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Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

FMR1-Related Disorders

Robert A Saul, MD, FACMG
Greenwood Genetics Center
Greenwood, SC
rsaul@ggc.org

Jack C Tarleton, PhD, FACMG
Fullerton Genetics Center
Asheville, NC
jack.tarleton@msj.org

Initial Posting: June 16, 1998.
Last Revision: August 5, 2008.

Summary

Disease characteristics. *FMR1*-related disorders include fragile X syndrome, fragile X-associated tremor/ataxia syndrome (FXTAS), and *FMR1*-related premature ovarian failure (POF). Fragile X syndrome occurs in individuals with an *FMR1* full mutation and is nearly always characterized by moderate mental retardation in affected males and mild mental retardation in affected females. Because *FMR1* mutations are complex alterations involving nonclassic gene-disrupting alterations (trinucleotide repeat expansion) and abnormal gene methylation, affected individuals occasionally have an atypical presentation with an IQ above 70, the traditional demarcation denoting mental retardation. Males with an *FMR1* full mutation accompanied by aberrant methylation may have a characteristic appearance (large head, long face, prominent forehead and chin, protruding ears), connective tissue findings (joint laxity), and large testes after puberty. Behavioral abnormalities, sometimes including autism spectrum disorder, are common. FXTAS occurs in males who have an *FMR1* premutation and is characterized by late-onset, progressive cerebellar ataxia and intention tremor. *FMR1*-related POF (age at cessation of menses <40 years) occurs in approximately 20% of females who have an *FMR1* premutation.

Diagnosis/testing. The diagnosis of *FMR1*-related disorders rests on the detection of an alteration in the *FMR1* gene. More than 99% of individuals with fragile X syndrome have a loss-of-function mutation in the *FMR1* gene caused by an increased number of CGG trinucleotide repeats (typically >200) accompanied by aberrant methylation of the *FMR1* gene. Other mutations within *FMR1* that cause fragile X syndrome include deletions, point mutations that disrupt RNA splicing, and a missense mutation. All individuals with FXTAS have *FMR1* premutation trinucleotide repeats ranging from 59 to approximately 200. Females with *FMR1*-related POF have *FMR1* trinucleotide repeats from high normal (35 repeats) into the premutation range. Both increased trinucleotide repeats and methylation changes in *FMR1* can be detected by clinically available molecular genetic testing.

Management. *Treatment of manifestations:* Fragile X syndrome: early developmental intervention, special education (individual attention, small class size, and avoiding sudden change and excessive stimulation), and vocational training; individualized pharmacologic management of behavioral issues that significantly affect social interaction; routine treatment of medical problems. FXTAS: supportive care for gait disturbance and/or cognitive deficits. POF: reproductive endocrine evaluation for treatment and counseling for reproductive options. *Agents/circumstances to avoid:* folic acid in individuals with poorly controlled seizures.

Genetic counseling. All mothers of individuals with an *FMR1* full mutation (expansion >200 CGG trinucleotide repeats) are carriers of an *FMR1* gene expansion. They and their family members are at increased risk of having offspring with fragile X syndrome and FXTAS. Males with FXTAS will transmit their *FMR1* premutation expansion to none of their sons and to all of their daughters, who will be premutation carriers. Carrier testing and prenatal testing are possible for pregnancies at increased risk if the diagnosis of an *FMR1*-related disorder has been confirmed in a family member.

Diagnosis

Clinical Diagnosis

Fragile X syndrome. A definite diagnosis of fragile X syndrome requires the presence of a loss-of-function mutation in *FMR1*, usually in a male with moderate mental retardation or a female with mild mental retardation.

Note: Because *FMR1* mutations are complex alterations involving nonclassic gene-disrupting alterations (trinucleotide repeat expansion) and abnormal gene methylation, affected individuals occasionally have an atypical presentation with an IQ above 70, the traditional demarcation denoting mental retardation.

Affected individuals have normal growth and stature and no associated malformations.

Fragile X-associated tremor/ataxia syndrome (FXTAS)

- **A definite diagnosis of FXTAS** requires the presence of a premutation in *FMR1* and white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem (the major neuroradiologic sign) with either intention tremor or gait ataxia (the two major clinical signs).

  Other minor neuroradiologic criteria include MRI white matter lesions in the cerebral white matter or moderate to generalized atrophy.

  Other minor clinical criteria include parkinsonism, moderate to severe working memory deficits, or executive cognitive function deficits.
- **A probable diagnosis of FXTAS** requires either one major neuroradiologic sign and one minor clinical sign or two major clinical signs.
- **A possible diagnosis of FXTAS** is based on one minor neuroradiologic sign and one major clinical sign [Grigsby et al 2005].

***FMR1*-related premature ovarian failure (POF).** *FMR1*-related POF is defined as cessation of menses before age 40 years in a woman with an *FMR1* premutation.

Testing

Chromosome analysis. Chromosome analysis using modified culture techniques to induce fragile sites is no longer used for diagnosis of fragile X syndrome because it is less sensitive and more costly than molecular genetic testing (see Molecular Genetic Testing).

Protein testing. Although protein testing is not performed routinely in most clinical laboratory settings, a few laboratories provide assays measuring the production of the product of *FMR1*, fragile X mental retardation 1 protein (FMRP) [Willemsen et al 1997]. See Testing.

Situations in which FMRP testing may be useful include screening of mentally retarded populations and characterization of cellular production of FMRP in individuals having unusual phenotypes. Because severity of the fragile X syndrome phenotype appears to correlate with

FMRP expression, assessment of FMRP production in some affected individuals has been proposed as a potential prognostic indicator of disease severity [Tassone et al 1999].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *FMR1* is the only gene known to be associated with *FMR1*-related disorders.

Allele sizes. *FMR1* alleles are categorized according to the trinucleotide repeat number contained in exon 1 and the methylation status of the repeat region. However, the distinction between allele categories is not absolute and must be made by considering both family history and repeat instability. The boundary between intermediate and premutation categories listed below differs slightly from the American College of Medical Genetics (ACMG) guidelines for diagnostic and carrier testing [Sherman et al 2005]. The ACMG guidelines describe the intermediate range as 41-60 repeats and the premutation range as 61-200 repeats, but state that "the definitions of premutation and intermediate alleles are blurred." The demarcation used here is based on there being no reports of maternal alleles and fewer than 59 repeats transmitted from mother to offspring who have fragile X syndrome. In support of the categorization used here, recent data describing the *FMR1* testing experience from a large commercial laboratory found no expansions of alleles containing fewer than 59 repeats during a single meiosis and suggested that the upper end of the intermediate or "gray zone" could be expanded to 58 repeats [Strom et al 2007].

- **Normal alleles:** Approximately 5-40 repeats
  - Alleles of this size are stably transmitted without any increase or decrease in repeat number.

    In stable normal alleles, the CGG region is interrupted by an AGG triplet after every nine or ten CGG repeats. These AGG triplets are believed to maintain repeat integrity by preventing DNA strand slippage during replication. (See Molecular Genetic Pathogenesis for a more complete discussion of pure repeats.)
  - Normal alleles with more than 35 CGG repeats are associated with increased risk of POF (see *FMR1*-related premature ovarian failure).
- **Mutable normal alleles**
  - **Intermediate alleles (also termed "gray zone"):** No consensus exists regarding the precise size of intermediate alleles, but it may be broadly defined as 41-58 repeats. Historically, the largest repeat included in the intermediate range has been 54; however, the intermediate range may extend slightly higher as no transmission of alleles with 58 or fewer repeats is known to have resulted in an affected individual to date.

    Note: (1) Because most clinical testing laboratories state that repeat measurements are plus or minus two to three repeats, it may be wise to consider reported test results with 55-58 repeats as potential premutations. (2) The risk for instability of alleles with 41-49 repeats when transmitted from mother to child is minimal. Any changes in repeat number are typically

very small (±1 or 2 repeats). (3) The frequency and magnitude of repeat instability increases with alleles containing more than 50 repeats [Sherman 2005]. (4) Nolin et al (2003) reported two instances of maternal transmission of 59-repeat alleles producing offspring with full mutations; 59 is the smallest repeat known to expand to full mutation in a single transmission. (5) An important predictor of repeat instability in large intermediate alleles (>50 repeats) is the number of "pure" CGG repeats without interrupting AGG repeats. Increasingly longer pure repeats, especially those with more than 35 uninterrupted CGG repeats, are more likely to become unstable [Eichler et al 1994].

- **Premutation alleles:** Approximately 59-200 repeats. Alleles of this size are not associated with mental retardation but do convey increased risk for FXTAS and POF. Because of potential repeat instability upon transmission of premutation alleles, women with alleles in this range are considered to be at risk of having children affected with fragile X syndrome.

  Note: The upper limit of the premutation range is sometimes noted as approximately 230. Both numbers (200 and 230) are estimates derived from Southern blot analysis, in which repeat size can only be roughly estimated.

- **Full mutation alleles:** More than 200 repeats, with several hundred to several thousand repeats being typical. Aberrant hypermethylation of the *FMR1* promoter region typically occurs in alleles in which the number of CGG repeats exceeds approximately 200.

Clinical testing

- **Targeted mutation analysis**
  - **Polymerase chain reaction (PCR)** specific for the trinucleotide repeat region of *FMR1* has high sensitivity for *FMR1* repeats in the normal and lower premutation range (≤100 to 120 repeats) (see Table 3).

    Note: (1) While the PCR assay alone yields accurate estimates of many *FMR1* allele sizes, it may fail to detect alleles in the upper premutation range and full mutation alleles with a high repeat number. (2) When PCR of the *FMR1* repeat segment reveals a normal or premutation allele in males, or two alleles of different size within the normal, intermediate, or premutation range in females, further testing may not be indicated. (3) PCR analysis of rare individuals who have cellular mosaicism for the *FMR1* repeat may give a false negative result. In cellular mosaicism, PCR detects alleles in the normal, intermediate, or low premutation ranges but fails to detect alleles in the high premutation or full mutation range [Orrico et al 1998, Schmucker & Seidel 1999]. Southern blot analysis detects these complex alterations in most cases.
  - **Southern blot analysis** detects all *FMR1* alleles including normal, larger-sized premutations, and full mutations, allowing a low-resolution estimation of trinucleotide repeat number. PCR analysis can then be used to obtain a more precise repeat estimate of normal and smaller premutation alleles.
- **Methylation status.** Southern blot analysis may be used to determine the methylation status of the *FMR1* promoter. PCR techniques that determine methylation status ("methylation PCR") have been developed in several clinical laboratories and may offer a more rapid test turnaround time [Das et al 1997, Weinhausel & Haas 2001].

- **Sequence analysis.** More than 99% of *FMR1* mutations detected in individuals with fragile X syndrome are repeat expansions. Although *FMR1* would be expected to have a mutation rate similar to other genes, there is a surprising paucity of reports of individuals with point mutations or other small alterations in *FNMR1* resulting in fragile X syndrome. To address the possibility that there may be a small subset of undetected individuals with fragile X syndrome who have rare intragenic mutations, a few clinical laboratories offer DNA sequence analysis of the *FMR1* promoter region and the 17 coding exons and flanking intronic regions.

  Note: (1) Small exonic deletions/duplications, insertions, and intragenic inversions can also be detected by sequence analysis. (2) Sequence analysis may fail to detect *FMR1* deletions of an entire allele in females.

- **Deletion analysis.** Deletions are typically detected in *FMR1* as a secondary finding when the trinucleotide repeat region is being interrogated by Southern blot analysis. Therefore, it is likely that *FMR1* deletions downstream of the repeat region, as well as other gene rearrangements, are underascertained. Nevertheless, both small deletions near the repeat region in exon 1 and large-scale deletions that completely remove *FMR1* continue to be reported regularly in the literature.

- **FISH analysis.** Fewer than 1% of individuals with fragile X syndrome have a partial or full deletion of the FMR1 gene (reviewed in Hammond et al 1997). Deletions not located in the repeat region of the gene may be missed on routine clinical testing for the trinucleotide repeat expansion; FISH may detect such deletions.

- **X-chromosome inactivation.** Although not routinely performed, DNA testing for nonrandom X-chromosome inactivation may be useful in evaluating females who have a full mutation. Random X-chromosome inactivation in a female predicts a 50:50 ratio of cells inactivating the maternally derived X chromosome and cells inactivating the paternally derived X chromosome. However, population studies find a distribution of ratios. Typically, a greater-than 90:10 ratio indicates unusual skewing of the X-chromosome inactivation ratio. In females who have an *FMR1* full mutation, nonrandom X-chromosome inactivation may result in more or less FMRP production with a resulting effect on the severity of the phenotype.

