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Congenital factor XIII deficiency in Switzerland

From the worldwide first case in 1960 to its molecular characterisation in 2005

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Summary

Coagulation factor XIII (FXIII) has a major role in the final stage of blood coagulation, is important for wound healing and maintaining pregnancy. Severe congenital FXIII deficiency is a rare disorder with 1 patient in 1–3 million. Untreated, it causes bleeding events, with intracranial haemorrhage being the major cause of death, impaired wound healing, and abortion. FXIII deficiency was traditionally diagnosed using the clot solubility test, but quantitative FXIII activity and antigen assays are preferred today. Treatment consists of replacement therapy with FXIII concentrates administered every 4–6 weeks. The molecular-genetic causes of FXIII deficiency are mutations in the genes coding for the FXIII A- and B-subunits. More than 60 mutations distributed throughout the FXIII A-subunit gene have been identified so far and 4 mutations in the FXIII B-subunit gene. The first case of congenital FXIII deficiency was reported in Switzerland in 1960. In Switzerland we observed a disproportionately high incidence, which can be explained in part by a founder effect.

In this article, we summarise general facts on severe congenital FXIII deficiency, and we characterise all FXIII deficient patients living in Switzerland, including the first case described in 1960 who is a member of a large family originating from the canton of Uri.

Key words: factor XIII; congenital FXIII deficiency; FXIII gene; FXIII mutations; haemophilia; FXIII structure

Structure and functions of blood coagulation factor XIII

Factor XIII (FXIII) is the final coagulation factor of the coagulation cascade. The zymogen circulates in plasma as a tetramer of two catalytic A-subunits and two carrier B-subunits (A_2B_2). The A-subunit consists of 731 amino acids and has a molecular weight of approx. 83 kDa, the B-subunit consists of 641 amino acids and has a molecular weight of approx. 80 kDa. In plasma, all A-subunits exist in complexed form, whereas there are free B_2 homodimers present in plasma. In platelets, monocytes, and macrophages, cellular FXIII occurs only as A_2 homodimer. The B-subunits are synthesised in the liver by hepatocytes. The A-subunits are assumed to be mainly of bone marrow origin, ie from megakaryocytes, monocytes and monocyte-derived macrophages, but hepatocytes might also contribute to plasma FXIII A-subunit synthesis [1–3]. However, it is not clear how the A-subunits are released into plasma since they lack a signal peptide for secretion. It is assumed that the A-subunits are released from cells as a consequence of cell injury, which is independent of the classical secretory pathway [4].

In plasma, thrombin, together with the cofactors fibrin(ogen) and Ca^{2+}, activates FXIII by cleavage of the activation peptide from the A-subunit, followed by dissociation of the A- and B-subunits, as shown in figure 1. Activated FXIII (FXIIIa), which is a transglutaminase, covalently cross-links fibrin polymers in two ways: by γ-dimerisation, Gln398 of the γ-chain in one fibrin molecule and Lys406 of the γ-chain in the next fibrin molecule are cross-linked, and by α-polymerisation, Gln328, Gln366, and Lys508 of α-chains in multiple fibrin molecules are cross-linked [1]. In addition, FXIIIa incorporates antifibrinolytic proteins such as α_2-antiplasmin and thrombin activatable fibrinolysis inhibitor (TAFI) into fibrin. Only by these reactions the fibrin clot obtains sufficient stability and becomes resistant to premature fibrinolysis [1–3].

