assoc w/16x ↑ risk		Bergendal et al [2014]
	Low-dose oral form has lowest thrombotic risk of hormonal contraception		Tepper et al [2016]
Oral HRT [1]	7x-25x ↑ relative risk	Risk ↑ w/↑ estrogen dose	Straczek et al [2005], Douketis et al [2011]
Transdermal HRT [1]	Lower relative risk than oral HRT	Preliminary data suggest may not ↑ thrombotic risk	Straczek et al [2005], Canonico et al [2010], ACOG [2013a]
SERMS [1]	Not well defined	Risk likely >2x ↑ over risk assoc w/ SERMS alone	Barrett-Connor et al [2006], Nelson [2013]
Obesity (BMI >30 kg/m^2)	5x-12x ↑ relative risk	Risk ↑ w/BMI	Severinsen et al [2010], Ribeiro et al [2016]
Overweight (BMI >25 - <30 kg/m^2)	4x-10x ↑ relative risk	Risk ↑ w/BMI	Severinsen et al [2010], Ribeiro et al [2016]
Organ transplantation	Not well defined		Ghisdal et al [2010], Pereboom et al [2011], Parajuli et al [2016]
Minor leg injury	23x-50x ↑ risk		van Stralen et al [2008], van Adrichem et al [2014]
Surgery	Unclear	Any excess risk conferred by Leiden variant heterozygosity likely small, compared to risk assoc w/ surgery	Joseph et al [2005], Charen et al [2015], van Adrichem et al [2015]
Age	After age 45 yrs lifetime risk = 17% (vs 8% in general population)	↑ age is an independent risk factor for VTE.	Bell et al [2016]
		Risk ↑ w/age, BMI, smoking, +FH	Juul et al [2004]
		Highest risk in persons age >70 yrs w/+FH	Karasu et al [2016]

+ FH = positive family history; COCs = combined oral contraceptives; HRT = hormone replacement therapy; SERMS = selective estrogen receptor modulators

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

Combined oral contraceptive (COC) use substantially increases the relative risk for VTE in women heterozygous for the Leiden variant.

The supra-additive effect of both a Leiden variant and use of COC was confirmed in multiple studies in which odds ratios 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 Leiden variant or doubly heterozygous for the Leiden

variant and the prothrombin 20210G>A variant the odds ratios for VTE ranged from 17 to 110 [Mohllajee et al 2006, van Vlijmen et al 2016].

Despite the marked increase in relative risk for VTE, the absolute incidence of VTE may be low because of the low baseline risk for VTE in young women.The incidence of VTE in COC users with either a Leiden variant or the prothrombin 20210G>A variant ranged 0.49 to 2.0 VTE/100 pill-years compared to 0.19 to 0/100 pill-years in COC users without these variants. The absolute VTE risk is substantially higher in COC users doubly heterozygous for the Leiden variant and the prothrombin 20210G>A variant or homozygous for either variant (0.86 vs 0.19/100 pill years) [van Vlijmen et al 2011, van Vlijmen et al 2016].

The thrombotic risk of COC 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 non-users [Renoux et al 2010, Eisenberger & Westhoff 2014]. Data comparing the VTE risk of combined estrogen/progestin HRT and unopposed estrogen are inconclusive [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 HRT is threefold increased in postmenopausal women with a factor V Leiden or prothrombin 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 than oral estrogen in women with inherited thrombophilic variants including the Leiden variant [Canonico et al 2010]. Women with a Leiden variant using transdermal estrogen had a risk similar to that of non-users with the variant. Among women with a Leiden variant the use of oral estrogen was associated with a fourfold increased risk for VTE over transdermal estrogen [Straczek et al 2005]. However, no prospective randomized trials have confirmed the safety of transdermal HRT in women with inherited thrombophilia.

Selective estrogen receptor modulators (SERMS). The risk for VTE in women with the Leiden variant who use SERMS is not well defined. Limited data suggest that SERMs such as tamoxifen and raloxifene are associated with a twofold increased risk for VTE, similar to the risk for HRT [Barrett-Connor et al 2006]. The thrombotic risk conferred by tamoxifen was higher than raloxifene in trials for primary prevention of breast cancer [Nelson 2013]. In light of the interaction of factor V Leiden with HRT, the risk is likely higher than that associated with SERMS alone.

Genotype-Phenotype Correlations

Other *F5* variants may affect clinical outcome in an individual heterozygous for the Leiden variant.

