



**STEVEN R. DEITCHER, MD**

Head, Section of Clinical Thrombosis,  
Department of Vascular Medicine,  
Cleveland Clinic

**ENRICO CAIOLA, MD**

Department of General Internal Medicine,  
Cleveland Clinic

**AMIR JAFFER, MD**

Department of General Internal Medicine,  
Cleveland Clinic

## FACTOR V LEIDEN AND PROTHROMBIN G20210A

# Demystifying two common genetic predispositions to venous thrombosis

### ABSTRACT

Two recently discovered genetic abnormalities substantially increase the risk of venous thromboembolism. Yet we do not advocate screening for these abnormalities except in cases in which the information gained would affect the course of action.

### KEY POINTS

We recommend testing in cases of idiopathic venous thromboembolism, venous thromboembolism in unusual sites, recurrent venous thromboembolism, and venous thromboembolism plus a family history of thrombosis; and in relatives of patients with known mutations if the results will affect a decision to take oral contraceptives or hormone replacement therapy, become pregnant, or undergo elective surgery.

The Leiden mutation in the gene for factor V renders factors V and Va more resistant to degradation by activated protein C. The G20210A mutation on the prothrombin gene results in increased prothrombin activity. Both have the end result of increasing thrombin generation.

Approximately 5% of white Americans are heterozygous for the factor V Leiden mutation, and 2% are heterozygous for the prothrombin G20210A mutation. Both mutations are much less common in African Americans and are rare in persons of Asian descent.

Persons who are heterozygous for either the factor V Leiden mutation or the prothrombin G20210A mutation have approximately a sevenfold increased risk of venous thromboembolism.

**J**UST BECAUSE a new test is available does not mean we should use it indiscriminately. A case in point is genetic testing for mutations that increase one's susceptibility to venous thromboembolism.

The recently discovered G1691A (Leiden) mutation in the gene for factor V and the G20210A mutation in the gene for prothrombin substantially increase the risk of thromboembolism in persons who carry them. Yet, in most cases, the knowledge that a patient carries one of these mutations serves no useful purpose, as it does not affect his or her treatment. Pending the results of ongoing clinical trials, physicians should use testing for hypercoagulability less, and focus on effective prevention and treatment of venous thromboembolism more.

This article addresses commonly asked questions about the factor V Leiden and prothrombin G20210A mutations and outlines an evidence-based, practical approach to testing for them.

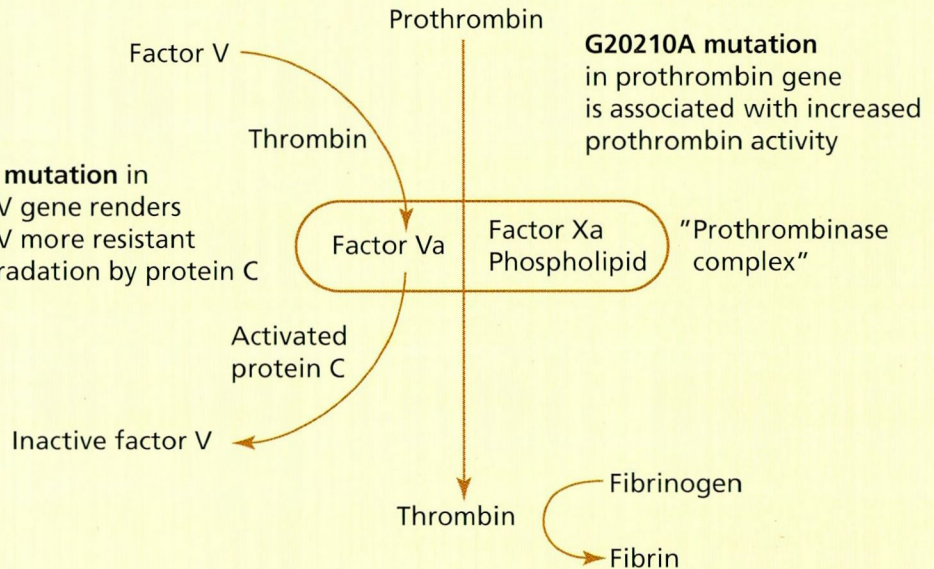
### WHAT ARE THE RISK FACTORS FOR VENOUS THROMBOEMBOLISM?

