Inheritance: Checking the family history

Haemophilia is inherited and another important step in diagnosis is to look back over your family history to see whether there are any other family members with haemophilia or who may have had a bleeding tendency.

Haemophilia and inheritance

A male or female who has the 'haemophilia' genetic alteration in their F8 (factor VIII) or F9 (factor IX) gene can pass this altered gene on to their children.

Because haemophilia is inherited, it occurs in families, and the altered gene is passed down the generations from parent to child.

No family history?

About one third of all cases appear in families with no previous history of the disorder. This happens when a new alteration in the genetic code of the F8 or F9 gene occurs by chance in an egg cell or sperm cell. The child who is conceived will have haemophilia or be a carrier and can pass the gene alteration on to their children.

Sometimes this genetic alteration has occurred a generation or two earlier and the family has been unaware until tested. For example, the alteration might have occurred originally at the time of a mother's conception so that when the mother of a child with haemophilia is tested, she finds she carries the gene. It may be that the grandmother was the original carrier - she passed the gene alteration onto her daughter who then passed the gene alteration onto her child who is diagnosed with haemophilia.

Testing the family

If someone is diagnosed with haemophilia or as being a haemophilia carrier, it is likely that other members of their family also have haemophilia or be a carrier. Diagnosis will also include checking the family history for bleeding problems. Other family members, both males and females, may also need to be tested for haemophilia.

Clotting factor genes and families

If you are thinking about genetic testing, it can be helpful to understand how haemophilia is passed on in families.

Haemophilia occurs when you have a mutation or alteration in the gene that makes clotting factor VIII (8) or factor IX (9). This gene alteration may have taken place for the first time in your generation or many generations ago. Once the gene alteration occurs, it is passed down from parent to child through the generations, creating a family history of haemophilia. The pattern of inheritance depends on whether a person is male or female. This is because the clotting factor gene is located on a sex chromosome.

Sex chromosomes and haemophilia

We all have millions of cells that make up our body. Each cell has 23 pairs of chromosomes, which contain our genetic information or 'genes'. The genetic information determines our individual characteristics, such as the colour of our hair or our eyes. It also determines how our body functions, for example, how blood clotting works in our body.

Twenty-two of these pairs of chromosomes look the same in both males and females and are called **autosomes**. The 23rd pair differ between males and females and are called the **sex chromosomes**.

Each parent contributes one of these sex chromosomes to their children:

- Females have two copies of the **X** chromosome, and receive one from each parent
- Males have one **X** chromosome, which they receive from their mother, and one **Y** chromosome, which they receive from their father.

Haemophilia

The genes for making factor VIII (8) and IX (9) are located on the X chromosome.

When there is a genetic alteration in the F8 or F9 gene causing haemophilia, this gene alteration will be found on the X chromosome.

Haemophilia and X chromosomes

Females	Males
• Because females have 2 **X** chromosomes, they have 2 copies of both the F8 and F9 genes, 1 inherited from each parent. • As a result, women and girls with an F8 or F9 gene alteration usually have another copy that functions normally. This helps factor VIII and IX to work properly in the blood clotting process and is often enough to control bleeding. • However, 20-30% of females have problems with blood clotting. This is because of a process called lyonization or skewed **X** inactivation – see below.	• Males have 1 **X** chromosome and therefore only have 1 copy of the F8 and F9 gene. • Males with an alteration on their F8 or F9 gene on their **X** chromosome do not have another F8 or F9 gene to help with blood clotting. They will all have haemophilia.

This can be a bit hard to follow! The inheritance diagram on page 11 might help to understand how it works.

Inheritance

If you are a female who has haemophilia or are an *asymptomatic* or *symptomatic haemophilia* carrier or you are a male with haemophilia, you will have an alteration in your F8 or F9 gene. This gene alteration may be passed on to your children.

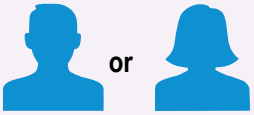
In genetics, females who have the gene alteration causing haemophilia are referred to as *carriers*.

Inheritance pattern in haemophilia

Haemophilia genetic inheritance

or

has an **X** chromosome with the "haemophilia" genetic alteration.



or

has an unaltered **X** chromosome.

