Important points

- Haemophilia is a genetic condition that causes people to continue bleeding for a long time unless treated. Bleeding is common into joints such as knees, ankles and elbows. Sometimes bleeding into muscles or internal organs can occur. The blood is unable to clot properly due to missing or abnormal proteins that enable blood to clot (*clotting factors*)
- **Haemophilia A** caused by having low levels of or no clotting factor 8, affects between 1 in 4,000-10,000 males; **Haemophilia B** caused by having low levels of or no clotting factor 9, affects about 1 in 20,000 males
- The genes that contain the information for the cells to make the clotting factors 8 and 9 are located on the X chromosome
- Women have two copies of the X chromosome (XX); those with a faulty clotting factor gene on one X chromosome and a working copy on the other partner X chromosome are genetic carriers for haemophilia and would not usually be affected
- Males have only one X chromosome and a Y (XY); those with a faulty clotting factor gene on their X chromosome will have haemophilia as they have no working gene copy on the Y chromosome
- For men and women to have the same amount of genetic information produced in their cells, one X chromosome copy is usually randomly 'switched off' or inactivated in a woman's cells. In about 10% of women who are genetic carriers for haemophilia, this 'switching off' system results in more of her cells containing the active X chromosome carrying the faulty clotting factor gene copy than the working copy, so she may be mildly affected with haemophilia
- The pattern of inheritance in families of the faulty gene causing haemophilia is described as **X-linked recessive inheritance**
- Where the mother is a carrier of a faulty X-linked clotting factor gene and the father has a working copy of the gene, **in every pregnancy**, the risks for having an affected child are different for their sons and daughters.
  - Their sons have 1 chance in 2, or a 50% chance, of inheriting the faulty gene for haemophilia and having the condition
  - Their daughters have 1 chance in 2, or a 50% chance, of inheriting the faulty clotting factor gene copy and being a genetic carrier for haemophilia. Carriers would usually be unaffected
- As a father passes his Y chromosome to his sons and his X chromosome to his daughters, where the father has haemophilia, **in every pregnancy, none of their children will have haemophilia**
  - Their **sons** will inherit the working X-linked faulty clotting factor gene copy from their mother and will therefore not have haemophilia
  - All of their **daughters** will inherit from **their mother the working copy** of the X-linked clotting factor gene and the **faulty copy from their father.** They will be carriers of the faulty X-linked clotting factor gene, although they will generally be unaffected by haemophilia
- If, in a couple, the man has haemophilia or the woman is a genetic carrier for haemophilia, they must seek genetic counselling for information about the condition and to discuss their risk for having an affected child with haemophilia and to discuss their reproductive options (see Genetics Fact Sheet 3)

For blood to flow normally in the blood vessels (arteries, veins and capillaries) a balance needs to be maintained between too much bleeding and too much clotting (coagulation). This is called *haemostasis* (haemo=blood, stasis=state of not flowing/moving).

A number of conditions result from the body's inability to prevent too much bleeding.

- If the clotting system forms clots too easily, then the result is formation of excess clots (*thrombophilia* - see Genetics Fact Sheet 39)
- This Fact Sheet discusses conditions where the clotting cannot adequately form a clot and the result is a bleeding condition called haemophilia

What is the blood clotting process?

Clotting of blood occurs when there is conversion of fluid blood into a coagulated, solid form to prevent further blood loss from damaged tissues, blood vessels or organs. This is a complicated process made up of two systems that work together to form a clot; problems in either system can yield conditions that cause either too much or too little clotting.

- One system involves cells called *platelets* that circulate in the blood combining to form a platelet 'plug' over damaged vessels
- The other system is based upon the actions of multiple proteins (including 'clotting factors') that act in conjunction to produce a clot. This system is called the *coagulation cascade* (see Genetics Fact Sheet 39)

Haemophilia

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

People with haemophilia do not bleed faster than anyone else, but will bleed continuously at the normal rate until they are treated. Internal bleeding is the major concern in haemophilia.

Bleeding into joints such as knees, ankles and elbows is common. This may be caused by injury, but in severe haemophilia, can begin spontaneously. Less commonly, bleeding into muscles or internal organs can occur.

There are two common 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.

What causes haemophilia?

Our genes are located on our chromosomes in our cells, and provide the information for the growth, development and function of our bodies (see Genetics Fact Sheet 1).

The clotting process in blood is very complex. There are many different 'factors' that are involved in this process. The information for the body to manufacture these factors is contained in the genes.

A gene that contains a variation in the information that stops it working properly is described as faulty. The variation that makes the gene faulty is called a *mutation*. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

There are different genes for the different clotting factors. Faulty clotting factor genes will result in the body manufacturing 'factors' which are impaired or not in the right amounts (see Genetics Fact Sheet 4).

