Saint Mary's Hospital

Information for Patients

The Fragile X or *FMR1* gene

Introduction

This leaflet describes the way that Fragile X Syndrome (FXS) is passed on in families due to changes in the *FMR1* gene. It also describes the different sizes of the gene and the effect these different sizes can have. It does not include detailed information about the symptoms of FXS or advice for management. The Fragile X Society has produced excellent booklets about many aspects of the condition in a variety of languages (www.FragileX.org.uk).

Inheritance

FXS is an inherited genetic condition and is caused by a change (sometimes called an alteration, mutation or expansion) in just one copy of the *FMR1* gene. Genes are the instructions our bodies use to grow and develop. All of our genes are packaged into structures called chromosomes. We have 2 copies of most chromosomes and therefore 2 copies of most genes (one from each parent). The *FMR1* gene is on the X chromosome which is significant because females have two X chromosomes but males have one X and one Y chromosome. This means that females have two copies of the *FMR1* gene while males have only one.

When males have children they pass on their only X chromosome to all their daughters and their Y chromosome to all their sons. When females have children they randomly pass on one or other of their X chromosomes to each of their children.

Repeats in the Fragile X *FMR1* gene

Part of the *FMR1* gene is made up of a number of small repeat units. The number of these repeats can be checked by testing a sample from an individual. For convenience a small blood sample is usually tested. The number of repeats varies between people but is usually less than 45 (normal size).

When the gene has between 45 and 55 repeats it is described as intermediate sized. An intermediate sized *FMR1* gene does not usually cause any clinical problems but it can gradually increase in size when it is passed on from one generation to the next and can become premutation sized.

A premutation is when the *FMR1* gene has more than 55 but less than 200 repeats. At this size the gene can still function but is unstable, with a tendency for bigger jumps in the number of repeats to happen when passed to the next generation. A premutation sized *FMR1* gene does not cause Fragile X Syndrome but can have some other clinical effects and can jump in size to become a full mutation in just one generation if passed on by a female.

A full mutation is when the gene has more than 200 repeats. The large size causes the gene to switch off (a process called methylation) which leads to symptoms of Fragile X Syndrome in males and some females.

Below we describe how the size of the Fragile X gene affects males and females differently.

