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# Understanding Inherited Bleeding Disorders: Genetic Mutations in Blood Coagulation Factors and Regulatory Proteins

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**Abstract**

Hereditary thrombotic diseases, or inherited bleeding disorders, are a group of genetic conditions that disrupt normal blood coagulation. These diseases result from mutations in genes encoding blood coagulation factors or other regulatory proteins, impairing the body's ability to regulate bleeding and clotting.

The most common inherited clotting disorders are hemophilia A and B, which are associated with deficiencies in clotting factors VIII and IX, respectively. Von Willebrand disease (VWD) is another prevalent disorder characterized by a deficiency or dysfunction of the Von Willebrand factor, a protein essential for coagulation. Additionally, the Factor V Leiden mutation is linked to an increased risk of blood clots.

The prevalence of inherited coagulation disorders varies significantly by region and subpopulation. It is estimated that 5,000 to 10,000 male newborns are born with hemophilia A or B each year. Von Willebrand disease is much more common, affecting about 1% of the global population. The Factor V Leiden mutation is found in significant percentages of certain populations, with 3–8% of Caucasians being carriers.

While antithrombin deficiency is more common in some areas, the incidence of other inherited clotting disorders, such as Factor XI, protein C and S deficiencies, and VWD, varies widely worldwide.

This study discusses the incidence of inherited clotting disorders and their impact on affected individuals and their families. It also covers new advancements in disease management, alternative therapy approaches, and contemporary diagnostic techniques, aiming to improve diagnoses, treatments, and outcomes for patients with hereditary clotting disorders.

## Introduction

Inherited factors, acquired alterations in the clotting system, or more frequently, a combination of acquired and inherited variables can all contribute to the

propensity to produce clots[1]. The frequency of hereditary bleeding diseases varies greatly. The most frequent ones are hemophilia A (1 in 5000 men) and VWD (affects 1 in 1000 live births, while numerous ultra-rare platelet abnormalities only occur in a few individuals [2,3,4]. Due to its hereditary nature, hemophilia is more common in communities with greater degrees of consanguinity. It is possible for females to carry the hemophilia gene without experiencing any symptoms or to have a partial expression of the relevant components. Although there is no sex preference for Von Willebrand disease, it is an autosomal dominant characteristic where symptoms are more common in women due to increased menstrual bleeding [5,6].

Patients who arrive in early infancy while having a family history of the problem, easy bruising, recurrent or severe bleeding (especially at atypical places), or any of these factors suggest that they may have a hereditary bleeding disorder [7].

Many hereditary bleeding diseases, such as VWD, platelet function abnormalities, hemophilia A and hemophilia B carrier status, and other less common coagulation factor deficiencies, can cause increased bleeding symptoms in women with inherited bleeding disorders [8].

FFP (fresh frozen plasma), cryoprecipitate, and concentrates of plasma-derived or recombinant factors are used to treat these patient's bleeding episodes. While the use of these products resulted in a noteworthy decrease in the morbidity and mortality rates after bleeding episodes among patients with hereditary bleeding disorders (HBDs), these replacement therapies have been linked to the spread of transfusion-transmissible infection (TTI), particularly viral infections like HTLV, HIV, HBV, and HCV [9,10].

There are two primary types of bleeding disorders: hereditary and acquired. We will focus on congenital coagulopathies, while acquired bleeding diseases will be viewed as falling outside the purview of the data offered here.

## Hemophilia A

*Definition and background*

Hemophilia, which literally translates to "love of blood" (from the Greek words "philia" and "hemo"), is the most frequent severe hereditary bleeding illness. The hemophilia A condition is relatively rare; however, it is one of the most prevalent X-linked inherited bleeding disorders that affects 1 in every 5000 males. It is caused by a deficiency or absence of clotting factor VIII, often known as FVIII. The severity of the condition is directly proportional to the amount of FVIII that has been reduced, which in turn is dependent on the kind of mutation that has occurred in the genes that code for the factors (F8) [11,12,15].

## Symptoms

The most prominent clinical signs of hemophilia are recurrent bleeding in the joints and muscles, which leads to severe and progressive musculoskeletal damage. Even preclinical hemarthrosis, if not handled properly, may lead to the development of hemophilic arthropathy, a debilitating disorder that is characterized by joint transformation, severe discomfort, lower quality of life, and ultimately the need for joint replacement. Persistent morbidity and early mortality are associated with this condition. These adverse outcomes can be avoided by using clotting factor concentrates provided through specialized care centers that offer home infusion therapy [13,14,16,17].

