Combined Factor V and Factor VIII Deficiency, Diagnosis, and Management

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9.1 Comparative Characteristics of Coagulation Factors V and VIII

Blood clotting factors V and VIII have a lot in common. They belong to proteins with high molecular weight. They do not have catalytic activity but are cofactors in the coagulation cascade. Factor (F) V is a cofactor of the prothrombinase complex and FVIII is a cofactor of the tenase complex. Factors V and VIII share similar domain structure (A_1-A_2-B-A_3-C_1-C_2) with high sequence identities between the A and C domains (~40% amino acid sequence homology) and undergo similar extensive post-translational modifications [1–4]. The functionally dispensable B domains of FV and FVIII share few sequence similarities, but both are heavily glycosylated [5]. Approximately, 80% of total blood FV circulates in plasma, whereas the remaining 20% is concentrated within platelet alpha granules. Plasma FV is produced in the liver while platelet FV is synthesized in the megakaryocytes or absorbed from plasma and then sequestered in the alpha granules [6]. Liver is the predominant site of FVIII synthesis by liver sinusoidal endothelial cells and hepatocytes. The main activators of FV and FVIII are thrombin and factor Xa. FV and FVIII have different half-lives. For FVIII it is 10–14 h, for factor V, on the average, 20 h, although according to various data, the time may vary between 6–36 h. These factors differ slightly in concentration and activity in plasma. The genes of blood clotting factors V and VIII are located on different chromosomes. This determines different inheritance paths for isolated FV or FVIII deficiencies. The FV gene is composed of 25 exons spanning a region of about 80 kb in the 1q24.2 chromosomal region [7]. The FVIII gene is located on the long arm of the X chromosome, occupies a region of the order of 186 bp, long and consists of 26 exons. The underlying cause of combined FV and FVIII deficiency (F5F8D) is in specific genetic mutations while

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Table 9.1 Comparative characteristics of coagulation factors V and VIII

Characteristics	FV	FVIII
Molecular weight	330 kDa	310 kDa
Biochemical function	cofactor	cofactor
Role in the coagulation cascade	prothrombinase complex	tenase complex
Structure	A_1–A_2–B–A_3–C_1–C_2	A_1–A_2–B–A_3–C_1–C_2
Synthesis	Hepatocytes, megakaryocytes	Hepatocytes, liver sinusoidal endothelial cells
Activators	FIIa, FXa	FIIa, FXa
Half-life	6–36 h	10–14 h
Location of the gene	1q24	Xq28
Plasma activity	70–120%	50–150%

isolated congenital deficiency of FV or FVIII is due to a defect in *F5* or *F8* genes, respectively. Comparative characteristics of FV and FVIII are presented in Table 9.1.

9.2 Combined Factor V and Factor VIII Deficiency

F5F8D (OMIM #227300 and #61362522) was first described in a pair in Swiss siblings by Oeri et al. in 1954 [8]. F5F8D is a rare bleeding disorder (RBD) that accounts for about 3% of all RBD and is the most common form of familial multiple coagulation factor deficiency (MCFD). F5F8D has been reported throughout the world. The prevalence in the general population is 1:1,000,000. Although the rate is higher (1:10,000) in populations where consanguineous marriages are acceptable. Most cases described are from Iran, Italy, Pakistan, Iraq, and India [9–14].

The disease has an autosomal recessive inheritance pathway, and men and women are equally affected. All homozygous individuals manifest the disease, this means complete penetrance. Heterozygous ones are usually asymptomatic [15].

F5F8D is characterized by simultaneous decrease of plasma FV and FVIII, usually between 5% and 30%. F5F8D is usually accompanied by mild to moderate bleeding tendency. Cases have been reported, however, with the activity of the factors to be as low as less than 5% with severe bleeding [10].

9.3 Etiology and Pathogenesis

Orei suggested that F5F8D is the result of a defect in a gene that encodes a common precursor of both blood clotting factors [8]. This hypothesis was refuted by Saito et al., who did not receive the effect of plasma transfusions from patients with hemophilia [16]. In what followed different genes encoding FVIII and FV were identified, in 1984 and 1992, respectively [17–19].

