Congenital Factor VII Deficiency

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10.1 Introduction

Congenital factor FVII (FVII) deficiency is a rare autosomal recessive bleeding disorder with the estimated prevalence of 1 per 500,000 in the general population, without ethnic or gender predilection [1, 2], but the prevalence is higher in regions with the high rate of consanguinity marriage [1, 3]. Clinical pictures in these patients range from asymptomatic condition to severe life-threatening hemorrhages [4, 5]. There is a relatively poor correlation between FVII coagulant activity (FVII:C) and bleeding tendency and mutation profile in congenital FVII deficiency [3, 6]. Severe clinical symptoms usually present in patients with less than 1% FVII:C, but some patients with severe deficiency don't experience severe bleeding episodes. The complete absence of functional FVII in knockout mice is incompatible with life, suggesting FVII deficiency is not associated with complete absence of functional FVII, but patients with residual FVII level can survive and are able to prevent lethal bleeding [7, 8]. The disorder is accompanied with a wide spectrum of bleeding problems including mild symptoms such as mucous membranes and skin hemorrhages and life-threatening hemorrhages such as central nervous system (CNS) bleeding. Iron deficiency due to menorrhagia is common in women with FVII deficiency [3]. This disorder can be managed by different therapeutic options including fresh frozen

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plasma (FFP), prothrombin complex concentrate (PCC), plasma-derived FVII (pd-FVII) products, and recombinant activated FVII (rFVIIa).

10.2 Factor VII Structure and Function

FVII is a low molecular weight protein (50 kDa) composed of 406 amino acids that is synthesized as single-chain molecule in the endoplasmic reticulum of hepatocytes. FVII has homology with FIX, FX, and protein C on the catalytic site and amino-terminal region [9]. In hepatocytes, FVII has a signal peptide that is required for secretion and a propeptide (removed intracellularly) that is necessary for γ-carboxylation of all glutamate residues within ~45 amino acids in N-terminus of FVII protein [10]. Coagulation FVII consists of four domains including one gamma-carboxyglutamic acid (*Gla*) domain on the N-terminal with ten glutamic acid residues (at residues 6, 7, 14, 16, 19, 20, 25, 26, 29, and 35). These ten glutamic acid residues undergo post-translational modification; convert to γ-carboxyglutamic acid with calcium-binding capacity. Binding of calcium to Gla domain leads to conformational changes and exposure of new epitopes that facilitate its subsequent binding to TF and phospholipid. Other FVII domains are two epidermal growth factor-like domains (*EGF1, EGF2*) and a catalytic serine protease (*SP*) domain in C-terminal (Fig. 10.1) [1, 10].

FVII in zymogen has the plasma half-life of 5 h that is the shortest half-life among the clotting factors, but the half-life of free FVIIa is 2 h, whereas the plasma half-life of most other activated coagulation factors is very short [1, 10]. FVII reversibly in a Ca^{2+}-dependent manner can bind to membranes with negatively charged phospholipids such as phosphatidylserine or phosphatidic via Gla domain [11, 12]. The majority of plasma FVII circulates as the single-chain inert zymogen (10 nmol/L (0.5 μg/mL)), and the minority circulates in the plasma as two-chain active protein (~10 to 110 pmol/L) [1, 3, 10, 13]. The key event in the activation of FVII is proteolysis of a single peptide bond between Arg-c15 (amino acid 152) and Ile-c16 (amino acid 153) in the connecting region of EGF2 and SP domains. This results in formation of two polypeptide chains: heavy chain with 254 amino acids (30 kDa) (residues 153–406), comprised of serine protease domain with Trypsin homology at C terminus, and light chain with 152 amino acids (20 kDa) (residues 1–152), composed of Gla and 2 EGF-like domains [1, 10, 14–16].

FVII chiefly interacts with TF via the Gla and EGF1 domains; however, two other domains can also interact with TF [15, 17]. FVII/TF complex is necessary for the restructuring of active site and full enzymatic activity of FVIIa, because free FVIIa has very weak catalytic activity [14, 15]. In addition to FVII/TF complex, several other coagulation factors including FXa, FIIa, and FIXa contribute to FVII activation; however, it seems that membrane-bound FXa is the most effective [18]. Once formed, the TF/FVIIa complex results in proteolytic activation of FIX and FX to FIXa and FXa, respectively, and generating few amount of thrombin that is able to produce a strong feedback amplification of coagulation cascade [10, 19]. Tissue factor pathway inhibitor (TFPI) and antithrombin (AT) are inhibitors of FVIIa, but only in complex form (FVIIa/TF) can it inhibit FVII [20, 21]. The TFPI is a Kunitz-type proteinase inhibitor and

