Factor VII Deficiency

Guglielmo Mariani, M.D.,[1] and Francesco Bernardi, Ph.D.[2]

ABSTRACT

The complex formed between the procoagulant serine protease activated factor VII (FVII) and the membrane protein tissue factor, exposed on the vascular lumen upon injury, triggers the initiation of blood clotting. This review describes the clinical picture of FVII deficiency and provides information on diagnosis and management of the disease. FVII deficiency, the most common among the rare congenital coagulation disorders, is transmitted with autosomal recessive inheritance. Clinical phenotypes range from asymptomatic condition, even in homozygotes, to severe disease characterized by life-threatening and disabling symptoms (central nervous system and gastrointestinal bleeding and hemarthrosis), with early age of presentation and the need for prophylaxis. In females, menorrhagia is prevalent and affects two thirds of the patients of fertile age. Although *FVII* gene mutations are extremely heterogeneous, several recurrent mutations have been reported, a few of them relatively frequent. The study of genotype-phenotype relationships indicates that modifier (environmental and/or inherited) components modulate expressivity of FVII deficiency, as reflected by patients with identical *FVII* mutations and discordant clinical phenotypes. Several treatment options are available for FVII deficiency: the most effective are plasma-derived FVII concentrates and recombinant activated FVII (rFVIIa). Treatment-related side effects are rare.

KEYWORDS: FVII deficiency, F7 database, F7 genotypes, FVII bleeding phenotype, replacement therapy

The complex formed between the procoagulant serine protease activated factor VII (FVIIa), a plasma vitamin K–dependent serine protease, and the integral membrane protein tissue factor (TF) exposed on the vascular lumen upon injury triggers the initiation of blood clotting. The action of the FVIIa-TF complex generates a burst of activated factors IX (FIXa) and X (FXa), which ultimately leads to formation of a stable fibrin clot.[1–3]

Inherited FVII deficiency is the most common among the rare congenital coagulation disorders and is characterized by autosomal recessive inheritance. Clinical heterogeneity is a feature of this hemorrhagic disorder, which ranges in severity from lethal to mild or even asymptomatic forms.[4–6] FVII deficiency is not believed to be associated with complete absence of functional FVII, as also reflected on studies on knockout mice,[7] which suggest that a complete lack of FVII is incompatible with life. The molecular genetics, FVII structure/function analysis, and pathophysiology of FVII deficiency have been extensively investigated.[8–14]

Comprehensive studies based on clinical issues and involving a very large patient population have greatly contributed to our knowledge of disease presentation and diagnosis.[6] The relationship between gender and bleeding tendency has been also investigated. It is known

[1]Dipartimento di Medicina Interna e Sanità Pubblica, Università dell'Aquila, L'Aquila 67010, Italy; [2]Dipartimento di Biochimica e Biologia Molecolare, Università di Ferrara, Ferrara 44100, Italy.

Address for correspondence and reprint requests: Prof. Guglielmo Mariani, M.D., Dipartimento di Medicina Interna e Sanità Pubblica, Università dell'Aquila, L'Aquila 67010, Italy (e-mail: mariani@cc.univaq.it).

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Table 1 Symptom Distribution in the International Registry on Factor VII Deficiency

	Patients ($N = 228$)	
Symptoms	***n***	**Percentage (%)**
Epistaxis	190	83
Easy bruising	143	62
Gum bleeding	95	42
Muscle hematoma	57	21
Hemarthrosis	58	22
GI bleeding	44	14
Hematuria	26	12
CNS bleeding	17	7
Postoperative bleeding	78	34

Note: Only symptoms present in at least 5% of patients are reported. The prevalence of menorrhagia is shown in Table 2.

that FVII levels are clearly modulated by *FVII* gene polymorphisms,[15,16] and databases of mutations are available for comparison.[8]

CLINICAL MANIFESTATIONS

The most frequent symptoms (Table 1) indicate that the disease is mild in the majority of cases, mimicking the clinical picture of a platelet disorder. However, severe to very severe cases are not infrequent, characterized, by disease presentation symptoms, by hemarthrosis, muscle hematomas, or even central nervous system (CNS) and gastrointestinal (GI) bleeding. Postoperative bleeding may also occur, and clotting tests may not be helpful in predicting the inherent bleeding risk.[17] In females, menorrhagia is prevalent[6] (Table 2) as per the other autosomally inherited congenital coagulation disorders.[18,19]

Table 2 Symptomatic FVII-Deficient Females in the International Registry on Factor VII Deficiency

Symptomatic FVII-Deficient Females ($N = 174$)		
Symptoms	***n***	**Percentage of Patients (%)**
Epistaxis	98	56
Easy bruising	83	48
Gum bleeding	59	34
Muscle hematoma	28	16
Hemarthrosis	28	16
GI bleeding	24	14
Hematuria	9	5
CNS bleeding	8	5
Thrombosis	5	3
Postoperative bleeding	40	30
Menorrhagia	100	63

Note: The incidence of menorrhagia has been determined in females aged >10 and <50 years.

