

# Factor V Leiden: An Overview

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This paper provides an update and an overview of factor V Leiden, an inherited condition, which predisposes affected individuals to thrombosis. Factor V Leiden occurs due to a single point mutation on chromosome one. Tests for factor V Leiden include screening for activated protein C (APC) resistance, and if positive, testing for the Factor V Leiden mutation.

**ABBREVIATIONS:** APC = activated protein C; APTT = activated partial thromboplastin time; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low molecular weight heparin; MI = myocardial infarction; PCR = polymerase chain reaction; PE = pulmonary embolism.

**INDEX TERMS:** activated protein C resistance; factor V Leiden; thrombosis.

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The human body maintains a delicate balance of procoagulant and anticoagulant processes by using a complex system of cofactors and inhibitors. The system uses a feedback mechanism to maintain the equilibrium.<sup>1</sup> When this balance is disrupted, there may be an episode of bleeding or a clotting event such as deep vein thrombosis (DVT) or pulmonary embolism (PE). Thrombophilia is used to describe the ten-

dency of some people to form abnormal blood clots.<sup>2</sup> The consequences are usually DVTs of the legs, and PE, which can both cause considerable suffering and even death.<sup>1</sup> Each year, approximately 201,000 new cases of venous thrombosis are diagnosed in the United States. Of these, 107,000 individuals develop DVTs and 94,000 develop PE.<sup>3</sup> Approximately 60,000 deaths in the United States each year are due to venous thromboembolism.<sup>3</sup>

Thrombophilia may be due to either an inherited condition or a condition that develops during life. Some examples of causes for development of non-hereditary thrombophilia are cancer, obesity, diabetes, and surgery.<sup>2</sup> Hereditary thrombosis, due to genetic mutations, is the cause of about half of the cases.<sup>1</sup> Causes for hereditary thrombophilia result from single gene mutations, and include protein C deficiency, protein S deficiency, antithrombin deficiency, prothrombin mutation, and factor V Leiden.<sup>4,5,6</sup> Other causes of thrombosis include antiphospholipid syndrome and elevated levels of factor VIII or homocysteine.<sup>6</sup> A study done by Bertina and others in 1994 showed that factor V Leiden is found in about 50% of the cases of familial thrombosis.<sup>7</sup>

It is important to note the difference between factor V deficiency and factor V Leiden. Factor V deficiency is an inherited disorder in which the clotting factor V is low, resulting in bleeding problems.<sup>8</sup> Factor V Leiden is also inherited, with normal factor levels but an abnormal form of factor V, which results in a tendency for thrombosis.<sup>8</sup> Factor V Leiden is an autosomal co-dominantly inherited disease, present in approximately three to seven percent of the Caucasian population, making it the most common cause of inherited thrombophilia.<sup>7,9</sup> It is most common in Northern European and Middle Eastern populations, while less common in Hispanic, Asian, African, and Native American populations.<sup>2</sup> Factor V Leiden is due to a single mutation on chromosome one, where guanine is replaced with adenine, causing the conversion of arginine 506 of factor V to glutamine.<sup>10</sup> This is the position where activated protein C (APC) must bind to the factor V molecule for normal anticoagulant response.<sup>10</sup>

When there is a vascular injury, thrombin is generated. The thrombin activates platelets, clots fibrinogen, and binds to

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the endothelial membrane protein thrombomodulin. This promotes the conversion of thrombin from a procoagulant to an anticoagulant protease, which activates protein C.<sup>1</sup> Protein C is a naturally occurring anticoagulant, and along with its cofactors protein S and antithrombin III, prevents ongoing thrombin production.<sup>10</sup> The factor V genetic mutation causes the synthesis of a factor V molecule that is not properly activated by APC, due to the binding site being altered from the mutation.<sup>7</sup> Factor V must be inactivated to prevent ongoing thrombin production. Since APC cannot properly bind, it leads to continued thrombin generation, and a state of hypercoagulation.<sup>10</sup>

The risk of thrombosis in individuals with factor V Leiden is increased five- to seven-fold for heterozygous persons, and increased 80-fold for homozygous individuals.<sup>11</sup> These patients usually experience their first thrombosis at a much earlier age (31 years versus 44 years) than persons without the mutation.<sup>12</sup> A study conducted by Rosendall and others suggested that factor V Leiden individuals who are homozygous will experience at least one event of thrombosis during their lifetime.<sup>12</sup>

