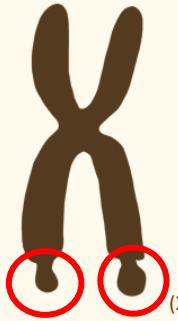
What is Fragile X Syndrome (FXS)?

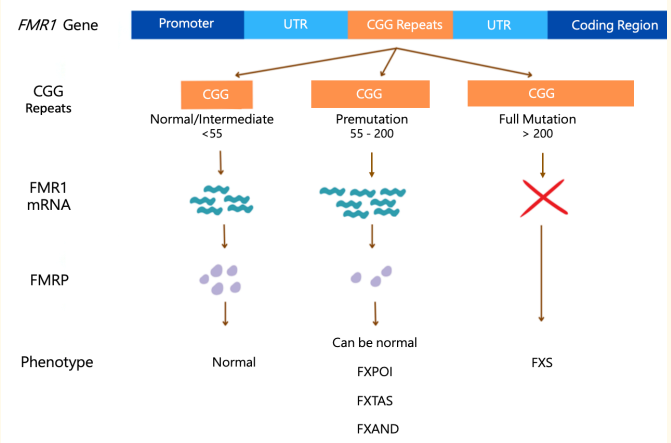
Fragile X Syndrome (FXS) is one of the most common genetic conditions that causes intellectual disability with varying severity. The word "fragile" describes the site of mutation on the X chromosome that appears broken.



What causes FXS?

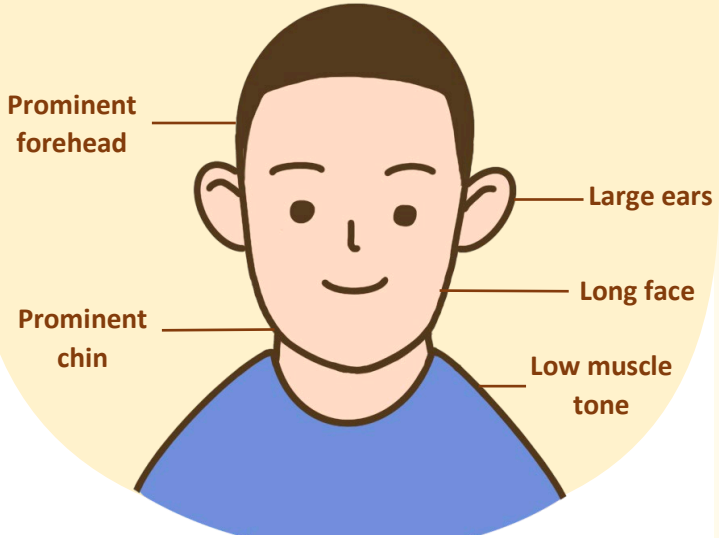
FXS is caused by an excessive increase of CGG trinucleotide repeats in the *FMR1* gene that is located on the X chromosome. The FMR1 gene plays a crucial role in the brain development by producing a protein called the Fragile X Mental Retardation Protein (FMRP).

When there is an excess of CGG trinucleotide repeats in the *FMR1* gene, the promotor region of the *FMR1* gene is hyper-methylated. The *FMR1* gene is then silenced, so no FMRP protein is produced. The absence of FMRP protein disturbs the biological mechanisms involved in learning and memory, resulting in cognitive challenges.



What are the signs and symptoms?

Physical Features:



* Large testes can also be a sign for males after puberty

Neuro-behavioural Features:

- Developmental delay/intellectual disability
- Language impairment
- Attention deficit/hyperactivity
- Seizures/epilepsy
- Features of autism spectrum disorder
- Deficits in social interaction
- Anxiety
- Difficulty in falling asleep

How to test for FXS?

FXS can be diagnosed through molecular testing. A blood test can be conducted to identify and count the number of the CGG trinucleotides repeats in the *FMR1* gene. Depending on the number of CGG repeats, the result can be classified into four categories: normal, grey zone, premutation and full mutation.

