Genes and inheritance

What is a carrier?

In genetics **all females who have the gene alteration for haemophilia** are described as **haemophilia carriers**, because they 'carry' the gene alteration.

Another important step in diagnosis is to draw a family tree to identify any other family members with haemophilia or who are haemophilia carriers.

Haemophilia and inheritance

Haemophilia occurs when you have a mutation or alteration in the gene that makes clotting factor VIII (8) or factor IX (9). The gene alteration is inherited and passed down the generations from parent to child.

This means that haemophilia 'runs' in families.

No family history?

About one third of all cases of haemophilia appear in families with no previous history of the disorder. This happens when a new alteration in 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 gene alteration has occurred a generation or two earlier and the family has not known about it until they are tested.

Testing the family

If someone is diagnosed with haemophilia or as being a haemophilia carrier, it is likely that other members of their family may also have haemophilia or may be a carrier. To find out other male and female family members 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.

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

Chromosomes are packages in our cells that contain our genes. They decide our individual characteristics, such as the colour of our hair or our eyes. Sex chromosomes are different in males and females. They determine which biological sex we are. They also determine how blood clotting works in our body.

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.

Inheritance

Any male or female with an alteration in their *F8* or *F9* gene can pass it on to their children.

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:

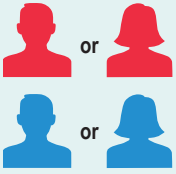
- If you have a son who inherits the gene alteration, he will have haemophilia.
- If you have a daughter who inherits the gene alteration, she will be a haemophilia carrier too and may have haemophilia.

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

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

Inheritance pattern in haemophilia

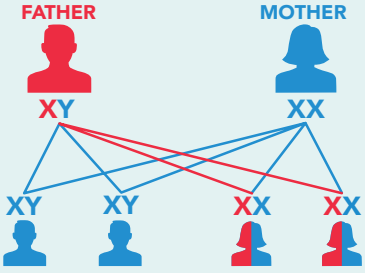
Haemophilia genetic inheritence



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

has an unaltered **X** chromosome.

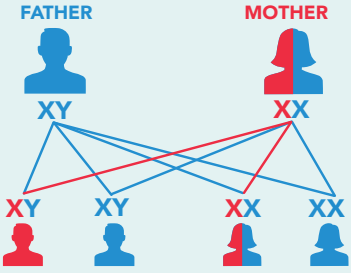
When the father has haemophilia and the mother is unaffected.



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.

Obligate carriers

Sometimes your inheritance pattern means you must have the gene alteration. In genetics this is called being an obligate carrier.

Obligate haemophilia carriers include:

- **ALL** daughters of a man with haemophilia
- Mothers of one child with haemophilia, and who have at least one other family member with haemophilia
- Mothers of one child with haemophilia, and who have a family member who is a haemophilia carrier
- Mothers of two or more children with haemophilia.

Why are female bleeding patterns different?

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

- Males with haemophilia in the same family will nearly always have the same severity – for example, a grandfather and a grandson will both have severe haemophilia.
- Factor levels in females who are carriers are unpredictable and can vary even within the same family.

Nur and Fatimah are sisters who are both haemophilia carriers.

Nur has low factor levels and mild haemophilia.

Fatimah has normal factor levels and no symptoms.

Their father has severe haemophilia.

Nur and Fatimah have inherited the same 'family' gene alteration that their father has, but this gene alteration causes severe haemophilia in males.

Both Nur and Fatimah can pass on the gene alteration to their children.

- **Their male children who inherit the gene alteration will have severe haemophilia.**
- **Their female children who inherit the gene alteration may have normal or low factor levels.**

Why are factor levels unpredictable in females?

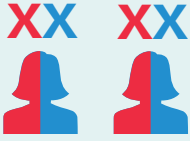
To understand factor levels in females who have a gene alteration for haemophilia, we need to look more closely at X chromosomes. Interested? Read on!

Haemophilia is due to a problem in one of the genes on the X chromosome – either the factor VIII (*F8*) gene or the factor IX (*F9*) gene.

AFFECTED MALES

A male with haemophilia (like Nur and Fatimah's father) has an **X chromosome with an *F8* or *F9* gene problem**.

Because he is male, he only has one X chromosome and so he has haemophilia.



AFFECTED FEMALES

Affected females (like Nur and Fatimah) have inherited **the X chromosome with the factor gene problem** from one parent (eg, their father).

However, females inherit two X chromosomes, one from each parent.

Usually their other parent will have **a normal X** (like Nur and Fatimah's mother).

So, although they have a **problem with a factor gene on one X**, affected females (like Nur and Fatimah) still have **a second normal factor gene on their other X**.

What happens to X chromosomes in females?

This is where it gets a bit more complicated.

In a female's body, only one of her two X chromosomes is needed in each of her cells.

The other X chromosome is permanently 'switched off' or inactivated.

This process is called **X-inactivation**.

X-inactivation is a random natural process that **happens in all females before birth**.

How does X-inactivation affect factor levels?

If a female is affected by haemophilia, she usually has **one normal X chromosome** and **one problem X** in each cell.

In some of her cells **the normal X** will be switched off

In the rest of her cells **the problem X** will be switched off.

This switching off process is random, so it is not possible to predict how many of her cells will have the normal X inactivated.

How much factor each cell makes depends on which X chromosome is switched off.

If more than half of a haemophilia carrier's normal X chromosomes are switched off, most of her cells might not be able to produce clotting factor properly. She could have low clotting factor levels and bleeding problems.

This is why two sisters who both carry the gene alteration for haemophilia can have different clotting factor levels.

50% of Fatimah's cells have an *F8* or *F9* gene that works properly.

This is enough for her blood to **clot normally**.

Only 30% of Nur's cells have an *F8* or *F9* gene that works properly.

This is why her blood doesn't clot well and she has **mild haemophilia**.

Why do some females have very low factor levels?

When females have very low factor levels, like the levels in moderate or severe haemophilia, this may sometimes be caused by other rare genetic conditions, for example, having two bleeding disorders or a different genetic disorder. Or in very rare cases, it could be that she has had the majority of her normal X chromosomes inactivated or inherited factor gene problems from both her parents.

This can be very complex and the girl or woman would need to have specialised advice, genetic counselling and genetic testing in liaison with a Haemophilia Treatment Centre and/or a Clinical Geneticist.