Haemophilia (2008), **14**, 1190–1200 DOI: 10.1111/j.1365-2516.2008.01857.x

ORIGINAL ARTICLE

Factor XIII deficiency

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Summary. Inherited factor XIII (FXIII) deficiency is a rare bleeding disorder that can present with umbilical bleeding during the neonatal period, delayed soft tissue bruising, mucosal bleeding and life-threatening intracranial haemorrhage. FXIII deficiency has also been associated with poor wound healing and recurrent miscarriages. FXIII plays an integral role in haemostasis by catalysing the cross-linking of fibrin, platelet membrane and matrix proteins throughout thrombus formation, thus stabilizing the blood clot. The molecular basis of FXIII deficiency is characterized by a high degree of heterogeneity, which contributes to the different clinical manifestations of the disease. There have been more than 60 FXIII mutations identified in the current literature. In addition, single nucleotide polymorphisms have been described, some of which have been shown to affect FXIII activity, contributing further to the heterogeneity in patient presentation and severity of clinical symptoms. Although there is a lifelong risk of bleeding, the prognosis is excellent when current prophylactic treatment is available using cryoprecipitate or plasma-derived FXIII concentrate.

Keywords: bleeding disorders, coagulation, factor XIII, factor XIII deficiency, fibrin stabilizing factor, protransglutaminase

Introduction

Prior to delving into the clinical and biochemical details which characterize this fascinating clotting factor, it is worth taking a moment to consider this important fact: factor XIII (FXIII) is not just another plasma protein in the clotting cascade. Like so many other discoveries, FXIII is defined by the function through which we first became aware of its existence, namely as a 'fibrin stabilizing factor' (FSF) in the earliest papers [1,2]. However, it is now apparent that FXIII is capable of cross-linking an ever-growing list of proteins, not only within plasma, but also proteins within the vascular matrix, platelets, endothelial cells and monocytes. Clearly intracellular FXIII plays an important role in the platelet and vascular bed in achieving haemostasis, thrombosis and healing. Although we focus this review article on the interaction of plasma proteins with FXIII, it is clear that intracellular FXIII, especially in platelet and vascular bed may play an equally important role in haemostasis.

In plasma, FXIII circulates as a pro-transglutaminase (FXIII-A_2B_2) composed of two catalytic A subunits (FXIII-A_2) and two non-catalytic B subunits (FXIII-B_2) held together by non-covalent bonds. The B subunits are found primarily in plasma, either free or in association with A subunits as part of the heterotetrameric form of FXIII. However, intracellular FXIII exists only as a homodimer of FXIII-A subunits (FXIII-A_2). A quick reference for the definitions of the various forms of FXIII discussed in this article is listed below in Table 1.

Substrates for intracellular FXIII-A_2 include myosin, actin, vinculin and filamin suggesting a major role for FXIII in cytoskeletal remodelling in platelet adhesion, aggregation and contraction. In the monocyte/macrophage cytosol, FXIII-A_2 facilitates Fcγ and complement receptor mediated phagocytosis and deficient patients have been shown to have impaired function in these activities [3]. Murine models of wound healing also support the important role of intracellular FXIII-A_2 in leucocyte and tissue remodelling and repair. Recent research on myocardial repair following infarction induced in FXIII–/–

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Accepted after revision 21 July 2008

Table 1. Factor XIII nomenclature.

Plasma FXIII	FXIII-A_2B_2
Cellular FXIII	FXIII-A_2
FXIII subunit A monomer	FXIII-A
FXIII subunit A dimer	FXIII-A_2
FXIII subunit B monomer	FXIII-B
FXIII subunit B dimer	FXIII-B_2
Inactive intermediate after thrombin cleavage	FXIIIa′
Ca^{2+} activated FXIII	FXIIIa*

knockout mice demonstrates significant reduction in leucocyte recruitment, phagocytosis and protease activity in the area of injury [4]. Finally, the production of FXIII-A_2 in the placenta, particularly the labyrinthine layer, confirms its important role in maintaining the integrity of placental attachment in the uterus [5–7]. This along with prevention of massive bleeding associated with microvascular bleeds is no doubt one of the major causes of miscarriage and foetal loss in deficient women.

This article focus on the haemorrhagic disorder resulting from deficiency of plasma FXIII because of absent A or B subunits, but there is still much to be learned regarding the relationship of intracellular A2 subunits and the integrity of the vascular bed, connective tissue and inflammation, all of which play a major role in thrombosis and healing.

