

Fragile X Syndrome

What is Fragile X Syndrome?

Fragile X syndrome is the most common inherited cause of learning difficulties. It occurs more commonly in boys than in girls. It causes a wide range of problems with learning and behaviour. Boys are usually more severely affected than girls.

How can Fragile X Syndrome affect a child?

Almost all boys with fragile X syndrome have some degree of learning difficulty, ranging from mild to severe. Most girls and women who have a fragile X chromosome are of normal intelligence, however up to a third have learning problems. In most affected girls and women, these learning problems are mild or moderate, but they can occasionally be severe.

Other problems in children with fragile X syndrome include delayed and distorted speech and language development. Some children and adults have problems such as repetitive behaviour, poor attention span and over-activity. Many affected children show some of the features of autism, such as poor eye contact, hand flapping, social anxiety, abnormal shyness and insistence on routine. Some children and adults develop epilepsy.

Physical features associated with fragile X syndrome include a relatively large head, a long face with prominent ears and a large jaw, however these features are rarely obvious. This lack of obvious physical features can lead to the diagnosis being missed or delayed.

What causes Fragile X Syndrome?

Fragile X syndrome is a genetic disorder. Genetic disorders are caused by one or more changed genes.

What are genes?

Our bodies are made up of millions of cells. Each cell contains a complete set of genes. We have thousands of genes. We each inherit two copies of most genes, one copy from our mother and one copy from our father. Genes act like a set of instructions, controlling our growth and how our bodies work. Any alteration in these instructions is called a mutation (or change). Mutations (or changes) can stop a gene from working properly. A mutation (change) in a gene can cause a genetic disorder. Genes are responsible for many of our characteristics, such as our eye colour, blood type or height.

What is wrong with the gene that causes Fragile X Syndrome?

The gene that causes fragile X syndrome is known. It is called FMR1. This gene contains information needed by our brain. If the gene has a mutation (change), the brain may not receive the information it needs, or it may get the wrong information. This causes the problems associated with fragile X syndrome. People with fragile X syndrome have a change (mutation) in FMR1, the fragile X gene.

Genes contain information used by our bodies in the form of a code. The code is contained in the order of chemicals that make up the gene. At the beginning of the normal fragile X gene, a small part of this code is repeated several times. In people with fragile X, this repeated part of the gene is larger than normal (they have more repeats). This is called an expansion, because part of the gene has expanded, or grown bigger. If the size of this expansion is too great, it interferes with the normal genetic instructions and leads to fragile X.

The size of the expansion varies.

- Children with up to 60 repeats at the beginning of the FMR1 gene do not have fragile X syndrome and have a normal FMR1 gene.
- Children with 60 to 200 repeats do not have fragile X syndrome, but they are said to be carriers of a premutation.
- Boys with over 200 repeats have fragile X syndrome. These boys will have some of the problems described in this information. A large expansion of over 200 repeats is called a full mutation.
- Girls with a full mutation may have Fragile X syndrome, but they may have fewer problems than affected boys.

Why is Fragile X Syndrome more common in boys than in girls?

Genes are carried on thread-like structures called chromosomes. Each of us has 46 chromosomes in every cell. We inherit our chromosomes from our parents, one set of 23 chromosomes from our mother and one set of 23 chromosomes from our father. So we have two sets of 23 chromosomes, or 23 pairs. The pairs of chromosomes are numbered according to size, starting with the largest chromosome, chromosome 1, through to chromosome 22. The remaining pair are called the sex chromosomes.

There are two kinds of sex chromosome, one called the X chromosome and one called the Y chromosome, and they control whether a person is male or female. Females have two X chromosomes. A female inherits one X chromosome from her mother and one X chromosome from her father. Males have an X and a Y chromosome. A male inherits an X chromosome from his mother and a Y chromosome from his father.

The gene that causes fragile X syndrome lies near the end of the X chromosome. Under a microscope, the X chromosome of a person with fragile X syndrome looks as if the tip of it has broken and is hanging off. This is how the disorder got its name.