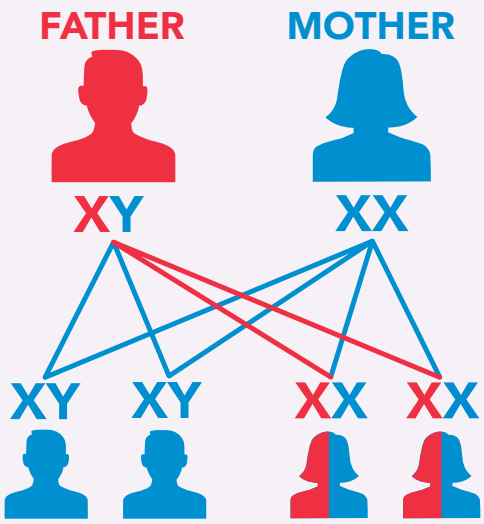
If you are a **female who is a haemophilia carrier**, there is a **50% chance with each of your pregnancies** that you will pass the gene alteration onto your baby:

- If you have a son who inherits the gene alteration, he will have haemophilia.
- If you have a daughter who inherits the gene alteration, she will be a carrier too and may have haemophilia.

If you are a **male with haemophilia**:

- **All (100%) of your daughters** will inherit the gene alteration from you. They will be carriers and some may have haemophilia
- **None of your sons** will inherit the gene alteration from you. They will not have haemophilia.

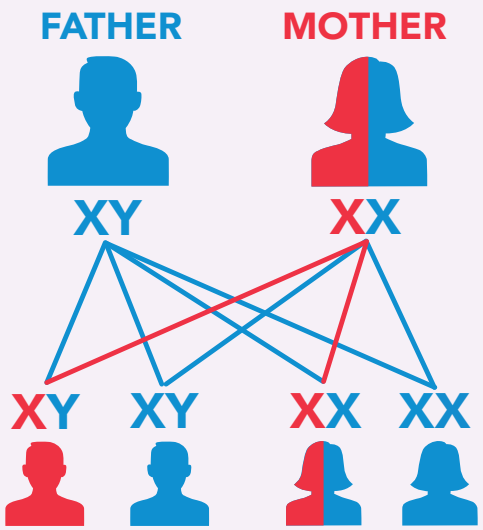
When the father has haemophilia and the mother is unaffected.



None of the sons will have haemophilia.

All of the daughters will carry the gene alteration. Some might have symptoms or have haemophilia.

When the mother carries the gene alteration causing haemophilia and the father is unaffected.



There is a 50% chance at each birth that a son will have haemophilia. There is a 50% chance at each birth that a daughter will carry the gene alteration. Some might have symptoms or have haemophilia.

Female bleeding patterns

Women and girls may wonder why their bleeding pattern is different to the males in their family.

In families with haemophilia, males who are affected will nearly always have the same severity – for example, a grandfather and a grandson will both have severe haemophilia.

However, factor levels in females who carry the gene alteration are unpredictable and can vary between family members. For example, if two sisters have the gene alteration, one might have low factor levels and have mild haemophilia, while the other has normal factor levels and no symptoms. A father might have severe haemophilia and his daughter might have mild haemophilia

X-inactivation

This is because of a process called **X-inactivation** or **lyonization**.

X-inactivation occurs during the development of a female embryo. All females have two copies of the X chromosome. In X-inactivation each cell in the female embryo randomly turns off (inactivates or silences) most of the genes on one of the X chromosomes, including the F8 or F9 gene. Through this process only one copy of the F8 or F9 gene is switched on in each cell at any time.

What happens in haemophilia?

Because the X-inactivation process is random, usually it is an approximately 50:50 chance as to which X chromosome is inactivated. But sometimes the ratio may be skewed (for example, 70:30). This means:

- If the normal X chromosome is silenced more often than the X chromosome with the F8 or F9 gene alteration, a female's clotting factor level can be low.
- When the X chromosome with the haemophilia gene alteration is turned off more often than the normal X chromosome, a female's clotting factor level can even be at the higher end of the normal range.

This is a random process and it is different in each female. This is why two sisters who both carry the gene for haemophilia can have very different clotting factor levels. X-inactivation also helps to explain why 20-30% of women and girls who have an F8 or F9 gene alteration have reduced clotting factor levels.

When females have low factor levels, particularly when their factor levels are very low or equivalent to their male relatives with haemophilia, this may be due to other rare genetic conditions, for example, having two bleeding disorders or a different genetic disorder. This is a very complex area and the girl or woman would need to have specialised advice and genetic testing in liaison with a Haemophilia Treatment Centre.

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NB: All photos in this booklet are stock images.

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More information

To find more information about haemophilia and carrying the gene alteration, or to find out how to get in touch with your local Haemophilia Foundation or a specialist Haemophilia Treatment Centre, contact:

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Important note

HAEMOPHILIA FOUNDATION AUSTRALIA