History

In 1944, Robbins [1] observed that the formation of insoluble fibrin occurred with calcium and an unknown 'serum factor'. Laki and Lorand confirmed Robbins' findings and concluded that the factor was a plasma protein and called it the FSF [2]. There have been several names for FSF, including Laki–Lorand or L–L factor, fibrinase, protransglutaminase and fibrin polymerase. In 1963, the International Committee of Blood Clotting Factors formally chose the designation of factor XIII. Muszbek *et al.* [8] recently published the recommended nomenclature for the various forms of FXIII so that unified abbreviations can be used for research publications.

Sixteen years after the discovery of FSF, Duckert *et al.* described the first clinical example of FXIII deficiency. In 1960, he evaluated a young boy in Switzerland with a severe bleeding diathesis. The only abnormal clotting test results were the thromboelastography (TEG) and the clot solubility screen. These assays are still in use today and can provide a valuable clinical tool to determine when the patient is at risk for bleeding or his response to therapy. An example of the TEG in a FXIIII deficient patient is seen in Fig. 1 The former study showed reduced

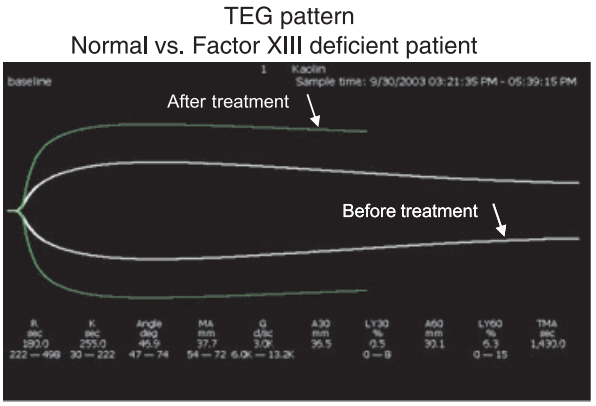

Fig. 1. Thromboelastogram (TEG) tracing of a severe FXIII-deficient patient is shown in white, with decreased clot size and strength in addition to increased lysis at 30 and 60 min. The green tracing is from the same patient following infusion of Fibrogammin P (FXIII concentrate) resulting in restoration of a normal TEG pattern.

maximal amplitude and a rapid decrease in clot size and strength, whereas the clot solubility assay revealed increased breakdown of clots in 5 M urea. After transfusing the patient with fresh frozen plasma, the clot solubility test normalized and his bleeding symptoms improved [9]. Subsequently, there have been numerous reports of patients with FXIII deficiency documenting their coagulopathy using the TEG and clot solubility assay [10].

Structure and function

Plasma FXIII, the heterotetramer (FXIII-A_2B_2), plays an integral role in haemostasis by catalysing the cross-linking of fibrin, a variety of integrins within the platelet membrane and matrix proteins throughout thrombus formation, thus strengthening and stabilizing the blood clot.

Plasma FXIII is converted from a pro-transglutaminase to activated FXIII (FXIIIa*) by thrombin in the presence of calcium ions and fibrin as seen in Fig. 2 FXIII-A contains both the thrombin cleavage site and the calcium-binding site required for catalytic activation [11]. The gene coding for the FXIII-A subunit (*F13A*) is located on chromosome 6p24–25, spanning 160 kb and consists of 15 exons interrupted by 14 introns encoding a mature protein of 731 amino acids (Fig. 3) [12].

FXIII-A is divided into the activation peptide, β-sandwich, catalytic core, β-barrel 1 and β-barrel 2 [13] (Fig. 3). Crystal structure of the A subunit revealed a catalytic triad in the central core domain formed through hydrogen bond interactions between Cys314, His373 and Asp396 [14].

