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Factor V Leiden Thrombophilia

[*Hereditary Resistance to Activated Protein C, Factor V Leiden Mutation. Includes: Hereditary Resistance to Activated Protein C, Factor V Leiden Mutation*]

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Summary

Disease characteristics. Factor V Leiden thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk of venous thromboembolism (VTE). Deep venous 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 a heterozygous factor V Leiden mutation has at most a modest effect on the risk of recurrence after initial treatment of a first VTE. Heterozygosity for factor V Leiden is associated with a two- to threefold increase in relative risk of pregnancy loss, and possibly other pregnancy complications such as preeclampsia, fetal growth retardation, and placental abruption. The clinical expression of factor V Leiden thrombophilia is influenced by: (1) the number of factor V Leiden alleles (heterozygotes have a slightly increased risk for venous thrombosis; homozygotes have a much greater thrombotic risk); (2) coexisting genetic thrombophilic disorders, which have a supra-additive effect on overall thrombotic risk; (3) acquired thrombophilic disorders: hyperhomocysteinemia, high factor VIII levels, malignancy; (4) circumstantial risk factors: travel, central venous catheters, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, advancing age, and surgery.

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 oral contraceptive use, and in individuals with a personal or family history of recurrent thrombosis.The diagnosis of factor V Leiden thrombophilia is made either using a coagulation screening test or by DNA analysis of the *F5* gene, which encodes the factor V protein. The term "factor V Leiden" refers to the specific G-to-A substitution at nucleotide 1691 in the gene for factor V that predicts a single amino acid replacement (R506Q) at one of three APC cleavage sites in the factor Va molecule.

Management. *Treatment of manifestations:* The first acute thrombosis is treated according to standard guidelines [course of intravenous unfractionated heparin or low molecular-weight heparin and concurrent oral administration of warfarin (except during pregnancy)]. The duration of oral anticoagulation therapy is debated. Long-term oral anticoagulation is considered in those with recurrent VTE, multiple thrombophilic disorders, or coexistent circumstantial risk factors and in factor V Leiden homozygotes. *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 heterozygotes. A short course of prophylactic anticoagulation when circumstantial risk factors are present may prevent initial thrombosis in factor V Leiden heterozygotes. *Prevention of secondary complications:* Enoxaparin prophylaxis in women heterozygous for factor V Leiden who have a history of recurrent pregnancy loss seems to increase the likelihood of a favorable pregnancy outcome. *Surveillance:* periodic reevaluation of individuals on long-term anticoagulation to assess risks (bleeding) vs. benefits. *Agents/circumstances to avoid:* oral contraceptives and HRT (homozygous women with or without prior VTE; heterozygous women and a history of VTE); asymptomatic heterozygous women using oral contraceptives should avoid third-generation formulations. *Testing of relatives at risk:* Molecular genetic testing can establish the genetic status of asymptomatic at-risk family members; however, the indications for family testing are unresolved. Clarification of factor V Leiden allele status may be useful in at-risk relatives considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age. Asymptomatic factor V Leiden heterozygotes and homozygotes should be aware of the signs and symptoms of VTE that require immediate medical attention and the potential need for prophylactic anticoagulation in high-risk circumstances.

Genetic counseling. Heterozygosity for the factor V Leiden allele and the associated risk for venous thrombosis are inherited in an autosomal dominant manner. Homozygosity for the factor V Leiden allele 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. While technically possible, prenatal testing does not seem relevant for this complex disorder, in which the genetic change is common in the general population and is predisposing to, but not predictive of, thrombosis.

Diagnosis

Clinical Diagnosis

No clinical features are specific for factor V Leiden thrombophilia. The diagnosis of factor V Leiden thrombophilia requires either the APC resistance assay as a coagulation screening test or DNA analysis of *F5*, the gene encoding factor V, to identify the Leiden mutation, a specific G-to-A substitution at nucleotide 1691 that predicts a single amino acid replacement (R506Q).

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 oral contraceptive use, and in individuals with a personal or family history of recurrent thrombosis.

The growing consensus is that **factor V Leiden testing should be performed** in the following circumstances [ACMG Consensus Statement 2001, CAP Consensus Conference Statement 2002, Manco-Johnson et al 2002, Bates et al 2004]:

- A first VTE before age 50 years
- A first unprovoked VTE at any age
- A history of recurrent VTE
- Venous thrombosis at unusual sites (e.g., cerebral, mesenteric, portal, and hepatic veins)

- VTE during pregnancy or the puerperium
- VTE associated with use of oral contraceptives or hormone replacement therapy (HRT)
- A first VTE in an individual with a first-degree family member with VTE before age 50 years
- Women with unexplained fetal loss after ten weeks' gestation

Factor V Leiden testing may be considered in the following individuals:

- Selected women with unexplained severe preeclampsia, placental abruption, or a fetus with intrauterine growth retardation
- A first VTE related to the use of tamoxifen or other selective estrogen receptor modulators (SERMs)
- Female smokers younger than age 50 years with a myocardial infarction or stroke
- Individuals older than age 50 years with a first provoked VTE in the absence of malignancy or an intravascular device
- Asymptomatic adult family members of probands with a known factor V Leiden mutation, especially those with a strong family history of VTE at a young age
- Asymptomatic female family members of probands with known factor V Leiden thrombophilia who are pregnant or are considering oral contraceptive use or pregnancy
- Women with recurrent unexplained first-trimester pregnancy losses with or without second- or third-trimester pregnancy losses
- Children with arterial thrombosis

Factor V Leiden testing is not recommended for the following:

- General population screening
- Routine initial test during pregnancy
- Routine initial test prior to the use of oral contraceptives, hormone replacement therapy (HRT), or SERM
- Prenatal or newborn testing
- Routine testing in asymptomatic children
- Routine initial test in individuals with arterial thrombosis. However, testing may be considered in individuals younger than age 50 years with unexplained arterial thrombosis (such as women with stroke associated with oral contraceptives)

Testing

Factor V Leiden is inactivated at a rate approximately ten times slower than normal factor V and 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, Zoller et al 1996].

The APC resistance assay is a coagulation screening test based on the aPTT; two versions are available:

- **The "original" APC resistance assay** involves performing an aPTT on the individual's plasma in the presence and absence of a standardized amount of exogenous APC; the two results are expressed as a ratio (aPTT + APC / aPTT – APC). This assay is based on the principle that when added to normal plasma, APC inactivates factors Va and VIIIa, which slows coagulation and prolongs the aPTT. The APC-resistant phenotype is characterized by a minimal prolongation of the aPTT in response to APC and a corresponding low ratio. The original assay has a sensitivity and specificity of 85%-90% for factor V Leiden. It is unreliable in individuals with a baseline prolonged aPTT resulting from warfarin or heparin anticoagulation, other coagulation defects, or a lupus inhibitor, and it may be altered by the hemostatic changes that occur during pregnancy or acute thrombosis.
- **The modified ("second-generation") APC resistance assay** overcomes these limitations, is now more widely available, and has a sensitivity and specificity for factor V Leiden approaching 100% [Kapiotis et al 1996]. In this assay, the individual's plasma is first diluted (1:4) in factor V-deficient plasma that contains polybrene, a heparin neutralizer. The addition of the factor V-deficient plasma corrects for deficiencies of all other coagulation proteins, neutralizes therapeutic concentrations of heparin, and also eliminates the effect of some lupus inhibitors. The assay can be used for individuals receiving warfarin or heparin anticoagulation and for many individuals with lupus inhibitors, as well as in the setting of acute thrombosis, pregnancy, or inflammation [Svensson et al 1997].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *F5*, the gene encoding factor V, is the only gene associated with factor V Leiden thrombophilia.

Clinical uses

- Diagnostic testing
- Predictive testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Note: It is the policy of *GeneReviews* to include clinical uses of testing available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Clinical testing

- **Targeted mutation analysis.** Targeted mutation analysis for factor V Leiden is performed by a variety of comparable methods [ACMG Consensus Statement 2001].

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Genetic Mechanism	Mutation Detection Rate	Test Availability
Targeted mutation analysis	G-to-A substitution at nucleotide 1691 in the *F5* gene	100%	Clinical Testing

Interpretation of test results. Molecular genetic tests are reliable in individuals on warfarin or heparin anticoagulation, and independent of thrombotic episodes.

Test results on DNA extracted from peripheral blood leukocytes should be interpreted with caution in the setting of liver transplantation or hematopoietic stem cell transplantation [Camire et al 1998, Loew et al 2005]. Diagnosis of factor V Leiden in hematopoietic stem cell transplant recipients requires molecular analysis of non-hematopoietic tissue [Crookston et al 1998].

Note: Hematopoietic stem cell transplantation from a donor with factor V Leiden thrombophilia should not increase the thrombotic risk in the recipient.

Resistance to APC resulting from factor V Leiden may be acquired or corrected by liver transplantation [Leroy-Matheron et al 2003, Willems et al 2003, Loew et al 2005]. "Acquired factor V Leiden" is suggested in a liver transplant recipient who has the combination of an abnormal APC resistance screening assay and a normal factor V genotype in DNA extracted from peripheral blood leukocytes. Diagnosis of factor V Leiden in liver transplant recipients requires molecular genetic testing of donor tissue.

Testing Strategy

- When appropriate clinical care requires testing for the factor V Leiden allele, either direct DNA-based genotyping or a factor V Leiden-specific functional assay is recommended. Although the modified APC resistance assay is highly sensitive and specific for the factor V Leiden mutation, DNA-based testing for the factor V Leiden allele is recommended in individuals with the following:
  - A low value based on the original APC resistance assay, in order to distinguish between factor V Leiden and other causes of APC resistance
  - Strong lupus inhibitors and a markedly prolonged baseline aPTT
  - Very low second-generation APC resistance assay values, in order to differentiate heterozygotes, homozygotes, and "pseudohomozygotes" who are heterozygous for both factor V Leiden and a second mutation causing a factor V deficiency
  - Borderline APC resistance assay values
- Individuals who test positive by a functional assay should then be further studied with the DNA test for confirmation and to distinguish heterozygotes from homozygotes.
- When relatives of individuals known to have factor V Leiden thrombophilia are tested, the DNA method is recommended [ACMG Consensus Statement 2001].

