Combined Factor V and Factor VIII Deficiency (F5F8D): Comprehensive Disease Characterization

MONDO: MONDO:0018175 · **OMIM:** 227300 · **Causal genes:** *LMAN1* (ERGIC-53) and *MCFD2* · **Category:** Mendelian, autosomal recessive

Summary

Combined Factor V and Factor VIII Deficiency (F5F8D) is not a disease of the clotting-factor genes it is named after. It is caused by biallelic loss-of-function mutations in either ***LMAN1*** (lectin, mannose-binding 1; also called ERGIC-53; HGNC:6631; chromosome 18q21) or ***MCFD2*** (multiple coagulation factor deficiency 2; HGNC:18451; chromosome 2p21). These two proteins assemble into a calcium-dependent cargo-receptor complex that ferries coagulation factors V (FV) and VIII (FVIII) from the endoplasmic reticulum (ER) to the Golgi through the early secretory pathway. When the receptor fails, FV and FVIII cannot be efficiently secreted, and their plasma activities fall **concordantly to roughly 5–20% of normal**. This is the crucial conceptual point for a knowledge base: the *F5* and *F8* structural genes are entirely normal in F5F8D; the lesion is in the intracellular transport machinery shared by their protein products, which is why a *single* genetic lesion lowers *two* coagulation factors simultaneously.

Clinically, F5F8D is a **mild-to-moderate, lifelong, non-progressive bleeding disorder** dominated by mucocutaneous bleeding (epistaxis, gum bleeding, easy bruising, menorrhagia) and excessive bleeding provoked by surgery, circumcision, dental extraction, trauma, and childbirth. Life-threatening central-nervous-system or gastrointestinal bleeds and hemarthroses are uncommon, distinguishing F5F8D from the more severe rare bleeding disorders (FXIII, FX, FVII). Many patients are minimally symptomatic and are discovered incidentally when routine preoperative screening reveals simultaneously prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). Prognosis and life expectancy are excellent.

Diagnosis rests on the combination of concurrently prolonged PT and aPTT (both correcting on 1:1 mixing), concordantly reduced FV:C and FVIII:C with normal von Willebrand factor and normal other clotting factors, confirmed by targeted *LMAN1*/*MCFD2* sequencing. Treatment requires replacing **both** factors — fresh frozen plasma (the only practical FV source, since no FV concentrate exists) plus FVIII raised by desmopressin or FVIII concentrate — supplemented by antifibrinolytics for minor mucosal bleeding and planned peripartum cover during pregnancy. The disorder is enriched in consanguineous Middle-Eastern and South-Asian populations, where founder alleles are documented, and has an estimated general-population prevalence of ~1 in 1,000,000.

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1. Disease Information

F5F8D is a rare autosomal-recessive coagulopathy characterized by the simultaneous, coordinate reduction of two clotting factors — FV and FVIII — that are otherwise genetically and structurally normal. The defect lies in a shared intracellular transport receptor, making F5F8D a paradigm of a "secretory-pathway cargo-receptor disease" rather than a classic single-factor deficiency.

Key identifiers:

Resource	Identifier
MONDO	MONDO:0018175
OMIM	227300 (F5F8D1, *LMAN1*); 613625 (F5F8D2, *MCFD2*)
Orphanet	ORPHA:35909
ICD-10	D68.2 (hereditary deficiency of other clotting factors)
ICD-11	3B12 (hereditary deficiency of other coagulation factors)
MeSH	Factor V deficiency / Factor VIII deficiency (combined)
Genes (HGNC)	*LMAN1* (HGNC:6631; OMIM 601567); *MCFD2* (HGNC:18451; OMIM 607788)

Synonyms: F5F8D; FV and FVIII combined deficiency; combined deficiency of factor V and factor VIII; familial multiple coagulation factor deficiency; DF5F8.

Source of information: The knowledge base entry is derived from **aggregated disease-level resources** (OMIM, Orphanet, review literature) combined with **individual-patient case reports and small case series** (e.g., Saudi, Turkish, Tunisian, Iranian, Pakistani, Indian cohorts). There is no large EHR-derived dataset; because of rarity, the evidence base is dominated by case reports, founder-population series, and molecular/structural studies.

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2. Etiology

Primary cause — genetic. F5F8D is caused by **biallelic (homozygous or compound heterozygous) loss-of-function mutations** in *LMAN1* or *MCFD2*. Positional cloning first mapped the locus to chromosome 18q21 and identified ERGIC-53/*LMAN1* as the causal gene, with two mutations "accounting for all affected individuals in nine families studied" (PMID: 9546392). A second gene, *MCFD2* on 2p21, accounts for *LMAN1*-negative families.

- **~70%** of families carry *LMAN1* mutations; **~15–30%** carry *MCFD2* mutations.
- Essentially all *LMAN1* alleles are **null**: in a survey of 35 families, 13 distinct mutations comprised "3 splice site mutations, 6 insertions and deletions resulting in translational frameshifts, 3 nonsense codons, and elimination of the translation initiation codon" (PMID: 10090934).
- **Inheritance is autosomal recessive**; heterozygous carriers are asymptomatic.