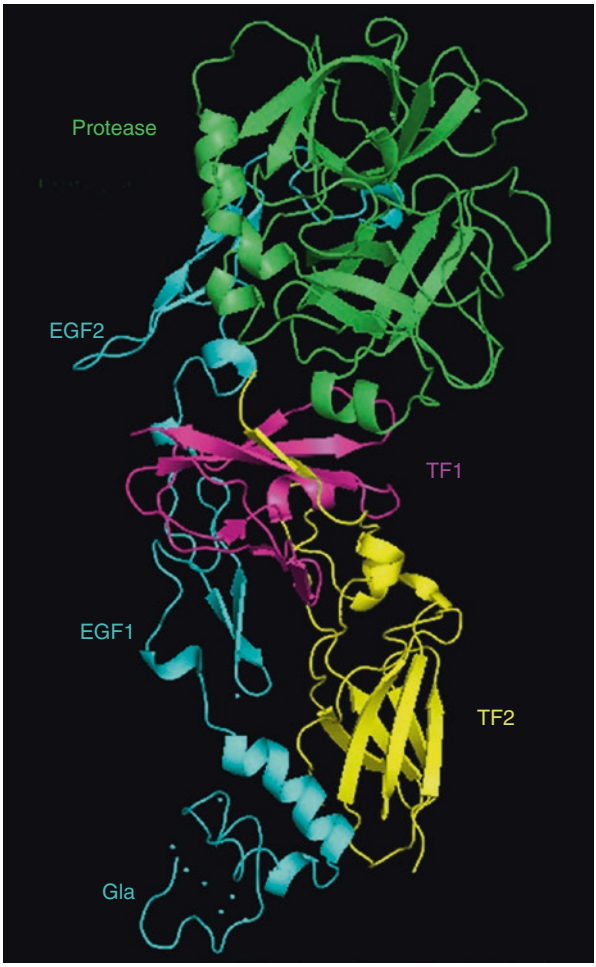

Fig. 10.1 The cartoon representation of activated factor VII (FVIIa)/soluble tissue factor (sTF) complex. FVII has four domains including gamma-carboxyglutamic acid (Gla), two epidermal growth like factor (EGF1, EGF2) domains, and serine protease domain. sTF contains two fibronectin type III domains (TF1 and TF2 represent of N- and C-terminal of sTF)

attaches to membrane surface via glycophosphatidylinositol (GPI)-linked. TFPI mainly is expressed by endothelial cells and partly by platelets [22]. The TFPI/FXa complex can inhibit FVIIa/TF complex and prevents further FX activation via inactivation of tetra-molecular (TF-FVIIa-TFPI-FXa) complex formation that rapidly inhibits the extrinsic coagulation pathway [20, 22]. Inhibitory function of TFPI/FXa, at least in part, is by inducing of TF-expressing cells to internalize the TF/FVIIa complexes, which leads to degradation of the majority of FVIIa [22, 23]. TFPI is synthesized by microvascular endothelial cells, megakaryocytes, and the liver [3, 24]. Heparin and various platelet agonists can increase the release of TFPI from the surface of endothelial cells. AT reaction is heparin dependent, and its reactivity with FVIIa is increased after FVIIa/TF complex formation. After binding of AT to FVIIa/TF complex, the affinity of FVIIa to TF is decreased and then FVIIa/AT complex releases into the bloodstream (Fig. 10.2) [3, 20]. FVIIa/AT complex is increased in many prothrombotic situations and seems to be the early marker of coagulation cascade activation [20].

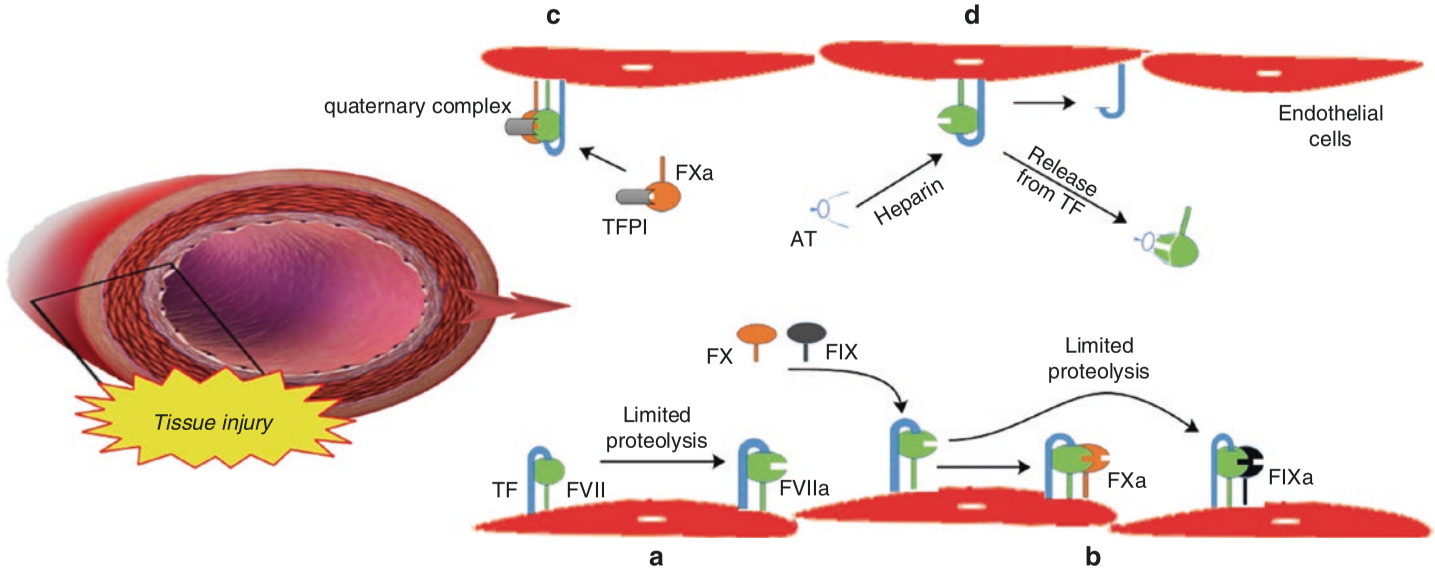

Fig. 10.2 In vivo activation and inhibition of factor VII (FVII). (**a**, **b**) FVII binds to tissue factor (TF) and is converted to its active form, FVIIa, by minor proteolysis and then activates factor X (FX) and factor IX (FIX). (**c**, **d**) Tissue factor pathway inhibitor (TFPI) and antithrombin (AT) are inhibitors of FVII/TF complex. TFPI/FXa complex can form an inactive tetra-molecular (TF-FVIIa-TFPI-FXa) complex that results in extrinsic coagulation pathway inhibition. In addition to direct deactivation of FXa, TFPI can prevent further FX activation after TFPI/TF/FVIIa complex formation. TFPI/FXa can induce internalization of TF/FVIIa complex that results in degradation of the majority of FVIIa (not shown). TFPI can also inhibit the early forms of prothrombinase (not shown). AT directly attaches to TF/FVIIa complex and causes segregation of FVIIa from TF by losing affinity of FVIIa for TF resulting in a release of FVIIa/AT into the bloodstream and therefore causing extrinsic coagulation pathway inhibition. AT activity can be strengthened by heparin

