



# Fragile X Screening

## INTRODUCTION

Fragile X, the most common heritable form of mental retardation, accounts for 2 to 3 percent of undiagnosed mental impairment. It is also the most common known cause of autism or autistic-like behaviors.

Fragile X syndrome causes a range of learning problems, ranging from mild mental retardation to severe cognitive or intellectual disabilities. Characteristic physical and behavioral features as well as delays in speech and language development are often present.

## OVERVIEW

Fragile X syndrome is caused by an expanded trinucleotide CGG repeat in the 5' untranslated region of the *FMRI* gene, which leads to hypermethylation and inhibition of gene transcription.

Fragile X behavioral features include hyperactivity, perseverative speech, social anxiety, poor eye contact, and hand flapping or biting.

Disease prevalence is one in 4,000 in males and one in 8,000 in females; females are generally more mildly affected than males because females have two X chromosomes, with one of the X's being randomly inactivated in each cell. If the brain retains a sufficient number of functional *FMRI* genes, the female may show little or no effect from the *FMRI* gene expansion.

## PREMUTATION VS. FULL MUTATION

The major factor that determines the presence or absence of fragile X syndrome is the number of CGG repeats in the *FMRI* gene on the X chromosome. If the number of CGG repeats exceeds 200 (full mutation), it triggers the methylation of the CpG island, a regulatory region for the *FMRI* gene, and the production of fragile X mental retardation protein is shut off, resulting in fragile X syndrome. All males with a full mutation will have fragile X syndrome and experience significant symptoms. Approximately 50 percent of females with a full mutation will also have symptoms of fragile X.

Individuals who have between 55 and 200 CGG repeats are in the premutation range and usually have no symptoms of fragile X syndrome. Older premutation carrier men may develop fragile X-associated tremor/ataxia syndrome (FXTAS), which is characterized by progressive cerebellar ataxia and intention tremor. Female premutation carriers may develop primary ovarian insufficiency or, rarely, FXTAS.

Both males and females can be carriers of *FMRI* expansions and pass it on to their children. Carrier prevalence in Caucasian females is one in 350, while carrier prevalence in Caucasian males is one in 1,000. Carrier females have up to a 50 percent risk of having an affected child, as their CGG repeat often expands into the full mutation range during the production of egg cells. The CGG repeat number rarely expands in males who carry a premutation; nevertheless, they will transmit the premutation to all of their daughters but none of their sons.

## TESTING

A healthcare provider may recommend fragile X syndrome testing for a child with mental retardation, developmental delay, or autism. Testing is especially important if the child also has physical or behavioral signs and symptoms of fragile X syndrome or a family history of fragile X syndrome or mental retardation of unknown cause.

Approximately half of all families do not learn of their child's fragile X syndrome diagnosis before having a subsequent pregnancy.

Women who are planning a pregnancy should be offered carrier testing for fragile X syndrome if they have a family history of fragile X syndrome, mental retardation, developmental delay, autism of unknown etiology, or personal history of early ovarian failure.

Due to carrier frequency, fragile X screening is also being routinely offered to expectant women even in the absence of any risk factors.

## ORDERING INDICATIONS

### **Fragile X (*FMR1*) Mutation Screen**

Fragile X (*FMR1*) mutation screen is recommended for:

- Newborn screening for infants without a family history of fragile X.
- Carrier screening for expectant women or those planning a pregnancy.

The fragile X (*FMR1*) mutation screen uses PCR followed by size analysis using capillary electrophoresis; reflex to the fragile X (*FMR1*) mutation diagnosis is preformed only if a premutation or full mutation allele is suspected.

If the screen is negative (i.e., no CGG repeat in the premutation or full mutation range), individuals are considered to be at very low risk for being affected with fragile X syndrome or having affected offspring.

If the screen is positive (i.e., with CGG repeat sizes in the premutation or full mutation range), individuals have an increased risk for having symptoms and/or affected offspring. Thus, reflex testing to fragile X (*FMR1*) mutation diagnosis is performed to determine the precise number of CGG repeats and methylation status.

### **Fragile X (*FMR1*) Mutation Diagnosis**

Fragile X (*FMR1*) mutation diagnosis is recommended for:

- Individuals with unexplained mental retardation, developmental delay, autism, or late-onset cerebellar ataxia and intention tremor of unknown etiology.
- Females experiencing primary ovarian insufficiency or fertility problems associated with elevated follicle-stimulating hormone levels.
- Confirmation of cytogenetic test results inconsistent with clinical phenotype.
- Prenatal or newborn testing for fetuses/infants of carrier mothers.
- Individuals with a family history of fragile X syndrome or mental retardation of unknown etiology.

The fragile X (*FMRI*) mutation diagnosis uses PCR analysis to determine the *FMRI* CGG repeat length; it also amplifies the sex-chromosome marker to confirm chromosomal sex.

## CONCLUSION

With a clinical and analytical sensitivity of 99 percent, ARUP's fragile X screening test costs significantly less than diagnostic testing and is beneficial for routine carrier screening. Only samples with a premutation or full mutation detected on the screening test are reflexed to more costly diagnostic testing to confirm the result and determine the precise number of CGG repeats.

## REFERENCES

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