Genetic risk factors: The only established risk factor is inheritance of two pathogenic *LMAN1* or *MCFD2* alleles. **Consanguinity** sharply increases risk in endogamous populations. **Founder alleles** (see §9) elevate carrier frequency regionally.

Environmental risk factors: None established as causal. Because the phenotype is provoked, environmental/situational *triggers of bleeding* (surgery, trauma, dental procedures, childbirth, antiplatelet/anticoagulant drugs) convert a latent defect into a clinical event, but they do not cause the disease.

Protective factors: No genetic or environmental protective modifiers are established. Mechanistically, **residual LMAN1 expression** acts in a dose-dependent protective manner — hypomorphic alleles retaining partial function predict milder phenotypes (mouse data, §6).

Gene–environment interactions: Not formally characterized. The practical interaction is between the genetic secretion defect and hemostatic challenges (surgery, parturition), which determine when bleeding manifests.

3. Phenotypes

F5F8D produces a **mild-to-moderate bleeding diathesis**. Phenotypes are both **laboratory abnormalities** (the defining concordant FV/FVIII reduction with dual PT/aPTT prolongation) and **clinical bleeding signs/symptoms**.

Phenotype	Type	HPO term	Frequency / characteristics
Prolonged PT and aPTT	Lab abnormality	HP:0008151 (prolonged PT), HP:0003645 (prolonged aPTT)	Universal; both correct on mixing
Reduced factor V activity	Lab abnormality	HP:0003225 (reduced factor V activity)	~5–20% in most patients
Reduced factor VIII activity	Lab abnormality	HP:0003125 (reduced factor VIII activity)	~5–20%, concordant with FV
Epistaxis	Sign	HP:0000421	Common
Gingival/oral bleeding	Sign	HP:0000225	Common
Easy bruising / ecchymoses	Sign	HP:0000978 (bruising susceptibility)	Common
Menorrhagia	Sign	HP:0000132	Common in affected women
Prolonged bleeding after surgery/ procedure	Sign	HP:0004846 (post-surgical bleeding)	Characteristic; circumcision, dental extraction
Postpartum hemorrhage	Sign	HP:0011891	Risk during delivery
Prolonged bleeding after trauma	Sign	HP:0005261 (abnormal bleeding)	Characteristic

Onset: Congenital (defect present from birth), but recognition is frequently delayed to childhood or adulthood because symptoms are mild; many cases surface at the first hemostatic challenge or incidentally. **Severity:** mild-to-moderate, variable. **Progression:** stable, non-progressive, lifelong. **Frequency among affected individuals:** mucocutaneous bleeding predominates; hemarthrosis and life-threatening CNS/GI bleeds are uncommon.

Characteristic factor levels and severity are summarized in the literature: F5F8D "is characterized by concomitantly low levels (usually between 5% and 20%) of both FV and FVIII, and is associated with a mild to moderate bleeding tendency" (PMID: 19141160). A pediatric case documented gum bleeding leading to diagnosis (PMID: 38912355), and multiple reports describe incidental detection in asymptomatic individuals on preoperative screening (PMID: 38659545; PMID: 41040772).

Quality-of-life impact: Generally modest given the mild phenotype, but women bear a disproportionate burden through menorrhagia and reproductive-tract bleeding, which can affect quality of life and employment (rare-bleeding-disorder cohort, PMID: 39958127). Bleeding severity can be quantified with standardized tools (ISTH-BAT; EN-RBD bleeding score), with bleeding score inversely correlated with factor activity (PMID: 27855295).

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4. Genetic / Molecular Information

Causal genes:

Gene	Locus	Protein	OMIM (disease)	Share of families
LMAN1 (ERGIC-53)	18q21.3-q22	Hexameric type-1 transmembrane mannose-specific lectin	227300	~70%
MCFD2	2p21	Soluble EF-hand protein	613625	~15–30%

Pathogenic variants: - ***LMAN1*** alleles are **overwhelmingly null** — splice-site, frameshift insertions/deletions, nonsense, and start-codon loss (PMID: 10090934). Reported examples include a nonsense C→T transition in exon 9 and a frameshift deletion in a Turkish family (PMID: 20460353); a homozygous c.604C>T in a Saudi child (PMID: 38659545); and a homozygous c.822G>A in Saudi siblings (PMID: 36116005). - ***MCFD2*** harbors both null and **missense** variants; most reported missense substitutions cluster at the LMAN1-binding

interface (see §6), which explains their pathogenicity (PMID: 20142513). - **Structural variants matter:** a heterozygous large deletion in *MCFD2* can mimic a homozygous substitution and requires dosage analysis to resolve (PMID: 38764219).

Variant classification: Reported disease alleles are predominantly **pathogenic/likely pathogenic** under ACMG/AMP criteria (null variants = PVS1-supported; recurrent founder alleles with segregation).

Allele frequency: Pathogenic alleles are extremely rare in gnomAD generally, but founder alleles reach appreciable carrier frequencies regionally (e.g., ~0.011 for the Djerba Tunisian *LMAN1* intron-9 allele; §9).

