TABLE 141-1 GENETIC AND LABORATORY CHARACTERISTICS OF INHERITED COAGULATION DISORDERS

Clotting Factor Deficiency	Inheritance	Prevalence in General Population	Laboratory Abnormality[a]			Minimum Hemostatic Levels	Treatment	Plasma Half-Life
			aPTT	PT	TT			
Fibrinogen	AR	1 in 1,000,000	+	+	+	100 mg/dL	Cryoprecipitate	2–4 d
Prothrombin	AR	1 in 2,000,000	+	+	–	20–30%	FFP/PCC	3–4 d
Factor V	AR	1 in 1,000,000	+/–	+/–	–	15–20%	FFP	36 h
Factor VII	AR	1 in 500,000	–	+	–	15–20%	FFP/PCC	4–6 h
Factor VIII	X-linked	1 in 5,000	+	–	–	30%	FVIII concentrates	8–12 h
Factor IX	X-linked	1 in 30,000	+	–	–	30%	FIX concentrates	18–24 h
Factor X	AR	1 in 1,000,000	+/–	+/–	–	15–20%	FFP/PCC	40–60 h
Factor XI	AR	1 in 1,000,000	+	–	–	15–20%	FFP	40–70 h
Factor XII	AR	ND	+	–	–	[b]	[b]	60 h
HK	AR	ND	+	–	–	[b]	[b]	150 h
Prekallikrein	AR	ND	+	–	–	[b]	[b]	35 h
Factor XIII	AR	1 in 2,000,000	–	–	+/–	2–5%	Cryoprecipitate/FXIII concentrates	11–14 d

[a]Values within normal range (–) or prolonged (+). [b]No risk for bleeding; treatment is not indicated.

Abbreviations: aPTT, activated partial thromboplastin time; AR, autosomal recessive; FFP, fresh-frozen plasma; HK, high-molecular-weight kininogen; ND, not determined; PCC, prothrombin complex concentrates; PT, prothrombin time; TT, thrombin time.

are clinically affected; women, who carry a single mutated gene, are generally asymptomatic. Family history of the disease is absent in ~30% of cases, and in these cases, 80% of the mothers are carriers of the de novo mutated allele. More than 500 different mutations have been identified in the *F8* or *F9* genes of patients with hemophilia A or B, respectively. One of the most common hemophilia A mutations results from an inversion of the intron 22 sequence, and it is present in 40% of cases of severe hemophilia A. Advances in molecular diagnosis now permit precise identification of mutations, allowing accurate diagnosis of women carriers of the hemophilia gene in affected families.

Clinically, hemophilia A and hemophilia B are indistinguishable. The disease phenotype correlates with the residual activity of FVIII or FIX and can be classified as severe (<1%), moderate (1–5%), or mild (6–30%). In the severe and moderate forms, the disease is characterized by bleeding into the joints (hemarthrosis), soft tissues, and muscles after minor trauma or even spontaneously. Patients with mild disease experience infrequent bleeding that is usually secondary to trauma. Among those with residual FVIII or FIX activity >25% of normal, the disease is discovered only by bleeding after major trauma or during routine presurgery laboratory tests. Typically, the global tests of coagulation show only an isolated prolongation of the aPTT assay. Patients with hemophilia have normal bleeding times and platelet counts. The diagnosis is made after specific determination of FVIII or FIX clotting activity.

Early in life, bleeding may present after circumcision or rarely as intracranial hemorrhages. The disease is more evident when children begin to walk or crawl. In the severe form, the most common bleeding manifestations are the recurrent hemarthroses, which can affect every joint but mainly affect knees, elbows, ankles, shoulders, and hips. Acute hemarthroses are painful, and clinical signs are local swelling and erythema. To avoid pain, the patient may adopt a fixed position, which leads eventually to muscle contractures. Very young children unable to communicate verbally show irritability and a lack of movement of the affected joint. Chronic hemarthroses are debilitating, with synovial thickening and synovitis in response to the intraarticular blood. After a joint has been damaged, recurrent bleeding episodes result in the clinically recognized "target joint," which then establishes a vicious cycle of bleeding, resulting in progressive joint deformity that in critical cases requires surgery as the only therapeutic option. Hematomas into the muscle of distal parts of the limbs may lead to external compression of arteries, veins, or nerves that can evolve to a compartment syndrome.

Bleeding into the oropharyngeal spaces, central nervous system (CNS), or retroperitoneum is life threatening and requires immediate therapy. Retroperitoneal hemorrhages can accumulate large quantities of blood with formation of masses with calcification and inflammatory tissue reaction (pseudotumor syndrome) and also result in damage to the femoral nerve. Pseudotumors can also form in bones, especially long bones of the lower limbs. Hematuria is frequent among hemophilia patients, even in the absence of genitourinary pathology. It is often self-limited and may not require specific therapy.

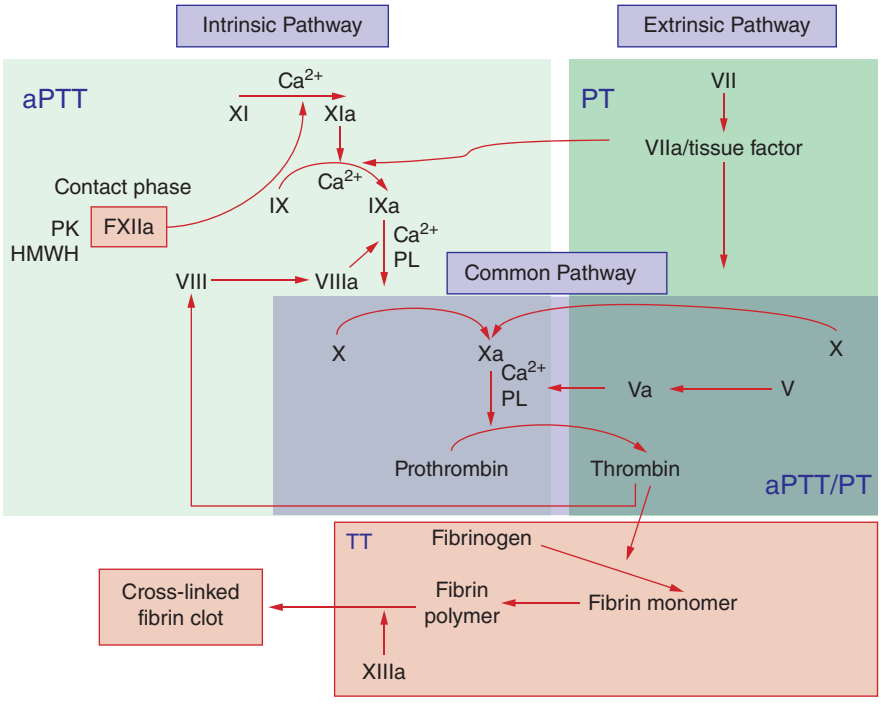

FIGURE 141-1 Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL).