

Important points

- Fragile X syndrome is characterised by particular physical features, varying degrees of learning difficulties and behavioural and emotional problems and affects about 1 in 4,000 males and between 1 in 5,000 and 1 in 8,000 females
- The condition is due to a change in the information in the *FMR-1* gene that impacts on the production of an important protein in the brain called the *FMR-1* protein
- Women have two copies of the X chromosome (XX); men have only one X chromosome and a Y (XY); there is no *FMR-1* gene copy on the Y chromosome
- The change in the information in the *FMR-1* gene is to the number of repeats in a sequence of one of the 'code words'. When the number of repeated code words increases over a critical number, the gene becomes faulty. The length of the repeat sequence can be described as short, medium and long. In most people, the repeat length size is short
- Individuals with the medium repeat size have a working copy of the gene but are **premutation carriers**. They **do not have fragile X syndrome**, so are not affected intellectually but are at risk for developing a neurological condition after about 50 years of age; women are also at risk for early menopause
- The long repeat size is a **full mutation** and its presence makes the gene faulty so that it can no longer do its normal job in the cell
- Men with a full mutation will have fragile X syndrome
- Women with the full mutation in one of their *FMR-1* gene copies and a working copy on the other partner X chromosome, will be carriers of the faulty gene (a **genetic carrier for fragile X syndrome**). They may be mildly affected with fragile X syndrome depending on how many of their cells are expressing the faulty *FMR-1* gene copy
- The pattern of inheritance in families of the faulty gene causing fragile X syndrome is described as **X-linked recessive inheritance** but is more complex than the usual pattern of inheritance of X-linked genes. The size of the repeated sequence can increase when inherited from the mother: a mother with a medium size repeat (premutation) can have children with a long repeat size in their *FMR-1* gene copies (full mutation)
- Where the mother is a carrier of the faulty *FMR-1* gene and the father has only a working copy of the gene, **in every pregnancy**, their **sons** have 1 chance in 2, or a 50% chance, of inheriting the faulty gene and having the condition. Their **daughters** have 1 chance in 2, or a 50% chance, of inheriting the faulty gene copy and being a usually less severely affected genetic carrier for fragile X syndrome
- Genetic testing can determine if an individual is a carrier of a medium or long *FMR-1* gene change where there is a family history of fragile X syndrome or a blood relative with the gene change
- Where one of the partners in a couple is a carrier of a changed *FMR-1* gene, the genetics team can provide information about the condition and discuss their risk for having an affected child with fragile X syndrome and their reproductive options (see Genetics Fact Sheet 3)

Characteristics of fragile X syndrome

A syndrome is a group of unusual physical, behavioural and/or intellectual features, which occur in a pattern in an individual and together describe the characteristics of a particular condition.

Fragile X syndrome is the second most common genetic cause of intellectual disability after Down syndrome (see Genetics Fact Sheet 28).

- Intellectual problems can vary from mild learning difficulties through to severe intellectual disability
- Emotional and behavioural problems may be present
- Females show varying degrees of the condition

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

Fragile X syndrome affects about 1 in 4,000 males and between 1 in 5,000 and 1 in 8,000 females.

Why is this syndrome called 'fragile X'?

The information that we inherit from our parents is contained in genes that are located on chromosomes. The chromosomes that are found in all the cells of the body can be seen under a microscope as shown in Genetics Fact Sheet 1.

Males and females have the same number of chromosomes (46) in each cell. Females, however have two X chromosomes (XX) while males have an X chromosome and a Y chromosome (XY): the other chromosomes (called the autosomes and numbered 1-22 according to their size) are the same in both males and females.

In those affected by fragile X syndrome it is usually possible to see a particular feature at the end of some of their X chromosomes when examined under a high powered microscope in a cytogenetics laboratory using special techniques. This feature is called a 'fragile site' (**fra X**) because it appears as a narrowing at the end of the chromosome.

What causes fragile X syndrome?

Located at the 'fragile site' on the X chromosome described above is a gene called *FMR-1*.

Everyone has the *FMR-1* gene that produces a protein called the FMRP protein. This protein is necessary for usual brain development and/or function. Fragile X syndrome is due to a variation in the information in the *FMR-1* gene that impacts on the production of the FMRP protein.

See Genetics Fact Sheets 4 & 5 for a full explanation of changes to the information in genes i.e. the genetic code.

What is the *FMR-1* gene change?

Our chromosomes are long strands of DNA on which the genes are located.

