

Capsule

Fragile X Syndrome

Fragile X syndrome is the most common cause of inherited mental retardation.¹ Individuals with fragile X syndrome have mental retardation that ranges from mild to severe. Autistic features and speech and language problems are also common. Approximately 1 in 1500 males and 1 in 2500 females have fragile X syndrome.²

Fragile X syndrome is an X-linked disorder caused by a variability in tandemly repeated trinucleotide sequences, CGG, near the 5' end of the *FMRI* gene. Normal alleles (gene variants) have fewer than 45 repeats and have no meiotic or mitotic instability.³ When 45 to 54 repeats are found, the allele size is considered “gray zone,” also referred to as borderline. It is highly unlikely that women with 45 to 54 repeats will have a child with fragile X syndrome, but it is possible that distant relatives or future generations could be at risk for fragile X syndrome. Family studies are necessary to determine the stability of the gene.³ People with 55 to 203 repeats are referred to as premutation carriers and usually do not have symptoms of fragile X syndrome; however, recent data suggest that premutation carriers may be at increased risk for developing mild cognitive/behavioral deficits, premature ovarian failure, and FXTAS (fragile X-associated tremor/ataxia syndrome).⁴ When more than 200 repeats are present, it is considered a full mutation. A full mutation results in fragile X syndrome.² Table 1 summarizes the correlation between severity and number of repeats.³

N° of Repeats	Condition
5 to 44	Normal
45 to 54	Gray zone, no measurable risk for affected children, but gene may be unstable
55 to 200	Premutation, carrier. May be at risk for mild cognitive/behavioral deficits, premature ovarian failure, and FXTAS (fragile X-associated tremor/ataxia syndrome)
200 or more	Full mutation, affected

The inheritance of fragile X syndrome is complex. Expansion of the fragile X premutation into a full mutation has only been

reported when the premutation is passed on by the mother;^{2,3} therefore, a woman who is a carrier of fragile X syndrome has (theoretically) a 50% chance with each pregnancy of passing on the unstable fragile X gene.³ The chance that the unstable gene will expand into a full mutation varies with the repeat size.¹

N° of Repeats	Risk of expansion to full mutation when passed to offspring by the mother
50 to 59	Negligible
60 to 69	17%
70 to 79	71%
80 to 89	82%
90 to 113	100%

Males can also be carriers of fragile X syndrome, but in general the fragile X gene is not expected to expand into the affected range when passed on through the male.³ Men who are carriers of fragile X syndrome are called “transmitting males.”¹ Men pass the Y chromosome to their sons; therefore, no son will inherit the fragile X gene from his father. Men pass the X chromosome to their daughters. Consequently, under normal circumstances, all of the daughters of a male carrier of fragile X syndrome will also be carriers.³ These daughters will be at increased risk of having affected children.

Historically, chromosome (cytogenetic) testing was used to diagnose fragile X syndrome.³ This method is no longer acceptable for diagnostic purposes because there are more sensitive technologies. DNA testing is available to determine the number of trinucleotide repeats in the *FMRI* gene. Two approaches are used since no one method can detect all *FMRI* variability. PCR techniques allow for accurate sizing of normal alleles, grey zone alleles, and small premutations. Larger premutations, full mutations, and women with the same size allele on both chromosomes are best analyzed by Southern blot analysis.^{1,3} In most cases, PCR is used as a first strategy, and equivocal results are verified and confirmed by Southern blot.

The American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG)

have recommended^{2,6} that testing for fragile X syndrome be offered to any child who has developmental delay or mental retardation (of no obvious cause), autistic-like features, or other physical findings and behavior consistent with fragile X syndrome. Any person who is considering a pregnancy or is pregnant should be offered carrier screening for fragile X syndrome if there is a family history of fragile X syndrome or a family history of mental retardation of uncertain etiology in either the male or female relatives.

Approximately 1 in 259 women have a fragile X premutation, and 20% of these women will experience premature ovarian failure.⁴ Fragile X testing is a consideration in women with premature ovarian failure.

Additionally, 1 in 810 males carries a fragile X premutation.⁴ Individuals with a premutation are at increased risk for FXTAS (fragile X-associated tremor/ataxia syndrome). This disease is more common in men and is characterized by gait ataxia, intention tremor, parkinsonism, and cognitive decline.⁴ The penetrance increases with age.⁵ Individuals with late-onset ataxia and intention tremor should be screened for fragile X syndrome premutations.⁵

Prenatal diagnosis is available for fragile X syndrome,³ and several options for testing are available. The most common tests are amniocentesis and chorionic villus sampling (CVS). These tests have different risks, benefits, and limitations that should be discussed with the appropriate health care provider.

