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# Hemophilia B

Synonyms: Christmas Disease, Factor IX Deficiency

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## Summary

### Clinical characteristics

Hemophilia B is characterized by deficiency in factor IX clotting activity that results in prolonged oozing after injuries, tooth extractions, or surgery, and delayed or recurrent bleeding prior to complete wound healing. The age of diagnosis and frequency of bleeding episodes are related to the level of factor IX clotting activity. In any individual with hemophilia B, bleeding episodes may be more frequent in childhood and adolescence than in adulthood.

- Individuals with **severe hemophilia B** are usually diagnosed during the first two years of life. Without prophylactic treatment, they may average up to two to five spontaneous bleeding episodes each month, including spontaneous joint or muscle bleeds, and prolonged bleeding or excessive pain and swelling from minor injuries, surgery, and tooth extractions.
- Individuals with **moderate hemophilia B** seldom have spontaneous bleeding, although it varies between individuals; however, they do have prolonged or delayed oozing after relatively minor trauma and are usually diagnosed before age five to six years. The frequency of bleeding episodes varies from once a month to once a year.
- Individuals with **mild hemophilia B** do not have spontaneous bleeding episodes; however, without pre- and postoperative treatment, abnormal bleeding occurs with surgery or tooth extractions. The frequency of bleeding may vary from once a year to once every ten years. Individuals with mild hemophilia B are often not diagnosed until later in life.

Approximately 30% of heterozygous females have factor IX clotting activity lower than 40% and are at risk for bleeding (even if the affected family member has mild hemophilia B), although symptoms are usually mild. After major trauma or invasive procedures, prolonged or excessive bleeding usually occurs, regardless of severity.

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## Diagnosis/testing

The diagnosis of hemophilia B is established in individuals with low factor IX clotting activity. Identification of a hemizygous *F9* pathogenic variant on molecular genetic testing in a male proband confirms the diagnosis. Identification of a heterozygous *F9* pathogenic variant on molecular genetic testing in a symptomatic female confirms the diagnosis.

## Management

*Treatment of manifestations:* Referral to a hemophilia treatment center (HTC) for assessment, education, genetic counseling, and treatment.

*Targeted therapy:* For those with severe disease, prophylactic infusions of factor IX concentrate to maintain factor IX clotting activity higher than 1% or as needed to prevent bleeding and allow normal activity improves outcomes and prevents chronic joint disease. Some individuals with moderate hemophilia bleed frequently enough to benefit from prophylaxis. Longer-acting products that allow weekly or biweekly dosing are now available. Intravenous infusion of plasma-derived or recombinant factor IX for acute bleeding episodes should be given as soon as possible after symptoms occur. Training in home infusion should be provided for individuals/families affected by moderate and severe hemophilia.

*Supportive care:* Physical therapy for evaluation and treatment of musculoskeletal disease; standard treatments for pain with help from a pain specialist as needed; standard treatments for transfusion-related infections contracted prior to virucidal treatment of plasma-derived concentrates.

*Surveillance:* For young children with severe or moderate hemophilia B, assessments every six to 12 months at an HTC; older children and adults with severe or moderate hemophilia B benefit from at least annual assessment at an HTC; for individuals with mild hemophilia B, assessment at an HTC every one to two years. Individuals with comorbidities may require more frequent visits. The assessment should include a review of bleeding episodes, adjustment of treatment plans as needed, a joint and muscle evaluation, an inhibitor screen, viral testing if indicated, and a discussion of any other issues related to the individual's hemophilia B as well as family and community support. Screening for alloimmune inhibitors is performed after treatment with factor IX concentrates has been initiated and in any individual with a suboptimal clinical response to treatment.

*Agents/circumstances to avoid:* Circumcision of at-risk males until hemophilia B is either excluded or treated with factor IX concentrate regardless of severity; activities with a high risk of trauma, particularly head injury; aspirin and all aspirin-containing products. Cautious use of other medications and herbal remedies that affect platelet function. Use precaution with intramuscular injections (apply pressure and ice; intramuscular injection may be scheduled after factor IX treatment or while on prophylaxis).

*Evaluation of relatives at risk:* It is appropriate to evaluate asymptomatic male and female at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of targeted therapy, supportive care, and surveillance. It is recommended that the genetic status of at-risk females be established prior to pregnancy or as early in a pregnancy as possible.

*Pregnancy management:* Maternal factor IX levels do not increase during pregnancy and heterozygous females may need factor IX infusion support for delivery and/or to treat or prevent postpartum hemorrhage. Heterozygous mothers should be monitored for delayed bleeding postpartum. Tranexamic acid can be used to prevent postpartum hemorrhage.

*Other:* Vitamin K does not prevent or control bleeding in hemophilia B.

## Genetic counseling

Hemophilia B is inherited in an X-linked manner. The risk to sibs of a male proband depends on the genetic status of the mother. The risk to sibs of a female proband depends on the genetic status of the mother and father. If the mother of the proband has an *F9* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%. If the father of the proband has an *F9* pathogenic variant, he will transmit it to all his daughters and none of his sons. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant are heterozygotes and may be at risk for bleeding. Once the *F9* pathogenic variant has been identified in an affected family member, genetic testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

# Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

## Suggestive Findings

Hemophilia B **should be suspected** in a male or female proband with any of the following clinical features, laboratory features, and/or family history.

**Clinical features**

- Hemarthrosis, especially with mild or no antecedent trauma
- Deep-muscle hematomas
- Intracranial bleeding in the absence of major trauma
- Neonatal cephalohematoma or intracranial bleeding
- Prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision *
- Prolonged or delayed bleeding or poor wound healing following surgery or trauma *
- Unexplained gastrointestinal bleeding or hematuria *
- Heavy menstrual bleeding, especially with onset at menarche
- Prolonged nosebleeds, especially recurrent and bilateral *
- Excessive bruising, especially with firm, subcutaneous hematomas

* Of any severity, or especially in more severely affected persons

**Laboratory features**

- Normal platelet count
- Prolonged activated partial thromboplastin time (aPTT) in severe and moderate hemophilia B; normal or mildly prolonged aPTT in mild hemophilia B
- Normal prothrombin time

**Family history** is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

**Male proband.** The diagnosis of hemophilia B **is established** in a male proband by identification of decreased factor IX clotting activity.

- **Severe hemophilia B.** <1% factor IX clotting activity

- **Moderate hemophilia B.** 1%-5% factor IX clotting activity
- **Mild hemophilia B.** 6%-40% factor IX clotting activity

Note: (1) The normal range for factor IX clotting activity is approximately 50%-150% [Khachidze et al 2006]. Individuals with factor IX clotting activity higher than 40% usually have normal coagulation in vivo. (2) Somatic mosaicism in males with hemophilia B has been described [Ketterling et al 1999, Miller 2021].

Identification of a hemizygous pathogenic (or likely pathogenic) variant in *F9* by molecular genetic testing can help predict the clinical phenotype, assess the risk of developing a factor IX inhibitor, and allow family studies (see Table 1).

**Female proband.** The diagnosis of hemophilia B **may be established** in a female proband with bleeding symptoms and decreased factor IX clotting activity, and/or by identification of a heterozygous pathogenic (or likely pathogenic) variant in *F9* by molecular genetic testing (see Table 1). Note: Factor IX clotting activity does not reliably identify heterozygous females, as only approximately 30% of females heterozygous for an *F9* pathogenic variant have factor IX clotting activity lower than 40% [Plug et al 2006].

Note: (1) Per ACMG/AMG variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this *GeneReview* is understood to include any likely pathogenic variant. (2) Identification of a hemizygous or heterozygous *F9* variant of uncertain significance does not establish or rule out the diagnosis.

## Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those with a phenotype indistinguishable from many other inherited disorders with prolonged bleeding are more likely to be diagnosed using genomic testing (see **Option 2**).

**Option 1**

**Single-gene testing.** Sequence analysis of *F9* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

**A multigene panel** that includes *F9* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

**Option 2**

When the phenotype is indistinguishable from many other inherited disorders characterized by prolonged bleeding, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 1.** Molecular Genetic Testing Used in Hemophilia B

| Gene [1] | Method | Proportion of Male Probands with a Pathogenic Variant [2] Detectable by Method |
|---|---|---|
| *F9* | Sequence analysis [3, 4] | 97%-100% [5] |
| | Gene-targeted deletion/duplication analysis [6] | 2%-3% [5] |

*1.* See Table A. Genes and Databases for chromosome locus and protein.
*2.* See Molecular Genetics for information on variants detected in this gene.
*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*4.* Routine sequence analysis should detect pathogenic variants in the *F9* proximal promoter located immediately upstream of the start codon (e.g., c.-49T>A, one variant associated with hemophilia B Leyden). Detection of disease-associated variants located farther upstream may require a targeted assay [Funnell & Crossley 2014]; see also Genotype-Phenotype Correlations and Table A, **Locus-Specific Databases**).
*5.* Mitchell et al [2010], Goodeve [2015], Johnsen et al [2022]
*6.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

# Clinical Characteristics

## Clinical Description

Hemophilia B in the untreated individual is characterized by spontaneous bleeding including intracranial bleeding, muscle and joint bleeding (usually in severe disease), immediate or delayed bleeding or prolonged oozing after injuries, tooth extractions, or surgery, or renewed bleeding after initial bleeding has stopped [Berntorp et al 2021, Mancuso et al 2021]. Intermittent oozing may last for days or weeks after tooth extraction. Prolonged or delayed bleeding or wound hematoma formation after surgery is common. After circumcision, males with hemophilia B of any severity may have prolonged oozing, or they may heal normally. In severe hemophilia B, spontaneous joint bleeding is the most frequent sign.

The age of diagnosis and frequency of bleeding episodes are generally related to the factor IX clotting activity (see Table 2). In any affected individual, bleeding episodes may be more frequent in childhood and adolescence than in adulthood. To some extent, this greater frequency is a function of both physical activity levels and vulnerability during more rapid growth.

**Individuals with severe hemophilia B** are usually diagnosed as newborns due to birth- or neonatal-related procedures or during the first year of life [Kulkarni et al 2009]. In untreated toddlers, bleeding from minor mouth injuries and large "goose eggs" from minor head bumps are common; these are the most frequent presenting symptoms of severe hemophilia B. Intracranial bleeding may also result from head injuries. The

untreated child almost always has subcutaneous hematomas; some have been referred for evaluation of possible nonaccidental trauma.

As the child grows and becomes more active, spontaneous joint bleeds occur with increasing frequency unless the child is on a prophylactic treatment program. Spontaneous joint bleeds or deep-muscle hematomas initially cause pain or limping before swelling appears. Children and young adults with severe hemophilia B who are not treated have an average of two to five spontaneous bleeding episodes each month. Joints are the most common sites of spontaneous bleeding; other sites include the muscles, kidneys, gastrointestinal tract, brain, and nose. Without prophylactic treatment, individuals with hemophilia B have prolonged bleeding or excessive pain and swelling from minor injuries, surgery, and tooth extractions.

**Individuals with moderate hemophilia B** seldom have spontaneous bleeding, although there is significant variability between individuals, and bleeding episodes may be precipitated by relatively minor trauma. Without pretreatment (as for elective invasive procedures) they do have prolonged or delayed oozing after relatively minor trauma and are usually diagnosed before age five to six years. The frequency of bleeding episodes requiring treatment with factor IX concentrates varies from once a month to once a year. Signs and symptoms of bleeding are otherwise similar to those found in severe hemophilia B.

**Individuals with mild hemophilia B** do not have spontaneous bleeding. However, without treatment, abnormal bleeding occurs with surgery, tooth extractions, and moderate to major injuries. The frequency of bleeding may vary from once a year to once every ten years. Individuals with mild hemophilia B are often not diagnosed until later in life when they undergo surgery or tooth extraction or experience major trauma.

**Heterozygous females** with a factor IX clotting activity level lower than 40% are at risk for bleeding that is usually comparable to that seen in males with mild hemophilia B. However, more subtle abnormal bleeding may occur with baseline factor IX clotting activity levels between 30% and 60% [Plug et al 2006, van Galen et al 2021].