Genetically Related (Allelic) Disorders

Two different mutations (designated as Factor V Cambridge, Factor V Hong Kong) at the arginine 306 activated protein C cleavage site in *F5* have been reported rarely in persons with thrombosis (see Pathologic allelic variants).

Clinical Description

Natural History

The clinical expression of factor V Leiden thrombophilia is variable. Many individuals with the factor V Leiden allele never develop thrombosis [Heit et al 2005]. Although most individuals with factor V thrombophilia do not experience their first thrombotic event until adulthood, some have recurrent thromboembolism before age 30 years.

Two studies found that heterozygosity for the factor V Leiden allele was not associated with an increase in mortality or reduction in normal life expectancy [Hille et al 1997, Heijmans et al 1998].

Venous Thromboembolism (VTE)—The primary clinical manifestation of factor V Leiden thrombophilia is venous thromboembolism (VTE) (see Clinical expression of factor V Leiden thrombophilia).

Deep venous 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. Factor V Leiden is associated with a sixfold increased risk of superficial vein thrombosis [Martinelli, Cattaneo et al 1999]. A significant fraction of individuals with venous leg ulcerations have APC resistance and the factor V Leiden allele [Larsson et al 1996, Munkvad & Jorgensen 1996, Zuber et al 1996]. Superficial vein thrombosis was the most common thrombotic complication reported in factor V Leiden homozygotes [Ehrenforth et al 2004].

Thrombosis in unusual locations may also occur, but less commonly.

- Factor V Leiden is associated with a three- to fourfold increased risk of cerebral vein thrombosis [Dentali et al 2006].
- Factor V Leiden thrombophilia has also been reported in central retinal vein occlusion, ovarian thrombosis, and hepatic vein thrombosis.
- An increased frequency of factor V Leiden has also been reported in children with cerebral and renal vein thrombosis [Heller et al 2003, Kuhle et al 2004].

Risk for VTE in adults. Multiple studies report that pulmonary embolism is less common than DVT in individuals with the factor V Leiden allele [Manten et al 1996, Vandenbroucke et al 1998]. Analysis of pooled data from these studies suggests that the prevalence of the factor V Leiden allele in individuals with isolated pulmonary embolism is approximately one half that in individuals with DVT [de Moerloose et al 2000]. Another study found that factor V Leiden heterozygotes had a nearly eightfold lower incidence of DVT involving the iliofemoral veins and significantly fewer extensive thromboses compared to individuals without the mutation [Karemaker et al 2000, de Moerloose et al 2000]. This observation could account for the lower risk of pulmonary embolism, as the iliofemoral veins are the most common source of pulmonary emboli [Bjorgell et al 2000]. Isolated DVT was also the most common major thrombotic event in a large cohort of factor V Leiden homozygotes [Ehrenforth et al 2004]. However, in a population-based cohort study, a factor V Leiden allele was not associated with a higher risk for DVT than for pulmonary embolism [Juul et al 2004].

A factor V Leiden allele was reported in 9%-12% of individuals with upper-extremity DVT, suggesting that the mutation confers a two- to sixfold increased risk of thrombosis in this location [Martinelli et al 2004, Blom et al 2005b].

Risk for VTE in children. Although venous thrombosis is far less common in children than in adults, the prevalence of thrombophilic disorders in children with thrombosis is higher than in a corresponding adult population. A combination of risk factors appears to be required to provoke thrombosis in children [Rosendaal 1997, Nowak-Gottl et al 2001, Revel-Vilk & Kenet 2006]. An increased prevalence of a factor V Leiden allele was found in neonates and children with venous thromboembolism in most, but not all studies. The variation in the reported prevalences of factor V Leiden likely reflects differences in study design and clinical characteristics of children studied [Revel-Vilk & Kenet 2006].

- APC resistance and a factor V Leiden allele were found in 21%-52% of children with venous thromboembolism in several small series [Nowak-Gottl et al 1996, Sifontes et al 1998].
- A heterozygous factor V Leiden mutation was found in 7.3% of unselected Argentinean children with DVT or pulmonary embolism, compared to 2.4% of controls, suggesting a three- to fourfold increase in thrombotic risk [Bonduel et al 2002].
- In contrast, another study of unselected children with venous thromboembolism found a low prevalence of the mutation, similar to that reported in the general population [Revel-Vilk et al 2003].

The majority of the individuals reported had other coexisting inherited and circumstantial risk factors in addition to the factor V Leiden mutation. For example, in one study, 50% of factor V Leiden heterozygotes had a coexisting thrombophilic disorder, and circumstantial risk factors were present in all children with venous thromboembolism.

In a prospective study, asymptomatic heterozygous and homozygous children who were family members of symptomatic probands with the factor V Leiden mutation had no thrombotic complications during an average follow-up period of five years [Tormene et al 2002]. Thus, the available data suggest that asymptomatic children with a factor V Leiden allele are at low risk for thrombosis except in the setting of strong circumstantial risk factors.

Recurrent Thrombosis—Risk for recurrent thrombosis in adults heterozygous for factor V Leiden alone. Recent evidence suggests that a heterozygous factor V Leiden mutation has at most a modest effect on the risk of recurrence after initial treatment of a first VTE.

Several earlier studies suggested that individuals heterozygous for factor V Leiden had a two- to fourfold increased risk of recurrent thrombosis [Simioni et al 1997, Simioni et al 2000], althouth other studies found no significant increase in risk [Eichinger et al 1997, De Stefano et al 1999, Lindmarker et al 1999]. A meta-analysis including 3104 individuals with a first VTE concluded that a heterozygous factor V Leiden mutation is associated with a significantly increased risk of recurrent VTE after a first event (odds ratio 1.4) [Ho et al 2006].

In contrast, two recent prospective cohort studies that evaluated the risk of recurrent thrombosis in unselected individuals with a first VTE followed for a mean of two years [Baglin et al 2003] and seven years [Christiansen et al 2005] concluded that heterozygotes for factor V Leiden did not have a greater risk of recurrent VTE than those without the mutation. In addition, a prospective study of families with a strong history of thrombosis found that persons with factor V Leiden had the lowest rate of recurrent VTE (3.5%/year) [Vossen, Walker et al 2005].

Risk for recurrent thrombosis in factor V Leiden homozygotes and heterozygotes with other risk factors. The risk of recurrent VTE in factor V Leiden homozygotes is not well

defined, but presumed to be higher than in heterozygotes. In a retrospective cohort study, 34% of factor V Leiden homozygotes had a history of recurrent VTE [Ehrenforth et al 2004]. A prospective follow-up of the Leiden Thrombophilia study reported a five year cumulative recurrence rate of 12.5% in a small group of factor V Leiden homozygotes not receiving long-term anticoagulation [Christiansen et al 2005]. Other studies included few or no factor V Leiden homozygotes, and those included were often on long-term anticoagulation [Vossen, Walker et al 2005].

Individuals who are heterozygous for both factor V Leiden and the prothrombin gene mutation or homozygous for factor V Leiden have a three- to ninefold higher risk of recurrence [De Stefano et al 1999, Lindmarker et al 1999, Meinardi et al 2002].

In one study, the annual incidence of recurrent VTE was 12%/year in persons with homozygous factor V Leiden or combined factor V Leiden and the prothrombin gene mutation, compared to 3%/year in those who were heterozygous for factor V Leiden alone [Gonzalez-Porras et al 2006].

The risk of recurrent VTE is four- to fivefold higher in factor V Leiden heterozygotes with hyperhomocysteinemia than in individuals with a factor V Leiden allele alone [Meinardi et al 2002].

Risk for recurrent thrombosis in children. The risk of recurrent VTE is likely higher in children with an initial spontaneous event, a strong family history of thrombosis, and multiple thrombophilic defects [Revel-Vilk & Kenet 2006].

Heterozygous and homozygous factor V Leiden mutations were found in 29% and 2.3% of children with a first spontaneous venous thrombosis, respectively.

Children with a factor V Leiden mutation had a four- to sixfold higher risk of recurrence, which occurred in 28% of homozygotes and 19% of heterozygotes, compared to 5% of those with a normal genotype [Nowak-Gottl et al 2001].

Risk for recurrent thrombosis in pregnant women. Women with a prior history of venous thrombosis probably have a higher risk of recurrence during pregnancy, although recurrence rates range from 0% to 15% among published studies. The risk is likely higher in women with a prior spontaneous event, and/or coexisting genetic or acquired risk factors. One prospective study evaluated the safety of withholding anticoagulation during pregnancy in 125 women with a history of venous thromboembolism. In subgroup analysis, women with a previous spontaneous thromboembolic event and thrombophilia (especially factor V Leiden), had the highest recurrence rate during pregnancy (20%, odds ratio 10). Women with either thrombophilia or a prior unprovoked VTE (but not both) had a recurrence rate of 13% and 7.7%, respectively [Brill-Edwards et al 2000].

Pregnancy Complications—Factor V Leiden thrombophilia may increase the risk of pregnancy loss and other obstetric complications. The available data indicate that heterozygosity for factor V Leiden is associated with a two- to threefold increase in relative risk of pregnancy loss, and possibly other complications such as preeclampsia, fetal growth retardation, and placental abruption; however, the precise risk is unknown pending prospective longitudinal studies. Overall, the probability of a successful pregnancy outcome is high.

Pregnancy loss. In addition to the increased risk of venous thromboembolism during pregnancy, a large number of case-control studies consistently found a high prevalence of factor V Leiden heterozygosity in women with unexplained recurrent pregnancy loss (30%),

compared to 1%-10% of controls (odds ratio range: 2-5) [Ridker et al 1998, Brenner et al 1999, Gris et al 1999, Kupferminc et al 1999, Martinelli et al 2000].