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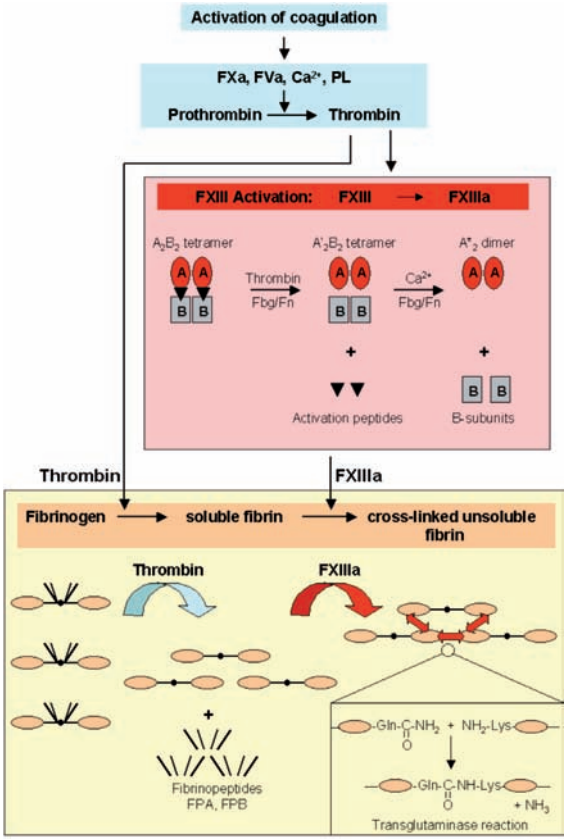
Figure 1

Activation and cross-linking reaction of FXIII
After activation of coagulation, thrombin is formed by the prothrombinase complex consisting of activated factors X and V (FXa, FVa), calcium ions (Ca^{2+}) and phosholipids (PL) (blue boxes). Thrombin converts fibrinogen into soluble fibrin by cleaving fibrinopeptides A and B (FPA, FPB) (yellow box) and initiates FXIII activation by cleaving FXIII activation peptide (red box). FXIII activation is completed by dissociation of the A- and B-subunit induced by Ca^{2+}. Both FXIII activation steps are enhanced by fibrinogen and fibrin (Fbg/Fn). Activated FXIII (FXIIIa) cross-links Lysine (Lys) and Glutamine (Gln) residues of soluble fibrin molecules in a transglutaminase reaction (yellow box).



FXIII plays also an important role in wound healing and tissue repair [5]. It cross-links proteins of the extracellular matrix such as fibronectin and collagen, enhances migration and proliferation of fibroblasts, modulates macrophage migration and phagocytosis, and enhances the function of the endothelial barrier. Recently, a direct proangiogenic effect on endothelial cells *in vitro* and promotion of angiogenesis in several *in vivo* animal models was described [6]. Furthermore, FXIII is necessary for the maintenance of pregnancy [7]. Maternal FXIII-A_2 is localised within the placenta at the interface between maternal and foetal tissue, where it is crucial for the formation of the cytotrophoblastic shell and the Nitabuch's layer. FXIII deficiency leads to poor formation of the cytotrophoblastic shell and the fibrinoid layers leading eventually to detachment of the placenta from the uterus [8].

Severe congenital FXIII deficiency: symptoms and epidemiology

Most patients with severe congenital FXIII deficiency suffer from a severe bleeding diathesis, but some patients have only mild symptoms. The first and most characteristic symptom is bleeding from the umbilical cord several days after birth. Other frequent bleeding events include superficial bruising and subcutaneous haematomas, intramuscular and joint haemorrhage, postoperative haemorrhage and bleeding after tooth extraction, and intracranial haemorrhage which is the major cause of death or disabling consequences. Typically, bleeding symptoms occur hours or days after trauma since the initially formed uncross-linked fibrin clot does not have sufficient stability and is prematurely dissolved by the fibrinolytic system. According to the various functions of FXIII, symptoms of congenital deficiency are not limited to bleeding. Many patients suffer from impaired wound healing and abnormal scar formation, and women frequently experience spontaneous abortions in the early pregnancy [9–11].