  FMRP assessment by immunohistochemical staining of a lymphocyte smear may be used as an indicator of X-chromosome inactivation ratios. Cells in which the active X chromosome has a full *FMR1* mutation should produce FMRP. In addition, FMRP assessment may be useful to determine protein production in males with methylation mosaicism, point mutations, or other mutation types that may not completely inactivate *FMR1*. An important caveat to X-chromosome inactivation studies is that such testing is typically performed using lymphocytes rather than brain tissues, where the mental and behavioral phenotype is manifested.

Research testing. 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.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *FMR1*-Related Disorders

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Targeted mutation analysis	**PCR.** CGG expansion in *FMR1* (allele sizes in the normal and lower premutation range)	>99%	Clinical Testing
	Southern blot. CGG expansion in *FMR1* (all repeat ranges); methylation status		
Sequence analysis	*FMR1* sequence variants	<1%	
FISH	Large (partial or whole-gene) *FMR1* deletions	<1%	
Deletion analysis [1]	• Large (partial or whole-gene) *FMR1* deletions	<1%	

1. Testing that identifies duplications/deletions not detectable by sequence analysis of genomic DNA; a variety of methods (e.g., quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification [MLPA], array CGH [see Testing]) may be used.

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- If the clinical phenotype is very consistent with fragile X syndrome and blood analysis is normal, testing of a second tissue type (e.g., skin fibroblasts) should be considered [MacKenzie et al 2006].

Testing Strategy

Establishing the diagnosis in a proband. Molecular genetic testing is appropriate for the following (see Figure 1):

- 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 who have a cytogenetic fragile X test result that is discordant with their phenotype, including (a) those who have a strong clinical indication (including risk of being a carrier) and who have had a negative or ambiguous cytogenetic test result and (b) those with an atypical phenotype who have had a positive cytogenetic test result

  Note: Chromosome analysis using modified culture techniques to induce fragile sites is no longer used for diagnosis of fragile X syndrome because it is less sensitive and more costly than molecular genetic testing.
- Males and females older than age 50 years who have progressive cerebellar ataxia and intention tremor with a positive family history of *FMR1*-related disorders in whom other common causes of ataxia have been excluded (see Ataxia Overview)
- Women with unexplained POF [Corrigan et al 2005]

Testing algorithm (see Figure 1):

Clarification of the genetic status of women seeking reproductive counseling who have a family history of *FMR1*-related disorders requires prior confirmation of the presence of an expanded (or altered) *FMR1* allele in the family or the presence of undiagnosed mental retardation.

Prenatal diagnosis for at-risk pregnancies requires prior confirmation of the presence of an expanded (or altered) *FMR1* allele in the family.

Note: Results from chorionic villus sampling (CVS) testing must be interpreted with caution because often the methylation status of *FMR1* is 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.

Preimplantation genetic diagnosis (PGD) for at-risk pregnancies requires prior confirmation of the presence of an expanded (or altered) *FMR1* allele in the family.

Genetically Related (Allelic) Disorders

No phenotypes other than fragile X syndrome, FXTAS, and POF are known to be associated with mutations in *FMR1*.

However, preliminary studies of the correlation of *FMR1* allele size variations in the normal and premutation range suggest a possible relationship to mild cognitive impairment in females [Allen et al 2005] and males [Loat et al 2006]. Varied results [Ennis, Murray et al 2006] demonstrate the need for further research.

A male with complex *FMR1* mosaicism (full mutation, premutation, and deletion) with only learning disability [Han et al 2006] also raises issues concerning gene and protein expression in *FMR1*-related phenotypes.

Clinical Description

Natural History

Males with full mutation alleles (fragile X syndrome). The phenotypic features of males with a full mutation and, hence, the fragile X syndrome, vary in relation to puberty (see below, Clinical Features in Males with Fragile X Syndrome).

Prepubertal males tend to have normal growth but large occipitofrontal head circumference (>50th percentile). Hypotonia, gastroesophageal reflux, and recurrent otitis media are problems in infancy that require medical attention [Hagerman & Hagerman 2002]. Other physical features 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 postpubertal males with fragile X syndrome often include tactile defensiveness, poor eye contact, perseverative speech, problems in impulse control, and distractibility. The behaviors tend to become more obvious over time. The comorbid diagnosis of autism occurs in nearly 25% of affected individuals [Hatton et al 2006].

Note: Recent evidence suggests an increased risk of autism spectrum disorder and/or attention deficit disorder in premutation carriers as well [Farzin et al 2006].

Ophthalmologic (strabismus), orthopedic (joint laxity), cardiac (mitral valve prolapse), and cutaneous (excess softness and smoothness) abnormalities have also been noted. Except for the strabismus, these issues typically do not require significant intervention.

Periventricular heteropia and other neuroradiologic abnormalities [Moro et al 2006] are consistent with abnormal neuronal migration and development suggested by the metabotropic

glutamate receptor (mGluR) theory of fragile X mental retardation (see Molecular Genetic Pathogenesis).

Clinical Features in Males with Fragile X Syndrome (adapted from Tarleton & Saul 1993)

Delayed developmental milestones (*)

- Sit alone (10 months)
- Walk (20.6 months)
- First clear words (20 months)

* = usual age of attainment for affected boys

Prepubertal features

- Developmental delay, especially speech
- Abnormal temperament: tantrums, hyperactivity, autism
- Mental retardation: IQ 30-50
- Abnormal craniofacies: long face, prominent forehead, large ears, prominent jaw

Postpubertal features

- Macro-orchidism
- Abnormal behavior: shyness, gaze aversion
- Ophthalmologic: strabismus
- Orthopedic: joint hyperextensibility, pes planus

Other features

- Cardiac: mitral valve prolapse
- Dermatologic: usually soft and smooth skin

Females heterozygous for full mutation alleles (fragile X syndrome). 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 milder involvement.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is characterized by late-onset progressive cerebellar ataxia and intention tremor in persons who have an *FMR1* premutation [Jacquemont et al 2004, Jacquemont et al 2006]. Other neurologic findings include short-term memory loss, executive function deficits, cognitive decline, dementia, parkinsonism, peripheral neuropathy, lower-limb proximal muscle weakness, and autonomic dysfunction [Loesch et al 2005, Bacalman et al 2006, Grigsby et al 2006, Louis et al 2006].