- An *F5* null variant *in trans* with the Leiden variant results in "pseudo-homozygous" APC resistance, which is indistinguishable from homozygous Leiden thrombophilia and may result in a more severe hypercoagulable state [Brugge et al 2005, Duckers et al 2011]. Coinheritance of an *F5* null variant is estimated in approximately 1:1,000 individuals heterozygous for a Leiden variant [Simioni et al 2005].
- The *F5* haplotype HR2, defined by the R2 variant (p.His1327Arg), may confer mild APC resistance. The HR2 haplotype *in trans* with the Leiden variant may confer greater thrombotic risk [Faioni et al 1999, de Visser et al 2000, Mingozzi et al 2003], but was not associated with a significantly higher risk for early or late pregnancy loss than presence of the Leiden variant alone [Zammiti et al 2006].

Penetrance

See Clinical Description.

Prevalence

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

Heterozygosity for the Leiden variant occurs in 3%-8% of the general US and European populations. The highest heterozygosity rate is found in Europe; the Leiden variant is extremely rare in Asian, African, and indigenous Australian populations.

- Within Europe, prevalence varies from 10%-15% in southern Sweden and Greece to 2%-3% in Italy and Spain.
- In the US, prevalence reflects the world distribution of the Leiden variant [Ridker et al 1997b], 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;
  - 1.25% of Native Americans.

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

The Leiden variant is present in:

- Approximately 15%-20% of individuals with a first DVT;
- Up to 50% of individuals with recurrent venous thromboembolism or an estrogen-related thrombosis.

Differential Diagnosis

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

Prothrombin-related thrombophilia is characterized by venous thromboembolism (VTE) manifest most commonly in adults as deep-vein thrombosis (DVT) in the legs or pulmonary embolism. The clinical expression of prothrombin-related thrombophilia is variable; many individuals heterozygous or homozygous for the *F2* thrombophilia variant (c.*97G>A, commonly known as 20210G>A) 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 this 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-related thrombophilia include: the number of c.*97G>A alleles; presence of coexisting genetic abnormalities including factor V Leiden; 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 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 Thrombophilia: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To assess the risk for thrombosis in an individual found to have the factor V Leiden variant, the following evaluations are recommended:

- For individuals heterozygous for the Leiden variant: the following testing for other inherited or acquired thrombophilic disorders is recommended by experts (but is not a hard-and-fast rule) given that double heterozygosity for the Leiden variant and *F2* thrombophilia variant 20210G>A occurs more commonly than protein C, S, and AT deficiencies (which are rare and unlikely to be found except in those with "high risk features" such as a strong family history) and antiphospholipid antibody (APLA) syndrome can occur at any age in anyone:
  - DNA testing *F2* thrombophilia 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 young age, or those with strong family history of VTE at 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 since 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 standard guidelines [Kearon et al 2012, Kearon et al 2016]. For initial treatment of VTE, current guidelines suggest a new oral anticoagulant (dabigatran, edoxaban, rivaroxaban, or apixaban) over warfarin because of a lower bleeding risk and greater convenience [Kearon et al 2016]. Of note, low molecular-weight heparin (LMWH) is given before dabigatran and edoxaban but not before rivaroxaban or apixaban.

For patients not treated with one of the new oral anticoagulants, administration of warfarin is started concurrently with LMWH or fondaparinux (except during pregnancy) and monitored with the international normalized ratio (INR). A target international normalized ratio (INR) of 2.5 (therapeutic range 2.0-3.0) provides effective anticoagulation, even in individuals homozygous for the 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 on two consecutive measurements over two days.

LMWH and warfarin are both safe in breastfeeding women (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 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 and prevention of thrombosis [Kearon et al 2012, Kearon et al 2016] as well as other clinical guidelines and expert opinion [Baglin et al 2010, Bauer 2010, National Clinical Guideline Centre 2012].
- Anticoagulation for at least three months is recommended for persons with DVT and/or PE associated with a transient (reversible) risk factor [Kearon et al 2012, Kearon et al 2016].

Long-term oral anticoagulation is recommended for individuals with a first or recurrent unprovoked (i.e., idiopathic) proximal DVT of the leg or pulmonary embolism (PE) who have a low or moderate bleeding risk [Kearon et al 2016]. The decision should be based on an assessment of potential risks and benefits regardless of Leiden variant status [EGAPP Working Group 2011].

Long-term anticoagulation is occasionally considered in individuals homozygous for the Leiden variant or with multiple thrombophilic disorders, particularly in the presence of additional risk factors (e.g., obesity) as the potential benefits from long-term anticoagulation may outweigh the bleeding risks [De Stefano & Rossi 2013].