*Diagnosis and treatment*

The one-stage clotting assay (OSCA) and the chromogenic substrate assay (CSA), both calibrated against plasma (FVIII) standards, are the two major methods used to measure plasma FVIII activity. However, the inability to identify the presence of abnormal bleeding might lead to diagnostic challenges. The use of factor replacement therapy in the prevention and treatment of bleeding problems has been considered the pinnacle of treatment. However, along with the worsening of arthropathy and the development of inhibitors, this has increased the demand for other methods of therapeutic strategies. These include extended half-life products and non-factor coagulation products, such as emicizumab, which enables patients to achieve successful hemostasis by replacing the lost activated factor VIII activity, which has been beneficial to prevent hemorrhage. Desmopressin, also known as D-amino D-arginine vasopressin, is a treatment option for people who have mild hemophilia A. In recent years, gene therapies have offered patients with hemophilia the possibility of a cure by producing permanent intrinsic production of factor VIII after the transfer of a functioning gene copy to substitute the hemophilic patient's incorrect gene.

This gives patients with hemophilia a reason to have hope for a cure. Hemophilia might be regarded as a "low-hanging fruit" for gene therapy due to the fact that even a little increase in blood factor levels (less than 2% of normal) results in a considerable improvement in the bleeding propensity, reducing it from severe to moderate and minimizing the majority of uncontrolled bleeding [18,19,20,21,22,23].

The diagnosis and treatment of hemophilia in newborns are complicated by a number of factors that are specific to this age group.

However, the bleeding sites may differ depending on the child's age. Bleeding episodes continue to predominate as the diagnostic trigger in youngsters. In the neonatal period, it is usual for bleeding to occur as a result of delivery-associated intracranial hemorrhage (ICH) and venipuncture. However, cartilage disease and head trauma are more likely to occur in later young people and teens. If morbidity and death are going to be kept to a minimum, prompt intervention by healthcare providers is an absolute need [24].

Presented coagulation products from the World Federation of Hemophilia's Humanitarian Aid Program (HAP) were used to treat more than 250,000 cases of excessive bleeding, manage nearly 4,000 surgical procedures, and establish bleeding preventative prophylaxis in roughly 2000 patients across 73 nationalities. In response to the initiative, a number of governments boosted their funding for hemophilia care, including the acquisition of independent modest quantities of therapeutic materials.

Exercise is frequently used to speed up the healing process after bleeding and to enhance joint functionality when there is arthropathy, according to suggestions from the World Federation of Hemophilia (WFH). In adults, they found that hydrotherapy relieves pain more effectively than land workouts. Exercise also helps in improving a person's quality of life as well as cardiovascular health because the risks of obesity and various metabolic and cardiovascular illnesses may be decreased by aerobic exercise. For building muscle strength, functional workouts like treadmill walking appear to be more helpful than static or quick exercises. These results are in line with the numerous non-controlled intervention accounts in the literature on hemophilia [25,26,27].

The ancient practice of circumcision is an important religious ceremony for Muslims and Jews as well as a significant social issue for the hemophilia patient and his relatives. A diagnosis of hemophilia does not always rule out the possibility of circumcision. The risk of major complications from hemorrhage is low but present. Patients with hemophilia have a significant societal challenge through the procedure of

circumcision, which has to be addressed [28,29].

**Hemophilia B:**

*Definition and background*

Hemophilia B is an X-linked hereditary bleeding disorder that primarily affects men. However, carrier females with low levels of factor IX (FIX) activity (factor IX concentrate) may also experience bleeding episodes[30].

Approximately 1 in 30,000 men worldwide are affected by hemophilia B, making it significantly less common than hemophilia A. Patients with hemophilia B may experience bleeding following dental extractions, bruising (ecchymosis), nosebleeds (epistaxis), and recurrent joint hemorrhages[31]. Compared to carriers of hemophilia A, pregnant carriers of hemophilia B are more likely to experience postpartum bleeding. This is because pregnancy-related elevations in factor VIII (FVIII) and FIX levels commonly occur in hemophilia A but not in hemophilia B[32].

Individuals with hemophilia B can have varying degrees of bleeding tendencies based on their levels of FIX coagulant activity. These levels can be classified as mild (5%–40%), moderate (1%–5%), or severe (<1%)[33]. However, new research indicates that individuals with hemophilia B have better long-term outcomes, including a lower risk of joint arthroplasty. They also exhibit a less severe bleeding phenotype and experience bleeding less frequently[34].

*Treatment*

Nowadays, the cornerstone of hemophilia treatment is prophylaxis, which involves regular infusions of FIX concentrate. However, various techniques have been developed to improve the pharmacokinetics of FIX clotting factors because their relatively short half-life necessitates frequent infusions, making it challenging for patients to maintain adherence[35]. The goal of hemophilia B therapy is to replace the deficient coagulation FIX. Currently, several FIX concentrates are available for replacement therapy, produced either through recombinant DNA technology or derived from donated human plasma. These products are well-established and enable patients to lead relatively normal lives. Additionally, recombinant FIX solutions with longer half-lives have been developed to enhance therapy efficacy. This innovation allows for more relaxed prophylactic dosing and reduces the overall treatment burden[36].