A small prospective study reported miscarriage in 11% of factor V Leiden heterozygotes compared to 4.2% of women without a factor V Leiden allele [Murphy et al 2000]. In another prospective study, factor V Leiden heterozygotes with a history of recurrent early miscarriage had a significantly lower live birth rate than women with a similar history of unsuccessful pregnancies but without the mutation. The live birth rate was 38% in factor V Leiden heterozygotes compared to 69% in women with a normal factor V genotype, suggesting that the mutation confers a three- to fourfold higher risk of an adverse pregnancy outcome [Rai et al 2002].

In a meta-analysis including 3000 women, a factor V Leiden allele significantly increased the risk of early first-trimester recurrent loss (odds ratio 2.1) and late recurrent and non-recurrent loss (odds ratios 7.8 and 3.2, respectively) [Rey et al 2003]. Two other meta-analyses also found a strong association with fetal loss [Dudding & Attia 2004, Kovalevsky et al 2004].

In contrast, a prospective follow-up study of thrombophilic women with no prior history of pregnancy loss found that a factor V Leiden allele conferred only a slight increase in risk of fetal loss (relative risk 1.4) [Vossen et al 2004].

- **Evidence of increased second- and third-trimester losses.** Some evidence suggests that thrombophilic women have a higher risk of loss in the second and third trimester. A large case-control study identified factor V Leiden as an independent risk factor for a first unexplained fetal loss after ten weeks' gestation (odds ratio 3.5) [Lissalde-Lavigne et al 2005]. Mulitple other studies and three meta-analyses suggest that factor V Leiden heterozygotes have a higher risk of late pregnancy loss than early first-trimester loss [Preston et al 1996, Rai et al 1996, Tormene et al 1999, Rey et al 2003, Dudding & Attia 2004, Kovalevsky et al 2004]. One possible explanation is that late-pregnancy losses reflect thrombosis of the placental vessels, in contrast to first-trimester losses, which are more commonly attributable to other causes. In several studies, the majority of placentas from women heterozygous for factor V Leiden and late fetal loss had evidence of thrombotic vasculopathy or infarction, supporting this hypothesis [Gris et al 1999, Martinelli et al 2000].
- **Evidence of increased first-trimester losses.** A factor V Leiden allele also increases the risk of early first-trimester loss [Rey et al 2003].

  Thirty-five per cent of all fetal losses in factor V Leiden heterozygotes were "pre-clinical" (prior to ultrasound confirmation of fetal heart activity), compared to 12% of those in women without the mutation [Tal et al 1999].

Preeclampsia, fetal growth retardation, and placental abruption. Although preeclampsia, fetal growth retardation, and placental abruption may also involve impaired placental perfusion, their association with thrombophilia remains controversial. The conflicting results reported in different studies may reflect the varying diagnostic and selection criteria, different ethnic groups, and small number of cases included.

- **Preeclampsia.** Multiple case-control studies found a significantly higher prevalence of factor V Leiden in women with preeclampsia (8%-26%) compared to women with normal pregnancies (2%-10%) with odds ratios ranging from two to six [Grandone et al 1997, Grandone et al 1999, Kupferminc et al 1999, Agorastos et al 2002, Mello et al 2005].

  Several large meta-analyses found an overall two to threefold increased risk of preeclampsa [Kosmas et al 2003, Dudding & Attia 2004, Lin & August 2005].

However, these risk estimates were based on pooled data from contradictory studies. The conflicting results reported may be due at least in part to differences in the severity of preeclampsia [Morrison et al 2002, Mello et al 2005]. Factor V Leiden has a stronger association with severe and early-onset preeclampsia than with mild forms of the disease [Mello et al 2005, Nurk et al 2006].

Women with thrombophilia including factor V Leiden and severe preeclampsia may have a higher risk of serious maternal complications and adverse perinatal outcomes than those without thrombophilia [Kupferminc et al 2000, Mello et al 2005].

In contrast, other studies found no association of the mutation with preeclampsia [Alfirevic et al 2001, Livingston et al 2001, Morrison et al 2002, De Maat et al 2004]. A factor V Leiden allele did not increase the risk of preeclampsia in three prospective studies of unselected women screened during the first trimester [Lindqvist et al 1999, Murphy et al 2000, Dizon-Townson et al 2005].

- **Fetal growth retardation.** The data on the risk of fetal growth retardation are more limited and conflicting. A factor V Leiden allele was found in 8%-35% of women with pregnancies complicated by fetal growth retardation compared to 2%-4% of controls (odds ratio range: 7-13) [Kupferminc et al 1999, Martinelli et al 2001, Kupferminc et al 2002]. Another study suggested that factor V Leiden heterozygotes have a twofold higher risk of delivering a neonate with fetal growth retardation [Grandone et al 2002]. Two recent meta-analyses found that a factor V Leiden allele was associated with a significant three- to fivefold increased risk of fetal growth retardation [Dudding & Attia 2004, Howley et al 2005].

  In contrast, two larger case-control studies found no significant association between factor V Leiden and fetal growth retardation [Infante-Rivard et al 2002, McCowan et al 2003].

  In several prospective studies of unselected pregnant women, the mutation did not increase the risk of fetal growth retardation [Lindqvist et al 1999, Murphy et al 2000, Dizon-Townson et al 2005].

- **Placental abruption.** The data on the risk of placental abruption are limited and conflicting. Factor V Leiden was found in 22%-30% of women with placental abruption compared to 3%-6% of control women (odds ratio range: 5-12) [Wiener-Megnagi et al 1998, Kupferminc et al 1999, Facchinetti et al 2003].

  Several other studies found no significant association [Lindqvist et al 1999, Alfirevic et al 2001, Prochazka et al 2003].

Clinical Expression of Factor V Leiden Thrombophilia—The clinical expression of factor V Leiden thrombophilia is influenced by four factors:

1 **The number of factor V Leiden alleles**

Factor V Leiden heterozygotes. The relative risk of venous thrombosis is increased approximately three - to eightfold in individuals who are heterozygous for the factor V Leiden allele. Lower relative risks are reported in heterozygotes identified from general population screening [Juul et al 2004, Heit et al 2005].

Factor V Leiden homozygotes. The relative risk of venous thrombosis is increased 18- to 80-fold in individuals who are homozygous. Although homozygotes have a higher thrombotic risk and tend to develop thrombosis at a younger age, the risk is much lower than that associated with homozygous protein C or S deficiency.

2 **Coexisting genetic abnormalities.** The presence of at least one factor V Leiden allele increases the risk associated with other inherited and acquired thrombophilic disorders (including protein C deficiency, protein S deficiency, and antithrombin deficiency), the prothrombin 20210G>A gene mutation, and hyperhomocystinemia [Ridker, Hennekens et al 1997]. The combination of factor V Leiden heterozygosity and most thrombophilic disorders has a supra-additive effect on overall thrombotic risk.

Prothrombin thrombophilia. Individuals with either a single factor V Leiden allele or prothrombin gene mutation had a four- to fivefold increase in thrombotic risk, in contrast to double heterozygotes who had a 20-fold increase in relative risk, illustrating the multiplicative effect of these two factors on overall thrombotic risk [Emmerich et al 2001]. A prothrombin 20210G>A allele was four- to fivefold more common in symptomatic factor V Leiden homozygotes with VTE than in controls with no thrombotic history [Ehrenforth et al 2004].

3 **Acquired thrombophilic disorders**

Hyperhomocysteinemia. In the Physicians' Health Study, individuals with either at least one factor V Leiden allele or hyperhomocystinemia had a three- to fourfold increased risk of idiopathic thrombosis, but the relative risk increased 22-fold in individuals with both abnormalities [Ridker, Hennekens et al 1997].

High factor VIII levels. Factor V Leiden heterozygotes with high factor VIII levels (>150% of normal) had a two- to threefold higher incidence of VTE than those with a factor V Leiden allele alone [Lensen et al 2001].

Malignancy. Cancer patients have an increased risk of VTE. A heterozygous factor V Leiden mutation increased the risk of VTE in patients with malignancy in several studies, although the results did not achieve statistical significance in one small study [Pihusch et al 2002, Blom et al 2005a, Kennedy et al 2005]. A large population-based case-control study found that factor V Leiden heterozygotes with malignancy had a twofold higher risk of VTE than cancer patients without the mutation, and a 12-fold higher risk than those with neither risk factor [Blom et al 2005a].

Cancer patients with a heterozygous factor V Leiden or prothrombin gene mutation had a 20-fold higher risk of developing an upper-extremity thrombosis than cancer patients with neither prothrombotic mutation [Blom et al 2005b].

4 **Circumstantial risk factors.** Other predisposing factors include: travel, central venous catheter use, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, age, and surgery. These predisposing factors are associated with the first thrombotic episode in at least 50% of individuals with a factor V Leiden allele.

In a retrospective study of a large cohort of symptomatic factor V Leiden homozygotes, the initial VTE was associated with circumstantial risk factors in 81% of women and 29% of men [Ehrenforth et al 2004]. Oral contraceptives and pregnancy were the most common predisposing factors in symptomatic women. Thirteen percent of major surgeries were complicated by VTE, suggesting a nearly 20-fold increase in risk. Leg trauma was associated with a ninefold increased risk of a first VTE, which occurred in 15% of factor V Leiden homozygotes compared to 1.8% of control individuals without the mutation.

VTE after travel. The combination of air travel and thrombophilia, including factor V Leiden, was associated with a 16-fold increased risk of VTE [Martinelli, Taioli et al 2003].

Central venous catheters. Individuals heterozygous for factor V Leiden have a two- to threefold increased risk of central venous catheter-related thrombosis [van Rooden et al 2004]. A factor V Leiden allele increases the risk of central venous catheter-associated thrombosis in individuals with advanced or metastatic breast cancer and those undergoing allogeneic bone marrow transplantation [Fijnheer et al 2002, Mandala et al 2004].

