



**EDUCATIONAL OBJECTIVE:** Readers will evaluate the risk of venous thromboembolism in patients who have the factor V Leiden mutation

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# Factor V Leiden: How great is the risk of venous thromboembolism?

## ABSTRACT

The factor V Leiden mutation, the most common inherited cause of thrombophilia, causes a mild hypercoagulable state. We describe a 29-year-old man, heterozygous for factor V Leiden, who developed extensive pulmonary emboli with concomitant bilateral deep venous thrombosis, likely provoked by prolonged immobility during a car trip. We then review the diagnosis, therapy, screening, and prognosis of venous thromboembolism related to factor V Leiden.

## KEY POINTS

The pathogenesis of venous thromboembolism is complex and multifactorial, often reflecting the interplay between environmental, clinical, and genetic factors.

Factor V Leiden increases the risk of venous thromboembolism but by itself does not appear to increase the risk of arterial thrombosis.

Often, people with factor V Leiden may have additional risk factors that increase the rate of venous clots, such as older age, surgery, obesity, immobility, prolonged travel, hospitalization, oral contraceptive use, hormonal replacement therapy, pregnancy, and malignancy.

General measures and precautions are needed to minimize the risk of venous thromboembolism in people with the factor V Leiden mutation, especially when modifiable factors are present, such as obesity and long periods of immobilization.

A 29-YEAR-OLD WHITE MAN with no chronic medical problems presents to the emergency department with shortness of breath, left-sided pleuritic chest pain, cough, and hemoptysis. These symptoms began abruptly 1 day ago and have persisted. He also has mild pain and swelling in both calves. He denies having any fever, night sweats, or chills. On further questioning, he reports having taken a long, nonstop driving trip that lasted 8 hours 1 week ago.

His medical history is negative, and he specifically reports no history of deep venous thrombosis or pulmonary embolism. He underwent appendectomy 10 years ago but has had no other operations. He does not take any medications. His family history is noncontributory and is negative for venous thromboembolism. He smokes and uses alcohol occasionally but not illicit drugs.

**Examination.** He appears to be in considerable distress because of his chest pain. His temperature is 100.4°F (38.0°C), blood pressure 125/70 mm Hg, heart rate 125 beats per minute, respiratory rate 26 breaths per minute, oxygen saturation 92% on room air, and body mass index 19 kg/m<sup>2</sup>.

Chest examination reveals diminished vesicular breathing in the left base, which is normal to percussion without added sounds. Both calves are swollen and tender to palpation without skin discoloration. The rest of his examination is normal.

**Laboratory values:**

- White blood cell count  $9.3 \times 10^9/L$  (reference range 4.5–11.0)

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**FIGURE 1.** The patient's chest radiograph shows small atelectatic changes in the left lung base (arrow).

- Hemoglobin 15.9 g/dL (14.0–17.5)
- Platelets  $205 \times 10^9/L$  (150–350)
- Sodium 140 mEq/L (136–142)
- Potassium 3.9 mEq/L (3.5–5.0)
- Chloride 108 mEq/L (96–106)
- Bicarbonate 23 mEq/L (21–28)
- Blood urea nitrogen 14 mg/dL (8–23)
- Creatinine 0.9 mg/dL (0.6–1.2)
- Glucose 95 mg/dL (70–110)
- International normalized ratio (INR) 0.90 (0.00–1.2)
- Partial thromboplastin time 27.5 seconds (24.6–31.8)
- Creatine phosphokinase 205 U/L (39–308)
- Troponin T < 0.015 ng/mL (0.01–0.045).

### **Pulmonary embolism is diagnosed**

Electrocardiography shows sinus tachycardia. Chest radiography shows small atelectatic changes at the left lung base (FIGURE 1). Pulmonary embolism is suspected, and a serum D-dimer level is obtained; it is 4,054 ng/mL (ref-

erence range < 500). Computed tomography of the chest confirms bilateral acute pulmonary emboli (FIGURE 2). Doppler ultrasonography of both legs reveals bilateral deep venous thrombosis. Echocardiography shows mildly elevated right ventricular systolic pressure at 47 mm Hg.