**Table 2.** Symptoms Related to Severity of Untreated Hemophilia B

| Severity | Factor IX Clotting Activity [1] | Symptoms | Usual Age at Diagnosis |
|---|---|---|---|
| **Severe** | <1% | • Frequent spontaneous bleeding<br>• Excessive &/or prolonged bleeding after minor injuries, surgery, or tooth extractions | Age ≤2 yrs |
| **Moderate** | 1%-5% | • Spontaneous bleeding uncommon<br>• Excessive &/or prolonged bleeding after minor injuries, surgery, or tooth extractions | Age ≤6 yrs |
| **Mild** | 6%-40% | • No spontaneous bleeding<br>• Excessive &/or prolonged bleeding after major injuries, surgery, or tooth extractions | Often later in life, depending on hemostatic challenges |

*1.* Clinical severity does not always correlate with the in vitro assay result.

**Complications of untreated bleeding.** The leading cause of death related to bleeding is intracranial hemorrhage [Zwagemaker et al 2021]. The major cause of disability from bleeding is chronic joint disease [Berntorp et al 2021]. Currently available treatment with clotting factor IX concentrates is normalizing life expectancy and reducing chronic joint disease for children and adults with hemophilia B [Mancuso et al 2021]. Prior to the availability of such treatment, the median life expectancy for the most severely affected individuals was in childhood. Excluding death from HIV, life expectancy for those severely affected individuals receiving adequate treatment was 63 years in 2000 [Darby et al 2007]. A more recent analysis from the Netherlands found life expectancy in men with hemophilia to be 77 years, six years less than the Dutch male population [Hassan et al 2021].

**Other.** Since the late 1960s, the mainstay of treatment of bleeding episodes has been factor IX concentrates that initially were derived solely from donor plasma. By the late 1970s, more purified preparations became available, reducing the risk for thrombogenicity but allowing viral transmission. HIV transmission from concentrates occurred between 1979 and 1985. Approximately half of these individuals died of AIDS prior to the advent of effective HIV therapy.

Viral inactivation methods and donor screening of plasmas were introduced by 1990 and a recombinant factor IX concentrate became available shortly thereafter [Monahan & Di Paola 2010]. A second recombinant factor IX concentrate was licensed by the FDA in 2013. Three long-acting modified recombinant factor IX concentrates are now FDA approved, extending the factor IX half-life three- to fivefold compared to unmodified products [Hart et al 2022]. In November 2022 the FDA approved the first gene therapy product (etranacogene dezaparvovec) for adults with hemophilia B.

Hepatitis B transmission from earlier plasma-derived concentrates was eliminated with donor screening and then vaccination introduced in the 1970s. Most individuals exposed to plasma-derived concentrates prior to the late 1980s became chronic carriers of hepatitis C virus. Viral inactivation methods implemented in concentrate preparation and donor screening assays developed by 1990 have essentially eliminated hepatitis C transmission from plasma-derived concentrates.

Alloimmune inhibitors occur much less frequently in hemophilia B than in hemophilia A although are more common than previously appreciated. Earlier data suggested a rate of 3%-5%, but more recent data suggests that it may be closer to 10%, almost exclusively in individuals with severe disease. The incidence appears to vary by population and underlying genetic variant [Puetz et al 2014, Male et al 2021, Johnsen et al 2022, Kihlberg et al 2022]. These individuals usually have partial- or whole-gene deletions or certain nonsense variants (see Genotype-Phenotype Correlations and Table A, **Locus-Specific Databases**). At times, the onset of an alloimmune response has been associated with anaphylaxis to transfused factor IX or development of nephrotic syndrome [DiMichele 2007, Chitlur et al 2009].

## Genotype-Phenotype Correlations

**Disease severity**

- Large deletions, nonsense variants, and most frameshift variants cause severe disease.
- Missense variants can cause severe, moderate, or mild disease depending on their location and the specific substitutions involved.

**Alloimmune inhibitors**

- Alloimmune inhibitors occur with the greatest frequency (40%-60%) in individuals with large partial (>50 bp) deletions, whole-gene deletions, or early-termination variants (<100 predicted amino acids) [Goodeve 2015, Saini et al 2015].
- Missense variants are rarely associated with inhibitors.

Unlike hemophilia A, severe hemophilia B is often caused by a missense variant, and several of these are associated with normal cross-reacting material (factor IX antigen) levels (see Table A, **Locus-Specific Databases**).

Uncommon variants within the carboxylase-binding domain of the propeptide cause increased sensitivity to warfarin anticoagulation in individuals without any baseline bleeding tendency [Oldenburg et al 2001] (see Management).

In hemophilia B Leyden, more than 20 different causative variants in the proximal *F9* promoter region have been described [Funnell & Crossley 2014, Miller 2021]. The severity of disease decreases after puberty; mild disease disappears, and severe disease becomes mild, depending on the specific pathogenic variant.

### Penetrance

All males with an *F9* pathogenic variant are affected and will have hemophilia B of approximately the same severity as all other affected males in the family; however, other genetic and environmental effects may modify the clinical severity to some extent.

Approximately 30% of heterozygous females have factor IX clotting activity below 40% and are at risk for a bleeding disorder; mild bleeding can occur in carriers with low-normal factor IX activity [Plug et al 2006].

### Nomenclature

Newly recommended terminology for heterozygous females designates five clinical- and laboratory-based categories [van Galen et al 2021]. For females with decreased (≤40%) factor IX clotting activity, the terminology is the same as that used for hemizygous males:

- Severe hemophilia B (<1% factor IX clotting activity)
- Moderate hemophilia B (1%-5% factor IX clotting activity)
- Mild hemophilia B (6%-40% factor IX clotting activity)

For heterozygous females with normal factor IX clotting activity:

- Individuals with a bleeding phenotype are termed "symptomatic hemophilia carriers";
- Individuals who do not have a bleeding phenotype are termed "asymptomatic hemophilia carriers."

### Prevalence

The birth prevalence of hemophilia B has been calculated to be five in 100,000 live male births, and 1.5 in 100,000 for severe hemophilia B [Iorio et al 2019].

The birth prevalence is thought to be approximately the same in all countries and all ethnicities, presumably because of the high spontaneous mutation rate of *F9* and its presence on the X chromosome.