Factor VII Deficiency and Thrombosis

Surprisingly, thrombotic episodes (particularly deep vein thrombosis), have been reported in 3 to 4% of patients with FVII deficiency, particularly in the presence of surgery and replacement treatments but "spontaneous" thrombosis may occur as well.[20,21]

FVII Deficiency in Women

As in the other autosomally inherited congenital bleeding disorders, menorrhagia is a frequent type of bleeding in FVII deficiency (Table 2),[6,17] accounting for a prevalence of two thirds of women aged 10 to 50 years, with a peak prevalence in teenagers. Menorrhagia may be associated with other gynecologic (i.e., hemoperitoneum related to ovarian cysts, metrorrhagia due to uterine fibromatosis) or obstetric (postpartum hemorrhage) problems.

In general, women with FVII deficiency do not display a bleeding tendency different from that observed in males (Table 2). In addition, the analysis of the bleeding-free survival is characterized by very similar median survival and curve shapes (data not shown).

FVII and Acquired Inhibitors

Very few anecdotal cases of inhibitors to FVII have been reported to date,[22–25] all of them occurring in relation to replacement therapies. The Seven Treatment Evaluation Registry (STER; where the inhibitors are checked in a centralized fashion) will probably allow us to draw better conclusions about the prevalence and features of this complication.

LABORATORY ASSAYS

Phenotype Analysis

The diagnosis of FVII deficiency is typically simple, relying on the discordance between the prolonged prothrombin time (PT) and the normality of the activated partial thromboplastin time (APTT) tests. Prolongation of the international normalized ratio (INR) may be from moderate (1.5 to 1.8) to high (>2.0), depending on the plasma FVII coagulant (FVII:C) levels.

The FVII:C assay is an important test for the diagnosis, but attention is required for the evaluation of levels around or below 1%, due to the potential presence of traces of FVII in deficient plasmas.[26] A carrier detection approach based on FVII activity and antigen determinations has also been proposed.[27]

Activated FVII (FVIIa) deficiency should be considered the crucial biochemical event in FVII deficiency, because this weak enzyme is the real trigger of blood coagulation. The assessment of FVIIa deficiency, which can be achieved by clotting-based assays (available