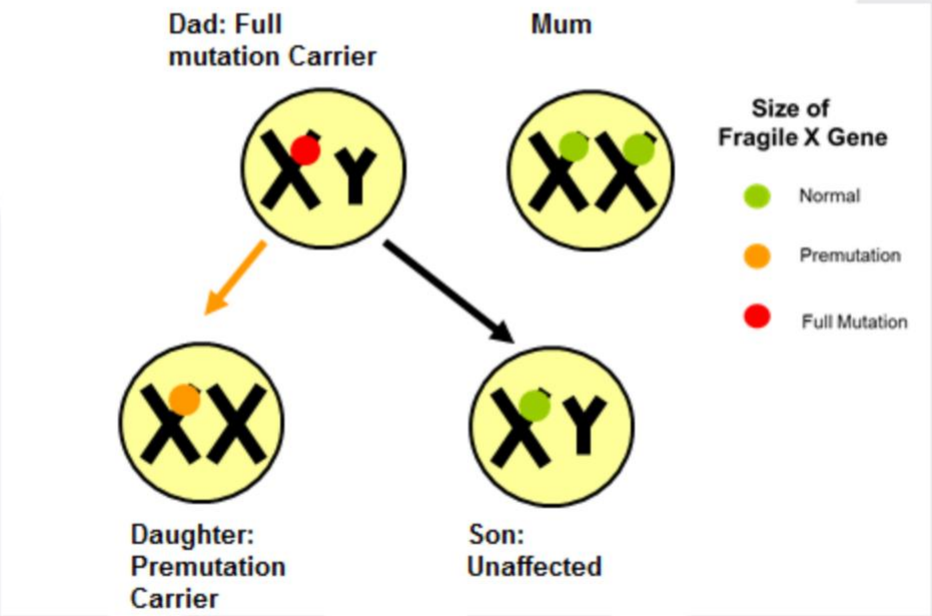
Males who have a full mutation

Males who inherit a full mutation will be affected by Fragile X Syndrome to some extent. The range and severity of symptoms varies widely and cannot be predicted by a genetic test looking at the exact number of repeats. The variability may be partly due to something called mosaicism. In FXS mosaicism is when someone with a full mutation also has some cells with a smaller, premutation sized *FMR1* gene or occasionally, because the full mutation sized *FMR1* gene is not completely switched off (methylated) in all cells. If the test shows evidence of mosaicism the doctor or genetic counsellor should have explained this at the time of giving the results. However, because the genetic test only looks at cells in the blood, there is no way of knowing whether there is any mosaicism in the cells that really matter like the brain.

There is currently no cure for FXS but there are a wide range of treatments and management strategies available which may benefit individuals and their families. Research is ongoing aimed at finding more effective treatments and hopefully a cure.

Diagram 1: If a male with a full mutation has children

It is rare for males with a full mutation to have children. When they have, their children (male or female) have not been affected by FXS. The daughters of a male with FXS have been found to have inherited a premutation rather than full mutation from their father (presumably because their father had a few sperm with a premutation sized *FMR1* gene). The sons of a man with FXS inherit their only copy of the *FMR1* gene from their mother and therefore are not at increased risk of being affected by, or a carrier of FXS, unless their mother also happens to be a carrier.

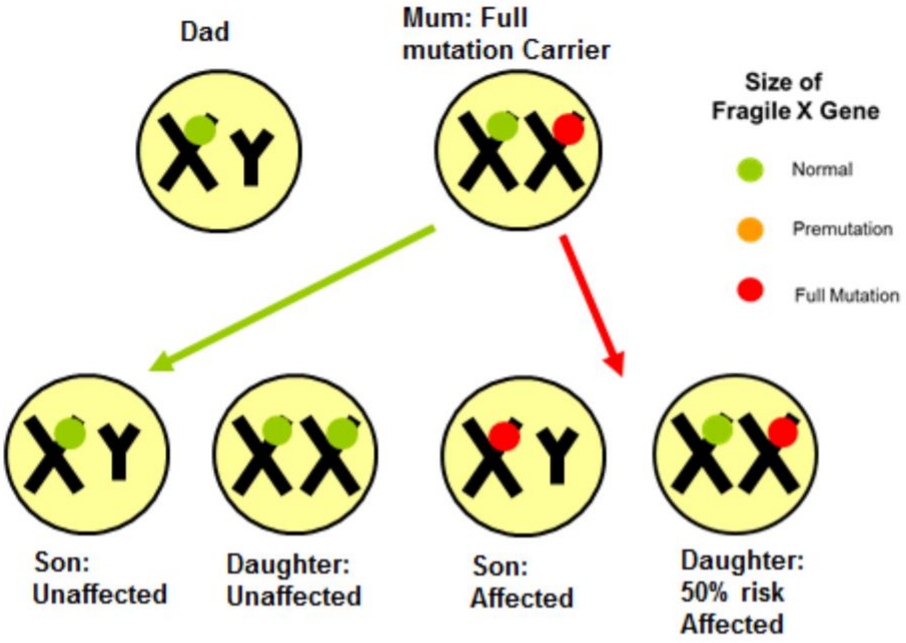


Females who have a full mutation

Only about 50% or 1 in 2 women who have inherited a full mutation develop symptoms of FXS. This is because they also have a second (usually normal) copy of the *FMR1* gene which can at least partly compensate. Females who are affected usually experience less severe symptoms than males who are affected. There are a small number of females with a full mutation who have a similar severity of FXS as an affected male. The genetic test cannot tell us in advance whether a female with a full mutation will develop any symptoms of FXS or how severe symptoms will be.

Diagram 2: If a female with a full mutation has children

Each child will have a 1 in 2 or 50% chance of inheriting her X chromosome with the normal sized *FMR1* gene and a 1 in 2 or 50% chance of inheriting her X chromosome with the full mutation sized *FMR1* gene. What this means for the child will depend on whether they are male or female.



