

Factor XIII B Subunit Deficiency — Comprehensive Disease Characterization

Disease: Factor XIII B Subunit Deficiency **MONDO ID:** MONDO:0013190 · **OMIM:** #613235 · **ORPHA:** 331 (Congenital FXIII deficiency) · **ICD-10:** D68.2 · **MeSH:** D005177 **Category:** Mendelian (autosomal recessive, rare bleeding disorder) **Gene:** *F13B* (HGNC:3534; chromosome 1q31.3; UniProt P05160)

Summary

Factor XIII B Subunit Deficiency is an ultra-rare, autosomal-recessive inherited bleeding disorder caused by biallelic loss-of-function variants in *F13B*, the gene encoding the non-catalytic **carrier/protective B subunit** of plasma coagulation Factor XIII (FXIII). Plasma FXIII circulates as a heterotetramer (FXIII-A₂B₂) in which two catalytic A subunits are bound and stabilized by two B subunits. The B subunit is a glycoprotein built from **10 repetitive sushi (complement control protein, CCP) domains**; it chaperones FXIII-A in the circulation, prevents its rapid clearance, and tethers it to the fibrinogen γ' -chain. When the B subunit is absent or severely reduced, the catalytic A subunit is cleared from plasma much faster than normal, so **plasma FXIII activity falls secondarily** even though A-subunit synthesis is intact. The result is deficient covalent cross-linking of fibrin and of α_2 -antiplasmin, producing mechanically weak, fibrinolysis-prone clots.

Clinically, the disease belongs to the congenital FXIII deficiency spectrum, whose hallmark features are **delayed umbilical-stump hemorrhage in the neonate, soft-tissue and intracranial bleeding, impaired wound healing, and recurrent pregnancy loss** — all occurring despite **normal routine coagulation screening** (PT, aPTT, fibrinogen). Importantly, B-subunit deficiency is considerably rarer and generally **milder** than severe A-subunit deficiency because residual A-subunit activity persists; the knockout mouse shows markedly reduced, but not absent, fibrin cross-linking. Diagnosis therefore requires a quantitative FXIII activity assay **plus subunit-specific antigen phenotyping** that reveals low/absent FXIII-B antigen with secondarily reduced FXIII-A antigen.

The single most clinically actionable distinction for this subtype concerns therapy: **recombinant FXIII-A₂ (catridecacog; NovoThirteen/Tretten)** does NOT correct **F13B defects**, because it supplies only the catalytic subunit without the carrier that stabilizes it. Patients with B-subunit deficiency must instead receive **plasma-derived FXIII concentrate (A₂B₂; Fibrogammin/Corifact)**, which supplies both subunits. Lifelong replacement prophylaxis — feasible because of FXIII's long half-life (~7–14 days) — reduces the annualized bleeding rate to essentially zero and transforms a historically high-mortality disease (intracranial hemorrhage being the leading cause of death) into a manageable chronic condition with near-normal life expectancy.

1. Disease Information

Factor XIII B Subunit Deficiency is a congenital rare bleeding disorder (RBD) within the broader entity of **congenital Factor XIII deficiency (FXIID)**. FXIII is the final enzyme of the coagulation cascade: a Ca²⁺-dependent transglutaminase that covalently cross-links fibrin to stabilize the clot. Congenital FXIII deficiency arises from biallelic variants in either of two genes — *F13A1* (catalytic A subunit) or *F13B* (carrier B subunit). The B-subunit form is defined by defects in *F13B*.

Key identifiers:

Resource	Identifier
MONDO	MONDO:0013190
OMIM	#613235 (Factor XIII, B subunit, deficiency of)
Orphanet	ORPHA:331 (Congenital factor XIII deficiency)
ICD-10	D68.2 (Hereditary deficiency of other clotting factors)
MeSH	D005177 (Factor XIII Deficiency)
Gene (HGNC)	HGNC:3534 (<i>F13B</i>)
UniProt	P05160 (Coagulation factor XIII B chain)

Synonyms / alternative names: Factor XIII deficiency due to B subunit defect; FXIII-B deficiency; congenital FXIII-B subunit deficiency; fibrin stabilizing factor B subunit deficiency.

Information source: Evidence is derived almost entirely from **aggregated disease-level resources and individual case reports**, not large EHR datasets. Because the subtype is ultra-rare (historically ~11 reported cases of congenital FXIII-B deficiency as of 2013; [PMID: 23407795](#)), the knowledge base is built from case reports, small cohorts of congenital FXIII deficiency (predominantly A-subunit), registry data from consanguineous populations, and one informative knockout mouse model.

"congenital FXIII-B deficiency is even rarer" — [PMID: 23407795](#)

2. Etiology

Primary cause — genetic. The disease is caused by **biallelic germline loss-of-function variants in *F13B*** (chromosome 1q31.3). It is inherited in a strictly autosomal recessive manner; both alleles must be defective to produce clinically significant deficiency ([PMID: 37314674](#)). There is no infectious or primary environmental cause of the congenital form. (A separate, non-inherited *acquired* FXIII deficiency exists — autoimmune or consumptive — but that is a distinct entity from this Mendelian B-subunit disease.)