Fragile X Syndrome, DNA Analysis 510065
CPT 83891; 83894; 83898; 83912
Synonyms Inherited Mental Retardation; Martin-Bell Syndrome
Test Includes Direct molecular analysis for fragile X
Special Instructions Please provide pertinent medical findings: name, age, and affected relatives, if any.
Specimen Whole blood, amniocyte culture (T25), or amniotic fluid (submission of maternal blood is required for fetal testing)
Volume 10 mL
Minimum Volume 3 mL
Container Lavender-stopper (EDTA whole blood) tube, yellow-stopper (ACD whole blood) tube, sterile culture tube, or flask
Storage Instructions Maintain specimen at room temperature.
Causes for Rejection Frozen or hemolyzed specimen; quantity not sufficient for analysis
Methodology Polymerase chain reaction (PCR) and gel electrophoresis (10 days); if Southern blot is indicated, additional 14 days

Fragile X Syndrome, Cytogenetics/DNA With Reflex to Multiprobe Subtelomere FISH (Telo-Scan) 510461
CPT 88230; 88262; 83891; 83894; 83898; 83912; 88289; 88291
Synonyms Fragile X with FISH reflex; FISH Subtelomeres with Fragile X Cytogenetics/DNA; Subtelomere FISH/ Chromosomes/ Fragile X DNA; Multiprobe Subtelomere FISH
Special Instructions Include name, age, and relevant clinical history. For prenatal testing, please call 800-533-0567.
Specimen Whole blood
Volume Two 10 mL tubes (10 mL in green-stopper tube and 10 mL in lavender-stopper tube)
Minimum Volume 2 mL (green-stopper tube) and 2 mL (lavender-stopper tube)
Container 10 mL green-stopper (sodium heparin whole blood) tube and 10 mL lavender-stopper (EDTA whole blood) tube
Storage Instructions Maintain specimen at room temperature.
Causes for Rejection Frozen specimen
Methodology Southern blot hybridization; cytogenetics

Fragile X Syndrome, Cytogenetics and DNA Analysis . . 510115
CPT 83891; 83894; 83898; 83912; 88230; 88262; 88289; 88291
Synonyms Chromosome Analysis, High Resolution and Fragile X DNA; Cytogenetics, High Resolution and Fragile X DNA; Inherited Mental Retardation; Martin-Bell Syndrome
Test Includes Direct molecular (DNA) analysis for fragile X plus complete high resolution chromosome analysis
Special Instructions Include name, age, and relevant clinical history. For prenatal testing, please call 800-533-0567.
Special Instructions Include name, age, and relevant clinical history
Specimen Whole blood
Volume Two 10-mL tubes (10 mL in lavender-stopper tube and 10 mL in green-stopper tube)
Minimum Volume 3 mL (lavender-stopper tube) and 2 mL (green-stopper tube)
Container 10-mL lavender-stopper (EDTA) tube and 10-mL green-stopper (sodium heparin whole blood) tube
Storage Instructions Maintain specimen at room temperature.
Methodology Polymerase chain reaction (PCR) and Southern blot hybridization; cytogenetics

References

1. Fu Y-H, Kuhl DPA, Pizzuti A, et al. Variation of the CGG repeat at the fragile X site results in genetic instability: Resolution of the Sherman paradox. *Cell*. 1991; 67:1047-1058.
2. American College of Obstetricians and Gynecologists. Fragile X syndrome. *ACOG Committee Opinion*. N° 161, October, 1995:25-26.
3. Maddalena A, Richards CS, McGinniss MJ, et al. Technical standards and guidelines for fragile X: The first of a series of disease-specific supplements to the standards and guidelines for clinical genetics laboratories of the American College of Medical Genetics. *Genet Med*. 2001; 3(3):200-205.
4. Hagerman PJ, Hagerman RJ. The Fragile X premutation: A maturing perspective. *Am J Hum Genet*. 2004; 74:805-816.
5. Jacquemont SJ, Hagerman RJ, Leehey MA, et al. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. *JAMA*. 2004; 291(4):460-469.
6. American College of Medical Genetics. Fragile X syndrome: Diagnostic and carrier testing. *Am J Med Gen*. 1994; 53:380-381.

To learn more about testing for fragile X syndrome or other genetic disorders, call 800-345-GENE.



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