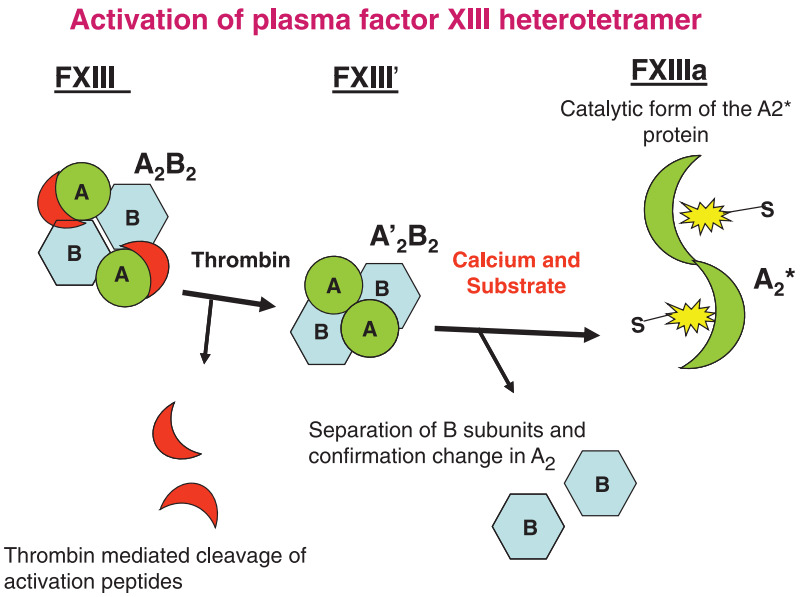

Fig. 2. Activation of plasma factor XIII heterotetramer.

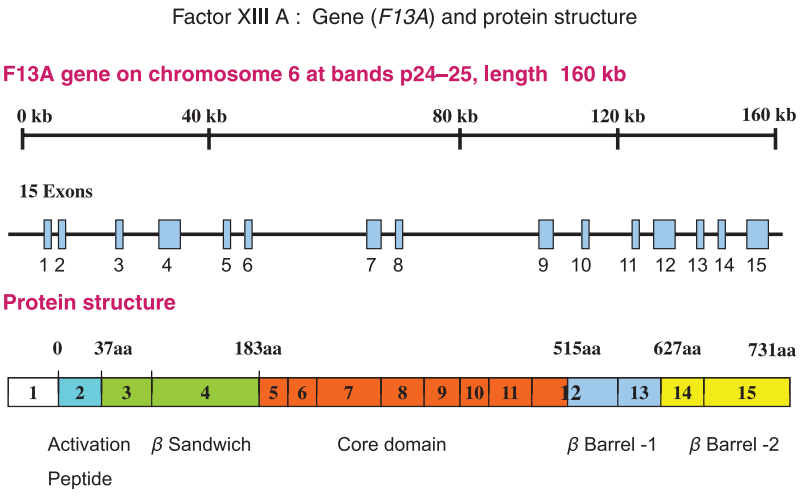

Fig. 3. Factor XIII A: gene (*F13A*) and protein structure.

In the first step of FXIII activation, thrombin cleaves off the FXIII N-terminal activation peptide (AP-FXIII) of 37 amino acid residues at position Arg37, forming the plasma FXIIIa′. In the presence of Ca^{2+} and fibrin, the B subunits then dissociate from the A subunits resulting in a conformational change thus leaving the active site cysteine accessible for the substrate [11] (Fig. 2). Activated FXIII-A_2 (FXIII-A_2*) then catalyses the cross-linking of fibrin or other target proteins which contain appropriate glutamine and lysine residues. Activated FXIII covalently cross-links fibrin through an $\epsilon(\gamma$-glutamyl)lysine link. FXIII can cross-link fibrin polymers by γ-dimerization, Gln 398 in one fibrin molecule and Lys406 of the next fibrin molecule. Polymerization can also occur through the alpha chains of Gln328, Gln366 and Lys508 in multiple fibrin molecules (see Figs 4 and 5) [15]. The active site contains cysteine residue (Cys311) which is found within the sequence Tyr-Gly-Gln-Cys-Trp. FXIII also forms a covalent bond with α_2-antiplasmin [16,17] and thrombin activatable fibrinolysis inhibitor, further stabilizing the thrombus, making it more resistant to proteolytic degradation by plasmin [16].

Additionally, FXIII also cross-links several other protein substrates in the plasma and subendothelium, including fibronectin, von Willebrand factor, vitronectin, collagen, coagulation factor V, thrombospondin and plasminogen activator inhibitor type 1 [11].

In contrast to plasma FXIII, thrombin does not play a role in activation of intracellular FXIII. When intracellular calcium level rises in the presence of

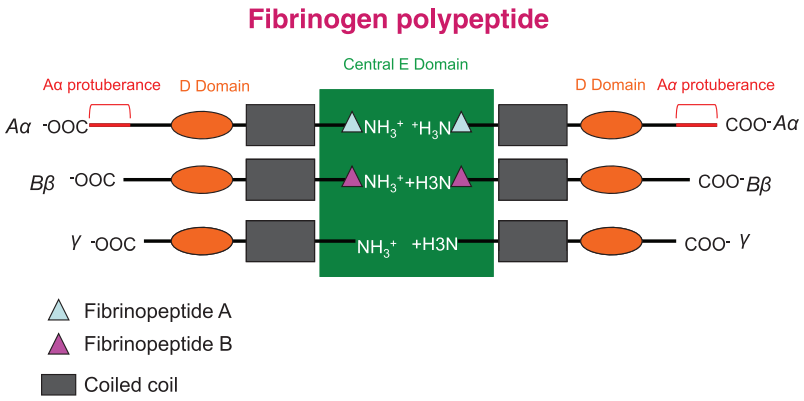

Fig. 4. Fibrinogen polypeptide.