**Hemophilia C**

*Definition and background*

Hemophilia C, a congenital factor XI deficiency (FXID), is associated with postoperative or post-traumatic bleeding, particularly in regions with high fibrinolytic activity like the nose, oral cavity, and urinary tract. The absence of clotting factor XI (FXI) causes this kind of illness.

Usually, one person out of every 100,000 has hemophilia C. FXID affects Ashkenazi Jews more frequently—roughly 8%. The two genetic variations that account for almost 90% of the aberrant alleles observed in the Jewish population are Glu117Stop (type II) and Phe283Leu (type III) [37,38,39].

*Diagnosis*

Current diagnostic techniques are unable to accurately predict bleeding tendencies in individuals with FXID due to the wide variation in symptoms across patients and their lack of correlation with plasma FXI levels. It seldom occurs spontaneously, commonly exhibits asymptomatic hemorrhagic tendencies,

and typically results in Hemorrhages related to trauma or surgery. In the lab, FXI deficiency is identified by simple, traditional methods. If an isolated, prolonged activated partial thromboplastin time (aPTT) is discovered during a systematic hemostasis test, a deficiency may be identified. Because of how much its sensitivity is influenced by the reagents used, aPTT is more likely to identify severe FXID [40,41,42].

*Treatment*

Preventive medicine is usually not necessary for daily activities, even for individuals with severe FXID. However, in cases where there has been substantial surgery or trauma, therapy can be required.

Anti-fibrinolytic like tranexamic acid are used for low-risk bleeding scenarios (dental surgery, menstrual bleeding). FXI concentrates, or FFP are used for high-risk situations (surgical prophylaxis, symptomatic bleeding). Anti-fibrinolytics and recombinant FVIIa concentrate can also be used together in certain situations, particularly when an individual has an FXI inhibitor. These therapies undergo a very detailed risk-benefit analysis due to the potential for serious adverse effects. FXI concentrations in particular could have a significant prothrombotic impact [43,44,45,46].

Replacement treatment may be linked to an increased risk of thrombosis, and there is no relationship between the degree of bleeding and FXI levels.

FFP at a dosage of 15 mL/kg with a target FXI activity level of 40% is frequently administered to patients diagnosed with severe FXID for about one week. For this ailment, this drug is thought to be the standard of care. Increased volume in people who already have congestive heart failure or renal failure is one of the potential issues that the medicine is associated with developing. The use of FFP might be made more difficult as a result of this increased risk. Patients who have levels of FXI in their plasma that are undetectable are also at risk of developing inhibitors as a result of being exposed to the concentrates. IgA-deficient patients are ineligible to receive treatment with these agents. Because of this, patients with undetectable FXI levels who have been previously exposed to FFP, FXI concentrates, or immunoglobulin must first undergo testing to determine whether or not they have antibodies to the drug before it may be prescribed for use [47,48,49,50].

**Von Willebrand factor (VWF)**

*Definition and background*

Von Willebrand disease (VWD) is characterized by a decrease in the level of von Willebrand factor (VWF) activity in the blood. When VWF activity is affected, either in quantity or quality, it results in a bleeding phenotype [51,52,53,54]. This plasma protein binds to and stabilizes blood clotting factor VIII (FVIII) and facilitates the initial adhesion of platelets at sites of vascular damage. Consequently, a decrease in FVIII concentration or impaired platelet adhesion due to deficiencies in VWF can lead to bleeding [55].

VWD is typically categorized into three subgroups. VWD type 1 is characterized by a partial quantitative deficiency of Von Willebrand factor (VWF). VWD type 2 involves qualitative deficiencies of VWF and can be further divided into several subtypes based on specific functional defects: 2A, 2B, 2N, and 2M. Lastly, VWD type 3, also known as severe VWD, is marked by an almost complete absence of VWF [56].

Since VWD is inherited, it affects men and women equally. However, women are more likely to experience symptoms due to the additional hemostatic challenges of menstruation and childbirth. While

type 3 and type 2N exhibit autosomal recessive inheritance, most cases of VWD are inherited in an autosomal dominant manner. The prevalence of VWD is about 1 in 100 when considering only abnormal laboratory findings. However, the clinical prevalence, which accounts for those with bleeding symptoms, is estimated to be closer to 1 in 1000[51,57].

There is no standardized laboratory method for identifying anti-VWF antibodies [58,59].

Patients with VWD may experience various types of bleeding, including mucocutaneous, gastrointestinal, and joint bleeding. Joint bleeding is more common in elderly patients and those with VWD types 2A and 3. Only individuals with a personal or family history of bleeding should be tested for VWD. Diagnosis is complicated by factors such as limited penetrance, variable expressivity, laboratory variability, and numerous modifiers that can affect a person's VWF levels [51].

VWF levels can be influenced by genetic, environmental, hormonal, and pathological factors. Pregnancy, aging, physical activity, the use of oral contraceptives, and exposure to cigarette smoke or air pollution all similarly increase the risk[60].

