### Condition Description

Fragile X syndrome is characterized by moderate intellectual disability, particularly in males. It has a prevalence of 1/4000 to 1/6000 in the general population, and is a leading genetic cause of intellectual disability. Males with fragile X syndrome may have a recognizable facial pattern with a long face, protruding ears, and a large head. Some males with fragile X have joint laxity. After puberty, males develop macroorchidism. Boys may have characteristic behaviors that vary with age: young children may have autistic-like features, hyperactivity or tantrums. Older children may have poor eye contact, shyness, and attention problems.

Females with fragile X may have a variable clinical presentation due to X-inactivation. Intellectual disability in females is typically mild. Other clinical findings and behaviors seen in males with fragile X have also been seen in females, with milder presentation and lower frequency.

Fragile X syndrome maps to the \( FMR1 \) gene on the X chromosome and is associated with a triplet (CGG) repeat expansion in the promoter of the \( FMR1 \) gene. CGG expansion leads to methylation and subsequent inactivation of the \( FMR1 \) gene. In individuals with normal alleles, the number of CGG repeats ranges from approximately 5-44. Individuals with approximately 55-200 CGG repeats are premutation carriers. The number of repeats in the premutation range is likely to expand in subsequent generations, particularly when passed through female meiosis. Individuals with fragile X syndrome have over 200 CGG repeats. Males with over 200 repeats are almost always affected. Mosaicism, the presence of two different sized repeats or extent of methylation, for pre and full mutation alleles has been reported in some individuals with \( FMR1 \) full CGG expansions.

Click here for the GeneReviews summary on this condition.


### Methodology

Both normal CGG repeat tracts and expanded CGG repeat tracts are detected by PCR amplification, using a CGG repeat-specific probe, and capillary electrophoresis. Expanded CGG repeat tracts will be reflexed to a gene specific PCR and sized by agarose gel electrophoresis. DNA methylation analysis will be performed on any full expansions detected. Methylation sensitive PCR for Males and Southern blot for females.

### Detection

All cases of fragile X syndrome caused by CGG expansion will be detected by this assay. Rare cases of fragile X syndrome caused by mutation of the \( FMR1 \) gene will not be detected by this assay.

### Reference Range

- Normal: Approximately 5-44 CGG repeats.
- Intermediate: Approximately 54-45 unmethylated CGG repeats.
- Premutation: Approximately 55-200 CGG repeats and methylation of expanded allele.
- Affected: Over 200 CGG repeats and methylation of expanded allele

### Specimen Requirements

**Type:** Whole Blood

Specimen Requirements:

- In EDTA (purple top) or ACD (yellow top) tube:
  - Infants (2 years): 3-5 ml
  - Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Related Tests
The EmArray 60K Chromosomal Microarray (VA) can be used to screen for chromosomal causes of mental retardation.

*FMR1* gene sequencing (FU) and deletion/duplication analysis (KQ) are appropriate for persons with a suspected clinical diagnosis of fragile X syndrome but normal CGG repeat length.

Testing for *FMR1*-related premature ovarian insufficiency (POI) (FK) is indicated for women experiencing ovarian dysfunction or menopause before the age of 40 or for women with sons diagnosed with fragile X syndrome.

Testing for *FMR1*-related tremor ataxia syndrome or FXTAS (FJ) is indicated for older men with late-onset, progressive cerebellar ataxia and intention tremor or for men with daughters who are carriers for fragile X.