Severe congenital FXIII deficiency is a rare, autosomal recessive inherited disease that affects all races and both sexes equally [9]. The incidence of congenital FXIII deficiency has been estimated at 1 in 2–5 million in the British population [10, 12] and extrapolated at 1 in 3 million worldwide [11], which is much lower than haemophilia A (1 in 5000–10 000) or haemophilia B (1 in 25 000–30 000). However, this low incidence may lead to unawareness and due to the fact that FXIII deficiency is not diagnosed by the routinely applied coagulation tests which detect the appearance of polymerised fibrin but not its stabilisation by FXIII, congenital FXIII deficiency may well be underdiagnosed. In Finland, the disease is unusually common, with 12 affected cases from 8 families in a total population of 5 million. Molecular-genetic analysis revealed a particular mutation which was present in 6 of the 8 families and led to the pro-

posal of a founder effect being responsible for the high incidence of FXIII deficiency in the Finnish population [13]. Generally, a founder effect may be considered the cause for a high incidence of rare inherited diseases; a new population established by only a small number of ancestors may result in an increase in rare alleles and a loss of genetic variation. A founder mutation can be evidenced by studying haplotypes of the respective gene in order to distinguish a founder mutation from independent hot-spot mutations. In addition, the incidence of severe congenital FXIII deficiency is also increased in populations where consanguineous marriages are common [10].

The first case: a Swiss story

In 1960, Duckert et al. described for the first time a case of severe congenital FXIII deficiency in their publication "A hitherto undescribed congenital haemorrhagic diathesis probably due to fibrin stabilising factor deficiency" [14]. They reported on a seven-year old Swiss boy who had already been hospitalised for surgical intervention of umbilical bleeding, treatment of a large haematoma on the head, trepanation of a subdural haematoma, a laceration and contusion on the head, and another contusion on the head. Bleeding occurred usually 24–36 hours after injury. His blood clots were loose and prone to rebleeding. He suffered from extremely slow and poor wound healing with wounds bleeding for weeks despite surgical intervention and compressive bandages. Wound healing took several weeks with the formation of a loose granulation tissue and resulted in extensive, irregular, and retracted scars. Laboratory analysis including bleeding time, Quick, thrombocytes, extrinsic and intrinsic coagulation factors, and the fibrinolytic system gave normal results.

The boy was the third son of consanguineous parents. His younger brother showed the same bleeding tendency, but his four other siblings and his parents were not affected. Further research on the family history revealed that two brothers of the maternal grandfather had died from severe bleeding events, and three female second cousins of the patient were also affected, of who two already died.

Based on the delayed bleeding episodes, the obvious lability of the patient's blood clots, and finally the clot solubility in 5 M urea, Duckert et al. suggested the deficiency of the fibrin stabilising factor which had been first described by Laki and Lorand in 1948 [15].

Today, the first patient is fortunately still in good health and took part in our recently published study on molecular characterisation of this first described FXIII deficient patient 47 years after diagnosis [16].

Severe congenital FXIII deficiency in Switzerland

In Switzerland, there is a disproportionately high incidence of severe congenital FXIII deficiency, with 14 patients in approximately 7.5 million inhabitants. Table 1 summarises the characteristics of these patients. Five patients are from central Switzerland, three from the canton of Bern, one patient is from Geneva, and five patients are originally from Eastern European countries.