Genetic risk factors. The disease-causing variants in *F13B* are themselves the causal risk factors; reported classes include missense (many causing secretion/folding defects — e.g., disruption of structural disulfides of sushi domains), nonsense, splice-site, and frameshift variants ([PMID: 31013569](#); [PMID: 26247044](#)). **Consanguinity** is the dominant risk factor for being born affected, since it greatly increases the chance of homozygosity for a rare recessive allele. In pediatric congenital FXIII cohorts, consanguinity rates reach ~75% ([PMID: 37314674](#)).

"Consanguinity was present in 15 (75%)" — [PMID: 37314674](#)

Environmental / modifier risk factors. No environmental exposures cause the congenital disease. Bleeding *events* are precipitated by trauma, surgery, childbirth, and the neonatal umbilical separation. Heterozygous carriers are usually asymptomatic but can bleed after a hemostatic challenge (surgery, trauma, delivery).

Protective factors. No specific protective genetic alleles are documented for this ultra-rare disorder. The principal "protective" circumstance is **residual FXIII-A activity**: because B-subunit loss only accelerates A-subunit clearance rather than abolishing A-subunit production, B-subunit deficiency tends to be milder than severe A-subunit deficiency ([PMID: 26247044](#); [PMID: 18224415](#)).

"Defects in the F13B gene (Factor XIII B subunit) occur more frequently in mild FXIII deficiency patients than in severe FXIII deficiency" — [PMID: 26247044](#)

Gene–environment interactions. The relevant interaction is **genotype × hemostatic challenge**: the underlying genetic deficiency is silent under routine screening and manifests when the coagulation system is stressed (neonatal umbilical healing, surgery, trauma, pregnancy/decidual bleeding).

3. Phenotypes

The phenotype of B-subunit deficiency mirrors the congenital FXIII deficiency spectrum but tends toward the **milder** end. Core manifestations ([PMID: 41583548](#); [PMID: 42230344](#); [PMID: 32360976](#)):

Phenotype	Type	Suggested HPO	Onset / Characteristics	Frequency
Delayed umbilical stump bleeding	Clinical sign	HP:0040187 / neonatal bleeding	Neonatal; classic first presentation	Very common in severe disease
Intracranial hemorrhage	Clinical sign	HP:0002170	Any age; most severe/life-threatening	~25–35% of severe patients; leading cause of death
Soft-tissue / subcutaneous hematoma, ecchymoses	Clinical sign	HP:0001009 / HP:0000978	Childhood onward	Common
Prolonged/delayed bleeding after trauma or surgery	Symptom	HP:0004846 (Abnormal bleeding)	Any age; episodic	Common
Impaired / delayed wound healing	Physical manifestation	HP:0001058 (Poor wound healing)	Any age	Characteristic
Recurrent spontaneous miscarriage	Clinical sign	HP:0008222 (Recurrent spontaneous abortion)	Reproductive age; episodic	~36% of affected women had ≥ 1 miscarriage (cohort)
Mucosal bleeding (epistaxis, oral)	Symptom	HP:0000421 / HP:0000163	Childhood onward	Common
Low plasma FXIII activity	Laboratory abnormality	HP:0012223 (Reduced factor XIII activity)	Congenital	Defining lab finding

"classically presents with delayed umbilical stump hemorrhage, soft-tissue and intracranial bleeding, impaired wound healing, and recurrent pregnancy loss" — [PMID: 41583548](#)

Onset: typically neonatal (umbilical bleeding) in severe cases; median symptom onset ~6 months and median diagnosis ~1 year in a South Indian pediatric congenital FXIII cohort ([PMID: 37314674](#)).

Severity / progression: variable and lifelong; bleeding is **episodic** (triggered by challenges) rather than continuously progressive. B-subunit deficiency is generally milder than severe A-subunit deficiency.

Quality-of-life impact: dominated by the burden of lifelong prophylaxis, fear of spontaneous intracranial bleeding, and reproductive complications (miscarriage, postpartum hemorrhage). Disease-specific QoL instruments for this ultra-rare subtype are not available; data are extrapolated from the FXIII deficiency literature.

4. Genetic / Molecular Information

Causal gene: *F13B* (HGNC:3534; chromosome **1q31.3**; UniProt **P05160**). It encodes the plasma FXIII B subunit, a secreted **glycoprotein of 10 repetitive sushi (CCP) domains**, each stabilized by two internal disulfide bonds ([PMID: 20880254](#)). The B subunit is synthesized in **hepatocytes** and secreted into plasma.