The genes for clotting factors 8 and 9 are located on the X chromosome. Haemophilia A and haemophilia B, are both due to changes in one copy of two different X-linked clotting factor genes.

What does it mean to have a faulty copy of the X-linked clotting factor 8 or 9 genes?

Having a faulty copy of an X-linked clotting factor gene affects men and women in different ways.

Men have only one X chromosome and a Y chromosome.

- If their X chromosome has a copy of a faulty clotting factor gene, they would have haemophilia
- The Y chromosome does not have the clotting factor genes so they have no working copy to provide the cells with the right information for the clotting factors

Women have two copies of the X chromosome.

Women with a faulty copy of a clotting factor gene on one of their X chromosomes, and a working copy of a clotting factor gene on the other partner X chromosome, can still produce the working clotting factor.

- They are carriers of the faulty gene involved ie. genetic carriers for haemophilia, and usually unaffected, although rarely they may be affected (see Genetics Fact Sheet 14 and later)
- Genetic carriers can pass the faulty gene copy on to their children

Are there any personal health implications for a woman who is a genetic carrier for haemophilia?

Women who are carriers of the X-linked faulty genes for clotting factors 8 or 9, ie. they are genetic carriers for haemophilia A or B, are *usually* not themselves affected.

To ensure that men and women have the same amount of genetic information sent to their cells, one of the X chromosomes in the cells of a woman is 'switched off' or inactivated (see Genetics Fact Sheet 14).

- This means that only one copy of the X chromosome genes in a woman is working, just like in men
- This is usually a random process
- Half of her cells will have the X chromosome copy with the faulty gene 'switched off' and the other half of her cells will have the X chromosome with the working copy 'switched off'
- This means that a woman who is carrier of a faulty clotting factor gene will produce half of the amount of clotting factor compared to a woman who has only working copies of the gene. This is, however, enough to stop the bleeding

In about 10% of women who are genetic carriers for haemophilia, this 'switching off' system is not random: more of her cells may contain the active X chromosome carrying the faulty clotting factor gene copy than the working copy. In these cases, the woman may have a mild form of haemophilia.

What is the pattern of inheritance of haemophilia in families?

The pattern of inheritance in families of both haemophilia A and haemophilia B is the same.

They are both genetic conditions (see Genetics Fact Sheet 2) that are passed from parents to children in their genes.

Two factors influence the pattern of inheritance of the faulty clotting factor genes causing haemophilia in families.

1. The genes for clotting factors 8 and 9 are on the X chromosome
2. The effect of the change in the genes is 'recessive' or hidden by the presence of the working copy of the gene (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance in families of the faulty gene causing haemophilia is therefore described as **X-linked recessive inheritance** (see Genetics Fact Sheet 10).

In *Figures 40.1* and *40.2*, the faulty clotting factor genes are represented by 'r' on the X chromosome; the working copy by 'R'.

As shown in *Figure 40.1*, where the mother is a carrier of the faulty clotting factor gene and the father has a working copy of the gene, the risks for their children is as follows:

- Their sons have 1 chance in 2, or a 50% chance, of inheriting the faulty gene for haemophilia and having the condition
- Their daughters have 1 chance in 2, or a 50% chance, of inheriting the faulty clotting gene copy and being a genetic carrier for haemophilia. Carriers would usually be unaffected

This is because there are four possibilities, **in every pregnancy**, for the combination of the clotting factor genes passed from the parents. There is

- 1 chance in 4, or 25% chance, that a **son** will inherit the X chromosome carrying the faulty clotting factor gene copy from his mother. In this case, his cells will not produce the right amount or no clotting factor at all and he will have haemophilia
- 1 chance in 4, or 25% chance, that a **son** will inherit the working copy of the gene from his mother and will not have haemophilia
- 1 chance in 4, or 25% chance, that a **daughter** will inherit the working copy of the gene from her mother and a working copy from her father. In this case she will not only be unaffected by the condition but she will also NOT be a carrier of the faulty clotting factor gene
- 1 chance in 4, or 25% chance, that a **daughter** will inherit the faulty clotting factor gene copy from her mother and a working copy from her father. She will be a genetic carrier like her mother and will generally be unaffected

What if the father has haemophilia?

The risk for passing on the faulty clotting factor gene copy to their child is different for their sons and daughters.