Treatment of VTE in Children

The treatment recommendations for adults (which concluded that presence of a Leiden variant should not influence the intensity or duration of anticoagulation) are generally followed in children as well [Chalmers et al 2011, Heleen van Ommen & Middeldorp 2011, Monagle et al 2012].

Children with a first VTE should receive initial treatment with either unfractionated heparin (UFH) or LMWH for at least five days. LMWH is favored over warfarin for continued therapy, especially in very young children and those with complex medical problems. Recommendations on the duration of antithrombotic therapy are based on the nature of the thrombotic event (spontaneous or provoked) [Chalmers et al 2011, 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 6-12 months after a first unprovoked VTE.

Expert opinion emphasizes the importance of a careful risk/benefit assessment in each individual [Heleen van Ommen & Middeldorp 2011].

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 Leiden variant because the 1%-3%/year risk for major bleeding from warfarin is greater than the estimated less than 1%/year risk for thrombosis.

Because the initial thrombosis in 50% of Leiden variant heterozygotes occurs in association with other circumstantial risk factors (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 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 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 [Guyatt et al 2012].

Surveillance

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

Agents/Circumstances to Avoid

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

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

Asymptomatic women heterozygous for the 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 hormone replacement therapy for severe menopausal symptoms should use a low-dose transdermal preparation, which has a lower thrombotic risk than oral formulations [Canonico et al 2007, Canonico et al 2010, Sweetland et al 2012].

Evaluation of Relatives at Risk

Although the genetic status of apparently asymptomatic at-risk family members can be established using molecular genetic testing for the Leiden variant, the indications for family testing are unresolved.

- In the absence of evidence that early identification of the Leiden variant leads to interventions that can reduce morbidity or mortality, decisions regarding testing should be made on an individual basis.
- Clarification of Leiden variant status may be considered in at-risk female relatives considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age if the results are likely to affect management.

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

Pregnancy Management

Prevention of Thrombosis During Pregnancy

No consensus exists on the optimal management of factor V Leiden thrombophilia during pregnancy; guidelines are derived from studies in non-pregnant individuals [Baglin et al 2010, Bates et al 2012]. All women with inherited thrombophilia should undergo individualized risk assessment in order to base decisions about anticoagulation on the number and type of thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

For pregnant women with a prior single episode of VTE provoked by a transient risk factor not related either to pregnancy or to the use of estrogen, clinical vigilance during pregnancy is suggested [Bates et al 2012].

LMWH is the preferred antithrombotic agent for prophylaxis and treatment during pregnancy [Bates et al 2012, ACOG 2013b].

The oral direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban are contraindicted 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].

Prophylactic anticoagulation during pregnancy **is recommended** for all women:

- With a history of unprovoked VTE including those heterozygous for the Leiden variant. LMWH should be given during pregnancy, followed by a six-week course of anticoagulation post partum [Bates et al 2012, ACOG 2013b];
- Heterozygous for the Leiden variant with a prior pregnancy or estrogen-related thrombosis who are also at increased risk for recurrence [Pabinger et al 2005, Bates et al 2012, ACOG 2013b].

Prophylactic anticoagulation during pregnancy **is suggested** for asymptomatic women who:

- Are homozygous for the Leiden variant;
- Are double heterozygotes for the Leiden variant and the prothrombin 20210G>A variant;
- Have other combined thrombophilic defects;
- Also have a positive family history for VTE.

In the absence of a positive family history for VTE, antepartum clinical vigilance and postpartum prophylaxis with LMWH is suggested as the greatest thrombotic risk is in the initial postpartum period [Bates et al 2012, ACOG 2013b].

Prophylactic anticoagulation during pregnancy **is not routinely recommended** in asymptomatic women heterozygous for the Leiden variant with no history of thrombosis. All women with a Leiden variant should be warned about potential thrombotic complications and counseled regarding the risks and benefits of anticoagulation during pregnancy [Bates et al 2012, ACOG 2013b].

Prevention of Thrombosis During the Postpartum Period

A six-week course of postpartum prophylaxis with LMWH is recommended for [Bates et al 2012, ACOG 2013b]:

- All women heterozygous for the Leiden variant with a prior history of VTE;
- Women heterozygous for the Leiden variant and a positive family history of VTE;
- All asymptomatic homozygous women.

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 [Baglin et al 2010, 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.