*Diagnosis*

Most people with VWD are likely to have normal results from screening tests such as total blood count, activated partial thromboplastin time (aPTT), and prothrombin time, limiting the usefulness of these tests. In more severe cases, individuals with type 2B may exhibit elevated aPTT and thrombocytopenia[51].

*Treatment*

Desmopressin can provide adequate hemostatic coverage to treat mucocutaneous bleeding and prevent bleeding during minimally invasive procedures in many patients with type 1 VWD and some with type 2A. To evaluate the potential for rapid clearance of the newly released protein, all patients considered for desmopressin treatment should undergo a therapeutic trial. During this trial, measurements of VWF: Ag, VWF: RCo, and FVIII: C should be taken for at least 4 hours after desmopressin administration [57,61]. When treating women with VWD experiencing menorrhagia, adjunctive therapy with antifibrinolytic agents, ideally tranexamic acid, is highly beneficial. The use of oral contraceptives or the levonorgestrel-releasing intrauterine device (Mirena) often achieves great results [51,61].

**Factor X**

*Definition and background*

Factor X (FX) is a crucial component of the blood coagulation cascade and a vitamin K-dependent clotting factor. Deficiency in FX can lead to a bleeding disorder characterized by heavy menstrual bleeding, easy bruising, nosebleeds, and prolonged bleeding after surgery or injury [62].

FX deficiency can be either congenital or acquired. Congenital FX deficiency is a rare autosomal recessive disorder caused by mutations in the F10 gene [63]. Acquired FX deficiency can arise from various conditions, including disseminated intravascular coagulation (DIC), vitamin K deficiency, renal disease, liver disease, warfarin treatment, and certain medications [64].

Rare bleeding disorders, such as FX deficiency, are classified as mild, moderate, or severe based on the residual amount of the deficient component. Historically, coagulation factor deficiencies were classified similarly to hemophilia: factor activity levels below 1% were considered severe, levels between 1% and 5% were considered moderate, and levels above 5% were considered mild. However, the specific type of coagulation factor deficiency affects bleeding patterns. Homozygous FX deficiency

is associated with a higher tendency to bleed compared to other coagulation factor deficiencies [65].

*Symptoms*

Bleeding can occur at any age in people with FX deficiency. Those with the most severe deficiency often begin experiencing bleeding as infants, including from the umbilical stump. Other severe bleeding events may include joint hemorrhages, bleeding after surgery, or intracranial bleeding[66].

*Treatment*

Minor bleeding issues are commonly managed with topical therapies and antifibrinolytic drugs. Nosebleeds Quick ReleaseTM powder is a hydrophilic polymer designed to stop nosebleeds effectively. Aminocaproic acid, available as a mouthwash, is used topically or orally to manage bleeding gums and recurrent nosebleeds. Fibrin glue preparations are applied to surgical sites to halt bleeding. Tranexamic acid, in addition to treating idiopathic menorrhagia, is a potent and well-tolerated antifibrinolytic medication beneficial for women experiencing bleeding issues. Fresh frozen plasma (FFP) or plasma-derived prothrombin complex concentrates (PCCs) are utilized to manage factor X deficiency. Refined FX concentrate is not currently available in the United States. FFP has been associated with allergic reactions and potential lung damage following blood transfusions. Integrated prenatal and menstrual care provided at a comprehensive hemophilia treatment center can benefit women dealing with menorrhagia and moderate factor X deficiency. Individuals who are heterozygous for factor X deficiency should undergo genetic counseling and hematological assessment before undergoing surgical procedures [67].

**Protein C deficiency**

*Definition and background*

Protein C (PC) is a plasma protein that is vitamin K-dependent in its function. It shares similar structural features with other coagulation mediators, including coagulation factor X and prothrombin.

PC deficiency could be acquired or inherited.

Acquired PC deficiency is a depletion of accessible PC in plasma or decreased PC synthesis due to vitamin K antagonist therapy, severe liver failure, or preterm problems.

Inherited PC deficiency is one of a diverse range of genetic illnesses linked to an increased risk of venous thromboembolism. Over 160 known mutations on PROC (a gene located on chromosome 2q14.3) result in PC deficiency [70,71].

While partial deficits (heterozygous forms) are far more common (1 in 200 to 1 in 500 births), severe PC deficiency (homozygous or compound heterozygous forms) is incredibly rare (1 in 500 000 to 1 in 750 000 births) [70,72].

**Pathophysiology**

PC's role is to maintain the physiologic function of coagulation within the body.

PC is transformed into its active thrombotic state by a thrombin-thrombomodulin complex 68 on the outermost layer of capillaries endothelial cells. Through its binding to plasminogen-activator inhibitor 1 (PAI-1), activated PC exerts an indirect profibrinolytic action by raising the rate of the action of tissue-type plasminogen-stimulating activation (tPA). Furthermore, thrombin activatable fibrinolysis inhibitor (TAFI) is less activated because to the decreased thrombin production, which raises the

profibrinolytic potential [73,74].