There are three major categories of risk factor for venous thromboembolism:

- Venous stasis, eg, due to prolonged immobilization after surgery
- Vascular endothelial cell injury, eg, due to trauma or cancer chemotherapy
- Hypercoagulable states, which can be either acquired (eg, due to pregnancy or oral contraceptive use) or inherited.

Venous thromboembolism can also arise without any identifiable precipitant, although research is revealing that most patients with





**FIGURE 1.** How genetic mutations can increase the risk of thromboembolism. A key molecule in the coagulation cascade is thrombin, which catalyzes the conversion of fibrinogen to fibrin. Two recently discovered mutations increase the risk of thromboembolism, at least in part, by leading to increased activity of thrombin.

**Most patients with "idiopathic" thromboembolism have an inherited disorder**

"idiopathic" venous thromboembolism actually have an inherited prothrombotic disorder. Before 1993, laboratory evaluations for inherited hypercoagulability consisted primarily of measurements of the functional activities of the natural anticoagulants antithrombin III, protein C, and protein S. Such an evaluation identified an underlying biochemical risk factor in only 15% to 20% of patients with idiopathic venous thromboembolism. The relatively recent discovery of the factor V Leiden and prothrombin G20210A mutations has dramatically enhanced our ability to identify an abnormality in such patients: now, more than 50% can be found to have an identifiable risk factor.

**■ HOW DO THESE MUTATIONS PREDISPOSE TO THROMBOSIS?**

To understand how the factor V Leiden and prothrombin G20210A mutations predispose to thrombosis, we must appreciate the pivotal role of thrombin in coagulation. Thrombin is generated from its precursor, prothrombin, by the "prothrombinase" complex of proteins.

An important cofactor in this conversion is factor Va (FIGURE 1).

Thrombin catalyzes the conversion of fibrinogen to fibrin. In addition, it activates platelets, factor VIII, factor V, and factor XIII. Therefore, any increase in the level or activity of thrombin tends to increase coagulation activation and the risk of thrombosis.

The factor V Leiden and G20210A mutations have effects that tend to increase thrombin activity, and carriers of these mutations as a group tend to have higher thrombin activity than do persons without these mutations. However, there is a great deal of overlap in thrombin levels between populations with and without these mutations. Therefore, it would be overly simplistic to ascribe the effects of these mutations solely to their effects on thrombin, although thrombin provides a useful conceptual framework.

**What are activated protein C resistance and the factor V Leiden mutation?**

Activated protein C, a natural anticoagulant, breaks down factor Va and factor VIIIa, resulting in less thrombin generation and less fibrin.





Conversely, anything that makes factor Va more resistant to being broken down by activated protein C will lead to more factor Va, more thrombin, and more fibrin.

**Factor V Leiden** is a single point mutation: a G-to-A substitution at nucleotide 1691 (ie, G1691A in the shorthand of genetics) of the gene that codes for factor V. Inherited in an autosomal-dominant fashion, it has the effect of rendering factors V and Va resistant to degradation by activated protein C.<sup>1</sup>

**Activated protein C resistance**, first described in 1993, is an umbrella term. More than 90% of cases are due to the factor V Leiden mutation, with the remaining 10% being due to pregnancy, oral contraceptive use, select antiphospholipid antibodies, and other factor V point mutations such as factor V Hong Kong and factor V Cambridge.<sup>2</sup> It is defined as a decreased plasma anticoagulant response to activated protein C *in vitro*.<sup>3,4</sup> In selected populations, it is the most common inherited risk factor for venous thromboembolism.<sup>5</sup>

The terms “factor V Leiden” and “activated protein C resistance” should not be used synonymously—activated protein C resistance in the absence of the factor V Leiden mutation remains an independent risk factor for venous thromboembolism.<sup>6</sup>

### What is the prothrombin G20210A mutation?

G20210A is another single point mutation: a G-to-A substitution at nucleotide 20210 of the 3'-untranslated region in the gene that codes for prothrombin, the precursor of thrombin. Persons with this mutation tend to have increased plasma prothrombin activity and an increased risk of venous and arterial thrombosis.<sup>7</sup> The increased plasma prothrombin activity is believed to mediate the prothrombotic effect: the more prothrombin, the more thrombin and the more fibrin.

