HARP
Hemophilia A
Research Program

Hemophilia A Genetics and Inheritance

What is Hemophilia A?

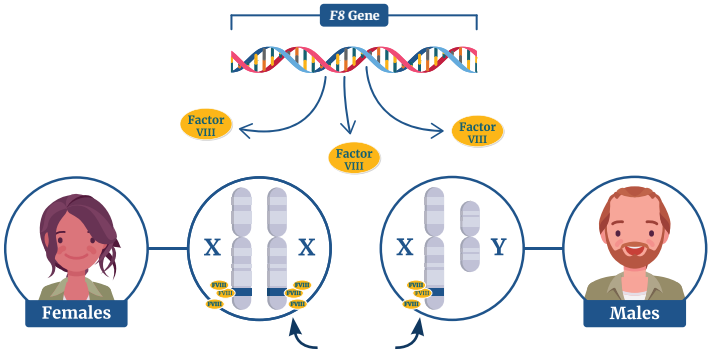
Hemophilia A is a **genetic bleeding disorder** caused by low levels of **factor VIII**, a protein needed for normal blood clotting.

When factor VIII levels are low, clots are fragile, and bleeding is harder to control.

Genetics of Factor VIII

Genes are sections of DNA that contain the instructions for making proteins. The *F8* gene is located on the **X chromosome, a sex chromosome.**

- Females usually have **two X chromosomes (XX)**.
- Males usually have **one X and one Y chromosome (XY)**.



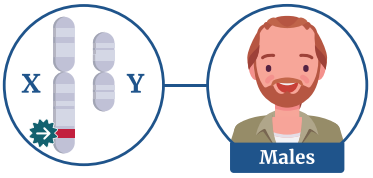
The blue bar represents the *F8* gene.

What is a Hemophilia Genotype?

A change in DNA is also called a DNA variant. Most variants don't cause problems. A variant that influences a trait or causes disease can also be called a genotype. **A hemophilia A genotype** is a DNA change that impacts the *F8* gene and causes low factor VIII levels.

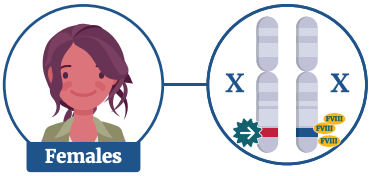
Males with Hemophilia A

XY males who inherit an affected X chromosome (an X with a genotype) will **have low factor VIII levels and hemophilia A.**



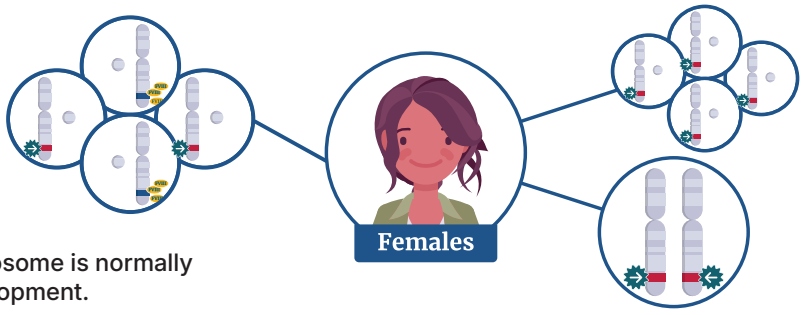
Females with a Hemophilia A Genotype

XX females who inherit an affected X chromosome usually have a **second normal X chromosome that can make some factor VIII.**



Causes of Low Factor VIII Levels in Females

Random X-inactivation



Skewed X-inactivation

No Normal X Chromosome

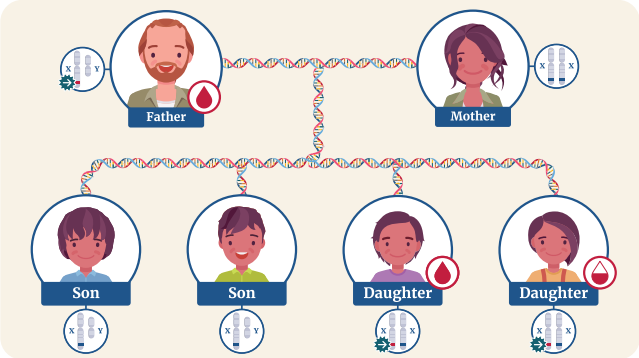
In females, one X chromosome is normally inactivated early in development.

In females with a genotype, about half of cells inactivate the affected X, and half of cells inactivate the normal X. **X-inactivation is a common reason for lower factor VIII levels in females.**

XX females can have hemophilia (low factor VIII levels) if the normal X chromosome is disproportionately silenced, or if both X chromosomes are abnormal.

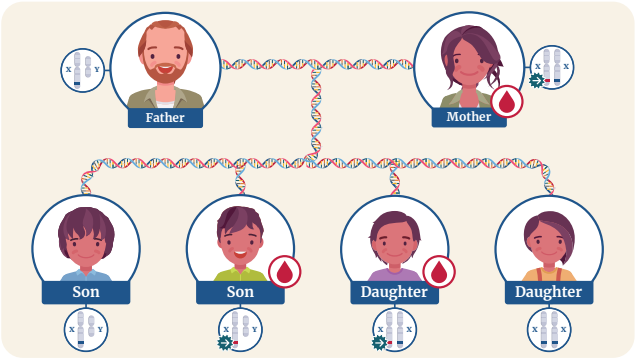
How is Hemophilia A Inherited?

If the Father has Hemophilia A:



- **All daughters** will inherit the X chromosome with the genotype and are at risk for bleeding and hemophilia A.
- **All sons** will be unaffected. They will not have hemophilia.

If the Mother has a Hemophilia Genotype:



- There is a **50% chance each son** will inherit the X chromosome with the genotype and have hemophilia A.
- There is a **50% chance each daughter** will inherit the genotype and be at risk for bleeding and hemophilia A.

Hemophilia Can Occur in a Family with No Apparent History

Reasons this can happen include:

- **A new (spontaneous) genetic change is causing hemophilia.** This accounts for about 30% of cases of severe hemophilia A. Occasionally, a new genotype can occur in other types of hemophilia.
- **Hemophilia was not recognized in the family,** usually due to small family size or milder bleeding.

Genetic Testing and Counseling

Genetic testing is recommended for anyone at risk to inherit hemophilia or who has hemophilia. Genetic counseling is always recommended.

Genetic counseling can provide:

- Education on genetic diseases and testing options
- Advice on issues associated with inherited disorders and testing
- Guidance and support for people with genetic conditions.

Where Can I Get More Information?

To find out more about the HARP:
https://harpf8.org/

To learn more about hemophilia:
https://www.ncbi.nlm.nih.gov/books/NBK1404/

To find a Genetic Counselor:
https://findageneticcounselor.nsgc.org/

https://harpf8.org

Development of this educational material was generously supported by funding from Sanofi. Sanofi had no editorial control or influence over the content.