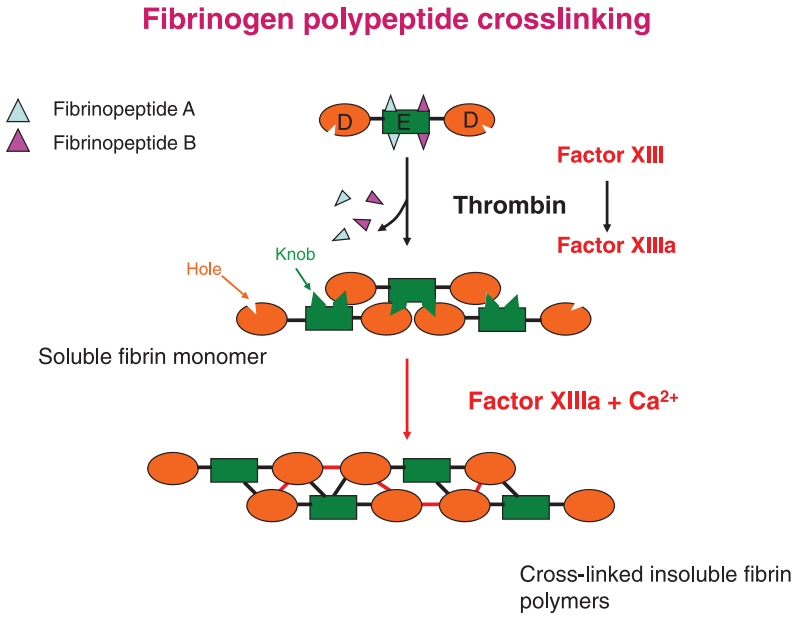

Fig. 5. Fibrinogen polypeptide cross-linking.

target substrate, platelet FXIII undergoes a non-proteolytic conformation change to its active form [18].

The liver is the major site of synthesis for FXIII-B, whereas it appears that the haematopoietic cells are responsible for the production of FXIII-A. Early on the strongest evidence to support the hepatic origins of the B subunit came from organ and stem cell transplantation. Wolpl *et al.* showed that after liver transplantation, the recipient's FXIII-B phenotype changed to the donor's phenotype, whereas the FXIII-A remained unchanged. In addition, the FXIII-A phenotype was converted to the donor's phenotype only after bone marrow transplantation [19]. The FXIII A2 is produced in megakaryocytes and monocytes from the earliest stages of myeloid development with circulating platelets containing around 50% of the total FXIII found in whole blood. Intracellular FXIII-A_2 (not FXIII-B) can be found in platelets, megakaryocytes, monocytes, tissue macrophages and placenta. Cellular FXIII-A_2 is immunochemically identical to plasma FXIII-A_2 and can combine with FXIII-B_2 to form the tetramer complex when released into the plasma.

The FXIII-B subunit gene (*F13B*) is located on chromosome 1q31–32.1 and spans approximately 28 kb in length and is composed of 12 exons interrupted by 11 introns encoding the mature protein of 641 amino acids (Fig. 6) [20,21]. The B subunit of FXIII is composed of 10 tandem repeats called glycoprotein-1 structures or Sushi domains because of their shape. One important function of the B subunit is the stabilization and transport of the hydrophobic A2 subunit in the aqueous environment of human plasma, thereby prolonging FXIII-A2 in circulation. Although there is a growing body of