Pregnancy. A factor V Leiden allele is associated with a five- to 16-fold increase in thrombotic risk during pregnancy and the puerperium, when compared to non-pregnant women without thrombophilia. A factor V Leiden mutation was confirmed by DNA testing in 20%-46% of women with pregnancy-associated venous thrombosis [Bokarewa et al 1996, Hirsch et al 1996, Hallak et al 1997, Grandone et al 1999, Gerhardt et al 2000, Hiltunen et al 2007]. For example, in one study, factor V Leiden thrombophilia was found in 44% of women with a history of venous thrombosis during pregnancy, compared to 8% of matched controls, with a corresponding ninefold increase in thrombotic risk [Gerhardt et al 2000].

Two recent meta-analyses found that a heterozygous factor V Leiden mutation is associated with an eightfold increased risk of pregnancy-related VTE [Biron-Andreani et al 2006, Robertson et al 2006]. The overall risk is likely higher in women with coexisting acquired or circumstantial risk factors. One study found the combination of a factor V Leiden allele and advanced maternal age (>35 years) and obesity (BMI >30) conferred a 44-fold and 75-fold increased risk, respectively, compared to younger and normal weight women without the mutation [Hiltunen et al 2007].

Women with multiple or homozygous thrombophilic defects have the highest risk of pregnancy-associated VTE. The risk of pregnancy-related VTE is increased 20- to 40-fold in women with homozygous factor V Leiden [Martinelli et al 2001, Gerhardt et al 2003, Robertson et al 2006].

The risk of thrombosis during pregnancy was increased more than 100-fold in women with both a factor V Leiden allele and the prothrombin gene mutation, illustrating the marked increase in overall risk when thrombophilic mutations are combined [Gerhardt et al 2000]. In studies of thrombophilic families, VTE complicated 4% of pregnancies in women doubly heterozygous for factor V Leiden and the prothrombin gene mutation, and 16% of pregnancies in factor V Leiden homozygotes, compared with 0.5% of those in unaffected relatives [Martinelli et al 2001; Middeldorp, Libourel et al 2001]. The prevalence of pregnancy-related VTE was 9% in a series of unselected homozygous women [Pabinger et al 2000].

Although presence of a factor V Leiden allele increases the relative risk of VTE during pregnancy and the puerperium, the true risk in asymptomatic heterozygotes is not well defined. The results of the following studies suggest that although factor V Leiden heterozygosity is an independent risk factor, the absolute incidence of thrombosis during pregnancy is low. Notes: (1) Two prospective studies of unselected pregnant women screened for factor V Leiden both observed very low rates of VTE in heterozygous women (1.1% and 0%, respectively) [Lindqvist et al 1999, Dizon-Townson et al 2005]. (2) No VTE events occurred during pregnancy or postpartum among a cohort of 129 women with factor V Leiden identified by general population screening [Heit et al 2005].

In several retrospective studies and meta-analyses, the estimated risk of VTE during pregnancy and the puerperium in factor V Leiden heterozygotes was in the range of one in 125 to 400 pregnancies [McColl et al 1997, Gerhardt et al 2000, Gerhardt et al 2003, Robertson et al 2006].

In contrast, women with homozygous factor V Leiden or combined thrombophilia have a much higher probability of VTE, in the range of one in 20 to one in 100 pregnancies [Martinelli et al 2001, Gerhardt et al 2003, Robertson et al 2006].

Oral contraceptive use. The use of oral contraceptives substantially increases the risk of venous thromboembolism (VTE) in women heterozygous for a factor V Leiden allele. A heterozygous mutation is found in 20%-35% of women with a history of venous thrombosis during oral contraceptive use [Hirsch et al 1996, Schambeck et al 1997]. In the Leiden Thrombophilia study, the risk of venous thrombosis was increased fourfold in oral contraceptive users, and sevenfold in women with a heterozygous factor V Leiden mutation. However, the risk was increased 35-fold in heterozygous women who used oral contraceptives, indicating a multiplicative rather than additive effect on overall thrombotic risk.

The supra-additive effect of a factor V Leiden allele and oral contraceptives was confirmed in other studies and a meta-analysis, with odds ratios ranging from 11 to 41 for the combination of both risk factors [Martinelli, Taioli et al 1999, Legnani et al 2002, Sidney et al 2004].

A meta-analysis found the combination of factor V Leiden and oral contraceptives conferred a 16-fold increase in relative thrombotic risk, which was fivefold higher than that observed with either risk factor alone [Wu et al 2005]. Heterozygous women who use oral contraceptives have a 30-fold higher risk of cerebral vein thrombosis than non-users without the mutation [Martinelli, Battaglioli et al 2003].

The corresponding risk is increased more than 100-fold in women homozygous for the factor V Leiden allele who use oral contraceptives. The risk of VTE is also markedly increased in oral contraceptive users who are doubly heterozygous for factor V Leiden and the prothrombin gene mutation, with reported odds ratios ranging from 17 to 110 [Mohllajee et al 2006].

Women with inherited thrombophilic disorders, such as factor V Leiden thrombophilia, tend to develop thrombotic complications sooner, with a much higher risk of thrombosis during the first year of oral contraceptive use [Bloemenkamp et al 2000].

Oral contraceptives containing the third-generation progestagen desogestrel are associated with a twofold higher risk of venous thromboembolism than second-generation preparations, with an especially high risk in factor V Leiden heterozygotes. The risk was increased 50-fold in factor V Leiden heterozygotes who used third-generation preparations containing desogestrel, compared to women without the factor V Leiden allele who were not using oral contraceptives.

Despite the marked increase in relative risk, the absolute incidence of VTE may still be low because of the low baseline risk in young healthy women. For example, the combination of factor V Leiden and oral contraceptives is estimated to result in an additional 28 VTE events per 10,000 women per year. Long-term use of oral contraceptives in asymptomatic factor V Leiden heterozygotes without complications has been reported, underscoring the multifactorial etiology of VTE [Girolami et al 2004].

Unopposed progestin contraception carries a much lower risk of thrombosis than estrogen-containing contraceptives, although the risk in thrombophilic women is not well defined. A retrospective study found that oral progestin alone did not increase

the risk of VTE in high-risk women with a history of thrombosis and/or thrombophilia, including 28 women with factor V Leiden [Conard et al 2004].

However, no prospective studies confirm the safety of progestin-alone contraception in women with factor V Leiden.

Hormone replacement therapy (HRT). Multiple studies have confirmed a significant (two- to fourfold) increase in relative risk of VTE in current users of HRT compared to non-users [Daly et al 1996, Grodstein et al 1996, Jick et al 1996, Perez-Guthann et al 1997, Hulley et al 1998, Varas-Lorenzo et al 1998, Grady et al 2000, Rossouw et al 2002].

The landmark Women's Health Initiative (WHI) randomized trial of estrogen and progesterone HRT versus placebo in postmenopausal women found that HRT was associated with a twofold increased risk of VTE [Rossouw et al 2002]. In a parallel WHI trial of estrogen-only HRT in women who had a hysterectomy, estrogen replacement increased the risk of VTE, although the risk was statistically significant only for DVT (hazard ratio 1.47) [Anderson et al 2004, Curb et al 2006].

Most of the observational studies of HRT excluded women with known thrombophilia. Based on the known interaction with estrogen, the use of HRT is expected to significantly increase the risk of VTE in women with a factor V Leiden allele. Evidence is now compelling that women with factor V Leiden who use HRT have a markedly increased risk of developing VTE. In one study, the combination of HRT use and activated protein C resistance was associated with a 13-fold increase in relative thrombotic risk compared to that found in women with neither risk factor [Lowe et al 2000]. Reinvestigation of this same group of women for prothrombotic mutations (factor V Leiden or the prothrombin gene mutation) demonstrated a 15-fold increased risk of venous thrombosis in HRT users with a heterozygous factor V Leiden mutation [Rosendaal et al 2002].

In another study of postmenopausal women with coronary heart disease, factor V Leiden heterozygotes who used HRT had a 14-fold higher thrombotic risk than non-users without the mutation. The estimated absolute incidence of VTE in women with coronary heart disease and factor V Leiden who used HRT was 15 VTE events per 1000 women per year, compared to two VTE events per 1000 women per year for non-users with a normal genoype [Herrington et al 2002]. A meta-analysis of the data from these confirmed that factor V Leiden heterozygotes who use HRT have a 13-fold higher risk of VTE [Wu et al 2005].

In a nested case-control study of the WHI, factor V Leiden heterozygotes who used estrogen and progestin HRT had a nearly sevenfold higher risk of VTE than non-users without the mutation [Cushman et al 2004]. The estimated absolute risk of VTE in factor V Leiden heterozygotes who used HRT was eight VTE events per 1000 women per year.

Some evidence suggests that the thrombotic risk from transdermal HRT is lower than the thrombotic risk from oral preparations, in women with and without prothrombotic mutations [Scarabin et al 2003, Straczek et al 2005]. In one study, women with factor V Leiden who used oral estrogen had a 16-fold higher risk of VTE than non-users without the mutation. In contrast, the thrombotic risk in women with factor V Leiden who used transdermal estrogen was similar to that in women with a mutation who did not use estrogen. Among women with factor V Leiden, the use of oral estrogen was associated with a fourfold higher risk of VTE than transdermal estrogen [Straczek et al 2005]. However, there are no prospective trials confirming the safety in women with thrombophilia and/or prior VTE.

Selective estrogen receptor modulators (SERMs). The limited data available suggest that SERMs, such as tamoxifen and raloxifene, are associated with a similar increase in thrombotic risk [Fisher et al 1998, Meier & Jick 1998, Cummings et al 1999, Abramson et al 2006, Barrett-Connor et al 2006].