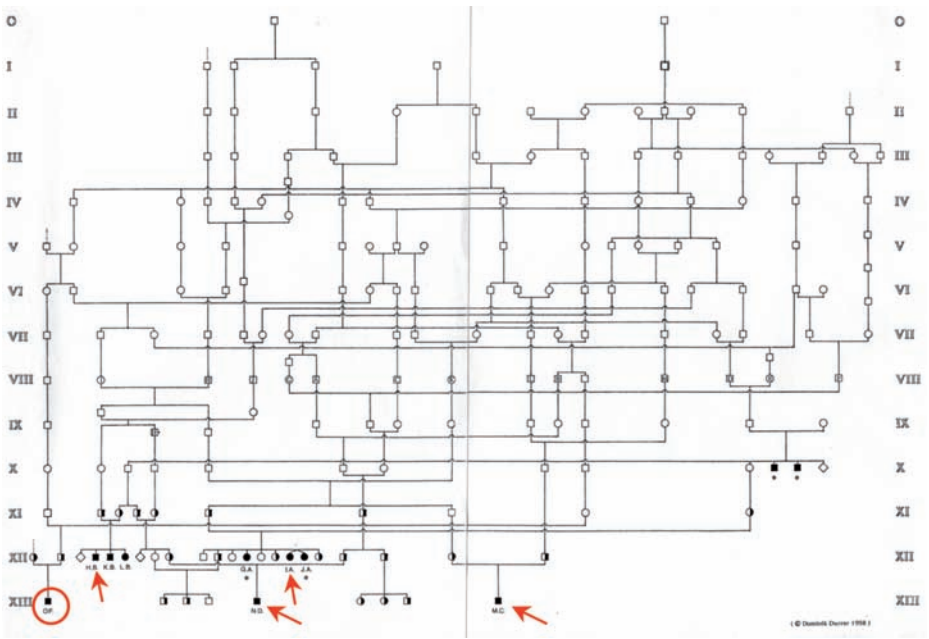


Figure 2

Pedigree of the tribe from the canton of Uri, from 1600 until today
Latin numbers represent the generations. Circle: female. Square: male. Filled symbols: individuals who are homozygous for FXIII deficiency and therefore affected by the disease. Semi-filled symbols: individuals who are heterozygous and therefore only carrier of the disease but not affected [17]. The five patients with severe FXIII deficiency taking part in our molecular-genetic analysis are indicated with red arrows (homozygous) or with a red circle (double heterozygous patient).

Table 1

Characteristics of the FXIII deficient patients living in Switzerland. Modified reproduction from [16] with permission from the publisher.

Patient (Sex)	Ethnic origin	Mutation in FXIII A-subunit gene	Year of birth	Age at diagnosis	Umbilical cord bleeding	Intracranial haemorrhage	Intramuscular haemorrhage	Joint haemorrhage	Subcutaneous haematomas	Defective wound healing	Post-operative bleeding	Other bleeding events	Prophylactic replacement therapy (every 4-6 weeks)	Approx. total annual dose of Fibrogammin® [U]
1 (m)	Kosovo	IVS5-1 G>A	1993	8 y							X			
2 (f)	Swiss	His716Arg Arg260Cys	1964	5 y			X	X	X	X			X	25 000
3 (m)[2]	Swiss	Arg77Cys	1991	5 d	X				X			Epistaxis	X	5250
4 (m)[2]	Swiss	Arg77Cys	1984	8 d	X	X[3]			X			Cephalhematoma, epistaxis	X	9000
5 (m)[1,2]	Swiss	Arg77Cys	1953	7 y	X	X	X	X	X	X		Retroperitoneal haemorrhage		1500
6 (f)	Swiss	Met159Arg	1983	6 m	X	X							X	4500
7 (m)	Swiss	Trp375Cys Arg260Cys	1992	1 y	X	X	X		X				X	5000
8 (m)[2]	Czech	IVS5-1 G>A	1964	5 y	X	X	X					Retroperitoneal haemorrhage		1000–1250
9 (m)[2]	Czech	IVS5-1 G>A	1959	10 y	X			X		X	X			1500
10 (m)	Swiss	Met159Arg Arg661stop	1958	13 y	X		X	X		X		Haematuria	X	3000
11 (f)	Macedonia	IVS5-1 G>A	1985	16 y		X						Haematuria	X	5000
12 (f)[2]	Swiss	Arg77Cys	1956	17 y	X	X	X	X	X	X	X	Abdominal haemorrhage	X	12 000
13 (f)	Serbian	Gly215Arg IVS10+1 G>A	1974	22 y	X		X			X		Corpus luteum, retroperitoneal haemorrhage	X	13000
14(m)[2]	Swiss	Arg77Cys Glu202delG	1974	3 y	X		X		X	X	X		X	13000

[1] First diagnosed FXIII deficient patient

[2] Patients 3, 4, 5, 12, and 14 are members of the large family shown in figure 2, and patients 8 and 9 are brothers.

