# Haemophilia A & haemophilia B

## What does it mean to carry the gene for haemophilia?

Everyone has the genes responsible for making factor VIII (8) and factor IX (9). These factors are necessary for blood to clot.

There are two types of haemophilia and they both have the same symptoms:

- **Haemophilia A** is the most common and is caused by not having enough of clotting factor VIII (8)
- **Haemophilia B** is caused by not having enough of clotting factor IX (9)

Haemophilia is caused by a change (often called a mutation) in the factor VIII or IX gene. This altered gene is commonly called the 'haemophilia gene'.

### Cells and chromosomes

Every person has millions of cells that make up their body. At the centre of each cell are 46 chromosomes arranged in pairs. The chromosomes contain the person's genetic information or 'genes', which determine the person's individual characteristics, such as the colour of their hair or their eyes.

### Sex determination

Everyone has a pair of 'sex' chromosomes, which decide what gender they are. Each parent contributes one of these chromosomes to their children. Females have two X chromosomes, 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.

**Women and girls** with an altered factor VIII or IX gene are often described as "carrying the gene" or a "carrier".

Photo by Daria Shevtsova from Pexels

Because **females** have two copies of the factor VIII or IX genes, one inherited from each parent, women and girls with an altered gene 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.

Most often a female who carries the gene will have normal clotting factor levels. In some cases she will have mildly reduced clotting factor levels. Sometimes her factor levels can be low enough to be classified as having haemophilia, usually mild haemophilia. In a few very rare cases girls and women can have extremely low factor levels and have severe haemophilia.

However, the Y chromosome does not have a gene to produce these factors. **Males** with an altered factor VIII or IX gene on their X chromosome do not have another factor VIII or IX gene to help with blood clotting and will have haemophilia.

# Inheritance

If you are a female who carries the gene for haemophilia or you are a male with haemophilia, you will have an alteration in your factor VIII (8) or IX (9) gene. This altered gene may be passed on to your children.

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

- If you have a son who inherits the gene, he will have haemophilia.
- If you have a daughter who inherits the gene, she will carry the gene too.

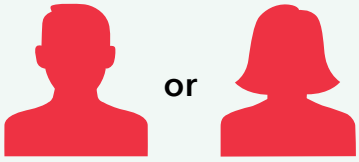
**If you are a male with haemophilia:**

- **All (100%) of your daughters** will inherit the altered gene from you and will carry the gene
- **None of your sons** will have haemophilia.

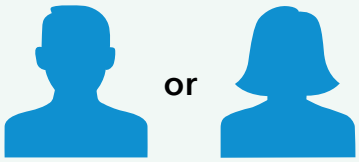
**This is tricky stuff to understand!**

The diagram below might help.
The red males are those with haemophilia; the red and blue females carry the gene - they have the X chromosome with the genetic alteration, and one unaltered X chromosome.

**Haemophilia genetic inheritance**

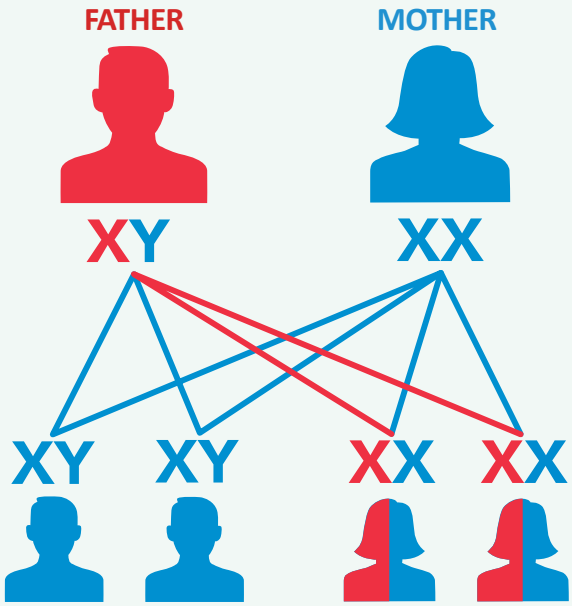



has an X chromosome with the "haemophilia" genetic alteration.



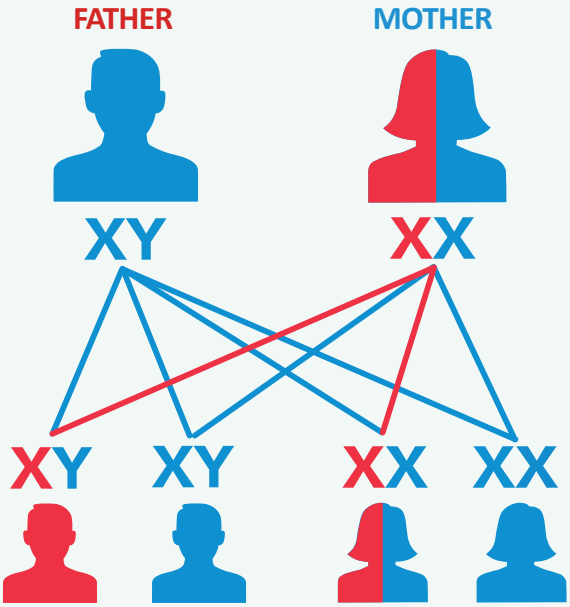

has an unaltered X chromosome.

