# Examining Factor V Leiden and vWF Deficiencies as Potential for Coexisting Thrombophilic and Hemophilic Diseases

A G Saunders, M G Kirk, K Ubhi

**Citation**

A G Saunders, M G Kirk, K Ubhi. *Examining Factor V Leiden and vWF Deficiencies as Potential for Coexisting Thrombophilic and Hemophilic Diseases* . The Internet Journal of Hematology. 2022 Volume 15 Number 1.

**DOI:** 10.5580/IJHE.56415

**Abstract**

Very few cases of combined thrombotic and hemophilic disorders have been published in the literature. This examines the pathophysiology and genetics of the most common bleeding and thrombotic diseases when existing together, vWF deficiency and Factor V Leiden, respectively. These patients present with special considerations in treatment that have not been well documented throughout the literature. After a review of the literature, it is presumed that both Factor V Leiden and vWF Disease can coexist in a patient. Although acting as antagonists, one case has found that a prothrombotic Factor V Leiden may compensate for low levels of factor VIII or IX, conferring a survival benefit in hemophiliacs. Existing in this prothrombotic state may potentially compensate by resulting in more efficient thrombin generation and easing the severing of clinical symptoms. In turn, by evaluating the pathophysiology and genetics of each disease in a clinical scenario, the paradox of both diseases existing in the same patient is examined.

## THE CLINICAL SCENARIO:

In your practice, a five-year-old boy comes to his well-child visit accompanied by his parents. He has a history significant for vWF deficiency, as discovered in his father. In addition, his mother has Factor 5 Leiden deficiency, but the child did not receive this deficiency. In your search of the literature, you find a documented case of coexisting vWD and Factor V Leiden confirmed to exist in a 30 year old pregnant patient. Could your patient also have inherited both diseases?

## THE CLINICAL QUESTION:

How does basic science level understanding of the disease process and genetics play a role in this case? Is it possible for these disease processes to coexist in the same patient? How would this diagnostics paradox play a role in the approach to the management of this illness?

## THE PATHOPHYSIOLOGY BEHIND THE DISEASE PROCESSES:

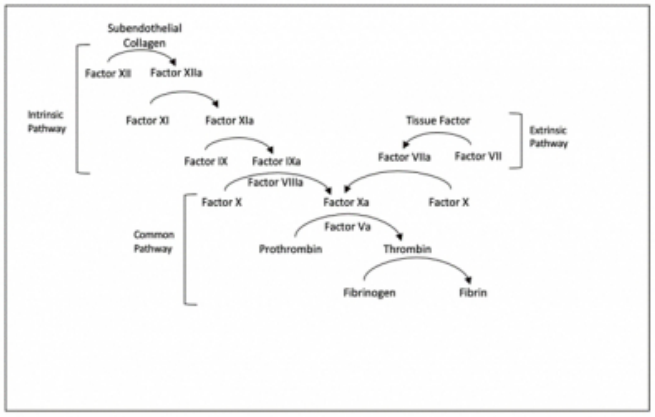
Von Willebrand disease (vWD) is the most common congenital bleeding disorder and is estimated to be prevalent in 1% of the general US population. Most cases are acquired in an autosomal dominant pattern, although some types are acquired in the autosomal recessive pattern or secondarily to other medical conditions, such as lymphoproliferative and autoimmune diseases. The most common type, Type 1, is classified by mild to moderate deficiency of vWF and factor VIII. The less common Type 2 is characterized by a dysfunctional vWF, while Type 3 has a complete absence of vWF and factor VIII. Deficiency or dysfunction of vWF leads to dysfunctional platelet adhesion, which inhibits formation of the platelet plug, which is necessary for primary hemostatic platelet linking. Decreased vWF also leads to decreased factor VIII concentration, as they are normally bound together in circulation. When factor VIII is unbound, it leads to its increased degradation, thus decreasing its levels in the blood. Decreased factor VIII activity impairs secondary hemostasis by being absent from the coagulation cascade8.

