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Hemophilia A

Synonym: Factor VIII Deficiency

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Summary

Clinical characteristics

Hemophilia A is characterized by deficiency in factor VIII clotting activity that results in prolonged bleeding 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 VIII clotting activity.

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

Approximately 30% of heterozygous females have factor VIII clotting activity below 40% and are at risk for bleeding (even if males in the family are only mildly affected). After major trauma or invasive procedures, prolonged or excessive bleeding usually occurs, regardless of severity. In addition, 25% of heterozygous females with normal factor VIII clotting activity report an increased bleeding tendency.

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Diagnosis/testing

The diagnosis of hemophilia A is established in an individual with low factor VIII clotting activity in the presence of a normal, functional von Willebrand factor level. Identification of a hemizygous *F8* pathogenic variant on molecular genetic testing in a male proband confirms the diagnosis. Identification of a heterozygous *F8* pathogenic variant on molecular genetic testing in a symptomatic female confirms the diagnosis.

Management

Treatment of manifestations: Referral to a hemophilia treatment center (HTC) to facilitate treatment (intravenous infusion of factor VIII concentrate is most effective when infused within one hour of bleeding onset); training to facilitate home infusions administered by parents or affected individuals; immune tolerance therapy. For those with mild disease, immediate treatment of bleeding with intravenous or nasal desmopressin acetate in those who have been shown to respond to desmopressin acetate or factor VIII concentrate.

Prevention of primary manifestations: For those with severe hemophilia A and those with moderate hemophilia A and frequent bleeding, prophylactic treatment with factor VIII concentrate infusions or subcutaneous administration of emicizumab. Adeno-associated viral (AAV)-mediated gene therapy for hemophilia A (valoctocogene roxaparvovec) was approved by the FDA for adults with severe disease in 2023.

Surveillance: For individuals with severe or moderate hemophilia A, assessments including inhibitor screen every six to 12 months at an HTC; for individuals with mild hemophilia A, assessment at an HTC every one to two years. Comorbidities may require more frequent visits.

Agents/circumstances to avoid: Circumcision of at-risk males until hemophilia A is either excluded or treated with factor VIII concentrate regardless of severity; activities with a high risk of trauma, particularly head injury; cautious, if any, use of medications and herbal remedies that affect platelet function, including aspirin. Use precaution with intramuscular injections (apply pressure; intramuscular injection may be scheduled after factor VIII treatment or while on emicizumab therapy).

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 treatment, preventive measures, 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: Monitor affected females during pregnancy and for delayed bleeding post partum unless it is known that their baseline factor VIII clotting activity is normal prior to pregnancy and there are no symptoms of bleeding.

Genetic counseling

Hemophilia A 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 *F8* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%. If the father of the proband has an *F8* 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 *F8* 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

Suggestive Findings

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

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 bleeding 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
- Normal prothrombin time

Establishing the Diagnosis

Male proband. The diagnosis of hemophilia A **is established** in a male proband by identification of decreased factor VIII clotting activity and a normal, functional von Willebrand factor level.

- **Severe hemophilia A.** <1% factor VIII clotting activity
- **Moderate hemophilia A.** 1%-5% factor VIII clotting activity
- **Mild hemophilia A.** 6%-40% factor VIII clotting activity

Note: Occasionally, in individuals with mild hemophilia A, a standard "one-stage" factor VIII clotting activity assay shows near-normal or low-normal factor VIII clotting activity (40%-80%), whereas in a "two-stage" or chromogenic assay, factor VIII clotting activity is low. Thus, low-normal in vitro clotting activity does not always exclude the presence of mild hemophilia A.

Identification of a hemizygous pathogenic (or likely pathogenic) variant in *F8* by molecular genetic testing can help predict the clinical phenotype, assess the risk of developing a factor VIII inhibitor, and allow family studies (see Table 1).

Female proband. The diagnosis of hemophilia A **may be established** in a female proband with bleeding symptoms, decreased factor VIII clotting activity (as described above for a male proband), and a normal, functional von Willebrand factor level; and/or by identification of a heterozygous pathogenic (or likely pathogenic) variant in *F8* by molecular genetic testing (see Table 1). Note: Factor VIII clotting activity does not reliably identify heterozygous females, as only approximately 30% of females heterozygous for an *F8* pathogenic

variant have factor VIII clotting activity lower than 40% [Plug et al 2006]. (Newly recommended terminology for heterozygous females is reviewed in Nomenclature.)

Note: (1) Per ACMG/AMP 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 variants" in this section is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *F8* 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). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see **Option 1**), whereas comprehensive genomic testing does not (see **Option 2**).