- The information in the gene is in the form of a genetic code made up of four 'letters': A, T, C and G. The letters represent the four basic chemicals in the DNA
- The information in each gene is arranged as a string of 'code words'; each 'word' is made up of three of the four letters e.g. ATC, CGG. Each 'code word' is therefore called a 'triplet'

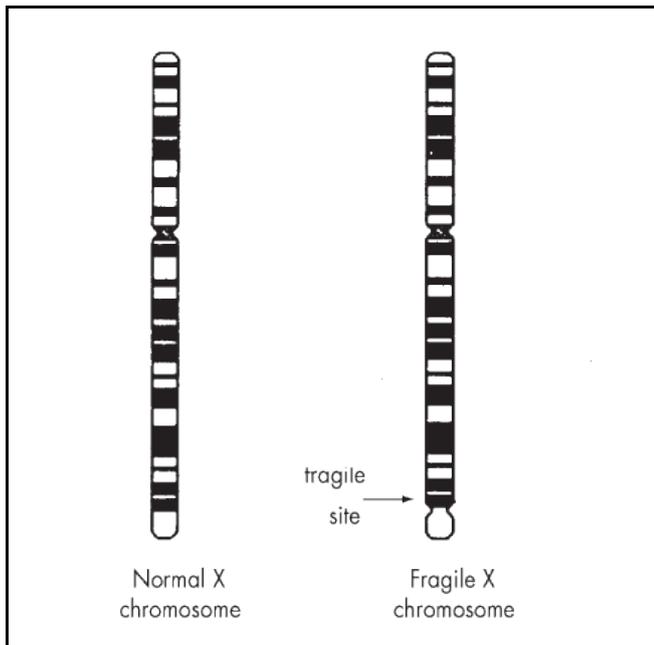


Figure 42.1: is a diagram of an X chromosome with a fragile site.

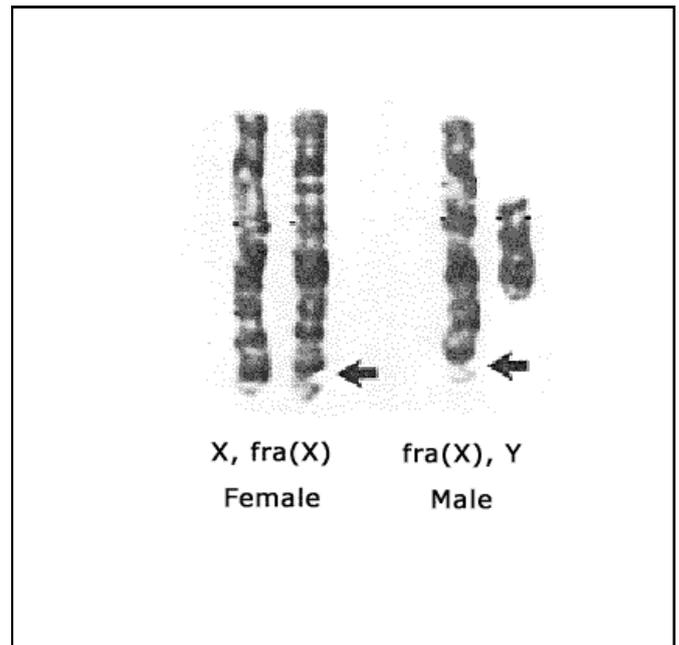


Figure 42.2: is a photograph of X chromosomes showing a fragile site from both a male and a female. (source: Greenwood Genetic Center (2002): *Counselling Aids for geneticists*. Greenwood Genetic Center, USA)

- In some genes, the same triplet is repeated within the DNA sequence. This is a sequence of 'triplet repeats' (see Genetics Fact Sheet 5). The number of times that a triplet code is repeated in a gene can be critical
- The triplet that is repeated in the *FMR-1* gene is made up of the letters 'CGG'. 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

The number of triplet repeats in the *FMR-1* gene

The number of times that the 'CGG' code word is repeated creates different lengths of the repeat sequence in the *FMR-1* gene (Table 42.2). The *FMR-1* gene that produces the important FMRP protein contains the code word 'CGG' repeated:

- A **short repeat** sequence, seen in **most people**: '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 in those who carry them or in their offspring. Genetic counselling is recommended to discuss this further
- A **medium repeat** sequence, seen in **some men and women**: 'CGG' is repeated between about 50 and 200 times. This medium repeat sequence is called a **premutation**. The *FMR-1* gene is still working even when it contains a medium repeat size sequence. People with a premutation do not have fragile X syndrome and are not affected intellectually. Genetic counselling is recommended to discuss this further
- A **long repeat** sequence seen in **men and women affected by fragile X syndrome**: 'CGG' is repeated over about 200 times. This **long repeat** sequence is called the **full mutation** and makes the *FMR-1* gene faulty: the gene no longer produces the important FMRP protein