Girls have two X chromosomes and therefore two copies of the fragile X gene. If one of a girl's fragile X genes has a full mutation and does not work properly, the other, normal copy of the gene may be able to compensate for it. This means that girls may be protected from some of the effects of having a fragile X gene with a change (mutation). In contrast, because boys have only one X chromosome, they also have only one fragile X gene. If their fragile X gene has a full mutation, the gene will not work properly and there is no other fragile X gene to compensate for it.

How is Fragile X Syndrome inherited?

Any woman who has more than 60 repeats in her Fragile X gene is at risk of having a child with Fragile X syndrome. This includes women who do not have Fragile X syndrome themselves, but carry the premutation or the full mutation.

A man who carries the premutation is at low risk of having a child with Fragile X syndrome.

The reason for this is that the part of the Fragile X gene with the change (mutation) is unstable when passed on by the mother. The number of repeats can be higher in the child than it was in the mother. For reasons that are not fully understood, this is very unlikely to happen if the father carries the premutation.

Will a parent who has a fragile X gene with a change (mutation) have a child with Fragile X Syndrome?

This depends on three things:

- How many repeats are passed on to the child.
- Whether the parent who has the fragile X gene with the change (premutation or full mutation) is the father or the mother.
- Which X chromosome is passed on from a mother who has a fragile X gene with a change (mutation).

The easiest way to understand this is to consider fathers and mothers separately. (This information is also summarised in Picture 1)

Father who carries a premutation (also known as a normal transmitting male)

- None of his sons will be affected as they inherit his Y chromosome, not his X chromosome.
- All of his daughters will inherit his premutation. Their (the daughters') children will be at risk of having fragile X syndrome.

Man who has a full mutation

- These men are affected with fragile X syndrome. It is very unusual for men affected with fragile X syndrome to have children.

Mother who carries a premutation

Each of her children has a 50%, or 1 in 2, risk of inheriting the premutation from her.

- If her children inherit the premutation, and if the premutation is passed on to them unchanged, then these children (boys or girls) will not have fragile X syndrome.
- If the premutation expands to a full mutation when passed on by the mother, then the child will inherit a full mutation. If the child is a boy, he will have fragile X syndrome. If the child is a girl, she may be affected by fragile X syndrome.

Mother who carries a full mutation

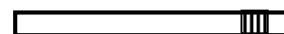
Each of her children has a 50%, or 1 in 2, risk of inheriting the full mutation from her.

- If a boy inherits the full mutation he will have fragile X syndrome
- If a girl inherits the full mutation she may be affected by fragile X syndrome.

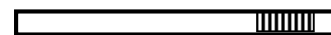
Picture 1. Will a parent who has a fragile X gene with a change (mutation) have a child with fragile X syndrome?

Key:

This shape represents an X chromosome that has a normal fragile X gene (no expansion, or unexpanded) (up to 60 repeats).



This shape represents an X chromosome that has a fragile X gene with a small expansion or premutation (60-200 repeats).



This shape represents an X chromosome that has a fragile X gene with a large expansion or full mutation (over 200 repeats).



This shape represents a Y chromosome.



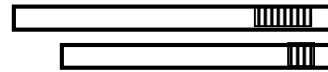
**Sex chromosomes in:
Father, carrier of a premutation
(normal transmitting male)**



Daughters: all his daughters will inherit his X chromosome. His daughters are premutation carriers.

Sons: all his sons inherit their father's Y chromosome. His sons will not be carriers and will not have fragile X syndrome.

**Sex chromosomes in:
Mother, carrier of a premutation**



Children (boys or girls): there is a 1 in 2, or 50%, chance that a child will inherit her X chromosome with the normal fragile X gene. These children will not be carriers and will not have fragile X syndrome.

There is a 1 in 2, or 50%, chance that her child (boy or girl) will inherit the mother's X chromosome with the premutation.