Option 1

Targeted analysis for inversions involving intron 22 or intron 1 can be performed first in (a) individuals with severe hemophilia A, (b) females with a family history of severe hemophilia A, or (c) females with a family history of hemophilia A of unknown severity in whom the family-specific pathogenic variant is not known (see Table 1).

Single-gene testing. Sequence analysis of *F8* should be done next if an intron 22 or intron 1 inversion is not detected. 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 (e.g., multiplex ligation-dependent probe amplification) to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *F8* and other genes of interest (see Differential Diagnosis) may also be considered 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. 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*. (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. (5) The ability of panels to detect structural variants in *F8*, a common cause of hemophilia A, should be confirmed. Currently most panels do not detect inversions involving intron 22, intron 1, or other large or complex structural variants.

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,** which does not require the clinician to determine which gene is likely involved, is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. The ability of the testing method to detect *F8* structural variants should be verified.

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 A

Gene [1]	Method	Proportion of Male Probands with a Pathogenic Variant [2] Detectable by Method	
		Severe hemophilia A	Moderate or mild hemophilia A
F8	Targeted analysis for intron 22 & intron 1 inversions [3]	~48% [4]	0% [4]
	Sequence analysis [5]	~43%-51% [6]	76%-99% [6]
	Multiplex ligation-dependent probe amplification [7]	1.5% [8]	0.2% [8]

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. Intron 22 and intron 1 inversions can be detected by multiple techniques (e.g., long-range PCR, inverse PCR, PCR-based "inverse shifting" procedure [Bagnall et al 2006, Rossetti et al 2008, Radic et al 2009]). Several intron 22 and intron 1 inversions have been identified; they occur following recombination between homologous sequences and can be accompanied by adjacent deletions or duplications (see Molecular Genetics).
4. An intron 22 inversion is identified in approximately 43%-45% of individuals with severe hemophilia A [Kaufman et al 2013, Johnsen et al 2022]. An intron 1 inversion is identified in 2%-5% of individuals with severe hemophilia A [Gouw et al 2012, Johnsen et al 2022]. These inversions have not been found in individuals with moderate or mild hemophilia A.
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Kemball-Cook et al [1998], El-Maarri et al [2005], Kaufman et al [2013], Johnsen et al [2022]
7. Multiplex ligation-dependent probe amplification (MLPA) is the most commonly used test method to detect *F8* deletions and/or duplications.
8. Deletions and duplications detected using MLPA in 2,353 males with severe hemophilia A or 1,709 males with moderate/mild hemophilia A in the My Life, Our Future project [Johnsen et al 2017]

Clinical Characteristics

Clinical Description

Hemophilia A in the untreated individual is characterized by spontaneous hemorrhage; immediate or delayed bleeding or prolonged bleeding after injuries, tooth extractions, or surgery; or renewed bleeding after initial bleeding has stopped [Berntorp et al 2021, Mancuso et al 2021]. Depending on the severity, intermittent bleeding 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 A of any severity may have prolonged bleeding, or they may heal normally without treatment. In severe hemophilia A, spontaneous joint bleeding is the most frequent manifestation.

The age of diagnosis and frequency of bleeding episodes in the untreated individual are related to the factor VIII 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 may be a function of both physical activity levels and vulnerability during more rapid growth.

Individuals with severe hemophilia A are usually diagnosed in the neonatal period (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 and are the most frequent presenting symptoms of severe hemophilia A. Intracranial bleeding can occur spontaneously in those with severe disease or following a head injury. The untreated child may have 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 adults with severe hemophilia A who are not treated prophylactically have an average of two to five spontaneous bleeding episodes each month. While joints are the most common sites of spontaneous bleeding, other sites include muscles, kidneys, gastrointestinal tract, and brain. Without prophylactic treatment, individuals with severe hemophilia A have prolonged bleeding that may result in excessive pain and swelling from minor injuries, surgery, and tooth extractions.

Individuals with moderate hemophilia A seldom have spontaneous bleeding, although there is significant variability among individuals; bleeding episodes may be precipitated by relatively minor trauma. Without pretreatment (as for elective invasive procedures) they have prolonged or delayed bleeding after relatively minor trauma and are usually diagnosed before age five to six years. In individuals not on prophylaxis, the frequency of bleeding episodes requiring treatment with factor VIII concentrates varies from once a month to once a year. Signs and symptoms of bleeding are otherwise similar to individuals with severe hemophilia A.

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

Affected females (heterozygotes, homozygotes, or compound heterozygotes) with low factor VIII clotting activity are at risk for bleeding that is comparable to that seen in males with a similar severity of hemophilia. In addition, 25% of females with normal factor VIII clotting activity have a bleeding phenotype. This may be due to the failure of factor VIII clotting activity to increase with stress [Plug et al 2006, Paroskie et al 2015, Candy et al 2018, van Galen et al 2021].