Both males and females with a premutation are at increased risk for FXTAS. The prevalence of FXTAS is estimated at 40% overall for males with premutations who are over age 50 years [Grigsby et al 2005]. Penetrance in males is age related (see Table 2).

Table 2. Risk of FXTAS by Age in Males with an *FMR1* Premutation

Age in Years	Risk
50-59	17%
60-69	38%
70-79	47%
≥80	75%

Although the precise risk for females has not yet been defined, it appears to be lower than that for males [Hagerman et al 2004, Biancalana et al 2005].

A retrospective longitudinal review of 55 males with premutations provides early natural history information of FXTAS [Leehey et al 2007]. The first sign to appear is usually tremor at approximately age 60 years. Ataxia tends to develop two years later, leading to increased tendency to fall and subsequent dependence on walking aids. Life expectancy after onset of symptoms ranged from five to 25 years.

Neuroradiologic signs (decreased cerebellar volume, increased ventricular volume, increased white matter hyperdensity) appear to correlate with premutation CGG repeat length [Cohen et al 2006].

***FMR1*-related premature ovarian failure (POF),** defined as cessation of menses before age 40 years, has been observed in carriers of premutation alleles [Murray et al 1999, Uzielli et al 1999, Hundscheid et al 2000, Bussani et al 2004, Machado-Ferreira et al 2004]. Ovarian failure has occurred as early as age 11 years. The diagnosis of POF does not eliminate the possibility of subsequent conception. A premutation carrier woman had a child with fragile X syndrome after her diagnosis with POF [Corrigan et al 2005, Nelson et al 2005]. It is estimated that 5%-10% of women may conceive after the diagnosis of POF is established [Nelson et al 2005].

An increased risk for POF and *FMR1* alleles containing trinucleotide repeats in the high normal (≥35 repeats) and intermediate ranges has been reported [Bretherick et al 2005, Bodega et al 2006]. Currently, no consensus exists for estimating an absolute risk for POF when a woman has high normal or intermediate repeat alleles. Sherman (2005) concluded that the risk for POF was 21% (estimates ranged from 15% to 27% in various studies) in premutation carriers, compared to a 1% background risk. In this review an odds ratio of 2.5 was estimated for intermediate repeat sizes of 41-58 [Wittenberger et al 2007]. (See Genotype-Phenotype Correlations, Premutation for additional risk estimates.)

Sullivan et al (2005) suggest that variation in the age at menopause in the general population might be related to *FMR1* CGG repeat size of less than 80, a finding further supported by data from Ennis, Ward et al (2006). A significant increase of alleles in the 35 to 54 range was found in women with POF [Bretherick et al 2005]. In all three studies, larger premutations (>80 CGG repeats) carried lower risk for POF.

Women with full mutation alleles are not at increased risk for POF.

Genotype-Phenotype Correlations

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

Table 3. Types of *FMR1* Repeat Expansion Mutations

Mutation Type	Number of CGG Trinucleotide Repeats	Methylation Status of *FMR1*	Clinical Status	
			Male	Female
Premutation	~59 to ~200	Unmethylated	At risk for FXTAS [1]	At risk for POF and FXTAS
Full mutation	>200	Completely methylated	100% with MR	~50% with MR, ~50% normal intellect
Repeat size mosaicism	Varies between premutation and full mutation in different cell lines	Partial: unmethylated in the premutation cell line; methylated in the full mutation cell line	Nearly 100% affected with MR; may be higher functioning [2] than males with full mutation	Highly variable: ranges from normal intellect to affected
Methylation mosaicism	>200	Partial: mixture of methylated and unmethylated cell lines		
Unmethylated full mutation	>200	Unmethylated	Nearly all have MR but often have high-functioning MR to low-normal intellect	

MR = mental retardation

1. Both males and females with premutations and manifestations of some symptoms of fragile X syndrome have been reported [Riddle et al 1998].

2. *FMR1* mutations are complex alterations involving nonclassic gene-disrupting alterations (trinucleotide repeat expansion) and abnormal gene methylation. This complexity at the gene level affects production of the FMR1 protein and may result in an atypical presentation in which affected individuals occasionally have an IQ above 70, the traditional demarcation denoting mental retardation.

Premutation. Males and females who have a fragile X premutation have normal intellect and appearance. As noted in Table 3, footnote 1, a few individuals with a premutation have subtle intellectual or behavioral symptoms including learning difficulties or social anxiety. The difficulties are usually not socially debilitating, and these individuals may still marry and have children.

It is estimated that 21% of premutation carriers will have POF [Sherman 2005]. The odds ratios for POF in premutation carrier females increases with increasing repeat sizes [Sherman 2005] (see Table 4). Although the numbers vary slightly, other studies confirm that these increased risks tend to plateau above 80-100 repeats [Bodega et al 2006; Ennis, Ward et al 2006].

Table 4. Odds Ratios for POF by Premutation Size

Premutation Size in CGG Repeats	Odds Ratio for POF
59-79	6.9
80-99	25.1
>100	16.4

Sherman 2005

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.

Approximately 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, approximately 50% of females who are heterozygous for the full mutation are intellectually normal. The variability among females is believed to result from the ratio in the brain of active X chromosomes with the *FMR1* full mutation to inactive X chromosomes with the normal *FMR1* allele.

Mosaicism. Mosaicism is present in approximately 15%-20% of individuals with *FMR1* mutations. Such mosaicism may be (1) "repeat size mosaicism," in which both full mutations and premutations are present (also termed "full mutation/premutation mosaicism"), or (2) methylation mosaicism, in which full mutations have varying degrees of methylation.

Although some data suggest that individuals with repeat size or methylation mosaicism perform at a higher intellectual level than those with completely methylated full mutations, such individuals are usually mentally retarded.

Rarely, individuals with methylation mosaicism or completely unmethylated full mutations and normal intellect have been reported. The milder phenotype appears to be related to FMRP production arising from transcription of unmethylated alleles [Tassone et al 1999]. Presumably, these individuals produce at least some FMRP because *FMR1* is unmethylated. The existence of these exceptional individuals suggests that repeat expansion and methylation of the gene are not absolutely coupled.