*Symptoms*

With age, the likelihood of blood clots rises in PC deficiency patients.

Predictable symptoms in mild forms of PC deficiency are vein clots (venous thromboembolism) and deep vein thrombosis (DVT) (the condition where blood clots form in the legs, brain, vein leading to the liver, big and small intestines, and other veins). Many patients may not have any symptoms at all.

The most serious predictable symptom in the severe form of PC deficiency is purpura fulminans, which is a sudden fatal thrombotic case mainly caused by PC deficiency and leads to coagulation in tiny blood capillaries within the skin, and progresses quickly to intravascular coagulation, skin necrosis, and thrombophilia (an excessive amount of blood clot formation)[69]. Some patients may express large purple patches or spots on the skin anywhere on the body.

The signs of neonatal acute PC deficiency may appear hours or days after birth. A significant absence of PC may result in recurrent venous thrombotic events, such as DVT and pulmonary embolism (PE) Throughout the newborn stage [75,76]. The patient's low serum levels (≤6%) in terms of PC appear to be a result of genetic PC abnormalities, coumarin impact, and disseminated intravascular coagulation (DIC). This finding raises the possibility that a lack of PC may seriously impair a newborn's capacity to regulate consumptive diseases [79].

*Diagnosis*

PC deficiency can be diagnosed by taking the patient's history, family history, and blood testing that determines the level of PC activity and quantity.

The long-term diagnosis of individuals with severe congenital PC deficiency is not well-documented [72].

*Treatment*

PC deficiency type and symptom intensity will determine the treatment.

No treatment: a majority of patients don't require therapy unless they are undergoing surgery, pregnant, have recently suffered trauma (such as a car accident), or are not physically active.

Anticoagulant treatment: if the patient has experienced a thrombotic (blood clotting) event.

Continuing anticoagulant medication raises the additive chance of bleeding disorders in adults, including burst ovarian cysts and subsequent pelvic hemorrhage in female patients.

In these individuals, standard suppressive treatment with estrogens is inappropriate unless the patient suffers from PC deficiency [77,78].

Patients who are on warfarin for an extended period should have regular checkups to ensure the drug is within its optimum range and the advantages outweigh the risks.

To ensure the INR is within the therapeutic range, doctors should closely evaluate the drug constantly [80].

When PC and protein S (PS) deficiencies are treated using a team-oriented approach, patient-centered treatment is improved, and a therapeutic relationship is formed for the best possible outcome [81,82,83].

**Antithrombin III deficiency**

*Definition and background*

Antithrombin (AT), a member of the serpin gene family and a heparin cofactor, is a significant protease

inhibitor that controls the activity of multiple serine proteases in the coagulation cascade [84,85].

AT-III deficiency classifications are quantitative (type I) or qualitative (type II) [93].

AT-III deficiency could be acquired or inherited.

Acquired AT-III deficiency depends on increased loss or higher consumption or decreased activity and synthesis of the AT-III gene.

Inherited AT-III deficiency is related to familial venous thromboembolic disease susceptibility. It is an autosomal dominant inheritance.

Occasionally, an individual with inherited AT deficiencies is affected due to being born with one defective copy of the AT-III gene from a parent who had the illness, with a prevalence rate of 1 in 500 to 1 in 5000 people in the general population.

The molecule responsible for most of the family deficits inheritance activity (AT-IIIgene) has undergone extensive characterization in recent years [94].

*Pathophysiology*

AT synthesis is mostly produced in the liver [87], which works as a physiological inhibitor of thrombin and factor X [88,89] (the two coagulation serine proteases). On the other hand, it can also inhibit plasmin and other coagulation factors [90,91].

AT-III is a non-vitamin K–dependent protease that suppresses coagulation by neutralizing the enzymatic activity of thrombin.

AT-III functions as a pseudosubstrate to inhibit factors IIa (thrombin), IXa, Xa, XIa, and XIIa, as well as kallikrein and plasmin, by covalently binding Arg393 from the AT-III reactive site loop to the serine protease active site. The serine protease inhibitor, AT-III, is encoded by the gene SerpinC1. This protease exhibits anticoagulant and anti-inflammatory properties. Similar to other serpins, AT can inactivate thrombin through the formation of a covalent 1:1 complex with the serine protease, which is the suicide substrate inhibition mechanism [92].

The most major coagulation factor inhibitor is AT-III. Any slight alterations in AT-III can dramatically influence the risk of thromboembolism[86].

*Symptoms*

Early signs of severe venous thromboembolism define the clinical picture of AT-III deficiency. Pregnancy, trauma, and infections are the triggers for the clinical symptoms.