Males who have a premutation

Males who have a premutation do not have FXS and usually have a normal IQ although they may have some difficulties in some areas such as decision making. Some studies suggest that male premutation carriers have an increased risk of emotional issues such as social anxiety or shyness and/or obsessional tendencies, similar to those seen in autistic spectrum disorder although less severe.

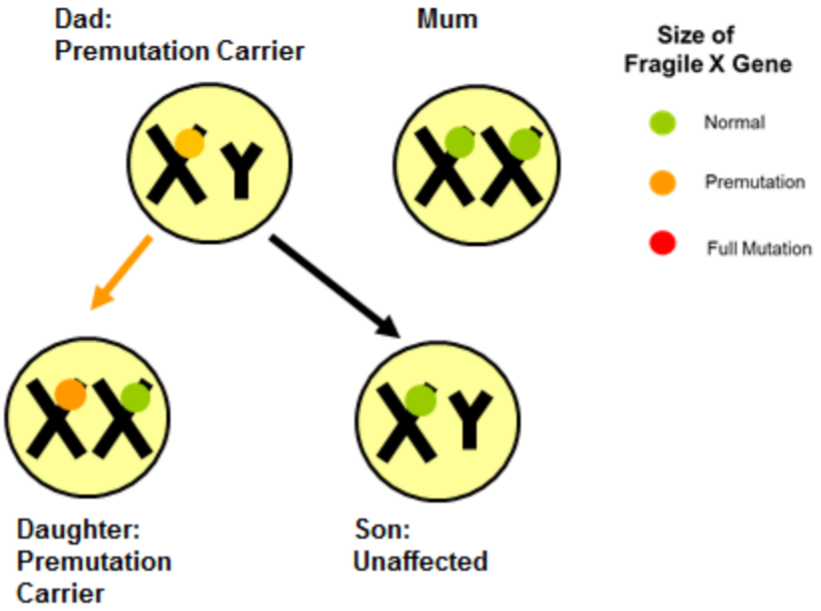
A proportion of males who have a premutation develop problems with movement, balance and/or memory later on in life. The chance of this happening increases significantly above age 50. The majority of men with a premutation will have some problems over age 70. This condition is called FXTAS (Fragile X Tremor Ataxia Syndrome) and although it is due to the repeats in the *FMR1* gene, the symptoms are very different to Fragile X syndrome. Males with Fragile X syndrome due to a full mutation do not appear to be at risk of developing FXTAS.

A link between being a premutation carrier and thyroid problems has been described in both sexes. Premutation carriers are advised to ask their GP to check their thyroid function.

If you have concerns that symptoms you or a family member are experiencing might be linked to being a premutation carrier, either get in touch with your genetics doctor/counsellor or discuss your concerns with your GP.

Diagram 3: If a male with a premutation has children

When a male passes on a premutation it remains roughly the same size and never gets bigger to become a full mutation. The daughters of a man with an *FMR1* premutation will always inherit their father's premutation. This means the daughters of a male premutation carrier are always also carriers and as they are female they are then at risk of having children affected by FXS themselves. The sons of a man with an *FMR1* premutation receive their only copy of the *FMR1* gene on the X chromosome they inherit from their mother and inherit a Y chromosome without the *FMR1* gene from their father. This means that a male premutation carriers sons are not affected by, or even carriers of FXS.



Females who have a premutation

Females who have a premutation do not have FXS and usually have a normal IQ and social skills although there is an increased risk of mental health problems ranging from social anxiety and shyness to more severe anxiety and depression. There can also be specific difficulties in some areas of learning such as mathematics.

