Fact sheet **09**

X-LINKED RECESSIVE INHERITANCE

This fact sheet talks about how genes affect our health when they follow a well understood pattern of genetic inheritance known as X-linked recessive inheritance.

IN SUMMARY

- Genes contain the instructions for growth and development. Some gene variations or changes may mean that the gene does not work properly or works in a different way that is harmful.
- A variation in a gene that causes a health or developmental condition is called a **pathogenic variant** or **mutation**.
- If a genetic condition happens when a gene on the X chromosome has a variation, this is called **X-linked inheritance**.
- An X-linked recessive gene is a gene located on the X chromosome and affects males and females differently.

CHROMOSOMES, GENES AND DNA

In all the cells of our body, our genes are found on chromosomes (long strings of genes). We have many thousands of genes that provide information for our body to grow, develop and stay healthy. The gene sends messages to the cell to make important chemical products such as proteins.

There are usually 46 chromosomes in each cell that are arranged into 23 pairs. One of each pair is passed on to us from our mother and the other from our father. 22 of these chromosome pairs are numbered. These numbered pairs are known as the autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Typically males have an X and a Y chromosome and females have two copies of the X chromosome.

Since the chromosomes come in pairs, there are also two copies of each of the genes.

The exception to this rule applies to the genes carried on the sex chromosomes called X and Y.

The genes in our DNA provide the instructions for proteins, which are the building blocks of the cells that make up our body. Although we all have variation in our genes, sometimes this can affect how our bodies grow and develop.

Generally, DNA variations that have no impact on our health are called **benign variants** or **polymorphisms**. These variants tend to be more common in people. Less commonly, variations can change the gene so that it sends a different message. These changes may mean that the gene does not work properly or works in a different way that is harmful. A variation in a gene that causes a health or developmental condition is called a **pathogenic variant** or **mutation**.

If a DNA change happens in only one copy of the pair of genes and this causes a health condition, it is called a **dominant variant**. If a health condition only occurs when both copies of the gene are changed, this is called a **recessive variant**.

Figure 9.1:
Chromosome picture (karyotype) from a male 46,XY.

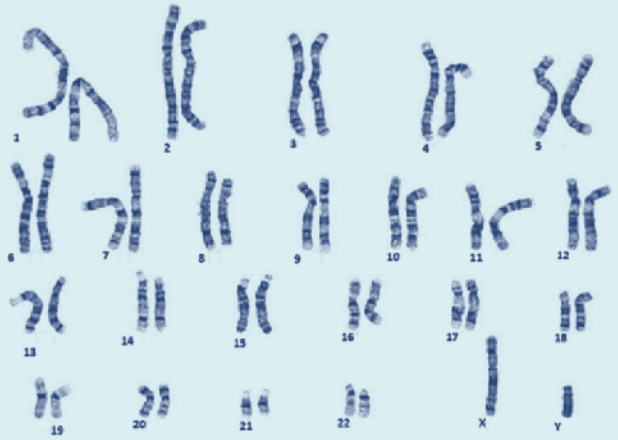

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Figure 9.2:
Where a non-working X-linked recessive gene copy with a variant is represented by 'r' and the working gene copy by 'R', there are several possibilities for a person depending on if they are male or female.

A.

- This typical female has the gene pair Rr on her X chromosomes. This means that one copy of the gene is working (R) and making the gene product in the right way, however the other copy (r) is not working
- When this person has a child, there is a 50% (1 in 2) chance of passing on a working (R) gene copy to each child and a 50% (1 in 2) chance of passing on the gene variant so the gene does not work (r).
- This person's children will either not develop symptoms of the genetic condition (see i. below) or be affected (see ii. below)
  - i. For most X-linked recessive conditions, genetic carrier females will not show symptoms themselves because enough cells have the working X chromosome switched on, and the non-working X chromosome switched off (inactivated)
  - ii. Some X-linked recessive conditions can show up in females who are genetic carriers. Sometimes this is because the X with the working copy of the gene is switched off or inactivated in more cells in the body.

B.

- This represents a typical unaffected female who has two working copies of the gene on her X chromosomes
- When this person has a child, there is a 100% chance of passing on the working copy of the gene to all sons and daughters. So none of the children will have the non-working copy of the gene causing the particular condition

C.

