

This fact sheet describes the condition Fragile X and includes a discussion of the symptoms, causes and available testing.

In summary

- Fragile X is a condition caused by a change in the *FMR-1* gene, on the X chromosome
- It is characterised by particular physical features, varying degrees of learning difficulties and behavioural and emotional problems
- Fragile X affects around 1 in 4,000 males and between 1 in 5,000 and 1 in 8,000 females.

WHAT IS FRAGILE X SYNDROME?

Fragile X syndrome is the most common known cause of inherited intellectual disability.

Intellectual problems in people with fragile X syndrome can vary from mild learning difficulties through to severe intellectual disability.

Emotional and behavioural problems may also be present.

Females with fragile X syndrome show varying degrees of the condition, but are usually less severely affected than males.

The features of the condition, and their severity, are related to the genetic information in the faulty gene causing the condition.

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WHAT CAUSES FRAGILE X SYNDROME?

Fragile X syndrome is caused by a variation in the genetic information in the *FMR-1* gene. Genes are made up of a string of three letter 'words', or **triplets**, using the letters A, T, C & G. The *FMR-1* gene codes for a protein called FMRP that is necessary for usual brain development and/or function. In the *FMR-1* gene, the triplet word 'CGG' can be repeated many times. When the number of 'CGG' repeats in the *FMR-1* gene increases over a critical number, the gene becomes so long that it becomes faulty and the production of the FMRP is disrupted.

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 (see Figure 1). 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. The *FMR-1* gene is located on the X chromosome (See figure 54.1).

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.

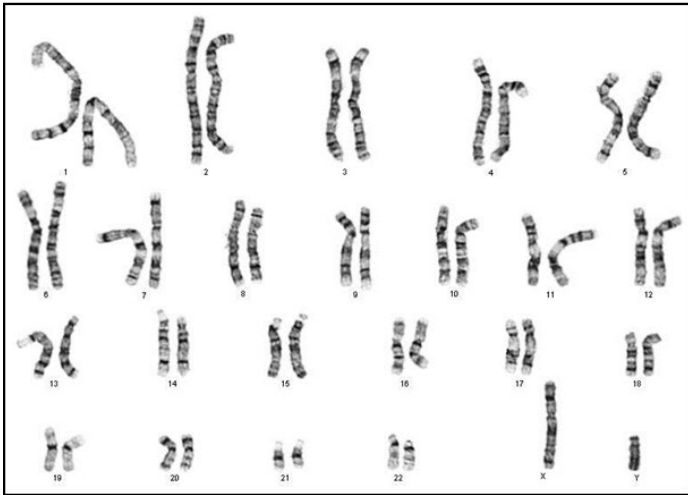


Figure 54.1: Chromosome picture (karyotype) from a male 46,XY.

HOW IS FRAGILE X SYNDROME INHERITED?

Fragile X syndrome follows a pattern of **X-linked recessive** inheritance in a family.

The *FMR-1* gene is an X linked gene because it is located on the X chromosome. Conditions involving genes on the X chromosome affect males and females differently.

Males have one X and one Y chromosome and so they will have only one copy of *FMR-1* in their cells to produce the FMRP protein. **Females** have two X chromosomes, so they have two copies of the *FMR-1* gene in every cell. However, one of the two gene copies is 'switched off' in their cells so the same amount of the FMRP protein is normally produced in males and females.

In **males** with fragile X syndrome, the *FMR-1* gene is faulty so the protein is either produced in a reduced amount or not at all. As this is less than the amount of protein needed by the body to function normally, they will be affected by fragile X syndrome.

A **female** may have one faulty copy of the *FMR-1* gene and one working copy. In females one of these copies will be 'switched off'. Some cells will be using the working copy and some the faulty copy. This means she will produce less than normal amounts of the FMRP protein. The body can still usually work normally with this reduced amount. Females with one faulty copy of *FMR-1* are described as **genetic carriers** as they carry one faulty copy of *FMR-1*. Sometimes, the 'switching off' process does not 'switch off' enough of the faulty gene.