- **Men** who have the full mutation in their *FMR-1* gene will have fragile X syndrome
- **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 partner X chromosome, will be **genetic carriers for fragile X syndrome**. They are often less severely affected. Around 60% will have some degree of learning problems that can vary from mild to severe. Once again, genetic counselling is recommended

The variability in expression of fragile X syndrome in females who are carriers of the full mutation is explained by the system of 'switching off' or inactivating one of the two X chromosomes in a woman's cells. 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 generally only one copy of most of the X chromosome genes in a female is working, just like in males. This is usually a random process. Half of the female's 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 female who is carrier of an X-linked faulty *FMR-1* gene that impacts on the production of the FMRP protein, will produce half of the amount of the protein compared to a female who has only working copies of the gene. This is, however, usually enough for normal function
- The severity of the symptoms of fragile X syndrome expressed by these women who are carriers of an *FMR-1* full mutation depends on the proportion of their cells expressing the faulty message

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

Table 42.1. Association of the number of repeats of the 'CCG' code word in the *FMR-1* gene with features of fragile X syndrome

Table 42.1 shows the association of the number of repeats of the 'CCG' code word in the *FMR-1* gene with its effects. Importantly, the gene will still produce the FMRP protein until the number of repeats of the repeated code words reaches about 200.

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

a) Individuals who have a medium repeat length sequence (premutation)

People with a **medium repeat length sequence** have no intellectual impairment and do not have fragile X syndrome but are **pre-mutation carriers** of the fragile X mutation. The *FMR-1* gene copy is still working.

- Despite the importance of the FMRP protein in brain function, this increase in length of the triplet repeat does not fully disrupt the *FMR-1* gene so enough protein for normal intellectual development and function is still produced
- Both men and women who are carriers of a medium repeat sequence, ie. premutation carriers, may *develop fragile X tremor/ataxia syndrome* which is a progressive neurological condition that usually starts after 50 years of age
- The risk increases with age:
 - In **men** the risk is approximately 1 in 2 (50%) by age 79
 - In **women** the risk is less but is not quantifiable at this time
- Women also have about 1 chance in 5 (20%) of going into menopause before the age of 40 (*premature ovarian failure*).

b) Males who have the long repeat sequence (full mutation)

The following features may not always 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

c) Females who have the long repeat length sequence (full mutation)

Usually women with the full mutation are more mildly affected than men.

- Around 60% have mild intellectual disability
- They may also present with hyperactivity or a shy personality and some will present with selective lack of speech (*mutism*)
- They may also have the emotional and behavioural characteristics seen in affected males described above

Inheriting the *FMR-1* gene

A **father** passes his X chromosome copy through his sperm to his **daughters** so all of his daughters will inherit an *FMR-1* gene copy from their father. Where a father has an *FMR-1* gene copy on his X chromosome containing a medium or long repeat length, the number of repeats in the *FMR-1* gene copy that his daughter will inherit:

- Usually stays the same
- In some rare cases can decrease
- Very rarely, may increase. This variability in expansion of the length of the repeat sequence has occurred even within members of the same family

A **mother** passes her X chromosome copies through her eggs to both **her sons and her daughters**. Where a mother passes the X chromosome copy on which the *FMR-1* gene copy containing a medium or long length repeat is located, the number of repeats in the *FMR-1* gene copy that her daughter will inherit may:

- Stay the same
- Be increased a little
- Be increased a lot

In other words, the *FMR-1* gene can become unstable when it contains repeats in the medium to long length range.

- The number of repeats in the *FMR-1* gene may increase when the gene is passed to a child from their mother through the egg and more rarely, from their father through the sperm
- This instability is thought to be due to the loss of chemical 'anchors' that keep the gene stable
- When the number of anchors lost is above a critical number, the *FMR-1* gene turns off and does not work, causing the symptoms of fragile X syndrome

What is the pattern of inheritance of fragile X syndrome inherited in families?

Two factors influence the pattern of inheritance of the faulty *FMR-1* gene causing fragile X syndrome in families.

1. The *FMR-1* gene is located on the X chromosome.
2. The effect of the variation in the *FMR-1* gene is 'recessive' or hidden by the presence of the working copy of the gene and is impacted by the length of the repeated sequence of the 'CCG' code words (see Genetics Fact Sheets 1, 4 & 5).