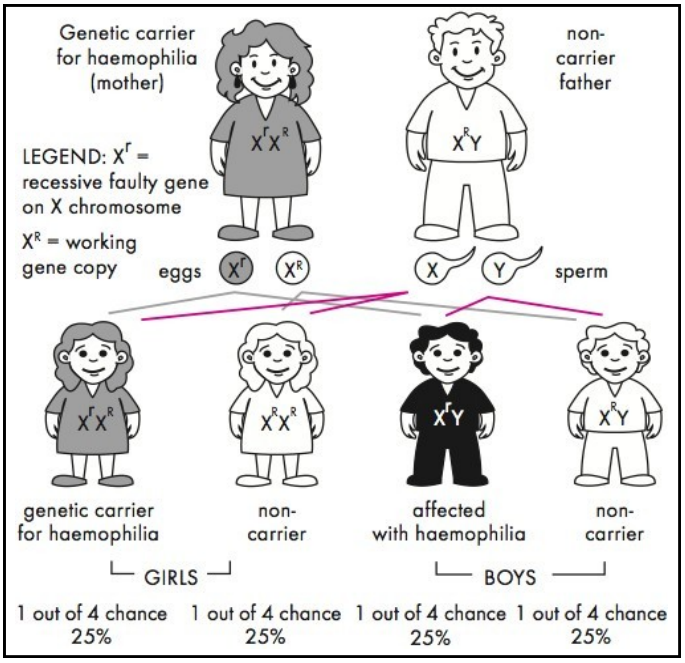

Figure 40.1: *X-linked recessive inheritance where the mother is a carrier of the faulty clotting factor gene copy. The faulty clotting factor gene copy is represented by 'r'; the working copy by 'R'.*

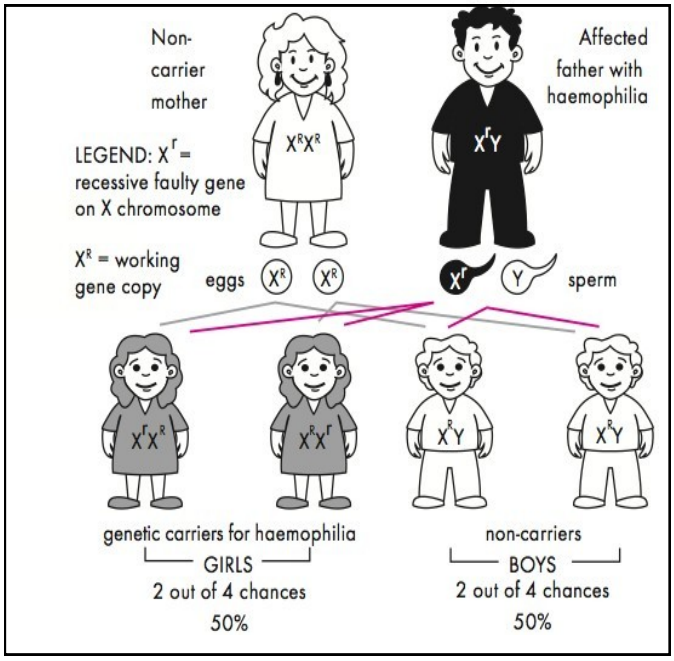

Figure 40.2: *X-linked recessive inheritance where the father has haemophilia due to having the faulty clotting factor gene copy. The faulty clotting factor gene copy is represented by 'r'; the working copy by 'R'.*

As shown in *Figure 40.2*, a father passes his Y chromosome to his sons and his X chromosome to his daughters. This means that where the father has haemophilia, **in every pregnancy,**

- None of their **sons** will inherit the faulty clotting factor gene copy from their father; they will only inherit their X chromosome from the mother that carries the working copy of the clotting factor gene. They will therefore not have haemophilia
- Their **daughters** will inherit **from their mother the working copy** of the clotting factor gene and **the faulty copy from their father**. They will be carriers of the X-linked faulty clotting factor gene, although they will generally be unaffected by haemophilia.

How can a woman find out if she is a genetic carrier for haemophilia?

It may be possible to determine if a woman is a carrier of a faulty clotting factor gene if she has a family history of haemophilia or a female blood relative who is a genetic carrier for haemophilia.

Genetic counselling (see Genetics Fact Sheet 3) can provide the most current information regarding these conditions and any tests which might be appropriate. Information and support is provided to all family members.

How can knowing about having the faulty clotting factor gene(s) help?

If in a couple, the man has haemophilia or the woman is a genetic carrier for haemophilia, they may seek genetic counselling for information about the condition, to discuss their risk for having an affected child with haemophilia and to discuss their reproductive options (see Genetics Fact Sheet 3).

Prenatal testing for haemophilia in pregnancy and testing an embryo before pregnancy in association with assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF) may be possible (see Genetics Fact Sheets 17C & 18).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 10, 14, 17C, 18, 39