Hemophilia B is about one fifth as prevalent as hemophilia A.

## Genetically Related (Allelic) Disorders

Certain missense variants within the propeptide portion of factor IX enhance sensitivity to warfarin by altering the binding of a gamma-carboxylase responsible for post-translational Gla residue formation [Oldenburg et al 2001].

The variant p.Arg384Leu, a missense gain-of-function change associated with markedly elevated circulating levels of factor IX and venous thrombosis at a young age, has been described in one family [Simioni et al 2009]. This amino acid change has been incorporated into *F9* constructs currently being used in gene therapy clinical trials [Nathwani 2019] and in the FDA-approved product (etranacogene dezaparvovec).

## Differential Diagnosis

A detailed history of bleeding episodes can help determine if an individual has a lifelong, inherited bleeding disorder or an acquired (often transient) bleeding disorder. Increased bleeding with trauma, tonsillectomy, or for a few hours following tooth extraction may be seen in individuals without a bleeding disorder. In contrast,

prolonged or intermittent oozing that lasts several days following tooth extraction or mouth injury, renewed bleeding or increased pain and swelling several days after an injury, or developing a wound hematoma several days after surgery almost always indicates a coagulation problem. An older individual with severe or moderate hemophilia B may have joint deformities and muscle contractures. Large bruises and subcutaneous hematomas for which no trauma can be identified may be present. Individuals with a mild bleeding disorder usually have no outward signs except during an acute bleeding episode. Of note, petechial hemorrhages indicate severe thrombocytopenia and are not a feature of hemophilia B.

**Bleeding disorders with low factor IX clotting activity**

- **Combined vitamin K-dependent factor deficiency** (OMIM PS277450) is associated with deficiency of prothrombin, factors VII, IX, and X, and proteins C and S. It is very rare, usually presenting in childhood with severe bleeding. Coagulation laboratory analysis shows a markedly prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). The prolonged PT, multiple coagulation factor deficiencies, and autosomal recessive inheritance would differentiate this from hemophilia B. Pathogenic variants in *GGCX* and *VKORC1* are causative.
- Common acquired deficiencies of vitamin K-dependent factors occur in individuals receiving **warfarin treatment** or those with **liver disease**. Vitamin K deficiency usually presents in the setting of other illnesses, although it may be solely nutritional. Warfarin therapy is by history. Clinical manifestations of liver disease are usually present when coagulation factors are decreased. These diagnoses can be distinguished from hemophilia B by a PT that is prolonged greater than the prolongation of the aPTT (versus an isolated prolonged aPTT in hemophilia B) and multiple coagulation factor deficiencies.

**Bleeding disorders with normal factor IX clotting activity.** See Table 3.

**Table 3.** Inherited Bleeding Disorders with Normal Factor IX Clotting Activity

| Gene(s) | Disorder | MOI | Clinical Features | Laboratory Findings / Comment |
|---|---|---|---|---|
| *F11* | Factor XI deficiency (OMIM 612416) | AR<br>AD | Both compound heterozygotes & homozygotes may exhibit bleeding similar to that seen in mild or moderate hemophilia B. | Heterozygotes have factor XI coagulant activity 25%-75% of normal; homozygotes have activity <1%-15%. [1] A specific factor XI clotting assay establishes the diagnosis. |
| *F12*<br>*KLKB1*<br>*KNG1* | Factor XII (OMIM 234000), prekallikrein (OMIM 612423), or high molecular-weight kininogen deficiencies (OMIM 228960) | AR | Not assoc w/clinical bleeding | Can cause prolonged aPTT |
| *F13A1*<br>*F13B* | Factor XIII deficiency (OMIM 613225, 613235) | AR | Umbilical stump bleeding in >80% of persons. Intracranial bleeding that occurs spontaneously or following minor trauma in 30% of persons. Subcutaneous hematomas, muscle hematomas, defective wound healing, & recurrent spontaneous abortion are also seen. Joint bleeding is rare. | All coagulation screening tests are normal; a screening test for clot solubility or a specific assay for factor XIII activity can confirm the diagnosis. Bleeding symptoms are reported in persons w/ levels <13% by quantitative assay. [2] |
| *F2*<br>*F5*<br>*F7*<br>*F10* | Prothrombin (factor II) (OMIM 613679), factor V (OMIM 227400), factor X (OMIM 227600), & factor VII (OMIM 227500) deficiencies | AR | Rare bleeding disorders. Persons may have easy bruising & hematoma formation, epistaxis, heavy menstrual bleeding, & bleeding after trauma & surgery. Hemarthroses are less common. Spontaneous intracranial bleeding can occur. | Factor VII deficiency should be suspected if the PT is prolonged & aPTT is normal. Persons w/deficiency of factors II, V, or X usually have prolonged PT & aPTT, but specific coagulation factor assays establish the diagnosis. |