Anticipation

Fragile X syndrome is a trinucleotide repeat disorder that may demonstrate anticipation in some families. Typically, anticipation occurs when less severely affected premutation or mosaic mutation carriers transmit unstable *FMR1* alleles to their offspring (e.g., transmission from a grandfather who carries a premutation to his daughter, whose premutation expands into a full mutation when she transmits it to her son, who has mental retardation as a result). However, the anticipation found in families with members affected with fragile X syndrome is not classic, as is that found in, for example, myotonic dystrophy type 1. Many families transmit premutation *FMR1* alleles for generations with little or no presentation of clinical symptoms until a full mutation is produced, resulting in an affected individual.

Prevalence

Fragile X syndrome. Prevalence estimates of males with fragile X syndrome 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, FRAXF) were likely included in the 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 to 25:100,000 males affected with the fragile X syndrome (using mental retardation as the hallmark clinical finding) [de Vries et al 1997].

A blinded study of 10,046 newborn males in Taiwan yielded one male with a full mutation and estimated prevalence of 1:1,674 for males with a premutation and 1:143 for intermediate (45-54) alleles [Tzeng et al 2005].

The prevalence of females affected with fragile X syndrome is presumed to be approximately one-half the male prevalence. A population-based prevalence study of affected African-American males revealed a higher estimate (39:100,000; 95% CI, 19-78:100,000) than reported previously for Caucasians, although confidence intervals overlap those estimated for Caucasians from this and other studies (27:100,000; 95% CI, 13-54:100,000) [Crawford et al 2002].

Unaffected female *FMR1* premutation carriers. The prevalence of females who are unaffected *FMR1* premutation carriers is high:

- In 10,624 French-Canadian women, 41 were found to have an *FMR1* premutation, representing a prevalence of 1:259 [386:100,000; 95% CI, 1:373-1:198 (268-505:100,000)] [Rousseau et al 1995].
- In 14,334 Israeli women of child-bearing age, 127 were found to have CGG repeats greater than 54, including three asymptomatic women with full mutations, representing a prevalence of 1:113 (885:100,000) [Toledano-Alhadef et al 2001].
- In nearly 2,300 women from the United States, the prevalence of premutations was 1:382 (262:100,000) and of intermediate alleles, 1:143 (699:100,000) [Cronister et al 2005].
- In the largest study to date from a laboratory database of more than 59,000 tests, the overall female carrier frequency was 1.3% (0.61% for full mutation, 1.7% for a premutation) [Strom et al 2007].

Females with *FMR1*-related POF. The prevalence of *FMR1* premutation in women with POF was recently shown to be 1:7 versus 1:15 for the general population [Bretherick et al 2005].

Males with FXTAS. An estimated 2%-4% of men with adult-onset cerebellar ataxia who represent simplex cases (i.e., a single occurrence in a family) have a premutation in *FMR1* [Brussino et al 2005, Cellini et al 2006].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Developmental delay/mental retardation. The signs of fragile X syndrome in early childhood are nonspecific, with developmental delay being an almost universal manifestation among 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 family history of mental retardation and a consistent physical and behavioral phenotype, and the absence of structural abnormalities of the brain or other birth defects [Curry et al 1997, Moeschler et al 2006]. 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 (~3%-6%) [Curry et al 1997, Shevell et al 2003].

Because cytogenetic abnormalities have been identified as frequently or more frequently than *FMR1* mutations in developmentally disabled or mentally retarded individuals referred for fragile X testing, chromosome analysis should be performed as a part of their laboratory evaluation [Moeschler et al 2006].

Conditions to be considered in the differential diagnosis include the following:

- **Sotos syndrome**. Sotos syndrome is characterized by typical facial appearance, overgrowth, and learning disability ranging from mild to severe. It is associated with behavioral problems, congenital cardiac anomalies, neonatal jaundice, renal anomalies, scoliosis, seizures, and a slightly increased risk of sacrococcygeal teratoma and neuroblastoma. Approximately 80%-90% of individuals with Sotos syndrome have a demonstrable mutation or deletion of *NSD1*.
- **Prader-Willi syndrome**. A small subset of people with fragile X syndrome have the hyperphagia and obesity characteristic of Prader-Willi syndrome. Prader-Willi syndrome is characterized by severe infantile hypotonia and feeding difficulties, followed by early childhood onset of excessive eating and development of morbid

obesity unless controlled. All individuals have developmental delay and cognitive impairment. Temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics are common. Hypogonadism (genital hypoplasia, incomplete puberty, and, in most, infertility), short stature, and characteristic facial appearance are common. Diagnosis is by DNA-based methylation testing to detect abnormal parent-specific imprinting within the Prader-Willi critical region on chromosome 15.

- **Autism**. Autistic-like behavior is frequently found in individuals with fragile X syndrome.
- **Attention deficit-hyperactivity disorder (ADHD).** Hyperactivity is frequently seen in individuals with fragile X syndrome.
- **Fragile XE 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 *FMR2* 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.
- **Adult-onset neurologic disorders.** The differential diagnosis for FXTAS is broad. One group of 56 individuals had 98 different diagnoses prior to the diagnosis of FXTAS. Most of these were in the following categories-parkinsonism, tremor, ataxia, dementia, autonomic dysfunction, and stroke [Biancalana et al 2005, Hall et al 2005].

It is estimated that 2%-4% of men with adult-onset cerebellar ataxia who represent simplex cases (i.e., a single occurrence in a family) have a premutation in *FMR1* [Brussino et al 2005, Cellini et al 2006].

Management

Evaluations Following Initial Diagnosis

Fragile X syndrome. To establish the extent of disease in an individual diagnosed with fragile X syndrome, the following evaluations are recommended:

- Complete developmental and educational assessments (including speech and language evaluation and occupational/physical therapy evaluation) for educational planning
- Behavioral and psychological assessment to determine the presence of concentration/attention problems, anxiety, obsessive-compulsive disorder, aggression, and depression
- In infants, feeding assessment (including attention to possible gastroesophageal reflux)
- Physical examination to evaluate for hypotonia and/or connective tissue findings, primarily joint hyperextensibility and pes planus
- Cardiac auscultation for mitral valve prolapse. If indicated by a murmur or click, consider echocardiography (usually in adulthood).
- History for possible seizure activity
- Ophthalmologic evaluation for possible strabismus

- In young children, history and physical examination for evidence of recurrent otitis media

FXTAS. To establish the extent of disease in an individual diagnosed with FXTAS, the following are recommended:

- Neurologic examination
- Behavioral and psychological assessment
- Neuroradiologic evaluation

POF. To establish the extent of disease in an individual diagnosed with POF, gynecologic evaluation including hormonal and/or ultrasonographic assessment is appropriate.