It became then obvious that the underlying cause of F5F8D was different from the one which causes isolated deficiency of FV or FVIII. The isolated FV or FVIII

deficiency results from defects in *F5* or *F8* genes, respectively. For many years, the mechanism by which a gene defect could cause the deficiency of these two different coagulation factors was unclear. In 1981, Soft and Levin suggested a common pathway of metabolism of both factors, disturbance of which leads to bleeding manifestations [20]. It was not until 1998 that Nichols et al. introduced null mutations in the *ERGIC53* (currently known as *lectin mannose binding 1-LMAN1*) gene, as the responsible genetic defect causing F5F8D [15, 21, 22]. LMAN1 protein was previously identified in the intermediate compartment between the endoplasmic reticulum (ER) and Golgi complex, but its function was not known [23]. Nichols et al. found out that LMAN1 was involved in transport of factors V and VIII from the ER to Golgi complex [22]. Mutations in *LMAN1* gene were identified in 70% of patients with F5F8D. This finding led to further genetic analysis. Finally, in 2003, Zhang et al. detected a second defect, referred to as multiple coagulation factor deficiency 2 (*MCFD2*) [24]. LMAN1 and MCFD2 form a receptor complex to transport specific secreted proteins, including FV and FVIII. In vitro studies suggest that LMAN1 acts as a cargo receptor for 2 lysosomal proteins, cathepsin C (CatC) and cathepsin Z (CatZ), and for α1-antitrypsin. FV and FVIII are synthesized on the rough ER and translocated into the ER lumen, where both proteins undergo N-linked glycosylation, proper folding, and quality control. Subsequently, proteins are packaged into coat protein complex-II (COPII) vesicles. These vesicles detach from the ER and connect to the endoplasmic reticulum—Golgi intermediate compartment (ERGIC). Retrieval (or retrograde transport) in coat protein I (COPI) vesicles returns many of the lost ER resident proteins back to the endoplasmic reticulum [25]. ERGIC is an organelle in eukaryotic cells which was first identified in 1988 using an antibody to the protein that has since been named ERGIC-53 [26]. This compartment mediates trafficking between the ER and Golgi complex, facilitating the sorting of cargo [27, 28].

The LMAN1–MCFD2 complex is the first known example of a specific ER-to-Colgi cargo receptor, discovered largely through the studies of F5F8D. The structure of the LMAN1-MCFD2 protein complex and **cargo transport by the LMAN1–MCFD2 complex** are shown in Fig. 9.1 [5, 25]. FV, FVIII, CatC, and CatZ bind the LMAN1–MCFD2 complex and are packaged into COPII vesicles. COPII vesicles bud from the ER membrane and fuse together forming the ERGIC. Anterograde transport of cargo protein to the Golgi occurs along microtubules. The LMAN1–MCFD2 complex is recycled back to the ER through COPI vesicles. Posttranslational modification of the cargo proteins occurs in the Golgi. CatC and CatZ are transported to the lysosomes. FV and FVIII are secreted outside of the cells.

LMAN1 is a homohexameric 53-kD type-1 transmembrane protein. MCFD2 is 16-kDa soluble protein-cofactor. They have similar half-lives. They form a stable, Ca^{2+}-dependent complex with 1:1 stoichiometry [29]. Separately, they do not provide transport FV and FVIII. The interaction of this complex with FV or FVIII is provided first of all by their B domains. Thus a qualitative or quantitative defect in LMAN1 or in MCDF2 leads to disorders in the secretion pathway

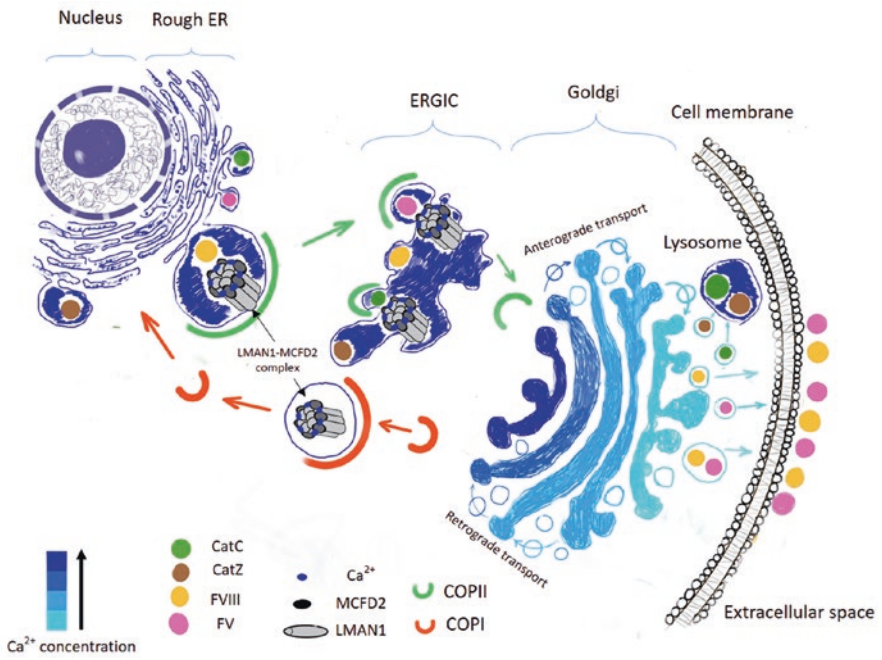

Fig. 9.1 Cargo transport by the LMAN1–MCFD2 complex

of FV and FVIII and impaired release into the circulation. A large number of different mutations have been described in *LMAN1* and *MCDF2* genes.

