

Funded by the NIH • Developed at the University of Washington, Seattle



# Fragile X Syndrome

(FRAXA, Martin-Bell Syndrome, Fragile X Mental Retardation, Marker X Syndrome)

**Authors:** Jack Tarleton, PhD; Fullerton Genetics Center  
Robert A Saul, MD; Greenwood Genetic Center

**Last update:**  
26 May 2000

**Last revision:**  
16 June 1998

**Initial posting:**  
10 June 1998

## Summary

**Disease characteristics.** Fragile X syndrome is characterized by moderate mental retardation in affected males and mild mental retardation in affected females.

**Diagnosis/testing.** The diagnosis of fragile X syndrome rests on the detection of an alteration in the *FMR1* gene (chromosome locus Xq27). More than 99% of affected individuals have a "full mutation" in the *FMR1* gene caused by an increased number of CGG trinucleotide repeats (>230) typically accompanied by aberrant methylation of the *FMR1* gene. Both increased trinucleotide repeats and methylation changes in *FMR1* can be detected by molecular genetic testing. Such testing is clinically available.

**Genetic counseling.** All mothers of a child with an *FMR1* gene full mutation (expansion >230 CGG trinucleotide repeats) are carriers of an *FMR1* gene expansion. They and their family members are at increased risk to have children with fragile X syndrome and should be offered molecular genetic testing and recurrence risk counseling based on the results. This counseling is complex and should be provided by a knowledgeable genetics professional. Prenatal testing is possible through molecular genetic testing of DNA from cells obtained by chorionic villus sampling (CVS) or amniocentesis, but should only be undertaken after carrier status has been confirmed and the couple has been counseled regarding the risk of recurrence.

## Diagnosis

The phenotypic manifestations of fragile X syndrome are not specific, and thus the diagnosis of fragile X syndrome rests on the detection of an alteration in the *FMR1* gene (chromosomal locus Xq27). Molecular genetic testing of the CGG trinucleotide repeat expansion in the *FMR1* gene detects more than 99% of cases. This testing is highly specific and widely available. Less than 1% of patients with fragile X syndrome have a deletion or point mutation in the *FMR1* gene; testing for these is available on a research basis only.

## Clinical Diagnosis

The diagnosis of fragile X syndrome is suspected in males with moderate mental retardation and females with mild mental retardation.

## Testing

**Chromosome analysis.** Chromosome analysis using modified culture techniques to induce fragile sites is no longer used for diagnosis of fragile X syndrome due to low sensitivity and increased costs when compared with DNA-based testing (see [Molecular Genetic Testing](#) below).

**Protein testing.** Although not routinely performed in most clinical laboratory settings, a few laboratories utilize testing for the product of *FMR1*, FMRP [[Willemssen et al 1997](#)]. Situations where FMRP testing may be useful include screening mentally retarded populations and characterization of cellular production of FMRP in individuals having unusual phenotypes. Since severity of the fragile X syndrome phenotype appears to be correlated to FMRP expression, assessment of FMRP production in some patients has been proposed as a potential prognostic indicator of disease severity [[Tassone et al 1999](#)].

## Molecular Genetic Testing

Routine clinical testing for mutations in the *FMR1* gene (chromosomal locus Xq27) generally determines the trinucleotide repeat number and the *FMR1* methylation status. The following types of alleles are observed:

- Normal alleles: 6 to ~54 CGG repeats
- Premutation (i.e., intermediate) alleles: ~55 to ~230 CGG repeats (An intermediate allele is not associated with symptoms, but on transmission to offspring can expand into a full mutation.)
- Full mutation (i.e., disease-causing) alleles: >230 CGG repeats

Methodologies for molecular genetic testing may vary from laboratory to laboratory as no one technical approach can ascertain all the possible mutation types in the *FMR1* gene found in patients with fragile X syndrome and carriers. Some clinical laboratories screen patient DNA samples by polymerase chain reaction (PCR) specific for the trinucleotide repeat region of the *FMR1* gene, a technique which has high sensitivity for *FMR1* repeats in the normal and lower premutation range (see [Table 3](#)). While the PCR assay alone yields accurate estimates of many allele sizes, it may fail to detect *FMR1* alleles in the upper premutation range and full mutation alleles with a high repeat number. Due to these limitations of PCR, many clinical laboratories perform Southern blot analysis and PCR assays. Southern blot analysis detects the presence of both full mutations and large premutations, allowing an approximate determination of trinucleotide repeat number. In addition, Southern blot analysis may be used to determine the *FMR1* methylation status.

When PCR of the *FMR1* repeat segment reveals a normal or premutation allele in male patients, or two alleles within the normal or premutation range in female patients, further testing may not be indicated. However, rare patients who have cellular mosaicism for the *FMR1* repeat may demonstrate PCR signals in the normal or premutation range when in fact a more complex *FMR1* mutation is present [[Orrico et al 1998](#), [Schmucker and Seidel 1999](#)], leading to potential false negative misdiagnosis.

Newer PCR approaches to testing which determine methylation status are being developed in several clinical laboratories and may offer a more rapid testing turnaround time [Das et al 1998].

The number and position of AGG repeats are known to be important in the overall stability of the CGG repeat sequence [Eichler et al 1994], but this analysis is currently available only in research settings.

Less than 1% of patients with fragile X syndrome have deletions of a portion or all of the *FMR1* gene (reviewed in DeBouille et al 1993, Lugenbeel et al 1995, Wang et al 1997). Unless detected fortuitously during testing for the *FMR1* trinucleotide repeat, point mutations will be missed on routine clinical testing for the trinucleotide repeat expansion, and deletions may or may not be missed. Testing for deletions and point mutations is available on a research basis only.

**Table 1. Molecular Genetic Testing Used in the Diagnosis of Fragile X Syndrome**

% of Patients	Genetic Mechanism	Test Type	Test Availability
> 99%	CGG expansion in <i>FMR1</i> gene	Southern analysis; PCR	Clinical <b>GENETests</b>
< 1%	Point mutation or deletion in <i>FMR1</i> gene		Research

## Testing Strategy

The testing strategy for a patient with a family history of fragile X syndrome differs somewhat from that of a patient with non-specific mental retardation of unknown etiology. To address the complexities of testing for fragile X syndrome in a clinical setting, the American College of Medical Genetics issued a [policy statement](#): *Fragile X Syndrome: Diagnostic and Carrier Testing* (July 22, 1994) which contains recommendations for fragile X diagnostic testing, population screening, and approaches to testing.