### ■ HOW COMMON ARE THESE MUTATIONS?

Activated protein C resistance has been found in approximately one third of patients with idiopathic venous thromboembolism referred for thrombotic tendency evaluation, and the prevalence may be as high as 60% in

**TABLE 1**

### Prevalence of the factor V Leiden mutation in various ethnic groups in the United States

ETHNIC GROUP	PREVALENCE
Whites	5.27%
Hispanics	2.21%
Native Americans	1.25%
African Americans	1.23%
Asian Americans	0.45%

DATA FROM RIDKER PM, MILETICH JP, HENNEKENS CH, BURING JE. ETHNIC DISTRIBUTION OF FACTOR V LEIDEN IN 4047 MEN AND WOMEN. IMPLICATIONS FOR VENOUS THROMBOEMBOLISM SCREENING. *JAMA* 1997; 277:1305–1307.

groups of highly selected thrombophilic patients.<sup>8,9</sup>

Up to 5% of healthy Americans are heterozygous for the factor V Leiden mutation, ie, they carry one normal copy of the factor V gene and one copy with the mutation.<sup>10</sup> This mutation seems to occur primarily in Caucasians but rarely in African Americans or Asians (TABLE 1).<sup>11</sup>

Heterozygosity for prothrombin G20210A is found in 18% of probands of thrombophilic families, 6% of patients with deep vein thrombosis, and 2% of normal white persons.<sup>7</sup> Like factor V Leiden, prothrombin G20210A has a varied geographic distribution, being twice as common in southern European populations as in northern European populations and uncommon in persons of African or Asian descent.<sup>12</sup>

### ■ WHAT IS THE RISK?

Persons heterozygous for the factor V Leiden mutation have a sevenfold increased lifetime risk of having a venous thromboembolic event<sup>13</sup>; persons homozygous for the mutation (ie, who have two abnormal copies) have an astounding 80-fold increased risk.

When factor V Leiden coexists with another prothrombotic stimulus, their combined effect may exceed the sum of the separate effects. For example, use of estrogen-containing oral contraceptive pills in women

**Homozygosity for factor V Leiden imparts an 80-fold risk**





with the mutation increases the risk considerably. Factor V Leiden alone has not been linked with an increased risk of recurrent venous thrombosis, but carriers of both the factor V Leiden mutation and the prothrombin G20210A mutation have a 2.6-fold increased risk of recurrent deep vein thrombosis after a first episode.<sup>14</sup>

Heterozygosity for prothrombin G20210A is associated with a twofold to sevenfold increased risk of venous thromboembolism.<sup>7</sup>

### Do these mutations increase the risk of arterial thrombosis?

While one case-control study showed an association between factor V Leiden and an increased risk of myocardial infarction in young women smokers, and other small case-control studies have suggested a link between arterial events and factor V Leiden, most available data indicate that activated protein C resistance and factor V Leiden are not associated with an increased risk of arterial thrombosis such as myocardial infarction and stroke.<sup>15,16</sup>

As for G20210A, a fourfold increased risk of myocardial infarction has been demonstrated particularly in young women carriers of this mutation.<sup>17</sup> A large case-control study of over 14,000 men, though, revealed no increased risk of stroke or myocardial infarction associated with G20210A.<sup>18</sup> No clear explanation for this apparent male-female disparity is currently available.

### ■ WHAT IS THE RISK IN WOMEN?

Women with factor V Leiden who take estrogen-containing oral contraceptives or are pregnant (with or without obstetric complications) have an increased relative risk of venous thromboembolism. For example, women without the mutation who take oral contraceptives have approximately a fourfold increased risk of venous thromboembolism compared with women not using oral contraceptives, but women with the mutation who take oral contraceptives have approximately a 35-fold increased risk.<sup>19</sup>

Moreover, in small case series, 40% to 60% of women with pregnancy-related venous thromboembolism had activated protein C

resistance or factor V Leiden.<sup>20</sup> Several recent studies identified factor V Leiden and other thrombophilic states as being associated with serious obstetric complications such as severe preeclampsia, abruptio placenta, fetal growth retardation, and stillbirth.<sup>21,22</sup>

On the other hand, there is no consensus on whether factor V Leiden is associated with recurrent pregnancy loss.<sup>23,24</sup> Furthermore, women carrying the factor V Leiden mutation have a low bleeding tendency following delivery, leading some investigators to suggest that the mutation provides a strong survival advantage.