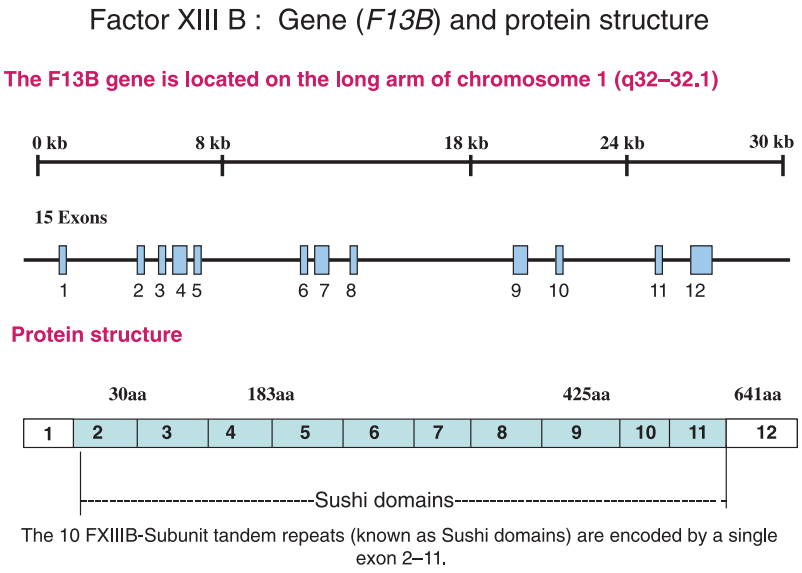

Fig. 6. Factor XIIIB: gene (*F13B*) and protein structure.

literature describing the role of B subunit in decreasing the degradation and inactivation of the A2 subunit by proteases, its most critical role is the localization of FXIII to the growing fibrin polymer, while the thrombin is still active, to initiate the cross-linking process. Localization is facilitated when FXIII-B portion of the Factor XIII A2B2 molecule binds specifically to the gamma chains of fibrinogen leading to polymerization, cross-linking and regulation of FXIII activity [22–25].

Factor XIII deficiency

Congenital FXIII deficiency can be due to defects in either FXIII-A genes (also known as type 2 defect) or FXIII-B genes (type 1 defect). Bleeding disorders as a result of mutations in the FXIII B subunit gene occurs infrequently (<5% of reported factor XIII deficiency cases). In severe FXIII-A deficiency (type 2), the A subunit is usually absent from plasma, platelets, monocytes and placenta.

The incidence of severe FXIII deficiency is one in 3–5 million people and is inherited in an autosomal recessive pattern [16]. This rare bleeding disorder affects people of all races and there is often a history of consanguinity within certain families of FXIII-deficient patients. Among non-consanguineous families, a higher incidence of compound heterozygosity is observed [7,26–28].

The first published genetic mutation leading to FXIII deficiency was reported by Webb *et al.* in 1992 [21]. With the advance of biotechnology, more than 70 FXIIIA or B subunit gene mutations have now been identified. At the time of this review, there are 67 mutations reported for FXIII-A with the vast majority being missense or nonsense mutations (Table 2). As seen in Fig. 7, mutations can occur throughout the gene, but concentrate between exons 3 and 14. A complete listing of all subunit A or B mutations (missense, nonsense, splice, insertions and deletions) can be found at the Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff website (http://www.hgmd.cf.ac.uk) and at the Factor XIII Registry Database website (http://www.f13-database.de).

To date, there are only four known mutations for FXIII-B, leading to the more rare form of FXIII deficiency. The few defects that have been reported in the B chain lead to a deficiency of the carrier protein (subunit B), which then leads to instability and reduction of plasma subunit A levels despite the presence of functional intracellular subunit A (type 1 defect) [16]. Most recently, three unrelated patients with severe FXIII deficiency were reported with failure of hepatocyte secretion of a truncated form of FXIII subunit B. This mutation, derived from a single-base deletion in the B subunit gene, resulted in impaired intracellular transport from the endoplasmic reticulum to the Golgi apparatus.

The FXIII gene has several common single nucleotide sequence variations, which encode amino acid substitutions. Five common coding polymorphisms have been identified in the FXIII-A subunit: Val34Leu, Tyr204Phe, Pro564Leu, Val650Ile and Glu651Gln. The Val34Leu variant is the most studied polymorphism, with the amino acid substitution occurring in the activation peptide sequence, three amino acids upstream from the thrombin-cleavage site. This poly-

Table 2. Factor XIII-A missense/nonsense mutations.