The risk of venous thromboembolism in women with factor V Leiden who use SERMs is unknown but likely higher than that associated with SERMs alone. There are several case reports of tamoxifen-associated thrombosis in women with factor V Leiden thrombophilia [Wietz et al 1997]. Two nested case-control studies of high-risk healthy women enrolled in the breast cancer prevention trials did not find a statistically significant effect of factor V Leiden on the risk of VTE associated with tamoxifen [Duggan et al 2003, Abramson et al 2006]. However, both studies were limited by the small number of cases included. In light of the interaction of factor V Leiden with HRT, it is likely that factor V Leiden thrombophilia will be shown to increase the risk of SERM-associated thrombosis in larger studies.

Organ transplantation. The prevalence of factor V Leiden in individuals who have undergone renal transplantation is similar to that in the general population, suggesting that it is not a risk factor for developing end-stage renal disease (ESRD) [Wuthrich et al 2001]. However, recent evidence suggests that the factor V Leiden mutation may contribute to thrombotic and other complications after renal transplantation [Kujovich 2004a]. In several retrospective studies, thromboembolic complications occurred in up to 39% of factor V Leiden heterozygotes, compared to 6%-15% of recipients without a factor V Leiden allele [Irish et al 1997, Wuthrich et al 2001]. The mutation conferred an overall fourfold increased risk of graft vein thrombosis and venous thromboembolism [Irish et al 1997].

Factor V Leiden has been associated with both delayed graft function and early graft loss [Wuthrich et al 2001, Hocher et al 2002]. In one study, factor V Leiden heterozygotes had a 12-fold higher risk of an early graft perfusion defect, and a markedly increased risk of graft loss within the first week (25%) compared to individuals with a normal genotype (<1%) (odds ratio 64) [Wuthrich et al 2001]. Factor V Leiden heterozygotes also had a significantly higher risk of graft loss within the first year in some [Ekberg et al 2000, Wuthrich et al 2001], but not all, studies [Pherwani et al 2003]. In the single study that screened kidney donors, grafts from donors heterozygous for factor V Leiden had a 30-day and one-year survival similar to those from donors without the mutation [Pherwani et al 2003].

Factor V Leiden may also increase the risk of acute rejection after renal transplantation. Although the number of individuals and frequency of rejection varied, a consistent pattern of more frequent rejection episodes was observed in recipients with a factor V Leiden allele. Several studies found that factor V Leiden heterozygotes have a three- to fourfold higher risk of acute rejection than those without the mutation [Ekberg et al 2000, Hocher et al 2002, Heidenreich et al 2003].

A recent study of renal transplantation outcomes in 394 stable recipients found that factor V Leiden heterozygotes were also significantly more likely to develop chronic graft dysfunction, reflected by both a steeper slope of the 1/creatinine-versus-time curve, and a higher annual increase in the rate of urinary protein excretion [Hocher et al 2002].

The contribution of factor V Leiden to thrombotic complications after other types of organ transplantation is not well defined. DVT, pulmonary embolism, and hepatic artery thrombosis have been reported in liver transplantation recepients whose donors were heterozygous or homozygous for factor V Leiden [Leroy-Matheron et al 2003, Willems et al 2003, Dunn et al 2006]. A retrospective study suggested that a liver

transplantation from a heterozygous donor was associated with a twofold overall risk of postoperative venous or hepatic vessel thrombosis [Hirshfield et al 1998]. Another study found that recipients with acquired activated protein C resistance after liver transplantation had a fourfold increased risk of subsequent venous thromboembolic complications [Loew et al 2005].

Age. The risk increases at a greater rate with advancing age in individuals with a factor V Leiden mutation, also suggesting that thrombosis involves acquired, as well as genetic, predisposing factors [Ridker, Glynn et al 1997]. In the Physicians' Health Study, a factor V Leiden allele was found in nearly one-third of men over age 60 years with an initial spontaneous unprovoked thrombotic event.

In a population-based cohort study, the risk of VTE was significantly increased only among factor V Leiden heterozygotes over age 60 years (relative risk 3.6) [Heit et al 2005]. Another prospective study found that the absolute risk of VTE in unselected individuals with factor V Leiden increased with age, body mass index (BMI), and smoking. The ten-year risk of VTE among factor V Leiden heterozygotes was 10% in smokers over age 60 with a BMI greater than 30 kg/m^2, in contrast to a less than 1% risk in nonsmokers younger than age 40 years who were not overweight [Juul et al 2004]. The corresponding absolute ten-year risks for factor V Leiden homozygotes with and without these risk factors were 51% and 3%, respectively.

Surgery. It is still unclear to what extent the factor V Leiden mutation adds to the overall thrombotic risk in individuals undergoing orthopedic surgery. In one study, individuals with APC resistance had a fivefold increased risk of symptomatic postoperative venous thromboembolism during the two months after elective hip or knee replacement [Lindahl et al 1999]. In contrast, in another study of individuals receiving standard prophylactic antithrombotic therapy, the mutation was not associated with a significantly increased risk of DVT during the immediate postoperative period [Ryan et al 1998].

Individuals heterozygous for factor V Leiden or the prothrombin gene mutation undergoing surgery had a nearly 13-fold higher risk of upper-extremity DVT than controls with neither risk factor [Blom et al 2005b].

Children. In several studies, 62%-91% of children with VTE had coexisting circumstantial risk factors, with central venous catheters, malignancy and congenital heart disease among the most frequently reported [Junker et al 1999, Revel-Vilk et al 2003].

Thrombosis NOT Convincingly Associated with Factor V Leiden Thrombophilia

—Arterial thrombosis. The role of factor V Leiden in arterial disease is controversial, with conflicting results from different studies. Most studies of unselected adult populations found no association between presence of a factor V Leiden allele and an increased risk of myocardial infarction or stroke [Cushman et al 1998]. A meta-analysis of 33 studies and including 25,053 individuals found no significant association with myocardial infarction, stroke, or peripheral vascular disease either collectively or individually [Kim & Becker 2003], However, a more recent larger meta-analysis found that a factor V Leiden allele conferred a moderately increased risk for coronary disease and myocardial infarction [Ye et al 2006]. Although consensus holds that the presence of a factor V Leiden allele is not a major risk factor for MI or stroke, some data suggest that it may contribute to the risk of arterial thrombotic events in selected subgroups of individuals.

Myocardial infarction. The results of several studies suggest that the factor V Leiden allele may contribute to myocardial infarction in younger individuals and in those with concomittant cardiovascular risk factors.

- One study reported a significantly increased risk of myocardial infarction in young women with other cardiovascular risk factors, particularly smoking. Young women with a heterozygous factor V Leiden mutation who smoked had a 30-fold increased risk of myocardial infarction compared to women with neither risk factor [Rosendaal et al 1997].
- Several other studies found that the simultaneous presence of prothrombotic mutations, including factor V Leiden, and one or more cardiovascular risk factors substantially increased the risk of acute myocardial infarction. The combination of a prothrombotic mutation and smoking was associated with the highest risk (odds ratio range: 6-18) [Doggen et al 1998, Inbal et al 1999].
- Two studies found a significantly higher prevalence of a factor V Leiden allele in young individuals with premature myocardial infarction and normal coronary angiography than in matched controls with significant coronary artery disease, with odds ratios of 2.6 and 4.7, respectively [Mansourati et al 2000, Van de Water et al 2000].
- A case-control study found that a heterozygous factor V Leiden mutation was associated with a significant two- to threefold increased risk of myocardial infarction. All of the individuals with factor V Leiden and myocardial infarction had coexisting cardiovascular risk factors [Middendorf et al 2004].
- The risk of arterial thrombosis in factor V Leiden homozygotes is unknown, as very few homozygous individuals were included in the available studies.

Stroke in adults. Most studies of unselected adult populations did not find a significant association between factor V Leiden and ischemic stroke [Cushman et al 1998, Lalouschek et al 2005]. There was no difference in the prevalence of factor V Leiden between unselected individuals with severe carotid atherosclerosis and healthy controls, even in the subgroup with symptomatic disease [Marcucci et al 2005]. Although the available data suggest that factor V Leiden is not a general risk factor for stroke, it may contribute in selected populations.

A factor V Leiden allele was associated with a threefold increased risk of stroke in individuals younger than age 45-50 years, and the risk was even higher in women in this age group (odds ratio range: 4-6) [Margaglione et al 1999, Aznar et al 2004].

The interaction of factor V Leiden with other vascular risk factors may increase the risk of ischemic stroke. Two studies found that young women with a factor V Leiden allele who used oral contraceptives had a nine- to 13-fold increased risk of stroke, compared to women with neither risk factor [Slooter et al 2005, Martinelli et al 2006]. Several studies also found a six- to ninefold increased risk of stroke in young adults and women up to age 60 years [Margaglione et al 1999, Lalouschek et al 2005, Slooter et al 2005]. The combination of a factor V Leiden allele with one or more other cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia) was associated with a nearly 11-fold increase in stroke risk [Margaglione et al 1999].

Arterial thromboembolism may also occur "paradoxically" through a patent foramen ovale in the heart of individuals with venous thrombosis [Karttunen et al 2003].

Stroke in children. Arterial ischemic stroke in children usually occurs in the setting of multiple predisposing factors [Barnes & Deveber 2006]. Data on the association of

thrombophilia with ischemic stroke are conflicting. The majority of published case-control studies found a significantly increased prevalence of factor V Leiden in children with ischemic stroke (17%-23%) compared to control children (3%-4%), with odds ratios of 4 to 5 [Zenz et al 1998, Nowak-Gottl et al 1999, Kenet et al 2000, Duran et al 2005]. Analysis of the data from five studies suggests that the mutation confers an overall fourfold increase in stroke risk [Barnes & Deveber 2006]. However, another meta-analysis reported that children with a factor V Leiden allele had a lower risk of a first ischemic stroke (odds ratio 1.2), which was not statistically significant [Haywood et al 2005].

Stroke in the fetus. Arterial thrombosis may also occur in the fetus as a result of placental venous thrombi entering the fetal circulation, crossing the foramen ovale, and entering the cerebral arterial vasculature [Thorarensen et al 1997].