9.4 Clinical Manifestations

Patients with F5F8D are not usually manifested by severe bleeding events. Common spontaneous bleeding symptoms include epistaxis, gum bleeding, easy bruising, and menorrhagia. The most frequent clinical manifestations of F5F8D are bleeding from trauma, surgery, tooth extraction, and childbirth. Hemarthrosis and gastrointestinal bleeding (GI) may also occur in these patients but with much less frequency. Hematuria, muscle hematoma, and central nervous system (CNS) hemorrhages have been only described in few cases [9–11, 30, 31]. The spectrum and frequency of clinical manifestations in patients with F5F8D in different populations are presented in Table 9.2.

Women with congenital bleeding disorders, including F5F8D, are more susceptible to severe course of the disease due to the physiological causes of bleeding due to menstruation, ovulation, and childbirth. Gynecological and obstetric problems in women with F5F8D require special attention. Spiliopoulos et al. analyzed clinical manifestations in 86 women suffering from F5F8D [32]. The most common

Table 9.2 Clinical manifestations in patients with combined factor V and factor VIII deficiency

Clinical manifestations	Incidence (number of patients with symptom/total number of patients)				
	Seligsohn et al. (n = 14)	Peyvandi et al. (n = 27)	Shetty et al. (n = 9)	Mansouritorghabeh et al. (n = 19)	Viswabandya et al. (n = 37)
Epistaxis	57%	77.8%	–	69.2%	18.9%
Gingival	64.3%	–	44.4%	–	48.6%
Ecchymosis/easy bruising	28.6%	–	44.4%	–	29.7%
Menorrhagia	100%	58.3%	50%	33.3%	66.7%
Post-circumcision bleeding	–	66.7%	–	46.1%	–
Excessive post-dental extraction bleeding	92.3%	82.3%	33.3%	92.3%	56.7%
Excessive post-surgical bleeding	75%	75%	–	83.3%	62.2%
Excessive post-partum hemorrhage	100%	75%	–	50%	–
After lacerations	42.8%	–	–	–	–
After abortion	80%	–	–	–	–
After cutting	–	–	77.8%	57.9%	–
Hemarthrosis	–	26%	–	36.8%	13.5%
Gastrointestinal bleeding	21.4%	7.4%	–	10.5%	2.7%
Hematuria	14.3%	–	–	–	–
Muscle hematoma	–	7.4%	–	–	–
Intracranial hemorrhage	–	3.7%	–	–	–

bleeding symptom is menorrhagia (49%). Other common manifestations are epistaxis (34%), easy bruising (19%), postoperative bleeding (17%), post-traumatic bleeding (15%), bleeding after dental extraction (11%), recurrent ovulation bleeding (4%). In total, 19 pregnancies were reported in 18 women. There was no miscarriage reported. The mode of delivery was mentioned in nine pregnancies, including four cesarean sections required for obstetric reasons and five spontaneous vaginal deliveries. Postpartum hemorrhage was reported in six women (32%). In one case, a newborn presented with spontaneous cephalohaematoma [33].

In comparison with isolated FV or FVIII deficiencies, F5F8D is not associated with a higher bleeding tendency [15]. A possible reason for this mild clinical phenotype has been provided by Shao et al., who suggested that low FV levels in F5F8D may ameliorate the bleeding tendency in these patients [34]. This finding was based on an in vitro thrombin-generation assay which surprisingly showed that low FV

level concomitant with low free tissue factor pathway inhibitor α (TFPIα) in F5F8D was associated with optimal procoagulant activity and addition of FV to plasma only leads to anticoagulation. Here, the anticoagulant activity of FV is attributed to the interaction with TFPIα as its carrier in circulation which consequently results in lower TFPIα in FV deficiency. TFPIα is a natural anticoagulant that regulates not only TF/FVIIa complex but also FXa. It has been indicated that FV also acts as a cofactor for TFPIα in the inhibition of FXa, owing to defective anticoagulation in case of low FV level.

9.5 Diagnosis

F5F8D typically manifests as prolongation of both the prothrombin time (PT) and activated partial thromboplastin time (APTT) and approximately concordant reduction in FV and FVIII activities. APTT-based activity assays and antigen assays reveal levels of between 5% and 20% for both FV and FVIII and rarely less than 5%. Factor antigen assays are not strictly necessary for diagnosis. PT and APTT are corrected by mixing studies using normal plasma. Mixing study helps rule out presence of inhibitors [2, 35].