[3] After cessation of prophylactic replacement therapy on his own initiative in 2004

Sex: m: male, f: female. Age at diagnosis: y: years, m: months, d: days.

The age at diagnosis varies markedly between 5 days and 22 years. The younger Swiss patients were diagnosed at a younger age due to a better awareness of the disease. All patients have experienced several of the typical bleeding events. Except for three patients, all are under regular prophylactic replacement therapy.

The cluster of congenital FXIII deficiency in central Switzerland has been investigated in a genealogical study by Durrer [17]. Studying old church registers, medical records, and family memories, he succeeded to trace back the hereditary disease to two ancestors in the 17th century and to reconstruct the complete pedigree of this tribe originating from the canton of Uri, as shown in figure 2. Durrer showed the familial relationship between the five patients from central Switzerland due to consanguineous marriages within the tribe and therefore proposed a founder effect for FXIII deficiency in this group of patients without knowledge of their molecular genetics. Between the other four Swiss patients there exist no known familial relationships. The remaining five patients are all originally from Eastern European countries, thus, a founder effect might also be involved. Since the molecular-genetic basis of FXIII deficiency in these 14 patients living in Switzerland, including the first described patient, has been unknown so far, we performed the molecular-genetic analysis to identify the causing mutations in the FXIII genes [16].

Molecular-genetic cause of FXIII deficiency

Two different genes code for the two FXIII subunits [1]. The gene coding for the A-subunit is located on chromosome 6, p24-25. It spans 160 kb and consists of 15 exons separated by 14 introns. The gene coding for the B-subunit is located on chromosome 1, q31-32.1. It spans 28 kb and consists of 12 exons and 11 introns. The molecular-genetic causes of congenital FXIII deficiency are mutations in the FXIII genes. More than 60 mutations in the A-subunit gene, and 4 mutations in the B-subunit gene, have been identified so far [18]. Approximately one third of the A-subunit gene mutations and two of the B-subunit gene mutations have been expressed in mammalian or yeast cell culture in order to support their causative nature in FXIII deficiency. Most of the mutations code for a single amino acid exchange (missense mutations) resulting in defective folding and instability of the mutant protein. In addition, mutations leading to stop codons (nonsense mutations), small deletions/insertions leading to frameshift and consequently to premature stop codons, and intronic mutations at splice sites leading to incorrect post-transcriptional processing of the messenger RNA (mRNA) have been reported. In the A-subunit gene, missense mutations occur in all exons except exons 1 and 13, and splice site mutations occur in introns 3, 5, 7, 8, 10, 11, and 14.

When we investigated the 14 FXIII deficient patients living in Switzerland, we identified ten different mutations in the A-subunit gene (table 1), among them four mutations which had been described previously and six novel mutations [16]. By cell expression of wild-type FXIII A-subunit and the mutant variants Arg77Cys, Met159Arg, Gly215Arg, Trp375Cys, and His716Arg, we confirmed their causative nature in FXIII deficiency. Our molecular-genetic analysis also confirmed the familial relationship between the five patients from central Switzerland, which Durrer [17] had de-