### **Factor V Leiden is diagnosed, and the patient recovers with treatment**

Anticoagulation is started in the emergency department.

Given this patient's young age and clot burden, a hypercoagulable state is suspected. Thrombophilia screening is performed, with tests for the factor V Leiden mutation, the prothrombin G20210A mutation, and antiphospholipid and lupus anticoagulant antibodies. The rest of the thrombophilia panel, including antithrombin III, factor VIII, protein C, and protein S, is deferred because the levels of these substances would be expected to change during the acute thrombosis.

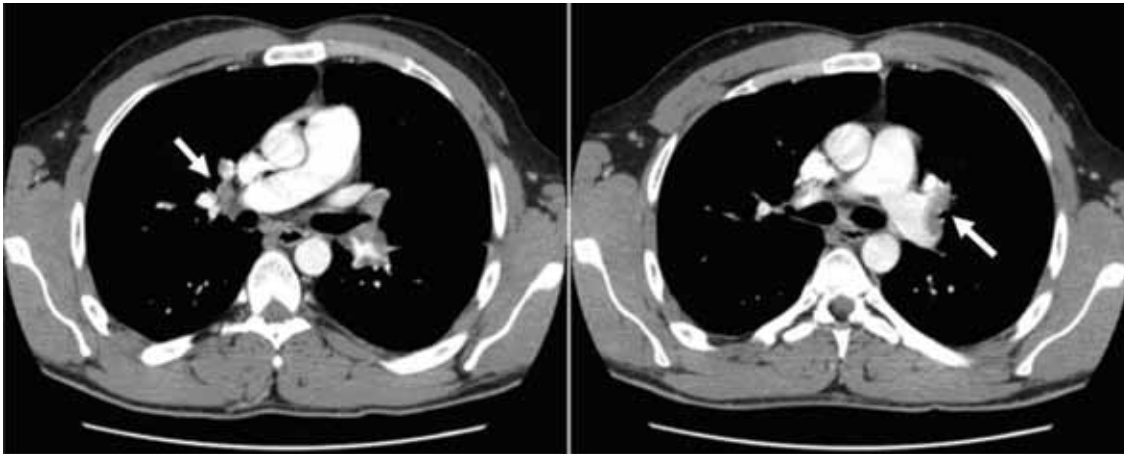
The direct test for factor V Leiden mutation is positive for the heterozygous type. The test for the prothrombin G20210A mutation is negative, and his antiphospholipid antibody levels, including the lupus anticoagulant titer, are within normal limits.

The patient is kept on a standard regimen of unfractionated heparin, overlapped with warfarin (Coumadin) until his INR is 2.0 to 3.0 on 2 consecutive days. His hospital course is uneventful and his condition gradually improves.

He is discharged home to continue on oral anticoagulation for 6 months with a target INR of 2.0 to 3.0. Two weeks after completing his anticoagulation therapy, his levels of antithrombin III, factor VIII, protein C, and protein S are all within normal limits.

### **■ FACTOR V LEIDEN IS COMMON**

Factor V Leiden is the most common inherited thrombophilia, with a prevalence of 3% to 7% in the general US population,<sup>1</sup> approximately 5% in whites, 2.2% in Hispanics, and 1.2% in blacks.<sup>2</sup> Its prevalence in patients with venous thromboembolism, however, is 50%.<sup>1,3</sup> The annual incidence of venous thromboembolism in patients with factor V Leiden is 0.5%.<sup>4,5</sup>



**FIGURE 2.** Computed tomography of the chest showed numerous filling defects within the upper and lower branches of the pulmonary artery (arrows), the right and left sides, suggestive of extensive acute pulmonary embolism. The main portions of the right and left main pulmonary artery and main central pulmonary artery are patent without embolus.

### ■ MORE COAGULATION, LESS ANTICOAGULATION

Factor V has a critical position in both the coagulant and anticoagulant pathways. Factor V Leiden results in a hypercoagulable state by both increasing coagulation and decreasing anticoagulation.