Bleeding phenotype of F5F8D is relatively similar to the clinical picture of isolated FV or FVIII deficiency, therefore some cases may be misdiagnosed as mild hemophilia A or FV deficiency and one of the factor defects may be overlooked [5]. Such errors revealed that there may be a bias in the exact number of patients with F5F8D in some countries specially where there are poor laboratory and genetic assays.

The concomitant presence of FV deficiency with either hemophilia A or von Willebrand disease (VWD) is the main differential diagnosis of F5F8D. These cases are extremely rare, but are described in the literature [36–39].

Based on VWD-specific tests, F5F8D and coinheritance of FV deficiency and VWD can be distinguished. Differentiation of F5F8D from coinheritance of FV deficiency and hemophilia A is mainly based on family history. In F5F8D, there may be no evidence of a positive family history; however, if present, the inheritance pattern is autosomal recessive [39].

Finally, molecular analysis of *MCFD2* and *LMAN1* genes can be used for confirmation of F5F8D, although it is not routinely performed [1]. Molecular analysis should start with the *LMAN1* gene, because 70% of mutations in patients with F5F8D are identified in this gene except in the Indian population [2].

9.6 Molecular Basis and Diagnosis

The gene encoding for LMAN1 with about 29 kb length and 13 exons (Fig. 9.2a) is located on the long arm of chromosome 18 (18q21.32). MCFD2 is encoded by a 19 kb gene on the short arm of chromosome 2 (2p21), containing 4 exons (Fig. 9.3a).

According to Human Gene Mutation Database (HGMD) 38 mutations in *LMAN1* and 20 mutations in *MCFD2* genes have been described so far (Tables 9.3 and 9.4)