Table 2. Symptoms Related to Severity of Untreated Hemophilia A

Severity	Factor VIII Clotting Activity [1]	Symptoms	Usual Age at Diagnosis
Severe	<1%	Frequent spontaneous bleeding; abnormal bleeding after minor injuries, surgery, or tooth extractions	Age ≤1 years [2]
Moderate	1%-5%	Rare spontaneous bleeding; abnormal bleeding after minor injuries, surgery, or tooth extractions	Age ≤6 years
Mild	6%-40%	No spontaneous bleeding; abnormal bleeding after 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.
2. Kulkarni et al [2009]

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 concentrates or the bispecific antibody emicizumab is normalizing life expectancy and reducing chronic joint disease for children and adults with hemophilia A [Mancuso et al 2021]. Prior to the availability of such treatment, the median life expectancy for the most severely affected individuals was in childhood, and such poor outcomes still exist in some communities. Excluding death from HIV, life expectancy for severely affected individuals in the UK receiving adequate treatment was reported in 2007 as 63 years [Darby et al 2007]. A recent analysis from the Netherlands found life expectancy in men with hemophilia to be 77 years, six years below the Dutch male population [Hassan et al 2021].

Other. Since the mid-1960s, the mainstay of treatment of bleeding episodes has been factor VIII concentrates that initially were derived solely from donor plasma. Viral inactivation methods and donor screening of plasmas were introduced by the mid-1980s and recombinant factor VIII concentrates were introduced in the early 1990s,

ending the risk of HIV transmission. Many individuals who received plasma-derived factor VIII concentrates from 1979 to 1985 contracted HIV. Approximately half of these individuals died of AIDS prior to the advent of effective HIV therapy.

Hepatitis B transmission from earlier plasma-derived concentrates was eliminated with donor screening and then vaccination 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 eliminated this complication.

Approximately 30% of individuals with severe hemophilia A develop alloimmune inhibitors to factor VIII, usually within the first 20 exposures to infused factor VIII [Hay et al 2011] and, less frequently, in those who have received more than 50 exposures [Kempton 2010] (see Management, Treatment of Manifestations). Among individuals with hemophilia A, inhibitors are more prevalent in Black and Hispanic individuals than White individuals. Certain genetic variants put individuals with mild or moderate disease at increased risk of inhibitor formation, particularly after prolonged exposure, as with surgery [d'Oiron et al 2008, Johnsen et al 2022].

Genotype-Phenotype Correlations

Evidence for an association between variant type and disease severity

- *F8* intron 22 inversions are associated with severe hemophilia A and account for 45% of individuals with severe hemophilia A [Kaufman et al 2013, Johnsen et al 2022]. Of these, 20% to 30% develop alloimmune inhibitors. Occasionally, individuals reported to have moderate hemophilia A are found to have *F8* inversions – a finding that may be explained by one of the following: either their factor VIII assays have contained some residual factor VIII clotting activity from a prior infusion; or the assay methods used were inaccurate at low levels. Intron 22 inversions may be associated with complex rearrangements [Johnsen et al 2022].
- An inversion between a 1-kb sequence in intron 1 and an inverted repeat 5' to *F8* [Bagnall et al 2002] is also associated with a severe phenotype, and some individuals have developed inhibitors.
- Single-nucleotide variants leading to new stop codons are essentially all associated with a severe phenotype, as are most frameshift variants. (An exception is the insertion or deletion of adenosine bases resulting in a sequence of eight to ten adenosines, which may result in moderate hemophilia A [Nakaya et al 2001].)
- Splice site variants often result in severe disease, but can result in mild or moderate disease, depending on the specific change and location.
- Missense variants occur in fewer than 20% of individuals with severe hemophilia A but are found in nearly all of those with a diagnosis of mild or moderate disease.

Penetrance

All males with an *F8* pathogenic variant will be affected and will have approximately the same severity of disease as 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 VIII clotting activity below 40% and are at risk for a bleeding disorder. In addition, 25% of heterozygous females with normal factor VIII clotting activity report an increased bleeding tendency [Plug et al 2006, van Galen et al 2021].

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 VIII clotting activity, the terminology is the same as that used for hemizygous males:

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

For heterozygous females with normal factor VIII 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"

Of note, 25% of females with normal factor VIII clotting activity have a bleeding phenotype.

Hemophilia A has also been referred to as "classic hemophilia."

Prevalence

The birth prevalence of hemophilia A has been calculated at 24.6:100,000 live male births, and 9.5:100,000 for severe hemophilia A [Iorio et al 2019].