The following is a summary of the recommendations.

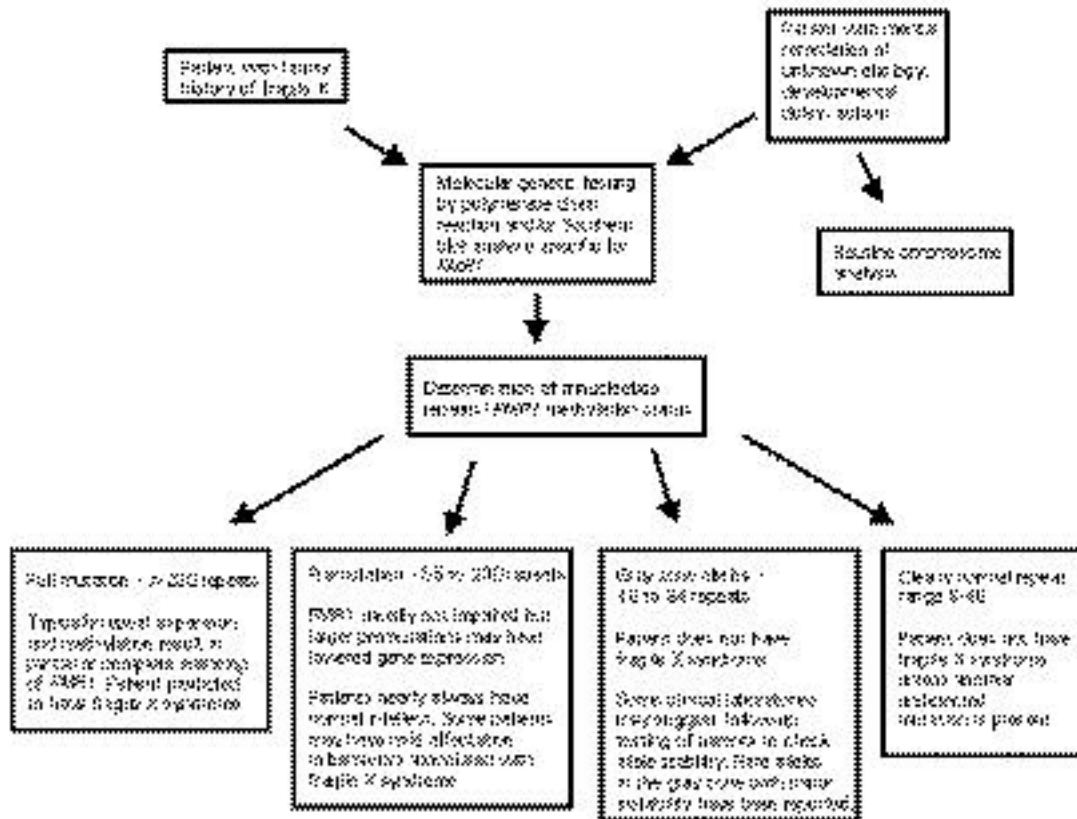
### Individuals for whom testing should be considered:

- Individuals of either sex with mental retardation, developmental delay, or autism, especially if they have a) any physical or behavioral characteristics of fragile X syndrome; b) a family history of fragile X syndrome; or c) male or female relatives with undiagnosed mental retardation
- Individuals seeking reproductive counseling who have a) a family history of fragile X syndrome or b) a family history of undiagnosed mental retardation
- Fetuses of known carrier mothers
- Patients who have a cytogenetic fragile X test result that is discordant with their phenotype. These include patients who have a strong clinical indication (including risk of being a carrier) and who have had a negative or ambiguous test result, and patients with an atypical phenotype who have had a positive test result.

### Approaches to testing:

- DNA analysis is the method of choice if one is testing specifically for fragile X syndrome and associated trinucleotide repeat expansion in the *FMR1* gene.
- If the etiology of mental retardation is unknown, DNA analysis for fragile X syndrome should be performed as part of a comprehensive genetic evaluation that includes routine cytogenetic analysis. Cytogenetic abnormalities have been identified as frequently or more frequently than fragile X mutations in mentally retarded individuals referred for fragile X testing [Curry et al 1997].
- For individuals at risk with an established family history of fragile X syndrome, DNA testing alone is sufficient. If the diagnosis of the affected relative was based on previous cytogenetic testing for fragile X syndrome, then at least one affected relative should be included in DNA testing.
- Prenatal testing of a fetus is indicated following a positive carrier test in the mother. When the mother is a known carrier, DNA testing can be offered to determine whether the fetus inherited the normal or mutant *FMR1* gene.
- Results from CVS testing must be interpreted with caution because the methylation status of the *FMR1* gene is often not yet established in chorionic villi at the time of sampling. CVS, while a standard technique for prenatal diagnosis, may lead to a situation in which follow-up amniocentesis is necessary to resolve an ambiguous result.
- Due to the complexity of *FMR1* trinucleotide repeat expansion and the accompanying methylation issues (see [Table 3](#)), the clinician should select a laboratory with known competence for *FMR1* molecular testing.

## Testing Algorithm



## Clinical Description

The phenotypic features of males with a full mutation and, hence, the fragile X syndrome, vary in relation to puberty (Table 2). Prepubertal males tend to have normal growth but large occipitofrontal head circumference (> 50th percentile). Other physical features that are not readily recognizable in the preschool-age child become more obvious with age. These involve the craniofacies (long face, prominent forehead, large ears, and prominent jaw) and genitalia (macro-orchidism), delayed attainment of motor milestones and speech, and abnormal temperament (hyperactivity, hand flapping, hand biting, temper tantrums, and occasionally autism). Behaviors in post-pubertal males with fragile X syndrome often include tactile defensiveness, poor eye contact, and perseverative speech. Ophthalmologic, orthopedic, cardiac, and cutaneous abnormalities also have been noted. The physical and behavioral features seen in males with fragile X syndrome have been reported in females heterozygous for the full mutation, but with lower frequency and with milder involvement.