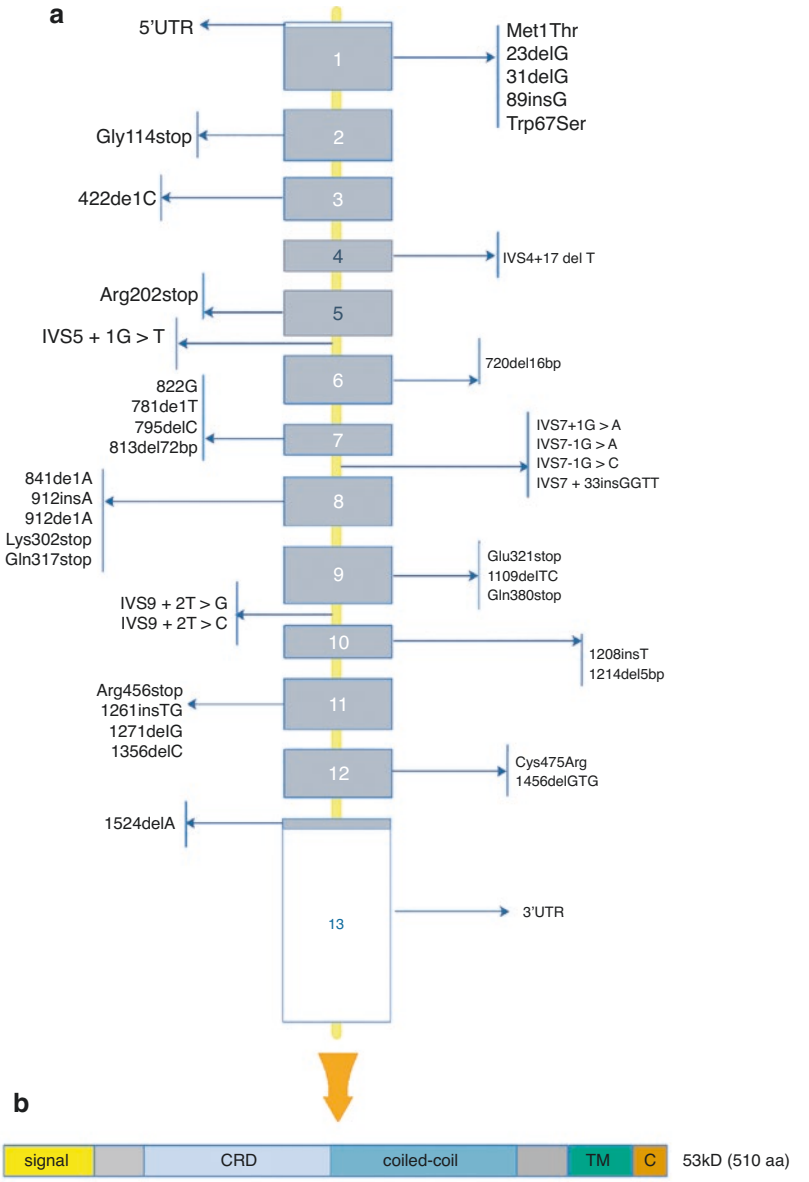

Fig. 9.2 (**a**) *LMAN1* gene and F5F8D causing mutations. *LMAN1* gene comprises 13 exons. Exons are shown in gray rectangles and are drawn to scale, and introns are indicated by yellow lines and are not to scale. White rectangles indicate 3′ UTR and 5′ UTR of gene. (**b**) Domains of LMAN1 protein. Signal peptide of LMAN1 contributes in translocation of LMAN1 into ER. The protein consists of 3 domains: luminal, transmembrane (TM), and short cytoplasmic (**c**). The luminal domain divides into two sub-domains, an N-terminal CRD and a membrane-proximal α-helical coiled domain, known as stalk domain. *LMAN1* lectin mannose binding 1, *UTR* untranslated region, *ER* endoplasmic reticulum, *CRD* carbohydrate recognition domain

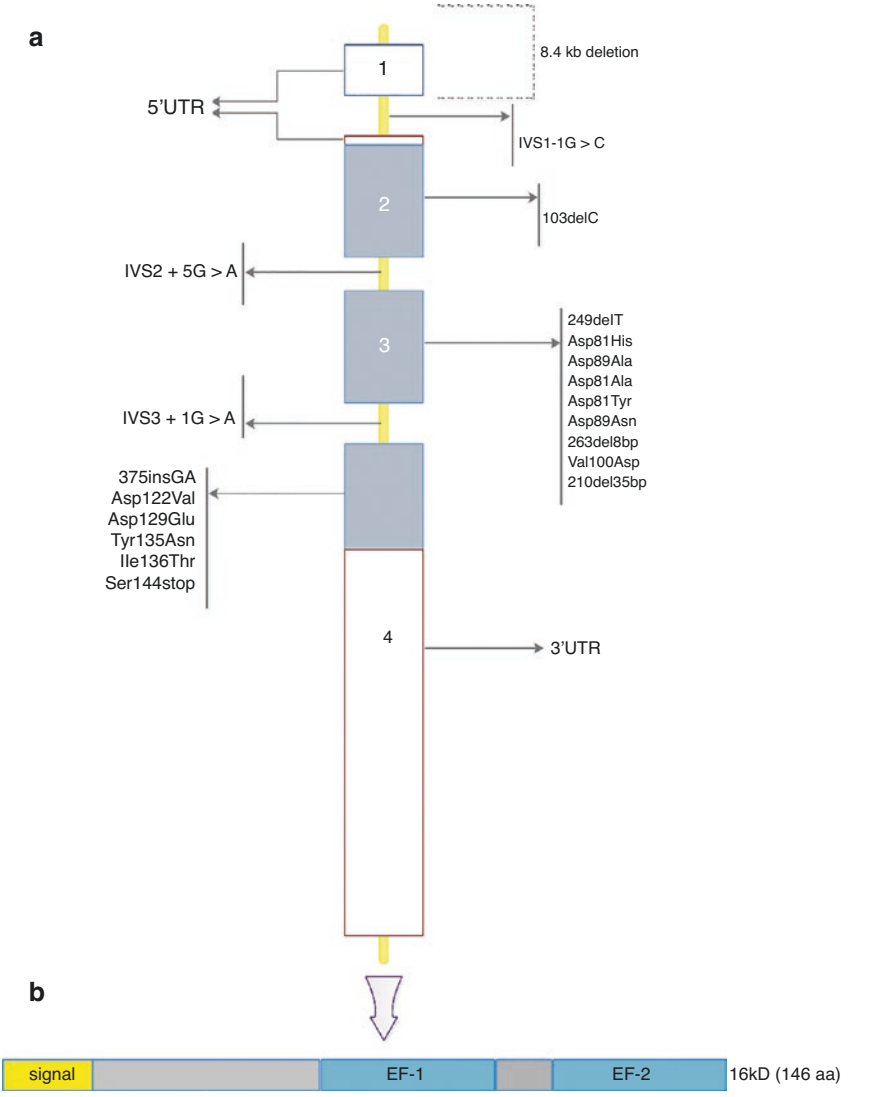

Fig. 9.3 (**a**) *MCFD2* gene and F5F8D causing mutations. Exons are indicated by gray rectangles and are drawn to scale. Introns are indicated by yellow lines and are not to scale. White rectangles indicate 3′ UTR and 5′ UTR of gene. (**b**) Domains of MCFD2 protein. MCFD2 is a small protein with 166 amino acids and three domains including a signal sequence for direction of MCFD2 into ER and two EF-hand motifs which probably can bind to Ca^{2+} ions. *MCFD2* multiple coagulation factor deficiency 2, *UTR* untranslated region, *ER* endoplasmic reticulum EF-hand motif: calcium-binding motif composed of two helixes (E and F) joined by a loop (helix-loop-helix)

(Figs. 9.2a and 9.3a) [1, 40, 41–45]. The most common mutations in *LMAN1* gene are insertion/deletion, nonsense, and splice site mutations, which lead to complete destruction of protein function (Table 9.3). The majority of mutations involving *MCFD2* gene is insertion/deletion, missense, and splice site (Table 9.4).

