TPMG Regional Genetics Laboratory

# Fragile X Testing

## What is fragile X syndrome?

Fragile X syndrome is an inherited condition that causes intellectual disability, behavior challenges, and small differences in the way a person looks. The level of intellectual disability can range from mild to severe. Common behavior problems include hyperactivity, attention deficit disorder, and autistic behaviors. Females with fragile X syndrome usually have milder symptoms than males. Fragile X syndrome is found in people from all parts of the world. It affects about 1 in every 4000 males and 1 in every 6000 females.

## What causes fragile X syndrome?

Fragile X syndrome is caused by a genetic change (mutation) in the Fragile X Mental Retardation (FMR1) gene. The FMR1 gene makes a protein that is found in the brain and other parts of the body. Almost all cases of fragile X are due to an expansion of the FMR1 gene. In one part of the gene three letters of the DNA code are repeated many times (CGG-CGG-CGG…). This is called a triplet repeat or a trinucleotide repeat. In most people there are fewer than 45 CGG repeats. When there are more than 200 CGG repeats, the gene gets turned off, causing fragile X syndrome. This is called a fragile X **full mutation**. Males with a full mutation will have fragile X syndrome, and about half of the females with a full mutation will have symptoms of fragile X syndrome.

## What is a fragile X premutation?

A person with between 55 and 200 CGG repeats carries a genetic change called a fragile X **premutation**. Both males and females can have a fragile X premutation. A person with a premutation does not have fragile X syndrome, but could pass the FMR1 gene to their children with more CGG repeats.

**Fragile X testing may be offered if you have:**

- Delayed development, intellectual disabilities, or autism
- Significant learning disabilities, especially when there are behavior problems or physical differences
- Someone in the family with fragile X syndrome
- A family history of intellectual disability that suggests fragile X syndrome
- Early menopause (before 40)
- Development of tremors, balance problems, and behavior changes without a known cause, especially if you are a male over 50

## Are there any medical problems for a person with a premutation?

Most people with a premutation do not have medical problems. However, some people with a fragile X premutation develop tremors (shaky hands), balance problems, and behavior changes as they age. This is called fragile X-associated tremor/ataxia syndrome (FXTAS). It is more common for a man with a premutation to develop FXTAS. Some women with a fragile X premutation may start menopause earlier than expected. This is called fragile X-associated primary ovarian insufficiency (FXPOI).

## Why should I consider fragile X testing?

Fragile X testing lets you know if your child could be born with fragile X syndrome. Testing can also let you know if you are at risk for FXTAS or FXPOI. A genetic counselor can help by reviewing your family history to find out whether fragile X testing may be indicated for you or someone in your family.

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### How is testing done?

Fragile X testing is usually done on a blood sample. Testing can also be done during pregnancy to check a fetus for fragile X. In the laboratory, the FMR1 gene is tested to see if a full mutation or a premutation is present.

### How accurate is testing?

Fragile X testing is highly accurate. More than 99% of mutations in the fragile X gene will be found by standard testing.

### What are the limitations of testing?

Fragile X testing does not test for all genetic causes of intellectual disability. If testing is being done because an individual or a family member has intellectual disability, more testing may be needed to look for other genetic causes of intellectual disability.

### How long does it take to get results?

Fragile X test results are usually ready in about two weeks.

### Fragile X can be passed from a parent to a child, but fragile X inheritance is complex.

The FMR1 gene is located on the X-chromosome and is called an X-linked condition. Inheritance is different for females and males.

- Females: Two X-chromosomes → Two copies of the FMR1 gene
- Males: One X-chromosome → One copy of the FMR1 gene
  PLUS One Y-chromosome → with no FMR1 gene

**Female Carriers:** A woman who carries either a premutation or a full mutation can pass the mutation to her sons and her daughters. There is a 50% (1 in 2) chance that the mutation will be passed on. The number of CGG repeats can get bigger when the FMR1 gene is passed from a mother to her child. This means that a child born to a woman with a premutation could have fragile X syndrome.

**Male Carriers:** A man with a premutation will pass the premutation to all of his daughters, but none of his sons (he passes the Y chromosome to his sons). The premutation rarely changes size when it is passed from a father to his daughters.

**Resources:**
National Fragile X Foundation - https://fragilex.org/