**Table 2. Clinical Features in Males with Fragile X Syndrome**

<b>Delayed developmental milestones (usual age of attainment for affected boys)</b>	<ul style="list-style-type: none"> <li>• Sit alone (10 months)</li> <li>• Walk (20.6 months)</li> <li>• First clear words (20 months)</li> </ul>
<b>Prepubertal</b>	<ul style="list-style-type: none"> <li>• Developmental delay, especially speech</li> <li>• Abnormal temperament tantrums, hyperactivity, autism</li> <li>• Mental retardation: IQ 30-50</li> <li>• Abnormal craniofacies: long face, prominent forehead, large ears, prominent jaw</li> </ul>
<b>Postpubertal</b>	<ul style="list-style-type: none"> <li>• Macro-orchidism</li> <li>• Abnormal behavior: shyness, gaze aversion</li> <li>• Ophthalmologic: strabismus</li> <li>• Orthopedic: joint hyperextensibility, pes planus</li> </ul>
<b>Other</b>	<ul style="list-style-type: none"> <li>• Cardiac: mitral valve prolapse</li> <li>• Dermatologic: usually soft and smooth skin</li> </ul>

Adapted from [Tarleton and Saul 1993](#)

## Genotype-Phenotype Correlations

The phenotype of males with an *FMR1* mutation is almost entirely dependent on the nature of the mutation; the phenotype of females with an *FMR1* mutation is dependent on both the nature of the *FMR1* mutation and random X-chromosome inactivation (Table 3).

**Table 3. Types of FMR1 Repeat Expansion Mutations**

Mutation Type	Number of CGG Trinucleotide Repeats	Methylation Status of <i>FMR1</i>	Clinical Status	
			Male	Female
<b>Premutation</b> <sup>1</sup>	~ 55 to ~230	Unmethylated	Usually unaffected <sup>2</sup>	Usually unaffected <sup>2</sup>
<b>Full mutation</b>	> 230	Completely methylated	100% affected	~50% affected, ~50% unaffected
<b>Repeat size mosaicism</b>	Varies between premutation and full mutation in different cell lines	Partial: unmethylated in the premutation cell line; methylated in the full mutation cell line	100% affected but may be higher functioning than males with full mutation	Highly variable - ranges from normal intellect to affected
<b>Methylation mosaicism</b>	> 230	Partial: mixture of methylated and unmethylated cell lines	100% affected but may be higher functioning than males with full mutation	Highly variable - ranges from normal intellect to affected
<b>Unmethylated full mutation</b>	> 230	Unmethylated	Nearly all are affected but often have high functioning MR to low normal intellect	Highly variable - ranges from normal intellect to affected

1. Also called "intermediate"

2. There are reports of both males and females with premutations and manifestations of some symptoms of fragile X syndrome [Hagerman et al 1994, Feng et al 1995, Hagerman et al 1996, Franke et al 1996, Riddle et al 1998]. In addition, women with premutations report premature ovarian failure at a higher frequency than found in the general population [Schwartz et al 1994, Partington et al 1996, Uzielli et al 1999, Murray et al 1999, Hundscheid et al 2000].

**Premutation (intermediate allele).** Males and females who have a fragile X premutation have normal intellect and appearance. As noted in Table 3, footnote 2 above, there have been multiple reports of individuals with a premutation and typically subtle intellectual or behavioral symptoms.

**Full mutation.** Males who have a full fragile X mutation generally have moderate to severe mental impairment and may or may not have a distinctive appearance. About 50% of females who have a full fragile X mutation are mentally retarded; however, they are usually less severely affected than males with a full mutation. Conversely, about 50% of females who are heterozygous for the full mutation are intellectually normal. This variability among females is believed to result from the distribution of X chromosome inactivation ratios in the brain.

**Repeat size mosaicism.** Although some data suggest that individuals with mosaicism perform at a higher intellectual level than individuals with completely methylated full mutations [McConkie-Rosell et al 1993], these individuals are, nonetheless, usually mentally retarded. Rarely, patients with methylation mosaicism or completely unmethylated full mutations and normal intellect have been reported [Rousseau et al 1994, Hagerman et al 1994, Smeets 1995]. Mosaicism is present in about 15% to 20% of individuals with *FMR1* mutations. Presumably these individuals produce at least some *FMR1* protein because the *FMR1* gene is unmethylated. The existence of these exceptional patients suggests that repeat expansion and methylation of the gene are not absolutely coupled.

## Prevalence

Prevalence estimates have been revised downward since the isolation of the *FMR1* gene in 1991. Original estimates of 80:100,000 males affected with the syndrome (often still quoted in the fragile X literature) were based on the cytogenetic detection of FRAXA for confirmation of the diagnosis of fragile X syndrome in mentally retarded males. Mentally retarded individuals coincidentally having other chromosomal fragile sites near FRAXA (e.g., FRAXD, FRAXE, and FRAXF) were likely included in these initial estimates. (Cytogenetic differentiation of these fragile sites is difficult because they are located in close proximity in the Xq27-q28 region.) More recent studies using molecular genetic testing of *FMR1* have estimated a prevalence of 16:100,000 to 25:100,000 males affected with the fragile X syndrome (using mental retardation as the hallmark clinical finding) [Murray et al 1996, Turner et al 1996, de Vries et al 1997]. The prevalence of females affected with the syndrome is presumed to be approximately one-half the male prevalence. The prevalence of females who are unaffected fragile X syndrome carriers has been found to be quite high; one study of a French-Canadian population [Rousseau et al 1995] found that 41 of 10,624 women had a premutation in *FMR1* for a prevalence of 1:259 (95% confidence interval 1/373-1/198).

## Differential Diagnosis

The signs of fragile X syndrome in early childhood are nonspecific, with developmental delay being an almost universal manifestation of affected individuals. Any child (male or female) with delay of speech, language, or motor development of unknown etiology should be considered for fragile X testing, especially in the presence of a positive family history of mental retardation, a consistent physical and behavioral phenotype, and absence of structural abnormalities of the brain or other birth defects [Curry et al 1997]. When fragile X molecular genetic testing is used regularly in this large and loosely defined group of unselected males with mental retardation, the yield of positive test results is relatively low - approximately 3-6% [Curry et al 1997].