Table 9.3 *LMAN1* gene mutations in patients with combined factor V and factor VIII deficiency (F5F8D)

Type of mutation	Nomenclature	Gene location
Initiation codon	Met1Thr	Exon 1
Frameshift	23delG	Exon 1
Frameshift	31delG	Exon 1
Frameshift	89insG	Exon 1
Missense	Trp67Ser	Exon 1
Non-sense	Gly114stop	Exon 2
Frameshift	422delC	Exon 3
Frameshift	IVS4 + 17 del T	Exon 4
Non-sense	Arg202stop	Exon 5
Splicing	IVS5 + 1G > T	Intron 5
Frameshift	720del16bp	Exon 6
Frameshift	781delT	Exon 7
Frameshift	795delC	Exon 7
Frameshift	813del72bp	Exon 7
Splicing	822G > A	Exon 7
Splicing	IVS7 + 1G > A	Intron 7
Splicing	IVS7-1G > A	Intron 7
Splicing	IVS 7–1G > C	Intron 7
Splicing	IVS7 + 33insGGTT	Intron 7
Non-sense	Lys302stop	Exon 8
Non-sense	Gln317stop	Exon 8
Frameshift	841delA	Exon 8
Frameshift	912insA	Exon 8
Frameshift	912delA	Exon 8
Non-sense	Glu321stop	Exon 9
Frameshift	1109delTC	Exon 9
Non-sense	Gln380stop	Exon 9
Splicing	IVS9 + 2 T > G	Intron 9
Splicing	IVS9 + 2 T > C	Intron 9
Frameshift	1208insT	Exon 10
Frameshift	1214del5bp	Exon 10
Frameshift	1261insTG	Exon 11
Non-sense	Arg456stop	Exon 11
Splicing	1271delG	Exon 11
Frameshift	1356delC	Exon 11
Missense	Cys475Arg	Exon 12
Deletion	1456delGTG	Exon 12
Frameshift	1524delA	Exon 13

LMAN1 lectin mannose binding 1

The most common mutation in the MCFD2 gene is IVS2 + 5G > A, which is identified in patients F5F8D from different geographical regions (India, Italy, USA, Serbia, and Germany). Some mutations such as 89insG (frameshift), IVS9 + 2 T > C (splicing), and M1T (c.2 T > C) (abolish initiation codon), which are exclusively seen in Middle Eastern Jewish, Tunisian Jewish and Italian origin, respectively, are

Table 9.4 *MCFD2* gene mutations in patients with combined factor V and factor VIII deficiency (F5F8D)

Type	Nomenclature	Location
Large deletion	8.4 kb deletion	Promoter and Exon 1
Splicing	IVS1–1G > C	Intron 1
Frameshift	103delC	Exon 2
Splicing	IVS2 + 5G > A	Intron 2
Frameshift	249delT	Exon 3
Frameshift	263del8bp	Exon 3
Frameshift	210del35bp	Exon 3
Missense	Asp81Tyr	Exon 3
Missense	Asp81His	Exon 3
Missense	Asp81Ala	Exon 3
Missense	Asp89Asn	Exon 3
Missense	Asp89Ala	Exon 3
Missense	Val100Asp	Exon 3
Splicing	IVS3 + 1G > A	Intron 3
Frameshift	375insGA	Exon 4
Missense	Asp122Val	Exon 4
Missense	Asp129Glu	Exon 4
Missense	Tyr135Asn	Exon 4
Missense	Ile136Thr	Exon 4
Nonsense	Ser144stop	Exon 4

MCFD2 multiple coagulation factor deficiency 2

suggestive of founder effect [1, 39]. Missense mutations in patients with F5F8D are significantly more often found in the *LMAN1* gene than *MCFD2* [46, 47].

The case of a compound patient with F5F8D is known. Nyfeler et al. studied a patient who was found to be a compound heterozygote for 2 novel mutations in MCFD2: a large deletion of 8.4 kb eliminating the 5′UTR of the gene and a nonsense mutation resulting in the deletion of only 3 amino acids (DeltaSLQ) from the C-terminus of MCFD2 [48].