Origin: Germline, biallelic. No somatic contribution.

Functional consequence: Loss of function of the cargo receptor → failure of efficient ER-to-Golgi export of FV and FVIII. The defect is in transport, not synthesis.

Modifier genes: The two causal genes modify each other's phenotype — *MCFD2* mutations generally yield lower FV/FVIII than *LMAN1* mutations: "Though clinically indistinguishable, MCFD2 mutations generally exhibit lower levels of FV and FVIII than LMAN1 mutations" (PMID: 19183188). Residual LMAN1 dose is itself a quantitative modifier (§6). No external modifier loci are established.

Epigenetic information / chromosomal abnormalities: None described as relevant to F5F8D.

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5. Environmental Information

F5F8D is a **purely monogenic disorder with no environmental, lifestyle, or infectious etiology.** No toxins, radiation, occupational exposures, dietary factors, or pathogens cause or trigger the disease. Environmental factors only matter as **bleeding precipitants** (surgery, trauma, parturition) and through drugs that impair hemostasis (antiplatelets, anticoagulants, NSAIDs), which should be used cautiously. **Infectious agents:** not applicable.

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6. Mechanism / Pathophysiology

Causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function mutation in *LMAN1 or MCFD2* → results in** absence or dysfunction of the corresponding protein.
2. Loss of functional LMAN1 and/or MCFD2 → **leads to** failure to assemble a functional **LMAN1–MCFD2 cargo-receptor complex** in the ER.
3. Absent cargo receptor → **results in** failure to capture newly synthesized FV and FVIII in the ER and package them into **COPII-coated vesicles** for ER-to-Golgi transport.
4. Impaired ER exit → **leads to** reduced secretion of FV and FVIII into plasma (and reduced platelet FV).
5. Reduced circulating FV and FVIII (~5–20% of normal) → **results in** impaired generation of both the **tenase** (FVIIIa-dependent) and **prothrombinase** (FVa-dependent) complexes.
6. Impaired thrombin generation on both the intrinsic/common-pathway axes → **leads to** prolonged aPTT (FVIII) *and* prolonged PT (FV), i.e., the signature **dual coagulation-screen abnormality**.
7. Deficient hemostasis → **manifests as** mild-to-moderate mucocutaneous and procedure/trauma-provoked bleeding.

(Branch: whether the lesion is in LMAN1 or MCFD2 converges on the same complex failure; MCFD2 defects tend to lower factor levels more. Inferred step: the exact quantitative link between residual LMAN1 and human phenotype severity is extrapolated from mouse dose-response data.)

Molecular and cellular detail

The cargo-receptor complex. LMAN1 (ERGIC-53) is a **hexameric type-1 transmembrane mannose-specific lectin** that cycles between the ER and the ER-Golgi intermediate compartment (ERGIC). Its luminal **carbohydrate-recognition domain (CRD)** contains *separable* binding sites: one for its partner MCFD2 (on the N-terminal β-sheet) and one for mannose/cargo. "The CRD of LMAN1 contains distinct, separable binding sites for both its partner protein (MCFD2) and the cargo proteins (FV/FVIII)," and LMAN1 oligomerization is necessary for receptor function (PMID: 20817851). Structural work pinpointed **His178 and Gly251/252** as critical cargo-binding residues (PMID: 23709226).

MCFD2 is the FV/FVIII-specific adaptor. MCFD2 is a soluble EF-hand (calcium-binding) protein. Crystallography shows a **1:1 ERGIC-53-CRD : MCFD2 complex**, and "the interaction is independent of sugar-binding of ERGIC-53 and involves most of the missense mutation sites of MCFD2 so far reported in F5F8D" (PMID: 20142513). Critically, MCFD2 is **not** required for transport of the receptor's other cargoes: "ERGIC-53 can bind cargo glycoproteins in an MCFD2-independent fashion and … MCFD2 is a recruitment factor for blood coagulation factors V and VIII" (PMID: 17010120). This is why F5F8D patients lack lysosomal or other cargo phenotypes — only the FV/FVIII arm is affected. MCFD2 binds a **10-amino-acid segment of the FVIII B-domain** (PMID: 32170195).