"FXIII-B is a glycoprotein consisting of 10 repetitive sushi domains each held together by two internal disulfide bonds" — [PMID: 20880254](#)

Variant classification and type: Reported *F13B* variants span **missense, nonsense, splice-site, and frameshift** classes; many missense variants cause **secretion or folding defects**, and disruption of the structural disulfide bonds of the sushi domains has functional consequences for a rare bleeding disorder ([PMID: 31013569](#); [PMID: 26247044](#)). Pathogenic variants act by **loss of function** (reduced/absent carrier subunit). The first sushi domain is important for A–B complex formation. Origin is **germline**; there is no somatic component. Per ACMG/AMP, null (nonsense/frameshift/splice) variants in this loss-of-function gene are typically classified pathogenic/likely pathogenic; many missense variants remain VUS pending functional (secretion) data.

Functional consequence: Loss of the B subunit does not abolish A-subunit synthesis but removes its carrier/stabilizer, so FXIII-A is cleared faster and plasma FXIII activity drops secondarily — a **loss-of-function, carrier-deficiency mechanism** confirmed by the knockout mouse (Section 6, [PMID: 18224415](#)).

Modifier genes: The principal modifier of plasma FXIII level in B-subunit deficiency is the status of the A-subunit pool itself (how quickly uncarried A is cleared). No independent modifier loci are well established for this subtype.

Epigenetic / chromosomal abnormalities: None are implicated. This is a single-gene point/indel mutation disorder; no recurrent aneuploidy, translocation, or methylation signature is associated.

Allele frequencies: Pathogenic *F13B* alleles are individually very rare in gnomAD; population carrier frequency of FXIII deficiency alleles is elevated in consanguineous populations (see Section 9). Precise per-variant gnomAD frequencies were not quantified in this investigation.

5. Environmental Information

The **congenital** disease has **no environmental, lifestyle, or infectious cause** — it is purely genetic. Environmental factors act only as **triggers of bleeding events** in an already-deficient individual: trauma, surgery, and childbirth. For completeness, an entirely separate **acquired** FXIII deficiency (not this Mendelian entity) can be caused by autoimmune inhibitors (e.g., SLE-associated) or consumption (e.g., major surgery, dilutional coagulopathy); those are distinct from B-subunit deficiency and are mentioned only to aid differential diagnosis. No toxins, radiation, pollutants, dietary factors, or pathogens cause the inherited B-subunit disease.

6. Mechanism / Pathophysiology

Ordered causal chain

1. **Biallelic loss-of-function variants in *F13B*** (missense/secretion-defect, nonsense, splice, or frameshift) **lead to** absent or severely reduced secretion of the FXIII B (carrier) subunit from hepatocytes.

2. Loss of circulating B subunit **results in** failure to chaperone and protect the catalytic FXIII-A subunit in plasma (the B subunit normally prevents fast clearance of FXIII-A and binds it to fibrinogen γ' -chain).
3. Unprotected FXIII-A **leads to** accelerated clearance of FXIII-A from the circulation, so **plasma FXIII activity falls secondarily** (partial, not complete, loss — *inferred* from the milder phenotype and directly *demonstrated* in the B-subunit knockout mouse, which shows markedly reduced but detectable cross-linking).
4. Low plasma FXIII activity **results in** deficient Ca^{2+} -dependent transglutaminase action, i.e., **reduced covalent cross-linking of fibrin γ - and α -chains and reduced cross-linking of α_2 -antiplasmin to fibrin.**
5. Deficient fibrin cross-linking **leads to** mechanically weak clots; deficient α_2 -antiplasmin cross-linking **leads to** loss of the principal antifibrinolytic mechanism → **premature clot lysis.**
6. **Branch A (hemostasis):** unstable, fibrinolysis-prone clots **result in** delayed/recurrent bleeding, soft-tissue and intracranial hemorrhage.
7. **Branch B (wound healing):** failure to cross-link the provisional wound matrix **results in** impaired leukocyte interaction and **poor wound healing / impaired mucosal repair.**
8. **Branch C (angiogenesis):** loss of FXIIIa action on endothelial VEGFR-2 / $\alpha v \beta 3$ integrin **results in** failure to downregulate antiangiogenic thrombospondin-1 → impaired angiogenesis/neovascularization (*inferred* contribution to healing/pregnancy defects).
9. **Branch D (reproduction):** loss of FXIII's role in **placental attachment results in** recurrent miscarriage and antenatal hemorrhage.

Supporting detail

Molecular / biochemical defect. Activated FXIII (FXIIIa) is a Ca^{2+} -dependent **transglutaminase** (EC 2.3.2.13) that forms ϵ -(γ -glutamyl)lysine isopeptide bonds. Its substrates include fibrin and α_2 -antiplasmin:

"These include antifibrinolytic proteins, with cross-linking of α_2 -antiplasmin to fibrin, and potentially fibrinogen, being the principal mechanism(s) whereby plasmin-mediated clot degradation is minimised" — [PMID: 25652913](#)

Angiogenesis. FXIIIa engages endothelial signaling:

"FXIII also acts on endothelial cell VEGFR-2 and $\alpha v \beta 3$ integrin, which ultimately leads to downregulation of the antiangiogenic protein thrombospondin-1, promoting angiogenesis and neovascularisation" — [PMID: 25652913](#)

Placentation. FXIII is required for placental attachment, explaining the high miscarriage rate:

"factor XIII is involved in placental attachment" — [PMID: 32360976](#)

Tissue repair. In an experimental colitis model, FXIII-deficient mice failed to resolve mucosal damage, and exogenous FXIII-A improved healing — confirming FXIII's role in mucosal/tissue repair ([PMID: 26098308](#)).