The birth prevalence is thought to be approximately the same in all countries and all races, presumably because of the high spontaneous mutation rate of *F8* and its presence on the X chromosome.

Genetically Related (Allelic) Disorders

A partial *F8* gene duplication resulting in markedly elevated factor VIII levels (>400%) and X-linked thrombophilia (OMIM 301071) has been described in two Italian families with venous thromboembolism [Simioni et al 2021].

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 bleeding 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 A 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 have no outward signs except during an acute bleeding episode. Of note, petechial hemorrhages indicate severe thrombocytopenia and are not a feature of hemophilia A.

Inherited Bleeding Disorders with Low Factor VIII Clotting Activity

Table 3. Inherited Bleeding Disorders with Low Factor VIII Clotting Activity

Gene(s)	Disorder	MOI	Clinical Features	Laboratory Findings / Comment
VWF	Type 1 von Willebrand disease (VWD)	AD	Mucous membrane bleeding incl epistaxis, bleeding w/dental extractions, heavy menstrual & postpartum	Partial quantitative deficiency of VWF (low VWF antigen, low factor VIII clotting activity, & low VWF activity). VWF levels can differentiate mild

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Laboratory Findings / Comment
			bleeding, & spontaneous bruises. Also may have trauma & procedure-related bleeding.	hemophilia A from VWD (persons w/hemophilia A have a normal VWF antigen level).
	Type 2A & 2B VWD	AD	Type 2A: Bleeding as in Type 1 VWD or may be more severe. 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 mild/moderate hemophilia A	VWF platelet binding is completely normal. Type 2N VWD is biochemically indistinguishable from mild hemophilia A. Mild hemophilia A can be distinguished from type 2N VWD by molecular genetic testing or measuring binding of factor VIII to VWF using ELISA or column chromatography.
	Type 3 VWD	AR	Frequent episodes of mucous membrane bleeding; joint & muscle bleeding similar to that seen in hemophilia A but usually w/more mucosal bleeding symptoms.	Complete or near-complete quantitative deficiency of VWF. VWF level is often <1% & factor VIII clotting activity is most commonly 2%-8%.
LMAN1 *MCFD2*	Combined factor V & factor VIII deficiency (OMIM 613625 & 227300)	AR	Very rare disorder w/mucocutaneous & bleeding w/trauma & surgery	Low factor VIII & factor V clotting activity levels (usually 10%-20%); prolonged PT & aPTT (Mild hemophilia A does not result in prolonged PT.)

AD = autosomal dominant; aPTT= activated partial thromboplastin time; AR = autosomal recessive; ELISA = enzyme-linked immunosorbent assay; MOI = mode of inheritance; PT = prothrombin time; VWF = von Willebrand factor

Inherited Bleeding Disorders with Normal Factor VIII Clotting Activity

Table 4. Inherited Bleeding Disorders with Normal Factor VIII Clotting Activity

Gene(s)	Disorder	MOI	Clinical Features	Laboratory Findings / Comment
F9	Hemophilia B	XL	Clinically indistinguishable from hemophilia A	Diagnosis is based on factor IX clotting activity <40%.
F11	Factor XI deficiency (OMIM 612416)	AR AD	Compound heterozygous & homozygous persons may exhibit bleeding similar to mild/moderate hemophilia A. Some heterozygotes have mucocutaneous bleeding symptoms.	Heterozygotes have factor XI coagulant activity 25%-75% of normal; homozygotes have activity <1%-15%. [1] A specific factor XI clotting assay establishes diagnosis.
F12 *KLKB1* *KNG1*	Factor XII (OMIM 234000), prekallikrein (OMIM 612423), & high molecular-weight kininogen deficiencies (OMIM 228960)	AR	Not assoc w/clinical bleeding	Can cause long aPTT

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Laboratory Findings / Comment
F2 *F5* *F7* *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 PT is prolonged & aPTT normal. Persons w/deficiency of factors II, V, or X usually have prolonged PT & aPTT, but specific coagulation factor assays establish diagnosis. [2]
FGA *FGB* *FGG*	Afibrinogenemia (OMIM 202400), hypofibrinogenemia (OMIM 202400), dysfibrinogenemia (OMIM 616004)	AR AD [3]	Afibrinogenemia is assoc w/manifestations similar to hemophilia A 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 level, w/latter usually in normal range. For all fibrinogen disorders thrombin & reptilase times are almost always prolonged & functional measurements of fibrinogen ↓.
F13A1 *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 specific assay for factor XIII activity can confirm diagnosis. Bleeding symptoms are reported in persons w/levels <13% by quantitative assay. [4]
GP1BA *GP1BB* *GP9* *ITGA2B*	Platelet function disorders: 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.