FVII with the initiation of coagulation pathway following complex formation with TF at injury site has a critical role in the coagulation cascade. This complex is an important activator of both extrinsic and intrinsic coagulation pathways by activating FVII, FIX, and FX [4]. It was shown that complete deletion of *F7* gene leads to mouse perinatal death, while mice and human with very low FVII level could survive [7, 25, 26]. Although the normal perinatal course was observed in FVII knockout mouse, major abdominal and intracranial hemorrhages (ICH) lead to death in such cases at birth or shortly after birth [8]. Generally, it is accepted that absence of FVII is incompatible with life [3, 19, 27].

TF also known as thromboplastin, coagulation FIII, or CD142 is a glycosylated, transmembrane protein that doesn't require proteolysis for activation [10]. It is well known that normal hemostasis process in some tissues with high TF-expression such as the brain, bowel, uterus, placenta, lungs, and heart mainly depends on the extrinsic pathway; therefore, decrease or absence of FVII can result in bleeding in some of these tissues [4, 7]. In addition to well-known role of TF in coagulation process, in complex with FVIIa, other functions including embryonic angiogenesis, oncogenic angiogenesis, tumor progression, leukocyte diapedesis, and regulation of inflammation and sepsis are described. This complex can also change cellular physiology in the TF-expression cells [28, 29].

10.3 Congenital Factor VII Deficiency

Congenital FVII deficiency (OMIM 227500) is an autosomal recessive bleeding disorder, for the first time described by Alexander in 1951 in a 4-year-old white girl who experienced prolonged umbilical cord bleeding at birth [30]. This bleeding disorder with a prevalence of 1 per 500,000 individuals is the most common rare bleeding disorders (RBD) [1, 5, 30]. Although the disorder has distributed over the world, it is more frequent in some areas such as the United Kingdom, United States, Brazil, Turkey, Italy, Slovak Republic, and Iran, according to the annual global survey of World Federation of Hemophilia (WFH). Although consanguinity is the main cause for high rate of disorder, in some countries like the United Kingdom, this was attributed to noticeable grow up of hygienic surveillance and the improved quality of life. The number of patients with congenital FVII deficiency might be underestimated probably due to undiagnosed asymptomatic patients and those with the mild bleeding tendency. FVII deficiency is categorized in two groups, including type I (quantitative deficiencies), which is characterized by simultaneous decreases in FVII activity and antigen levels, and type II (qualitative defects) with only decreases in factor activity with normal or near-normal FVII antigen level (Table 10.1) [5]. Clinical manifestations of the disorder are highly variable both in severity and type of bleeding, with poor correlation between residual plasma factor activity and severity of bleeding [4, 31]. The FVII reference range is between 70% and 140%, and usually, less than 2% FVII activity (FVII:C) is related to increased risk of severe bleeds during the newborn and young childhood periods [1, 6]. The disorder is due to mutations in *F7* gene, and a wide spectrum of mutations has been identified

Table 10.1 Classification of congenital factor VII deficiency and results of coagulation tests

	aPTT	PT	FVII:C	FVII:Ag
Normal people	Normal	Normal	Normal	Normal
FVII deficiency (type I)	Normal	Prolonged	Decreased	Decreased
FVII deficiency (type II)	Normal	Prolonged	Decreased	Normal or nearly normal

aPTT activated partial thromboplastin time, *PT* prothrombin time, *FVII:C* factor VII coagulant activity, *FVII:Ag* factor VII antigen

within this gene. Most of the identified mutations are new and restricted to the special area or specific family and could be used for carrier detection, precise diagnosis, and prenatal diagnosis in affected families.

The presence of abnormal bleeding, accompanied by isolated prolonged PT, is the first clue for suspicion to FVII deficiency, but in general, clinical presentations, physical examination, family history, and laboratory assessments can be used for precise diagnosis of the disorder. Several therapeutic options such as fresh frozen plasma (FFP), plasma-derived FVII (pd-FVII), prothrombin complex concentrate (PCC), activated PCC (aPCC), and more recently recombinant FVIIa (rFVIIa) are available for patients with FVII deficiency.

10.4 Acquired Factor VII Deficiency

Acquired FVII deficiency can be present as the isolated or combined deficiency as a part of vitamin K-dependent coagulation factors deficiency [1, 32, 33]. Acquired isolated FVII deficiency is an extremely rare disorder, but the frequency was underestimated, because clinical symptoms of the disorder may be mild to moderate with slightly prolonged PT [32–34]. Different conditions such as malignancies, severe systemic sepsis, infectious agents, drugs (penicillin), and aplastic anemia as well as stem cell transplantation and presence of an inhibitory antibody may be accompanied with acquired isolated FVII deficiency [1, 33, 35, 36]. In some cases, no underlying condition of FVII deficiency (idiopathic) was identified [33]. The pathogenesis and the possible mechanism of FVII deficiency are not clear in these situations [33]. Simultaneous deficiency of FVII with other coagulation factors may arise in different conditions including [1]:

- Problem in synthesis, particular in liver failure that leads to decrease of all coagulation factors.
- A defective synthesis, especially during hypovitaminosis K syndrome caused by insufficient intake, malabsorption, or anticoagulant therapy with vitamin K antagonists such as warfarin, acenocoumarol (Sinthromin), and phenprocoumon (Marcoumar). These conditions only lead to vitamin K-dependent coagulation factor deficiency (FII, FVII, FIX, and FX) and the decrease of protein C and protein S levels. Warfarin inhibits the vitamin K-dependent reductase and the vitamin K-dependent quinone reductase and leads to disturbing in the recycling of vitamin K to its enzymatically active form and its carboxylation activity (Fig. 9.4).