Upstream vs downstream. *Upstream:* the *F13B* mutation and loss of carrier subunit. *Midstream:* accelerated FXIII-A clearance and low plasma FXIII activity. *Downstream:* deficient cross-linking → unstable clots, impaired healing, impaired placentation → clinical bleeding and pregnancy loss.

Cell types / processes involved: hepatocytes (CL:0000182) synthesize the B subunit; the A subunit's major plasma pool derives from cells of **megakaryocyte/platelet lineage** (CL:0000556 megakaryocyte; CL:0000233 platelet) per lineage-tracing studies ([PMID: 26312861](#)); endothelial cells (CL:0000115) are the target of FXIIIa's angiogenic action.

Suggested ontology terms: GO:0007596 (blood coagulation), GO:0018149 (peptide cross-linking), GO:0042730 (fibrinolysis), GO:0001525 (angiogenesis), GO:0042060 (wound healing), GO:0003810 (protein-glutamine γ -glutamyltransferase/transglutaminase activity); CHEBI:29108 (calcium(2+)).

7. Anatomical Structures Affected

- **Primary site:** the **blood / plasma / circulatory system** (UBERON:0000178 blood; UBERON:0001969 blood plasma) — the compartment where the FXIII-A₂B₂ complex operates.
- **Organs affected by bleeding:** **brain** (UBERON:0000955) — intracranial hemorrhage is the most feared complication; **skin and subcutaneous soft tissue** (UBERON:0002097) — ecchymoses, hematomas; **mucosa** (oral/nasal); **umbilical stump** in the neonate; **spleen**

(rare spontaneous rupture reported); **uterus/placenta** (UBERON:0000995 / UBERON:0001987) — miscarriage, decidual bleeding, postpartum hemorrhage.

- **Body systems:** hematologic/cardiovascular (primary), nervous system (secondary via ICH), reproductive system (secondary via miscarriage/PPH), integumentary (bruising/wound healing).
 - **Tissue/cell level:** **hepatocytes** (synthesis of B subunit), **endothelial cells**, **platelets/megakaryocytes** (A-subunit pool), leukocytes (wound matrix interaction).
 - **Subcellular:** the mature protein acts **extracellularly** (secreted; GO:0005576 extracellular region / GO:0005615 extracellular space); synthesis involves the hepatocyte **ER/secretory pathway** (relevant to missense secretion-defect variants).
 - **Lateralization:** not applicable — bleeding is systemic and site-dependent on challenge, not lateralized.
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8. Temporal Development

Onset: congenital — the deficiency is present from birth. Classic first manifestation is **neonatal delayed umbilical stump bleeding**. In milder B-subunit disease, presentation may be later (post-traumatic or post-surgical bleeding). Cohort median symptom onset ~6 months; median diagnosis ~1 year ([PMID: 37314674](#)).

Course: chronic, lifelong, with an **episodic** bleeding pattern (events provoked by trauma, surgery, delivery; spontaneous intracranial bleeding is the dangerous exception). Severity is generally stable over life (set by genotype), not progressive.

Critical periods / windows of opportunity: the **neonatal period** (umbilical bleeding, early ICH risk) and **pregnancy** (miscarriage, decidual and postpartum bleeding) are windows of heightened vulnerability where prophylaxis is especially important. The long FXIII half-life (~7–14 days) provides a wide therapeutic window allowing infrequent (e.g., monthly) replacement dosing.

Remission: no spontaneous remission of the genetic deficiency; bleeding is controlled (treatment-induced "functional remission") by replacement therapy.

9. Inheritance and Population

Inheritance: autosomal recessive; biallelic *F13B* loss-of-function required. Heterozygotes have mild deficiency (activity ~20–60%) and are usually asymptomatic but may bleed after hemostatic challenge (PMID: 37832789).

"heterozygosity at FXIII genetic loci results in mild FXIII deficiency, characterized by circulating FXIII activity levels ranging from 20% to 60%" — PMID: 37832789

Epidemiology:

Measure	Value	Source
Congenital FXIII deficiency incidence	~1 in 3–5 million	PMID: 37314674
Worldwide prevalence (FXIIID)	~1 in 2 million	PMID: 25615432
Iran prevalence (vs worldwide)	~12-fold higher (~473 patients)	PMID: 25615432
FXIII-B subtype (reported cases)	~11 historically (as of 2013)	PMID: 23407795
Mild/heterozygous deficiency prevalence	~0.8% (German-Caucasian donors); ~1 per 1,000–5,000 general; up to 3.5% in SE Iran	PMID: 37832789; PMID: 36940714

"a rare bleeding disorder (RBD) of autosomal recessive inheritance, with an incidence of 1 in 3-5 million" — PMID: 37314674

"An approximately 12-fold higher prevalence of FXIIID is estimated in Iran in comparison with overall worldwide frequency" — PMID: 25615432

Penetrance / expressivity: biallelic severe disease is highly penetrant for bleeding risk; expressivity is variable (B-subunit form milder than severe A-subunit form). No genetic anticipation (not a repeat-expansion disorder).