Conditions to be considered in the differential diagnosis include Sotos' syndrome, Prader-Willi syndrome, autism, and attention deficit-hyperactivity disorder (ADHD). Before molecular genetic testing was available, some patients with fragile X syndrome were incorrectly diagnosed as having Sotos syndrome, based on similarities in craniofacial features. Autistic-like behavior and hyperactivity are frequently found in patients with fragile X syndrome.

**FRAXE.** Mild mental retardation (not as severe as that typically seen in fragile X syndrome) without consistent physical features has been described in males with expanded CCG repeats in the *FMR2* gene at the FRAXE fragile site. FRAXA and FRAXE are distinct fragile sites, albeit in close proximity on the X chromosome. The genes spanning the two fragile sites are designated *FMR1* (FRAXA) and *FMR2* (FRAXE). However, the genes do not have any detectable similarity at the DNA level and the associated clinical entities are discrete [Hamel et al 1994, Mulvey et al 1995]. To find information on laboratory testing for FRAXE syndrome, see [GENETests](#).

## Management

No specific treatment for fragile X syndrome is available. Supportive therapy for children with fragile X syndrome currently consists of [Hagerman 1996a, 1996b]:

- Behavioral techniques to assist with some of the behavioral phenotype
- Pharmacological management of behavioral issues that significantly affect social interaction. No particular pharmacological treatment has been shown to be uniquely beneficial; therapy must be individualized and monitored closely.
- Educational intervention aimed specifically at the known impediments to learning

Parents and teachers of children with fragile X syndrome have recognized the need for individual attention, small class size, and the avoidance of sudden change. More specific guidelines are available through education resources (see [Resources](#)).

## Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal or cultural issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see [GENETests](#). —ED.

### Mode of Inheritance

Fragile X syndrome is inherited in an X-linked dominant manner.

### Risk to Family Members

**Parents of a proband.** The mother of a child with an *FMR1* full mutation (i.e., expansion of >230 trinucleotide repeats) is a carrier of an *FMR1* gene expansion and may be affected. The parent of an unaffected female premutation carrier may be a father who is a premutation carrier (i.e., a "transmitting male") or a mother who is a premutation carrier. The mother of a transmitting male has a premutation allele.

**Sibs of a proband.** The risk to sibs depends upon their gender, the gender of the carrier parent, and the size of the expanded allele in the carrier parent.

#### Offspring of an individual with a full mutation.

- **Males** who inherit the full mutation are expected to have mental retardation and generally do not reproduce.
- **Females** who inherit the full mutation have an approximately 50% risk of mental retardation. Whether or not they have phenotypic manifestations, they have a 50% chance of transmitting the full mutation in each pregnancy.

#### Offspring of an individual with a premutation.

- **Males** who are premutation carriers are considered "transmitting males." The premutation is inherited by all of their daughters and none of their sons. When premutations are transmitted by the father, small increases in trinucleotide repeat number may occur, but these do not result in full mutations. (In actuality, premutations transmitted from father to daughter may often regress slightly in repeat number.) All daughters of transmitting males are unaffected premutation carriers. It is important to remember that the offspring of these daughters who are premutation carriers (i.e., the grandchildren of the transmitting male) are at risk for fragile X syndrome.
- **Females** who are premutation carriers have a 50% risk of transmitting an abnormal (premutation or full mutation allele) in each pregnancy. The risks of a female premutation carrier having affected offspring (with a full mutation) based on premutation size were summarized by [Warren and Nelson \(1994\)](#) and [Nolin et al \(1996\)](#) ([Table 4](#)). While the likelihood for repeat instability increases with the increasing CGG trinucleotide repeat number, the risk percentages in [Table 4](#) should be viewed as approximations because they are derived from a relatively small number of patients and are based solely on the trinucleotide repeat number. Very rarely, regression of trinucleotide repeat number, such as regression of a premutation of 110 repeats in a mother to 44 repeats in her daughter, has been reported [[Vits 1994](#) and others].

**Table 4. Risk that a Mother with a Premutation will have an Affected Child with a Full Mutation**

Number of Maternal Premutation CGG Repeats	Approximate % Risk of Having an Affected Son	Approximate % Risk of Having an Affected Daughter <sup>1</sup>
56-59	7%	3.5%
60-69	10%	5%
70-79	29%	15%
80-89	36%	18%
90-99	47%	24%
>100	50%	25%

Adapted originally from [Warren and Nelson 1994](#); modified according to [Nolin et al 1996](#).

1. Unlike classical X-linked dominant disorders where all females with a mutation are affected, only about 50% of females with a full mutation are mentally retarded. This variability in phenotype is likely to be related to variability in X chromosome inactivation, a phenomenon independent of *FMR1* mutations.

**Other family members of a proband.** The proband's maternal aunts and their offspring may be at risk to be carriers or affected (depending upon their karyotype and family relationship).

**Carrier testing.** Carrier testing of at-risk females is available on a clinical basis and involves determination of the trinucleotide repeat number and the *FMR1* methylation status. (See [Molecular Genetic Testing](#)).

Fragile X syndrome is a trinucleotide repeat disorder that demonstrates anticipation.

### Related Genetic Counseling Issues

The presence of premutation carriers within families leads to pedigrees with generation skipping occurs or seemingly spontaneous occurrences of fragile X syndrome with no previous family history of the disorder.

### Prenatal Testing

Prenatal testing for fetuses at increased risk for *FMR1* full mutations can be performed using DNA extracted from cells obtained by amniocentesis at 16-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation (see [Molecular Genetic Testing](#) and [Guidelines](#)). While the *FMR1* Southern blot patterns for DNA derived from amniocytes are identical to those found in adult tissues, differences in *FMR1* methylation patterns may occur in DNA derived from cells obtained by CVS, making the distinction between large premutations and small full mutations difficult. As a result, for accurate genetic counseling, follow-up amniocentesis or testing using PCR may be necessary to determine the size of the *FMR1* alleles in a methylation-independent manner.