Factor 5 Leiden, also known as Activated protein C (APC) resistance, is also inherited in an autosomal dominant fashion. It is prevalent in the heterozygote states in approximately 5% of the general population. In the normal physiologic pathway, APC inactivates factor V, which is a clotting factor in the coagulation cascade. The inactive factor V then results in decreased thrombin activation, which is the

final step in the coagulation cascade. Usually, this would decrease the rate of clotting. However, when Factor V is resistant to cleavage by APC, Factor C remains active and increases thrombotic events. Most cases of Factor V Leiden are caused by a DNA point mutation that substitutes guanine for adenine, which results in an Arg506Gln mutation on the mRNA codon near the polypeptide cleave site of factor V, rendering the factor resistant to cleavage by APC. This creates a resistant pathway to inactivation and a thrombophilic physiologic situation. As most cases are heterozygous, some patients are homozygous for the mutation (<1% of the general population) and are at a higher risk of thromboembolism[1].

**Figure 1**

Coagulation cascade. Intrinsic pathway is measured by aPTT. Extrinsic pathway is measured by PT. vWF normally stabilizes Factor VIII. A deficiency in vWF leads to decreased levels of Factor VIII.




## SYMPTOMS & PRESENTATION OF DISEASES:

Von Willebrand disease presentation varies between individuals, as the severity of symptoms subsequently varies among the different types of this disease. Many patients are often asymptomatic. Patients who develop symptoms of vWD often have mucocutaneous bleeding, such as recurrent or uncontrolled epistaxis, unexplained ecchymoses, bleeding of the gingiva, petechiae, or prolonged bleeding time from minor injuries such as dental procedures. 92% of patients who menstruate who have vWD often suffer from mennorrhagia[10]. In severe cases, patients may also present with life-threatening bleeding9.

Factor 5 Leiden often presents with thromboembolism at a young age, often with onset at an age younger than 50 years old. These are often unprovoked or associated with weak risk factors. The thrombus may also be in an unusual location, such as a portal vein thrombosis or central retinal vein occlusion. As this condition is autosomal dominant, there may also be a strong family history of thromboembolism. Factor V Leiden patients are also at increased risk of recurrent or multiple venous thrombus embolism. Patients with the ability to become pregnant are also at risk for frequent obstetrical complications, such as recurrent pregnancy loss, preeclampsia, intrauterine fetal demise, and intrauterine growth restriction[2]. Few patients may also present with stroke symptoms or arterial thromboembolism at a young age with no cardiovascular risk factors7.

## HOW THE DISEASES ARE DIAGNOSED:

Von Willebrand disease is diagnosed partly by patient history, as they will often have had recurrent episodes of unexplained bleeding and positive family history for similar symptoms. Coagulation studies often show an increased bleeding time, normal or prolonged aPTT, and a normal PT and platelet count. Quantitative assessment for vWF antigen levels and factor VIII will also be decreased [11]. A more specific test is the ristocetin cofactor assay, which measures the ability of vWF to aggregate platelets. Ristocetin is an antibiotic that activates vWF, which then if present in the sample, will bind glycoprotein Ib on platelets. If ristocetin is added to blood that does not contain or has decreased levels of vWF, it will be unable to aggregate platelets or have a cofactor level <30 IU/dL. In a patient with vWD, their platelets will be able to aggregate normally in other assays, and such has in combination ADP and collagen[11].

Factor 5 Leiden is often identified following an unprovoked, thromboembolic event. Routine investigations should be performed as the initial workup, including CBC to rule out a myeloproliferative neoplasm, BMP to examine the potential for thrombosis originating from a nephrotic syndrome, Liver Enzyme studies to look for underlying liver disease that can cause coagulation factor dysfunction, and coagulation studies. More specific thrombophilia testing is warranted in select cases, as patients prone to VTEs are often treated accordingly without needing a diagnosis of Factor V Leiden. Factor V Leiden specific studies are performed first by an Activated protein C resistance assay, then followed by genetic testing for Factor V Leiden if positive[3]. If these patients are at increased risk for malignancy, appropriate cancer screening is recommended as underlying thromboembolism can indicate an underlying malignancy[4]. Screening may be considered in asymptomatic patients with

a personal history of thromboembolism who wish to start hormonal contraception, patients who wish to start contraception and have a strong family history of thromboembolism, and patients at risk who are pregnant or considering fertility counseling[5].

