

This fact sheet describes the genetic condition haemophilia and includes the symptoms, cause and any treatment or testing which is available.

In summary

- Haemophilia is a genetic condition that causes continued bleeding due to the blood's inability to clot properly
- There are two main genes involved in Haemophilia, known as *F8* and *F9*. Both genes are found on the X chromosome
- Haemophilia is an X-linked recessive condition and usually affects males only.

WHAT IS HAEMOPHILIA?

Haemophilia is a genetic condition that causes people to continue bleeding for a long time unless treated. It is due to missing or abnormal clotting factors that impact on the blood clotting process.

The blood clotting system is activated in response to blood vessel injury. Part of the clotting process involves the activation of specialised proteins called **clotting factors** numbered 1 to 10 whose primary role is to 'plug' an injured blood vessel, like a band-aid. Haemophilia occurs due to missing or abnormal clotting factor 8 or 9. People with haemophilia do not bleed faster than anyone else, but will bleed continuously at the normal rate.

There are two types of Haemophilia:

- **Haemophilia A:** also known as classic haemophilia, is caused by having low levels of or no clotting factor 8. It affects approximately 1 in 4,000 to 1 in 10,000 males.

- **Haemophilia B:** also known as Christmas disease, is caused by having low levels of or no clotting factor 9. It affects approximately 1 in 20,000 males.

Spontaneous bleeding in to joints such as knees, ankles and elbows is common and can result in osteoarthritis. Internal bleeding and bleeding into muscle is the major concern. Treatment involves injections of the missing clotting factor, both prophylactically and following a bleed.

WHAT CAUSES HAEMOPHILIA?

There are two genes involved in haemophilia and both are found on the X chromosome. The *F8* gene produces the clotting factor 8 (Factor VIII) and the *F9* gene produces the clotting factor 9 (Factor IX). A mutation in the *F8* or *F9* gene results in a deficiency in these clotting factors and the blood cannot form clots properly.

Our body is made up of millions of cells, and in each cell there are instructions, called genes, that make all the necessary structural components and chemicals for the body to function. These genes are packaged onto little long strands known as chromosomes.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product produced by the gene, called a protein, is impaired or even absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

HOW IS HAEMOPHILIA INHERITED?

Haemophilia follows a pattern of **X-linked recessive inheritance**. X-linked refers to the fact that the haemophilia genes are located on the X chromosome, which is one of the sex chromosomes. Recessive means that severe symptoms occur when there are no normal copies of the haemophilia gene.

If males have a mutation in one of their haemophilia genes, they will develop signs and symptoms of haemophilia because they only have one copy of the haemophilia genes (on their one X chromosome).

Females, on the other hand, have two copies of their haemophilia genes, one on each X chromosome pair. If one of the haemophilia genes has a mutation they still have a normal, working copy on the other X chromosome and will usually produce about 50% of the associated clotting factors (Factor VIII or Factor IX) needed in the blood clotting process. This amount is usually sufficient for normal clot formation and they will usually not show any signs or symptoms of haemophilia.

Sometimes, females with a haemophilia gene mutation on one of their X chromosomes will produce <50% of the associated clotting factor and may show signs of a mild bleeding disorder. All daughters and mothers of an affected male should have their baseline clotting factor activity calculated and risk of bleeding assessed.

Unaffected women who have a mutation in a haemophilia gene on one of their X chromosomes are referred to as **genetic carriers** as, although they do not have symptoms of the condition, they can still pass it on to their children.

If a mother is a genetic carrier for a haemophilia gene (Figure 52.1), in every pregnancy there is:

- 1 chance in 4, (25% chance) that a son will inherit the Y chromosome from his father and the X chromosome with the haemophilia gene mutation from his mother. In this case, no working gene will be made. He will be affected with haemophilia.

- 1 chance in 4, (25% chance) that a son will inherit the Y chromosome from his father and X chromosome with the working copy of the haemophilia gene from his mother. He will not be affected by the condition.
- 1 chance in 4, (25% chance) that a daughter will inherit the X chromosome with a working copy of the haemophilia genes from both her father and her mother. In this case she will not be affected by the condition and she will NOT be a carrier for haemophilia.
- 1 chance in 4, (25% chance) that a daughter will inherit the X chromosome with a working copy of the haemophilia gene from her father and the X chromosome with the haemophilia gene mutation from her mother. She will be a genetic carrier for haemophilia like her mother and will usually be unaffected.