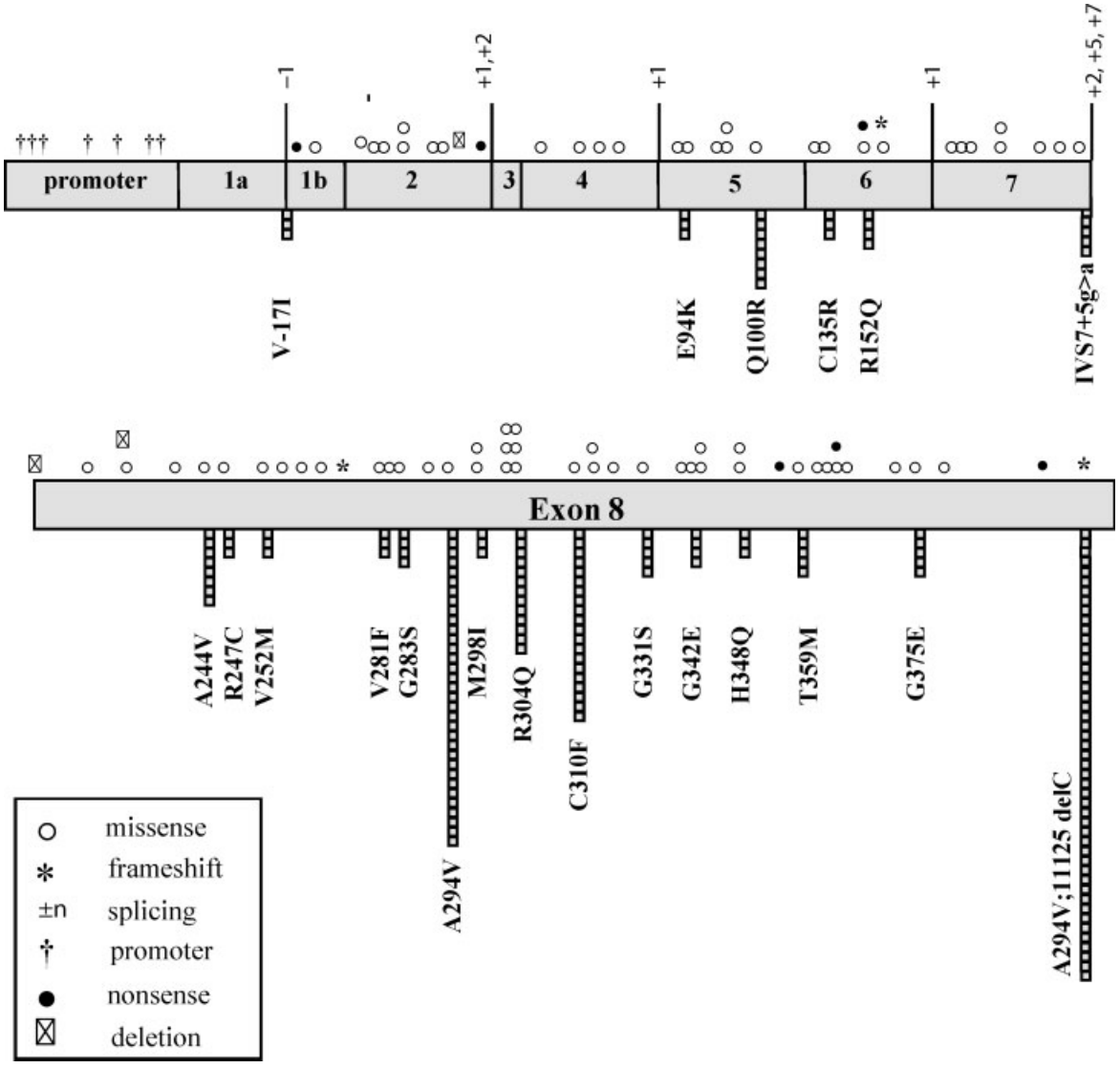

Figure 1 Mutational spectrum in FVII deficiency from the International Registry on Factor VII Deficiency (IRF7). Gray horizontal bars denote promoter and cDNA segments. Splicing mutations are indicated through the position in the consensus splicing sequence. Mutations present in more than five alleles are reported under the bars; one square = two alleles.

from Stago, Asnières sur Seine, France) or enzyme-linked immunosorbent assay (ELISA), is not performed routinely in this bleeding disorder. Normal levels of FVIIa range from 5 to 15 ng/mL (i.e., 1 to 3% of the inactive zymogen form). It is worth noting that the PT assay performed with recombinant-thrombin time (TF) is extremely sensitive to tiny amounts of FVIIa. Factor VII antigen can be quantitatively assayed with polyclonal antibodies to FVII by an ELISA assay (available from Stago)[28] or by using an amidolytic method.[4] An antigen assay is useful to identify the dysfunctional forms of FVII deficiency, characterized by a discrepancy between clotting assay values and antigen levels.

The generation of FXa in plasma, or using recombinant molecules, has been estimated using the FXa fluorogenic substrate MeSO2-D-CHA-Gly-Arg-AMCAcOH (American Diagnostica, Stamford, CT, USA).[26]

Thrombin generation has also been used to evaluate features of FVII-deficient patients. A small amount of FVII is able to guarantee an appreciable thrombin generation.[29]

Genotype Analysis

The *FVII* gene (*F7*) is located on chromosome 13q34,[30] 2.8 kb upstream of the *FX* gene (*FX*), and contains nine exons (Fig. 1) encoding the FVII protein circulating in plasma as a 406-amino-acid single chain (50 kDa).[31] FVII proteolytic activation generates two chains: the light chain, which contains the gamma-carboxyglutamic acid (Gla) domain and two epidermal growth factor–like

Table 3 Recurrent/Frequent Mutations Found in FVII Deficiency and Associated Phenotypes

Mutation	CRM Status	Clinical Phenotype	FVII:C % (% pooled normal plasma)
Q100R	Reduced	Severe	<1
A244V	Minus	Mild	3–7
A294V	Reduced	Moderate	3–8
A294V; 11125delC	Minus	Moderate to severe	1–3
R304Q	Plus	Mild	1–37*
C310F	Plus	Mild to moderate	1–4
G331S	Plus	Mild to moderate	1
T359M	Minus	Mild	1–4
IVS7+5 g>a	Minus	Severe	1

• The wide variation depends on the thromboplastin used in the clotting assays.