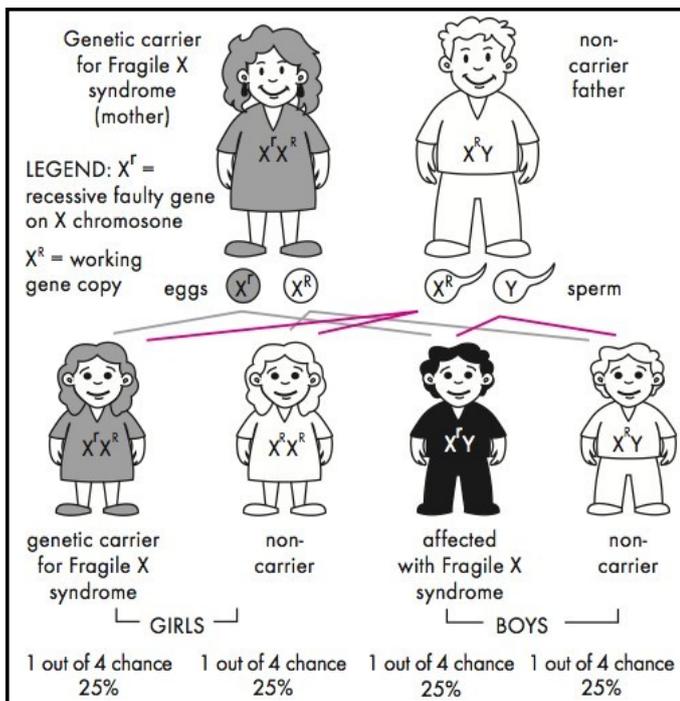


Figure 42.3: The copy of the X-linked recessive *FMR-1* gene containing the long sequence (full mutation) is faulty and is represented by 'r'. The copy of the X-linked recessive *FMR-1* gene containing the short sequence (working copy) is represented by 'R'.

The pattern of inheritance in families of the faulty *FMR-1* gene causing fragile X syndrome is therefore described as **X-linked recessive inheritance** but is more complex than usually seen with this pattern of inheritance (see Genetics Fact Sheet 10).

a) 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) 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 ie. a full mutation. In this case, the *FMR-1* gene in the child turns off and does not work, causing the symptoms of fragile X syndrome

- 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 the fragile X syndrome
- The length of the repeated sequence may remain as a medium length ie. a premutation. In this case, the children will be premutation carriers

c) When the mother is a carrier of the fragile X 'full mutation'

In Figure 42.3, the faulty *FMR-1* gene containing the long repeat sequence ie. the 'full mutation', is represented by 'r' on the X chromosome; the working copy containing the short sequence by 'R'. The Y chromosome does not have a *FMR-1* gene copy.

This means that, in every pregnancy there is

- 1 chance in 4, or 25% chance, that a **son** will inherit the Y chromosome from his father and the **faulty copy of the X-linked *FMR-1* gene** from his mother. In this case, no gene product or the right amount will be able to be made by his cells. He will generally be affected by fragile X syndrome
- 1 chance in 4, or 25% chance, that a **son** will inherit the Y chromosome from his father and the **working copy of the X-linked gene** from his mother. He will not be affected by the condition
- 1 chance in 4, or 25% chance, that a **daughter** will inherit **both copies of the X-linked genes**: one copy from her father and one from her mother. In this case she will not only be unaffected by the condition but she will also NOT be a carrier of the X-linked recessive faulty gene
- 1 chance in 4, or 25% chance, that a **daughter** will inherit from her mother the **faulty copy of the X-linked *FMR-1* gene and the working copy** from her father. She will be a genetic carrier like her mother and will generally be more mildly affected than her brother

Testing for the *FMR-1* faulty gene

The change in the *FMR-1* gene on the X chromosome causes the chromosome to appear as if it has a 'fragile' end. When looking at the chromosomes using a microscope (*karyotyping*), the X chromosome copies carrying the faulty gene may appear to have a 'fragile site'.

This has been superseded however, by genetic testing (known as DNA testing) by looking at the number of CGG code word repeats in the *FMR-1* gene (see Genetics Fact Sheet 21). DNA testing has been shown to be more reliable in identifying individuals who are either affected, or genetic carriers of fragile X syndrome.

How can knowing about having the faulty *FMR-1* gene help?

This information can be helpful when considering an individual's risk for having affected children and their reproductive options.

Where a baby is at risk for having fragile X syndrome, testing in pregnancy is available (see Genetics Fact Sheet 17C). In association with assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), testing of the embryo may be available (see Genetics Fact Sheet 18). In such testing, the length of the repeated code word sequence in the *FMR-1* gene can be determined.

A discussion with a genetic counsellor will assist in enabling a couple to make an informed decision with the most up-to-date information (see Genetics Fact Sheet 3).

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 10, 14, 17C, 18, 21, 28