# Thrombophilia

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## Key Points

- Mutations in several different genes are associated with an increased risk for venous thrombosis (VT).
- The lifetime risk for VT associated with the most common mutations is modest. For example, the lifetime risk for VT associated with factor V Leiden, a gene variant present in 5% of individuals of European descent, is estimated to be about 12% to 20%.
- However, inheritance of two copies of the factor V Leiden mutation, or the factor V Leiden mutation and a mutation in a second gene associated with VT, confers a high lifetime risk for VT.

## Learning Objectives

Participants will be able to:

- List the most common gene variants associated with increased risk for venous thrombosis;
- Explain the potential benefits and harms of testing for genetic susceptibility to venous thrombosis;
- Make judgments about clinical settings in which thrombophilia testing is appropriate.

## Family History Issues

A family history of venous thrombosis or pulmonary embolism may identify individuals at increased risk for inherited susceptibility to VT. If multiple relatives are affected, or relatives were affected at a young age, the likelihood of an inherited predisposition to venous thrombosis is increased.

## Red Flags 

The occurrence of venous thrombosis before age 40 years and in the absence of known risk factors for VT may be an indicator of an inherited

condition that confers a high lifetime risk for venous thrombosis.

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## Case 39. Two Patients Presenting to a Walk-In Clinic with Symptoms of a Blood Clot

**Patient #1**

Ms. Y, a 42-year-old woman, comes to the emergency room with a red, swollen leg. Physical examination suggests venous thrombosis (VT); a Doppler study confirms the diagnosis. The resident who saw the patient reports that she is moderately obese, smokes, and is on birth control pills. She has just returned from a visit with a close friend who lives 500 miles away (a 12-hour car ride). She has no other health problems. There is a possible family history of a pulmonary embolus in a great-aunt. The resident suggests testing for factor V Leiden, noting that the patient's relatively young age makes a genetic cause of her VT more likely.

**Patient #2**

Mr. J is a 20-year-old college student who has been bothered by a sore leg for three days. Physical examination suggests venous thrombosis (VT); a Doppler study confirms the diagnosis. The resident who saw the patient reports that the patient is healthy and physically active; he plays soccer three to four times a week. He has no known medical problems. The patient is not aware of any family history of blood clots. The resident was unable to identify any risk factors for VT. After hearing her fellow resident present Patient #1 (Ms. Y above), the resident says, "I suppose we could do factor V Leiden testing in this patient too, but I thought it was a useless test. It won't change the management of the patient, will it?"

## Clinical Care Issues

Both of these patients need anticoagulant therapy to treat their VT. Identification of a genetic predisposition will not change initial management.

However, genetic risk information has the potential to change long-term management in a small proportion of patients with VT. Identification of a genetic risk might also be of interest to family members. Consideration of

genetic testing needs to take into account the range of genetic and non-genetic risk factors associated with venous thrombosis, as outlined in Risk Assessment.

In addition, the potential benefits and risks associated with genetic information need to be considered, as outlined in Genetic Counseling and Testing, Interventions and Ethical/Legal/Social/Cultural Issues.

## Risk Assessment

VT is a multifactorial disorder, caused by the interactive or additive effect of genetic and non-genetic factors.

**Gene mutations and venous thrombosis.** Several gene mutations have been identified as factors in susceptibility to VT (Table 1). Most have modest effects. However, the combination of two moderate susceptibility factors may increase risk significantly. As shown in Table 1, a person with one copy of the factor V Leiden (FVL) mutation — the most common gene mutation associated with increased risk for VT — has a two- to sevenfold higher risk of developing VT than a person without this mutation. However, the absolute risk is not high: in a population-based study, the cumulative lifetime risk for VT for a person with FVL was estimated to be about 12% [Juul et al 2004]. Two other prospective studies of people with FVL (mean age in the early 40s) estimated the annual incidence of VT associated with FVL to be 0.58% [Middeldorp et al 2001] and 0.28% [Simioni et al 1999]; assuming an average risk of 0.43% and 50 years at risk, these figures would lead to an estimated lifetime of risk of a little over 20%.