(EGF) domains, and the heavy chain, which contains the catalytic domain. The FVII gene and protein are structurally homologous to other serine proteases of coagulation, and particularly to FIX, FX, and protein C.

The *FVII* gene has been extensively investigated by DNA sequencing of all coding regions, exon/intron boundaries and the promoter region, by sequencing methods that enable very efficient detection of mutations in patients with FVII deficiency. Moreover, the expression of mutations detected in FVII-deficient patients have been investigated by recombinant FVII molecules obtained in cultured eukaryotic cells transfected with the expression vectors after site-directed mutagenesis of the human FVII cDNA.[26,31] The processing of altered FVII molecules has also been investigated by FVII chimeric FVII green fluorescent protein constructs.[32]

Mutations of the *FVII* gene[8] have been characterized in the vast majority of FVII-deficient patients. Mutations are very heterogeneous (Fig. 1), and missense changes are the most frequent lesions (70 to 80%). Splicing-site changes are also well represented.[33] Nonsense mutations and small deletions are rare, particularly in the homozygous condition.[32] A frequent allele[13] bearing a double change, the missense Ala294Val mutation and a single nucleotide deletion, 11125delC, causing an elongated protein with an additional 28 residues occurs in an appreciable number of subjects, particularly in central Europe (several mutations located in CpG sequences, known to be "hot spot" mutation sites, have been found in several patients coming from different countries). Virtually all the patients with moderate and severe disease are either homozygotes or double heterozygotes for mutations, the clotting and clinical phenotypes of double heterozygotes and homozygotes being virtually indistinguishable. The homozygous condition has a variable prevalence in different countries and has been associated with consanguinity caused by genetic isolates or ethnic habits.

Plasma levels of FVII in the general population are known to be affected by several polymorphisms in the *FVII* gene.[16] Although carriership of polymorphic alleles known to be associated with low FVII:C levels could contribute to the clinical phenotype, epidemiologic evidence is still scanty.

Genotyping of exons, splicing and promoter regions has found causative mutations in the vast majority of patients.[8] In a few patients (<10%), no mutation has been found after this type of screening. However, the extensive sequencing of the whole gene, which would corroborate these observations, has not been reported. This makes FVII deficiency caused by mutations in genes different from the *FVII* gene still an open question.

Phenotype-Genotype Correlation

Patients homozygous for the same mutation do not always belong to the same class of severity (Table 3), indicating phenotypic heterogeneity in the presence of identical *FVII* gene mutations.[29] These observations, as well as the report of several symptomatic heterozygotes, suggests a role for environmental factors and/or other genetic components[34] in the modulation of both the function of the clotting process and the penetrance of FVII deficiency.

PROBLEMS WITH LABORATORY DIAGNOSIS

The diagnostic efficiency of the FVII:C assay is highly dependent on the thromboplastin sensitivity (i.e., reagent ISI, or international sensitivity index). In general, recombinant thromboplastins structurally identical to the human TF are the most sensitive for the detecting the defect (give the longest clotting times), and should therefore be used to assay FVII levels when there is the suspicion of such deficiency. It is important to note, however, that the FVII:C assay measures both the zymogen (FVII) and the active enzyme (FVIIa).[34]

The quality of deficient plasmas is also important for accurate measurement of very low levels of FVII. In general, small amounts of residual FVII are present in these reactants, which makes it difficult to assay residual FV in patients with very severe defects (i.e., those in whom we expect levels consistently lower than 1%). Accordingly, levels of FVII around or below 1% are often questionable. More sensitive activity methods are those based on thrombin generation assays, especially when fluorogenic substrates for the detection of thrombin are used; these methods are made more sensitive by using highly diluted TF to trigger the reaction.[29]

Several FVIIa assays have recently become available using one of two assay methods. One is "clot-based" (the TF is of bovine origin) and the other utilizes ELISA

Table 4 Therapeutic Materials Available for the Treatment of Congenital FVII Deficiency

Therapeutic Materials	Potency (IU/mL)	Advantages	Disadvantages
FFP	1	Cheap. Easily available.	Limited effectiveness. Unsuitable for surgery. Circulatory overload.
PCCs (virus attenuated)	5–10	Suitable for surgery.	Concentration of the other vitamin K–dependent factors higher than FVII. Presence of ''activated'' factors. Risk of thrombosis.
pdFVII (virus attenuated)	20–40	Effective. Suitable for surgery.	Concentration of the other vitamin K–dependent factors higher than FVII. Risk of thrombosis. Inhibitors (?).
rFVIIa (shortly in the serum-free formulation)	>25,000	Very effective. No risk of viral transmission. No risk of thrombosis.	Inhibitors (?).

technology. The usefulness of these assays is questionable in FVII deficiency, whereas assessment of FVIIa by antigen assay would help to identify the dysfunctional variants. It is also important to mention that the clotting FVIIa assay should preferably be performed at specialized centers due to several technical challenges.