### Relative risk vs absolute risk

Although the *relative risk* is useful in evaluating whether a factor is associated with an increased risk, it is not necessarily the best measure to assess the importance of a factor to an individual patient, for whom the *absolute risk* is more relevant.

For example, Vandenbroucke et al<sup>25</sup> report that the background incidence of thromboembolism in women of childbearing age who do not carry the factor V Leiden mutation is extremely low at 0.8 per 10,000 woman-years; among women with the mutation the incidence is 5.7. With oral contraceptive use, the incidence increases to 3.0 in women without the mutation and 28.5 in women with the mutation.

In light of these numbers, should a woman with factor V Leiden take oral contraceptives? Her risk might be five times higher than it would be if she did not take contraceptives, and 36 times higher than for a woman without the mutation who does not take contraceptives. Yet her absolute risk of 28.5 events per 10,000 woman-years is still fairly low. Furthermore, withholding oral contraceptives from all women with factor V Leiden would most likely result in an increased incidence of unwanted pregnancies, and pregnancy itself places a woman with this mutation at increased risk for venous thromboembolism.

Hormone replacement therapy is similarly associated with a twofold to fourfold increased risk of venous thromboembolism, perhaps because both hormone replacement therapy and oral contraceptives are associated with an acquired, relative activated protein C resis-

**Factor V Leiden alone does not rule out contraceptive use**



tance.<sup>26-28</sup> Because the baseline incidence of thrombosis is higher in postmenopausal women than in women of reproductive age, hormone replacement therapy results in a greater number of women developing thrombosis than does oral contraceptive use in younger women.

This increase in absolute risk, however, is very likely to be outweighed by the many health benefits of hormone replacement therapy, which include increased bone density and possible reduced risk of myocardial infarction and a reduced incidence of Alzheimer disease.<sup>29</sup> Whether women with factor V Leiden or prothrombin G20210A or both have an even more accentuated risk for venous thromboembolism when they use hormone replacement therapy has not been thoroughly studied. Until data are available that clarify this issue, we recommend that therapy be individualized on the basis of the woman's cardiovascular risk factors and personal and family history of venous thromboembolism.

Prothrombin G20210A is associated with a 10-fold increased risk of cerebral vein thrombosis and when combined with oral contraceptive use is associated with a 150-fold increased risk of this uncommon condition.<sup>30</sup> Women carriers of prothrombin G20210A have a 10-fold increased risk of venous thromboembolism during pregnancy and the postpartum period.

#### ■ WHO SHOULD BE TESTED?

The appropriate use of testing should avoid unnecessary patient anxiety and the non-evidence-based use of antithrombotic agents. Costly and specialized testing such as genetic analysis for the factor V Leiden and prothrombin G20210A mutations should be limited to situations in which the results will have an impact on patient care. Clear goals of testing should be determined before testing is performed. Simply knowing that a patient has a mutation is not part of best medical practice.

In general, testing should be done if the information gained will guide the type or intensity of antithrombotic therapy, affect the duration of therapy, assist with assessing a patient's prognosis, or guide family screening.

We feel that patients should be tested for

activated protein C resistance and the prothrombin G20210A mutation, as part of a comprehensive panel of tests designed to identify the most common and relevant acquired and inherited hypercoagulable states, if they have any of the following:

- Idiopathic venous thromboembolism
- Venous thromboembolism in unusual sites
- Recurrent venous thromboembolism, even with a known risk factor such as venous insufficiency after deep venous thrombosis
- Venous thromboembolism plus a family history of thrombosis.

Family members of a patient with known activated protein C resistance, factor V Leiden, or prothrombin G20210A may benefit from screening if the results will affect a decision to take oral contraceptives or hormone replacement therapy or to become pregnant. Family screening may affect an individual's decision to undergo elective surgery, because of a possible increased risk of postoperative venous thromboembolism in carriers of factor V Leiden or prothrombin G20210A or both. Widespread preoperative screening, though, is unlikely to be cost-effective.