Founder effects / consanguinity: consanguinity drives prevalence in Iran (Sistan & Baluchestan Province has the highest global incidence), Tunisia, Pakistan, and Sudan. A documented **Japanese founder-effect *F13B* mutation** underlies a severe congenital FXIII-B deficiency case (patient homozygous for it):

"Sistan and Baluchestan Province has not only the highest number of patients with FXIIID in Iran but the highest global incidence" — [PMID: 25615432](#)

"He was found to be homozygous for a Japanese founder-effect mutation of F13B" — [PMID: 23407795](#)

Demographics: affected individuals cluster in consanguineous populations (Middle East, South Asia, North Africa). Sex ratio in congenital FXIII cohorts is roughly balanced (male:female ~1.2–1.5:1), though women carry additional reproductive morbidity.

10. Diagnostics

Why it is missed: routine coagulation screening is **normal**. PT, aPTT, and fibrinogen do not detect FXIII deficiency because FXIII acts after fibrin polymerization. This causes frequent underdiagnosis and decades-long diagnostic delay (recurrent ICH despite normal screens is a recurring theme in case reports).

"Routine coagulation screening tests are normal and diagnosis relies on quantitative FXIII activity assays with or without antigenic phenotyping" — [PMID: 41583548](#)

ISTH/SSC diagnostic algorithm ([PMID: 24286209](#)):

1. **Quantitative FXIII activity assay** (ammonia-release / amine-incorporation) — markedly reduced.
2. **Immunological antigen assays** measuring total FXIII, FXIII-A antigen, FXIII-B antigen, and the A₂B₂ complex.
3. **Inhibitor testing** (cross-mixing / 5-step mixing) to exclude acquired autoimmune deficiency.

4. Plasma-derived FXIII dosing / recovery test, with molecular (DNA sequencing) confirmation of *F13B*.

Subunit assignment (the key step for this subtype): - FXIII-A deficiency: absent FXIII-A antigen, **normal FXIII-B antigen**. - FXIII-B deficiency: **low/absent FXIII-B antigen** with **secondarily reduced FXIII-A**.

"Four immunological assays detected essentially no FXIII protein, FXIII-A antigen, and A2 B2 antigen, but normal FXIII-B antigen" — [PMID: 24286209](#) (illustrates the mirror-image logic that identifies the subunit at fault)

Genetic testing: single-gene *F13B* sequencing (or a rare-bleeding-disorder / FXIII gene panel) confirms the diagnosis and enables carrier and prenatal testing. WES/WGS can be used when the phenotype is unclear. **Legacy test:** the **urea / acetic-acid clot solubility test** is an insensitive legacy screen (only abnormal at very low activity) but is still used where activity assays are unavailable.

Differential diagnosis: von Willebrand disease, platelet function disorders, other rare factor deficiencies, and **acquired FXIII deficiency** (autoimmune/consumptive) — all distinguished by specific FXIII activity, antigen phenotyping, inhibitor testing, and *F13B* sequencing.

Screening: cascade (family) genetic screening and carrier testing in affected consanguineous families; prenatal/antenatal diagnosis available where the familial mutation is known.

11. Outcome / Prognosis

Dominant risk — intracranial hemorrhage (ICH): ICH is the most severe and life-threatening manifestation and the **leading cause of death** in severe congenital FXIII deficiency, affecting up to ~25–35% of severe patients untreated. In a Tunisian cohort of 7 severe patients, 3/7 had intracranial bleeding and 1 died of ICH ([PMID: 28704210](#)).

"Intracranial hemorrhage represents its most severe and life-threatening manifestation" — [PMID: 42230344](#)

"One patient was died because of intracranial hemorrhage" — [PMID: 28704210](#)

With prophylaxis: regular FXIII replacement **reduces the annualized bleeding rate to essentially zero**, converting a high-mortality disease into a manageable chronic condition with near-normal life expectancy.

"Prophylaxis was effective with an annualized bleeding rate of zero" — [PMID: 28581691](#)

Subtype note: B-subunit deficiency tends to be **clinically milder** than severe A-subunit deficiency because residual A-subunit activity persists.

Morbidity: recurrent bleeding, poor wound healing, reproductive loss (miscarriage, postpartum hemorrhage). **Prognostic factors:** baseline FXIII activity, adherence to prophylaxis, and prior ICH.

12. Treatment

Principle: lifelong **FXIII replacement prophylaxis**, feasible because FXIII has a long half-life (~7–14 days), allowing infrequent (often monthly) dosing.