Exon	Amino acid change	References
3	Asn60Lys	Anwar R *et al.* 1995
3	Arg77Cys	Duan *et al.* 2002
3	Arg77His	Peyvandi *et al.* 2004
3	Glu102Lys	Anwar 2002
4	Met159Arg	Schroeder *et al.* 2006
4	Arg171Stop	Standen and Bowen 1993
5	Gly210Arg	Vysokovsky *et al.* 2004
5	Gly215Arg	Schroeder *et al.* 2006
6	Leu235Arg	Birben *et al.* 2003
6	Met242Thr	Mikkola *et al.* 1994
6	Arg252Ile	Mikkola *et al.* 1996
6	Arg260Cys	Ichinose 1998
6	Arg260Leu	Vysokovsky *et al.* 2004
6	Arg260His	Kangsadalampai 1999
6	Gly262Glu	Onland *et al.* 2005
7	Tyr283Cys	Souri *et al.* 2001
7	Ser295Arg	Anwar R *et al.* 2000
7	Val316Phe	Onland *et al.* 2005
7	Ala318Val	Vysokovsky *et al.* 2004
8	Arg326Gln	Mikkola *et al.* 1996
8	Arg326Stop	Anwar 2005
8	Leu354Pro	Anwar *et al.* [28]
9	Trp375Cys	Schroeder *et al.* 2006
9	Arg382Ser	Peyvandi *et al.* 2003
9	Ala394Val	Izumi 1998
9	Thr398Asn	Vysokovsky *et al.* 2004
9	Gln400Stop	Kangsadalampai *et al.* 1996
10	Arg408Gln	Anwar R *et al.* 1995
10	Ser413Leu	Niya *et al.* 1999
10	Ser413Trp	Duan *et al.* 2003
10	Val414Phe	Aslam 1997
10	Gly420Ser	Kangsadalampai *et al.* [52]
10	Tyr441Stop	Anwar 1995
11	Gly501Arg	Board 1993
12	Leu498Pro	Mikkola *et al.* 1996
12	Asn541Lys	Birben *et al.* 2002
12	Gly562Arg	Takahashi *et al.* 1998
14	Leu660Pro	Inbal *et al.* 1997
14	Arg661Stop	Mikkola *et al.* 1994
14	Leu667Pro	Aslam 1995
15	Trp691Stop	Anwar 2005
15	His716Arg	Schroeder *et al.* 2006

morphism exists in approximately 20% of white European, 40% of Pima Native American and 13% of South Asian populations [29,30].

Studies have shown that the Leu34 allele variant promotes accelerated cleavage of the activation peptide once activated by thrombin [31]. In addition, the two other polymorphisms, Tyr204Phe and Pro564-Leu, have been linked with increased risk of haemorrhagic stroke in young women [32]. The Tyr204Phe substitution has been reported to be associated with an increased risk of miscarriages [33]. The Glu651Gln and Val 650Ile polymorphisms are the least studied single nucleotide polymorphisms.

Some studies have shown that the Leu34 variant was associated with a decreased risk of myocardial infarction in several different human studies [34–36], but other scientists have not found this association [37–40]. Controversy has surrounded the role of Val34Leu in coronary artery disease, with the literature supporting both sides of the debate. The FXIII-B subunit also has common polymorphisms, His95Arg being the most well known. No known change of function in the FXIII-B subunit has been associated with this polymorphism to date.

The FXIII gene mutations and polymorphisms result in a high level of heterogeneity of disease presentation. Mutations occurring along the gene can affect different areas of the protein, such as the B subunit binding site or the activation site. This heterogeneity in the gene is responsible for the wide range of clinical manifestations of patients with FXIII deficiency.

Clinical presentation and disease management

FXIII deficiency is associated with severe bleeding, spontaneous intracranial haemorrhages, poor wound healing and spontaneous abortions. Patients with severe congenital FXIII deficiency usually present with plasma FXIII levels less than 1% and severe bleeding diatheses. Heterozygote patients can have reduced levels of FXIII-A and FXIII-B and will usually be clinically asymptomatic. Our understanding of the heterogeneous nature of factor XIII deficiencies and their clinical course derives primarily through the excellent data base and registries established in Europe and internationally over the last decade [41,42].

Early manifestations of the disease can occur in the neonatal period with umbilical bleeding presenting a few days after birth. Umbilical bleeding is a characteristic and frequent finding occurring in 80% of cases [7]. The incidence of intracranial haemorrhage has been reported to be 25–30%, a much higher frequency than that reported in haemophilia A or B, and is also the main cause of death or disability in patients with congenital FXIII deficiency. In FXIII-deficient patients, clots may form normally but begin to breakdown 24–48 h later because of weak cross-linking of fibrin, leading to subsequent episodes of bleeding. Ecchymoses, intramuscular bleeding, post-operative haemorrhage and mucosal bleeding post-dental extraction can also occur.