If the premutation is passed on unchanged, the child will also be a carrier of the premutation.

If the premutation expands to a full mutation when passed on by the mother, the child will have the full mutation. If this child is a boy, he will have fragile X syndrome.

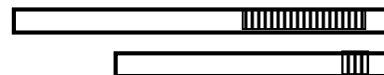
If this child is a girl, she may be affected by fragile X syndrome.

**Sex chromosomes in:
Man with a full mutation**



These men are all affected with fragile X syndrome. It is very unusual for men with fragile X syndrome to have children.

**Sex chromosomes in:
Mother, carrier of a full mutation**



Children (boys or girls): There is a 1 in 2, or 50%, chance that a child will inherit the mother's X chromosome with the normal fragile X gene. These children will not be carriers and will not have fragile X syndrome.

There is a 1 in 2, or 50%, chance that her child (boy or girl) will inherit the mother's X chromosome with the full mutation. If the child is a boy, he will have fragile X syndrome. If the child is a girl, she may be affected by fragile X syndrome.

Can a premutation cause a carrier any problems?

People who are carriers of the premutation are at low risk of having any of the learning and behavioural problems seen in fragile X syndrome, but there are some other, poorly understood problems that may affect some people who are carriers.

- Women who are carriers of the premutation are more likely to have an early menopause (before the age of 40 years). They may have problems having children. This does not affect all women with the premutation. More research is needed to understand which women are at most risk.
- After the age of 50 years, some men who are carriers of the premutation develop a tremor (shaking), and difficulties with walking and balance. This is caused by a neurological (nervous system) or brain disorder. More research is needed to understand the cause of this disorder and why it occurs only in some men who carry the premutation.

How is Fragile X Syndrome diagnosed?

Genetic testing is available to find out whether a person has the premutation or the full mutation. The test is done on a small blood sample. It is also possible to do a test during pregnancy to find out whether a baby may be affected with fragile X syndrome. This kind of test is called prenatal diagnosis.

The importance of making a diagnosis of Fragile X Syndrome

Making a diagnosis of fragile X syndrome in a child is important, as it will allow the child to receive specialist help in areas of education, speech and language development and behaviour. A diagnosis of fragile X syndrome in adults can help with the understanding and management of specific problems they may have. Making the diagnosis of fragile X is important, as there may be relatives who are at risk of having affected children. These relatives might benefit from genetic counselling, carrier testing and from the offer of prenatal diagnosis.

Where can I get more information about Fragile X Syndrome?

This is only a brief guide to fragile X syndrome and its causes. More information can be obtained from your local regional genetics centre or from:

The Fragile X Society

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6 Stortford Road,
Great Dunmow,
Essex,
CM6 1H7*

Telephone: 01371 875100

Email: info@fragilex.org.uk

FAX: 01371 859915

Web: www.fragilex.org.uk

The Genetic Interest Group

*Unit 4D, Leroy House
436 Essex Rd
London
N1 3QP*

Telephone: 0207 704 3141

Web: www.gig.org.uk

Email: mail@gig.org.uk

Contact a Family

*209-211 City Rd
London EC1V 1JN*

Telephone: 020 7608 8700

FAX: 020 7608 8701

Helpline 0808 808 3555 or Textphone 0808 808 3556

(Freephone for parents and families, 10am-4pm, Mon-Fri)

e-mail: info@cafamily.org.uk

Web: www.cafamily.org.uk

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Glossary (difficult words and their meanings): Fragile X Syndrome

This glossary is intended only to explain terms used in the information: Fragile X Syndrome. Words shown in **bold** are defined elsewhere in the glossary.

autism. A condition which affects interaction and communication with other people.

cell. The human body is made up of millions of cells, which are like building blocks. There are many specialised types of cells. These include skin cells, brain cells, and blood cells. Cells in different parts of the body look different and do different things. Every cell (except for eggs in women and sperm in men) contains all the body's **genes**.

chromosomes. Thread-like structures which can be seen under the microscope and contain the **genes**. Usually people have 46 chromosomes in every **cell**. There are two sex chromosomes and 22 other pairs of chromosomes. Twenty-three chromosomes come from the mother, and twenty-three come from the father. One chromosome of each pair comes from each parent. (As an analogy: a chromosome is like a book; a **gene** is like a story in the book).

epilepsy. A disorder of the **nervous system**. Affected people may have fits of varying type or severity.

expansion. Increased number of **repeats** in the Fragile X **gene**.