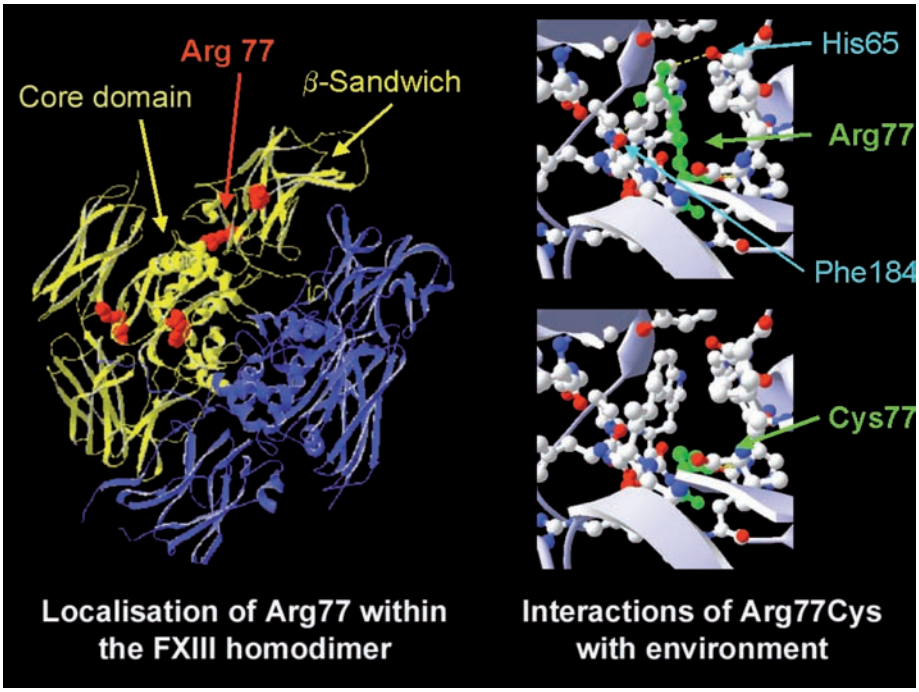


Figure 3

Structural analysis of the mutation Arg77Cys found in the tribe of Uri
Left: FXIII A_2 homodimer (the two monomers are displayed in yellow and blue). Wild-type Arg77 is located at a critical site between the β-sandwich and core-domain.
Right: Top: Wild-type Arg77 (green) forms hydrogen bonds (yellow dashes) with His65 and Phe184.
Bottom: Mutant Cys77 (green) forms no hydrogen bonds and leaves an open gap.
(Modified from [16] and reproduced with permission from the publisher)

duced from his large pedigree. These five patients, including the first case described in 1960, carry a point mutation in exon 3, codon 77 of the FXIII A-subunit gene, resulting in the exchange of the amino acid arginine (Arg) by cysteine (Cys). Expression of the mutant Cys77 protein in cell culture yielded only traces of FXIII A-subunit protein (less than 1% of the Cys77 mutant compared to wild-type), confirming that this Arg77Cys mutation was causative for FXIII deficiency. Structural analysis (figure 3) revealed that the wild-type Arg77 forms hydrogen bonds with two neighbouring amino acids and therefore may have an important role in stabilisation of the protein structure. The mutant Cys77, however, does not maintain these hydrogen bonds and leaves an open gap because of its smaller side chain. It is therefore likely to destabilise the environment leading to defective folding and/or premature decay of the FXIII protein. Durrer also predicted that four patients were homozygous for one mutation, whereas one patient had to be compound heterozygous carrying two different mutations from his father and mother side, since his mother is of different origin. We could also confirm this prediction and showed that four patients are indeed homozygous for the Arg77Cys mutation, and that one patient has the Arg77Cys mutation on one allele and a deletion of a guanosine (G) nucleotide in codon 202, Glu202 delG, on the other allele. This deletion induces a shift of the reading frame during the translation process resulting in a premature stop codon five codons downstream. Consequently, the major part of the FXIII A-subunit polypeptide including the essential active site region is not translated from mRNA into protein. The Glu202 delG mutation has not been described so far. Interestingly, the Arg77Cys mutation has also been found in Chinese patients [19]. For more information on the other mutations found in the Swiss patients please refer to our original publication [16].

Diagnosis and treatment

Diagnosis of congenital FXIII deficiency cannot always been made right after birth since the severity of clinical signs can differ between individuals and major bleeding episodes do not always occur in the first weeks of life. However, because of the potentially fatal bleeding complications, the possible diagnosis of severe congenital FXIII deficiency should not be delayed in any individual with an unknown bleeding tendency.