Genotype-Phenotype Correlations

Individuals homozygous for factor V Leiden have a higher risk for thrombosis than heterozygotes (see Clinical Description. However, the clinical course of an acute thrombotic episode is not more severe or more resistant to anticoagulation in homozygotes than in heterozygotes.

"Pseudo-homozygous" APC resistance. Other genetic abnormalities may affect the expression of a heterozygous factor V Leiden allele. One example is "pseudo-homozygous" APC resistance, which occurs in individuals who are doubly heterozygous for the factor V Leiden mutation and a factor V null mutation. Rather than attenuating the effect of the factor V Leiden mutation, coexisting factor V deficiency appears to enhance it, producing a more severe APC-resistant phenotype, reflected by a extremely low APC resistance ratio [Brugge et al 2005]. Factor V Leiden pseudohomozygotes show a degree of APC resistance indistinguishable from that of individuals homozygous for the mutation [Brugge et al 2005]. The diagnosis of pseudohomozygous APC resistance is based on the combination of a heterozygous factor V Leiden mutation, reduced factor V activity levels (approximately 50% of normal), and a low APC resistance ratio in the range typical for a homozygous mutation. Several different mutations associated with a quantitative factor V deficiency have been described, including one polymorphism (the "R2 allele") found in up to 7.5% of the Italian population [Castaman et al 1997, Castoldi et al 1998, Simioni et al 2005].

Coinheritance of a factor V null allele is estimated in approximately 1/1000 individuals heterozygous for factor V Leiden [Simioni et al 2005]. Most of the individuals described have had a history of thrombosis. Recent data suggest that individuals with pseudohomozygous APC resistance have an increased thrombotic risk comparable to that of factor V Leiden homozygotes [Simioni et al 2005]. Pseudohomozygous APC resistance has also been reported in individuals doubly heterozygous for factor V Leiden and factor V Cambridge [Santamaria et al 2005].

In rare cases, both a null allele and factor V Leiden mutation occur on the same chromosome in cis configuration. In these individuals, the resulting quantitative factor V deficiency prevents expression of the factor V Leiden mutation [Dargaud et al 2003].

Factor V polymorphisms. A factor V gene haplotype (HR2) defined by the R2 polymorphism (A4070G) may confer mild APC resistance and interact with the factor V Leiden mutation to produce a more severe APC resistance phenotype [Bernardi et al 1997, de Visser et al 2000, Mingozzi et al 2003]. In one study, coinheritance of the HR2 haplotype increased the risk of venous thromboembolism associated with factor V Leiden by approximately threefold [Faioni et al 1999]. However, double heterozygosity for factor V Leiden and the R2 polymorphism was not associated with a significantly higher risk of early or late pregnancy loss than a

heterozygous factor V Leiden mutation alone [Zammiti et al 2006]. Whether the HR2 haplotype alone is an independent thrombotic risk factor is still unclear. Several studies have suggested that the HR2 haplotype is associated with a twofold increase in risk of venous thromboembolism [Alhenc-Gelas et al 1999, Jadaon & Dashti 2005]. In contrast, other studies found no significant increase in thrombotic risk [de Visser 2000, Luddington et al 2000, Dindagur et al 2006].

Penetrance

Factor V Leiden heterozygotes identified from general population screening had a low absolute incidence of VTE of approximately two VTE events per 1000 persons per year in several studies [Juul et al 2004, Heit et al 2005]. The cumulative incidence of VTE was 6.5% at age 65 years. Homozygotes had an absolute incidence of 15 VTE events/1000 persons/year [Juul et al 2004].

The risk of thrombosis is higher in studies of asymptomatic factor V Leiden heterozygotes from thrombophilic families than in unselected individuals identified by population screening. Four retrospective studies of relatives of unselected symptomatic and asymptomatic factor V Leiden heterozygotes also reported a low thrombotic risk. The results were remarkably consistent, with the absolute incidence of venous thrombosis ranging from 0.19%/year to 0.45%/year, compared to 0.10%/year in individuals without a factor V Leiden allele [Middeldorp et al 1998, Simioni et al 1999, Lensen et al 2000, Martinelli et al 2000]. Venous thrombosis occurred in 7%-12% of relatives with factor V Leiden heterozygosity compared to 2%-3% of individuals without a factor V Leiden allele, consistent with other estimates that the lifetime risk of thrombosis in a heterozygote is approximately 10% [Grody et al 2001]. At least 50% of thrombotic events were associated with other risk factors, especially pregnancy. One study found a higher thrombotic risk in relatives from families with a factor V Leiden allele in which multiple family members had a history of thrombosis. The absolute incidence of venous thrombosis in heterozygous first-degree relatives was 1.7%/year, suggesting that a strong family history is a risk factor for thrombosis [Martinelli et al 2000]. A systematic review of these four studies found a pooled nearly fourfold increased relative risk of venous thromboembolism [Langlois & Wells 2003]. In three prospective cohort studies, the overall incidence of VTE in asymptomatic factor V Leiden heterozygotes was in the range of 0.1% to 0.67% per year. The majority (50%-75%) of thrombotic episodes were associated with other risk factors despite the common use of prophylactic anticoagulation during high-risk periods [Middeldorp, Meinardi et al 2001; Simioni et al 2002; Vossen, Conard et al 2005].

Anticipation

Anticipation is not observed.

Prevalence

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

Heterozygosity for factor V Leiden occurs in 3%-8% of the general US and European populations. The highest heterozygosity rate is found in Europe; the mutation 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 mutation [Ridker, Miletich et al 1997]. It is present in:

- 5.2% of Caucasian Americans
- 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 factor V Leiden is approximately 1:5000.

The factor V Leiden mutation 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

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

APC resistance. Although 95% of cases of APC resistance reflect the presence of the factor V Leiden mutation, 5% of individuals have repeatedly abnormal APC resistance tests in the absence of the factor V Leiden allele. Depending on the screening assay used, some cases may represent acquired APC resistance caused by high factor VIII levels, pregnancy, or a lupus anticoagulant effect. Two studies suggested that APC resistance not caused by the factor V Leiden allele is also a risk factor for venous thrombosis [de Visser et al 1999, Rodeghiero & Tosetto 1999]. In another study, resistance to APC was associated with an increased risk of stroke and TIA, independent of the factor V Leiden mutation [van der Bom et al 1996]. In rare cases, other genetic abnormalities may produce an APC-resistant phenotype (see Molecular Genetics).

Thrombophilic disorders. The differential diagnosis of venous thromboembolism includes several other inherited and acquired thrombophilic disorders. Because these thrombophilic disorders are not clinically distinguishable, laboratory testing is required for diagnosis in each case. Laboratory testing should be considered even after the identification of the factor V Leiden allele, as it often coexists with other disorders.

Inherited

Prothrombin thrombophilia. The mutation 20210G>A in the 3' untranslated region of the gene encoding prothrombin is found in 2% of the general population, 6% of individuals presenting with a first DVT, and up to 18% of individuals with a personal and family history of thrombosis. Coinheritance of both a factor V Leiden allele and the prothrombin gene mutation occurs in approximately one in 1000 in the general population and 1%-5% of individuals with venous thromboembolism [De Stefano et al 1999, Emmerich et al 2001].

A specific point mutation (677C>T) in the gene *MTHFR*, encoding methylenetetrahydrofolate reductase results in a variant thermolabile enzyme with reduced activity for the remethylation of homocysteine. Homozygosity for 677C>T predisposes to mild hyperhomocysteinemia, usually in the setting of suboptimal serum concentration of folate. Homozygosity for 677C>T occurs in 10%-20% of the general population.

Inherited abnormalities or deficiencies of the natural anticoagulant proteins C, S, and antithrombin are approximately tenfold less common than the factor V Leiden allele, 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 are rare and infrequently cause thrombophilia and thrombosis.

Acquired

High plasma concentration of homocysteine occurs in 10% of individuals with a first VTE and is associated with a two- to threefold increase in relative risk The plasma concentration of homocysteine reflects genetic as well as environmental factors and is more directly associated with thrombotic risk than molecular genetic testing of the *MTHFR* gene.

Antiphospholipid antibodies (APA) comprise a heterogeneous group of autoantibodies directed against proteins bound to phospholipids. Anticardiolipin antibodies and the related anti-beta$_2$-glycoprotein 1 antibodies are detected by solid-phase immunoassays. High titer IgG anticardiolipin antibodies and persistent lupus inhibitors are most strongly associated with arterial and venous thromboembolism [Galli et al 2003]. Antiphospholipid antibodies are frequently identified in individuals with factor V Leiden allele but can also cause APC resistance in the absence of the factor V Leiden mutation. The acquired APC resistance associated with APA should be distinguished from the spuriously low APC resistance ratio that occurs in individuals with a prolonged aPTT resulting from a lupus inhibitor. Testing for antiphospholipid antibodies should include assays for both anticardiolipin antibodies and lupus inhibitors, as only 50% of individuals with the antiphospholipid antibody syndrome have both types of antibodies.

Elevated clotting factor levels. A factor VIII level greater than 150% of normal is an independent risk factor for venous thromboembolism, conferring a four- to fivefold increase in risk in several studies [Koster et al 1995, Bank et al 2005]. High factor VIII concentrations also significantly increase the risk of recurrent thrombosis [Kyrle et al 2000].

Elevated plasma concentrations of factor IX and factor XI are associated with an approximately twofold increased risk of venous thromboembolism [Meijers et al 2000, van Hyickama et al 2000].

Elevated plasma prothrombin levels greater than 110%-115% of normal are associated with a twofold increased risk of VTE in the absence of prothrombin 20210G>A heterozygosity [Poort et al 1996, Legnani et al 2002]. The combination of oral contraceptives and high levels of prothrombin, factor V, or factor XI had a supra-additive effect on thrombotic risk (odds ratio range: 10-13) [van Hylckama Vlieg & Rosendaal 2003]. However, it is still unclear whether assessment of clotting factor concentrations should be included in a thrombophilia evaluation [Kamphuisen et al 2001].