Around 2 in 10 women with a premutation develop a condition called primary ovarian insufficiency (POI). POI can cause fertility problems and/or an early menopause. Women who are concerned about their fertility can be referred to a specialist reproductive medicine doctor for an assessment of their ovarian function and discussion of possible options such as egg freezing. An early menopause can have long term health implications and women who go through the menopause below age 50 are usually

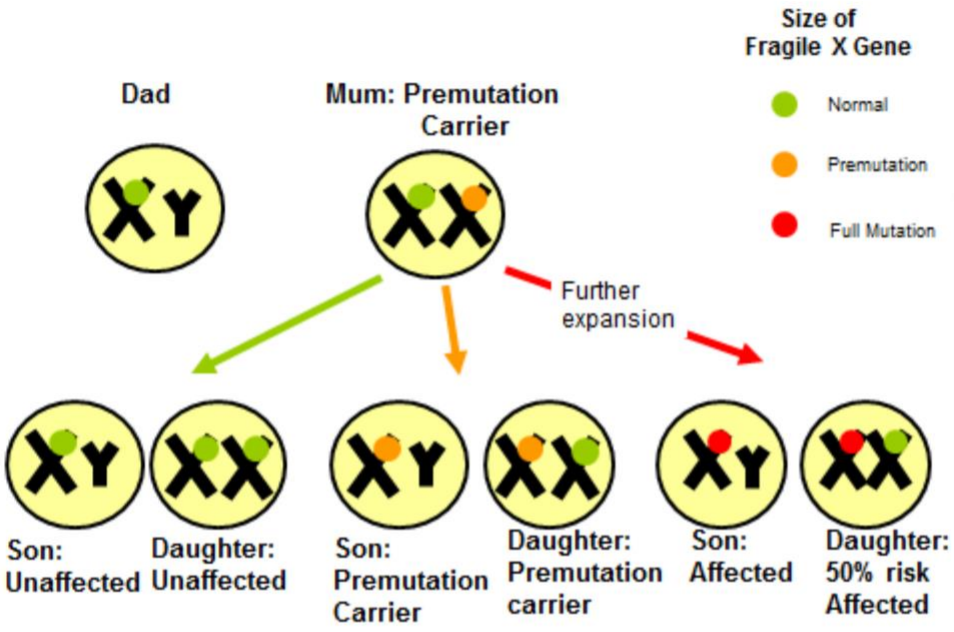
recommended to have some hormone replacement therapy (HRT) until at least age 50. Women who are concerned about this should speak to their GP or genetic counsellor who can refer them for specialist assessment and advice if necessary.

Although more common and more severe in male premutation carriers, a small proportion of females with a premutation develop problems with movement, balance and/or memory later on in life due to a condition called Fragile X Tremor Ataxia Syndrome (FXTAS). A link between being a premutation carrier and thyroid problems in both sexes has also been suggested and premutation carriers are advised to ask their GP to check their thyroid function.

Diagram 4: If a female with a premutation has children

A female with a premutation has a 1 in 2 chance of passing on the larger copy of the *FMR1* gene to each of her children. When passed on by a female, a premutation will either stay within the premutation size range or expand to become a full mutation. It is not possible to accurately predict the chance of a gene changing from a premutation to a full mutation when it is passed on, although in general the likelihood increases with increasing premutation size.

If a female passes on a premutation sized *FMR1* gene, her child (male or female), will be a carrier of a premutation but will not have FXS. If the premutation expands to become a full mutation when it is passed on, a son would be affected by FXS and a daughter would have around a 1 in 2 chance of having symptoms of FXS.



Further Information and support

The Fragile X Society is an excellent source of information and support for individuals and families affected by Fragile X Syndrome or any of the *FMR1* related disorders.

Address: The Fragile X Society
Rood End House
6 Stortford Road
Great Dunmow
Essex
CM6 1DA

Telephone: 01371 875 100
E-mail: info@fragilex.ork.uk
Website: www.fragilex.org.uk

Alternatively get in touch with the Genomic Medicine Department:

Manchester Centre for Genomic Medicine
Sixth Floor
Saint Mary's Hospital
Oxford Road
Manchester
M13 9WL

Telephone: (0161) 276 6506 (Reception)

Department staffed Monday-Friday, 9.00am to 5.00pm.

Website: www.mangen.co.uk

Please let us know if you would like this leaflet in another format (e.g. large print, Braille, audio).

Seen in clinic by (doctor):_____

Or

(Genetic Counsellor):_____

Telephone number:_____

Family reference number:_____