**Table 1**

Diagnosis of Von Willebrand Disease and Factor V Leiden.

| Von Willebrand Disease | Factor V Leiden |
|---|---|
| Patient history<br>• Recurrent episodes of unexplained bleeding<br>• Family history<br>Coagulation studies<br>• Increased bleeding time<br>• Normal or prolonged aPTT<br>• Normal PT<br>• Normal platelet count<br>Ristocetin cofactor assay<br>• No platelet aggregation<br>• Cofactor level <30 IU/dL | Patient history<br>• Unprovoked thromboembolic event<br>○ CBC to rule out myeloproliferative neoplasm<br>○ BMP to rule out nephrotic syndrome<br>○ Liver enzyme studies to rule out liver disease<br>• Family history of thromboembolism<br>Coagulation studies<br>• Normal bleeding time, aPTT, PT, platelet count<br>Activated protein C resistance assay<br>• If positive, follow with genetic testing for Factor V Leiden |

## TREATMENT OF DISEASES AND HOW TREATMENT WORKS:

Von Willebrand disease patients are treated with prophylaxis for procedures and only as hemophilic symptoms occur. Most commonly, patients are treated with Desmopressin, a synthetic version of antidiuretic hormone. Desmopressin stimulates vWF release from endothelial cells but is ineffective in patients with Type 3 vWD. Concentrated vWF and factor VIII can be given as prophylaxis, cases of severe bleeding, or if desmopressin has been ineffective. In cases of acquired vWD, concentrates have been found to be less effective, and the best treatment for these patients is treatment of the underlying cause[9].

Factor 5 Leiden patients are often managed with secondary prevention with appropriate anticoagulation and modification of risk factors for thromboembolism. Acute treatment of arterial thrombosis can consist of revascularization and fibrinolytics, depending on patient presentation. Venous thrombosis acute treatment consists of anticoagulation administration[1]. Primary prevention in asymptomatic patients is often not necessary, although some patients may benefit from modification of risk factors for thromboembolism[6].

**Table 2**

Treatment approach for Von Willebrand Disease and Factor V Leiden.

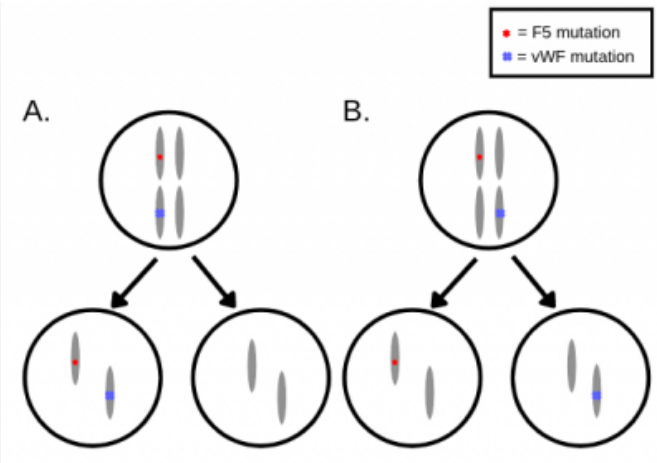
| Von Willebrand Disease | Factor V Leiden |
|---|---|
| Desmopressin<br>• Symptomatic treatment<br>• Prophylaxis for procedures<br>Concentrated vWF and factor VIII<br>• If desmopressin is ineffective<br>• Symptomatic treatment<br>• Prophylaxis for procedures<br>Treatment of underlying cause | Management of thromboembolic risk factors<br>Anticoagulation<br>• Acute venous thrombosis management<br>Revascularization and fibrinolytics<br>• Acute arterial thrombosis management |

## GENETIC INHERITANCE OF A COEXISTING VWF AND FACTOR V LEIDEN DEFICIENCIES:

Both Factor V Leiden and von Willebrand factor are typically inherited in an autosomal dominant pattern. Factor V Leiden also displays incomplete penetrance, which means that every person who has the mutation does not always go on to develop the disease. The gene that codes for Factor V is often referred to as F5. F5 is located on chromosome 1 and is most often mutated by a missense substitution that renders Factor V unable to be cleaved by APC13. vWF is located on chromosome 12 [14]. Due to the law of independent assortment, it is feasible that these disease processes could be inherited in the same patient, as the inheritance of these alleles should not influence the inheritance of the other.

