You may have been tested for the condition known as factor V Leiden (pronounced factor five lye-den) because you or someone in your family has had a blood clot in one of the deep veins of the body (also called deep vein thrombosis, or DVT) or a blood clot that traveled to the lung (also called a pulmonary embolism, or PE). Thrombophilia is the term used to describe the propensity of some people to form abnormal blood clots, and it may be either a condition that developed during your lifetime or that you inherited through your family. Some examples of situations in which thrombophilia develops include cancer, diabetes, obesity, and surgery. This Cardiology Patient Page will concentrate on factor V Leiden, the most common cause of inherited thrombophilia.

How Does the Blood Keep From Clotting When Flowing Through the Bloodstream?

The job of the blood is to deliver oxygen and nutrients to all the tissues of the body. Blood must remain in fluid form and does so through a series of complex biochemical reactions. Blood also has a mechanism to counteract to these reactions, if necessary, to stop bleeding in the case of injury to the blood vessels. This is the process of coagulation, which consists of enzymes forming a clot to plug leaks in blood vessels while other blood enzymes repair the damage. There is a delicate balance at work to ensure that there is enough — but not too much — clotting power in the blood. Not enough clotting power leads to bleeding problems, whereas too much clotting power (thrombophilia) can lead to the formation of dangerous blood clots. The state of this normal balance between bleeding and clotting differs from person to person, and many things can upset the balance (Figure).

What Is Factor V?

Factor V is a protein in the blood that is required for normal clotting to occur in response to injury. To understand how factor V works, it is important to understand the basics of blood coagulation (see box). Throughout the course of a normal day, the blood vessels sustain many nicks and scrapes on the inside that we cannot see. The blood coagulation mechanism is therefore activated many times during the day to repair the damage.

How Normal Blood Clots When a Blood Vessel Is Injured

1. Blood clotting cells (platelets) are drawn to the site of injury on the blood vessel, where they form a loose plug over the leaky area.
2. Enzyme reactions occur on the surface of the platelets to generate strands of fibrous material called fibrin. Fibrin acts as a biological “band-aid” to hold the platelets firmly to the injured site and prevent blood from leaking out. This combination of platelets and fibrin is called a clot. Factor V is a helper in the enzyme reactions that form the fibrin in the clot.
3. When enough fibrin has been made, a substance called activated protein C (APC) inactivates factor V, helping stop the clot from growing any larger than necessary.
4. The clot remains in place while other enzymes repair the damaged blood vessel.

What Is Factor V Leiden?
People with factor V Leiden have a mutation in the gene for factor V. Factor V Leiden is an abnormal version of factor V that is resistant to the action of APC. Thus, APC cannot easily stop factor V Leiden from making more fibrin. Once the coagulation process is turned on in people with factor V Leiden, it turns off more slowly than in people with normal factor V. Having factor V Leiden, therefore, results in a condition known as APC resistance.

How Did I Get Factor V Leiden?
You inherit all your genes, including factor V Leiden, from your parents. You have two copies of every gene, one from your mother and one from your father. You may have inherited one copy of the factor V Leiden gene from one parent and one copy of the normal factor V gene from the other parent, making you heterozygous for the factor V Leiden gene mutation. This means that you have about 50% of normal factor V and about 50% of abnormal factor V Leiden in your blood. Sometimes both parents pass factor V Leiden to their offspring, making it possible to have two abnormal genes. If this applies to you, then you are homozygous for factor V Leiden, and 100% of your factor V is the abnormal Leiden variant.

How Is the Diagnosis Made?
The diagnosis of factor V Leiden is made by a blood test. Initially, a screening test may be done to determine if you have APC resistance. Because factor V Leiden is only one of several causes of APC resistance, you may have a DNA test (also done on the blood) to see if you have factor V Leiden if your blood shows APC resistance. This test will also determine whether you have the heterozygous or homozygous form. Sometimes the initial screening test for APC resistance is omitted and only the DNA test is performed.

What Are the Implications of Having Factor V Leiden?
Heterozygous factor V Leiden is found in about 5% of the white population and is most common in people of Northern European descent and in some Middle Eastern populations, whereas the homozygous form is found in fewer than 1%. Factor V Leiden is less common in the Hispanic populations and is rare in Asian, African, and Native American populations.

Factor V Leiden is associated with an increased risk of developing an episode of DVT (with or without a PE). Approximately 1 in every 1000 people will develop a DVT or PE each year, and this increases from about 1 in 10 000 for those in their twenties to about 5 in 1000 for those in their seventies. Heterozygous factor V Leiden increases the risk of developing a first DVT by 5- to 7-fold (or 5 to 7 in 1000 people each year). Thus, even though the relative risk of developing a DVT seems high, the absolute risk of having a DVT is still quite low with factor V Leiden. Factor V Leiden is thus a weak risk factor for developing blood clots; in fact, most people who have heterozygous factor V Leiden never develop blood clots. Homozygous factor V Leiden increases the risk of developing clots to a greater degree, about 25- to 50-fold. If you have the heterozygous form of factor V Leiden, the lifetime risk of developing a DVT is 10% or less, but may be higher if you have close family members who have had a DVT. Very often, people with factor V Leiden have additional risk factors that contributed to the development of blood clots (Table). Having factor V Leiden alone does not appear to increase the risk of developing arterial thrombosis, that is, heart attacks and strokes.