Classification of *FMR1* allele

No. of CGG Repeats	Category	Potential Clinical Manifestation
<45	Normal	None
45-54	Grey Zone	None
55-200	Premutation	**Female:** Fragile X associated Primary Ovarian Insufficiency (FXPOI) **Both male and female**: 1. Fragile X associated Tremor/Ataxia Syndrome (FXTAS) 2. Fragile X associated Neuropsychiatric Disorders (FXAND)
>200	Full Mutation	Fragile X Syndrome (FXS)

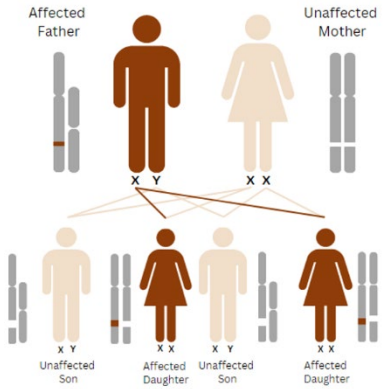
Normal people have fewer than 45 CGG repeats. People who have a premutation (55-200 CGG) in the *FMR1* gene do not have FXS, but they might develop other *FMR1*-related disorders. They can also give birth to children with a premutation or full mutation (FXS).

How is FXS inherited?

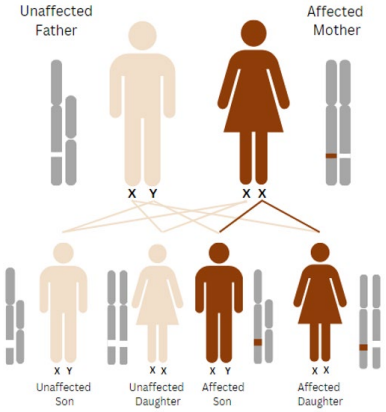
FXS affects an estimation of 1 in **4000 to 7000** males and 1 in **6000 to 11000** females. Males have one X and one Y chromosome, while females have two X chromosomes. Since FXS is an X-linked dominant disease, males are at a higher risk of having developmental delay and intellectual disability (ID) that are more severe than females. While 50% of affected females have normal intellect, the rest may present with a spectrum of delay, ID and autism spectrum disorder.

1 Father with Premutation + Unaffected Mother

An affected father (XY) can only pass the *FMR1* premutation allele to his daughter(s) but not to his son(s). The daughter will become a premutation carrier as the CGG repeats usually remain stable if transmitted from father.



Unaffected Father + Affected Mother 2



All children regardless of sex have a 50% chance of inheriting the altered gene from an affected mother with one altered X and one normal X chromosome. Most grey zone alleles are stable, whereas premutation alleles may undergo further expansion into full mutations.

Reproductive options for at-risk couples

Pregnant women who are FMR1 premutation/full mutation carriers can consider prenatal FXS testing through:

- Amniocentesis
- Chorionic villus sampling (CVS)

Pre-implantation genetic testing (PGT) alongside IVF (in-vitro fertilization) can be used to prevent transmission of FXS to the next generation.

What can I do if my child has FXS?

While there is currently no cure for FXS, special education and training are available for children with FXS to acquire essential life skills effectively. These treatment services can enhance verbal communication, motor abilities and social interactions, which can improve the quality of life of FXS patients and their families.

For further enquiry, you may contact us.

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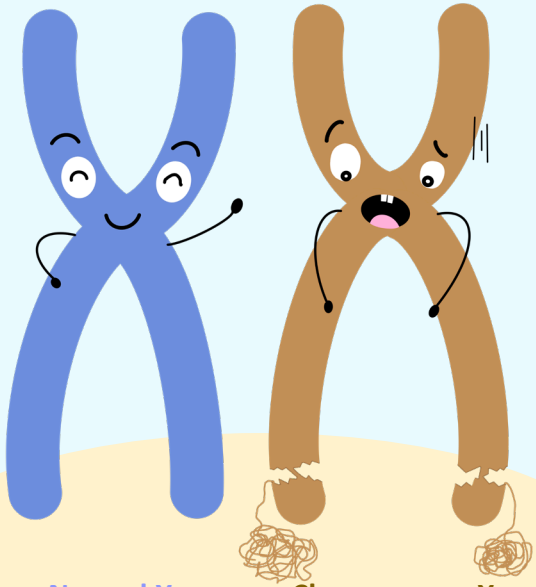

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