## Molecular Genetics

**Table 5. Molecular Genetics of Fragile X Syndrome**

Gene Symbol	Locus	Normal Gene Product	Genomic Databases
<i>FMR1</i>	Xq27	FMR1 protein	<a href="#">OMIM</a> <a href="#">LocusLink</a> <a href="#">GeneCards</a> <a href="#">GDB</a> <a href="#">GenAtlas</a>

## Molecular Genetic Pathogenesis

Nearly all mutations (>99%) in the *FMR1* gene resulting in fragile X syndrome occur as trinucleotide repeat (CGG) expansion accompanied by aberrant methylation of the gene. Deletions and point mutations in *FMR1* account for the remaining mutations found in patients with the syndrome. Repeat expansion only occurs when a premutation or full mutation is transmitted by females to their offspring. Methylation of the CGG expansion results in decreased or completely absent *FMR1* transcription and the loss of the protein encoded by the gene (FMRP) (see [Abnormal product](#) below).

## Fragile X Syndrome

- **Gene:** [FMR1/FRAXA](#)
- **Abnormal product:** It is evident from patients having deletions in *FMR1* that gene loss resulting in the absence of the protein product causes fragile X syndrome. FMRP is a nucleocytoplasmic shuttling protein which binds several mRNAs, including its own mRNA, forms messenger ribonucleoprotein complexes, and associates with translating ribosomes [[Ceman et al 1999](#)]. While FMRP is expressed in many tissues, it is most abundant in neurons and appears to play a role in structural and functional maturation of synapses [[Weiler and Greenough 1999](#)].
- **Pathologic variants:** Expansion of the CGG repeat copy number beyond about 230, accompanied by hypermethylation of the deoxycytosine residues in the *FMR1* promoter, inhibits or reduces *FMR1* transcription, resulting in the loss of the protein product (FMRP) [[Pieretti et al 1991](#), [Sutcliffe et al 1992](#)] and giving rise to the expression of the cytogenetic fragile site, FRAXA [[Verkerk et al 1991](#), [Oberle et al 1991](#), [Yu 1991](#), [Kremer et al 1991](#)]. It is the loss of FMRP that produces the fragile X syndrome.

Rare patients with deletions of all or part of *FMR1* (reviewed in [Hammond et al 1997](#)) or point mutations in *FMR1* [[De Bouille et al 1993](#), [Lugenbeel et al 1995](#), [Wang et al 1997](#)] have been reported but account for much less than 1% of patients with fragile X syndrome. The existence of patients with deletions has confirmed that the syndrome is due to the lack of *FMR1* expression. Occasionally, a patient is identified who appears to have no cells in which the abnormal methylation events have occurred even when >230 CGG repeats are found. These are usually described as "unmethylated full mutations." Patients having partial methylation of full mutations ("methylation mosaics") also are observed. Cellular mosaicism also occurs in some patients in which premutation and full mutation cell lines are present.

## Gene Involved: *FMR1*

- **Chromosomal locus:** Xq27 [[Verkerk et al 1991](#)]
- **Normal allele:** The *FMR1* gene occupies 38 kilobases of genomic DNA and has 17 exons [[Eichler et al 1993](#)] contained in a messenger RNA of ~4kb [[Verkerk 1991](#)]. A trinucleotide repeat, composed primarily of CGG, is contained in the untranslated portion of exon 1 ending 69 base pairs upstream of the translational start - near the 5' end of the gene [[Ashley et al 1993](#)]. Variation of the repeat copy number ranges in normal (i.e., stable) alleles from 6 to ~54 CGG repeats with a trimodal distribution around 30 repeats with minor peaks around 20 and 40 repeats [[Fu et al 1991](#), [Snow et al 1993](#)]. Alternative splicing of *FMR1* occurs toward the 3' end of the mRNA [[Eichler et al 1993](#), [Ashley et al 1993](#), [Verkerk et al 1993](#)].
- **AGG repeats:** Increase in the number of the CGG trinucleotide repeats contained in the *FMR1* gene occur exclusively during transmission from female carriers (see [Genetic Counseling](#)). The risk of increase in the size of the expansion from maternal alleles varies depending upon the copy number of CGG repeats contained in premutation alleles and the presence of AGG triplets embedded in the CGG repeat segment [[Eichler et al 1994](#), [Kunst and Warren 1994](#)]. In most *FMR1* alleles the sequence of CGG trinucleotide repeats is interrupted by an AGG repeat at repeat 9 or 10 and 19 or 20 (and occasionally repeat 30) [[Eichler et al 1994](#)]. These AGG repeats appear to "anchor" the segment against repeat expansion, probably by disruption of DNA secondary structures that may form during DNA replication. Sequences of uninterrupted CGG repeats beyond the last AGG repeat ("pure CGG trinucleotide repeats") greater than about 33-39 triplets appear to increase the instability of maternal alleles and increase the risk for expansion of the number of trinucleotide repeats upon transmission to offspring [[Eichler et al 1994](#), [Kunst and Warren 1994](#)]. Alleles in the premutation range typically contain long stretches of pure CGG trinucleotide repeats beyond the last AGG triplet. Various alleles containing identical numbers of CGG trinucleotide repeats may have different risks for instability, depending upon the number and location of AGG repeats within the CGG trinucleotide repeat segment.
- **Normal product:** The product of *FMR1* is termed FMRP (FMR1 protein). FMRP is found in the cytoplasm of many cell types but is most abundant in neurons [[Devys et al 1993](#)]. The protein contains two KH binding domains found in other proteins with RNA-binding properties and appears to function as an RNA-binding protein that interacts with a subset of mRNAs [[Devys et al 1993](#), [Verheij et al 1993](#), [Ashley et al 1993](#), [Gibson et al 1993](#), [Siomi et al 1994](#)]. FMRP also contains both a nuclear localization signal and a nuclear export signal. In the cytoplasm, FMRP is usually found associated with poly(A)<sup>+</sup> mRNA in activity-translating polyribosomes and may be an mRNA chaperone from the nucleus to the translational machinery [[Khandjian et al 1996](#), [Corbin et al 1997](#)].

## Resources

GeneClinics provides information about selected national organizations and resources for the benefit of the reader. GeneClinics is not responsible for information provided by other organizations. —ED.