Delayed wound healing and recurrent spontaneous miscarriages are all common symptoms of severe FXIII deficiency. In addition to its function in haemostasis, FXIII has a role in angiogenesis, a

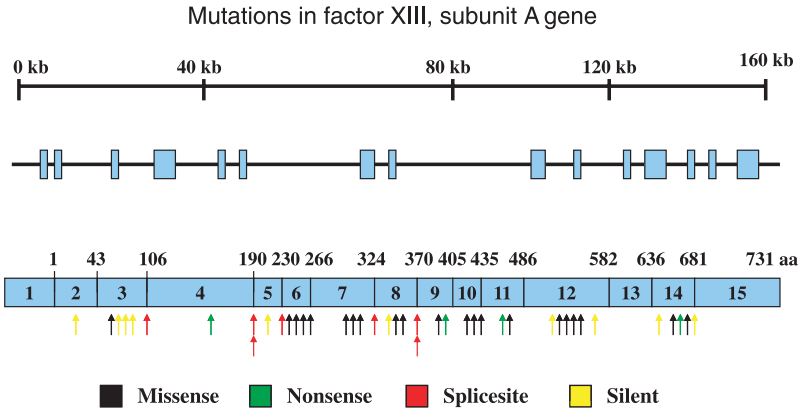

Fig. 7. Diagram of selected mutations in factor XIII, subunit A gene. Exons are indicated numerically. Locations of selected mutations are represented with arrows. Classification of the different mutations are represented by either a black arrow indicating a missense, a green arrow indicating a nonsense, a red arrow indicating a splice site deficiency or a yellow arrow indicating a silent mutation.

process affecting wound healing and tissue repair [43]. FXIII deficiency not only causes increased uterine bleeding during pregnancy but also leads to poor formation of the cytotrophoblastic shell increasing risk for placental detachment and eventual miscarriage within the first trimester [44]. Recommendations for factor infusions during pregnancy are significantly different from dosing regimens for prophylaxis or surgery (see below), but aggressive management can result in successful delivery of a full-term infant.

The classification used to correlate factor activity with disease severity in haemophilia A or B, namely: severe, moderate or mild disease, cannot easily be applied to FXIII deficiency because the assays used thus far cannot accurately measure FXIII levels less than 5% activity. Until a more sensitive assay becomes widely available to measure activity, it will be difficult to determine the levels that place patients at greatest risk for bleeding. Certainly, an abnormal clot solubility that indicates a level of less than or equal to 1% has been shown to correlate with the characteristic umbilical bleeding seen after birth and has a high risk of intracranial haemorrhage in the first decade of life.

Acquired FXIII deficiency is much more common and in this setting, deficiency in the enzyme is caused by an inhibitor, usually an autoantibody binding to plasma FXIII and interfering with normal function. Acquired FXIII deficiencies can be associated with severe bleeding complications because of inhibitors directed against FXIII, or they can present with mild bleeding symptoms in association with an underlying condition [7]. Inhibitors can develop in association with medications such as isoniazid, penicillin and phenytoin [45].

Acquired FXIII deficiency has been associated with systemic lupus erythematosus, leukaemias, severe liver disease, disseminated intravascular coagulation and inflammatory bowel disease [45]. In patients with acquired FXIII deficiency, factor levels range from 50 to 75% of normal. This type of FXIII deficiency occurs more frequently in middle-aged or elderly individuals who present with spontaneous or post-traumatic deep haematomas. Treatment may include anti-CD20 (rituximab), steroids, IVIG or even plasmapheresis, generally with good response and resolution of the inhibitor.

Diagnosis

The results of standard laboratory clotting tests, such as prothrombin time, activated partial thromboplastin time, fibrinogen level, platelet count and bleeding time, are all *normal* in FXIII-deficient patients. The first case of FXIII deficiency was detected by an abnormal urea clot lysis test result. Using a solution of 1% monochloracetic acid or 5 M urea, clots will under go lysis if a patient has FXIII levels of <1%. The clot solubility test is only sensitive at very low levels of FXIII (zero or very close to zero and will be normal if the FXIII activity level rises up to 1–3% [7]. If the urea clot solubility test result is positive for lysis, a sample may be sent for a quantitative analysis of FXIII activity. There are four quantitative assay kits commercially available in Europe: the Berichrom FXIII (Dade Behring, Marburg, Germany), the REA-chrom FXIII (Reanal, Budapest, Hungary) and the Pefakit Factor XIII (Pentapharm, Basel, Switzerland), and a new fluorometric assay developed by N-zyme BioTec (Darmstadt, Germany). The Berichrom FXIII and the REA-chrom both use photometric methods to measure the ammonia released in the first step of the transglutaminase reaction. The Pefakit uses an amine incorporation assay to measure amines covalently cross-linked to a protein substrate. Development of the new fluorometric test was based on isopeptidase activity of FXIIIa described by Parameswaran *et al.* [46,47]. Normal FXIII activity levels range from 50 to 220%. Plasma levels between 5 and 30% have

been shown to be sufficient in preventing spontaneous bleeding. At the time of this publication, only the Berichrom assay is FDA approved for use within the US. Genetic analysis is performed to aid in family counselling, prenatal screening and further characterization of specific bleeding risk. Laboratories performing specific FXIII mutational analysis are listed below.