This mutation causes factor V to be resistant to being cleaved and inactivated by activated protein C, a condition known as APC resistance. As a result, more factor Va is available within the prothrombinase complex, increasing coagulation by increased generation of thrombin.<sup>6-8</sup>

Furthermore, a cofactor formed by cleavage of factor V at position 506 is thought to support activated protein C in degrading factor VIIIa (in the tenase complex), along with protein S. People with factor V Leiden lack this cleavage product and thus have less anticoagulant activity from activated protein C. The increased coagulation and decreased anticoagulation appear to contribute equally to the hypercoagulable state in factor V Leiden-associated APC resistance.<sup>9-11</sup>

Heterozygosity for the factor V Leiden mutation accounts for 90% to 95% of cases of APC resistance. A much smaller number of people are homozygous for it.<sup>1</sup>

People who are homozygous for factor V Leiden are at higher risk of venous thromboembolism than those who are heterozygous

for it, since the latter group's blood contains both factor V Leiden and normal factor V. The normal factor V allows anticoagulation via the second pathway of inactivation of factor VIIIa by activated protein C, giving some protection against thrombosis. In people who are homozygous for factor V Leiden, the lack of normal factor V acting as an anticoagulant protein results in a higher thrombotic risk.<sup>9-11</sup>

### Other factor V mutations may also cause APC resistance

Although factor V Leiden is the only genetic defect for which a causal relationship with APC resistance has been clearly determined, other, rarer hereditary factor V mutations or polymorphisms have been described, such as factor V Cambridge (Arg306Thr)<sup>12</sup> and factor V Hong Kong (Arg306Gly).<sup>13</sup> These mutations may result in APC resistance, but their clinical association with thrombosis is less clear.<sup>14</sup> Factor V Liverpool (Ile359Thr) is associated with a higher risk of thrombosis, apparently because of reduced APC-mediated inactivation of factor Va and because it is a poor cofactor with activated protein C for the inactivation of factor VIIIa.<sup>15</sup>

An R2 haplotype has also been described in association with APC resistance.<sup>16,17</sup> The phenomenon may be due to a reduction in activated protein C cofactor activity.<sup>9</sup> However, not all studies have been convincing regarding the role of this haplotype in clinical disease.<sup>18</sup>

**Prevalence of  
factor V Leiden:  
5% in whites,  
2.2% in Hispanics,  
1.2% in blacks,  
and 50%  
in people  
with venous  
thrombo-  
embolism**

Coinheritance of this haplotype with factor V Leiden may increase the risk of venous thromboembolism above that associated with factor V Leiden alone.<sup>19</sup>

Although factor V Leiden is the most common cause of inherited APC resistance, other changes in hemostasis cause acquired APC resistance and may contribute to the thrombotic tendency in these patients.<sup>20–22</sup> The most common causes of acquired APC resistance include elevated factor VIII levels,<sup>23–25</sup> pregnancy,<sup>26–28</sup> use of oral contraceptives,<sup>29,30</sup> and antiphospholipid antibodies.<sup>31</sup>

### ■ USUALLY MANIFESTS AS DEEP VEIN THROMBOSIS

Factor V Leiden usually manifests as deep vein thrombosis with or without pulmonary embolism, but thrombosis in unusual locations also occurs.<sup>32</sup>

The risk of a first episode of venous thromboembolism is two to five times higher with heterozygous factor V Leiden. However, even though the relative risk is high, the absolute risk is low. Furthermore, despite the higher risk of venous thrombosis, there is no evidence that heterozygosity for factor V Leiden increases the overall mortality rate.<sup>4,33–36</sup>

In people with homozygous factor V Leiden or with combined inherited thrombophilias, the risk of venous thromboembolism is increased to a greater degree: it is 20 to 50 times higher.<sup>7,8,37–39</sup> However, whether the risk of death is higher is not clear.

### ■ VENOUS THROMBOEMBOLISM IS MULTIFACTORIAL

The pathogenesis of venous thromboembolism is multifactorial and involves an interaction between inherited and acquired factors. Very often, people with factor V Leiden have additional risk factors that contribute to the development of venous clots, and it is very unusual for them to have thrombosis in the absence of these additional factors.