AD = autosomal dominant; aPTT= activated partial thromboplastin time; AR = autosomal recessive; GI = gastrointestinal; MOI = mode of inheritance; PT = prothrombin time

1. Duga & Salomon [2013]

2. Combined (multiple) deficiencies are usually acquired disorders, although a few families have hereditary deficits of the vitamin K-dependent factors, often resulting from deficiency of gamma-carboxylase.

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.

4. Menegatti et al [2017]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hemophilia A, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Hemophilia A

System/Concern	Evaluation	Comment
Hematologic	• Personal & family history of bleeding to help predict disease severity • CBC w/platelet count, esp if history of nose bleeds, GI bleeding, mouth bleeding, or (in females) heavy menstrual bleeding or postpartum hemorrhage • Referral to HTC • *F8* 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 A 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 [Srivastava et al 2020]. Treatment should be coordinated through a hemophilia treatment center (HTC).

Intravenous infusion of plasma-derived or recombinant factor VIII for bleeding episodes within an hour of noticing symptoms:

- 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. Laboratory expertise in assessment of factor VIII activity is needed to monitor for under- and overdosing in treatment for major surgery and severe bleeds.
- In individuals on emicizumab, the activated partial thromboplastin time and one-stage factor VIII assay will not accurately reflect factor VIII activity (they will overestimate activity). A bovine-based chromogenic factor VIII assay is needed to assess underlying factor VIII activity levels. Individuals on emicizumab with bleeding or requiring major surgery will need factor VIII supplementation. A specialist in hemophilia treatment should be consulted.
- Parents of young children with severe hemophilia A should be trained to administer the infusions. Home treatment allows for prompt treatment and facilitates prophylactic therapy. Emicizumab therapy may be chosen in young children to provide hemostatic protection while avoiding intravenous infusions.
- Hemophilia nurse specialists play a key role in education about the disease, home infusion, and injection training, as well as provide family support.

Pediatric issues. Special considerations for care of infants and children with hemophilia A include the following [Chalmers et al 2011, Srivastava et al 2013]:

- Infant males with a family history of hemophilia A should not be circumcised unless hemophilia A is either excluded or, if present, is treated with factor VIII concentrate directly before and after the procedure with consideration of the risks versus benefit of factor VIII exposure.

- Immunizations should be administered preferably subcutaneously, but when required, intramuscular injections can be given in those treated with factor VIII concentrate, or in some individuals prolonged pressure on the vaccination site may successfully prevent excessive bleeding.
- Effective dosing of factor VIII requires an understanding of different pharmacokinetics in young children.

DDAVP® (desmopressin acetate). For individuals with mild hemophilia A who have been documented to respond to DDAVP®, including symptomatic females, immediate treatment of bleeding can be achieved with DDAVP®. A single intravenous dose often doubles or triples factor VIII clotting activity. Alternatively, a multiuse nasal formulation of DDAVP® may be more convenient. A high-concentration formulation (1.5 mg/mL) must be used.

Note: Hemophilia A genotype influences DDAVP® response [Castaman et al 2009, Nance et al 2013], and testing for response should be performed prior to clinical use.

Immune tolerance therapy. Alloimmune inhibitors to factor VIII greatly compromise the ability to manage bleeding episodes [Meeks & Batsuli 2016]. High-titer inhibitors can often be eliminated by immune tolerance therapy [Hay et al 2012]. Individuals with large gene deletions are less likely to respond to immune tolerance than individuals with other types of *F8* variants [Coppola et al 2009].

Physical therapy. Physical therapists play a key role in the care of individuals with hemophilia A, evaluation and treatment of musculoskeletal disease, and 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 A 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 of hepatitis B and C viruses since 1990. All individuals with hemophilia A who have active hepatitis C infections should be offered the current, very effective treatment for viral eradication.

Prevention of Primary Manifestations

Prophylactic treatment is considered the standard of care by the National Hemophilia Foundation and the World Federation of Hemophilia for individuals with severe hemophilia A and those with moderate hemophilia A and frequent bleeding.

- Regular factor VIII concentrate infusions given prophylactically in young boys before or just after their first few joint bleeds can nearly eliminate spontaneous bleeding and prevent chronic joint disease [Manco-Johnson et al 2007].
- The bispecific antibody emicizumab is administered subcutaneously on a regular schedule and provides very effective prophylaxis in individuals with hemophilia A with and without inhibitors [Callaghan et al 2021].