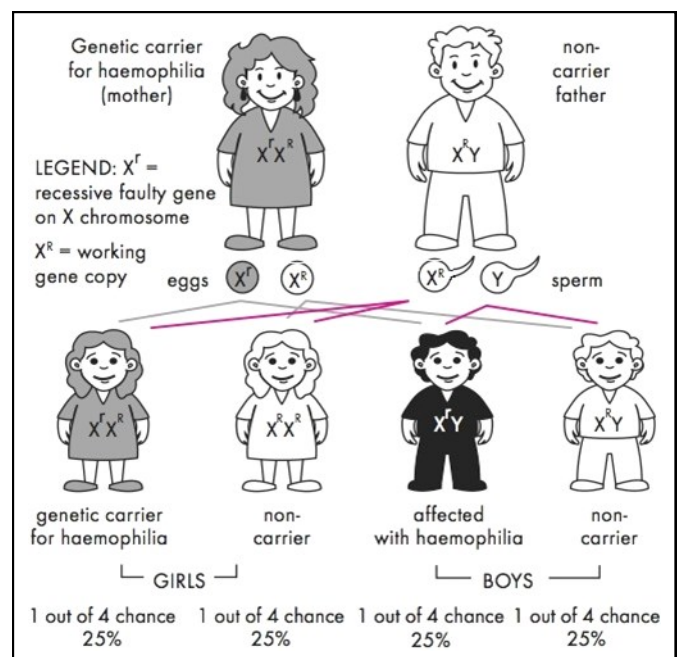


Figure 52.1: X-linked recessive inheritance where the mother is a carrier of a haemophilia gene mutation on one of her X chromosomes. The X-linked recessive mutation is represented by 'r'; the working copy by 'R'.

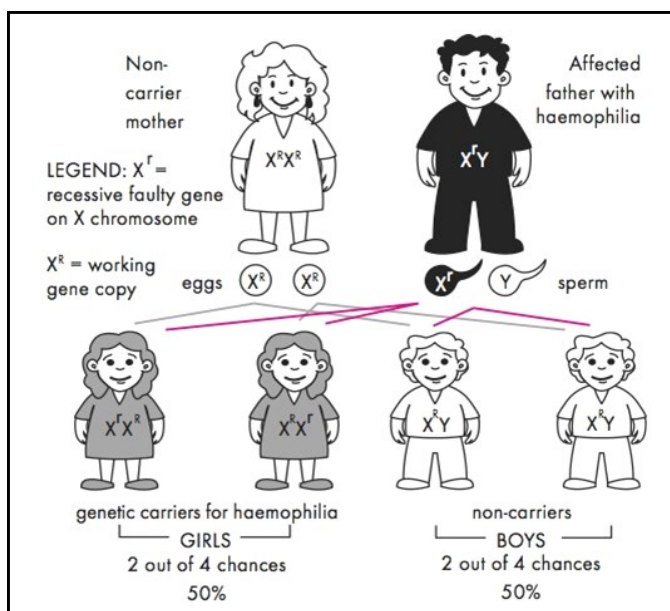


Figure 52.2: X-linked recessive inheritance where the affected father has the faulty copy of the haemophilia gene mutation. The X-linked recessive faulty gene copy is represented by 'r'.

If a father is affected with haemophilia (Figure 52.2), in every pregnancy:

- All sons will inherit the Y chromosome from their father and the X chromosome with a working copy of the haemophilia gene from their mother and will therefore not have the condition.

All daughters will inherit the X chromosome with the haemophilia gene mutation from their father (as this is his only X chromosome) and the X chromosome with a working copy of the haemophilia gene from their mother.

They will be genetic carriers for haemophilia and can pass the mutation on to their children. They will usually be unaffected by the condition.

IS THERE ANY TESTING AVAILABLE FOR HAEMOPHILIA?

Diagnostic testing

If a diagnosis of haemophilia is suspected, special blood tests to look at the levels of clotting factors may be arranged by your health care practitioner. This will indicate the severity and type of haemophilia. Genetic testing is available to confirm a diagnosis, although a mutation is not always identified in people affected with haemophilia. When a person is confirmed to have haemophilia, their first degree relatives (parents, children, brothers and sisters) may have up to 1 chance in 2 (50%) of being a genetic carrier if female, or affected if male.

Testing for carrier status

Female carriers of Haemophilia may not have abnormal levels of clotting factor. Genetic testing is the only way to confidently confirm or exclude your carrier status if the gene mutations have been identified in your family.

Prenatal testing and PGD

For females who are known genetic carriers for haemophilia, testing may be available during a pregnancy to determine whether the baby will be unaffected, affected or a genetic carrier for haemophilia. It may also be possible to undergo **pre-implantation genetic diagnosis (PGD)** screening for haemophilia on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes be explored.

Treatment

The type of treatment you or your child receives depends on several things, including how severe the haemophilia is, the activities you will be doing, and the dental or medical procedures you will be having. Replacement therapies, where you are given an infusion of concentrated clotting factors to replace those that are missing or in low concentration, may be offered as needed. Your health care practitioner will discuss what treatment options are relevant to you.