Note: The diagnosis of POF does not eliminate the possibility of subsequent conception. A premutation carrier woman had a child with fragile X syndrome after being diagnosed with POF [Corrigan et al 2005, Nelson et al 2005]. It is estimated that 5%-10% of women with POF may conceive after the diagnosis [Nelson et al 2005].

Treatment of Manifestations

Fragile X syndrome. No specific treatment is available. Supportive therapy for children with fragile X syndrome currently consists of the following:

- Recognition of the need for special education and anticipatory management such as the avoidance of excessive stimulation whenever possible may ameliorate some of the behavioral difficulties.
- Pharmacologic management of behavioral issues that significantly affect social interaction has been useful. No particular pharmacologic treatment has been shown to be uniquely beneficial; therapy must be individualized and closely monitored.
- Early educational intervention, special education, and vocational training 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).
- Anticipatory management for behavioral difficulties, e.g., the avoidance of excessive stimulation whenever possible
- Pharmacologic management of behavioral issues that significantly affect social interaction. No particular pharmacologic treatment has been shown to be uniquely beneficial; therapy must be individualized and closely monitored. A closely monitored and integrated program of behavioral management and pharmacologic treatment with an experienced developmental team may prove to be beneficial.
- Routine medical management of strabismus, seizures mitral valve prolapse

FXTAS. No specific treatment is available. Supportive care for problems with gait and/or cognitive deficits may require assistance with activities of daily living.

POF. No specific treatment is available. Gynecologic or reproductive endocrinologic evaluation can provide appropriate treatment and counseling for reproductive options.

Agents/Circumstances to Avoid

Folic acid should be avoided in individuals with poorly controlled seizures [Hagerman 2002].

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

FMR1-related disorders are inherited in an X-linked dominant manner.

Risk to Family Members

Parents of a proband

- The mother of an individual with an *FMR1* full mutation (i.e., hypermethylated allele of >200 trinucleotide repeats) is a carrier of a premutation or full mutation and may be affected.
- An unaffected female premutation carrier may have a father who is a premutation carrier (i.e., a "transmitting male") or a mother who is a premutation carrier or an intermediate allele carrier.
- The mother of a male with a premutation has a premutation allele or an intermediate allele.
- Women with premutations are at risk for POF and FXTAS.
- Men with premutations are at risk for FXTAS.

Sibs of a proband. The risk to sibs depends on 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** with a full mutation have mental retardation and generally do not reproduce.

- **Females** who inherit the full mutation are at an approximately 50% risk for mental retardation. Whether or not a female has phenotypic manifestations, her offspring are at a 50% risk of inheriting the full mutation.

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 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.
- **Females** who are premutation carriers have a 50% risk of transmitting an abnormal (premutation or full mutation) allele in each pregnancy.

  Very rarely, contraction of trinucleotide repeat number, such as contraction of a premutation of 110 repeats in a mother to 44 repeats in her daughter, has been reported [Vits et al 1994 and others].

  The risk of the mother's premutation becoming a full mutation on transmission to her offspring is correlated with:

  - The number of CGG trinucleotide repeats in the premutation
  - The interruption of the CGG repeats in the premutation by occasional AGG repeats (See AGG repeats, Molecular Genetic Pathogenesis.)

Note: Because most clinical laboratories do not examine the AGG repeat status, risk assessment for expansion of a maternal premutation to a full mutation on transmission to offspring is nearly always based on the number of CGG trinucleotide repeats in the premutation. Data adapted from Nolin et al (2003) and presented in Table 5 estimate the risk of a maternal premutation expanding to a full mutation upon transmission to offspring. These data are corrected for potential ascertainment bias that may have affected previous risk estimates [Warren & Nelson 1994, Nolin et al 1996]. Additional data from FMR1 testing in a large commercial laboratory support relatively low risks of repeat expansion of premutation alleles less than 75 (5%) and higher risks when 75-100 repeats are present (30%). All alleles of 90 or more repeats were observed to expand to full mutations in this sample population [Strom et al 2007].

Table 5. Risks for Expansion from a Maternal Premutation to a Full Mutation When Transmitted to Offspring

Number of Maternal Premutation CGG Repeats	Total Maternal Transmissions	Expansions to Full Mutations (%) [1]
55-59	27	1 (3.7%)
60-69	113	6 (5.3%)
70-79	90	28 (31.1%)
80-89	140	81 (57.8%)
90-99	111	89 (80.1%)
100-109	70	70 (100%)
110-119	54	53 (98.1%)
120-129	36	35 (97.2%)
130-139	18	17 (94.4%)
140-200	19	19 (100%)

Adapted from Nolin et al (2003)

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

Offspring of an individual with an intermediate allele. Offspring of an individual with an intermediate allele may occasionally have a minor variation in repeat size (i.e., a change of 1 or 2 repeats), and are at negligible risk of being affected. Intermediate alleles ranging from 50 to 58 repeats may be somewhat more unstable than those with fewer than 50 repeats, and potentially may become premutation size (>58 repeats). Thus, the risk to offspring of an individual with a larger intermediate allele of inheriting a premutation allele is low but greater than that of the general population.

Other family members of a proband. The proband's maternal aunts and their offspring may be at risk of being carriers or being affected (depending on their gender and family relationship).

Carrier Detection

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.)

Popluation-based carrier testing. Fragile X syndrome carrier screening has been offered to women not known to be at risk in the prenatal genetic counseling setting [Cronister et al 2005]. Fewer than 8% of women elected such testing. Anido et al (2005) analyzed women's attitudes toward carrier testing and suggest that non-carrier women from the general population would be unprepared to learn that they are carriers.

Related Genetic Counseling Issues

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

Grandchildren of transmitting males. The daughters of transmitting males are premutation carriers; thus, their offspring are at risk for fragile X syndrome.

Early diagnosis of fragile X syndrome. The first indication of fragile X syndrome within a family is usually the diagnosis in an affected child. A survey to assess the timing of a diagnosis in an affected child and genetic counseling for the family indicated that in approximately half of the families surveyed, the diagnosis was made more than a year after the child's development or behavior first raised concerns. Half of the surveyed families reported having subsequent pregnancies before diagnosis of the first affected child. These findings emphasize the importance of increased opportunities for early diagnosis so that children and families can receive all possible benefits, including genetic counseling and intervention services [Centers for Disease Control and Prevention 2002].