**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.
Some might have symptoms or have haemophilia.

**When the mother carries the altered gene 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. Some might have symptoms or have haemophilia.

## No family history

Because haemophilia is inherited, it occurs in families, and the altered gene is passed down from parent to child. However, **in about one third of all cases there is no family history of the disorder**. This situation can happen when a new genetic mutation occurs during a baby's conception. When the child is born they will have the altered gene and can pass it on to their children. Another possibility is that the genetic mutation might actually have occurred in the mother's conception so that when the mother of a child with haemophilia is tested, she finds she carries the gene.

If someone is diagnosed with haemophilia or as being a carrier, other members of their family may be affected too. Confirming a diagnosis often includes checking the family history for bleeding problems. Other family members, including females, may also need to be tested.

**If you would like more information about inheritance**, read the **Haemophilia booklet** by visiting the webpage: https://www.haemophilia.org.au/about-bleeding-disorders/haemophilia Or request a copy of the booklet from your Haemophilia Treatment Centre.

## Bleeding symptoms

**Most girls and women who carry the altered gene causing haemophilia do not have symptoms of a bleeding disorder.** If at least one of their X chromosomes has a factor VIII or IX gene that works, their body can usually produce normal or near normal levels of clotting factor and they do not have bleeding problems.

**However, some females who have the gene may have a bleeding tendency.** These girls and women used to be described as symptomatic carriers. If a female's factor levels fall in the range for mild haemophilia (5 – 40% of normal clotting factor), she is now recognised as having mild haemophilia. In very rare cases, a few females have particularly low factor levels causing them to have moderate or severe haemophilia.

Some females with factor levels between 40% and 60% may also experience abnormal bleeding.

Females with very low clotting factor levels may also have:

- Bleeding episodes that happen for no obvious reason.
- Bleeding into joints and muscles which can cause swelling, loss of movement and pain.

### FACTOR LEVELS AND SEVERITY

The normal level of factor VIII or IX in a person's blood is between 50% and 150%

| | |
|---|---|
| Mild haemophilia | 5 – 40% of normal clotting factor |
| Moderate haemophilia | 1 – 5% of normal clotting factor |
| Severe haemophilia | Less than 1% of normal clotting factor |

# Female bleeding patterns

In males with haemophilia the severity is nearly always the same within the same family. This means, for example, a grandfather and a grandson will both have severe haemophilia. However, factor levels in girls and women who have the altered gene are unpredictable and can vary between family members. For example, a father with severe haemophilia can have a daughter with mild haemophilia, or if two sisters carry the gene, one can have normal factor levels, and the other can have low factor levels and have mild haemophilia.

## Why does this happen?

This is because of a process called **lyonization**.

The lyonization process usually occurs very early in female embryo development. All females have two copies of the X chromosome. In lyonization each cell in the female embryo randomly turns off (inactivates) one of the X chromosomes. This is to "balance out" the amount of X chromosome material in each cell in a female's body so that females do not end up with a doubling up of their genetic material.

## What happens in haemophilia?

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

- If the normal X chromosome (without the haemophilia gene mutation) is turned off more often than the X chromosome with the haemophilia gene mutation then a girl or woman's clotting factor level can be low.
- If the X chromosome with the haemophilia gene mutation is turned off more often than the normal X chromosome then a girl or woman's clotting factor level can even be at the higher end of the normal range.

It is important to understand that 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. This process also helps to explain why approximately 20-30% of women and girls who have the haemophilia gene alteration have a reduced clotting factor level.

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. 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.

Photo by Bahaa A. Shawqi from Pexels

# The calico cat

**The calico cat is often used to help explain lyonization (X chromosome inactivation).**

The coat of a calico cat is a mix of orange, black and white fur. Calico cats are nearly always female and so they have two X chromosomes. The gene for the orange fur is on one X chromosome and the gene for the black fur is on the other X chromosome. When these cats are an embryo, each of their cells will turn off one of their X chromosomes.

If the X chromosome with the gene for black fur is turned off, the cell will create orange fur. If the X chromosome with the gene for orange fur is turned off, the cell will create black fur.

The amount of black and orange fur on a calico cat will depend on how many of either the black or orange X chromosomes are inactivated (turned off).

Because the X chromosomes are turned off randomly, the fur coat of every calico cat will have a different pattern of orange and black. The white colour is created by another gene.

**Source:** LeMieux, J. Calico Cats Are A Walking Genetics Lesson. American Council on Science and Health, July 27, 2016.
Available from: https://www.acsh.org/news/2016/07/27/calico-cats-are-a-walking-genetics-lesson

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