Individuals will typically have blood clot symptoms. The most common symptoms of blood clots in the arms or legs are discomfort, redness, and swelling. AT-III deficiency has been linked to ischemic damage, including stroke, in children more than in adults. Women with AT deficiency have a higher risk of venous thromboembolism (VTE) during pregnancy and the postpartum phase. This risk is particularly significant in women who have already experienced VTE in the past. It is advised that pregnant AT deficiency women undergo a comprehensive evaluation of their risk for VTE, remembering genetic mutations, previous conditions, pregnancy-specific risk factors, and the degree and type of AT deficiency [95].

AT deficiency is linked to a higher risk of pulmonary embolism and deep vein thrombosis, two important causes of morbidity and mortality [96].

*Diagnosis*

AT-III deficiency can be diagnosed by physical examination, patient history, and blood tests that measure AT levels.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the laboratory tests used in AT-III deficiency diagnosis.

More precise diagnosis and prenatal diagnosis in families with the fully described variants is possible using more recent diagnostic procedures that employ synthetic oligonucleotide probes and restriction fragment length polymorphisms [99].

*Treatment*

In asymptomatic patients with AT deficiency, long-term anticoagulant thromboprophylaxis is not advised due to the high risk of bleeding. On the other hand, advise short-term thromboprophylaxis in clinical situations with high risks, such as trauma, surgery, and the management of pregnancy[97].

Individuals with genetic AT deficiency may be treated with fresh frozen plasma, heparin, human recombinant AT, and plasma-derived AT [97].

Several carriers will require cautious, long-term anticoagulation and thromboprophylaxis, particularly in high-risk circumstances like pregnancy and surgery.

For individuals with antithrombin deficiency, antithrombin concentrates represent a significant toolkit for the treatment and prophylaxis of acute venous thrombosis [98].

Functionally active AT-III, created using recombinant DNA technology, has the potential to eventually displace human chromatographically separated AT-III as the recommended course of treatment for clinically significant deficient conditions.

**Fibrinogen deficiency:**

*Definition and background*

Fibrinogen serves as crucial for effective hemostasis as it influences the production of blood clots, platelet aggregation, and fibrinolysis [100,101,102] .

Unlike certain other inherited bleeding illnesses, inherited forms of fibrinogen anomalies are uncommon and poorly characterized clinically[101].

Genetic fibrinogen abnormalities can impact the amount or value of circulating fibrinogen, resulting in hypo- and afibrinogenemia and dysfibrinogenemia, respectively. The majority of hypofibrinogenemia patients do not exhibit any symptoms, however they are susceptible to bleeding upon injury. Random bleeding and a comparatively elevated risk of thrombosis are both linked to dysfibrinogenemia[103].

*Prevalence*

It has been suggested that 8% of rare coagulation-related conditions are hereditary fibrinogen abnormalities[104]. The most serious kind of the condition, afibrinogenemia, is thought to affect approximately 1 in 1000000 people[105].

*Symptoms and diagnosis*

Thrombotic episodes might be the only symptomatic indicator of functional fibrinogen deficits in nearly 25% of instances. There is an uncommon form of thrombophilia that is likely underdiagnosed because of normal findings from routine coagulation tests and the potential lack of hemorrhagic episodes[106].

Based on a typical hemostasis evaluation, the biological diagnosis is made. Although the specificity and sensitivity of standard tests in dysfibrinogenemia rely on reagents and procedures, all coagulation tests that use the generation of fibrin as the endpoint are affected. Confirming the diagnosis by genetic study can improve the prediction of the patient's phenotype[107].

*Treatment*

When treating bleeding episodes in hereditary fibrinogen abnormalities, replacement therapy works well. Patients are given cryoprecipitate, fibrinogen concentrates, or fresh frozen plasma (FFP), depending on where they live[108].

**Factor V deficiency:**

*Definition and background*

Factor V (FV) is a plasma cofactor protein, not enzymatically active, and known as proccelerin or labile factor. It is involved in the coagulation and activation of prothrombin to thrombin by the prothrombinase complex.

FV deficiency is a bleeding disease brought on by mutations located in the FV gene, or genes encode parts of a potential cargo receptor that carries factor VIII and FV from the endoplasmic reticulum to the Golgi apparatus. Very low or undetectable plasma FV levels are present in patients with FV deficiency, primarily impacting mucosal tracts.

FV deficiency could be inherited or acquired.

Inherited FV deficiency is a bleeding illness passed down in an autosomal recessive pattern with mild to severe hemorrhagic symptoms. The homozygous form of the disorder affects 1 in 1,000,000 people in the general population [109]. Heterozygous carriers are typically asymptomatic and have FV levels that are roughly half normal.

Acquired FV deficiency ( AFVD) is a rare clinical syndrome that causes hemorrhagic consequences of various severity due to the development of antibodies against FV (FV inhibitors). It may be caused by surgery involving bovine thrombin, certain antibiotics (especially β-lactams), malignancies, infections, liver disease, and autoimmune disorders.