- Consumption syndromes, especially disseminated intravascular coagulation (DIC) or hyperfibrinolysis that leads to consuming of all coagulation factors.

As mentioned, FVII has the shortest plasma half-life among clotting factors; thus, decrease in plasma level of FVII occurs faster than other coagulation factors. Therefore, diagnosis of isolated FVII deficiency should be made with caution [1].

10.5 Clinical Manifestations

Patients with congenital FVII deficiency have variable bleeding diathesis with poor correlation between FVII activity and bleeding tendency [1, 33]. The clinical phenotype is very heterogeneous and ranges from asymptomatic condition to life-threatening diathesis. The clinical phenotype of these patients could be categorized into two main categories [1, 3, 37]:

- Asymptomatic that composed about one-third of patients
- Symptomatic with two subgroups:
  - Nonsevere: Mild to moderate with mucocutaneous bleeding (mimic platelet disorders) including approximately two-third of affected patients. These patients usually don't require medical intervention.
  - Severe with life- or limb-threatening hemorrhages (CNS bleeding, gastrointestinal (GI) bleeding, or hemarthrosis) that composed about 10–15% of patients [1, 3, 37].

Asymptomatic patients might be randomly diagnosed or identified during family studies, especially in cases with other affected family member (s). According to a large study, 71% of homozygous and 50% of compound heterozygous patients are symptomatic, while only 19% of heterozygous subjects are symptomatic [2]. Based on another large study, most common bleeding features among patients with FVII deficiency are epistaxis, easy bruising, gum bleeding, hematoma, hemarthrosis, post-operative bleeding, and menorrhagia, and less common bleeding features are hematuria, GI bleeding, and CNS bleeding (Table 10.2) [2, 6, 27, 37–40]. Severe clinical presentations generally occur at young ages (soon after birth or when they are toddler) in severely affected patients [9, 37]. Severe chronic iron deficiency due to menorrhagia is common in women with FVII deficiency [3]. Patients with plasma FVII level <2% may present severe bleeding, while those with >20% are generally asymptomatic. Interestingly, bleeding can be observed among patients with plasma levels between 20% and 50%, while asymptomatic subjects with plasma level <1% were also reported [9]. Prediction of hemorrhagic risk may not be possible, even in the presence of laboratory assays such as thrombin generation test, FVIIa and FVII antigen level (FVII:Ag) assays, and TFPI measurement [41]. CNS bleeding is less common condition and is an important problem, mainly in children under 6 months with severe FVII deficiency and associated with high rate of morbidity and mortality [3, 9]. Bleeding episodes in FVII deficiency may mimic hemophilia (hemophilia

Table 10.2 Clinical manifestations of patients with congenital factor VII deficiency

	Mariani et al. (*n*: 174[a]) (%)	Mariani et al. (*n*: 139[b]) (%)	Mariani et al. (*n*: 228) (%)	Herrmann et al. (*n*: 217) (%)	Peyvandi et al. (*n*: 28) (%)	Mariani et al. (*n*: 24) (%)
CNS bleeding	4.6	6.5	7	1	17	–
GI bleeding	13.8	14.4	14	9	–	17
Hemarthrosis	16.1	21.6	22	12	21	67
Epistaxis	56.3	66.2	83	58	64	62
Easy bruising	47.7	43.2	62	37	32	29
Gum bleeding	33.9	25.9	42	25	–	33
Menorrhagia	62.9	–	–	57 (of 106 female)	60 (of 10 female)	90 (of 10 female)
Hematomas	16.1	20.9	21	20	12	46
Hematuria	5.2	12.2	12	7	10	29
Post-operative bleeding	29.8	30.4	34	–	55	–
Thrombosis	3	–	–	–	–	–

CNS central nervous system, *GI* gastrointestinal

[a]The incidence of menorrhagia has been reported in female aged >10 and <50 years and all of patients are female

[b]Only males

type) with the present of hemarthrosis and hematoma or may mimic primary hemostasis defects with menorrhagia, epistaxis, or ecchymosis [9]. In addition to bleeding episodes, thrombotic events with the unknown mechanism (particularly deep vein thrombosis) also may occur in ~3% of patients with severe FVII deficiency, especially those patients undergoing surgical interventions or those under replacement therapy; however, spontaneous thrombosis also may occur [42, 43]. Although severe clinical events were observed in homozygous or compound heterozygotes, heterozygous are usually asymptomatic [2, 27].

10.6 Diagnosis

The first case with congenital FVII deficiency was described by prolonged PT in 1951 [30]. The diagnosis was made based on clinical presentations, physical examination, family history, and laboratory assessments [38]. Occasionally, the disorder could be identified during routine work up. In general, the mean age of diagnosis in inherited FVII deficiency is 8 years [1]. FVII deficiency is usually suspected by the presence of isolated prolonged PT that is corrected by 50:50 mixing of patient's plasma with normal pooled plasma. In this setting, the activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen concentration, and platelet count are usually normal. Evaluation of FVII coagulant activity (FVII:C) (with twice repeating) leads to confirmation of disorder [3, 38]. In general, the mainstay in the diagnosis of FVII deficiency is FVII:C assay. Exclusion of vitamin K deficiency or other acquired causes of clotting factor deficiencies is useful, but not necessary, because concomitant prolongation of aPTT is observed in these conditions [3].