Management

Prophylaxis and bleeding

Traditional treatment for FXIII deficiency includes cryoprecipitate and fresh frozen plasma. As the half-life of endogenous FXIII is long, ranging from 5 to 11 days, prophylactic therapy with fresh frozen plasma in doses of 10 mL kg^{-1} can be given every 4–6 weeks. Cryoprecipitate can be administered in doses of 1 bag per 10–20 kg every 3–4 weeks [48]. In general, prophylactic therapy is recommended for patients with a history of intracranial haemorrhage. On-demand therapy for acute or recurrent bleeding should incorporate the TEG, clot solubility, severity of the bleed and bleeding history to determine frequency of dosing for each patient.

Currently in the US, most patients are being treated with plasma-derived pasteurized FXIII concentrates (Fibrogammin P; CSL Behring, Marburg, Germany) under clinical trial with more than 60 centres and investigators at the Children's Hospital of Orange County (djn0@choc.org). Fibrogammin P has been used for prophylaxis in Europe, Canada Asia and in the US. Dosage regimens vary widely depending on patient response and pharmacokinetics. This variation is not surprising given the heterogeneity of FXIII-deficient patients, the presence or absence of intracellular FXIII subunits or activity modifying polymorphisms. Dosages ranging from 10 to 35 U kg^{-1} may be necessary to prevent bleeding for prophylaxis. Because of the long half-life of Fibrogammin P (5–11 days), dosing can be administered at 4- to 6-week intervals. Treatment with FXIII concentrate (Fibrogammin P) resulted in restoration of normal clotting pattern as measured by thromboelastography [49].

Surgery and pregnancy

Decidual bleeding usually begins from 5 to 6 weeks' gestation leading to spontaneous abortion if replacement therapy is not given. Perinatal management should maintain FXIIIA levels at least 2–3%, and ideally greater than 10% to prevent miscarriage [44]. Administration of FXIIIA concentrate at 250 IU every week is sufficient to maintain plasma FXIIIA level greater than 10% in early gestation (less than 22 weeks gestation). Higher dosing at 500 IU weekly is adequate replacement for later in pregnancy. At time of delivery, a large dose at 1000 IU is recommended to achieve levels greater than 30% to avoid bleeding complications [50].

For surgical procedures, FXIII may need to be given more frequently to maintain levels above 10–20% and prevent poor healing. However, there are no prospective, controlled trials to validate ideal levels in these clinical scenarios.

Another investigational therapy is human recombinant FXIII-A_2 (rFXIII-A_2), a homodimer that binds with the patient's own endogenous circulating FXIII-B subunits to form the heterotetramer FXIII-A_2B_2. This product has a half-life of 6–9 days [51]. Interestingly, Lovejoy *et al.* [51] clearly showed that the half-life of infused recombinant FXIII-A_2 is significantly shorter in patients with FXIII-B deficiency. Results of the phase 1 clinical trial showed that this product was safe and effective as a possible alternative treatment plan for FXIII-deficient patients [51]. Recombinant FXIII-A_2 (Novo Nordisk; Bagsvaerd, Denmark) is currently awaiting a phase 3 trial.

Prognosis

Although there is a lifelong risk of bleeding with FXIII deficiency, the prognosis is excellent because of the good response to treatment with FFP, cryoprecipitate or plasma-derived FXIII concentrate. Because the half-life of FXIII is long, prophylaxis is easily accomplished for those patients with the worst bleeding history and the incidence of inhibitor development is extremely low.

Individuals with interest in area

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Molecular analysis

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FXIII-A and FXIII-B subunit mutational analysis and testing, contact Dr Diane Nugent (djn0@choc.org) or Dr Loan Hsieh (lhsieh@choc.org) at the Department of Hematology, Children's Hospital of Orange County.

Disclosures

The authors stated that they have no interests that might be perceived as posing a conflict or bias.

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