This means the amount of protein produced is not enough. As a result female genetic carriers may show symptoms of fragile X syndrome.

Effects of the length of the repeat sequence in the *FMR-1* gene

The number of times that the 'CGG' triplet is repeated creates different lengths of the repeat sequence in the *FMR-1* gene (Table 54.1).

A. Individuals who have a normal repeat length (6 to 50 repeats of 'CGG'): Most people have a **short repeat sequence**, when 'CGG' is repeated between about 6 and 50 times. The most common repeat length is about 30 times. These repeat numbers are variable in different families. Some repeats of 40 or more can be unstable although they do not cause Fragile X syndrome in those who carry them or in their offspring. Genetic counselling is recommended to discuss this further.

B. Individuals who have a medium repeat length (50 to 200 repeats of 'CGG'): This medium repeat sequence is called a **premutation** and occurs when 'CGG' is repeated between about 50 and 200 times. People with a premutation do not have fragile X syndrome and are not usually affected intellectually. Genetic counselling is recommended to discuss this further.

B. Individuals who have a medium repeat length (50 to 200 repeats of 'CGG'): This medium repeat sequence is called a **premutation** and occurs when 'CGG' is repeated between about 50 and 200 times. People with a premutation do not have fragile X syndrome and are not usually affected intellectually. Genetic counselling is recommended to discuss this further.

- Despite the length of the repeat, it does not fully disrupt the *FMR1* gene so enough protein is still produced for normal intellectual development and function
- Both men and women who are premutation carriers may develop *fragile X tremor/ataxia syndrome* (FXTAS), which is a progressive neurological condition that usually starts after 50 years of age
- The risk of developing fragile X tremor/ataxia syndrome for men increases with age. Approximately 20 – 40% of male premutation carriers will develop FXTAS after the age of 60. The risk for women is less, but not clearly defined at this time
- Women who are premutation carriers have a 1 in 5 (20%) chance of going into menopause before the age of 40, known as premature ovarian insufficiency (POI).

C. Males who have the long repeat sequence (more than 200 repeats of 'CGG'): This long repeat sequence is called the **full mutation** and makes the *FMR-1* gene faulty. A **long repeat** is when 'CGG' is repeated over about 200 times and the gene no longer produces the important FMRP protein. Men who have the full mutation will have fragile X syndrome. The following features may be present, and may vary in severity:

- ◇ *Developmental delay:* Including intellectual disability (100% of males); speech delay; delay in the development of physical skills and co-ordination difficulties
- ◇ *Behavioural or emotional problems:* Including attention problems with or without hyperactivity; speech disturbances; hand flapping and biting, gaze aversion, repetitive speech mimicry and preoccupation with objects; sensory problems such as aversion to touch, loud noises, bright lights and strong smells; anxiety and mood instability with aggression and depression, especially in young men after puberty
- ◇ *Medical conditions:* Including epilepsy (up to 20%); heart problems; recurrent ear infections and eye problems
- ◇ *Physical characteristics* (may be subtle in childhood): Including large prominent ears; long face; large testicles; high, broad forehead; high arched palate and connective tissue problems, eg flat feet, loose joints, scoliosis.

D. Females who have the long repeat sequence (full mutation - genetic carriers): Women who have the full mutation in one copy of their *FMR-1* gene on the X chromosome and the working (short) sequence in the other copy of the *FMR-1* gene on their other X chromosome, will be **genetic carriers for fragile X syndrome**. They are often more mildly affected than men. Once again, genetic counselling is recommended.

- Women who are genetic carriers of an *FMR-1* full mutation will produce less FMRP protein, but this is usually enough for normal function
- A woman who is a carrier of a full mutation can be unaffected or affected, depending on the amount of FMRP protein that she produces.
 - ◇ Around 60% have intellectual disability that can vary from mild to severe
 - ◇ They may be hyperactive or have a shy personality and some will lack speech (*mutism*)
 - ◇ They may also have the emotional and behavioural characteristics seen in affected males described previously.