- **National Fragile X Foundation**  
 Newsletter: *The Foundation Quarterly*. Subscriptions through National Fragile X Foundation  
 PO Box 190488  
 San Francisco, CA 94119-0488  
**Phone:** 800-688-8765; 510-763-6030  
**Fax:** 510-763-6223  
**Email:** natlfx@sprintmail.com  
**Web:** [www.nfxf.org](http://www.nfxf.org)
- **FRAXA Research Foundation**  
 Newsletter: *FRAXA Research Foundation Newsletter*. Subscription through FRAXA  
 45 Pleasant St  
 Newburyport, MA 01950  
**Phone:** 978-462-1866  
**Fax:** 978-463-9985  
**Email:** info@fraxa.org  
**Web:** [www.FRAXA.org](http://www.FRAXA.org)
- **NCBI Genes and Disease Webpage**

**Web:** [www.ncbi.nlm.nih.gov/disease/FMR1.html](http://www.ncbi.nlm.nih.gov/disease/FMR1.html)

## References

### Statements and Guidelines Regarding Genetic Testing

- American College of Medical Genetics (1994) [Policy statement](#) on Fragile X syndrome: diagnostic and carrier testing
- National Society of Genetic Counselors (2000) [Recommendations](#): genetic counseling for fragile X syndrome

### Articles on Fragile X Syndrome **MEDLINE**

[About GeneClinics Medline Searches](#)

### Literature Cited

- Ashley CT, Sutcliffe JS, Kunst CB, Leiner HA, Eichler EE, Nelson DL, Warren ST (1993) Human and murine FMR-1: alternative splicing and translational initiation downstream of the CGG-repeat. *Nat Genet* 4:244-51 [[Medline](#)]
- Ceman S, Brown V, Warren ST (1999) Isolation of an FMRP-associated messenger ribonucleoprotein particle and identification of nucleolin and the fragile X-related proteins as components of the complex. *Mol Cell Biol* 19:7925-32 [[Medline](#)]
- Corbin F, Bouillon M, Fortin A, Morin S, Rousseau F, Khandjian EW (1997) The fragile X mental retardation protein is associated with poly(A)<sup>+</sup> mRNA in actively translating polyribosomes. *Hum Mol Genet* 6:1465-72 [[Medline](#)]
- Curry CJ, Stevenson RE, Aughton D, Byrne J, Carey JC, Cassidy S, Cunniff C, Graham JM Jr, Jones MC, Kaback MM, Moeschler J, Schaefer GB, Schwartz S, Tarleton J, Opitz J (1997) Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics. *Am J Med Genet* 72:468-77 [[Medline](#)]
- Das S, Kubota T, Song M, Daniel R, Berry-Kravis EM, Prior TW, Popovich B, Rosser L, Arinami T, Ledbetter DH (1997) Methylation analysis of the fragile X syndrome by PCR. *Genet Test* 1:151-5 [[Medline](#)]
- De Boule K, Verkerk AJ, Reyniers E, Vits L, Hendrickx J, Van Roy B, Van den Bos F, de Graaff E, Oostra BA, Willems PJ (1993) A point mutation in the FMR-1 gene associated with fragile X mental retardation. *Nat Genet* 3:31-5 [[Medline](#)]
- de Vries BB, van den Ouweland AM, Mohkamsing S, Duivenvoorden HJ, Mol E, Gelsema K, van Rijn M, Halley DJ, Sandkuijl LA, Oostra BA, Tibben A, Niermeijer MF (1997) Screening and diagnosis for the fragile X syndrome among the mentally retarded: an epidemiological and psychological survey. Collaborative Fragile X Study Group. *Am J Hum Genet* 61:660-7 [[Medline](#)]
- Devys D, Lutz Y, Rouyer N, Belloq JP, Mandel JL (1993) The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. *Nat Genet* 4:335-40 [[Medline](#)]
- Eichler EE, Holden JJ, Popovich BW, Reiss AL, Snow K, Thibodeau SN, Richards CS, Ward PA, Nelson DL (1994) Length of uninterrupted CGG repeats determines instability in the FMR1 gene. *Nat Genet* 8:88-94 [[Medline](#)]
- Eichler EE, Richards S, Gibbs RA, Nelson DL (1993) Fine structure of the human FMR1 gene [published erratum appears in *Hum Mol Genet* 1994 Apr;3(4):684-5] *Hum Mol Genet* 2:1147-53 [[Medline](#)]
- Feng Y, Zhang F, Lokey LK, Chastain JL, Lakkis L, Eberhart D, Warren ST (1995) Translational suppression by trinucleotide repeat expansion at FMR1. *Science* 268:731-4 [[Medline](#)]
- Franke P, Maier W, Hautzinger M, Weiffenbach O, Gansicke M, Iwers B, Poustka F, Schwab SG, Froster U (1996) Fragile-X carrier females: evidence for a distinct psychopathological phenotype? *Am J Med Genet* 64:334-9 [[Medline](#)]
- Fu YH, Kuhl DP, Pizzuti A, Pieretti M, Sutcliffe JS, Richards S, Verkerk AJ, Holden JJ, Fenwick RG Jr, Warren ST, et al (1991) Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. *Cell* 67:1047-58 [[Medline](#)]
- Gibson TJ, Rice PM, Thompson JD, Heringa J (1993) KH domains within the FMR1 sequence suggest that fragile X syndrome stems from a defect in RNA metabolism. *Trends Biochem Sci* 18:331-3 [[Medline](#)]
- Hagerman RJ, Hull CE, Safanda JF, Carpenter I, Staley LW, O'Connor RA, Seydel C, Mazzocco MM, Snow K, Thibodeau SN, et al (1994) High functioning fragile X males: demonstration of an unmethylated fully expanded FMR-1 mutation associated with protein expression. *Am J Med Genet* 51:298-308 [[Medline](#)]
- Hagerman RJ, Staley LW, O'Conner R, Lugenbeel K, Nelson D, McLean SD, Taylor A (1996) Learning-disabled males with a fragile X CGG expansion in the upper premutation size range. *Pediatrics* 97:122-6 [[Medline](#)]
- Hagerman RJ (1996a): Medical follow-up and pharmacotherapy. In: Hagerman RJ and Cronister A (eds) *Fragile X Syndrome: Diagnosis, Treatment and Research*, 2 ed. The Johns Hopkins University Press, Baltimore, pp 283-331
- Hagerman RJ (1996b): Physical and behavioral phenotype. In: Hagerman RJ and Cronister A (eds) *Fragile X Syndrome: Diagnosis, Treatment and Research*, 2 ed. The Johns Hopkins University Press, Baltimore, pp 3-87
- Hamel BC, Smits AP, de Graaff E, Smeets DF, Schoute F, Eussen BH, Knight SJ, Davies KE, Assman-Hulsmans CF, Oostra BA (1994) Segregation of FRAXE in a large family: clinical, psychometric, cytogenetic, and molecular data. *Am J Hum Genet* 55:923-31 [[Medline](#)]
- Hammond LS, Macias MM, Tarleton JC, Shashidhar Pai G (1997) Fragile X syndrome and deletions in FMR1: new case and review of the literature. *Am J Med Genet* 72:430-4 [[Medline](#)]
- Hundscheid RD, Sistermans EA, Thomas CM, Braat DD, Straatman H, Kiemeny LA, Oostra BA, Smits AP (2000) Imprinting effect in premature ovarian failure confined to paternally inherited fragile X premutations. *Am J Hum Genet* 66:413-8 [[Medline](#)]
- Khandjian EW, Corbin F, Woerly S, Rousseau F (1996) The fragile X mental retardation protein is associated with ribosomes. *Nat Genet* 12:91-3 [[Medline](#)]
- Kremer EJ, Pritchard M, Lynch M, Yu S, Holman K, Baker E, Warren ST, Schlessinger D, Sutherland GR, Richards RI (1991) Mapping of DNA instability at the fragile X to a trinucleotide repeat sequence p(CCG)<sub>n</sub>. *Science* 252:1711-4 [[Medline](#)]