**Table 1. Gene Variants Contributing to Venous Thrombosis Susceptibility (Thrombophilia)**

| Gene Variant | Prevalence (%) | Relative Risk (RR) |
|---|---|---|
| Factor V Leiden (FVL) | 1-5 | 2-7 |
| Prothrombin G20210A (PT) | 1-4 | 3 |
| Protein C deficiency | 0.4 | 8 |
| FVL and PT | 0.1 | 20 |
| Protein S deficiency | 0.13 | 20 |
| Antithrombin deficiency | 0.2 | 50 |

| | | |
|---|---|---|
| FVL homozygote (2 copies of FVL) | 0.02 | 22-80 |

Sources: Reich et al 2003, Juul et al 2004

**Non-genetic risk factors for venous thrombosis.** Most VT occurs in association with one or more non-genetic risk factors (Table 2), even among people with the common gene mutations FVL and PT.

**Table 2. Non-Genetic Risk Factors for Venous Thrombosis (VT)**

| Level of Risk | Risk Factor |
|---|---|
| **Strong**<br>(odds ratio >10) | • Fracture of hip or leg<br>• Hip or knee replacement within the last 3 months<br>• Major abdominal or pelvic surgery within the last 3 months<br>• Major trauma<br>• Spinal cord injury |
| **Moderate**<br>(odds ratio 2-9) | • Arthroscopic knee surgery<br>• Central venous line<br>• Chemotherapy<br>• Congestive heart failure or respiratory failure<br>• Hormone replacement therapy<br>• Malignancy<br>• Oral contraceptive therapy<br>• Paralytic stroke<br>• Pregnancy/ postpartum<br>• Previous venous thromboembolism |
| **Weak**<br>(odds ratio <2) | • Bed rest >3 days<br>• Immobility due to sitting (e.g., prolonged car or air travel)<br>• Age (>40 years)<br>• Laparoscopic surgery<br>• Obesity<br>• Pregnancy/ antepartum<br>• Varicose veins<br>• Smoking |

Sources: Anderson & Spencer 2003, Juul et al 2004, Kroegel & Reissig 2003

### Recurrent venous thrombosis

Although the common gene variants FVL and PT increase risk for VT, they do not appear to increase the rate of recurrent VT significantly when they are present in the heterozygous state [De Stefano et al 1999, Ridker et al 2003].

However, patients with higher genetic risk also appear to have a higher risk for recurrent VT. For example, one study found that people with both FVL and PT had a two- to fourfold higher recurrence risk for VT, compared to people who were heterozygous for the FVL mutation [De Stefano et al 1999]. Similarly, a population-based study estimated the lifetime risk for VT at 80% for people homozygous for the FVL mutation, compared to 12% for FVL heterozygotes [Juul et al 2004]. Another study observed a VT recurrence risk almost twice as high in FVL homozygotes than in heterozygotes [Procare Group 2003].

## Genetic Counseling and Testing

### Testing of Ms. Y and Mr. J

The residents have raised the question of genetic testing for Ms. Y and Mr. J, the two patients with VT seen in the walk-in clinic. A stronger case can be made for testing Mr. J than for Ms. Y.

Mr. J developed a VT at a young age and in the absence of any known non-genetic risk factors. From an epidemiological perspective, this presentation increases the likelihood of a significant genetic risk that, if found, would result in a recommendation for long-term anticoagulation — for example, an antithrombin deficiency or homozygous FVL. Although he does not report any family history of VT, his presentation is sufficiently unusual to merit consideration of a genetic diagnosis. In addition, it is not unusual for young adults to be unaware of disease history in their relatives; further exploration of the family history (for example, by asking Mr. J to ask his parents about medical problems in relatives) might reveal relatives with a history of VT or pulmonary embolism. In order to find the rare gene variants that are associated with higher risk (Table 1), experts recommend testing with a thrombophilia panel when the suspicion for genetic risk is high.