*Table 3. continued from previous page.*

| Gene(s) | Disorder | MOI | Clinical Features | Laboratory Findings / Comment |
|---|---|---|---|---|
| *F8* | Hemophilia A | XL | Clinically indistinguishable from hemophilia B | Diagnosis is based on a factor VIII clotting activity level <40% in the presence of a normal VWF level. |
| *FGA*<br>*FGB*<br>*FGG* | Afibrinogenemia (OMIM 202400), hypofibrinogenemia (OMIM 616004), dysfibrinogenemia (OMIM 616004) | AR<br>AD [3] | Afibrinogenemia is assoc w/ manifestations similar to hemophilia B except that bleeding from minor cuts is prolonged due to lack of fibrinogen to support platelet aggregation. Hypofibrinogenemia & dysfibrinogenemia can be assoc w/mild-to-moderate bleeding symptoms. Rarely persons w/dysfibrinogenemia are at risk for thrombosis. | In dysfibrinogenemia there is discordance between functional & antigenic levels, w/ latter usually in normal range. For all fibrinogen disorders thrombin & reptilase times are almost always prolonged & functional measurements of fibrinogen are ↓. |
| *GP1BA*<br>*GP1BB*<br>*GP9*<br>*ITGA2B* | Platelet function disorders incl Bernard-Soulier syndrome (OMIM 231200) & Glanzmann thrombasthenia (OMIM 273800) | AR | In Bernard-Soulier syndrome, Glanzmann thrombasthenia, & storage pool & nonspecific secretory defects: skin & mucous membrane bleeding, recurring epistaxis, GI bleeding, heavy menstrual bleeding, & excessive bleeding during or immediately after trauma & surgery. Joint, muscle, & intracranial bleeding is rare. | Diagnosis is established using platelet aggregation assays, flow cytometry, & platelet electron microscopy. |
| *VWF* | Type 1 von Willebrand disease (VWD) | AD | Mucous membrane bleeding incl epistaxis, bleeding w/dental extractions, heavy menstrual & postpartum bleeding, & spontaneous bruises. Also may have trauma & procedure-related bleeding. | Partial quantitative deficiency of VWF (low VWF antigen, low factor VIII clotting activity, & low VWF activity). (Persons w/hemophilia B have a normal VWF level & a normal factor VIII activity.) |
| | Type 2A & 2B VWD | AD | in type 2A, bleeding as in Type 1 VWD or may be more severe. In type 2B, bleeding as in Type 1 VWD or may be more severe. Also may have thrombocytopenia. | Qualitative deficiency of VWF w/↓ of high molecular-weight multimers (more loss in type 2A). Measures of VWF platelet or collagen binding activity are ↓, while VWF antigen & factor VIII clotting activity may be low-normal to mildly ↓. |
| | Type 2M VWD | AD | Bleeding as in type 2A VWD | Qualitative deficiency of VWF w/similar ↓ in function as seen in type 2A; but assoc w/normal multimer pattern. |
| | Type 2N VWD | AR | Clinically indistinguishable from hemophilia B | VWF platelet binding is completely normal. Biochemically, type 2N VWD is indistinguishable from hemophilia B; however, hemophilia B can be distinguished from type 2N VWD by molecular genetic testing. |

*Table 3. continued from previous page.*

| Gene(s) | Disorder | MOI | Clinical Features | Laboratory Findings / Comment |
|---|---|---|---|---|
| | Type 3 VWD | AR | Frequent episodes of mucous membrane bleeding. Joint & muscle bleeding similar to that seen in hemophilia B. | Complete or near-complete quantitative deficiency of VWF. VWF level is often <1% & factor VIII clotting activity is most commonly 2%-8%. |

AD = autosomal dominant; aPTT= activated partial thromboplastin time; AR = autosomal recessive; GI = gastrointestinal; MOI = mode of inheritance; PT = prothrombin time; VWF = von Willebrand factor; XL = X-linked
*1.* Duga & Salomon [2013]
*2.* Menegatti et al [2017]
*3.* Afibrinogenemia is inherited in an autosomal recessive manner. Hypofibrinogenemia can be inherited in either an autosomal dominant or an autosomal recessive manner. Dysfibrinogenemia is inherited in an autosomal dominant manner.

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hemophilia B, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 4.** Recommended Evaluations Following Initial Diagnosis in Individuals with Hemophilia B

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Hematologic** | • Personal & family history of bleeding to help predict disease severity<br>• CBC w/platelet count, esp if history of nose bleeds, GI bleeding, mouth bleeding, or (in females) heavy menstrual bleeding or postpartum hemorrhage<br>• Referral to HTC<br>• *F9* molecular testing to aid in determining disease severity, likelihood of inhibitor development, & testing of family members | |
| **Musculoskeletal** | Joint & muscle eval, esp if person reports history of hemarthrosis or deep-muscle hematomas | |
| **Infectious disease** | Screening for hepatitis A, B, & C as well as HIV if blood products or plasma-derived clotting factor concentrates were administered prior to 1990 | |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & their families re nature, MOI, & implications of hemophilia B to facilitate medical & personal decision making |

CBC = complete blood count; GI = gastrointestinal; HTC = hemophilia treatment center; MOI = mode of inheritance
*1.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

The World Federation of Hemophilia has published treatment guidelines for the management of individuals with hemophilia. Treatment should be coordinated through a hemophilia treatment center (HTC).

### Targeted Therapy

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure.* —ED

Prophylactic treatment is recommended by the National Hemophilia Foundation and the World Federation of Hemophilia for individuals with severe hemophilia B and is administered as infusions of standard or extended half-life factor IX concentrate as needed to maintain factor IX clotting activity above 1% or to prevent bleeding and allow normal activities [Srivastava et al 2020]. Some individuals with moderate hemophilia B bleed frequently and also benefit from prophylaxis. Modified recombinant factor IX concentrates extend the half-life three- to fivefold, allowing significantly fewer infusions compared to use of standard half-life products [Hart et al 2022]. Choice of product should be individualized based on clinical factors and activity levels. Initiation of prophylactic infusions of factor IX concentrate in young boys before or just after their first few joint bleeds has been shown to nearly eliminate spontaneous bleeding and prevent chronic joint disease [Manco-Johnson et al 2007]. Experience, primarily in hemophilia A, has shown that lower-dose prophylaxis used in countries with fewer resources can decrease bleeding and improve outcomes [Srivastava et al 2020]. In addition, factor IX concentrates are used to treat acute bleeding and prevent bleeding and allow healing in individuals with hemophilia B undergoing procedures.

**Intravenous infusion of factor IX concentrates (recombinant or plasma-derived)** is used to treat acute bleeding or prevent bleeding on a long-term basis (prophylaxis) or prior to and following procedures.

- For acute bleeding, treatment should be given as soon as possible after symptoms occur. For those trained in home infusion this can be done promptly in the home.
- Dosing is weight based and target levels and duration of treatment vary by the severity of bleeding and/or the risk associated with the surgery or procedure.
- Prophylactic regimens are instituted based on disease severity and may be informed by bleeding symptoms or instituted prior to joint bleeding.
- Parents of children age two to five years with severe hemophilia B should be trained to administer the infusions. Older children should be trained in self-infusion. Home treatment allows for prompt treatment and facilitates prophylactic therapy.