FV differs from FV Leiden with one nucleotide in its DNA structure. FV deficiency is a rare para-hemophilia (poor clotting) disorder known as Owren's disease. On the other hand, FV Leiden mutation is the most common hereditary hypercoagulability disorder. Bleeding is more likely in people with FV deficiency, whereas thrombosis is more likely in those with FV Leiden mutation.

*Pathophysiology*

FV is produced by the liver (hepatocytes), which generate plasma-derived FV, and megakaryocytes, which generate platelets and platelet-derived FV [110]. FV is triggered by activated factor X, thrombin, and activated protein C (aPC).

There are three pathways in the coagulation cascade: intrinsic, extrinsic, and common pathway. Some of these pathways will combine to create complexes that can function as proteases [111,112]. The role of FV is coagulating the cascade's common. FV and FX combine to generate a prothrombinase complex in the coagulation cascade. This prothrombinase complex helps halt bleeding by promoting the formation of a fibrin and platelet clot.

Since FV is found in both plasma and platelet α-granules, diseases affecting platelet granules are

associated with low levels of FV also [113].

*Symptoms*

The symptoms of FV deficiency vary in severity, even between members of the same family.

In many cases, the symptoms are so mild that they don't cause any problems.

However, often early in life, if the level of FV is very low or absent, some symptoms can occur.

These symptoms may include strokes, abnormal bleeding after giving birth, nose bleeds, easy bruising, bleeding gum following dental work, sudden shortness of breath (SOB), rapid heartbeats, chest pain when breathing in, heavy prolonged menstrual periods and occasionally bleeding inside the lungs and intestinal tract.

*Diagnosis*

FV deficiency could be diagnosed using a sample of blood for a prothrombin blood test (PT), activated partial thromboplastin time test (aPTT), and thrombin clotting time (TCT).

*Treatment*

Since FV cannot be obtained in replacement form like other factors, fresh frozen plasma (FFP) is typically infused in its place. Solvent-detergent FFP may have a more consistent level of FV than regular FFP.

It is rare for people with FV deficiency to get FV inhibitors following FFP. Options for these patients include rFVIIa concentrate and activated prothrombin complex concentrate (FEIBA). According to reports, people with severe FV deficiency respond well to the latter.

Platelet concentrates may be added in cases of acute severe bleeding. An FV source that is less susceptible to inactivation by circulating antibodies could be obtained by platelet transfusions [114].

Tranexamic acid is a medication used to increase the number of proteins that stabilize blood clots briefly.

*Combined FV/FVIII Deficiency*

A rarely occurring disease. Less than 100 patients from 60 families worldwide have combined FVIII and FV deficiency. Moderate to mild instances predominate.[115]

**Factor XIII Deficiency**

*Definition and background*

Factor XIII (FXIII) is a tetrameric zymogen composed of two FXIII-A units and two FXIII-B subunits[116,117].FXIII plays a vital role in angiogenesis, the maintenance of pregnancy, wound healing, bone metabolism, and even cardioprotection, in addition to its well-known role in hemostasis.

FXIII deficiency (FXIIID) is considered a rare bleeding disorder with an incidence of one per two million. It is accompanied by life-threatening bleeding, including intracranial hemorrhage (ICH), recurrent spontaneous miscarriages, and bleeding from the umbilical cord.[118]

FXIIID can appear in both acquired and congenital forms, resulting in aberrant bleeding tendencies and decreased clot stability. Compared to the autosomal recessive congenital type, acquired FXIIID is more common and results from factors such as hemodilution, reduced synthesis, and hyperconsumption. On rare occasions, autoantibodies directed against FXIII subunits may develop in people with acquired FXIII insufficiency. On the other hand, the majority of individuals with the congenital type of FXIIID

normally have deficiencies in the A (FXIII-A) and B (FXIII-B) subunits[119].

*Pathophysiology*

There are two subunits in FXIII: the active enzyme (the "A" subunit) and the carrier protein (the "B" subunit). Through an epsilon (gamma-glutamyl)lysine link, activated FXIII covalently crosslinks fibrin, modifying the structure of the clot. Through the same link, it also crosslinks more proteins into the clot, such as fibronectin and alpha-2-plasmin inhibitor (alpha-2PI). Most individuals suffering from the inherited deficiency exhibit no FXIII activity and no A subunit protein in their platelets, plasma, and monocytes. At the molecular level, the deficiency is most likely a single-point mutation that varies depending on the family and not a significant gene rearrangement or deletion. Given the severity of the bleeding diathesis, prophylaxis is desirable and has proven to be highly effective because low plasma levels are sufficient for hemostasis and plasma XIII has a long in vivo half-life[120].

Numerous medical conditions, including major surgery, pulmonary embolism, stroke, leukemia, myelodysplastic syndrome, Crohn's disease, ulcerative colitis, Henoch-Schönlein purpura, liver cirrhosis, sepsis, and disseminated intravascular coagulation, have been linked to acquired FXIII deficiency with significant reductions in FXIII levels. FXIII-A subunit levels fall to 20% to 70% in these acquired FXIII-deficient states due to either increased consumption or decreased production [120,121].

