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Mutations and blood clots

how point mutations in clotting factor genes conspire to increase the risk of thrombosis

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Clotting is essential, yet can be fatal. Pathological activation of the clotting cascade can lead to the formation of a blood clot, typically a deep vein thrombosis (DVT) in the legs. This blood clot may then be carried in the bloodstream to the lungs. This is known as a pulmonary embolism and is a medical emergency, being one of the leading causes of sudden death.

After trauma, the formation of a thrombus is essential to stem bleeding. A cascade of pro-enzymes, enzymes, and cofactors interact with damaged vessel endothelium to converge on a common pathway with the formation of a fibrin clot. The clot acts as a mechanical plug to prevent bleeding and is vital for normal vascular function. Disturbance of this pathway can be deadly; too little clotting results in bleeding disorders such as hemophilia, whereas excessive clotting produces blood clots that can block the lungs.

There are many factors that lead to an excessive propensity to clot, or thrombophilia. These can be classified by: (1) changes in blood vessel wall (2) changes in blood flow and (3) changes in blood constituents. Among the genetic components that underlie problems with blood constituents are mutations of clotting factor genes. These cause a deficiency of the body's natural anticoagulants, such as protein C, protein S, or antithrombin III (see figure). However, the most common inherited mutation that predisposes to thrombosis is the factor V Leiden mutation.

Factor V acts toward the end of the clotting cascade, where it is a co–factor for the Xa-dependent proteolytic cleavage of prothrombin to thrombin. Thrombin then catalyzes the conversion of soluble fibrinogen to a solid fibrin clot. Activated factor V (Va) is kept in check by a serine protease called activated protein C (APC). APC stops factor V from working by cleaving sites on its heavy chain; in particular at the sites Arg 506 and Arg 306. Thus, APC is important in limiting clot formation.

Factor V Leiden is a single point mutation resulting in an amino acid substitution of arginine for glutamine at Arg 506. The mutation affects factor V's APC-binding site, therefore preventing factor V inactivation. Carriers of this APC-resistant factor V suffer from a propensity to inappropriate clot formation.

What if you are a carrier of factor V Leiden? It is a common mutation, with a prevalence of 2% in Caucasian populations. It is especially found in patients with DVTs and increases the risk of thrombosis during pregnancy or while taking oral contraceptives. It is also associated with an increased risk of miscarriage. Although it is the most important genetic risk factor that we know of, the overall probability of thrombosis is still low with a single mutation. However, with the co-inheritance of other clotting factor polymorphisms, such as that of prothrombin which increases levels of prothrombin in the blood, the risk of thrombosis now becomes more significant.

Further investigation of the clotting factor mutations will help explain the hereditary basis of thrombophilia. Most importantly, however, the main causes of DVT are not inherited but are acquired. Despite our genetic make-up, a healthy lifestyle is our most important weapon for keeping thrombosis at bay.

Search PubMed for factor V mutations in pregnancy.

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What are the consequences of factor V mutations in pregnancy?

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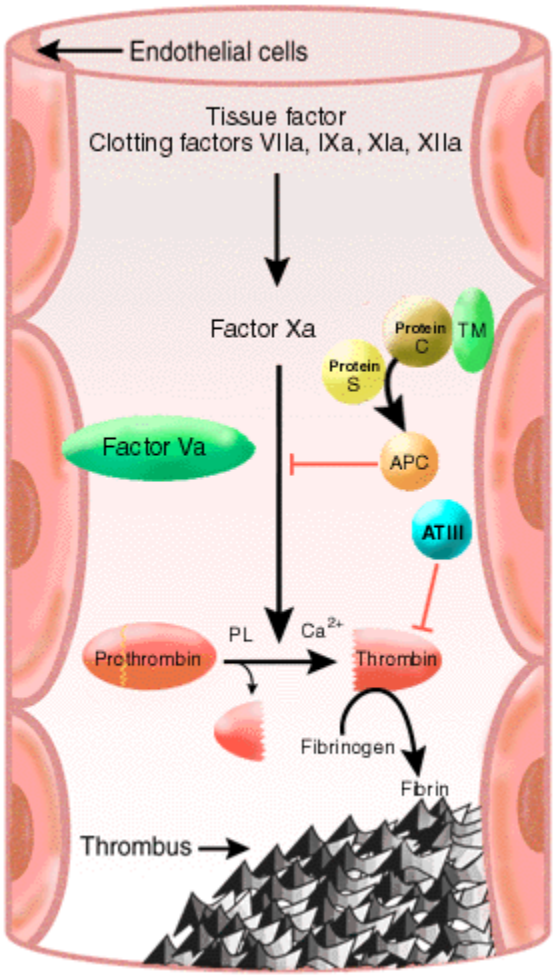

Coagulation cascade.
Key:

Black arrows = activation

Red arrows = inactivation

APC = activated protein C

TM = thrombomodulin, a protein bound to endothelial cell membranes to which protein C binds

PL = phospholipid

Ca^{2+} = calcium

Each reaction in the coagulation cascade involves the conversion of a clotting factor precursor into an active protease by proteolysis, regulated by cofactors and calcium. The end point is the generation of enough thrombin to catalyze the formation of fibrin, which then polymerizes and crosslinks to form a clot. Under pathological conditions, the mutation in **factor V** renders it resistant to inactivation by APC. Hence mutated factor V pushes the cascade towards excessive blood clot formation. Mutations in the upstream region of the **prothrombin** gene result in increased levels of prothrombin in the blood, again encouraging the formation of a thrombus. Protein C, protein S and antithrombin III all have anti-coagulant action. Deficiencies of proteins C and S usually result in a syndrome of recurrent venous thrombosis and pulmonary embolism. Deficiency of antithrombin III is usually mild.