Genotype-guided product selection — the critical point for B-subunit deficiency:

Product	Composition	Corrects FXIII-A deficiency?	Corrects FXIII-B deficiency?
Plasma-derived FXIII concentrate (Fibrogammin/Corifact)	A ₂ B ₂	Yes	Yes — required
Recombinant FXIII-A ₂ (catridecacog; NovoThirteen/Tretten)	A subunit only	Yes	No
Cryoprecipitate / FFP	Contains FXIII	Yes (older option)	Yes (older option)

"recombinant FXIII-A2 is appropriate for F13A1 defects but not patients with F13B variants" — [PMID: 41583548](#)

The rationale: recombinant A₂ lacks the carrier B subunit, so in B-subunit deficiency the infused A would itself be rapidly cleared; only the A₂B₂ plasma-derived concentrate supplies the missing carrier. **Plasma-derived FXIII is therefore the mainstay for B-subunit deficiency.** Its safety profile is favorable — in FXIII-knockout mice it corrected clot kinetics/strength and was **not associated with thrombus formation up to 350 IU/kg** (PMID: 27069637).

Dosing thresholds (pregnancy): maintain plasma FXIII activity $\geq 2\text{--}3\%$, **ideally** $>10\%$ to prevent decidual bleeding and miscarriage, escalating from ~ 250 IU/week early to ~ 500 IU/week after ~ 23 weeks, targeting $>20\text{--}30\%$ for labor (PMID: 17371605).

"the level of plasma A-subunit of factor XIII antigen (XIIIA-Ag) or factor XIII activity (XIII-act) must be at least 2%-3%, and, if possible, higher than 10% to prevent decidual bleeding and miscarriage during the pregnancy" — PMID: 17371605

"factor XIIIA concentrate is better than fresh frozen plasma or cryoprecipitate for replacement therapy" — PMID: 17371605

Acute bleeds/surgery: replacement before procedures and to treat active bleeding; perioperative FXIII concentrate enables safe major surgery. **Suggested NCIT intervention terms:** coagulation factor replacement therapy; "Factor XIII Concentrate"; prophylactic therapy.

Advanced therapeutics: no gene, cell, or RNA therapies are approved for this disorder; management is replacement-based. Genetic counseling and prenatal diagnosis are offered for family planning. **Thrombotic risk** of replacement is low but non-zero and individualized dosing (avoiding full normalization) is advised in high-risk contexts (PMID: 42527937).

13. Prevention

Because the disease is congenital and genetic, "prevention" operates at two levels:

- **Primary (preventing affected births): genetic counseling, carrier/cascade screening, and prenatal diagnosis** in affected consanguineous families where the *F13B* mutation is known; preimplantation genetic diagnosis is theoretically applicable.

- **Secondary/tertiary (preventing complications in affected individuals): lifelong prophylactic FXIII replacement** to prevent spontaneous ICH and other bleeds; peri-procedural prophylaxis before surgery/delivery; continuous FXIII replacement throughout pregnancy to prevent miscarriage and postpartum hemorrhage.

"our data confirmed the high incidence of miscarriage in women with factor XIII deficiency. Good outcome of pregnancies required prophylaxis" — [PMID: 32360976](#)

No vaccine or environmental/public-health intervention is relevant. Patient education and medical-alert documentation help avoid diagnostic anchoring (e.g., misdiagnosis as von Willebrand disease).

14. Other Species / Natural Disease

- **Model species: *Mus musculus*** (NCBI Taxon 10090) — engineered knockouts exist (Section 15). Orthologous gene: mouse *F13b*.
 - **Naturally occurring disease:** No well-characterized spontaneous FXIII-B deficiency is catalogued in companion animals or wildlife in the reviewed literature; the disorder is primarily studied in humans and engineered mice. (OMIA was not confirmed to list a natural animal FXIII-B deficiency in this investigation.)
 - **Evolutionary conservation:** the FXIII-A₂B₂ system and the carrier/stabilizer function of the B subunit are conserved in mouse, where knockout recapitulates the human carrier mechanism — supporting conservation of the disease mechanism.
 - **Zoonotic potential:** none — this is a non-transmissible inherited disorder.
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15. Model Organisms

Principal model — **FXIII-B knockout mouse** (Souri et al., [PMID: 18224415](#)): targeted deletion of mouse *F13b* (and separately *F13a*).

Phenotype recapitulation: Homozygous *F13b*^{-/-} mice are **viable and fertile** but have **prolonged bleeding times** and **markedly reduced (not absent)** plasma fibrin cross-linking and thrombin-dependent amine incorporation — milder than *F13a*^{-/-} mice, in which cross-linking is undetectable. Subunit gene expression is regulated independently.