It is important to distinguish between this AH13 and typical hemorrhagic acquired FXIIID. Compared to ordinary hemorrhagic acquired FXIII deficiency, AH13 tends to be more severe and necessitates immunosuppressive treatment to eliminate autoantibodies as well as FXIII replacement therapy to halt the bleeding [122].

**Diagnosis**:

Normal conventional coagulation assays require specific FXIII assays for diagnosis, making FXIIID diagnosis particularly problematic. This difficulty is further complicated in developing nations.

In order to reduce the number of patients with undiagnosed FXIIID, test quality in less-equipped laboratories should be enhanced. In suspected cases, common mutations particular to a country may help with diagnosis through focused genetic investigation in reference laboratories. However, not all countries will be able to afford genetic analysis, and it might miss spontaneous mutations[123].

It is more difficult to diagnose FXIIID because all standard coagulation tests are normal in this condition. More specialized testing is needed for a precise diagnosis of FXIIID, including qualitative and quantitative tests like antigen assays and FXIII activity, as well as molecular studies to confirm FXIIID.

The most popular technique for detecting FXIIID is the clot solubility assay; however, it is not standardized.

Since the clotting factors and solubilizing agents are the main factors that affect this method's sensitivity, the FXIII activity test is recommended for FXIIID screening. The photometric assay is a common choice among assays for measuring FXIII activity; however, because commercial assays lack sample blanks, FXIII activity is overestimated in this assay, which can be fatal in cases of severe FXIIID. In such cases, the fluorometric assay is a suitable substitute that prevents the overestimation seen in the photometric assay.

The primary molecular method for confirming FXIIID has remained full sequencing of the FXIII genes, as there are no mutational hotspots in the FXIII-A and FXIII-B genes, despite a few recurring

mutations in specific populations [124] .

*Treatment*

Treatment options include antifibrinolytic medication, FXIII replacement, and/or inhibitor eradication. However, with acquired FXIIID, thresholds and treatment targets are unclear[125].

FXIII concentrate and recombinant FXIII are being used to treat ICH, prophylaxis, minor and significant hemorrhage, and effective delivery in women who have recurrent pregnancy loss[118].

The creation of dependable preventive treatment is possible with the availability of safe and effective factor XIII concentrates. Currently, two virus-inactivated factor XIII concentrates obtained from plasma are being produced. The first, called Fibrogammin P, is sold in Japan, Europe, South Africa, and South America. Under an investigational new drug application approved by the Food and Drug Administration, it is distributed in the US.

In the UK, the use of a second factor XIII concentrate is restricted to "named patient" situations only. When such factor XIII concentrates are given at the right intervals, patients with factor XIII insufficiency can live normal lives free from severe bleeding episodes[126].

## Conclusion

In conclusion, this review has explored the complex genetic mutations underlying inherited bleeding disorders, focusing on blood coagulation factors and regulatory proteins. We have highlighted the diversity of mutations that contribute to disorders such as hemophilia A and B, von Willebrand disease, and rare coagulopathies. By elucidating the molecular mechanisms and pathophysiological consequences of these mutations, we emphasized their clinical implications, including variability in disease severity and therapeutic responses.

Additionally, this review highlights the importance of advancing our understanding of these genetic variations to enhance diagnostic precision and therapeutic strategies. Future research should aim to further elucidate genotype-phenotype correlations, explore novel therapeutic targets, and improve personalized treatment approaches. By integrating genetic insights with clinical practice, we can pave the way for improved patient management and outcomes in inherited bleeding disorders.

Ultimately, this work contributes to the broader goal of translating genetic knowledge into clinical advancements, fostering a deeper appreciation for the complexity of inherited bleeding disorders and guiding future research endeavors in this critical area of hematology.

## Declarations

**Conflict of interest:** The authors declare no conflict of interest.

**Ethical approval :**The authors agreed that the corresponding author is responsible for the process of submission. The authors declared no submission to any other journal at the same time. The data mentioned in this review article are original.

**Human participants and/or animals:** This review does not perform experimental work on animals or humans. The data were collected from the web base.

**Informed consent:** This work procedure was in accordance with the ethical values of research institutes and Helsinki declaration.

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**Author's contribution:**

Mohammad helped in searching about hemophilia A.

Rand helped in searching about hemophilia B.

Hala helped in searching about hemophilia C.

Sadeen helped in searching about (Von Willebrand Factor).

Shama helped in searching about factor x deficiency.

Ansam helped in searching about protein C deficiency and fibrinogen deficiency and edited the final version of the manuscript.

Aya helped in searching about antithrombin III deficiency and protein V deficiency and edited the final version of the manuscript.

Mohammad AlGhzawi helped in searching about factor XIII deficiency and edited the final version of the manuscript.

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