## Feature | Disease Facts
---|---
### Synonyms
- Hageman trait, Hageman factor deficiency.

### Epidemiology
Rare disorder, actual prevalence unknown because disease is usually asymptomatic. Relatively more common in the Netherlands.

### Etiology and Pathogenesis
Factor XII is a single-chain beta-globulin serine protease with a molecular weight of 80,000 - 84,000 daltons and a plasma concentration of approximately 30 pg/mL. Proteolytic cleavage of factor XII is mediated by charged surfaces (glass, kaolin, cel-lite, dextran sulfate, endotoxin, urates, crude collagen, sulfatides), autoactivation, and kallikrein. Prekallikrein, factor XI, factor VIII, plasminogen, and complement C1 are proteolytically cleaved by activated factor XII (factor XIIa) into their active forms.

Hageman factor fragments and kallikrein link the contact system to the kinin system, the intrinsic fibrinolytic system, and the complement system in addition to liberating renin from prorennin and priming neutrophils for chemotactic activity. An antithrombotic role for factor XII as a platelet aggregation inhibitor or plasminogen activator has been proposed. C1 esterase inhibitor is the major inhibitor of factor XIIa. Antithrombin III (AT-III), alpha-2-antiplasmin, and alpha-2-macroglobulin also inhibit factor XIIa.

Acquired factor XII deficiency is most common in patients with nephrotic syndrome. The pathological basis of this acquired deficiency has not been established since urinary loss of factor XII alone may not account for the reduced plasma activity of this factor.

### Pattern of Inheritance
Factor XII deficiency is usually transmitted as an autosomal recessive trait, although dominant and codominant patterns of inheritance have been reported in some families.

Plasma levels of factor XII vary from 0.17 to 0.83 U/mL in different studies, with about one-half showing levels below the normal range. Homozygotes (or double heterozygotes) have very low levels < 0.01 U/mL of factor XII. Most individuals with homozygous factor XII deficiency are cross-reacting material negative (CRM-).

### Clinical Presentation
**Congenital Factor XII Deficiency.** Factor XII deficiency is the most common cause of an isolated prolongation of the aPTT in a nonbleeding child or adult; consequently, most patients are detected during a routine preoperative coagulation study. Most patients withstand severe challenges to the hemostatic system, such as dental extractions or major surgery, without bleeding, although easy bruising or epistaxis has been reported in an occasional factor XII-deficient patient.
**Clinical Presentation (Cont’d)**

In contrast to the usual lack of bleeding manifestations, there is an increased incidence of serious thromboembolic problems in patients with hereditary factor XII deficiency. The first patient discovered to have factor XII deficiency, John Hageman, died of a pulmonary embolus and an unusually high incidence of strokes, deep venous thrombosis, and myocardial infarction has been described in other patients with factor XII deficiency, as well as in families with the anomaly. The incidence of serious thromboembolic disease has been reported as 1-8% in different studies.

**Acquired Factor XII Deficiency.** Activation of the contact factor system is seen in a wide variety of disease states, including the nephrotic syndrome, endotoxin-induced sepsis and shock, disseminated intravascular coagulation, adult respiratory distress syndrome, polycythemia vera, hepatic cirrhosis, and other diseases. Although decreased contact factor levels have been demonstrated in these diseases, the pathophysiologic significance of this findings is uncertain. A spontaneous increase in factor XII activity occurs in pregnancy and with the use of oral contraceptives. A spontaneous increase in factor XII also occurs with cold storage of plasma (cold-promoted activation).

**Laboratory Features**

The platelet count, bleeding time, prothrombin time, and thrombin time are normal in patients with isolated factor XII deficiency. The aPTT is markedly prolonged in patients with homozygous factor XII deficiency, but corrects to the normal range by 1:1 mixing with normal plasma, aged normal serum, and adsorbed normal plasma. The "Fletcher factor" screening test (10-min incubation of the patient's plasma) does not correct the prolonged aPTT to near normal. Prothrombin consumption and thromboplastin generation are retarded.

Individuals with heterozygous factor XII deficiency have normal to mildly prolonged aPTT values. The immediate family members (who are potential heterozygotes) of a patient found to have a homozygous contact factor deficiency should be screened to prevent future expensive evaluations of a mildly prolonged APTT.

The definitive diagnosis of factor XII deficiency requires a specific factor XII assay utilizing factor XII deficient plasma.

**Treatment**

No treatment necessary for hereditary type. Management of nephrotic syndrome in acquired type.

**References**

Factor XII Deficiency

References