- This represents a typical affected male who has an X-linked recessive gene on the X chromosome. There is no working copy of the gene and therefore they will not be making the gene product in the right way and will show symptoms of that particular condition
- When this person has a child, there is a 100% chance (all of his daughters) will inherit the non-working copy of the gene with a variant (r). Their sons will not inherit the X chromosome, but rather the Y chromosome, which means they will not have inherited the non-working gene copy with the variant from him.

D.

- This represents a typical unaffected male who has a working copy of the gene on the X chromosome. Their body cells can therefore make the gene product in the right way and will not show symptoms of that particular condition.
- When this person has a child, there is a 100% chance (all of his daughters) will inherit the working copy of the gene. Their sons will not inherit the X chromosome, but rather the Y chromosome which means that all sons will not have inherited the gene variant either.

An **autosomal** gene is a gene located on a numbered chromosome and usually affects males and females in the same way.

An **X-linked** gene is located on the X chromosome and usually affects males and females differently.

A CLOSE LOOK AT X-LINKED INHERITANCE

This type of inheritance refers to the inheritance of a gene variant on the X chromosome. Typically males have one X chromosome and one Y chromosome whereas females have two copies of the X chromosome and no Y chromosome (see *Figure 9.1*). Because of this, males will only have one copy of each X chromosome gene while females will have two.

In females, although each body cell has two X chromosomes, only one is used for making the gene product and the other X chromosome is switched off.

This process of switching off is known as **X-inactivation**. This usually happens randomly so that in some of the female's cells, one particular X will be inactivated (switched off) and in another cell, that X will be active (switched on).

WHAT DOES IT MEAN IF YOU HAVE AN X-LINKED RECESSIVE GENE VARIANT?

Variants on the X chromosome are most often recessive. This means that if there is a working copy of the same gene in each cell of a person, they will not usually show symptoms of the condition. In other words, the working copy of the gene is a backup for the other non-working copy of the gene.

For example, in *Figure 9.2A*, the female has two copies of the gene because there are two X chromosomes. One of the X chromosomes has a recessive variant and the other has a working copy of the gene.

This person is a genetic carrier and although only one of the gene copies is sending the right instructions to make the gene product, the cell can usually work with this.

In many X-linked recessive conditions, females who carry a gene variant will not have any symptoms of the condition (*Figure 9.2Ai*).

Some conditions, however, may affect females who are genetic carriers and this is thought to be due to the X inactivation process switching off the X with the working gene copy in more body cells (*Figure 9.2Aii*). So the working copy of the X-chromosome is not switched on enough to protect this person from developing the condition.

Males who have the recessive gene variant on their X chromosome do not have a second chromosome with a working copy of the gene.

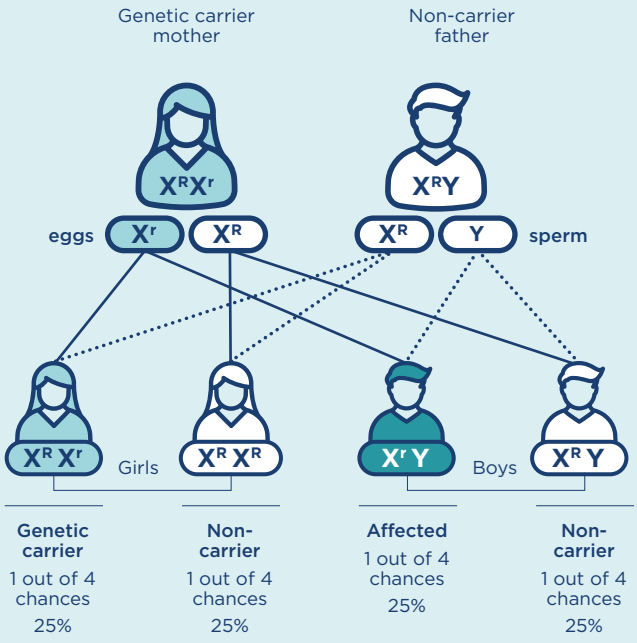
Therefore, they will not be able to send the right message to the cells to make the gene product, and will have the condition (see *Figure 9.2C*).

HOW ARE X-LINKED RECESSIVE GENE VARIANTS PASSED DOWN THROUGH THE FAMILY?