- Kunst CB & Warren ST (1994) Cryptic and polar variation of the fragile X repeat could result in predisposing normal alleles. *Cell* 77:853-61 [[Medline](#)]
- Lugenbeel KA, Peier AM, Carson NL, Chudley AE, Nelson DL (1995) Intragenic loss of function mutations demonstrate the primary role of FMR1 in fragile X syndrome. *Nat Genet* 10:483-5 [[Medline](#)]
- McConkie-Rosell A, Lachiewicz AM, Spiridigliozzi GA, Tarleton J, Schoenwald S, Phelan MC, Goonewardena P, Ding X, Brown WT (1993) Evidence that methylation of the FMR-1 locus is responsible for variable phenotypic expression of the fragile X syndrome. *Am J Hum Genet* 53:800-9 [[Medline](#)]
- Martin JP and Bell J (1943) A pedigree of mental defect showing sex-linkage. *J Neurol Psychiatry* 6: 151-4
- Mulley JC, Yu S, Loesch DZ, Hay DA, Donnelly A, Gedeon AK, Carbonell P, Lopez I, Glover G, Gabarron I, et al (1995) FRAXE and mental retardation. *J Med Genet* 32:162-9 [[Medline](#)]
- Murray A, Webb J, MacSwiney F, Shipley EL, Morton NE, Conway GS (1999) Serum concentrations of follicle stimulating hormone may predict premature ovarian failure in FRAXA premutation women. *Hum Reprod* 14: 1217-8 [[Medline](#)]
- Murray A, Youings S, Dennis N, Latsky L, Linehan P, McKechnie N, Macpherson J, Pound M, Jacobs P (1996) Population screening at the FRAXA and FRAXE loci: molecular analyses of boys with learning difficulties and their mothers. *Hum Mol Genet* 5: 727-35 [[Medline](#)]
- Nolin SL, Lewis FA 3rd, Ye LL, Houck GE Jr, Glicksman AE, Limprasert P, Li SY, Zhong N, Ashley AE, Feingold E, Sherman SL, Brown WT (1996) Familial transmission of the FMR1 CGG repeat. *Am J Hum Genet* 59: 1252-61 [[Medline](#)]
- Oberle I, Rousseau F, Heitz D, Kretz C, Devys D, Hanauer A, Boue J, Bertheas MF, Mandel JL (1991) Instability of a 550-base pair DNA segment and abnormal methylation in fragile X syndrome. *Science* 252:1097-102 [[Medline](#)]
- Orrico A, Galli L, Dotti MT, Plewnia K, Censini S, Federico A (1998) Mosaicism for full mutation and normal-sized allele of the FMR1 gene: a new case. *Am J Med Genet* 78:341-4 [[Medline](#)]
- Partington MW, Moore DY, Turner GM (1996) Confirmation of early menopause in fragile X carriers. *Am J Med Genet* 64:370-2 [[Medline](#)]
- Pieretti M, Zhang FP, Fu YH, Warren ST, Oostra BA, Caskey CT, Nelson DL (1991) Absence of expression of the FMR-1 gene in fragile X syndrome. *Cell* 66:817-22 [[Medline](#)]
- Riddle JE, Cheema A, Sobesky WE, Gardner SC, Taylor AK, Pennington BF, Hagerman RJ (1998) Phenotypic involvement in females with the FMR1 gene mutation. *Am J Ment Retard* 102:590-601 [[Medline](#)]
- Rousseau F, Heitz D, Biancalana V, Blumenfeld S, Kretz C, Boue J, Tommerup N, Van Der Hagen C, DeLozier-Blanchet C, Croquette MF, et al (1991) Direct diagnosis by DNA analysis of the fragile X syndrome of mental retardation *N Engl J Med* 325:1673-81 [[Medline](#)]
- Rousseau F, Robb LJ, Rouillard P, Der Kaloustian VM (1994) No mental retardation in a man with 40% abnormal methylation at the FMR-1 locus and transmission of sperm cell mutations as premutations. *Hum Mol Genet* 3:927-30 [[Medline](#)]
- Rousseau F, Rouillard P, Morel ML, Khandjian EW, Morgan K (1995) Prevalence of carriers of premutation-size alleles of the FMR1 gene-- and implications for the population genetics of the fragile X syndrome *Am J Hum Genet* 57: 1006-18 [[Medline](#)]
- Schmucker B & Seidel J (1999) Mosaicism for a full mutation and a normal size allele in two fragile X males. *Am J Med Genet* 84:221-5 [[Medline](#)]
- Schwartz CE, Dean J, Howard-Peebles PN, Bugge M, Mikkelsen M, Tommerup N, Hull C, Hagerman R, Holden JJ, Stevenson RE (1994) Obstetrical and gynecological complications in fragile X carriers: a multicenter study. *Am J Med Genet* 51:400-2 [[Medline](#)]
- Siomi H, Choi M, Siomi MC, Nussbaum RL, Dreyfuss G (1994) Essential role for KH domains in RNA binding: impaired RNA binding by a mutation in the KH domain of FMR1 that causes fragile X syndrome. *Cell* 77:33-9 [[Medline](#)]
- Smeets HJ, Smits AP, Verheij CE, Theelen JP, Willemsen R, van de Burgt I, Hoogeveen AT, Oosterwijk JC, Oostra BA (1995) Normal phenotype in two brothers with a full FMR1 mutation. *Hum Mol Genet* 4:2103-8 [[Medline](#)]
- Snow K, Doud LK, Hagerman R, Pergolizzi RG, Erster SH, Thibodeau SN (1993) Analysis of a CGG sequence at the FMR-1 locus in fragile X families and in the general population. *Am J Hum Genet* 53: 1217-28 [[Medline](#)]
- Sutcliffe JS, Nelson DL, Zhang F, Pieretti M, Caskey CT, Saxe D, Warren ST (1992) DNA methylation represses FMR-1 transcription in fragile X syndrome. *Hum Mol Genet* 1:397-400 [[Medline](#)]
- Tarleton JC & Saul RA (1993) Molecular genetic advances in fragile X syndrome. *J Pediatr* 122:169-85 [[Medline](#)]
- Tassone F, Hagerman RJ, Ikle DN, Dyer PN, Lampe M, Willemsen R, Oostra BA, Taylor AK (1999) FMRP expression as a potential prognostic indicator in fragile X syndrome. *Am J Med Genet* 84:250-61 [[Medline](#)]
- Turner G, Webb T, Wake S, Robinson H (1996) Prevalence of fragile X syndrome. *Am J Med Genet* 64:196-7 [[Medline](#)]
- Uzielli ML, Guarducci S, Lapi E, Cecconi A, Ricci U, Ricotti G, Biondi C, Scarselli B, Vieri F, Scarnato P, Gori F, Sereni A (1999) Premature ovarian failure (POF) and fragile X premutation females: from POF to fragile X carrier identification, from fragile X carrier diagnosis to POF association data. *Am J Med Genet* 84:300-3 [[Medline](#)]
- Verheij C, Bakker CE, de Graaff E, Keulemans J, Willemsen R, Verkerk AJ, Galjaard H, Reuser AJ, Hoogeveen AT, Oostra BA (1993) Characterization and localization of the FMR-1 gene product associated with fragile X syndrome. *Nature* 363:722-4 [[Medline](#)]
- Verkerk AJ, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DP, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang FP, et al (1991) Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell* 65:905-14 [[Medline](#)]
- Verkerk AJ, de Graaff E, De Boule K, Eichler EE, Konecki DS, Reyniers E, Manca A, Poustka A, Willems PJ, Nelson DL, et al (1993) Alternative splicing in the fragile X gene FMR1 [published erratum appears in *Hum Mol Genet* 1993 Aug;2(8):1348] *Hum Mol Genet* 2:399-404 [[Medline](#)]
- Vits L, De Boule K, Reyniers E, Handig I, Darby JK, Oostra B, Willems PJ (1994) Apparent regression of the CGG repeat in FMR1 to an allele of normal size. *Hum Genet* 94:523-6 [[Medline](#)]
- Wang YC, Lin ML, Lin SJ, Li YC, Li SY (1997) Novel point mutation within intron 10 of FMR-1 gene causing fragile X syndrome *Hum Mutat* 10:393-9 [[Medline](#)]
- Warren ST & Nelson DL (1994) Advances in molecular analysis of fragile X syndrome *JAMA* 271:536-42 [[Medline](#)]
- Weiler IJ & Greenough WT (1999) Synaptic synthesis of the Fragile X protein: possible involvement in synapse maturation and elimination. *Am J Med Genet* 83:248-52 [[Medline](#)]