FMR1. Scientific abbreviation for the **gene** which is changed in people with **Fragile X syndrome**. The **Fragile X gene**.

fragile X. Characteristic appearance of the **X chromosome** of affected people, under the microscope. The **X chromosome** looks as if its tip has broken off.

full mutation. Large **expansion** (over 200 **repeats**) in the **Fragile X gene**. Boys and men who have the full **mutation** have **Fragile X syndrome**. Girls and women who have the full **mutation** may have **Fragile X syndrome**, but may have fewer problems than affected males.

gene. Information needed for the body to work, stored in a chemical form on **chromosomes**. Changes or **mutations** in genes alter the information and this can change how the body works. Most genes are in pairs, one from the mother and one from the father. The two genes of a pair are at matching places on a pair of **chromosomes**. Genes on the **X chromosome** and the **Y chromosome** of males are not paired with each other; they do not match. (As an analogy: a gene is like a story in a book, changes in genes are like changes in a story).

genetic. Caused by **genes**, concerning **genes**.

genetic counselling. Information and support for people who have a history of a **genetic** condition in their family, or who are concerned about their risk for inheriting or passing on a **genetic** condition.

menopause. Time of changes in a woman's body, before and after her last **period**.

mutation. A change in a **gene**. Some mutations are not harmful. Sometimes when a **gene** is changed, its information is altered so it does not work properly. (As an analogy: a change or mutation in a **gene** is like a missing or extra letter in a word in a story). In Fragile X syndrome, the mutation is an increase in the number of **repeats** of part of a **gene**. This increased number is called an **expansion**.

nervous system. The brain and the nerve supply to the body. It controls movement and senses, such as touch and pain.

neurological. Affecting the **nervous system**.

Permutation. An **expansion** (60 to 200 **repeats**) in the **fragile X gene**, not enough to cause **fragile X syndrome**.

prenatal diagnosis. Test during a pregnancy for the presence or absence of a **genetic** disorder in the baby.

repeats. In **fragile X syndrome**, the change (**mutation**) that causes the disease is in a part of the **fragile X gene** that is repeated. A test can show the size of the repeated part of the **fragile X gene**. People who have **fragile X syndrome** have too many repeats. (As an analogy, repeats are like repeated letters or syllables in a word; if more repeated letters or syllables are added, the sense of the word may be lost)

sex chromosomes. The X **chromosome** and the Y **chromosome**. The sex chromosomes control whether a person is male or female. Females have two X **chromosomes**. Males have one X and one Y **chromosome**.

syndrome. A group of features which occur together in affected people. Affected people share some or all of the features of the syndrome.

transmitting. A term used to describe a man who has a **premutation** in his **fragile X gene** and can pass it to his children, but is not affected with **fragile X syndrome**

tremor. Shaking or trembling.

X chromosome. One of the **sex chromosomes**. Females have two X **chromosomes** Males have one X **chromosome** and one Y **chromosome**.

XX. This represents the **sex chromosomes** of a female. Females have two X **chromosomes**. One X **chromosome** is inherited from each parent.

XY. This represents the usual **sex chromosomes** of a male. Males have one **X chromosome** and a **Y chromosome**. A male inherits his **X chromosome** from his mother and his **Y chromosome** from his father.

Y chromosome. One of the **sex chromosomes**. Males have one **Y chromosome** and one **X chromosome**. Females have two **X chromosomes**.

This glossary is intended only for use by patients and families, with the genetic information to which it refers.

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Glossary 11