The greatest benefit of prophylaxis is seen in affected individuals who start therapy before age 2.5 to three years. Routine prophylaxis begun later in childhood or in adulthood significantly decreases bleeding episodes [Valentino et al 2012, Manco-Johnson et al 2013, Mondorf et al 2013]. Previously it was recommended that factor VIII clotting activity be maintained above 1%, but it is now clear that this goal will not prevent bleeding in many individuals; a personalized approach is recommended. Low-dose prophylaxis regimens have been used to successfully prevent bleeding in young boys in resource-constrained countries [Srivastava et al 2020]. The World Federation of Hemophilia Humanitarian Aid program facilitates such an approach in many countries [Pierce et al 2022].

Newer modified factor VIII recombinant products with longer half-lives allow less frequent infusions, although until recently half-life extension has been modest due to the dependency of factor VIII on von Willebrand factor (VWF) for stabilization. A new factor VIII product (efanesoctocog alfa) was approved by the FDA in 2023 for prophylaxis and treatment of bleeding in children and adults with hemophilia A that is independent of VWF and has a much longer half-life compared to other factor VIII products [von Drygalski et al 2023].

Valoctocogene roxaparvovec, an adeno-associated viral (AAV)-mediated gene therapy for hemophilia A, received conditional marketing authorization by the European Medicines Agency in August 2022 and was approved by the FDA in 2023 for treatment of adults with severe disease without antibodies to AAV-5 or factor VIII. The major side effect has been a transaminitis in most individuals, for which a course of corticosteroids is prescribed. The factor VIII levels attained are generally in the mild hemophilia range, although there is variability among affected individuals and levels have been shown to decrease over time. Bleeding episodes and factor product use are significantly decreased compared to prior gene therapy [Ozelo et al 2022, Samelson-Jones & George 2023].

Surveillance

Persons with hemophilia who are 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 A 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 as needed. Early signs and symptoms of possible bleeding episodes are reviewed. The assessment should also include a joint and muscle evaluation, an inhibitor screen, a discussion of any other problems related to the individual's hemophilia A, and family and community support.

Screening for alloimmune inhibitors is indicated at least once during the first ten to 20 treatment days in children with severe hemophilia, and then every three to six months after treatment with factor VIII concentrate has been initiated either for bleeding or prophylaxis. After 50 to 100 exposure days, annual screening and screening prior to elective surgical procedures is sufficient. Testing for inhibitors should be performed in any individual with hemophilia A whenever a suboptimal clinical response to treatment is suspected, regardless of disease severity. Use of emicizumab for prophylaxis in young children usually alters exposure to factor VIII and may change the approach to monitor for inhibitors.

Older children and adults with severe or moderate hemophilia A 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 A.

Individuals with mild hemophilia A 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 A should not be circumcised unless hemophilia A is excluded; or, if present, the infant should be treated with factor VIII concentrate directly before and after the procedure. The benefit versus the risk of factor VIII exposure in early life should be considered.
- Medications and herbal remedies that affect platelet function, including aspirin, should be avoided unless there is strong medical indication, such as in 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].
- Intramuscular injections without factor treatment should be avoided. Pressure on the site after intramuscular injection in children has been reported without factor coverage. Individuals on emicizumab or prophylactic factor VIII infusions may be given intramuscular injections.
- Activities that involve a high risk of trauma, particularly of head injury, should be avoided.

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 treatment, preventive measures, and surveillance. A thorough family history may identify relatives who are at risk but have not been tested (particularly in families with mild hemophilia A).

Evaluation of at-risk males

- Assay of factor VIII 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 VIII clotting activity in the neonatal period, or molecular genetic testing for the family-specific *F8* pathogenic variant can establish or exclude the diagnosis of hemophilia A in newborn males at risk.
- Note: Ideally, the cord blood for factor VIII 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. If not available, a standard blue top tube can be used.
- Infants with a family history of hemophilia A should not be circumcised unless hemophilia A is either excluded or, if present, factor VIII concentrate is administered immediately before and after the procedure to prevent delayed bleeding and poor wound healing. The benefit versus the risk of exposure to factor VIII in early childhood should be considered.

At-risk females. Approximately 30% of heterozygous females have factor VIII clotting activity lower than 40% and are at risk for bleeding that is usually comparable to that seen in males with a similar severity of hemophilia A. Abnormal bleeding is reported in some females with a borderline abnormal factor VIII clotting activity or higher [Plug et al 2006, Paroskie et al 2015]. Twenty-five percent of females with normal factor VIII clotting activity have a bleeding phenotype. Very occasionally, a female will have particularly low factor VIII clotting activity that may result from heterozygosity for an *F8* pathogenic variant associated with skewed X-chromosome inactivation or, on rare occasion, biallelic *F8* pathogenic variants [Pavlova et al 2009].