In patients with acquired isolated FVII deficiency, isolated prolongation of PT was occurred, while aPTT is normal. However, prolonged aPTT might have occurred in some patients with the presence of lupus anticoagulant (LA). In this situation, FVII:C should be determined and isolated FVII deficiency should be confirmed. Evaluation of other vitamin K-dependent clotting factors might be helpful to rule out other disorders. For further investigation, mixing study should be performed. After mixing study, if PT was prolonged, the presence of specific FVII inhibitor is suspected, and the Bethesda assay could confirm the presence of specific FVII inhibitor [33]. In this way, the absence of bleeding history, the presence of malignancy (or other underlying conditions), as well as absence of family history of congenital FVII deficiency could be useful during the process of diagnosis.

10.6.1 Factor VII Coagulant Activity

FVII:C should be performed for diagnosis of FVII deficiency. FVII:C usually determines by one-stage prothrombin time-based assay [44]. The source of thromboplastin, calibration materials, and quality of the reagents can affect the results of FVII:C [45]. Three types of thromboplastin reagents with different sensitivities including rabbit brain, ox[1] brain, or human recombinant thromboplastin are available [44, 46].

According to the type of thromboplastin, different results might be obtained; however, variability that is caused by qualitative FVII defects such as FVII Padua, FVII Nagoya, and FVII Tondabayashi is more profound. For example, in Padua variant (Arg304Gln in exon 8) which usually associates with no bleeding history and the normal range of FVII:Ag, disparate results toward different thromboplastins could be obtained, so that normal results using ox brain thromboplastin and abnormal results by use of rabbit brain thromboplastin might be obtained [1, 47]. It should be noted that variable reactivity of different thromboplastins only occurs in type II deficiency such as Padua, not type I deficiency [1, 47]. In this setting, based on structural similarity of recombinant thromboplastins and human TF, use of this product is more reliable than other thromboplastins for FVII assay.

In spite of the presence of certified reference materials for the accuracy of calibrators, the different calibration materials may have variable interlaboratory precision, especially in cases with FVII level below 20% [1].

The quality of the FVII-deficient reagents impresses accuracy of FVII:C assay, especially when FVII-deficient plasma has residual FVII:C. This issue can lead to overestimation of FVII:C in patients with low plasma level of FVII [45]. According to 2016 Clinical and Laboratory Standards Institute (CLSI) document H48-Ed2, the mean activity of FVII-deficient plasma in the one-stage clotting assay should be less than 1% [48]. Indeed, contamination of thromboplastin with small amounts of FVIIa can decrease sensitivity to patient's plasma FVII:C, while it increases sensitivity to patient's plasma level of FV, FX, and prothrombin [1, 49]. Finally, it should be noted that plasma FVII level is raised in some circumstances, such as female gender, increasing age, and hyperlipidemia, especially hypertriglyceridemia [50].

[1] Ox is derived from oxen and commonly referred as castrated adult male cattle.

10.6.2 Factor VIIa Assay

In addition to the pivotal role of TF-FVIIa pathway in the initiation of the coagulation cascade, it has the important effect on the inflammatory pathway, regulation of inflammation and sepsis [28].

When recombinant activated FVII (rFVIIa) was introduced for treatment of patients with hemophilia having inhibitor, FVII deficiency, and other bleeding events such as retropubic prostatectomy, the interest for concentrates FVIIa assay was increased [1, 51, 52]. Although PT and FVII:C assay could also be used for monitoring of rFVIIa treatment, but as mentioned above, the FVII:C and PT results vary greatly among laboratories (mostly due to type of thromboplastin), even if different assays used thromboplastins with similar sensitivity. Therefore, FVIIa assay may be more effective than PT and FVII:C for monitoring of these patients [1, 51]. FVIIa assay is not recommended for diagnosis of FVII deficiency [1, 51]. The assessment of FVIIa could be performed by different methods: the first method relies on clotting-based assay using recombinant soluble mutant TF molecule (sTF1–219), a TF without transmembrane and cytoplasmic domains. STF cannot activate FVII, but its FVIIa cofactor activity is conserved [53, 54]. Normal plasma FVIIa level using this technique is 0.5–8.4 ng/mL (mean 3.6 ng/mL), encompassing 1–3% of the total inactive zymogen form [3, 54], based on the specificity of the FVIIa assay [55]. The second method is based on enzyme linked immunosorbent assay (ELISA), using the high specific antibody against two-chain FVIIa that cannot reactive with FVII. An obvious discrepancy might be observed between results of these two methods [54, 55]. The ELISA can detect approximately 0.0125 ng/mL (±0.01 ng/mL) of FVIIa, but the correlation between both methods is excellent [3].

The FVII:Ag could be determined by different methods including ELISA or immunoturbidimetric assays (IRMAs) with epitope-specific monoclonal antibodies against free-circulating FVII. Distinguish between type I and II defects is feasible, by using the FVII:Ag assay. The FVII:Ag level is not a good predictor of severity of bleeding tendency, but it can help understanding of mutational mechanisms of FVII deficiency [1, 38].

10.7 Molecular Basis

The *F7* gene spans 12.8 kb on chromosome 13q34 and contains nine exons and five short tandem repeats. These minisatellite DNA sequences cover more than a quarter of the intron sequence and more than one-third of 3′ untranslated region (UTR) of mRNA. The *F7* gene is located approximately 2.8 kb upstream of the *F10* gene and located near another vitamin K-dependent protein *Z* gene [4, 16, 27, 56]. *F7* gene and protein are structurally homologous with other vitamin K-dependent coagulation factors, particularly FIX, FX, and protein C. The overall base compositions of the *F7* gene in exons and introns are similar (60% G-C and 40% A-T), which is similar to the protein C and the *F10* genes [16]. *F7* gene consists of nine

exons. Exons 1a and 1b (the latter is an alternatively spliced target in 90% of factor VII mRNA transcripts) and a part of exon 2 encode 5′ UTR and mainly a part of the pre-pro leader. Exon 2 encodes Gla domain. Exon 3 encodes the hydrophobic aromatic stack, exons 4 and 5 encode two epidermal-like growth factor (EGF) domains, exons 6 and 7 are responsible for encoding of activation region, and, finally, exon 8 encodes the catalytic domain and 3′ UTR including poly (A) tail (Fig. 10.3) [3].