However, laboratory analysis of FXIII activity and/or antigen levels is not available everywhere. Because FXIII acts when fibrin has already been formed, it is not detected by routine coagulation assays. In the past, severe FXIII deficiency could only be diagnosed using the clot solubility test. In this test, plasma samples are allowed to clot and the clot is then resuspended in diluted urea or monochloroacetic acid solutions. Presence of FXIII makes the clot insoluble whereas dissolution of the clot indicates FXIII deficiency. This assay allows only semi-quantitative FXIII determination. Additionally, careful consideration of the preanalytic condition is mandatory, since any plasma or FXIII administration within the weeks before testing will give "normal" results, with some 5% of normal FXIII plasma concentration already being sufficient for giving a urea-resistant clot. For these reasons, quantitative FXIII activity and antigen assays are more recommended. The most commonly used commercial assay, Berichrom® FXIII (by Dade Behring AG, Marburg, Germany), is based on a photometric method and can be carried out on several automatic coagulation analysers. The assay has one disadvantage: it may give too high results in the low FXIII range due to interference with high ammonia concentrations in the test plasma, what can be avoided by doing mixing studies with normal plasma. Therefore, FXIII activity levels below 15% obtained with this assay should be carefully reviewed as there might be no or only traces of FXIII in the sample. For this reason, we recommend the Pefakit® FXIII Incorporation Assay (by Pentapharm Ltd, Basel, Switzerland) or enzyme-linked immunosorbent assay (ELISA) methods for determination of FXIII activity or FXIII antigen levels, respectively, especially for diagnosis or therapy monitoring of FXIII deficiency. The Pefakit® FXIII Incorporation Assay measures FXIII cross-linking activity and the ELISAs directly detect the FXIII A-subunit or B-subunit proteins by specific antibodies. Both Pefakit® and ELISAs are highly sensitive and therefore reliable in the low range. Unfortunately, these methods are quite time-consuming and cannot be carried out automatically, and the ELISAs are mainly in-house assays. Unlike in haemophilia A and B, in severe FXIII deficiency there exist no different degrees of severity relating to residual FXIII activity and/or antigen plasma levels, since FXIII deficiency causing mutations always lead to complete absence of the protein. So far, no cases of only partially reduced FXIII activity and/or antigen levels are known.

If the diagnosis of severe congenital FXIII deficiency is confirmed, prophylactic replacement therapy is mandatory because of the sometimes fatal or severely disabling bleeding complications after only minor trauma. The treatment normally consists of prophylactic administration of FXIII concentrate, commercially available as Fibrogammin® HS (by ZLB Behring, Bern, Switzerland). In prophylaxis studies this concentrate has proven to be efficient in bleeding control and safe with no development of inhibitors or viral seroconversion

[20]. Thanks to the long half-life of FXIII in plasma, approximately 10 days, it is sufficient to administer FXIII concentrate only every 4–6 weeks. With regular replacement therapy, patients can lead a normal life. Under special conditions, eg pregnancy or surgical interventions, FXIII levels should be monitored more closely as higher or more frequent dosage of FXIII may be required [21, 7]. Recently, recombinant FXIII products have been developed and first clinical trials have been carried out [22, 23]. Heterozygous carriers of FXIII deficiency have about 50% of normal FXIII plasma levels and usually do not need any therapy since their haemostasis functions normally under most conditions.

International registry

Since April 2006, the international registry on severe congenital FXIII deficiency is open to the public on the World Wide Web under http://www.f13-database.de. The registry is maintained by V. Ivaskevicius and J. Oldenburg, University of Bonn, Germany, and supported by the Factor XIII and Fibrinogen Subcommittee of the Scientific and Standardisation Committee (SSC), which serves as the scientific working arm of the International Society on Thrombosis and Haemostasis (ISTH). The aim of this registry is to collect data on all FXIII deficient patients to gain more knowledge on this rare hereditary disease. In addition, the website provides detailed information on FXIII and FXIII deficiency.

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