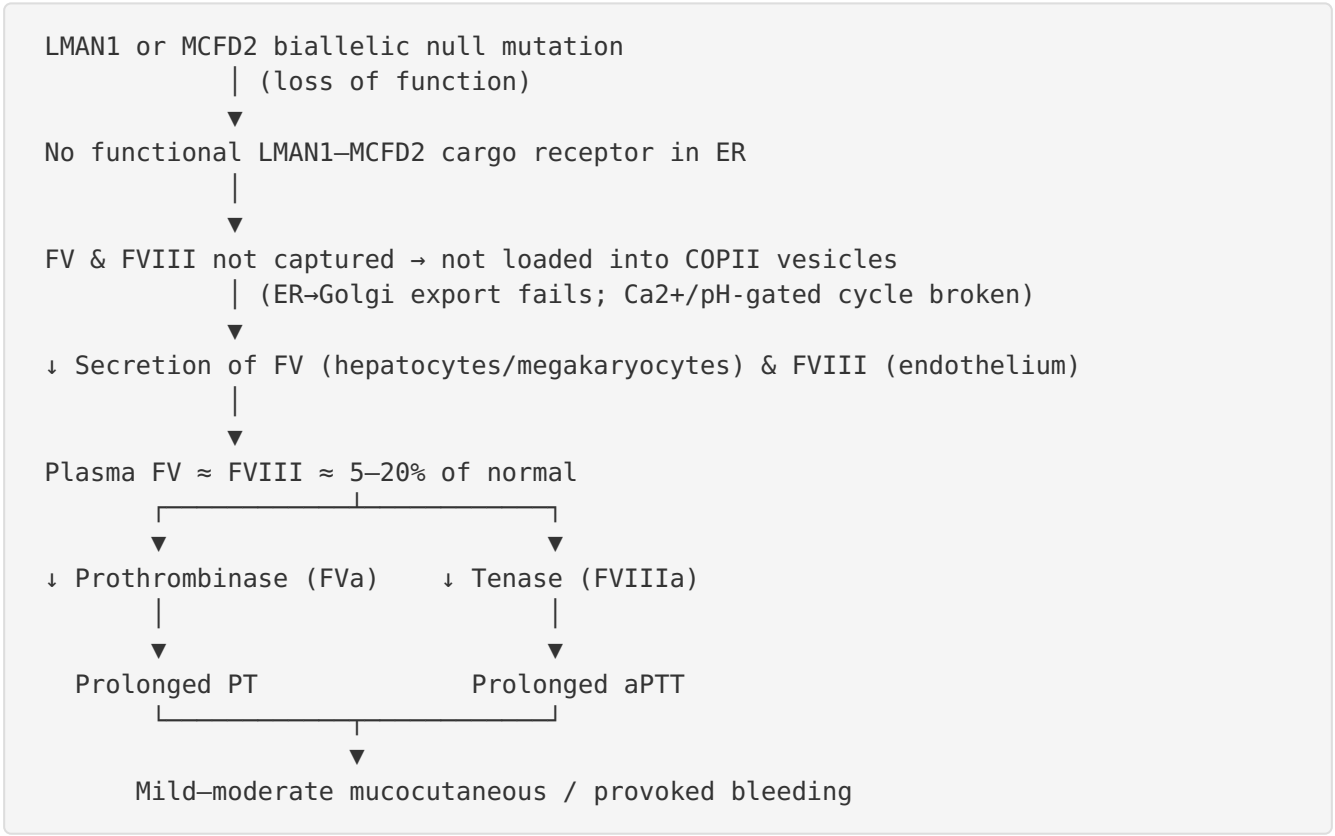
Division of labor. Cell-line studies indicate that **MCFD2 performs cargo binding/transport while LMAN1 acts as a shuttle carrier of MCFD2**: overexpression of MCFD2 alone rescues FV/FVIII secretion in LMAN1-deficient cells, and N-glycan binding by LMAN1 is not strictly essential for transport (PMID: 36490287).

pH/Ca^{2+}-triggered cargo cycle. Cargo capture in the ER is **Ca^{2+}-dependent at neutral pH**; a conserved CRD histidine acts as a pH/Ca^{2+} sensor so that mild acidification and lower Ca^{2+} in the ERGIC trigger glycoprotein release: "Acidification of cells inhibited the association of ERGIC-53 with the known cargo … and dissociation of this glycoprotein in the ERGIC was impaired by organelle neutralization" (PMID: 14718532).

Broader cargo repertoire. The LMAN1–MCFD2 receptor also exports **cathepsin C and cathepsin Z** (PMID: 15849265; PMID: 17010120), **alpha-1-antitrypsin** (PMID: 18283111), and **Mac-2BP/LGALS3BP** (PMID: 23550150). Because MCFD2 is dedicated to FV/FVIII, humans with MCFD2 mutations lose only FV/FVIII transport; the other cargoes are handled MCFD2-independently.

Cell types and tissues. FVIII is synthesized primarily by **endothelial cells**, not hepatocytes — conditional-knockout mouse studies "demonstrate that endothelial cells are the primary biosynthetic source of murine FVIII and that hepatocytes make no significant contribution to the plasma FVIII pool" (PMID: 24719406). FV is produced by hepatocytes and megakaryocytes (platelet FV).

ASCII mechanistic model



Suggested GO / CL terms: GO:0006888 (ER-to-Golgi vesicle-mediated transport); GO:0030134 (COPII-coated ER-to-Golgi transport vesicle); GO:0005537 (mannose binding); GO:0007596 (blood coagulation); GO:0005509 (calcium ion binding). CL:0000182 (hepatocyte); CL:0000115 (endothelial cell); CL:0000556 (megakaryocyte). UBERON:0002107 (liver); UBERON:0001981 (blood vessel). CHEBI:29108 (calcium(2+)); CHEBI:4208 (D-mannose).