Fragile X tremor ataxia syndrome (FXTAS) in males with premutation alleles. When a child is diagnosed with fragile X syndrome and his mother is found to have a premutation allele, his maternal grandfather is then known to be at risk of developing FXTAS.

Premature ovarian failure (POF) in females with premutation alleles. The increased risk for POF (i.e., age at menopause <40 years) in female premutation carriers should be taken into account when providing genetic counseling.

Note: The diagnosis of POF does not eliminate the possibility of subsequent conception. A premutation carrier woman had a child with fragile X syndrome after being given the diagnosis POF [Corrigan et al 2005, Nelson et al 2005]. It is estimated that 5%-10% of women with POF may conceive after the diagnosis [Nelson et al 2005].

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of availability of prenatal testing is before pregnancy.

It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal testing for fetuses at increased risk for *FMR1* full mutations can be performed using DNA extracted from cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or CVS at approximately ten to 12 weeks' gestation (see Molecular Genetic Testing and Published Statements and Policies). The *FMR1* Southern blot patterns for DNA derived from amniocytes are identical to those found in adult tissues; however, 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. Thus, for pregnancies evaluated by CVS, follow-up amniocentesis or testing using PCR may be necessary to determine the size of the *FMR1* alleles in a methylation-independent manner.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. Technical improvements enabling better testing of *FMR1* in single embryonic cells produced for PGD have recently been reported. Implantation of embryos detected with normal alleles led to unaffected offspring [Burlet et al 2006, Malcov et al 2007]. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of *FMR1*-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
FMR1	Xq27.3	Fragile X mental retardation 1 protein

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for *FMR1*-Related Disorders

300623	FRAGILE X TREMOR/ATAXIA SYNDROME; FXTAS
300624	FRAGILE X MENTAL RETARDATION SYNDROME
309550	FMR1 GENE; FMR1

Table C. Genomic Databases for *FMR1*-Related Disorders

Gene Symbol	Entrez Gene	HGMD
FMR1	2332 (MIM No. 309550)	FMR1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

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

Hagerman et al (2001) and Jacquemont et al (2004) review evidence of dysregulation of the *FMR1* gene in the premutation range, which may explain many of the clinical observations. Paradoxically, Kenneson et al (2001) found a decrease in FMRP and an increase in transcription of *FMR1* in premutation carriers. These findings suggest that mRNA over-production from *FMR1* premutations may exert an effect on intracellular transport of mRNAs produced by *FMR1* and other genes. Thus, FXTAS and POF resulting from *FMR1* premutations may be manifestations of an RNA metabolism defect.

The mGluR theory of fragile X mental retardation is based on the observation that activated group 1 metabotropic glutamate receptors (mGluRs) mediate long-term depression of transmission at hippocampal synapses, a process that requires translation of preexisting mRNA near synapses. Evidence strongly indicates that the FMRP represses translation of specific mRNAs. Loss of FMRP increases long-term depression of transmission at hippocampal synapses in the *fmr-1* mouse model and likely has the same effect in individuals with the fragile X syndrome. The mGluR theory of fragile X syndrome hypothesizes that in the absence of the FMRP, mGluR-dependent protein synthesis may be exaggerated and result in the fragile X syndrome phenotype [Bear et al 2004].

Normal allelic variants: *FMR1* occupies 38 kb of genomic DNA and has 17 exons contained in a messenger RNA of approximately 4 kb. 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. Variation of the repeat copy number in normal (i.e., stable) alleles ranges from six to 40 CGG repeats, with a trimodal distribution consisting of a major peak at around 30 repeats and minor peaks at around 20 and 40 repeats. Alternative splicing of *FMR1* occurs toward the 3' end of the mRNA.

- **AGG repeats:** An increase in the number of the CGG trinucleotide repeats contained in *FMR1* occurs exclusively during transmission from female carriers (see Genetic Counseling). The risk of increase in the size of the expansion of maternal premutation alleles depends on the number of CGG repeats and the presence of AGG triplets

embedded in the CGG repeat segment [Eichler et al 1994, Kunst & 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 approximately 33-39 triplets appear to increase the instability of maternal alleles and increase the risk for expansion of the number of trinucleotide repeats on transmission to offspring [Eichler et al 1994, Kunst & 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 on the number and location of AGG repeats within the CGG trinucleotide repeat segment.

Pathologic allelic variants: Expansion of the CGG repeat number beyond approximately 200, 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) and giving rise to the expression of the cytogenetic fragile site, FRAXA. It is the loss of FMRP that results in the fragile X syndrome phenotype.

Rare individuals with deletions of all or part of *FMR1* (reviewed in Hammond et al 1997) or point mutations in *FMR1* [De Boulle et al 1993, Lugenbeel et al 1995, Wang et al 1997] have been reported but account for far fewer than 1% of those with fragile X syndrome. The existence of affected individuals with deletions has confirmed that the syndrome is caused by the lack of *FMR1* transcription. Occasionally, an individual will appear to have no cells in which the abnormal promoter methylation events have occurred even when more than 200 CGG repeats are found. Such individuals are usually described as having "unmethylated full mutations." Individuals having partial methylation of full mutations ("methylation mosaics") are also observed. Cellular mosaicism, in which both premutation and full-mutation cell lines are present, also occurs in some individuals. (For more information, see Genomic Databases table.)

Normal gene product: The product of *FMR1*, fragile X mental retardation 1 protein (FMRP), is found in the cytoplasm of many cell types but is most abundant in neurons. 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 containing G-quartet motifs. FMRP contains both a nuclear localization signal and a nuclear export signal, suggesting that it functions as a nucleocytoplasmic shuttling protein that binds several mRNAs, including its own mRNA, forms messenger ribonucleoprotein complexes, and associates with translating ribosomes [Ceman et al 1999]. FMRP is expressed in many tissues; it also appears to play a role in structural and functional maturation of synapses by serving as a translational suppressor in postsynaptic spaces [Weiler & Greenough 1999].