**Figure 2**

Independent assortment of chromosomes carrying F5 mutation and vWF mutation. Situations A and B illustrate how chromosomes carrying mutations for F5 on chromosome 1 and for vWF on chromosome 12 could potentially independently assort during meiosis. As seen in situation A, this independent assortment can lead to an individual inheriting both mutated F5 and vWF.




## DISCUSSION:

After a review of the literature, it is presumed that both Factor V Leiden and vWF Disease can coexist in a patient.

Although acting as antagonists, one case has found that a prothrombotic Factor V Leiden may compensate for low levels of factor VIII or IX, conferring a survival benefit in hemophiliacs. Existing in this prothrombotic state may potentially compensate by resulting in more efficient thrombin generation and easing the severing of clinical symptoms. It has been proposed that this is what accounts for Factor V Leiden's high prevalence in the population, as at one point, it may have conferred evolutionary survival in areas that historically had a high prevelance of caucasians[18]. Furthermore, high factor VIII levels have also been found to paradoxically worsen Factor V Leiden disease. This further reinforces the idea that an acquired vWF deficiency causing low factor VIII levels may be beneficial in a patient suffering from Factor V Leiden, and that presence of a higher factor VIII level may act as an additional risk factor for venous thromboembolism in a Factor V Leiden patients [19].

A case in the literature presents a woman who inherited both diseases. She was reported to suffer from Factor V Leiden and vWF Disease Type 1 in pregnancy. Her history was significant for easy bruising, but in this case, she was prescribed thromboprophylaxis with enoxaparin as pregnancy is a hypercoagulable state and as it has been documented that factor VIII and vWF levels normalize, removing any bleeding risk [15]. She went on to deliver her child with no complications and was continued on postpartum prophylaxis. Management of these patients remains controversial in the literature, as the use of thromboprophylaxis with no prior venous thromboembolism consists of few case-control studies [16]. Another case study from the literature also reports a family with inherited combined deficiency of Factor V Leiden and vWF has been reported, further demonstrating the ability of a clotting and bleeding disorder to exist together [17]. Little evidence supports how these patients would present either acutely or chronically, if they would present as clinically distinct from vWD or Factor V Leiden, if their symptoms would resemble one condition more than the other, or if they would be clinically silent due to the thrombophilic-hemophilic paradox.

Future research should focus on cases like these of combined thrombophillic-hemiphilic patients in order to provide better care for these unique presentations. Although it is easy to see how the pathophysiology of these diseases can exist in a physician's basic science training, clinical medicine has to tease out the fine details from a patient's presentation to keep this scenario on their differential diagnosis list. Primary care physicians would most often be the first to see these patients unless they are presently acutely to the ED for either a thrombosis or coagulopathy. In both of these cases, starting these patients on either thrombolytic or coagulopathy medications would be a tough call to make in this case and would call for consultation from hematology or established guidelines that would lead precedent in treatment. Novel diagnostics or a novel diagnostics algorithm may also have to exist to diagnose these patients as more research is done into the prevalence of these disease processes coexisting. If the coinheritance is high, testing for VWD may infer testing of Factor V Leiden to be performed, and vice versa.

In the clinical scenario presented, the five-year-old boy had only inherited vWF deficiency. However, through a review of the literature, it was possible for the child to have inherited both diseases. Therefore, precautions must be taken with this child for vaccinations as he has a higher incidence of bleeding problems and will continue to have an increased risk of bleeding throughout his life, due to his present vWF deficiency. When he is ready to have children of his own, he needs to be cognizant that he could transmit his disease, but does not need to worry about passing on Factor V Leiden from his mother.