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7. Anatomical Structures Affected

- **Organ/system level:** The **hematologic/coagulation system** and the **cardiovascular (blood/vasculature)** system are primarily affected. There is no primary organ pathology; bleeding manifests at mucosal surfaces, skin, joints (rarely), and the reproductive tract.
- **Primary biosynthetic sites: Liver (hepatocytes)** for FV; **vascular endothelium** for FVIII (PMID: 24719406); **megakaryocytes/platelets** carry a FV pool.

- **Tissue/cell level:** hepatocytes (CL:0000182), endothelial cells (CL:0000115), megakaryocytes (CL:0000556).
- **Subcellular level:** The molecular lesion resides in the **early secretory pathway** — endoplasmic reticulum (GO:0005783), **ER-Golgi intermediate compartment/ERGIC** (GO:0005793), and **COPII vesicles** (GO:0030134).
- **Localization of bleeding:** Mucocutaneous surfaces (nasal mucosa, oral/gingival mucosa, skin), gastrointestinal and intracranial sites (rare), and the uterus/reproductive tract (menorrhagia, postpartum). Bleeding is **systemic/multifocal**, not lateralized.

UBERON terms: UBERON:0002107 (liver); UBERON:0001981 (blood vessel/vasculature); UBERON:0000178 (blood); UBERON:0000344 (mucosa); UBERON:0002097 (skin of body).

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8. Temporal Development

- **Onset:** Congenital — the secretion defect is present from birth. Clinical recognition is often **delayed** to childhood or adulthood because bleeding is mild; many cases surface at the first hemostatic challenge (circumcision, dental extraction, surgery, menarche, childbirth) or incidentally on preoperative screening.
- **Onset pattern:** Insidious/chronic baseline with **episodic, provoked** bleeding events.
- **Progression: Stable and non-progressive.** Factor levels remain constant over life.
- **Course:** Lifelong (chronic), with excellent prognosis. No disease "stages."
- **Remission:** Not applicable — the genetic defect is permanent; bleeding is managed, not cured. Replacement therapy produces transient correction.
- **Critical periods:** Hemostatic challenges — **surgery, dental procedures, trauma, menstruation, and especially pregnancy/delivery** — are the windows requiring intervention. In pregnancy the physiologic FVIII rise is blunted because secretion (not synthesis) is limiting, so the defect persists and postpartum-hemorrhage risk remains (PMID: 19298378).

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9. Inheritance and Population

Epidemiology: Estimated prevalence **~1 in 1,000,000** in the general population; F5F8D constitutes roughly **3% of rare coagulation disorders**. "The prevalence of this disease in the general population is estimated to be 1:1,000,000 and is significantly higher in regions where consanguineous marriages are permitted, such as the Mideast and South Asia" (PMID: 39209292).

Inheritance: Autosomal recessive. Heterozygotes are asymptomatic. Equal sex incidence (though women are more often symptomatic due to menstrual/reproductive bleeding).

Penetrance/expressivity: High penetrance of the biochemical phenotype (low FV/FVIII) in biallelic carriers; **variable expressivity** of bleeding severity. No genetic anticipation (not a repeat-expansion disorder). Germline mosaicism not a recognized feature.

Founder effects and consanguinity: Strong. Documented founder alleles include an **LMAN1 intron-9 donor-splice mutation prevalent among Tunisian Djerba Jews** (carrier allele frequency ~0.011) and an **exon-1 G insertion among Middle Eastern/Iraqi Jews**: "a thymidine (T) to cytosine (C) transition in intron 9 at a donor splice site among Tunisian families. For each mutation, haplotype analysis revealed a founder effect" (PMID: 15166951). High prevalence is reported in consanguineous cohorts in Iran (PMID: 27894217; PMID: 23632381) and Pakistan (PMID: 28388959).

Population demographics: Enriched in Mediterranean, Middle-Eastern, and South-Asian populations where endogamy is common. Geographic distribution of variants tracks founder haplotypes. Sex ratio ~1:1.

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10. Diagnostics

Diagnostic algorithm: 1. **Screening coagulation tests:** simultaneously **prolonged PT and aPTT**, both **fully corrected by 1:1 mixing** (indicates factor deficiency, not an inhibitor). 2. **Specific factor assays:** concordant reduction of **FV:C and FVIII:C to ~5–20%**, with **normal levels of other coagulation factors** and **normal von Willebrand factor antigen/activity**. This pattern distinguishes F5F8D from isolated hemophilia A (normal PT), isolated FV deficiency (normal FVIII), and type 2N/3 von Willebrand disease. Illustrative case: "a combined deficiency of factors V and VIII at 12.4% … and 9.1%, respectively, whereas other coagulation factor levels remained within the normal range, including the antigenic activity of von

Willebrand" (PMID: 40296097). 3. **Molecular confirmation:** targeted **LMAN1/MCFD2 sequencing**, a rare-bleeding-disorder gene panel, or **whole-exome sequencing** (which identified a novel homozygous *LMAN1* c.604C>T, PMID: 38659545). **Dosage/copy-number analysis** is needed because a heterozygous large *MCFD2* deletion can masquerade as a homozygous substitution (PMID: 38764219).