"homozygous mice of either FXIII-A- or FXIII-B-deficiency did have prolonged bleeding times" — [PMID: 18224415](#)

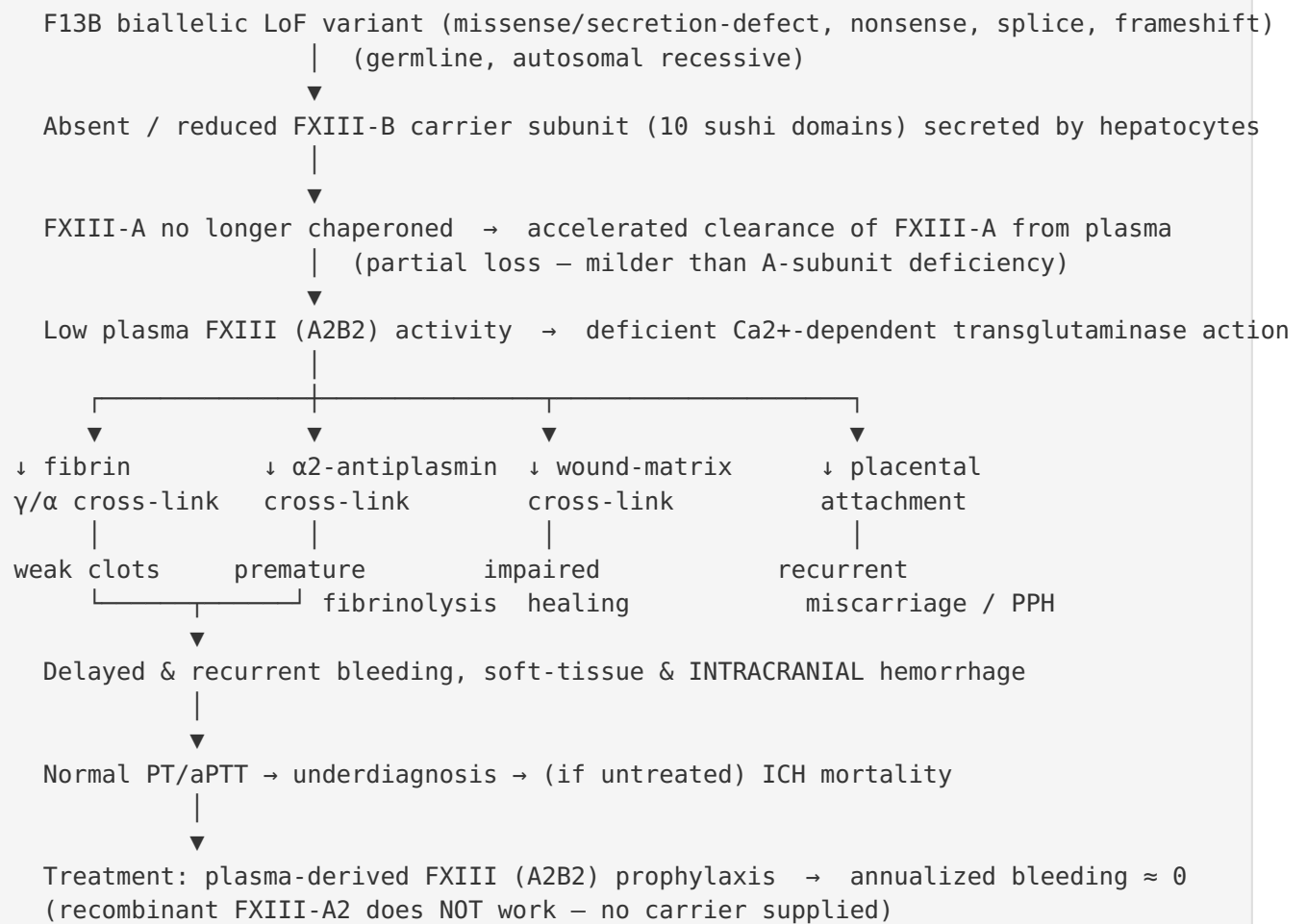
"fibrin-crosslinking in plasma were undetectable in the FXIII-A-deficient mice and markedly reduced in the FXIII-B-deficient mice" — [PMID: 18224415](#)

Direct mechanistic validation (the carrier mechanism): injecting **recombinant human FXIII-B into *F13b*^{-/-} mice raised plasma FXIII-A levels, fibrin cross-linking, and amine-incorporation activity** — demonstrating that the B subunit maintains/stabilizes circulating FXIII-A.

"rFXIII-B was injected into FXIII-B-deficient mice, FXIII-A levels, fibrin crosslinking, and amine-incorporation activities increased in their plasma, indicating that FXIII-B assisted the maintenance of FXIII-A levels in the circulation" — [PMID: 18224415](#)

Related models / applications: FXIII-A knockout mice reveal tissue-repair functions — e.g., impaired resolution of mucosal damage in DSS colitis, rescued by recombinant FXIII-A ([PMID: 26098308](#)) — and a floxed-*F13a1* mouse mapped the cellular source of plasma FXIII-A to the megakaryocyte/platelet lineage ([PMID: 26312861](#)). **Model limitation:** the *F13b*^{-/-} mouse is milder than the human severe phenotype and does not reproduce the full spectrum of human obstetric complications. **Resources:** MGI for mouse *F13b*/*F13a1* alleles.