Women affected by factor V Leiden have additional risks for thrombosis. Hormone use increases the risk of DVT and PE in women. Healthy women taking oral contraceptives have a three- to four-fold increased risk of DVT or PE.<sup>2</sup> Further, women with factor V Leiden who are taking oral contraceptives, have an increased risk of about 35 fold when compared to factor V Leiden women who do not take oral contraceptives.<sup>2</sup> Factor V Leiden post-menopausal women using hormone replacements therapy have a 15 fold increased risk of developing an event of thrombosis.<sup>2</sup>

Djordjevic and others studied the prevalence of factor V Leiden in a group of 45 women with first episode of DVT during pregnancy or puerperium (the period of state of confinement during and just after childbirth).<sup>13</sup> The results showed that 44.4% of the women were heterozygous for factor V Leiden, and 2.2 % of the women were homozygous. This study suggests that testing for factor V Leiden is recommended in women with a history of DVT during pregnancy and puerperium.<sup>13</sup>

Another study conducted by Prochazka and others examined whether being a carrier of the factor V Leiden gene was associated with an increased risk of premature separation of the placenta.<sup>14</sup> They studied 135 women with confirmed diagnosis of abruptio placentae, and compared them to a control

group of 198 pregnant women who completed delivery. The results showed women with abruptio placentae were carriers of factor V Leiden in 15.5 % of the cases, compared to 5.1 % of the control group. Their conclusion was that factor V Leiden is a risk factor for premature placental separation.<sup>14</sup>

Middendorf and others performed a study on factor V Leiden and its role in patients with myocardial infarction (MI).<sup>15</sup> The study included 507 patients with documented MIs. The prevalence of factor V Leiden in patients with MI was 8.7%, compared to the control group's prevalence of 3.7%. They concluded that their study showed a significant increase in the prevalence of the factor V Leiden mutation, leading them to the conclusion that patients with factor V Leiden mutation have a predisposition for MI.<sup>15</sup> Their study also showed factor V Leiden patients had a lower prevalence of hyperlipidemia and hypertension and rate of smoking than the total population of patients with MI. They propose this may show that traditional risk factors for MI may be less important in patients with factor V Leiden mutations.<sup>15</sup> Hille (as cited by Middendorf, 2004) observed a nine fold increase in mortality from coronary heart disease in patients under age 45, who were the parents of factor V Leiden children.<sup>15</sup>

### LABORATORY TESTING

Individuals who have a history of venous thrombosis or a family history of a high incidence of venous thrombosis should be screened for hereditary causes of thrombophilia.<sup>16</sup> Tests ordered should include Factor V Leiden (APC resistance), protein S deficiency, protein C deficiency, antithrombin assay, Prothrombin G20210A mutation, factor VIII activity, homocysteine level, and Lupus anticoagulant.<sup>5,6,17</sup> Studies have shown that up to one-third of families affected with a hereditary form of thrombosis have two genetic defects, one of which is factor V Leiden.<sup>5</sup>

When testing for factor V Leiden, a screening test is done to determine APC resistance. This test was first described in 1993 by Dahlback and others.<sup>18</sup> The activated partial thromboplastin time (APTT) was measured both in the presence and absence of exogenous APC. The normal response was a prolonged APTT in presence of APC, because of the inactivation of factors Va and VIIIa. Abnormal response was a failure of prolongation of APTT due to a resistance of added APC.<sup>18</sup> The limitations of the assay include that it can not be used for patients who are on heparin or warfarin therapy, due to a preexisting prolonged APTT results.<sup>16</sup> Other coagulation defects such as a lupus inhibitor, haemostatic changes during pregnancy, or acute thrombosis could also affect the test

result.<sup>16</sup> Due to these interferences, the assay has a sensitivity and specificity of 85%-90 % for factor V Leiden.<sup>16</sup>