- All daughters and mothers of an affected male and other at-risk females should have molecular genetic testing for the family-specific *F8* pathogenic variant. Heterozygous females should have a baseline factor VIII 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 A be established prior to pregnancy or as early in a pregnancy as possible.

If the heterozygous female has hemophilia A (factor VIII clotting activity <40%) or has normal factor VIII clotting activity and a bleeding phenotype, she will be somewhat protected by the natural rise of factor VIII clotting activity during pregnancy, which may even double by the end of the third trimester. Factor VIII clotting activity should be measured early in pregnancy and at least once in the third trimester to plan for delivery. If the

level is well within the "non-pregnant" normal range (the optimal level is not clearly established but some recommend >100% for delivery and >50% for neuroaxial anesthesia), delivery can proceed as clinically indicated if the fetus is confirmed not to be affected by hemophilia. Postpartum factor VIII clotting activity may decrease soon after delivery, and postpartum hemorrhage may ensue [Leebeek et al 2020]. Tranexamic acid 1 gram intravenously immediately following cord clamping and then orally for seven to 14 days or as needed can be used to prevent secondary postpartum hemorrhage.

Newborn males at risk for hemophilia. Controversy remains as to indications for cesarean section versus vaginal delivery [Leebeek et al 2020]. In retrospective data analysis of 580 males newborn to age 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

Clinical trials for gene therapy for hemophilia A are under way; one product, valoctocogene roxaparvovec, received conditional marketing authorization by the European Medicines Agency in 2022 and approval by the FDA in 2023. The gene therapies currently in or having recently completed Phase III trials use liver-targeted adeno-associated (AAV) vectors. 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 as well as safety need further study [Leebeek & Miesbach 2021, Samelson-Jones & George 2023]. Additional approaches to gene therapy are under study in preclinical models and early-phase trials, including with lentiviral vectors [Butterfield et al 2020].

Drugs that "rebalance" coagulation are under study, including completed Phase III or late-phase trials for an inhibitor of antithrombin (fitusiran) and inhibitors of tissue pathways (concizumab and marstacimab) in individuals with hemophilia A with and without inhibitors [Lewandowska et al 2022]. Additional bispecific antibodies that mimic the activity of factor VIII are in development and/or in clinical trials.

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 A.

Cryoprecipitate is no longer recommended to treat hemophilia A because it is not treated with a virucidal agent and contains a lower concentration of factor VIII than concentrates. However, it can be used in emergencies if no factor products are available.

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 A 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 disorder, nor will he be hemizygous for the *F8* 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 A. If a male is the only affected family member (i.e., a simplex case), it is possible that:
  - The mother is heterozygous for an *F8* pathogenic variant. Overall, the mother of a male proband who represents a simplex case has an approximately 80% chance of being heterozygous. If the proband has an intron 22 inversion, the mother has a 98% of being heterozygous, because most intron 22 inversions occur in spermatogenesis.
  - Note: In a Swedish study of individuals with severe hemophilia A who represented simplex cases, the mother of the proband was found to be heterozygous in 28 out of 45 families [Mårtensson et al 2016].
  - The mother has somatic/germline mosaicism. Studies have shown varying frequencies of mosaicism ranging from 13% to 22.5% in the mothers of apparent simplex cases [Lannoy & Hermans 2020].
  - 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. Specialized testing approaches designed to detect low-level mosaicism have been developed [Mårtensson et al 2016].
  - The mother is not heterozygous for an *F8* 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 *F8* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- On rare occasion, biallelic *F8* pathogenic variants have been reported in females with particularly low factor VIII clotting activity [Pavlova et al 2009]. A proband with biallelic pathogenic variants may have inherited *F8* pathogenic variants from both her mother and her father or may have one *de novo* and one inherited pathogenic variant.
- 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 *F8* pathogenic variant, the chance of the mother 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. Approximately 30% of heterozygous females have a factor VIII clotting activity lower than 40% and are at risk for bleeding;

25% of heterozygous females with normal factor VIII clotting activity report an increased bleeding tendency (see Penetrance).

- All sibs should have factor VIII clotting activity assayed unless molecular genetic testing confirms that they have not inherited the *F8* 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 *F8* 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 *F8* pathogenic variant, he will transmit it to all his daughters and none of his sons.

Offspring of a male proband. Affected males transmit the *F8* pathogenic variant to all of their daughters and none of their sons.

Offspring of a female proband. Women with an *F8* 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 *F8* 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 *F8* 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 A.

Heterozygote Detection

Molecular genetic testing for identification of female heterozygotes is most informative if the *F8* pathogenic variant has been identified in an affected family member. If an affected family member is not available for testing, targeted analysis for inversions involving intron 22 or intron 1 can be performed followed by single-gene testing approaches if an intron 22 or intron 1 inversion is not detected (see Molecular Genetic Testing, **Option 1**).