These factors include older age, surgery, obesity, prolonged travel, immobility, hospitalization, oral contraceptive use, hormonal replacement therapy, pregnancy, and malignancy. They increase the risk of venous

thrombosis in normal individuals as well, but more so in people with factor V Leiden.<sup>40–43</sup>

Testing for other known causes of thrombophilia may also be pursued. These include elevated homocysteine levels, the factor II (prothrombin) G20210A mutation, anticardiolipin antibody, lupus anticoagulant, and deficiencies of antithrombin III, protein C, and protein S.

Factor V Leiden by itself does not appear to increase the risk of arterial thrombosis, ie, heart attack and stroke.<sup>33,38,44–46</sup>

### Family history: A risk indicator for venous thrombosis

Family history is an important indicator of risk for a first venous thromboembolic event, regardless of other risk factors identified. The risk of a first event is two to three times higher in people with a family history of thrombosis in a first-degree relative. The risk is four times higher when multiple family members are affected, at least one of them before age 50.<sup>47</sup>

In people with genetic thrombophilia, the risk of thrombosis (especially unprovoked thrombosis at a young age) is also higher in those with a strong family history than in those without a family history. In those with factor V Leiden, the risk of venous thromboembolism is three to four times higher if there is a positive family history. The risk is five times higher in carriers of factor V Leiden with a family history of venous thromboembolism before age 50, and 13 times higher in those with more than one affected family member.<sup>47</sup>

Possible shared environmental factors or coinheritance of other unidentified genetic factors may also contribute to the higher susceptibility in thrombosis-prone families.

### ■ TESTING FOR APC RESISTANCE AND FACTOR V LEIDEN

The factor V Leiden mutation can be detected directly by genetic testing of peripheral blood mononuclear cells. This method is relatively time-consuming and expensive, however.

At present, the most cost-effective approach is to test first for APC resistance using a second-generation coagulation assay—the modified APC sensitivity test. In this clot-based method, the patient's sample is prediluted

**Even with factor V Leiden, people rarely develop venous thromboembolism without additional risk factors**

ed with factor V-deficient plasma to eliminate the effect of lupus anticoagulants and factor deficiencies that could prolong the baseline clotting time, and heparin is inactivated by polybrene. Then either an augmented partial-thromboplastin-time-based assay or a tissue-factor-dependent factor V assay is performed.

This test is nearly 100% sensitive and specific for factor V Leiden, in contrast to the first-generation, or classic, APC sensitivity test, which lacked specificity and sensitivity for it.<sup>9–11,48–60</sup> This modification also permits testing of patients receiving anticoagulants or who have abnormal augmented partial thromboplastin times due to coagulation factor deficiencies.

A positive result on the modified APC sensitivity test should be confirmed by a direct genetic test for the factor V Leiden mutation. An APC resistance assay is unnecessary if a direct genetic test is used initially.

#### ■ HOW LONG TO GIVE ANTICOAGULATION AFTER VENOUS THROMBOEMBOLISM?

Patients who have had an episode of venous thromboembolism have to be treated with anticoagulants.

In general, the initial management of venous thromboembolism in patients with heritable thrombophilias is no different from that in any other patient with a clot. Anticoagulants such as warfarin are given at a target INR of 2.5 (range 2.0–3.0).<sup>32</sup> The duration of treatment is based on the risk factors that resulted in the thrombotic event.

After a first event, some authorities recommend anticoagulant therapy for 6 months.<sup>32</sup> A shorter period (3 months) is recommended if there is a transient risk factor (eg, surgery, oral contraceptive use, travel, pregnancy, the puerperium) and the thrombosis is confined to distal veins (eg, the calf veins).<sup>32</sup>

Factor V Leiden does not necessarily increase the risk of recurrent events in patients who have a transient risk factor. Therefore, people who are heterozygous for this mutation do not usually need to be treated lifelong with anticoagulants if they have had only one episode of deep vein thrombosis or pulmonary embolism, given the risk of bleeding associated with anticoagulation, unless they

have additional risk factors.