A wide spectrum of mutations was identified within *F7* gene, and whole gene sequencing including exons, introns, boundaries, and the promoter regions is recommended for mutation detection in patients with congenital FVII deficiency. This is mostly due to a large number of identified mutations within *F7* gene, the short length of the gene, and merely possibility in detection of a recurrence mutation [1]. In general, 90–92% of mutated alleles could be identified with the current routine direct sequencing methods, and ~10% of gene mutation could not be found. Although new techniques, such as next-generation sequencing (NGS), certainly can improve this situation, some of the cases with congenital FVII deficiency may occur due to mutations in different another genes that can make FVII deficiency still an open question [1, 19]. A wide spectrum of normal gene variations and disease-causing mutations, including missense, nonsense, splice site mutations, and insertions/deletions, were observed in *F7* gene. Several functional and nonfunctional polymorphisms have also been observed (Table 10.3) [3, 19, 57–64]. For example, functional promoter polymorphism at position −402 (G > A) of the ATG codon leads to increased FVII:C, while promoter polymorphism at position −401 (G > T) associated with decreased plasma FVII level [58]. Arg413Gln substitution in exon 7 (classically known as R353Q variant) arises from G to A substitution at nucleotide 10,976 and generally associated with another polymorphism, a decanucleotide (10-bp sequence) insertion at position −323 in the 5′-flanking region of the *F7* gene, resulting in 20 to 30% reduction in FVII level [3, 58]. In vitro functional analysis of two adenine (g.11293_11294insAA) insertion polymorphisms located in the 3' UTR of *F7* gene revealed the steady-state decreases of FVII mRNA level [57].

According to available data, most of the mutations in *F7* gene, similar to other congenital bleeding disorders, are point mutation. Missense mutations (79%) are the most frequent while nonsense mutations are the rarest mutations (4%) (Fig. 10.4). Exon 8 as the largest exon (1.6 kb) [16] in *F7* gene that is responsible for encoding of the catalytic domain has a considerable number of mutations.

Prenatal diagnosis (PND) can be used in patients with congenital FVII deficiency, but it is more suitable for those families with severe factor deficiency and history of life-threatening bleeding such ICH [1, 65].

10.8 Management

Due to highly variable clinical presentations and low correlation between severity of clinical presentations and FVII:C level, bleeding risk prediction and management of these patients remained debated. The mainstay of treatment in patients with