Table 54.1 shows the association between the number of repeats of the 'CGG' triplet code word in the *FMR-1* gene and its effects. Importantly, the gene will still produce the FMRP protein until the number of repeats reaches about 200.

| Length of repeats of the 'CGG' code word | Description of the <i>FMR-1</i> gene change | Impact | |
|------------------------------------------|---------------------------------------------|-----------------------------------------|-----------------------------------------------------------------------|
| | | Males | Females |
| Short | Normal | Unaffected | Unaffected |
| Medium | Pre-mutation | Men usually unaffected genetic carriers | Women usually unaffected genetic carriers |
| Long | Full mutation (gene is faulty) | Men affected | Women may be unaffected or affected less severely than affected males |

Table 54.1: Association of the number of repeats of the 'CGG' triplet in the *FMR-1* gene with features of fragile X syndrome

Inheriting the *FMR-1* gene

The pattern of inheritance in families of the faulty *FMR-1* gene causing fragile X syndrome is more complex than other X-linked conditions because the length of the triplet repeat (CGG) can increase when passed from a mother to her child. This is called **maternal anticipation**.

a) What happens when the father is an unaffected carrier of the fragile X premutation?

Fathers only pass their Y chromosome to their sons. So fathers cannot pass the X chromosome with the changed *FMR-1* gene containing a medium length sequence, to their sons. When the father has a premutation in his *FMR-1* gene:

- All of his **sons** will inherit the working copy of the *FMR-1* gene from their mother; they will **not** have fragile X syndrome and will not be premutation carriers
- All of his **daughters** will inherit his X chromosome and so all his daughters will be carriers of the *FMR-1* gene containing a medium length sequence (premutation carriers).

The number of repeats of the 'CGG' code word in the *FMR-1* gene usually does not increase when passed by a father to his daughter(s) as the expansion in length of the *FMR-1* gene does not usually occur in sperm.

b) What happens when the mother is an unaffected carrier of the fragile X premutation?

Mothers pass one copy of their X chromosome through their egg to a son or a daughter. When passing the X chromosome containing the medium repeat length sequence (premutation) to their children:

- The repeated sequence may increase in length to become a long sequence i.e. a full mutation. In this case, the *FMR-1* gene does not work

- Virtually all boys who inherit the full mutation from their mother will have learning problems, ranging in severity, and the physical, behavioural and emotional problems seen in fragile X syndrome
- The length of the repeated sequence may remain as a medium length i.e. a premutation. In this case, the children (male and female) will be premutation carriers.

c) What happens when the mother is a carrier of the fragile X 'full mutation'?

In Figure 54.2, the fragile X full mutation gene is shown as (X^f) and the working copy of the fragile X gene is shown as (X^R)

For every pregnancy, there is:

- **1 in 4 (25%) chance that a son will have fragile X syndrome** having inherited the fragile X full mutation (X^f) from his mother and a Y chromosome from his father
- **1 in 4 (25%) chance that a son will not have fragile X syndrome** having inherited the working copy of the fragile X gene (X^R) from his mother and a Y chromosome from his father
- **1 in 4 (25%) chance that a daughter will not have fragile X syndrome** and will not be a carrier, having inherited two working copies for the fragile X gene from both her parents ($X^R X^R$)
- **1 in 4 (25%) chance that a daughter will be a carrier or have fragile X syndrome** having inherited the full mutation copy of the fragile X gene from her mother (X^f) and the working copy from her father (X^R)