Abnormal gene product: It is evident from affected individuals with deletions in *FMR1* that gene loss and the consequent lack of FMRP causes fragile X syndrome. The pathogenic mechanism whereby premutation alleles result in FXTAS or POF is not well understood. However, in contrast to the loss-of-function mutations producing fragile X syndrome, FXTAS and POF may result from RNA toxicity related to overexpression of premutations.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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
www.FRAXA.org

National Fragile X Foundation
Journal: The Foundation Quarterly. Subscriptions through National Fragile X Foundation
PO Box 190488
San Francisco CA 94119-0488
Phone: 800-688-8765; 925-938-9300
Fax: 925-938-9315
Email: NATLFX@FragileX.org
Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)
www.FragileX.org

National Library of Medicine Genetics Home Reference
Fragile X syndrome

NCBI Genes and Disease
Fragile X syndrome

National Ataxia Foundation
2600 Fernbrook Lane Suite 119
Minneapolis MN 55447
Phone: 763-553-0020
Fax: 763-553-0167
Email: naf@ataxia.org
www.ataxia.org

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
www.wemove.org

Teaching Case-Genetic Tools
Cases designed for teaching genetics in the primary care setting.
Case 16. A Two-Year-Old Boy with Developmental Delay

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Chapter Notes

Revision History

- 5 August 2008 (cd) Revision: deletion/duplication testing available clinically
- 7 March 2008 (cd) Revision: FISH analysis available clinically
- 20 December 2007 (me) Comprehensive update posted to live Web site
- 15 March 2007 (cd) Revision: correction of the wording and the discrepancy associated with only using premutation when gray zone (AKA intermediate) FMR1 alleles also present increased risk
- 25 April 2006 (bp) Revision: Table 4 updated according to Nolin et al (2003)
- 1 March 2006 (cd) Revision: updated ACMG practice guideline
- 2 December 2005 (jt) Revision: sequence analysis of *FMR1* clinically available; updated genetic counseling recommendations
- 24 May 2005 (rs/jt) Comprehensive update: change in scope of GeneReview from fragile X syndrome to *FMR1*-related disorders
- 13 September 2004 (me) Comprehensive update posted to live Web site
- 20 April 2004 (jt) Revisions: Testing Algorithm; FXTAS

- 22 November 2002 (me) Comprehensive update posted to live Web site
- 26 May 2000 (me) Comprehensive update posted to live Web site
- 16 June 1998 (pb) Review posted to live Web site
- May 1996 (jt) Original submission

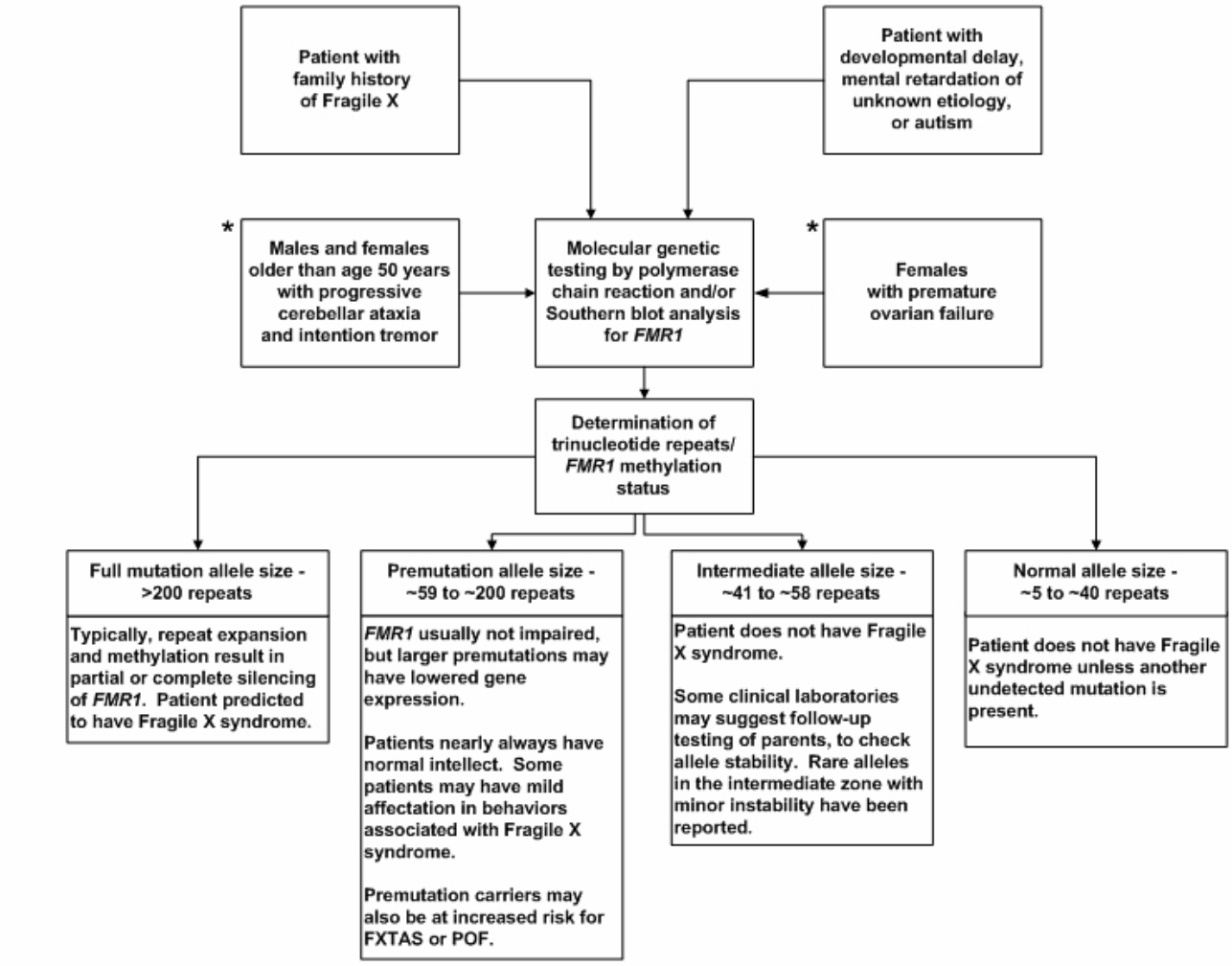

Figure 1. Testing algorithm for *FMR1*-related disorders. The boxes identified with asterisks (*) identify individuals to be considered for *FMR1* molecular testing. See Testing Strategy, Establishing the diagnosis in a proband for further discussion [Maddalena et al 2001, Sherman et al 2005].