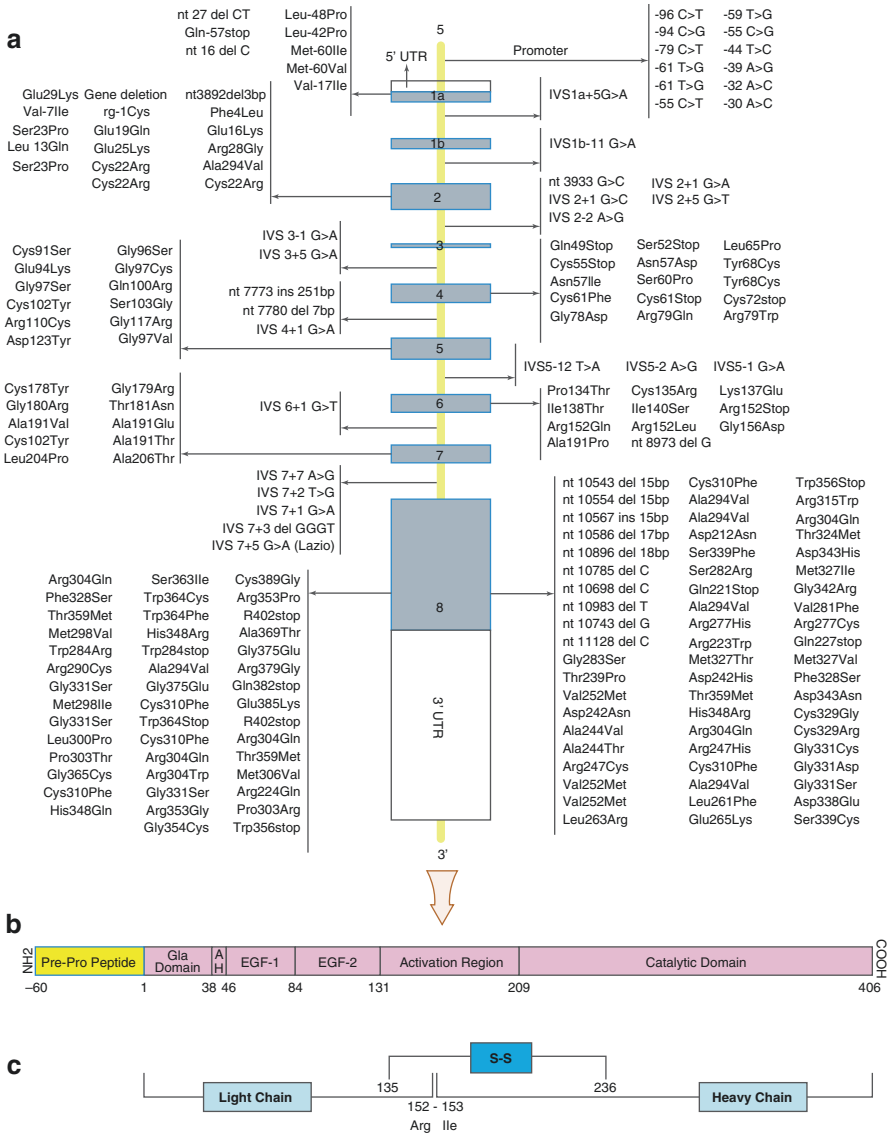

Fig. 10.3 *F7* gene and FVII protein structures and spectrum of gene mutations in *F7* gene. (**a**) *F7* gene contains nine exons that encode FVII protein. Exon 1b, usually alternatively spliced in 90% of FVII mRNA transcript. (**b**) The FVII protein contains pre-pro sequence, Gla, EGF1, EGF2, and catalytic serine protease domains. (**c**) Cleavage at Arg152-Ile153 location, leads to generation of two-chain active molecule which join together by a disulfide bond between Cys135 and Cys236. Light chain contains residues +1 to 152 and heavy chain contains residues 153 to 406. *FVII* factor VII, *Gla* gamma-carboxyglutamic acid, *EGF* epidermal growth factor

Table 10.3 *F7* gene polymorphisms

Polymorphism type	Location	Frequency	Effect on FVII:C
Decanucleotide [CCTATATCCT] insert	5′ region (−323)	0.77 0.23	Decrease[a]
G/T dimorphism	5′ region (−401)	0.91 0.09	Decrease
G/A dimorphism	5′ region (−402)	0.71 0.29	Increase
Intron 1a (G73A)	Intron 1a	0.79 0.21	Decrease[a]
Dimorphism (his 115)	Exon 5	0.80 0.20	–
VNTR repeat (37 bp monomer repeat, 9716ins)	Intron 7	0.30 0.70	Increase[b]
G/A dimorphism	Intron 7	0.82 0.18	NM
Arg353Gln polymorphism	Exon 8	0.80 0.20	Decrease[a]
G/A dimorphism (Ser 333)	Exon 8	0.99 0.01	–
2 adenine (g.11293_11294 insAA) insert	3′ UTR	0.85 0.15	Decrease[c]

NM not mentioned

[a]The 10 bp insertion, and the Arg353Gln polymorphism indicate a strong linkage disequilibrium and therfore it is not clear whether the G73A allele or 10 bp insertion contributed per se to lowering FVII:C

[b]The high mRNA expression in quantitative mRNA analysis has shown that this polymorphism probably is associated with incresed plasma FVII level, although there are contradictory results in this regard

[c]The effect of other polymorphisms was not excluded

congenital FVII deficiency is on-demand replacement therapy that means the stop of bleeding as soon as possible after the occurrence of bleeding. In patients with the history of life-threatening bleeding such as ICH, secondary prophylaxis is recommended. Primary prophylaxis could be used for those patients with severe factor deficiency and risk of life-threatening bleeding. Different therapeutic choices including FFP, pd-FVII, PCC, aPCC, and rFVIIa are available for patients with FVII deficiency (Table 10.4) [1, 27].

The recommended dose and therapeutic target levels of FVII for on-demand, prophylaxis, and in surgeries are summarized in Table 10.5 [66].

rFVIIa (eptacog alfa) is the structurally similar product to plasma-derived coagulation factor VIIa but is manufactured using DNA biotechnology [67, 68]. The first report of successful treatment with rFVIIa was in 1988 with NovoSeven® (rFVIIa; NovoSeven, Novo Nordisk, Copenhagen, Denmark) in patient with severe

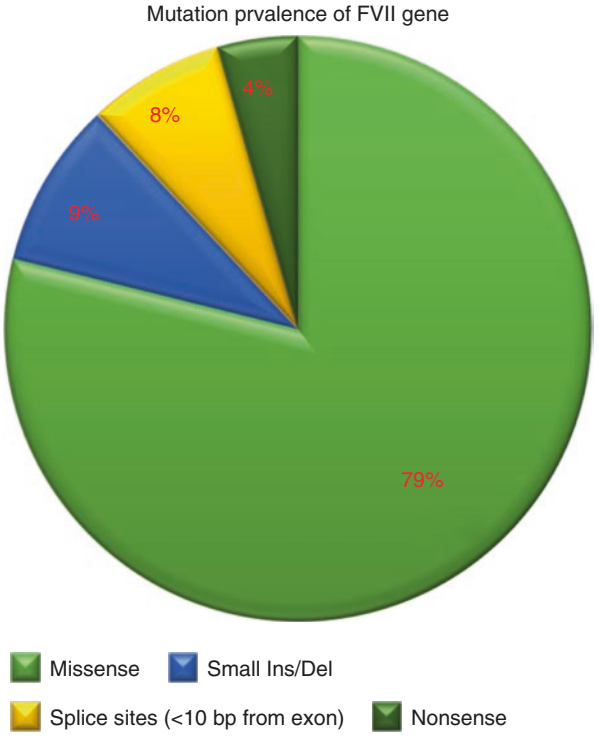

Fig. 10.4 Mutation prevalence of *F7* gene. Most common mutations of *F7* gene are missense mutations (79%), while small Ins/Del (9%), splice sites (8%), and nonsense (4%) mutations form other mutations in *F7* gene

Table 10.4 Available therapeutic options for patients with factor VII deficiency

Factor	Advantage	Disadvantage
FFP	Easily available, cheap	Limited effectiveness, need to high volumes for treatment, fluid overload, risk of viral transmission
Pd-FVII	Effective; suitable for surgery	Unavailable in some countries, other vitamin K-dependent factor concentrations are higher than factor VII, risk of viral transmission, risk of TE
rFVIIa	Very effective Low dosage requirement for treatment No risk of viral transmission Not immunogenic in patients with hemophilia Not produces an anamnestic response in hemophilia patients with inhibitors Very low thrombogenicity	Risk of TE, expensive
PCC	Suitable for surgery	Risk of TE, concentration of other vitamin K-dependent factors is higher than factor VII and presence of activated factors Variable amount of factor VII