9.7 Genotype-Phenotype Correlation

The study of the relationship between genotype and plasma activity of factors and clinical manifestations is an important aspect. This knowledge helps to predict the prognosis of the disease, the levels of activity of the coagulation factor that determine protection from bleeding episodes, in order to determine appropriate prevention and management strategies.

According to a study by Zhang et al. it was suggested that mutations involving *MCFD2* are associated with lower levels of FV and FVIII, compared with *LMAN1* mutations (mean values of 9.6% vs. 13.7% for FV and 10.0% vs. 16.0% for FVIII). This finding supports a genotype-phenotype relationship in patients with F5F8D [47]. But FV and FVIII plasma activity cannot be used to predict a defective gene.

On the other hand, there is a correlation between the activity of FV and FVIII, regardless of which gene the mutation is in. This confirms damage to the common secretion pathway of molecules FV and FVIII. No significant differences were observed between male and female patients for either FV or FVIII levels. Another interesting fact is lack of any significant difference in FV and FVIII levels in patients with blood group O compared with non-O blood groups.

As mentioned earlier circulating FV exists in both plasma and platelets. Zhang et al. showed that platelet FV levels are reduced to the same extent as FV levels in plasma, for both the *LMAN1* group and the *MCFD2* group [47].

According to The European Network of Rare Bleeding Disorders (EN-RBD) data there is a strong association between coagulation factor activity level and clinical bleeding severity for combined FV and FVIII, as well as for fibrinogen, FVIII and FXIII deficiencies. The study group consisted of 18 F5F8D patients. The mean value of factors activity for asymptomatic patients is 44%, for patients with bleeding that occurred after trauma or drug ingestion (antiplatelet or anticoagulant therapy) is 34%, for patients with spontaneous minor bleeding is 24% and for patients with spontaneous major bleeding is 15% [49].

9.8 Management

The bleeding tendency in F5F8D is not more severe than isolated FV or FVIII defect. Clinical management of F5F8D does not rely on molecular diagnosis [1]. Clinical presentations are usually mild, thus on-demand therapy is usually preferred for management of bleeding in surgical procedures or in time of delivery and in cases of traumatic bleeding events. In F5F8D, there is no need for prophylaxis except for specific cases with severe recurrent bleeding events [50].

The treatment of bleeding episodes is dependent on the nature of the bleed and the affected individual's FV and FVIII levels. Mild bleeding or moderate episode usually respond to anti-fibrinolytic agents, like aminocapronic acid 15–20 mg/kg intravenously or 1 g per os 3–4 times daily. Severe spontaneous or post-traumatic/postoperative bleeding, as well as preparation for major surgical interventions, requires hemostatic replacement therapy. A large number of products that replace FVIII are available. In contrast, there are no FV concentrates accessible. The extreme lability of human FV in plasma, used in preparing FV-deficiency plasma by aging, is the main reason why isolated procedures yielding an undegraded product have not been reported previously. The lability can presumably be explained by the high susceptibility of FV to proteolysis during blood collection as well as during the initial purification steps [51–53].

In 2018, Bulato et al. published data on the development of a novel plasma-derived FV concentrate. This concentrate was tested for the in vitro correction of severe FV deficiency in patients with FV deficiency and both, standard tests and all thrombin generation parameters normalized [54]. FV concentrates, however, are currently still unavailable as a therapeutic option. Available therapy includes virus-inactivated fresh frozen plasma (FFP) which contains FV and FVIII. The

therapeutic goal is to achieve 20–25% FV activity and at least 50% FVIII. FFP infusion is usually sufficient to restore FV activity to hemostatic level, but may not be enough for FVIII activity. Additional transfusion is required of plasma-derived or recombinant FVIII concentrate. The initial dose of FFP usually is 15–25 mg/kg and FVIII concentrate is 20–40 IU/kg (depending on the intensity of the hemorrhagic syndrome and basic plasma activity FV and FVIII) [2, 15, 35, 55]. Repeated administration with a reduction in dosage is recommended after 12 h. Analysis of APTT, PT, FV, and FVIII activities is necessary to assess the effectiveness of therapy and prescribe the next transfusion regimen. After major surgical interventions, it is recommended to maintain the activity of FV at least 20–25% and FVIII at least 50% within 72 h. Replacement therapy should be continued until the wound heals. Screening coagulation tests (APTT, PT) are routine and are performed in laboratories everywhere. Not all laboratories are equipped to assess the activity of blood clotting factors. Hence, relying only on screening tests for the laboratory control of hemostatic replacement therapy is a challenge. In the described clinical observation by Yakovleva et al., the analysis of hemostasis parameters during the perioperative period in F5F8D patient allowed to conclude that full compensation of screening parameters is not required, and the maintenance of APTT within 50 s and the quick prothrombin within 50% is sufficient to prevent hemorrhagic complications in the perioperative period [56]. It is necessary to remember about possible complications of this therapy, such as volume overload, allergic reaction, and the production of alloantibodies when using FFP and the development of inhibitors when using FVIII concentrates. Such cases are rare, but they are described in the literature [2, 35, 57, 58].