- Willemsen R, Smits A, Mohkamsing S, van Beerendonk H, de Haan A, de Vries B, van den Ouweland A, Sijm A, Galjaard H, Oostra BA (1997) Rapid antibody test for diagnosing fragile X syndrome: a validation of the technique. *Hum Genet* 99:308-11 [[Medline](#)]
- Yu S, Pritchard M, Kremer E, Lynch M, Nancarrow J, Baker E, Holman K, Mulley JC, Warren ST, Schlessinger D, et al (1991) Fragile X genotype characterized by an unstable region of DNA. *Science* 252:1179-81 [[Medline](#)]

## Profile History

### Authors

Jack Tarleton, PhD [MEDLINE](#)  
Fullerton Genetics Center, Mission St. Joseph's Health System, Asheville, NC

Robert A Saul, MD [MEDLINE](#)  
Greenwood Genetic Center, Greenwood, SC

[About GeneClinics Medline Searches](#)

### Last Update/Revision

26 May 2000

### Revision History

- 26 May 2000 (CA) Editorial updates entered
- 07 Apr 2000 (CA) Author updates entered
- 31 Mar 2000 (JT & RS) Author updates submitted
- 15 Feb 2000 (CA) Initial editorial updates entered
- 16 Jun 1998 (PB) Author edits
- 25 Feb 1998 (JT & RS) Revision submitted
- May 1996 (JT & RS) Original version

---

**Copyright© 2001, University of Washington, Seattle**  
**[All Rights Reserved](#)**

---

**Funded by** [National Library of Medicine](#), [National Human Genome Research Institute](#), [National Cancer Institute](#), and [Office of Rare Diseases](#) of the NIH

**Administrative support from** [University of Washington](#), Seattle