Pd-FVII plasma-derived FVII, *FFP* fresh frozen plasma, *rFVIIa* recombinant FVIIa, *TE* thrombotic events, *PCC* prothrombin complex concentrates

Table 10.5 Recommended dose and therapeutic target levels for factor VII on on-demand and prophylaxis treatment in patients with factor VII deficiency

Recommended and maintaining level	Plasma half-life	On-demand dosages	Major surgery	Minor surgery	Long-term prophylaxis dosages
>20%	2–4 h	Pd-FVII concentrate (30–40 U/kg)	rFVIIa: Before surgery: 15–30 μg/kg After surgery: continue the same dose for first day with 4–6 h interval, and then change interval to 8–12 h or Pd-FVII concentrate: 8–40 IU/kg with similar intervals	Tranexamic acid 15–20 mg/kg or 1 g 4 times daily or antifibrinolytics[a]	FFP: 10–15 mL/kg 2 times/week Pd-FVII: 30–40 U/kg 3 times/week

Pd-FVII plasma-derived FVII, *FFP* fresh frozen plasma, *rFVIIa* recombinant FVIIa
[a]This recommendation needs further research because the quality of evidence is moderate

hemophilia A during synovectomy [69]. AryoSeven™ as a new generic rFVIIa claimed that it has biosimilarity with NovoSeven® and is similar in clinical safety and efficacy with NovoSeven® [70–72]. rFVIIa has been approved for treatment of patients with congenital FVII deficiency, congenital hemophilia B with high-responding inhibitors, acquired hemophilia, and Glanzmann thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets and recommended as the first-line therapeutic option for hemophilia A patients with high-responder inhibitors [67, 68]. rFVIIa also was used in surgical bleeding related to dilutional or consumptive coagulopathies or in patients with impaired liver function [73]. In addition, the rFVIIa could be used in various conditions, such as spontaneous bleeding, hemarthrosis, and major surgical procedures. Inhibitor development is one of the most important problems in the administration of rFVIIa [74]. According to FDA report, the risk of the thrombotic events associated with rFVIIa is 2% of treated patients in rFVIIa clinical trials. The very low frequency of thrombotic events, no virus transmission, and scarce production of inhibitory antibodies are advantages of rFVIIa, and expensiveness and short half-life of rFVIIa even than FVII and FVIIa are disadvantages of rFVIIa [1].

PCC is another therapeutic choice for patients with FVII deficiency. PCC usually contains FII (prothrombin), FIX, FX, and the variable amount of FVII. In general, two commercially types of PCC are available, including 3-factor PCC (with absent or low levels of FVII) and 4-factor PCC (with high level of FVII) (Table 10.6), [75–81] and another form is activated PCC (FEIBA) which contains 4-factors in

Table 10.6 Characteristics of some available four-factor prothrombin complex concentrates (PCC)

PCC	Manufacturer/country	Hemophilia B (factor IX)	Acquired deficiency (e.g., VKA)	Congenital deficiency (specific factor not available)	Other factor deficiency, such as factor II, VII, X
Beriplex P/N	CSL Behring GmbH/ Germany		√	√	
Kcentra[a]	CSL Behring GmbH/ Germany		√		
Cofact	Sanquin/the Netherlands		√	√	
Kaskadil	LFB/France		√		√ (FII & FX)
Octaplex	Octapharma/Vienna, Austria		√		√ (FII & FX)
Prothromplex Total 600 IU	Baxalta Innovations GmbH/Vienna, Austria		√	√	
Proplex T[b]	Baxter/Glendale, USA	√			√ (FVII)

PCC prothrombin complex concentrates, *VKA* vitamin K antagonists, *FIX* factor IX, *FII* factor II, *FVII* factor VII, *FX* factor X

[a]Kcentra is indicated for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients during acute major bleeding (it does not have indication in patients without acute major bleeding)

[b]Proplex T is indicated for the treatment of bleeding episodes in patients with factor VIII deficiency with inhibitors

inactive (FII, FIX, and FX) and activated (FVII) forms [82–84]. The amount of FVII is variable in different manufactured PCC that is usually indicated by the manufacturer; thus, after requirement calculation could be administered [3]. Some PCC may contain the additional components such as anticoagulants, protein C, protein S, protein Z, and antithrombin III as well as heparin, to mitigate thrombotic risk [83, 85, 86]. Overall clotting factors of these concentrates are approximately 25 times higher than normal plasma [87]. Some advantages of PCC over the FFP include relatively constant high level of vitamin K-dependent coagulation factors (FII, FVII, FIX and FX), a more rapid decrease in INR value, and no need for matching the blood groups, or thawing the product [84, 88]. Several reports indicated both venous and arterial thrombosis associated with PCC; therefore, utilization of these concentrates in patients with liver disease and major trauma and neonates (because of relatively immature livers) is not recommended. The incidence of thrombotic events in patients treated with 4-factor and 3-factor PCC is 1.8% and 0.7%, respectively [84]. Another disadvantage of PCC is high concentration of other vitamin K-dependent factors than FVII [1, 27, 89–91].

The pd-FVII is the useful product for prophylaxis in children with severe FVII deficiency and for long-term prophylaxis in the range of 30–40 U/Kg, 3 times/week. Pd-FVII was successfully used for surgery with doses ranging from 8 to 40 U/Kg every 4–6 h. For major surgeries, FVII level must be kept above 20 U/dl. Similar to PCC, FVII concentration of pd-FVII is less than other vitamin K-dependent coagulation factors [3, 27, 92]. Acquired FVII deficiency is usually treated as same as inherited FVII deficiency by FFP, PCC, aPCC, and pd-FVII or rFVIIa. However, in these cases, underlying disease should be treated.

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