In the case of Ms. Y, there is less reason to suspect an inherited cause of her VT. She is over 40, and her VT occurred in the setting of several mild risk factors (smoking; obesity; recent long car ride) and one moderate risk factor

(oral contraceptive use) for VT. Although there is a history of VT in a great-aunt, this relative is not closely related to Ms. Y (a great-aunt is a third-degree relative), and unless further investigation revealed additional cases of VT in the family, this history is not particularly suggestive of an inherited cause. Because Ms. Y has had VT, she is more likely to have FVL or PT than a person from the general population; nevertheless, a positive test result for one of these gene mutations would not change her clinical management.

**Implications of testing for family members.** If a genetic predisposition to VT were identified in either Mr. J or Ms. Y, other family members would be also at risk of having the genetic predisposition. In the case of inherited conditions associated with very high risk for VT (such as homozygous FVL and antithrombin deficiency) preventive use of anticoagulation might be considered. For example, prophylactic low-dose heparin is recommended during pregnancy for women who are homozygous for FVL [Bates et al 2004]. The benefit of genetic risk knowledge is less clear for heterozygous FVL or PT. Some family members might consider this information of value. For example, a woman with FVL might decide against the use of oral contraceptives (OC) because the risk for VT is higher in women with FVL who use OC (although the absolute risk is small even for women with FVL) [Vandenbroucke et al 1994]. There is no urgency in pursuing testing for this purpose, and genetic counseling may help family members to think about the pros and cons of testing.

### Genetic counseling

After diagnosis of a genetic condition associated with a high risk for VT, genetic counseling provides the patient and family with information about how the genetic condition is inherited and who else in the family might be at risk. For example, if Mr. J were found to be homozygous for FVL, his siblings would each have a 25% chance of also being homozygous; his parents would each have a single copy of FVL. In addition to providing information about the genetic condition and testing options, the genetic counselor can give the family a chance talk about their concerns, and provide emotional support, which is often helpful for families as they absorb the implications of a genetic diagnosis.

## Interventions

If genetic testing reveals a single copy of FVL or PT, the identification of genetic risk does not change clinical management of VT. Awareness of risk could potentially influence some choices. For example, a woman with FVL

might choose not to use oral contraceptives or hormone replacement therapy; or knowledge of FVL or PT status might cause a person to take precautions to reduce VT risk, such as avoiding prolonged sitting during air travel. However, the efficacy of such measures is unknown.

If genetic testing reveals an inherited conditions associated with high lifetime risk for VT and increased VT recurrence risk, such as homozygous FVL or antithrombin deficiency, clinical recommendations are affected. For patients with VT, prolonged (lifetime) anticoagulant therapy is recommended. For patients who have not had a VT, prophylactic anticoagulation is recommended in high-risk situations such as pregnancy, surgery, and long air flights.

## Ethical/Legal/Social/Cultural Issues

**Potential risks of genetic information.** Knowledge of genetic risk could have harmful personal or social effects. For example, a pilot interview study suggested that knowledge of FVL status may lead to worry, guilt related to passing risk on to children, stigmatization by others, or insurance discrimination [Bank et al 2004]. These risks need to be weighed against the medical value of the information.

**Cultural value placed on information.** A high value is placed on information in the US medical culture. For example, some experts may opt for thrombophilia testing in order to seek an explanation for a VT event, even if test results will not change clinical management [Reich et al 2003]. This approach leads to a potential treatment risk. When a genetic risk is identified, both the doctor and the patient are likely to be tempted to pursue treatment, with its attendant risks, in spite of the absence of evidence that the treatment improves health outcome.

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## Resources

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

- **National Library of Medicine Genetics Home Reference**

**Factor V Leiden thrombophilia**

- ***GeneReview*: Factor V Leiden Thrombophilia**
- **GeneTests Online Medical Genetics Information Resource**

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