A modified or second generation method was developed that shows sensitivity and specificity values for factor V Leiden that are near 100%.<sup>16</sup> The modified assay requires that the plasma is first diluted 1:4 with factor V deficient plasma that also contains a heparin neutralizer.<sup>16</sup> This step corrects for inaccuracies due to other deficient factors, neutralizes therapeutic concentrations of heparin, and eliminates the effects of some lupus inhibitors.<sup>16</sup> The modified assay can be used for patients undergoing warfarin or heparin therapy, and in cases of acute thrombosis, pregnancy, or inflammation.<sup>16</sup> Since lupus anticoagulant may be a potential interferent in the modified assay, patients with lupus anticoagulant should be evaluated for the factor V Leiden mutation by genetic testing.<sup>19</sup>

Bertina and others (as cited by Major, 2000) reported that the factor V Leiden mutation is present in more than 95% of the individuals studied with APC resistance.<sup>20</sup> All patients testing positive for APC resistance should be tested for the factor V Leiden mutation. Polymerase chain reaction is the "gold standard" for testing for the mutation of factor V Leiden.<sup>19</sup> However, other DNA-based methods are commercially available, including an invasive signal amplification reaction assay called the Invader assay, by Third Wave Technologies, Inc., Madison, Wisconsin.<sup>19</sup> This test uses florescent probes, one for the wild-type, and one for factor V Leiden.<sup>18</sup> In several studies conducted, this assay correctly identified 95.8%-100% of the individuals, when compared with PCR.<sup>19</sup>

Testing of asymptomatic family members for factor V Leiden is controversial. The testing could facilitate counseling on reducing risk factors and informing the patients of symptoms of DVT and PE.<sup>2</sup> The detrimental effects of the testing are anxiety, withholding certain treatments, such as oral contraceptives, and the possibility of the individual's being denied insurance or employment.<sup>2</sup> Thus, a positive test could cause unwanted consequences, while a negative test could cause a false sense of security and cause family members to ignore other risks. It is recommended that individuals discuss the implications of testing with their physicians.<sup>2</sup>

There are some additional risk factors that, when in combination with factor V Leiden, increase the risk of thrombosis. These include age, obesity, cancer, immobility, hospitalization, surgery, trauma, pregnancy, taking oral contraceptives or hormone replacement therapy, chronic medical conditions, and air travel.<sup>2</sup> Some risk factors such as genetics and age are

not alterable, but other factors can be controlled by lifestyle modifications or medications.<sup>2</sup>

## TREATMENT

Treatment after a first event of thrombosis with a reversible risk factor is usually three months of anticoagulant therapy.<sup>21</sup> The anticoagulant therapy of choice is usually a course of IV unfractionated heparin or subcutaneous low molecular weight heparin (LMWH), followed by oral warfarin therapy.<sup>16</sup> The target international normalized ratio (INR) is 2.5, with a therapeutic range of 2.0 to 3.0.<sup>16</sup> After recurrent events, anticoagulant therapy is usually continued for 12 months or indefinitely.<sup>21</sup> If a factor V Leiden individual has never had a clot, no routine treatment is recommended; however, the patient should be counseled about eliminating other risk factors. Temporary treatment may be necessary during high risk periods, such as surgery.<sup>2</sup> It is recommended that homozygous and heterozygous patients with another prothrombotic genetic defect take anticoagulant therapy in all risk situations, and lifelong anticoagulant therapy is considered even after a single thrombotic event.<sup>11</sup>

## SUMMARY

In summary, factor V Leiden contributes to a large number of individuals experiencing a state of hypercoagulation, which may lead to DVT, PE, and MI. Factor V Leiden occurs due to a single point mutation on chromosome one, and leads to the synthesis of a factor V molecule that is not properly activated by APC.<sup>7,10</sup> Factor V Leiden is an autosomal co-dominantly inherited disease, present in approximately three percent to seven percent of the Caucasian population, making it the most common cause of inherited thrombophilia.<sup>7,9</sup> Women with factor V Leiden who are taking hormones are at a significantly higher risk for developing a thrombotic event. Women with factor V Leiden are at a higher risk for DVT during pregnancy or puerperium, and at a higher risk for abruption placentae.

Testing symptomatic individuals begins with a test for activated protein C resistance, and then if positive, genetic testing is performed. Testing asymptomatic individuals for factor V Leiden is controversial. It is important for individuals to be aware of their family history, and to report any familial history of thrombosis to their physician, so they can be screened for factor V Leiden if the physician deems it necessary. Positive lifestyle changes, and treatment when deemed necessary, can prevent blood clots in a significant number of these individuals.

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