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Fragile X Syndrome

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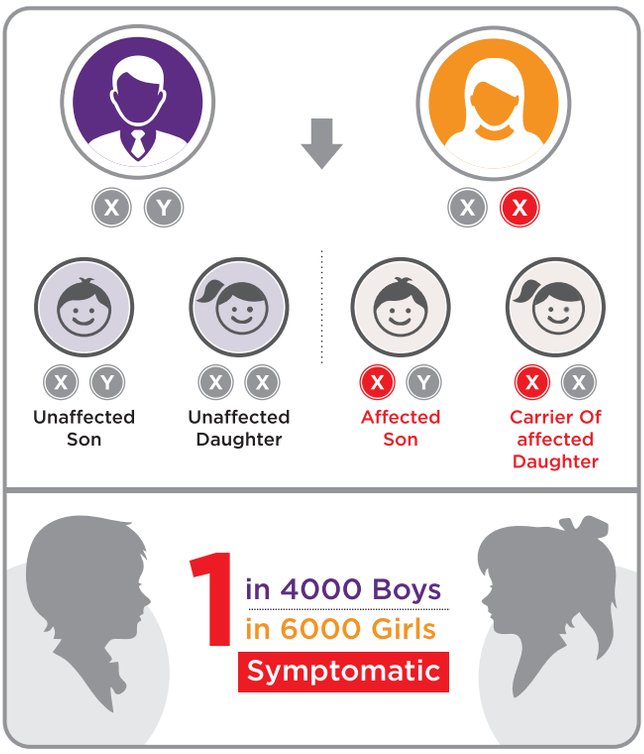
What is Fragile X Syndrome ?

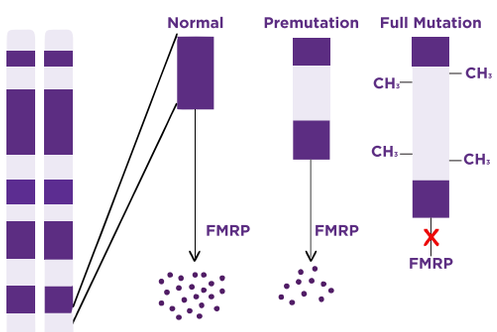
Fragile X (Fr-X) syndrome is one of the common causes of intellectual disability and autism. This condition, being X-linked, disproportionately affects males, with females being mildly affected. In India, it is estimated that 2-4 lakh people are affected with this condition, with approximately 1 in 300 females being carriers of the condition.[1]

Fr-X is an X-linked recessive disorder - Mothers who carry the Fragile X premutation have a 50% chance of passing the expanded *FMR1* gene to their children. Children will either be carriers (if female) or they will have Fr-X syndrome (if male). Carrier men will pass the premutation to ALL their daughters (carriers) but none of their sons.



What causes Fr-X Syndrome?

Fr-X syndrome is caused by a mutation in the *FMR1* gene that is located on the X chromosome. Nearly all affected individuals (99%) have an increased number of copies of a portion of the FMR1 gene, called the CGG repeat region ("trinucleotide" or "triplet" repeat region).



The expansion of the CGG repeat region to more than 200 repeats ("full mutation") silences the *FMR1* gene, causing loss of the FMRP protein, leading to the symptoms of Fr-X syndrome. [6]

CGG Repeats	Results	Clinical Features
<45	Normal	▸ No Symptoms of Fr-X syndrome ▸ No Risk of repeat expansion in the next generation
46-54	Gray Zone/ Intermediate	▸ No Symptoms of Fr-X syndrome ▸ Increased risk of repeat expansion to pre-mutation in the next generation
55-200	Pre-mutation	▸ FMR1 related disorders (FX-TAS, FX-POI) ▸ Risk of full mutation in the next generation
>200	Full Mutation	▸ Affected males have symptoms consistent with Fr X Syndrome ▸ Affected females may have milder symptoms[3]

What are *FMR1*- related disorders?

Individuals who carry CGG repeats between 55 – 200 (pre-mutation) are at risk for having children or grandchildren with Fr-X syndrome. They are also at risk for two adult onset disorders.

Primary Ovarian insufficiency (POI):

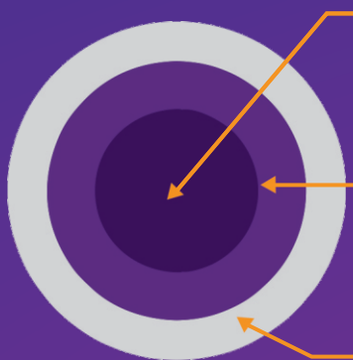
Pre-mutation carrier women may have irregular menstrual cycles and early menopause by the time they are 40 years old. POI may cause elevated Follicle stimulating hormone (FSH) and infertility.

Fragile X Tremor Ataxia Syndrome (Fx-TAS):

Pre-mutation carriers (both men and women), over the age of 50, may experience Parkinson-like features. Men are usually more affected than women.

When to consider *FMR1* gene testing?

1 in 33 children with autism may have Fragile X Syndrome



As a **DIAGNOSTIC TEST** in individuals symptomatic for Fr-X syndrome-Autism, developmental & intellectual delays (ID/DD), and physical features of Fr-X syndrome.

As a **CARRIER SCREENING TEST** when there is a family history of Fr-X or Fr X related disorders or undiagnosed cause of ID

As a **PREDICTIVE TEST** in individuals suspected of Fr-X related disorders and known carrier mothers for risk of expansion.

This test is not recommended to be used as a general population screening test. [4]

How do you test for Fr-X syndrome?

- Triple repeat primer polymerase chain reaction (TP-PCR) is a method of DNA amplification that can detect triplet nucleotide repeat regions on the *FMR1* gene to accurately and efficiently detect the number of CGG repeats for both affected and carrier individuals.
- The sensitivity of this technology makes it an ideal tool for personalized diagnosis of both premutation and full-mutation patients. [5]
- TP -PCR test is performed on whole blood sample (EDTA) and results can be expected in 15 working days.

What to expect from *FMR1* test report ?

- TP-PCR gives the exact number of CGG repeats and provides accurate and personalized risk assessment.
- TP-PCR resolves the challenges associated with apparent homozygous females, because the normal allele will not outcompete the expanded allele. Hence this test can clearly specify – if the female sample is homozygous or heterozygous, with two numbers representing the repeats identified on each allele.
- TP-PCR assay also resolves the difficulty of detecting mosaic males. Hence the test also gives information on mosaicism in your patient to accurately describe the prognosis.
- This kit promises confident amplification of CGG repeats upto 1.8Kb of expansion, which no other kit has published/promised till date.

Can the TP-PCR test provide a personlized risk assessment in carriers?

The number of CGG repeats in a pre-mutation carrier can be used to predict the risk of repeat expansion from parent to child. [6]

CGG repeats	55-59	60-69	70-79	80-89	90-99	100+
Risk (%) of expansion to >200 repeats	3.7	5.3	31.1	57.8	80.1	98

Why TP-PCR is better ?

	Conventional PCR	TP-PCR
Simultaneous amplification of *FMR1* gene and CGG repeats	X	✓
Differentiates between homozygous and heterozygous	X	✓
Exact number of repeats provided for >200 repeats	X	✓
Detection of all allele expansions, including low abundance full mutation size mosaics	X	✓
Requires Southern Blot	✓	X
Diagnostic sensitivity of 99%	X	✓
Diagnostic specificity of 98.4%	X	✓
Overall accuracy of 99%	X	✓

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