Monitoring of replacement treatment in FVII deficiency is currently best achieved using a FVII activity assay, which is, as outlined previously, sensitive to both the zymogen and FVIIa, although extremely sensitive to the latter.[35] The FVIIa assay is only effective for monitoring FVIIa. For routine monitoring at the bedside, the PT-INR may be sufficient,[35] because its normalization roughly correlates with the hemostatic levels. In fact, levels close to 50% of the reference plasma FVII content are associated with the lowest "normal" INR values (1.15 to 1.18).

PRENATAL DIAGNOSIS

Prenatal diagnosis in severe FVII deficiency has been successfully performed both by coagulation assays and by molecular genetic methods, although the former method is technically challenging. The presence of repeated regions, and of polymorphic variation of repeats within the *FVII* genes, requires careful design of PCR primers to detect gene rearrangements.[36,37]

TREATMENT

Patients with FVII deficiency can be offered several therapeutic options (Table 4), which may result in a very effective correction of the disease. Fresh-frozen plasma (FFP) is still used in developing countries, the most important drawback being the blood volume overload and a relatively high risk of transmitting blood-borne viruses. Plasma-derived FVII (pdFVII) concentrates are essentially prothrombin complex concentrates (PCCs) with a higher content of FVII but are effective for any therapeutic requirement. Together with the regular PCCs, pdFVII concentrates were reported to be associated with posttreatment thrombosis.[19]

Recombinant FVIIa is to be considered the optimal replacement therapy as FVIIa is the enzyme to be replaced; it can be used at a low dose (15 to 30 μg/kg body weight) compared with dosing in hemophilic patients with inhibitors.[38]

Prophylaxis has been a debated issue in FVII deficiency, especially because of the very short half-life of infused FVII in the blood, and especially in childhood where prophylaxis is of particular importance. Recent anecdotal observations suggest that secondary prophylaxis can be performed with FFP (very low concentration of FVII) infusions. Moreover, ex vivo studies showed that infused recombinant FVIIa disappears quickly from the circulation but persists extravascularly, bound to pericytes.[39] These observations would support the feasibility of prophylaxis in FVII deficiency, but larger trials are needed to assess the optimal schedule. At any rate, the main target for prophylaxis are the newborns who have had early and severe (CNS, GI) bleeds.

The same uncertainty holds for prophylaxis courses for the prevention of bleeding and after surgical interventions: a wide array of dosages and schedules has been employed. In some cases, surgery has been performed without any replacement therapy, namely in patients with a poor bleeding history,[40] but these patients were not homogenous in terms of genotype or clotting phenotype. For both bleeding prevention and treatment of spontaneous bleeds, pdFVII concentrates and recombinant FVIIa seem to be equally effective, although no formal comparative studies have been published. As for the

single, standard dose capable of inducing hemostatic levels, it ranges from 15 to 25 μg/kg body weight for recombinant FVIIa and from 10 to 30 IU/kg body weight for the pdFVII preparations (STER registry, unpublished data). Due to the short half-life, more than one daily administration should be given, if possible. Both preparations are suitable for home care.

With regard to the kinetics of infused FVII, scant data are available, which, nonetheless, confirms the very short half-life, especially in children.[41,42]

The complications of treatment, excluding transmission of blood-borne viruses (very rare today), are confined to the occurrence of thrombosis[20,21] (as a rare complication of replacement therapy or sometimes spontaneous), or the even rarer appearance of inhibitors to FVII (with a probable prevalence of ~1% of the treated patients).[43]

Treatment in Women: Pregnancy, Delivery, and Menorrhagia

As outlined before, menorrhagia is prevalent in women with a severe deficiency, especially after menarche. This is almost invariably associated with iron deficiency and iron-deficiency anemia. The occurrence of frequent menorrhagic menses may require treatment or even an ad hoc "prophylaxis" consisting of replacement therapy (as previously outlined) during the first days of the menses. Pregnancy itself does not require special precautions, whereas delivery should occur under the coverage of a short-term replacement therapy.[43]

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