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.

Factor VIII clotting activity, or its ratio to von Willebrand factor level, is not a reliable test for determining genetic status: it can only be suggestive if low. Only an estimated 30% of heterozygous females have factor VIII 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 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 *F8* pathogenic variant has been identified in an affected family member, molecular genetic prenatal and preimplantation genetic testing for hemophilia A are possible.

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
- **MedlinePlus**
  Hemophilia A
- **National Hemophilia Foundation**
  Phone: 212-328-3700; 888-463-6643
  Email: info@hemophilia.org
  www.hemophilia.org
- **NCBI Genes and Disease**
  Hemophilia A
- **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

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 A: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
F8	Xq28	Coagulation factor VIII	Hemobase: Hemophilia A mutation registry CDC Hemophilia A Mutation Project - F8 Factor VIII Variant Database F8 @ LOVD	F8	F8

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 A (View All in OMIM)

300841	COAGULATION FACTOR VIII; F8
306700	HEMOPHILIA A; HEMA

Molecular Pathogenesis

Factor VIII is synthesized primarily in the liver sinusoidal endothelial cells and circulates as an inactive clotting cofactor that has been cleaved in the B domain prior to secretion. In circulation, factor VIII is stabilized by binding to von Willebrand factor (VWF). Once activated by trace amounts of thrombin, it is released from VWF and binds to phospholipid membrane surfaces such as those provided by activated platelets. There it interacts with factor IXa to become the "intrinsic system" factor X activator [Stoilova-McPhie et al 2002]. Intrinsic factor X activation is a critical step in the early stages of coagulation.

Mechanism of disease causation. Loss of function. Abnormal gene products vary from deficiency caused by absence of detectable protein (including the majority of individuals with severe hemophilia A) to those with normal levels of a dysfunctional protein. Pathogenic variants may result in reduced levels of factor VIII clotting activity and antigen caused by impaired secretion of factor VIII or instability of factor VIII in circulation. Certain premature termination codons, gene inversions, or large gene alterations causing severe hemophilia A are at an especially increased risk of being complicated by inhibitor development [Gouw et al 2012, Astermark et al 2013, Eckhardt et al 2013, Meeks & Batsuli 2016, Johnsen et al 2022].

***F8*-specific laboratory technical considerations.** Gene inversions account for approximately 45% of the *F8* pathogenic variants in individuals with severe hemophilia A [Johnsen et al 2022]. *F8* inversions usually occur through recombination between a sequence located within intron 22 and one of two additional copies of homologous sequence that are located 400-500 kb 5' from *F8* (about half the distance to the telomere of the long arm of the X chromosome) [Bagnall et al 2006]. Of the two most frequent types, crossover with the distal telomeric sequence (designated as int22h3) is more frequent than with the proximal sequence (designated as int22h2). Infrequently, a third telomeric copy is present and may lead to an alternate intron 22 inversion; alternative patterns can also be seen when the inversion is accompanied by large partial-gene deletions or duplication-insertion events [Andrikovics et al 2003]. A different recurrent inversion occurs between a 1-kb

sequence in intron 1 (designated int1h-1) that is repeated in the reverse orientation (designated int1h-2), approximately 140 kb 5' (telomeric) to *F8* [Bagnall et al 2002]; intron 1 inversions occur in up to 3% of families with severe hemophilia A.

Table 6. Notable *F8* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000132.4	c.-257T>G	--	Assoc w/mild hemophilia A [Riccardi et al 2009]
NM_000132.4 NP_000123.1	c.1244C>T	p.Ala415Val	Founder variant reported in persons from France [Lassalle et al 2018]
	c.6046C>T	p.Arg2016Trp	Founder variant reported in persons from northern Italy [Garagiola et al 2015]
	c.6104T>C	p.Val2035Ala	Founder variant reported in persons from Newfoundland & Labrador [Scully et al 2018]

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.

Chapter Notes

Author Notes

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

- 27 July 2023 (sw) Revision: AAV-mediated gene therapy valoctocogene roxaparvovec approved by the FDA

- 27 October 2022 (sw) Comprehensive update posted live
- 22 June 2017 (bk) Revision: based on Hemophilia B update
- 2 February 2017 (sw) Comprehensive update posted live
- 5 June 2014 (me) Comprehensive update posted live
- 22 September 2011 (me) Comprehensive update posted live
- 25 March 2008 (me) Comprehensive update posted live
- 17 August 2005 (me) Comprehensive update posted live
- 8 May 2003 (me) Comprehensive update posted live
- 21 September 2000 (me) Review posted live
- April 2000 (art) Original submission

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