We do not advocate screening all pregnant women or patients with malignancy, as screening in these groups is unlikely to affect management. Pregnant women with a past history of venous thromboembolism require pharmacologic prophylaxis against venous thromboembolism during pregnancy regardless of the presence of factor V Leiden or prothrombin G20210A. The future management of women with pregnancy-associated venous thromboembolism, oral contraceptive-associated venous thromboembolism, or complicated pregnancies is unlikely to be affected by testing for this mutation.

#### ■ HOW SHOULD PATIENTS BE TESTED?

Testing for activated protein C resistance can serve as a screening test for the factor V Leiden mutation. This test is relatively inexpensive and has been automated in several special coagulation laboratories to provide a rapid turnaround time. Recent modifications to the test, including the predilution of

## Test for activated protein C resistance before factor V Leiden





patient plasma with factor V-deficient plasma, have made it extremely sensitive and specific for factor V Leiden, and it can be performed in patients receiving full doses of anticoagulant agents.<sup>31</sup>

The test results are often reported as the plasma clotting time measured in a sample supplemented with purified activated protein C, divided by the plasma clotting time measured without exogenous activated protein C. A normal ratio (in our laboratory 1.95 or higher) essentially rules out factor V Leiden.

**Factor V gene analysis** performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis is more costly and time-consuming but is the sole means of truly differentiating between heterozygous and homozygous factor V Leiden.

Factor V Leiden PCR should be performed if the activated protein C ratio is equivocal or if the ratio is low and one wants to determine if the patient is heterozygous or homozygous for factor V Leiden. We also advocate screening first for activated protein C resistance instead of proceeding directly to factor V Leiden PCR analysis because of the importance of detecting non-factor V Leiden-associated activated protein C resistance.

The prothrombin G20210A mutation can only be reliably and routinely identified using molecular biological techniques. Measurements of functional prothrombin activity do not sufficiently differentiate between carriers and noncarriers of this gene mutation.<sup>7</sup> The test is accurate even if the patient is taking heparin or warfarin.

### ■ HOW SHOULD AFFECTED PATIENTS BE MANAGED?

No evidence-based clinical guidelines exist for managing symptomatic or asymptomatic patients with activated protein C resistance, factor V Leiden, or prothrombin G20210A.

Clinical experience dictates that asymptomatic persons who are heterozygous for the factor V Leiden or prothrombin G20210A mutations receive prophylactic anticoagulation only in situations known to predispose to venous thromboembolism. In an episode of acute thrombosis, they should be treated in

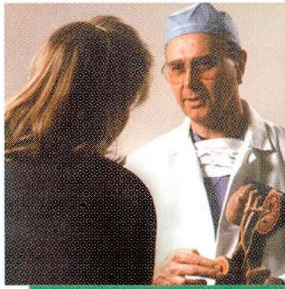
a standard fashion. The presence of activated protein C resistance or prothrombin G20210A plus another hypercoagulable state, or homozygous factor V Leiden alone, should prompt the clinician to seriously consider long-term anticoagulant therapy following an initial episode of venous thromboembolism. The presence of one of these mutations alone is not an absolute contraindication to oral contraceptive use, hormone replacement therapy, or pregnancy. The absolute risks and benefits of any intervention must be carefully estimated and individualized for each patient. ■

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**No evidence-based guidelines exist for factor V Leiden or G20210A**



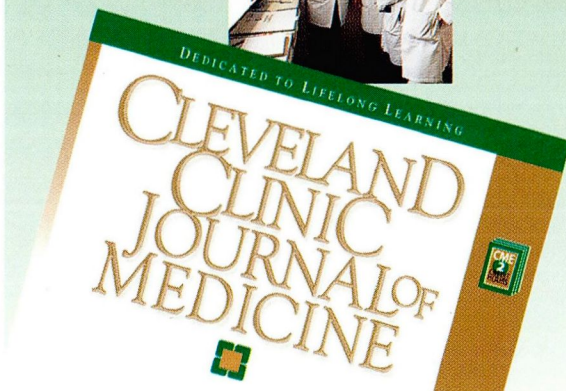
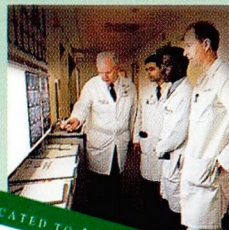


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**ADDRESS:** Steven R. Deitcher, MD, Department of Vascular Medicine, S60, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, e-mail [deitchs@ccf.org](mailto:deitchs@ccf.org).