## References

1. Gottlieb JL. Activated Protein C Resistance, Factor V Leiden, and Central Retinal Vein Occlusion in Young Adults. Arch Ophthal .1998; 116(5): p.577. doi: 10.1001/archopht.116.5.577
2. Connors JM. Thrombophilia Testing and Venous Thrombosis. N Engl J Med .2017; 377(12): p.1177-1187. doi: 10.1056/nejmra1700365
3. Kakkos SK, Gohel M, Baekgaard N, et al.. European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. Eur J Vasc Endovasc Surg .2021; 61(1): p.9-82. doi: 10.1016/j.ejvs.2020.09.023
4. Van Es N, Le Gal G, Otten H-M, et al. Screening for Occult Cancer in Patients With Unprovoked Venous Thromboembolism. Ann Intern Med .2017; 167(6): p.410. doi: 10.7326/m17-0868
5. Colucci G, Tsakiris DA. Thrombophilia screening revisited: an issue of personalized medicine. J Thromb Thrombolysis .2020; 49(4): p.618-629. doi: 10.1007/s11239-020-02090-y.
6. Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis .2016; 41(1): p.154-164. doi: 10.1007/s11239-015-1316-1.
7. Page C, Rubin LE, Gusberg RJ, Dardik A. Arterial thrombosis associated with heterozygous factor V Leiden disorder, hyperhomocysteinemia, and peripheral arterial disease: importance of synergistic factors. J Vasc Surg. 2005;42(5):1014-1018. doi:10.1016/j.jvs.2005.06.019

8. Centers for Disease Control and Prevention. What is von Willebrand Disease?. https://www.cdc.gov/ncbddd/vwd/facts.html
9. National Heart, Lung, and Blood Institute. The Diagnosis, Evaluation and Management of von Willebrand Disease. https://www.nhlbi.nih.gov/sites/default/files/media/docs/vwd.pdf
10. The American College of Obstetricians and Gynecologists. Committe Opinion: Von Willebrand Disease in Women. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/12/von-willebrand-disease-in-women#.
11. Coller BS, Gralnick HR. Studies on the mechanism of ristocetin-induced platelet agglutination. Effects of structural modification of ristocetin and vancomycin. J Clin Invest 1977; 60:302.
12. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. Br J Haematol 2014; 167:453.
13. Jennifer Bushwitz; Michael A. Pacanowski & Julie A. Johnson (2006-10-11). "Important Variant Information for F5". PharmGKB.
14. Aerssens J, Chaffanet M, Baens M, et al. Regional assignment of seven loci to 12p13.2-pter by PCR analysis of somatic cell hybrids containing the der(12) or the der(X) chromosome from a mesothelioma showing t(X;12)(q22;p13). Genomics. 1994;20(1):119-121. doi:10.1006/geno.1994.1136
15. Middeldorp S, Henkens CM, Koopman MM, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med 1998; 128: 15-20.
16. Schapkaitz E, Jacobson BF. A case of a combined commonly inherited bleeding and clotting disorder. S Afr Med J. 2010;100(1):10.
17. Akutsu Y, Mori K, Suzuki S, et al. Rinsho Ketsueki. 1990;31(3):365-370.
18. Franchini M, Lippi G. Factor V Leiden and hemophilia. Thromb Res. 2010;125(2):119-123. doi:10.1016/j.thromres.2009.11.003
19. De Mitrio V, Marino R, Scaraggi FA, et al. Influence of factor VIII/von Willebrand complex on the activated protein C-resistance phenotype and on the risk for venous thromboembolism in heterozygous carriers of the factor V Leiden mutation. Blood Coagulation & Fibrinolysis : an International Journal in Haemostasis and Thrombosis. 1999 Oct;10(7):409-416. PMID: 10695766.

## Author Information

**Alexis G. Saunders, BS**
SUNY Upstate Medical University
Syracuse, NY, USA

**Melanie G. Kirk, BS BA**
SUNY Upstate Medical University
Syracuse, NY, USA

**Kuldesh Ubhi, MD**
SUNY University at Buffalo
Buffalo, NY, USA