Conditions in which indefinite anticoagulation may be required after careful consideration of the risks and benefits are:

- Life-threatening events such as near-fatal pulmonary embolism
- Cerebral or visceral vein thrombosis
- Recurrent thrombotic events
- Additional persistent risk factors (eg, active malignant neoplasm, extremity paresis, and antiphospholipid antibodies)
- Combined thrombophilias (eg, combined heterozygosity for factor V Leiden and the prothrombin G20210A mutation)
- Homozygosity for factor V Leiden.<sup>32,46,48</sup>

Factor V Leiden by itself or combined with other thrombophilic abnormalities is not associated with a higher risk of recurrent venous thromboembolism during warfarin therapy (a possible exception is the combination of factor V Leiden plus antiphospholipid antibodies).<sup>32,34</sup> Furthermore, current evidence suggests that no thrombophilic defect is a clinically important risk factor for recurrent venous thromboembolism after anticoagulant therapy is stopped. All these facts indicate that clinical factors are probably more important than laboratory abnormalities in determining the duration of anticoagulation therapy.<sup>32,35,36,61–63</sup>

#### ■ PRIMARY PROPHYLAXIS IN PATIENTS WITH FACTOR V LEIDEN

Factor V Leiden is only one of many risk factors for deep vein thrombosis or pulmonary embolism. If carriers of factor V Leiden have never had a blood clot, then they are not routinely treated with an anticoagulant. Rather, they should be counseled about reducing or eliminating other factors that may add to their risk of developing a clot in the future.

Usually, the effect of risk factors is additive: the more risk factors present, the higher the risk.<sup>46,50</sup> Sometimes, however, the effect of multiple risk factors is more than additive.

Some risk factors, such as genetics or age, are not alterable, but many can be controlled by medications or lifestyle modifications. Therefore, general measures and precautions are recommended to minimize the risk of thrombosis. For example:

**The most cost-effective way to detect factor V Leiden is to test first for APC resistance using the modified APC sensitivity test**

**Losing weight** (if the patient is overweight) is an important intervention for risk reduction, since obesity is probably the most common modifiable risk factor for developing blood clots.

**Avoiding long periods of immobility** is recommended. For example, if the patient is taking a long car ride (more than 2 hours), then stopping every few hours and walking around for a few minutes is a good way to keep the blood circulating. If the patient has a desk job, getting up and walking around the office periodically is advised. On long airplane trips, a walk in the aisle every so often and preventing dehydration by drinking plenty of fluids and avoiding alcohol are recommended.

**Wearing elastic stockings** with a graduated elastic pressure may prevent deep venous thrombosis from developing on long flights.<sup>63–65</sup>

**Staying active** and getting regular exercise through such activities as walking, bicycling, or swimming are helpful.

**Avoiding smoking** is critical.<sup>50,63</sup>

**Thromboprophylaxis** is recommended for most acutely ill hospitalized patients, especially those confined to bed with additional risk factors. Guidelines for prophylaxis are based on an individualized risk assessment and not on thrombophilia status. Prophylactic anticoagulation is routinely recommended for patients undergoing major high-risk surgery, such as an orthopedic, urologic, gynecologic, or bariatric procedure. Any excess thrombotic

risk conferred by thrombophilia is likely small compared with the risk of surgery, and recommendations on the duration and intensity of thromboprophylaxis are not based on thrombophilic status.<sup>46,48</sup>

**Education.** Pain, swelling, redness of a limb, unexplained shortness of breath, and chest pain are the most common symptoms of deep vein thrombosis and pulmonary embolism.<sup>46,50</sup> It is crucial to teach patients with factor V Leiden to recognize these symptoms and to seek early medical attention in case they experience any of them.

### ■ SCREENING FAMILY MEMBERS FOR THE FACTOR V LEIDEN MUTATION

Factor V Leiden by itself is a relatively mild thrombophilic defect that does not cause thrombosis in all carriers, and there is no evidence that early diagnosis reduces rates of morbidity or mortality. Therefore, routine screening of all asymptomatic relatives of affected patients with venous thrombosis is not recommended. Rather, the decision to screen should be made on an individual basis.<sup>50,66</sup>

Screening may be beneficial in selected cases, especially when patients have a strong family history of recurrent venous thrombosis at a young age (younger than 50 years) and the family member has additional risk factors for venous thromboembolism such as oral contraception or is planning for pregnancy.<sup>32,48,49,66</sup> ■

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