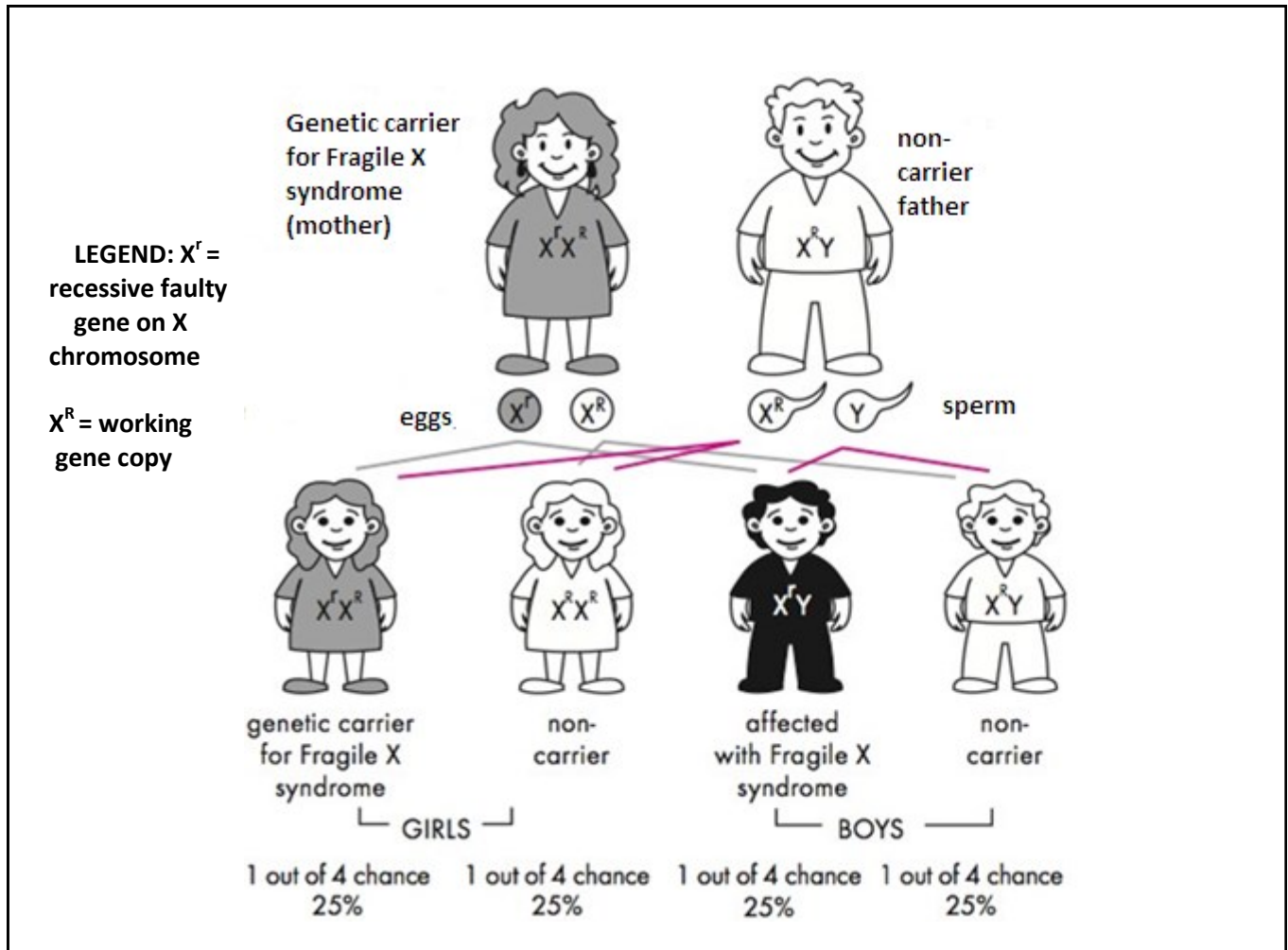


Figure 54.2: The copy of the X-linked *FMR-1* gene containing the long sequence (full mutation) is faulty and is represented by 'r'. The copy of the X-linked *FMR-1* gene containing the short sequence (working copy) is represented by 'R'.

IS THERE ANY TESTING AVAILABLE FOR FRAGILE X?

Genetic testing (known as DNA testing) for fragile X syndrome can be performed by looking at the number of CGG repeats in the *FMR-1* gene. DNA testing has been shown to be reliable in identifying individuals who are either affected, or carriers of fragile X syndrome.

Prenatal testing and PGD

For couples where one partner is known to be a carrier of a *FMR-1* mutation, testing may be available during a pregnancy to determine whether the baby will be unaffected, affected or a carrier for fragile X syndrome.

It may also be possible to undergo **pre-implantation genetic diagnosis (PGD)** screening for fragile X syndrome 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 can be explored.