**Pediatric issues.** Special considerations for care of infants and children with hemophilia B include the following [Chalmers et al 2011, Srivastava et al 2020]:

- Infant males with a family history of hemophilia B should not be circumcised unless hemophilia B is either excluded or, if present, is treated with factor IX concentrate directly before and after the procedure.
- Immunizations should be administered subcutaneously if known to be an effective route; intramuscular injections may be managed with pressure and ice and, if possible, under factor IX coverage.
- Effective dosing of factor IX requires an understanding of different pharmacokinetics in young children.

**Immune tolerance therapy.** Alloimmune inhibitors to factor IX greatly compromise the ability to manage bleeding episodes [Hay et al 2006]. Their onset can be associated with anaphylactic reactions to factor IX infusion and nephrotic syndrome [DiMichele 2007, Chitlur et al 2009]. Immune tolerance can be challenging, although it can be effective [Astermark et al 2021], and long-term bypassing therapy, primarily recombinant activated factor VII (rFVIIa) or an investigational drug, may be needed for treatment.

## Supportive Care

**Physical therapy.** Physical therapists play a key role in the care of individuals with hemophilia B in the evaluation and treatment of musculoskeletal disease and in advising on physical activities to maintain healthy joints. The use of musculoskeletal ultrasound aids in the evaluation of bleeding and helps to guide treatment.

**Pain.** Most individuals who have had repeated musculoskeletal bleeding experience acute and chronic pain. Addressing pain through multiple modalities is an important part of comprehensive hemophilia B care. Individuals often benefit from treatment by a pain specialist.

**Treatment for transfusion-related infections.** Standard treatments per infectious disease specialist. Note: Virucidal treatment of plasma-derived concentrates has eliminated the risk of HIV transmission since 1985, and hepatitis B and C viruses since 1990. All individuals with hemophilia B who have active hepatitis C infections should be offered the current, very effective treatment for viral eradication.

## Surveillance

Persons with hemophilia followed at an HTC (see Resources) have lower mortality than those who are not [Soucie et al 2000, Pai et al 2016].

Young children with severe or moderate hemophilia B should be evaluated at an HTC (accompanied by their parents/guardians) every six to 12 months and as needed to review their history of bleeding episodes and adjust treatment plans. Early signs and symptoms of possible bleeding episodes are reviewed. The assessment should also include a joint and muscle evaluation, an inhibitor screen, viral testing if indicated, and a discussion of any other issues related to the individual's hemophilia B as well as family and community support.

Because of the risk of severe allergic reactions with development of alloantibodies, it is recommended that the first 20 factor replacement treatments be given in a medical setting where resuscitation medications and equipment are available. Risk can be stratified if the genetic variant is known. Those with large partial deletions, complete gene deletions, and early termination variants (<100 predicted amino acids) are at highest risk [Hart et al 2022]. Screening for alloimmune inhibitors is performed after treatment with factor IX concentrates has been initiated for either bleeding or prophylaxis (see Genotype-Phenotype Correlations). Testing for inhibitors should also be performed in any individual with hemophilia B whenever a suboptimal clinical response to treatment is suspected.

Older children and adults with severe or moderate hemophilia B benefit from at least annual assessment at an HTC (see Resources) and periodic assessments to review bleeding episodes and treatment plans, evaluate joints and muscles, screen for inhibitors, perform viral testing if indicated, provide education, and discuss other issues relevant to the individual's hemophilia B.

Individuals with mild hemophilia B can benefit from an assessment at an HTC every one to two years. Affected individuals with comorbidities and other complications or treatment challenges may require more frequent visits.

## Agents/Circumstances to Avoid

The following agents/circumstances should be avoided:

- Infant males with a family history of hemophilia B should not be circumcised unless hemophilia B is excluded; or, if present, the infant should be treated with factor IX concentrate directly before and after the procedure.
- Use precaution with intramuscular injections without factor IX treatment. Pressure on the site after intramuscular injection in children has been reported without factor IX coverage. Individuals on prophylactic factor IX infusions may be given intramuscular injections after factor IX treatment or factor IX may be given specifically for this indication.
- Activities that involve a high risk of trauma, particularly of head injury, should be avoided.
- Medications and herbal remedies that affect platelet function, including aspirin, should be avoided unless there is strong medical indication, such as individuals with a cardiovascular indication. Individuals with severe hemophilia usually require clotting factor prophylaxis to allow aspirin and other platelet-inhibitory drugs to be used safely [Angelini et al 2016].

Older, intermediate-purity plasma-derived "prothrombin complex" concentrates should be used cautiously (if at all) in hemophilia B because of their thrombogenic potential.

## Evaluation of Relatives at Risk

It is appropriate to evaluate asymptomatic male and female at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of targeted therapy, supportive care, and surveillance. A thorough family history may identify relatives who are at risk but have not been tested (particularly in families with mild hemophilia B).

**Evaluation of at-risk males**

- Assay of factor IX clotting activity from a cord blood sample obtained by venipuncture of the umbilical vein (to avoid contamination by amniotic fluid or placenta tissue), assessment of factor IX clotting activity in the neonatal period, or molecular genetic testing for the family-specific *F9* pathogenic variant can establish or exclude the diagnosis of hemophilia B in newborn males at risk.

  Note: (1) The cord blood for factor IX clotting activity assay should be drawn into a syringe containing one tenth volume of sodium citrate to avoid clotting and to provide an optimal mixing of the sample with the anticoagulant. (2) Factor IX clotting activity in cord blood in a normal-term newborn is lower than in adults (mean: ~30%; range: 15%-50%); thus, the diagnosis of hemophilia B can be established in an infant with activity lower than 1% but is equivocal in an infant with moderately low (15%-20%) activity.

- Infants with a family history of hemophilia B should not be circumcised unless hemophilia B is either excluded or, if present, factor IX concentrate is administered immediately before and after the procedure to prevent delayed oozing and poor wound healing. The benefit versus the risk of exposure to factor IX concentrate in early childhood should be considered.

**At-risk females.** Approximately 30% of heterozygous females have factor IX clotting activity lower than 40% and may have abnormal bleeding. In a Dutch survey of heterozygous females, bleeding symptoms correlated with baseline factor clotting activity; there was suggestion of a very mild increase in bleeding even in those with 40% to 60% factor IX clotting activity [Plug et al 2006]. Joint range of motion in female carriers with factor VIII or factor IX activity lower than 40% was significantly different from that measured in normal controls and inversely related to factor level [Sidonio et al 2014].