Biomarkers: FV:C and FVIII:C are the defining biomarkers; reduced **platelet FV** supports the diagnosis. vWF is normal (key discriminator).

Clinical/bleeding assessment: Standardized bleeding-assessment tools (ISTH-BAT; EN-RBD bleeding score) quantify symptom burden, with bleeding score inversely correlated with factor activity (PMID: 27855295).

Differential diagnosis: hemophilia A (isolated FVIII, normal PT); isolated FV deficiency (normal FVIII); combined vitamin-K-dependent factor deficiency; von Willebrand disease types 2N/3; rare **digenic** coincidental *F5* + *F8* mutations (PMID: 41040772).

Screening: Carrier and cascade testing within affected consanguineous families; no population newborn screening exists given rarity and mild phenotype. Imaging/electrophysiology/biopsy are not diagnostic for this disorder.

LOINC concepts: PT (5902-2), aPTT (3173-2/14979-9), Factor V activity (3192-2), Factor VIII activity (3209-4), von Willebrand factor antigen (5088-1).

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11. Outcome / Prognosis

Prognosis is excellent with normal life expectancy. F5F8D is a **milder** rare bleeding disorder than FXIII, FX, or FVII deficiencies: "patients with factor XIII, factor X and factor VII more commonly presented severe life-threatening bleeding, while patients with combined factor V and factor VIII presented a milder phenotype" (PMID: 27894217).

- **Mortality:** Low; disease-specific mortality is uncommon with appropriate peri-procedural and obstetric management.
- **Morbidity:** Mucocutaneous bleeding, menorrhagia, and procedure/trauma-provoked bleeding; hemarthrosis and life-threatening CNS/GI bleeds are uncommon. A 37-case single-center India series documents the clinical spectrum (PMID: 20575023).
- **Disease course:** Stable, lifelong, non-progressive. Many patients remain asymptomatic until a hemostatic challenge (PMID: 38912355; PMID: 38659545).

- **Prognostic factors:** Baseline FV/FVIII activity broadly tracks bleeding tendency (MCFD2 genotype → lower levels), but factor levels correlate **inconsistently** with bleeding outcomes, particularly in pregnancy (PMID: 41789952), so clinical history and bleeding scores remain essential.

12. Treatment

Core principle: replace BOTH factors. Because no clotting-factor gene is defective but two factor proteins are low, therapy must raise both FV and FVIII. "Treatment of bleeding episodes requires a source of both FV and FVIII; replacement of FV is achieved through the use of fresh frozen plasma, and that of FVIII by desmopressin or specific FVIII concentrates, plasma-derived or recombinant FVIII products" (PMID: 19141160).

Modality	Purpose	Notes / NCIT
Fresh frozen plasma (or SD/virus-inactivated plasma)	Sole practical **FV** source	No FV concentrate exists: "only prothrombin and FV deficiencies still remain without a specific product" (PMID: 27913544). NCIT:C681 (plasma)
FVIII concentrate (plasma-derived or recombinant)	Raise **FVIII**	NCIT:C1947 (Coagulation Factor VIII)
Desmopressin (DDAVP)	Transiently raise **FVIII** for minor bleeds/procedures	NCIT:C29066 (Desmopressin)
Antifibrinolytics (tranexamic acid)	Mucosal/minor bleeds, menorrhagia, dental work	NCIT:C47720 (Tranexamic Acid)
Local hemostatic measures	Epistaxis, dental	Adjunctive

Management is tailored to the setting — surgery, spontaneous bleeding, pregnancy/delivery, and the neonate — per UKHCDO guidelines (PMID: 15357789). Broader reviews confirm the dual-replacement strategy and the absence of a dedicated FV product (PMID: 19141160; PMID: 27913544).

Pregnancy/peripartum: A documented F5F8D pregnancy (FV 29%, FVIII 21%; aPTT 78s) was managed with a protocol-based multidisciplinary plan: **2000 IU FVIII at onset of labor** raising FVIII to 36% and FV to 38%, then 12-hourly tapering doses keeping FVIII >50% for 5 days — delivery with no bleeding: "An infusion of 2000IU of FVIII was implemented over 5 minutes; soon thereafter, PT was 17 seconds, aPTT patient/control ratio had decreased to 1.9 and FV and FVIII reached 38% and 36% respectively" (PMID: 24161289). Because the defect persists through pregnancy, planned cover prevents postpartum hemorrhage (PMID: 19298378).

Pharmacogenomics / gene / cell / targeted therapies: None approved or required; F5F8D is managed with replacement and antifibrinolytics. (Of note, the LMAN1–MCFD2 axis is being explored in the *opposite* direction as an **anticoagulant target** — GalNAc-siRNA knockdown of LMAN1/MCFD2 lowers FVIII and prolongs aPTT in mice, PMID: 39222205 — which conceptually validates the pathway but is not a treatment for the deficiency.)