There is experience with the use of desmopressin (DDAVP) in F5F8D patients. It promotes a short-term (60–120 min) doubling of FVIII activity. DDAVP can be used in F5F8D patients in whom the activity of FVIII is slightly reduced. In this case, it can be an alternative to FVIII concentrates. The dosage DDAVP is 260 μg intranasal or 0.3 μg/kg subcutaneous. It is necessary to remember about the depletion of the effect with prolonged use [59–64].

Recombinant activated coagulation factor VIIa (rFVIIa) has been introduced to improve hemostasis in hemophilia A/B patients with inhibitors, patients with Glanzmann's thrombasthenia, but many reports describe an off-label use in other bleeding conditions. The literature describes cases of successful use of rFVII in patients with F5F8D. In one case, rFVII was used due to uncontrolled hemorrhagic syndrome, despite of the ongoing therapy of FFP and FVIII concentrate [65]. In another case, hemostatic therapy with rFVII was carried out due to the development of anaphylactic reaction to the transfusion of FFP [66].

Also, an alternative option is the use of platelet transfusions, the alpha granules of which contain FV [2]. Several cases of platelet concentrate use have been described in patients with F5F8D and FV deficiency, including with the presence of FV inhibitor [58, 67, 68].

There is no information in the literature about the use of cryoprecipitate in F5F8D patients. Most authors believe that the cryoprecipitate does not contain FV. However, Yakovleva et al. had a positive experience of using cryoprecipitate to

control bleeding syndrome in F5F8D patients. Experimental research evaluated the activity of clotting factors in cryoprecipitate samples from different donors immediately after defrosting and after 1 h showed sufficient FV activity [69].

Nonsteroidal anti-inflammatory drugs, antiplatelet drugs, psychotropic drugs and a number of other medicines can aggravate the hypocoagulation condition in patients. Their appointment should be strictly justified and, if necessary, combined with hemostatic therapy.

9.9 Family Planning, Pregnancy, Childbirth

When planning a family and genetic counseling, it is necessary to take into account that the disease is autosomal recessive and inheritance does not depend on gender. If one of the parents suffers from F5F8D (i.e. is homozygous), then the risk of having a child with a heterozygous carrier is 50%. The birth of a child with F5F8D has to be expected if both parents are F5F8D patients or with a risk of 25% if both parents are heterozygous carriers.

Throughout pregnancy, the level of FV does not change, while the level of FVIII increases [64, 70]. Thus, the diagnosis of F5F8D is difficult during pregnancy. In this case, a family history is important if F5F8D was established in relatives. Factor assays should be performed in the third trimester and used to develop a hemostatic plan for delivery. Women with F5F8D have to be considered potentially at risk for developing postpartum hemorrhage [32, 65]. F5F8D is not a contraindication to normal vaginal delivery. The method of delivery is determined by obstetric indications [71]. For delivery, it is necessary to reach a level of FV more than 20% and FVIII more than 50%. Initial dosage FFP is 15–25 ml/kg once in established labor or before cesarean section, then 10 ml/kg once every 12 h for at least 3 days with supplementary with FVIII concentrate [2, 15, 35, 72].

Due to the mild bleeding phenotype of F5F8D, prenatal diagnosis is not usually recommended. However, if wish to be performed, both parents should be carriers of the disorder and it may be known by already having an affected child. Chorionic villus sampling (CVS) has to be performed at 10–12 gestational weeks. Then fetal DNA is evaluated for the specific mutations, which were found in parents and affected child [2]. Currently, Non-Invasive Prenatal Testing (NIPT) is being introduced into clinical practice, based on the analysis of extracellular fetal DNA circulating in the blood of a pregnant woman after 10 weeks of pregnancy. In the future NIPT may become a common tool for prenatal diagnosis of monogenic diseases [73, 74].

F5F8D can be diagnosed in the neonatal period using cord or peripheral blood. According to Andrew et al. FV and FVIII activities in healthy term neonates are 36–108 IU/ml and 61–139 IU/ml, respectively, with FV activity increasing further within 1 week [75]. Also, a recent study by Mitsiakos et al. showed that in healthy newborns, FV and FVIII activity positively correlates with gestational age and birth weight [76]. F5F8D very rarely presents with bleeding in neonates. Neonatal intracranial hemorrhage has not been described in this condition. There are no reports of prophylaxis in F5F8D newborns [15].

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