- All daughters and mothers of an affected male and other at-risk females should have molecular genetic testing for the family-specific *F9* pathogenic variant. Heterozygous females should have a baseline factor IX clotting activity assay to determine if they are at increased risk for bleeding.
- It is recommended that the genetic status of at-risk females be established prior to pregnancy or as early in a pregnancy as possible.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

**Obstetric issues.** It is recommended that the genetic status of a female at risk for hemophilia B be established prior to pregnancy or as early in a pregnancy as possible.

Unlike for factor VIII, maternal factor IX levels do not increase during pregnancy, and heterozygous females are more likely to need factor IX infusion support for delivery and/or to treat or prevent postpartum hemorrhage. In females with hemophilia B, postpartum hemorrhage has been a prominent feature, even in women without heavy menstrual bleeding [Yang & Ragni 2004]. To prevent postpartum hemorrhage, tranexamic acid 1 gm intravenously immediately following cord clamping and then orally for seven to 14 days postpartum or as needed with or without factor IX concentrate as indicated by factor IX clotting activity can be used.

If the female has a baseline factor IX clotting activity below approximately 40%, she by definition has hemophilia B and is at risk for excessive bleeding, particularly postpartum, and may require therapy with factor IX concentrate [Yang & Ragni 2004].

**Newborn males.** Controversy remains as to indications for cesarean section versus vaginal delivery [Leebeek et al 2020]. In a retrospective study of 580 males age birth to two years with hemophilia A and hemophilia B, 17 suffered intracranial hemorrhages with delivery, and all but one were delivered vaginally [Kulkarni et al 2009]. This finding supports the recommendation of cesarean section for infants with hemophilia; however, 12 of the 17 were born to women not known to be heterozygous, suggesting that a planned delivery may mitigate risks. A more recent large study showed a similar risk of intracranial hemorrhage after planned vaginal delivery as reported in the general population [Andersson et al 2019]. The relative risks of cesarean section versus vaginal delivery should be considered and discussed with the family and obstetrician so that a coordinated plan can be developed. Regardless of delivery mode, instrumentation with vacuum assistance or forceps must be avoided.

### Therapies Under Investigation

**Gene therapy for hemophilia B.** Clinical trials for gene therapy for hemophilia B are under way, and one product was approved by the FDA in 2022. Those that are currently in or have recently completed Phase III clinical trials use liver-targeted adeno-associated vectors (AAV) and include the *F9* Padua variant (p.Arg384Leu), which results in a transgene with increased specific activity. These vectors use liver-restricted promoters to target synthesis to the natural site of factor IX synthesis. Therapeutic levels have been achieved in many, although not all, individuals in studies to date, and short-term steroids are often needed for elevated transaminases. Long-term durability and safety need further study [Leebeek & Miesbach 2021].

**Hemostasis rebalancing agents.** Several products are under study that alter the balance of hemostasis so that individuals in which hemostasis is defective, such as those with hemophilia B, can have a more normal hemostatic response [Mancuso et al 2021].

Hemostasis rebalancing agents in late-phase clinical trials include antithrombin inhibitors and tissue factor pathway inhibitors. These have shown efficacy in hemophilia B and are particularly promising for individuals with hemophilia B and prevalent inhibitors.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

### Other

Vitamin K does not prevent or control bleeding in hemophilia B.

Fresh frozen plasma is no longer recommended to treat hemophilia B because it is not treated with a virucidal agent.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

### Mode of Inheritance

Hemophilia B is inherited in an X-linked manner.

## Risk to Family Members

**Parents of a male proband**

- The father of an affected male will not have the disease, nor will he be hemizygous for the *F9* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a female has more than one affected child and no other affected relatives and if the familial pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- Approximately 30% of affected males have no family history of hemophilia B. If a male is the only affected family member (i.e., a simplex case), it is possible that:
    - The mother is heterozygous for an *F9* pathogenic variant.
    - The mother has somatic/germline mosaicism. Somatic mosaicism is reported in ≤11% of families [Ketterling et al 1999, Miller 2021].

      Note: Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
    - The mother is not heterozygous for an *F9* pathogenic variant, and the affected male has a *de novo* pathogenic variant.
- Molecular genetic testing of the mother is recommended to assess her genetic status and to allow reliable recurrence risk assessment.

**Parents of a female proband**

- A heterozygous female proband may have inherited the *F9* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother and the father can help determine if the pathogenic variant was inherited.

**Sibs of a male proband.** The risk to the sibs depends on the genetic status of the mother:

- If the mother of the proband has an *F9* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
    - Males who inherit the pathogenic variant will be affected.
    - Females who inherit the pathogenic variant will be heterozygotes. Heterozygous females with a factor IX clotting activity level lower than 40% are at risk for bleeding that is usually comparable to that seen in males with mild hemophilia. However, more subtle abnormal bleeding may occur with baseline factor IX clotting activity levels between 30% and 60% [Plug et al 2006].
- All sibs should have factor IX clotting activity assayed unless molecular genetic testing confirms that they have not inherited the *F9* pathogenic variant present in the family.

**Sibs of a female proband.** The risk to sibs depends on the genetic status of the mother and father:

- If the mother of the proband has an *F9* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50% (see **Sibs of a male proband**).
- If the father of the proband has an *F9* pathogenic variant, he will transmit it to all his daughters and none of his sons.

**Offspring of a male proband.** Affected males transmit the *F9* pathogenic variant to all of their daughters and none of their sons.

**Offspring of a female proband.** Females with an *F9* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

**Other family members**

- The maternal aunts and maternal cousins of a male proband may be at risk of having an *F9* pathogenic variant.
- The risk to other family members of a female proband depends on the status of the proband's mother and father: if a parent has the *F9* pathogenic variant, the parent's family members may be at risk.

Note: Molecular genetic testing can often determine the point of origin of a *de novo* pathogenic variant. Determining the point of origin of a *de novo* pathogenic variant is important for determining which branches of the family are at risk for hemophilia B.

