# Mechanism and pathophysiology of activated protein C-related factor V leiden in venous thrombosis


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Sir,

Factor V Leiden (FVL) is the most common heritable cause of venous thrombosis. It is caused by a single nucleotide substitution resulting in an R506Q mutation, resulting in factor V resistance to activated protein C (APC) inactivation. The carriers of FVL have an increased susceptibility to venous thrombosis, which is further increased in the presence of other genetic or environmental risk factors. Factor V resistance to APC has an incidence of 4.8% in general population.[1] In contrast, the second most common genetic mutation that results in thrombosis (G20210A Prothrombin mutation) occurs in 2.7% of normal patients, with the frequency increasing up to 7.1 to 16% in affected patients.[2] FVL mutation is more frequently found in cases of venous thrombosis than protein C or S deficiency, Prothrombin G20210A mutation and antithrombin deficiency combined.

The genetical and molecular basis for APC resistance involves a mutation in the coagulation factors (FV) gene at nucleotide1691 that causes the mutation Arg 506 Gln. Two reports of functional activity studies suggested that the variant Gln 506–FVa is resistant to cleavage by APC. Two large studies have examined the association between FVL and venous thrombosis. The Leiden Thrombophilia Study (LETS), a case-control study of unselected Dutch patients younger than 70 years of age without cancer who experienced a first episode of deep venous thrombosis (DVT). Secondly, the Longitudinal Investigation of Thromboembolism Etiology (LITE) study was a prospective cohort study involving 21 680 men and women age ranging from 65 to 100 years that evaluated baseline risk factor including FVL, in relation to future DVT or pulmonary embolism. Both studies found an increased risk in persons with the mutation for developing venous thrombosis. The relative risk for FVL heterozygotes was 8.1 fold in LETS and 3.7 fold in the LITE study and the relative risk for FVL homozygotes was 80 fold and 24 fold, respectively. The weaker association of FVL with thrombosis in the LITE study may be due to the younger age of patients in LETS and the use of oral contraceptives in LETS vs LITE, while disorders of the vessel wall and paraneoplastic hypercoagulability (Trousseau syndrome) may have accounted for a greater fraction of thrombosis cases in the LITE study.[3,4] The mean age for presentation with venous thrombosis is 44 years for heterozygotes and 31 years for homozygotes. The incomplete penetrance of thrombotic phenotype in FVL, in contrast to other hereditable coagulopathies, suggests other genetic or environmental modifiers that, if identified, might

help predict which patients are at greatest risk. FVL heterozygotes are estimated to have only a 10% lifetime risk of thrombosis; homozygosity, found in 1% of patients with the FVL mutation, is serious but compatible with life. By contrast, homozygosity for protein or double heterozygosity for deficiencies in both protein C and protein S (levels 1%) results in neonatal purpura fulminans. Other precipitating events or genetic risk factors greatly add to the risk of an episode of venous thrombosis in patients with FVL and are usually required before patients with FVL become symptomatic. These additional factors include genetic defects such as antithrombin deficiency, prothrombin G20210A mutation, and deficiency of proteins C or S, or exogenous risk factors (e.g., oral contraceptive use, pregnancy, surgery, or prolonged stasis). This suggests a "two hit" model in which the relative risk for thrombosis increases synergistically in the presence of other predisposing genetic mutations. Although FVL is more prevalent in selected patients with venous thrombosis, it tends to be a weaker risk factor for thrombosis. The highest annual risk for venous thrombosis is seen in patients with antithrombin deficiency (annual risk, 0.87 to 1.6%), while the annual risk in patients with FVL is only 0.25 to 0.45%.

To conclude, APC resistance caused by FVL mutation is a strong risk factor for venous thrombosis. FVL remains an important heritable cause of hypercoagulability. Clinical suspicion should be high in cases of unexplained venous thrombosis. APC resistance and FVL mutation can be diagnosed with high sensitivity and specificity with use of clotting time-based functional assays and genetic assays, respectively, allowing for evidence-guided clinical decision making regarding the benefit of long-term anticoagulation.

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