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Sonic Genetics

Information for patients

Female carriers of fragile X syndrome

The healthcare professional responsible for your care has given you this leaflet because you have been identified by reproductive carrier screening as a carrier of fragile X syndrome. The genetics of FXS are complex, and this leaflet provides only a brief overview of this disorder. We recommend that you also discuss your test result with your doctor or genetic counsellor. There is a separate leaflet for male carriers of FXS.

What is fragile X syndrome?

Each year, one in 4,000 boys[1] and one in 6,000 girls[1] in Australia are born with fragile X syndrome (FXS). This inherited genetic disorder can cause a wide range of disability, from learning difficulties (typically in females) through to moderate intellectual disability (typically in males). FXS is the most common cause of inherited intellectual disability. People with FXS can also have anxiety, autism, epilepsy and a range of emotional and behavioural problems. There is no cure for FXS.

Genetic disorders can be caused by inheriting faulty genes. Our genes are made of DNA and tell the body how to work. The genes are packaged into 22 pairs of chromosomes in every cell in the body. In addition, men have an X and a Y chromosome in each cell, while women have two copies of the X chromosome in each cell. The FXS gene (its scientific name is FMR1) contains information that is important for brain development. The FXS gene is located on the X chromosome, and so women have two copies of the FXS gene while men have only one.

FXS is due to an abnormality in the FXS gene that varies in size. The size of this abnormality determines the chance of the FXS gene failing to function in a normal way. Overall, approximately one in 330[1] women has an abnormal FXS gene. If the abnormality is small, the FXS gene functions normally. If the abnormality is large, the FXS gene will not perform normally. A woman has two copies of the FXS gene, and the effect of a large abnormality in one FXS gene may be masked by the presence of the second, normal FXS gene. A man has only one copy of the FXS gene; a small abnormality will have no effect on intellectual ability but a large abnormality causes FXS. The situation is complicated even further because the size of the abnormality in the FXS gene can increase when passed from parent to child.

How does a child inherit fragile X syndrome?

When a couple has a child, the child inherits an X chromosome from the mother and an X chromosome or Y chromosome from the father. If the child has two X chromosomes (one from each parent), the sex of the child is female; if the child inherits an X chromosome from the mother and Y chromosome from the father, the sex of the child is male.

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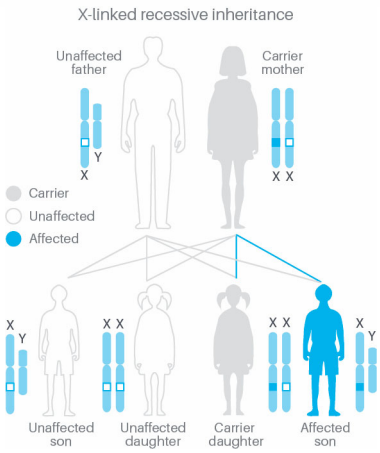
A female carrier of FXS has an abnormal FXS gene on one X chromosome and a normal FXS gene on the other. Her child has a one in two (50%) chance of inheriting the abnormal FXS gene from her. If the sex of her child is male (having one X chromosome), the significance of this abnormal FXS gene will depend on the size of the abnormality. If the sex of her child is female (having two X chromosomes), the significance of this abnormal FXS gene will still depend on the size of the abnormality, but will be milder than in a boy.

As an abnormal FXS gene is passed down from mother to child over generations, the abnormality can become larger and progressively interfere with the normal function of the FXS gene. Your doctor will advise you about the size of abnormality in the FXS gene identified in you and the impications for both you and your children.



What does being a fragile X syndrome carrier mean for me and my child?

The significance of this test result will vary according to the size of the abnormality in your FXS gene.

If you have a small abnormality in the FXS gene (a 'pre-mutation')

- The FXS pre-mutation does not cause intellectual disability. Some female carriers with a pre-mutation develop premature ovarian failure (before the age of 40). There is also a small chance of developing a tremor disorder later in life.
- If the pre-mutation is inherited by your child, it may increase in size and severity to become a full mutation (see below). In **every pregnancy**, there is a one in four chance (25%) of having a son who will inherit either the pre-mutation (the son is unaffected) or a full mutation (the son is affected by FXS). There is a one in four chance (25%) of having a daughter who is a carrier of FXS who will inherit either the pre-mutation (daughter does not have intellectual disability) or a full mutation (may be affected by FXS). There is a two in four chance (50%) that the child (son or daughter) will inherit the normal FXS gene, be unaffected and not be a carrier of FXS.

If you have a large abnormality in the FXS gene (a 'full mutation')

- You may have some signs of FXS or be unaffected.
- In **every pregnancy,** there is a one in four chance (25%) of having a son with the abnormal FXS gene who will develop FXS. There is a one in four chance (25%) of having a daughter who is a carrier of FXS; she may or may not be affected by FXS. There is a two in four chance (50%) that the child (son or daughter) will inherit the normal FXS gene, be unaffected and not be a carrier of FXS.

There is a small group of women with an abnormality in the FXS gene that is clearly larger than normal but not large enough to be a pre-mutation. This is called an **intermediate abnormality in the FXS gene**. If you have such an abnormality, this is not associated with intellectual disability, premature ovarian failure or the development of tremor in later life. In every pregnancy, there is a one in two chance of passing the the intermediate FXS gene to your child; the abnormality may expand in size and become a pre-mutation, but it is very unlikely to cause FXS in your son or daughter.

The significance of an abnormal FXS gene in a child primarily depends on the size of the abnormality in the mother's FXS gene and on the chance of the abnormality becoming larger when passed to a child. The father's FXS gene usually has little impact. It is also possible that the father has a small abnormality (pre-mutation) in the FXS gene and is unaffected; this is usually not of significance for immediate reproductive decision-making. We have developed a separate leaflet for unaffected men with a small abnormality in the FXS gene.

What can I do if I am a carrier of FXS?

If you are not pregnant, you and your partner have time to think about your carrier test result when discussing your options for family planning. These options include testing the baby in early pregnancy for FXS (prenatal testing). Another option is using IVF and then testing the embryo for FXS before implantation. There are other options, such as using a donor egg, or having no testing for FXS at all. You should discuss these options with your doctor.

If you are pregnant, your options include prenatal testing or no testing for FXS. You should discuss these options with your doctor.

Hearing about your carrier result will usually be unexpected. Some people find this information confronting or confusing at the very time that decisions need to be made. You need information and support when making these decisions.

Your doctor may suggest that you discuss these issues with a genetic counsellor, a healthcare professional who can help you and your partner make an informed decision. Sonic Genetics offers free genetic counselling for couples where the women is shown to be a carrier of FXS. Your doctor can refer you for this service; conditions apply and can be discussed with your doctor.

Your doctor or genetic counsellor will not tell you what to do: the right decision is what you decide is best for you and your family.

Your test result is important for your relatives

If you are a carrier of FXS, you probably inherited the faulty gene from one of your parents. That means that close family members, such as brothers, sisters and cousins, may also be carriers. We recommend that you tell them about your result and the availability of reproductive carrier screening, so that they can make their own informed decisions about family planning.

Further information is available at The Centre for Genetics Education, genetics.edu.au

[1] Archibald A, Smith M, Burgess T, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. *Genet Med*. 2018; **20**(5):513-526

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