How Is Factor V Leiden Treated?
If you have had a DVT or PE, then you were most likely treated with blood thin-
Hormone Use

The use of hormones, such as oral contraceptive pills (OCPs) and hormone replacement therapy (HRT, including estrogen and estrogen-like drugs) taken after menopause, increases the risk of developing DVT and PE. Healthy women taking OCPs have a 3- to 4-fold increased risk of developing a DVT or PE compared with women who do not take OCPs. Women with factor V Leiden who take OCPs have about a 35-fold increased risk of developing a DVT or PE compared with women without factor V Leiden and those who do not take OCPs. This would translate to an about 35 per 10 000 chance per year of use on average for women in their twenties with factor V Leiden. Likewise, postmenopausal women taking HRT have a 2- to 3-fold higher risk of developing a DVT or PE than women who do not take HRT, and women with factor V Leiden who take HRT have a 15-fold higher risk. This is about a 15 to 40 per 1000 chance per year of use, on average, for women in their fifties with factor V Leiden. Women with heterozygous factor V Leiden who are making decisions about OCP or HRT use should take these statistics into consideration when weighing the risks and benefits of treatment.

Pregnancy

Factor V Leiden increases the risk of developing a DVT during pregnancy by about 7-fold. Women with factor V Leiden who are planning pregnancy should discuss this with their obstetrician and/or hematologist. Most women with factor V Leiden have normal pregnancies and only require close follow-up during pregnancy. For those with a history of DVT or PE, treatment with an anticoagulant during a subsequent pregnancy can prevent recurrent problems.

What Are the Implications for My Family Members?

Who Should Be Tested?

Patients who develop a DVT or PE and are from a family with a confirmed factor V Leiden diagnosis should be tested. Likewise, even if there is no family history of factor V Leiden, anyone who has had a DVT or PE that is unexplained, recurrent, occurred at a young age (under 50), occurred during pregnancy, was associated with hormone use, or developed in an unusual site (such as the veins of the brain or abdomen) may benefit from testing for factor V Leiden and other causes of hereditary thrombophilia.

Testing asymptomatic family members of people with factor V Leiden is controversial. An advantage to testing is that finding factor V Leiden allows for counseling to reduce other risk factors and for education on the signs and symptoms of DVT or PE so that early diagnosis and treatment may be instituted. The downside of testing family members is that finding the gene mutation may lead to untoward anxiety, withholding certain treatments (such as OCP), and possibly to discrimination in insurance or employment. A positive test, therefore, may have unwanted consequences and a negative test may lead to a false sense of security and induce family members to ignore other risk factors. Family members of people with factor V Leiden should discuss the implications of being tested with their family doctor or a hematologist before they are tested. Asymptomatic family members of a person who has had a DVT or PE should always be counseled about reducing risk factors whether or not factor V Leiden or other hereditary thrombophilia is present. Women in families with factor V Leiden might consider being tested if decisions about OCP or HRT are being made.

What Can I Do to Minimize My Risk Caused by the Presence of Factor V Leiden?

Factor V Leiden is only one of many risk factors for the development of DVT or PE. Usually, the effect of risk factors is additive: the more risk factors you have, the higher the risk. Sometimes, however, the effects of multiple risk factors are more than additive. A woman who has factor V Leiden and takes OCPs, for example, has a 35-fold increased risk of developing a DVT, which is higher than the increased risk associated with simply adding together the risk of factor V Leiden (5-fold increased risk) and OCP use (4-fold increased risk). The table lists additional risk factors for developing DVT. Some risk factors, like genetics or age, are not alterable, but many factors can be controlled by medications or lifestyle modifications. For example, obesity is probably the most common modifiable risk factor for developing blood clots, so losing weight (if you are overweight) is an important intervention for risk reduction. Avoiding long periods of immobility is recommended. For example, if you are 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. On long airplane trips, walk in the aisle every so often and prevent dehydration by drinking.
plenty of fluids and avoiding alcohol. If you have a desk job, get up and walk around the office periodically. If you are hospitalized or require surgery, make sure your doctor knows that you have factor V Leiden so that measures such as the temporary administration of blood thinners may be taken to prevent DVT. Finally, it is important to recognize symptoms of blood clots and seek early medical attention: pain, swelling, and/or redness of a limb or unexplained shortness of breath and/or chest pain are the most common symptoms of DVT and PE.

**PRACTICAL STEPS TO MINIMIZE RISK**

- Try to maintain ideal body weight for your sex and height.
- Stay active and try to get regular exercise through such activities as walking, bicycling, or swimming.

**Continued**

- Avoid prolonged periods of immobility. For example, stop the car, get out, and walk around every few hours during a long trip. On an airplane, drink plenty of water to avoid dehydration, walk the aisles, and avoid alcohol. Wearing elastic stockings with a moderate level of compression (15 to 20 mm Hg) may prevent DVT from developing on long flights.
- Don’t smoke.
- If you have other chronic medical conditions, such as diabetes, high cholesterol, or congestive heart failure, work with your doctors to try to keep these problems under good control.
- Let your doctors know that you have factor V Leiden so that they can administer blood thinners or provide you with mechanical compression boots for your legs if you are hospitalized or need surgery.

**Additional Resources**

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