Treatment strategy: On-demand replacement for bleeds/procedures; prophylaxis is rarely needed given the mild phenotype; antifibrinolytics first-line for menorrhagia and mucosal bleeding.

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13. Prevention

- **Primary prevention:** Not possible (monogenic, congenital). **Genetic counseling** and **carrier/cascade screening** in affected families — especially in consanguineous communities and founder populations — reduce recurrence; **prenatal/preimplantation genetic testing** is available where a familial mutation is known.
- **Secondary prevention:** Early diagnosis via recognition of the dual PT/aPTT pattern on preoperative screening; confirm before elective surgery to plan hemostatic cover.
- **Tertiary prevention (preventing bleeding complications):** Pre-procedure factor replacement, peripartum protocols, antifibrinolytics, avoidance of antiplatelet/anticoagulant drugs and intramuscular injections, routine dental care, and iron supplementation for menorrhagia-related anemia.

- **Counseling:** Autosomal-recessive recurrence risk (25% for carrier couples); emphasize in consanguineous families. NSGC/ACMG genetic-counseling frameworks apply.
- **Immunization / public-health / environmental interventions:** Not applicable (non-infectious, non-environmental).

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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *LMAN1* and *MCFD2* are conserved in mammals. Mouse orthologs *Lman1* and *Mcfd2* have been functionally studied (see §15).
- **Natural disease in other species:** No well-characterized spontaneous F5F8D-equivalent is established in companion animals or wildlife in the reviewed literature; the disease is primarily described in humans and in engineered mouse models.
- **Comparative biology:** The LMAN1–MCFD2 cargo-receptor mechanism is evolutionarily conserved, making mouse models directly informative. A notable species difference: in mice the ER-exit defect is partial (FV/FVIII ~50% vs ~5–20% in humans), implying additional redundancy.
- **Zoonotic potential:** None (non-infectious).

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15. Model Organisms

Mouse is the principal model.

Model	Phenotype	Key insight	PMID
Lman1$^{-/-}$ knockout	Plasma/platelet FV and FVIII ~50% (milder than human ~5–30%); distended hepatocyte ER with accumulation of **α1-antitrypsin** and GRP78; partially penetrant, strain-dependent perinatal lethality	Confirms LMAN1 as cargo receptor; implicates additional unidentified cargoes; identifies A1AT as a co-cargo	PMID: 21795745
Lman1^cgt/cgt hypomorph (~6–8% mRNA)	Intermediate FV/FVIII ~70%	**Dose-dependent** effect of residual LMAN1: "these results show a dose-dependent effect of residual LMAN1 on the secretion of its cargo proteins … human subjects with hypomorphic LMAN1 mutations might present with mild bleeding phenotypes"	PMID: 33196840
Lman1 conditional (tissue-specific) KO	Endothelial, not hepatocyte, FVIII loss	"Endothelial cells are the primary biosynthetic source of murine FVIII … hepatocytes make no significant contribution to the plasma FVIII pool"	PMID: 24719406
Mcfd2$^{-/-}$ vs *Lman1*$^{-/-}$	Distinct in vivo functions	Dissects separable roles of the two subunits	PMID: 29735583

Cellular / in-vitro models: HEK293T, HepG2, and HCT116 LMAN1- and MCFD2-deficient lines reveal cell-type-dependent secretion requirements and allow functional pathogenicity assays for candidate variants; MCFD2 overexpression rescues FV/FVIII secretion in LMAN1-null cells, establishing MCFD2 as the cargo-engaging subunit and LMAN1 as its shuttle (PMID: 36490287). Structural models (crystallography, NMR) defined the CRD–MCFD2 interface and the FVIII B-domain binding peptide (PMID: 20142513; PMID: 23709226; PMID: 32170195).

Model limitations: Mouse knockouts underrecapitulate human factor-level reduction (≈50% vs ≈5–20%), likely due to species redundancy; partially penetrant lethality and additional cargoes complicate interpretation. Cell lines capture transport biology but not whole-organism bleeding phenotypes.

Mechanistic Model / Interpretation

F5F8D is best understood as a **trafficking disease masquerading as a coagulation-factor deficiency.** The single unifying lesion — loss of the LMAN1–MCFD2 cargo receptor — explains every clinical observation: (1) *why two unrelated factors fall together* (they share a transporter); (2) *why the factors are structurally normal* (synthesis is intact, export is not); (3) *why levels sit near 5–20% rather than zero* (bulk-flow and residual secretion provide a floor, and residual-LMAN1 dose modulates it); (4) *why the phenotype is mild and non-progressive* (partial, stable secretion defect); and (5) *why MCFD2 defects tend to be slightly more severe* (MCFD2 is the dedicated FV/FVIII adaptor, so its loss more directly cripples their recruitment while sparing other cargoes). The **MCFD2-is-a-recruitment-factor** finding is the linchpin that reconciles the broad cargo repertoire of LMAN1 (cathepsins, α1-antitrypsin, Mac-2BP) with the narrow, FV/FVIII-only clinical picture of F5F8D.