Mechanistic Model (Synthesis)



Evidence Base

PMID	Title (abbrev.)	Supports
20880254	<i>Factor XIII: novel structural and functional aspects</i>	B-subunit 10-sushi-domain architecture; carrier role
26247044	<i>Structural/functional influences of FXIII-B heterozygous mutants</i>	F13B defects over-represented in mild deficiency
41583548	<i>Factor XIII Deficiency: Biology, Testing, Treatment</i>	Clinical phenotype; normal screening; rFXIII-A2 not for F13B
23407795	<i>Alloantibodies against FXIII B subunit</i>	Ultra-rarity (~11 cases); Japanese F13B founder effect
18224415	<i>FXIII-B administration in F13b KO mice</i>	Direct validation of carrier mechanism ; milder than A-KO
25652913	<i>FXIII: multifunctional transglutaminase</i>	Antifibrinolytic & angiogenic mechanisms
32360976	<i>French cohort obstetric outcomes</i>	Placental role; miscarriage; prophylaxis need
37314674	<i>Congenital FXIII deficiency in children</i>	Incidence 1/3–5M; AR; consanguinity 75%
25615432	<i>FXIII deficiency in Iran</i>	Geographic epidemiology; 12× Iran prevalence
24286209	<i>ISTH/SSC classification of FXIII deficiency</i>	Antigen phenotyping algorithm (A vs B)
17371605	<i>Congenital FXIII deficiency & deliveries</i>	Pregnancy FXIII thresholds; product preference
27069637	<i>Nonclinical safety of plasma-derived FXIII</i>	Safety up to 350 IU/kg, no thrombosis
28704210	<i>FXIII deficiency in south Tunisia</i>	ICH as cause of death
28581691	<i>Recombinant FXIII prophylaxis phase 3b</i>	Annualized bleeding rate of zero on prophylaxis
42230344	<i>Delayed diagnosis of FXIII deficiency in infant</i>	ICH severity; diagnostic delay
26098308	<i>FXIII in experimental colitis</i>	Tissue-repair / mucosal-healing role

PMID	Title (abbrev.)	Supports
26312861	<i>Cellular source of plasma FXIII-A</i>	Megakaryocyte/platelet origin of A-subunit
37832789	<i>Heterozygous FXIII deficiency</i>	Heterozygote activity 20–60%; prevalence ~0.8%
36940714	<i>Heterozygous FXIII deficiency insights</i>	Prevalence 1/1,000–5,000; 3.5% in Iran
31013569	<i>Disruption of FXIII-B structural disulfides</i>	Missense/disulfide-defect variant class

Evidence source types: human clinical (cohorts, case reports, ISTH guidelines), model organism (mouse knockouts), in vitro (variant/structure studies), and review/computational syntheses.

Limitations and Knowledge Gaps

- Subtype-specific data scarcity.** Only ~11 congenital FXIII-B deficiency cases were reported historically ([PMID: 23407795](#)). Much phenotype/epidemiology data is extrapolated from the far more common **A-subunit** form; true B-subtype frequencies, penetrance, and natural history remain imprecise.
- No dedicated B-subunit QoL or natural-history studies.** QoL and disability metrics are inferred from the general FXIII literature.
- Allele-frequency precision.** Individual pathogenic *F13B* allele frequencies in gnomAD were not quantified in this investigation.
- Mechanistic branches partly inferred.** The angiogenesis (thrombospondin-1) and placentation contributions to the B-subtype phenotype are supported mechanistically but not specifically demonstrated in B-subunit-deficient humans.
- Model limitations.** The *F13b^{-/-}* mouse is milder than severe human disease and does not fully model human obstetric complications.
- No OMIA-confirmed natural animal disease** was identified for the B subtype.

Proposed Follow-up Actions

1. **Quantify *F13B* pathogenic-allele frequencies** in gnomAD/population databases and compile a variant table (HGVS nomenclature, ACMG classification, secretion phenotype) to refine carrier estimates.
 2. **Assemble an international FXIII-B case registry** to define subtype-specific phenotype, penetrance, obstetric risk, and treatment response separately from the A subtype.
 3. **Confirm ontology mappings** (MONDO:0013190 ↔ OMIM #613235 ↔ ORPHA:331) and verify gnomAD constraint metrics for *F13B*.
 4. **Pharmacokinetic/clinical confirmation** that plasma-derived A₂B₂ concentrate normalizes FXIII-A survival specifically in B-subunit-deficient patients (mirroring the mouse rescue), to formalize the genotype-guided product rule.
 5. **Prospective obstetric cohort** under plasma-derived FXIII prophylaxis to establish miscarriage-prevention thresholds in B-subunit deficiency specifically.
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Report compiled from a 5-iteration autonomous investigation: 12 confirmed findings across all 15 template sections, 42 papers reviewed. Evidence spans human clinical cohorts, ISTH/SSC guidelines, a mechanistically decisive knockout-mouse model, and in-vitro variant studies.