## Heterozygote Detection

Molecular genetic testing for identification of female heterozygotes is most informative if the *F9* pathogenic variant has been identified in an affected family member. If an affected family member is not available for testing, molecular genetic testing can be performed first by sequence analysis, and if no pathogenic variant is identified, then by gene-targeted deletion/duplication analysis.

See Management, Evaluation of Relatives at Risk, **At-risk females** for information on evaluating at-risk female relatives for the purpose of early diagnosis and treatment.

Note: Factor IX clotting activity does not reliably identify heterozygous females, as only approximately 30% of females heterozygous for an *F9* pathogenic variant have factor IX clotting activity lower than 40% [Plug et al 2006].

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

See the World Federation of Hemophilia treatment guidelines for recommendations regarding psychosocial support for individuals with hemophilia and their families.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is recommended that the genetic status of a female at risk be established prior to pregnancy or as early in a pregnancy as possible (see Management, Pregnancy Management).
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are heterozygous, or are at risk of being heterozygous.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *F9* pathogenic variant has been identified in an affected family member, or if it cannot be identified but linkage can be established in the family, prenatal and preimplantation genetic testing are possible [Laurie et al 2010].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **Canadian Hemophilia Society**
  Canada
  **Phone:** 800-668-2686
  **Email:** chs@hemophilia.ca
  hemophilia.ca
- **National Hemophilia Foundation**
  **Phone:** 212-328-3700; 888-463-6643
  **Email:** info@hemophilia.org
  www.hemophilia.org
- **The Haemophilia Society**
  United Kingdom
  **Phone:** 020 7939 0780
  **Email:** info@haemophilia.org.uk
  haemophilia.org.uk
- **World Federation of Hemophilia**
  Canada
  **Phone:** 514-875-7944
  **Fax:** 514-875-8916
  **Email:** wfh@wfh.org
  wfh.org
- **Hemophilia Treatment Center (HTC) Directory**
  Centers for Disease Control and Prevention
  HTC directory
- **MedlinePlus**
  Hemophilia B

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Hemophilia B: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|

*Table A. continued from previous page.*

| | | | | | |
|---|---|---|---|---|---|
| *F9* | Xq27.1 | Coagulation factor IX | Hemobase: Hemophilia B mutation registry<br>F9 @ LOVD<br>Factor IX Mutation Database<br>CHBMP F9 Mutation List<br>Factor IX Gene (F9) Variant Database | F9 | F9 |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for Hemophilia B (View All in OMIM)

| | |
|---|---|
| 300746 | COAGULATION FACTOR IX; F9 |
| 306900 | HEMOPHILIA B; HEMB |

## Molecular Pathogenesis

Factor IX is synthesized in hepatocytes and circulates as a zymogen at 90 nmol/L (5 µg/mL). During coagulation initiation in vivo, it is activated by factor VIIa / tissue factor, and in coagulation amplification and propagation by factor IXa, in a reaction in which the activation peptide is cleaved. Activated factor IX is the intrinsic factor X activator, requiring its cofactor, activated factor VIII, a lipid surface, and calcium. Molecular interactions across multiple regions of the factor IXa molecule are involved in factor Xa activation [Kristensen et al 2016]. This activation is a critical early step that can regulate the overall rate of thrombin generation in coagulation.

Factor IX includes several distinct domains [Kanagasabai et al 2013, Rallapalli et al 2013]. From the 5' end, these domains are:

- Signal peptide and propeptide domain: cleaved to yield the mature protein, a secreted 415-amino acid peptide;
- GLA domain;
- Two domains homologous with epidermal growth factor;
- Connecting sequence: includes the activation peptide;
- Catalytic domain: typical of serine proteases.

Post-translational modifications include glycosylation, sulfation, phosphorylation, beta-hydroxylation, and gamma-carboxylation. A gamma-carboxylase binds to the propeptide before cleavage and, in a vitamin K-dependent step, converts the first 12 glutamic acid residues (near the amino-terminus) to gamma-carboxyglutamic residues (GLA domain). The GLA domain then binds calcium ions and adopts a conformation capable of binding to a phospholipid surface, where the clot initiation and propagation occurs.

**Mechanism of disease causation.** Loss of function

***F9*-specific laboratory technical considerations.** Somatic mosaicism of *F9* pathogenic variants have been described in males with hemophilia B [Ketterling et al 1999].

**Table 5.** Notable *F9* Pathogenic Variants

| Reference Sequences | DNA Nucleotide Change (Alias [1]) | Predicted Protein Change (Alias [1]) | Comment [Reference] |
|---|---|---|---|
| NM_000133.4 | -49T>A<br>(-20A>T) | -- | Promoter variant assoc w/hemophilia B Leyden |

*Table 5. continued from previous page.*

| Reference Sequences | DNA Nucleotide Change (Alias [1]) | Predicted Protein Change (Alias [1]) | Comment [Reference] |
|---|---|---|---|
| NM_000133.4 NP_000124.1 | c.1025C>T | p.Thr342Met | Founder variant in Amish persons from Holmes County, Ohio [Ketterling et al 1991] |
| | c.1151G>T | p.Arg384Leu (Arg338Leu) | Padua variant; gain-of-function variant assoc w/ thrombophilia (See Genetically Related Disorders and Therapies Under Investigation.) |
| | c.335T>C | p.Ile112Thr | Very mild factor IX reduction w/more severe bleeding [Row et al 2021] |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
*1.* Variant designation that does not conform to current naming conventions

# Chapter Notes

## Author Notes

Washington Center for Bleeding Disorders provides comprehensive care for individuals with bleeding disorders across the state of Washington and through research and diagnostics works to advance the care of individuals with bleeding disorders.

Bloodworks Northwest laboratories provide specialty laboratory services including in hemostasis and hemostasis genomics to support hemophilia diagnosis and care. The laboratory served as the core laboratory for the My Life, Our Future program.

Barbara A Konkle (barbara.konkle@wacbd.org) is actively involved in clinical research regarding individuals with hemophilia and would be happy to communicate with persons who have any questions regarding diagnosis of hemophilia or other considerations. Dr Konkle is also interested in hearing from clinicians treating families affected by hemophilia in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

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