Genetics of Hypercoagulable and Hypocoagulable States

Daulath Singh, MD[a,*], Arjun Natarajan, MBBS, MD[b], Sucha Nand, MD[a], Hanh P. Mai, DO[a]

KEYWORDS

• Factor V Leiden • Prothrombin gene mutation • Protein C and S deficiencies
• Antithrombin deficiency • Antiphospholipid syndrome • von Willebrand disease • Hemophilia

KEY POINTS

- Hemostasis is a tightly regulated process, and a delicate equilibrium exists between prothrombotic and antithrombotic factors.
- Hypercoagulable states can be acquired or inherited.
- Inherited thrombophilia can be inherited in a heterozygous or homozygous fashion with varying degrees of penetrance.
- Antiphospholipid syndrome is associated with significant venous and arterial thrombosis as well as obstetric complications.
- Inherited bleeding disorders include von Willebrand disease and hemophilia.

Under physiologic conditions, equilibrium exists between thrombotic and antithrombotic mechanisms. Primary hemostasis involves the interaction of endothelial cells, von Willebrand factor (VWF), and platelets to form a temporary platelet plug. Secondary hemostasis, also known as the coagulation cascade, involves a series of enzymatic reactions culminating in the formation of a stable fibrin clot (**Fig. 1**).[1,2] Venous stasis, hypercoagulability (either inherited or acquired causes), and vascular injury are predisposing risk factors for thrombosis.[3] Protein C, S, and antithrombin (AT) are natural anticoagulants of the coagulation cascade. Thrombin converts protein C to activated protein C (APC), which, in combination with protein S inactivates factors Va and VIIIa, providing a negative feedback loop to effectively limit thrombin production. AT binds to and inactivates thrombin, factor Xa, as well as other clotting factors.

It has been known for centuries that inherited defects in the coagulation system can lead to bleeding diatheses. However, the counterargument, which is inherited defects leading to the increased risk of pathologic thrombosis, has been elucidated only in the last few decades.[2,4] Over the last century, research has been performed to identify the genetic causes of thrombophilia. A hereditary thrombophilia results when there is a deficiency in a clotting protein, which can be inherited in a homozygous or heterozygous fashion. Homozygosity is the loss of 2 gene copies, resulting in the total loss of the protein product. Heterozygosity refers to the loss of one gene copy, where there is still some functional product present. The severity of the clinical

Disclosure: The authors have nothing to disclose.

[a] Department of Hematology and Oncology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153, USA; [b] Department of Internal Medicine, Advocate Illinois Masonic Medical Center, 533 West Barry Avenue, Unit 7K, Chicago, IL 60657, USA
* Corresponding author.
E-mail address: Daulath.singh@lumc.edu