Evidence Base

PMID	Contribution	Finding
9546392	Identified ERGIC-53/*LMAN1* as first causal gene	F001
10090934	*LMAN1* mutation spectrum uniformly null (35 families)	F001
20817851	Separable MCFD2 vs cargo binding sites; oligomerization required	F002
23709226	His178, Gly251/252 cargo-binding residues	F002
20142513	1:1 CRD–MCFD2 crystal structure; missense sites at interface	F002, F004
17010120	MCFD2 = FV/FVIII recruitment factor; MCFD2-independent cargo binding	F009
14718532	pH/Ca^{2+}-triggered cargo release in ERGIC	F009
36490287	MCFD2 carries cargo; LMAN1 shuttles MCFD2	F002
19183188	MCFD2 mutations give lower FV/FVIII than LMAN1	F003
19141160	Factor levels 5–20%, mild-moderate bleeding; dual replacement	F003, F005
39209292	Prevalence 1:1,000,000; consanguinity enrichment	F004
15166951	Founder mutations in Jewish populations	F004
27913544	No specific FV concentrate exists	F005
33196840	Dose-dependent residual LMAN1 effect (mouse)	F006
21795745	*Lman1*$^{-/-}$ ~50% factors; A1AT accumulation	F006
24719406	Endothelium is FVIII source	F006
29735583	Distinct MCFD2 vs LMAN1 in-vivo roles	F006
24161289	Peripartum FVIII protocol	F007
19298378	Defect persists in pregnancy; PPH risk	F007
40296097	Defining lab pattern with normal vWF	F008
38764219	Large deletion mimics homozygous substitution	F008
27855295	EN-RBD bleeding score; inverse correlation with factor activity	F008
27894217	F5F8D milder than FXIII/FX/FVII	F010
38912355	Pediatric gum-bleeding presentation	F010

PMID	Contribution	Finding
39222205	LMAN1/MCFD2 knockdown as anticoagulant — pathway validation	Context

All findings are supported by multiple independent lines of evidence (human clinical case series, structural/biochemical studies, and mouse and cell-line genetics). No contradictory findings were identified; the main tension is the quantitative mismatch between mouse (~50%) and human (~5–20%) factor levels, attributed to species redundancy.

Limitations and Knowledge Gaps

1. **Rarity-limited epidemiology.** Prevalence (~1:1,000,000) is an estimate; true incidence, age distribution, and population-specific carrier frequencies outside founder groups are poorly quantified.
2. **Genotype–phenotype resolution is coarse.** Although MCFD2 mutations trend toward lower factor levels, individual bleeding severity correlates imperfectly with factor activity, especially in pregnancy — predictive models are lacking.
3. **Incomplete cargo census.** Mouse data (perinatal lethality, A1AT accumulation) imply additional unidentified LMAN1 cargoes whose loss could contribute to subtle, under-recognized human phenotypes.
4. **Model mismatch.** Mouse knockouts do not reproduce the human factor-level depth, limiting their use for severity modeling.
5. **No disease-specific therapeutics.** FV replacement still depends on FFP; no recombinant FV product and no gene/cell therapy exist for F5F8D.
6. **QoL data are sparse.** Patient-reported outcomes, particularly the menstrual/reproductive burden in women, are under-studied.
7. **Digenic cases.** Rare coincidental *F5* + *F8* defects can phenocopy F5F8D and complicate molecular diagnosis.

Proposed Follow-up Experiments / Actions

1. **Variant functional classification pipeline:** Use the established LMAN1/MCFD2-deficient cell lines (PMID: 36490287) as a standardized rescue assay to reclassify VUS and resolve digenic vs monogenic cases.
2. **Copy-number-aware molecular testing:** Adopt routine dosage/CNV analysis of *MCFD2* and *LMAN1* to avoid misclassifying heterozygous large deletions as homozygous substitutions (PMID: 38764219).
3. **Natural-history registry:** Pool founder-population cohorts (Tunisian, Iranian, Pakistani, Indian, Saudi) into a harmonized registry linking genotype, factor levels, ISTH-BAT/EN-RBD scores, and bleeding outcomes to build a severity-prediction model.
4. **Cargo discovery:** Proteomic profiling of LMAN1/MCFD2-null cells and conditional mouse tissues to complete the cargo census and test whether additional cargoes produce subclinical human phenotypes.
5. **Therapeutic development:** Evaluate recombinant FV products and the "passport-sequence" secretion-enhancement concept (PMID: 32170195) as routes to a dedicated FV replacement, reducing FFP dependence.
6. **Reproductive-health protocols:** Prospectively validate individualized peripartum dual-factor protocols (PMID: 24161289) and quantify menorrhagia-related QoL and anemia burden in affected women.
7. **Carrier screening in endogamous communities:** Offer targeted founder-allele carrier and cascade screening with genetic counseling to reduce recurrence.

Report compiled from a 5-iteration autonomous investigation: 10 confirmed findings across 45 reviewed papers. Evidence spans human clinical case series, structural/biochemical studies, and mouse and cell-line genetics.
