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# Neu INSIGHTS



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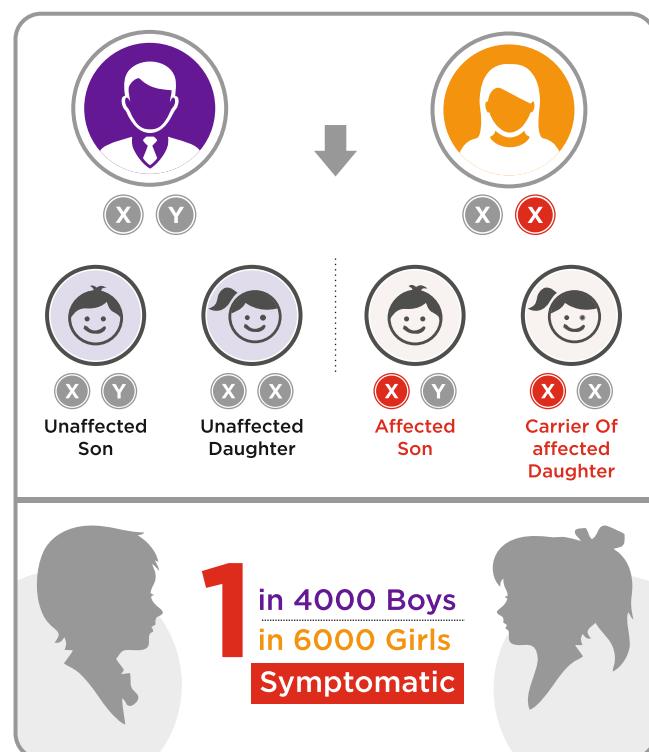


## Fragile X Syndrome

# 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.<sup>[1]</sup>

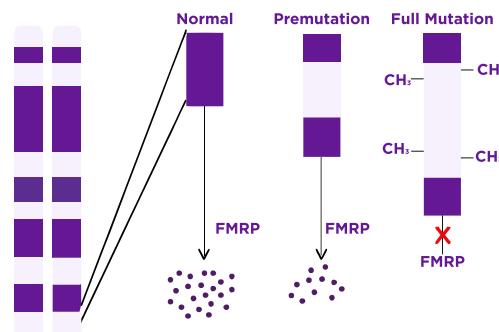
Fr-X is an X-linked recessive disorder - Mothers who carry the Fragile X pre-mutation have a 50% chance of passing the expanded *FMR1* gene to their children. Children will either be carriers (if female) or they will have Fr-X syndrome (if male). Carrier men will pass the pre-mutation to ALL their daughters (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.<sup>[6]</sup>



CGG Repeats	Results	Clinical Features
<45	Normal	<ul style="list-style-type: none"> <li>No Symptoms of Fr-X syndrome</li> <li>No Risk of repeat expansion in the next generation</li> </ul>
46-54	Gray Zone/ Intermediate	<ul style="list-style-type: none"> <li>No Symptoms of Fr-X syndrome</li> <li>Increased risk of repeat expansion to pre-mutation in the next generation</li> </ul>
55-200	Pre-mutation	<ul style="list-style-type: none"> <li>FMR1 related disorders (FX-TAS, FX-POI)</li> <li>Risk of full mutation in the next generation</li> </ul>
>200	Full Mutation	<ul style="list-style-type: none"> <li>Affected males have symptoms consistent with Fr X Syndrome</li> <li>Affected females may have milder symptoms<sup>[3]</sup></li> </ul>

# 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):

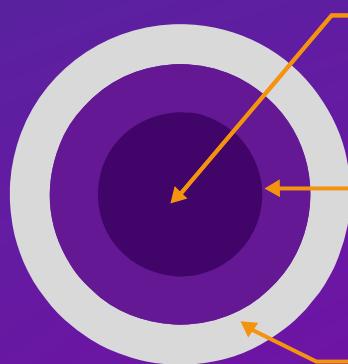
Pre-mutation carrier women may have irregular menstrual cycles and early menopause by the time they are 40 years old. POI may cause elevated Follicle stimulating hormone (FSH) and infertility.

## 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.<sup>[4]</sup>

## 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 pre-mutation and full-mutation patients.<sup>[5]</sup>
- ▶ 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. <sup>[6]</sup>

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	✗	✓
Differentiates between homozygous and heterozygous	✗	✓
Exact number of repeats provided for >200 repeats	✗	✓
Detection of all allele expansions, including low abundance full mutation size mosaics	✗	✓
Requires Southern Blot	✓	✗
Diagnostic sensitivity of 99%	✗	✓
Diagnostic specificity of 98.4%	✗	✓
Overall accuracy of 99%	✗	✓

## Reference

Indhumathi, N., Singh, D., Chong, S. S., Thelma, B. K., Arabandi, R., & Srisailpathy, C. R. (2012). Fragile X CGG repeat variation in Tamil Nadu, South India: a comparison of radioactive and methylation-specific polymerase chain reaction in CGG repeat sizing. *Genetic testing and molecular biomarkers*, 16(2), 113-122. <https://doi.org/10.1089/gtmb.2011.0102>

Committee Opinion No. 469: Carrier Screening for Fragile X Syndrome. (2010). *Obstetrics & Gynecology*, 116(4), 1008-1010. doi:10.1097/aog.0b013e3181fae884

Sherman, S., Pletcher, B. A., & Driscoll, D. A. (2005). Fragile X syndrome: Diagnostic and carrier testing. *Genetics in Medicine*, 7(8), 584-587. doi:10.1097/01.gim.0000182468.22

Monaghan, K. G., Lyon, E., Spector, E. B., & erican College of Medical Genetics and Genomics (2013). ACMG Standards and Guidelines for fragile X testing: a revision to the disease-specific supplements to the Standards and Guidelines for Clinical Genetics Laboratories of the American College of Medical Genetics and Genomics. *Genetics in medicine : official journal of the American College of Medical Genetics*, 15(7), 575-586. <https://doi.org/10.1038/gim.2013.61>

Spector, E., Behlmann, A., Kronquist, K., Rose, N. C., Lyon, E., & Reddi, H. V. (2021). Laboratory testing for fragile X, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine*, 23(5), 799-812. doi:10.1038/s41436-021-01115-y

Willemsen, R., Levenga, J., & Oostra, B. (2011). CGG repeat in the *FMR1* gene: size matters. *Clinical Genetics*, 80(3), 214-225. doi:10.1111/j.1399-0004.2011.01723.x

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