Neurosurg Clin N Am 29 (2018) 493–501
https://doi.org/10.1016/j.nec.2018.06.002

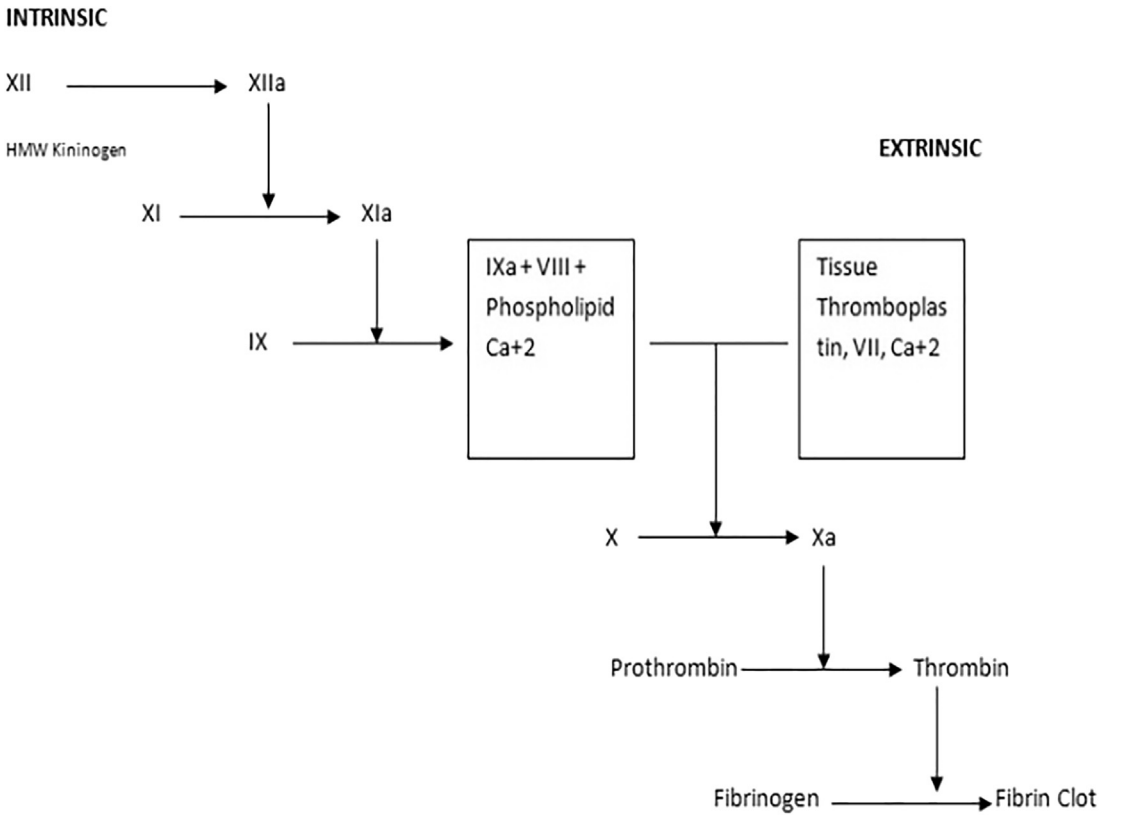

Fig. 1. Extrinsic and intrinsic pathways of coagulation. HMW, high molecular weight. (*From* Aneeque M. Coagulation cascade. Available at: https://www.slideshare.net/muhammadakhan754365/coagulation-cascade-dr-m-aneeque; with permission. Accessed March 16, 2018.)

phenotype or thrombotic risk depends on the homozygous or heterozygous state.[1,5] The common causes of inherited thrombophilia include factor V Leiden (FVL), prothrombin gene mutation, protein C, protein S, and AT deficiencies.

INHERITED AND ACQUIRED HYPERCOAGULABLE STATES

Factor V Leiden or Activated Protein C Resistance

APC is a potent inhibitor of the coagulation system. It cleaves the activated forms of factors V and VIII. In 1993, Dahlback and colleagues discovered that patients with resistance to APC developed clinical thrombosis, and the mode of inheritance appeared to be autosomal dominant. In 1994, Bertina and colleagues described a single point mutation in the factor V gene resulting in susceptibility of inactivation by APC. Factor V gene has been mapped to chromosome 1 (1q21-25) and is closely linked to the AT gene.[6] The term "activated protein C resistance" was developed because of the observation that APC in patients' plasma failed to prolong the partial thromboplastin time (PTT). A substitution mutation at nucleotide 1691 results in the replacement of arginine by glutamine. This gene product, called factor V Leiden (FVL), also known as factor V Q506 or Arg506Gln, is named after the city in the Netherlands where it was first identified. FVL is a variant of the normal gene and is not susceptible to cleavage at position 506 by APC (**Fig. 2**). Consequently, more factor Va is available within the prothrombinase complex, thereby increasing the generation of thrombin. FVL is the most common cause of heritable thrombophilia.[1,2,7] The prevalence of heterozygous FVL is 3% to 8% in the Caucasian population and 1.2% in African Americans. Homozygous FVL occurs in 1 in 500 to 1600 Caucasians.[2] Based on published case control studies, there is a 5- to 10-fold increase in thrombosis risk in heterozygous carriers and approximately 80-fold increase in thrombosis risk for homozygous carriers.[7] A study of 306 members from 50 Swedish families found that 40% of homozygous individuals had an episode of venous thrombosis by age 33, compared with 20% of heterozygous individuals, and 8% of normal.[1,6,7] The risk of recurrent venous thromboembolism (VTE)