Other

Although thrombosis has been reported in association with abnormalities in other coagulation or fibrinolytic proteins such as heparin cofactor II and PAI-1, a causal association has not been established.

Management

Evaluations Following Initial Diagnosis

Individuals heterozygous for the factor V Leiden allele should be tested for other inherited or acquired thrombophilic disorders. Testing should include the following:

- DNA testing for the prothrombin gene mutation (G-to-A substitution at nucleotide 20210)
- Measurement of total plasma concentration of homocysteine
- Multiple phospholipid-dependent coagulation assays for a lupus inhibitor
- Serologic assays for anticardiolipin antibodies (and in some cases anti-beta$_2$-glycoprotein 1 antibodies)

In 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) testing should also include assays of the following:

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

Although routine measurement of factor VIII levels is not recommended, testing may be useful in selected cases [Chandler et al 2002]. It is still unclear whether assessment of clotting factor concentrations should be included in a thrombophilia evaluation [Chandler et al 2002].

Treatment of Manifestations

Thrombosis—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 with a course of intravenous unfractionated heparin or low molecular weight heparin [Buller et al 2004]. Oral administration of warfarin is started concurrently with heparin (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 with homozygous factor V Leiden [Baglin et al 1998]. Heparin 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. The use of warfarin is safe in breast-feeding women.

The duration of oral anticoagulation therapy should be tailored to the individual, based on an assessment of the risks of VTE recurrence and anticoagulant-related bleeding. Approximately 30% of individuals with an incident VTE develop recurrent thrombosis within the subsequent ten years [Prandoni et al 1996]. Because individuals remain at risk for recurrence even after ten years, VTE is now considered a chronic disease. The optimal duration of anticoagulation for individuals who are heterozygous for the factor V Leiden allele is debated. Individuals with a spontaneous thrombosis and no identifiable provoking factors or persistent risk factors require a longer course of anticoagulation (e.g., ≥6-12 months). In contrast, individuals with transient (reversible) risk factors such as surgery require a shorter course of therapy [Hirsh et al 1997, Buller et al 2004]

Long-term oral anticoagulation should be considered in individuals with recurrent VTE, multiple thrombophilic disorders, or coexistent circumstantial risk factors and in individuals homozygous for the factor V Leiden allele. In these individuals at high risk for recurrence, the potential benefits from long-term warfarin may outweigh the bleeding risks.

Although unfractionated and low molecular-weight heparin and warfarin are still the primary antithrombotic agents in use, new antithrombotic agents are available for prophylaxis and treatment of arterial and venous thromboembolism. A pentasaccharide (fondaparinux) and

several direct thrombin inhibitors (lepirudin, argatroban) are approved for use in specific circumstances [Weitz et al 2004].

Graduated compression stockings should be worn for at least two years following an acute DVT.

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 allele because the 1%-2%/year risk of major bleeding from warfarin is greater than the estimated less than 1%/year risk of thrombosis.

Prophylactic anticoagulation. Because the initial thrombosis in factor V Leiden heterozygotes occurs in association with other circumstantial risk factors in 50% of cases, a short course of prophylactic anticoagulation during exposure to hemostatic stresses may prevent some of these episodes.

Prophylactic anticoagulation should be considered in high-risk clinical settings such as surgery, pregnancy, or prolonged immobilization, although currently no evidence confirms the benefit of primary prophylaxis for all asymptomatic carriers.

Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment in each individual case. Factors that may influence decisions about the indication for and duration of anticoagulation include age, family history, and other coexisting risk factors. Recommendations for prophylaxis at the time of surgery and other high risk situations are available in consensus guidelines [Geerts et al 2004].

Pregnancy. No consensus exists on the optimal management of factor V Leiden thrombophilia during pregnancy; guidelines are similar to those for individuals who are not pregnant [Bates et al 2004, Kujovich 2004b]. Until more specific guidelines are defined by prospective trials, decisions about anticoagulation should be individualized based on the thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

Prophylactic anticoagulation during pregnancy:

- **Is not routinely recommended** in asymptomatic heterozygous women with no history of thrombosis. These women should be warned about potential thrombotic complications, counseled about the risks and benefits of anticoagulation during pregnancy, and offered a four- to six-week course of anticoagulation after delivery, as the greatest thrombotic risk is in the initial postpartum period.
- **Is recommended** for women with a factor V Leiden allele and a history of unprovoked VTE. Unfractionated or low molecular-weight heparin should be given during pregnancy, followed by a four- to six-week course of anticoagulation postpartum.
- **Should be considered** for heterozygous women with a prior estrogen-related thrombosis who are also at an increased risk of recurrence [Bates et al 2004, Pabinger et al 2005].
- **Should be considered** for asymptomatic women with homozygous factor V Leiden or double heterozygosity for factor V Leiden and the prothrombin 20210G>A mutation, or with other combined thrombophilic defects, especially those with circumstantial risk factors (obesity, immobilization, multiple gestation) [Barbour et al 2001, Bates et al 2004].

Graduated elastic compression stockings are recommended for all women with a prior DVT [Bates et al 2004].

Prevention of Secondary Complications

Prevention of pregnancy loss. The current data on antithrombotic therapy in women with inherited thrombophilia and recurrent pregnancy loss are limited to several observational studies and two randomized trials.

In one study, 50 women with thrombophilia (including 20 factor V Leiden heterozygotes) and recurrent pregnancy loss were treated with enoxaparin throughout 61 subsequent pregnancies. The live birth rate was 75% with enoxaparin prophylaxis, compared to 20% in prior untreated pregnancies [Brenner et al 2000].

Another study reported a similar live birth rate of 77% with enoxaparin prophylaxis compared to 44% in untreated historical control women, suggesting a threefold greater likelihood of a favorable outcome. The beneficial effect of anticoagulation was most pronounced in women with factor V Leiden thrombophilia, although the small number of individuals studied precluded definitive conclusions [Carp et al 2003].

A prospective randomized trial compared prophylactic-dose enoxaparin and low-dose aspirin in women with factor V Leiden, the prothrombin 20210G>A mutation, or protein S deficiency and a single unexplained fetal loss. Enoxaparin prophylaxis was associated with a significantly higher live birth rate of 86% compared to 29% with aspirin, suggesting a 15-fold higher likelihood of a successful outcome. In the subgroup of women with heterozygous factor V Leiden (n=72) the live birth rate was 94% with enoxaparin prophylaxis, compared to 33% with aspirin, suggesting a 34-fold higher likelihood of a successful pregnancy outcome [Gris et al 2004].

A prospective randomized trial (Live-Enox) compared two different prophylactic doses of enoxaparin in thrombophilic women with a history of recurrent pregnancy loss (including 55 heterozygous for factor V Leiden). Both prophylactic doses (40 mg/day and 80 mg/day) achieved similar high live birth rates of 84% and 78%, respectively. These rates were substantially higher than the 23% live birth rate in prior untreated pregnancies [Brenner, Hoffman et al 2005].

No prospective randomized trials including an untreated control group confirming the benefit of low molecular weight heparin in preventing pregnancy loss in thrombophilic women have been performed. However, the concordant results of the studies cited above suggest that anticoagulation may improve pregnancy outcome in thrombophilic women.

Antithrombotic prophylaxis should be considered in selected women with factor V Leiden and unexplained pregnancy loss after an informed discussion of the risks and the data suggesting benefit [Kujovich 2005]. The evolving consensus in favor of prophylactic anticoagulation is reflected by the recent recommendations of the Seventh American College of Chest Physicians' Conference (ACCP) on antithrombotic therapy [Bates et al 2004]. ACCP guidelines suggest prophylactic-dose low molecular-weight or unfractionated heparin and low-dose aspirin for women with inherited thrombophilia and recurrent pregnancy loss or a single second- or third-trimester loss [Bates et al 2004].

Other pregnancy complications. Data supporting the benefit of antithrombotic therapy in thrombophilic women with other pregnancy complications are considerably more limited. In the Live-Enox study, the incidence of preeclampsia, placental abruption, and fetal growth retardation was substantially lower with enoxaparin prophylaxis than in prior untreated

pregnancies [Brenner, Bar et al 2005]. A study of thrombophilic women with prior fetal loss who received either enoxaparin or aspirin during a subsequent pregnancy showed that those who received enoxaparin had newborns with significantly higher birth weights and fewer classified as small for gestational age [Gris et al 2004]. However, neither study was designed to evaluate these complications as primary outcomes. ACCP guidelines suggest low-dose aspirin and prophylactic-dose low molecular-weight or unfractionated heparin for thrombophilic women with a history of severe or recurrent preeclampsia or placental abruption [Bates et al 2004]. Decisions about antithrombotic therapy in women with factor V Leiden and pregnancy complications should be based on an individual risk/benefit assessment. Assessment of the maternal thrombotic risk during pregnancy should also be incorporated into the decision regarding prophylaxis.

Surveillance

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

Selected 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. (See Prevention of Primary Manifestations.)

Agents/Circumstances to Avoid

Women with a factor V Leiden allele and a history of VTE should avoid oral contraceptive use and HRT.

Asymptomatic women who are heterozygous for factor V Leiden should be counseled on the risks of oral contraceptive and HRT use and should be encouraged to consider alternative forms of contraception and control of menopausal symptoms.

Asymptomatic heterozygous women electing to use oral contraceptives should avoid third-generation formulations because of their higher thrombotic risk.

Homozygous women with or without prior VTE should avoid oral contraceptives.

For heterozygous women who require short-term hormone replacement therapy for severe menopausal symptoms, low-dose transdermal preparations may have a lower thrombotic risk [Scarabin et al 2003, Straczek et al 2005].

Testing of Relatives at Risk

The genetic status of asymptomatic at-risk family members can be established using molecular genetic testing; however, the indications for family testing are unresolved. In the absence of evidence that early diagnosis of factor V Leiden reduces morbidity or mortality, decisions regarding testing should be made on an individual basis.

Clarification of factor V Leiden allele status may be useful in women considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age.