Risk to Family Members

Parents of a proband

- Most individuals with factor V Leiden thrombophilia are heterozygous for the Leiden variant, which they have inherited from a parent who is also heterozygous for the Leiden variant.
- More rarely, individuals with factor V Leiden thrombophilia are homozygous for the Leiden variant, having inherited one Leiden variant from each parent.
- Occasionally – because of the relatively high frequency of the Leiden variant in the general population – one parent is homozygous for the Leiden variant or both parents are heterozygous for the 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 for the Leiden variant has been performed on the parents of the proband.

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 Leiden variant, each sib of the proband is at a 50% risk of being heterozygous for the Leiden variant.
- If one parent is homozygous for the Leiden variant, each sib of the proband has a 100% chance of being heterozygous for the Leiden variant.
- If both parents are heterozygous for the Leiden variant, each sib of the proband has a 25% chance of being homozygous for the Leiden variant, a 50% chance of being heterozygous for the Leiden variant, and a 25% chance of inheriting both normal factor V alleles.

Offspring of a proband

- **Heterozygous proband**
  - Each child has a 50% chance of inheriting the Leiden variant.
  - If the proband's reproductive partner is also heterozygous for the Leiden variant, each of their children has a 25% chance of inheriting two Leiden variants, a 50% chance of inheriting one Leiden variant, and a 25% chance of inheriting neither Leiden variant.

- **Homozygous proband**
  - A proband homozygous for the Leiden variant will transmit the Leiden variant to all offspring.
  - If the proband's reproductive partner is heterozygous for the Leiden variant, each of their children has a 50% chance of inheriting two Leiden variants and a 50% chance of inheriting one Leiden variant.

Other family members of a proband. 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 factor V Leiden 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 who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the Leiden variant has been identified in a family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for factor V Leiden thrombophilia are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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

Gene structure. *F5* is encoded by 25 exons spanning approximately 75 kb. Using legacy nomenclature amino acid numbering begins 28 amino acids after the ATG transcription start site. The factor V Leiden variant is referred to as p.Arg506Gln using legacy nomenclature, and p.Arg534Gln using standard HGVS nomenclature.

Factor V Leiden variant. The c.1691G>A (p.Arg534Gln) variant occurs in one of three activated protein C (APC) cleavage sites in factor V, which are required for factor V inactivation by APC. This variant is frequent in the population (see Prevalence) leading to speculation of a survival advantage associated with the heterozygous state (see supplemental information: history; pdf).

Other variants in *F5* at APC cleavage sites, p.Arg334Thr (commonly known as p.Arg306Thr and factor V Cambridge) and p.Arg334Gly (commonly known as p.Arg306Gly), are not major risk factors for thrombosis, but may contribute when combined with other genetic or acquired risk factor (see supplemental information: history).

For more information on the variants p.Arg334Thr and p.Arg334Gly, see supplemental information: variants (pdf).

Table 3. Selected *F5* Variants

Variant Classification	DNA Nucleotide Change (Standard Naming Convention [1])	Predicted Protein Change (Standard Naming Convention [1])	Reference Sequence
Variants in factor V APC sites	c.1001G>C	p.Arg334Thr [2] (p.Arg306Thr)	NM_000130.5 NP_000121.2
	c.1000A>G	p.Arg334Gly (p.Arg306Gly)	
Factor V Leiden variant	c.1691G>A (c.1601G>A)	p.Arg534Gln (p.Arg506Gln)	
Factor V R2 variant [2]	c.3980A>G	p.His1327Arg [3] (p.His1299Arg)	

Variants listed in the table have been provided by the author. *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 designations that do not conform to current naming conventions are given because they are widely used in the literature. Names in parentheses follow standard naming conventions (varnomen.hgvs.org) and take into account the entire factor V precursor protein synthesized from F5, beginning with the first nucleotide of the initiating methionin (AUG residue). Reference sequences correspond to the standard naming conventions.
2. Factor V Cambridge
3. R2 variant; see Genotype-Phenotype Correlations.

Normal gene product. *F5* encodes coagulation factor V (FV), a key regulator in the coagulation cascade. Once activated, FV functions as a cofactor that accelerates clot formation. FV is inactivated when cleaved by activated Protein C (APC) at two APC sites in FV.

Abnormal gene product. Protein with the factor V Leiden variant (p.Arg534Gln) is inactivated at an approximately tenfold slower rate than normal due to this amino acid change resulting in less efficient APC cleavage. FV with the Leiden variant persists longer in the circulation, resulting in increased thrombin generation and a mild hypercoagulable state, reflected by elevated levels of prothrombin fragment F1+2 and other activated coagulation markers [Martinelli et al 1996, Zöller et al 1996, Dahlbäck 2008].

Chapter Notes

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