If the mother is a carrier of an X-linked recessive gene variant

The chances of a mother who is a carrier of an X-linked recessive gene variant having a child with the condition are different for her sons and daughters.

Figure 9.3:
X-linked recessive inheritance where the mother is a carrier of the non-working copy of the X-linked gene. The X-linked recessive non-working gene copy is represented by 'r'; the working copy by 'R'.



In *Figure 9.3*, where the non-working X-linked recessive gene copy is represented by 'r' and the working copy by 'R', the mother is a carrier of an X-linked recessive gene health condition and the father has only a working copy of the gene. There are four possibilities in every pregnancy that the child can receive from the parents.

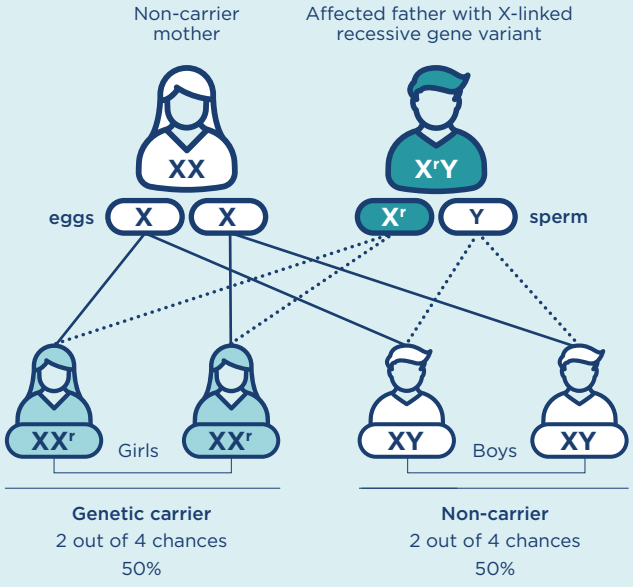
For such a couple, this means that in every pregnancy there is:

- 1 chance in 4, (25% chance) that a **son** will inherit the Y chromosome from their father and **X-linked recessive non-working gene copy with the variant** from the mother. In this case, the body cells cannot make gene product in the right way. This person will therefore have the condition
- 1 in 4, (25%) chance that a **son** will inherit the Y chromosome from their father and **the working copy of the X-linked gene** from the mother. This person will therefore not have the condition

- 1 in 4, (25%) chance that a **daughter** will inherit **both working copies of the X-linked genes**: one copy from their father and one from the mother. A daughter will therefore be unaffected by the condition. In addition they will also NOT be a carrier of the X-linked recessive gene copy with the variant
- 1 in 4, (25%) chance that a **daughter** will inherit from their father the **working copy of the X-linked gene** and the **X-linked recessive non-working gene copy with a variant** from the mother. This person will be a genetic carrier of the condition like the mother and will usually be unaffected.

In summary, if pregnant with a son, there is a 50% (1 in 2) chance that the child will have the condition and if pregnant with a daughter, a 50% (1 in 2) chance they will be a genetic carrier of the condition.

Figure 9.4:
X-linked recessive inheritance where the father has the non-working copy of the X-linked gene. The non-working X-linked recessive gene copy is represented by 'r'.



If the father is affected by an X-linked recessive genetic condition

If the father is affected by an X-linked recessive genetic condition, the chance of passing on the non-working recessive gene copy is different for his sons and daughters.

As shown in *Figure 9.4*, there are two possibilities in every pregnancy that the child can receive from the parents. The father passes his Y chromosome to his sons and his X chromosome to his daughters.

For such a couple, this means that in every pregnancy:

- All **sons** will inherit the **working X-linked gene copy** from their mother and the **Y chromosome from their father** and will therefore not have the condition
- All **daughters** will inherit a **working copy of the X-linked gene** from their mother and **X-linked recessive gene variant** from their father. They will be carriers of the variant and can pass this on to their children. They will usually not have the condition.

WHAT GENETIC CONDITIONS ARE CAUSED BY AN X-LINKED RECESSIVE GENE VARIANT?

The most common conditions that are caused by an X-linked recessive gene variant are haemophilia, Duchenne muscular dystrophy and fragile X syndrome.

Usually female genetic carriers of an X-linked recessive condition do not develop health concerns by being a genetic carrier.

Clues for why a female might be a genetic carrier of an X-linked recessive gene variant include having a family history of a condition that usually only affects males.