Asymptomatic factor V Leiden heterozygotes and homozygotes should be aware of the signs and symptoms of venous thromboembolism that require immediate medical attention and the potential need for prophylactic anticoagulation in high-risk circumstances. They should be informed that although a factor V allele is an established risk factor, it does not predict thrombosis with certainty because the clinical course is variable, even within the same family.

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

Therapies Under Investigation

Novel inhibitors of the initiation of coagulation and fibrin formation are still investigational [Weitz et al 2004]. None of these new antithrombotic agents are specific for factor V Leiden or thrombophilia in general.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

The phenotypes associated with factor V Leiden are inherited in an incomplete autosomal dominant manner.

Risk to Family Members — Proband Heterozygous for Factor V Leiden

Parents of a proband

- In most instances, one parent of a proband heterozygous for the factor V Leiden allele is also heterozygous for the factor V Leiden allele.
- Because of the relatively high prevalence of this allele in the general population, occasionally one parent is homozygous or both parents are heterozygous.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If one parent of a heterozygous proband is heterozygous, each sib of the proband has a 50% risk of being heterozygous for the factor V Leiden allele.
- If one parent is homozygous, each sib of the proband has a 100% risk of being heterozygous for the factor V Leiden allele.

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

Offspring of a proband

- Each offspring of a proband heterozygous for the factor V Leiden allele has a 50% chance of inheriting the factor V Leiden allele.
- If the proband's reproductive partner is heterozygous, each offspring has a 25% risk of being homozygous for the factor V Leiden allele, a 50% risk of being heterozygous for the factor V Leiden allele, and a 25% chance of being homozygous for both normal factor V alleles.

Risk to Family Members — Proband Homozygous for Factor V Leiden

Parents of a proband

- In most instances, both parents of an individual homozygous for the factor V Leiden mutation are heterozygous for factor V Leiden.
- Because of the relatively high prevalence of this allele in the general population, occasionally one parent is homozygous and the other parent is heterozygous.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If the parents of a proband homozygous for the factor V Leiden allele are heterozygotes, the sibs of the proband have a 25% risk of being homozygous for the factor V Leiden allele, a 50% risk of being heterozygous for the factor V Leiden allele, and a 25% chance of inheriting both normal factor V alleles.
- If one parent is homozygous for the factor V Leiden allele and the other parent is heterozygous, the sibs of the proband have a 50% chance of being homozygous for the factor V Leiden allele and a 50% chance of being heterozygous.

Offspring of a proband

- Each offspring of a proband homozygous for the factor V Leiden allele has a 100% chance of inheriting one factor V Leiden allele.
- If the affected person's reproductive partner is heterozygous, each offspring has a 50% chance of inheriting two factor V Leiden alleles and a 50% chance of inheriting one factor V Leiden allele.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. The family members of a person found to be heterozygous or homozygous for factor V Leiden are at risk.

Related Genetic Counseling Issues

Informed consent. Specific informed consent is not generally required for factor V Leiden genetic testing. However, prior to testing, individuals should be made aware that genetic test results have implications regarding risk to other family members and that attendant issues of confidentiality and possible insurance discrimination may arise [Grody et al 2001].

Testing at-risk family members. The presence of one or two factor V Leiden alleles can be identified in asymptomatic at-risk family members using molecular genetic testing.

The indications for testing at-risk family members are unresolved. Since heterozygosity for the factor V Leiden allele confers only a mildly increased risk of thrombosis, routine testing of at-risk family members is not recommended.

The low absolute thrombotic risk in asymptomatic heterozygotes argues against a general policy of testing at-risk family members. In the absence of evidence that early diagnosis of the heterozygous state reduces morbidity or mortality, the decision to test at-risk family members should be made on an individual basis. Clarification of factor V Leiden allele status may be beneficial in women considering use of oral contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age. At-risk family members often request factor V Leiden testing prior to exposure to recognized risk factors or simply from a desire to know their status. Individuals requesting testing for factor V Leiden and those identified as heterozygotes should be counseled regarding the implications of the diagnosis, including the need for prophylactic anticoagulation in high risk settings and the signs and symptoms that require immediate medical attention. They should be informed that although the presence of the factor V Leiden allele is an established risk factor, it does not predict thrombosis with certainty because the clinical course is variable even within the same family.

Testing of at-risk individuals during childhood. Asymptomatic at-risk individuals younger than age 18 years are not usually tested because thrombosis rarely occurs before young adulthood, even in homozygous individuals. Earlier testing may be considered in families with other known thrombophilic disorders or a strong history of thrombosis at a young age. The subcommittee for perinatal and pediatric hemostasis of the International Society for Thrombosis and Haemostasis has published guidelines for laboratory testing for thrombophilia in pediatric patients. A complete evaluation for genetic and acquired thrombophilic disorders is recommended for children with thrombosis [Manco-Johnson et al 2002] (See also the National Society of Genetic Counselors resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.)

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The diagnosis of factor V Leiden should be confirmed in an affected family member before prenatal testing is performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for factor V Leiden are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which one or two Factor V Leiden alleles have been identified in a parent. For laboratories offering PGD, see Testing. Although technically possible, PGD for factor V Leiden is rarely requested as the disorder may never cause thrombosis, and effective treatment is available.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Factor V Leiden Thrombophilia

Gene Symbol	Chromosomal Locus	Protein Name
F5	1q23	Coagulation factor V

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Factor V Leiden Thrombophilia

188055	THROMBOPHILIA DUE TO DEFICIENCY OF ACTIVATED PROTEIN C COFACTOR
227400	FACTOR V DEFICIENCY

Table C. Genomic Databases for Factor V Leiden Thrombophilia

Gene Symbol	Entrez Gene	HGMD
F5	2153 (MIM No. 227400)	F5

For a description of the genomic databases listed, click here.

Normal allelic variants: Haplotype analysis of the factor V gene strongly suggests that the mutation at nucleotide 1691 was a single event that occurred 20,000-30,000 years ago, after the evolutionary separation of Caucasians from Asians and Africans [Zivelin et al 1997]. The high prevalence of factor V Leiden among Caucasians suggests a balanced polymorphism with some type of survival advantage associated with the heterozygous state. Some investigators speculate that the mild hypercoagulable state conferred by the mutation might have had a beneficial effect in reducing mortality from bleeding associated with childbirth or trauma in pre-modern times [Zivelin et al 1997]. One retrospective study reported a significantly reduced risk of intrapartum bleeding complications in women heterozygous for factor V Leiden compared to women without the mutation [Lindqvist et al 1998]. Factor V Leiden hterozygotes undergoing elective cardiac surgery had significantly less blood loss and a lower risk of requiring a blood transfusion than individuals with a normal factor V genotype [Donahue et al 2003]. Another study suggested that the mutation is associated with a fivefold lower risk of spontaneous intracranial hemorrhage, consistent with the proposed protective effect [Corral et al 2001]. A study of women who had successful in vitro fertilization suggested that factor V Leiden enhances embryo implantation, thereby favoring the early survival of heterozygotes [Gopel et al 2001]. Analysis of a large randomized trial of individuals with severe sepsis showed that factor V Leiden heterozygotes had a threefold greater probability of survival, confirming animal models of sepsis that suggest a similar survival benefit [Kerlin et al 2003]. Although each of these hypothesized beneficial effects could account for the persistence of the mutation, a survival advantage remains to be confirmed.

Pathologic allelic variants: Two different mutations at the R306 APC cleavage site have been reported, only one of which is associated with APC resistance. A G-to-C point mutation in the codon for the R306 APC cleavage site (factor V Cambridge) was identified in a British individual with a history of thrombosis and APC resistance in the absence of the factor V Leiden mutation [Williamson et al 1998]. The mutation predicts the replacement of R with T at position 306, the second of three sequential APC cleavage sites in the factor V molecule. The same mutation was found in the individual's mother, who also had an abnormally low APC resistance value. However, it was not found in 600 other individuals presenting with thromboembolism or in a population of normal blood donors, suggesting that it is a very rare factor V variant. Factor V Cambridge was not found in several other series of individuals with VTE or unexplained recurrent pregnancy loss, or in healthy controls from other ethnic groups [Djordjevic et al 2004, Zammiti et al 2006].

A different mutation in the same codon predicting an R-to-G substitution at position 306 in factor V was identified in two of 43 Chinese individuals with a history of thrombosis and one control individual [Chan et al 1998]. The R306G mutation was not associated with APC resistance in the one individual tested with a coagulation screening assay. However, in a recombinant system, factor V Cambridge and the R306G variants showed identical APC resistance patterns with ratio values intermediate between those of wild type factor V and factor V Leiden [Norstrom et al 2002]. Another study found the R306G mutation in 4.7% of Hong Kong Chinese individuals, but did not identify it as a risk factor for thrombosis [Liang et al 1998].

Although the available evidence suggests that the R306T and R306G mutations alone are not major risk factors for thrombosis, they may contribute when combined with other genetic or acquired risk factors. There are anecdotal reports of double heterozygosity for factor V Cambridge and factor V Leiden or the prothrombin 20210G>A mutation in individuals with VTE [Santamaria et al 2005, Jeanne-Yvonne et al 2006].

Normal gene product: Coagulation factor V

Abnormal gene product: The point mutation predicts the replacement of a single amino acid (R506Q) at one of three APC cleavage sites in the factor Va molecule. The mutant factor V Leiden is inactivated at an approximately tenfold slower rate than normal and 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, Zoller et al 1996].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

The National Alliance for Thrombosis and Thrombophilia
PO Box 66018
Washington DC 20035-6018
Email: nattinfo@nattinfo.org
www.nattinfo.org

National Library of Medicine Genetics Home Reference
Factor V Leiden thrombophilia

March of Dimes
The Thrombophilias and Pregnancy

Teaching Case-Genetic Tools
Cases designed for teaching genetics in the primary care setting.
Case 39. Two Patients Presenting to a Walk-In Clinic with Symptoms of a Blood Clot

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Chapter Notes

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