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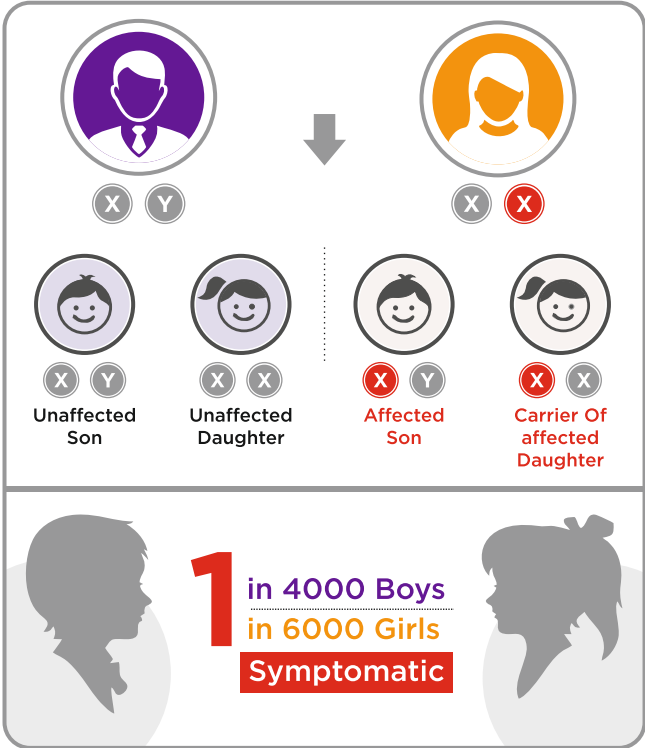
Fragile X Syndrome

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What is Fragile X Syndrome ?

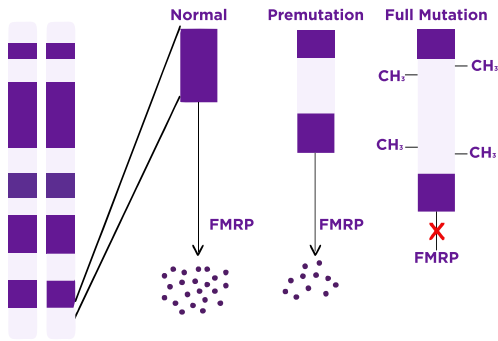
Fragile X (Fr-X) syndrome is one of the common causes of intellectual disability and autism. This condition, being X-linked, disproportionately affects males, with females being mildly affected. In India, it is estimated that 2-4 lakh people are affected with this condition, with approximately 1 in 300 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	<ul style="list-style-type: none">▶ No Symptoms of Fr-X syndrome▶ No Risk of repeat expansion in the next generation
46-54	Gray Zone/ Intermediate	<ul style="list-style-type: none">▶ No Symptoms of Fr-X syndrome▶ Increased risk of repeat expansion to pre-mutation in the next generation
55-200	Pre-mutation	<ul style="list-style-type: none">▶ <i>FMR1</i> related disorders (FX-TAS, FX-POI)▶ Risk of full mutation in the next generation
>200	Full Mutation	<ul style="list-style-type: none">▶ 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):

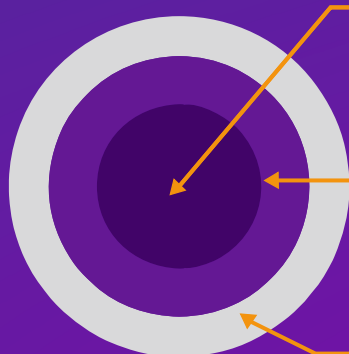
Pre-mutation carrier women may have irregular menstrual cycles and early menopause by the time they are 40 years old. POI may cause elevated Follicle stimulating hormone (FSH) and infertility.

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 personalized 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 <i>FMR1</i> 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	✓

Reference

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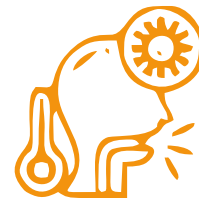
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