

## Fragile X Mental Retardation Syndrome DNA Screen

### Background

In almost all cases (>99%), fragile X mental retardation syndrome is caused by both expansion and abnormal hypermethylation of the *FMRI* gene on chromosome Xq27.3. An abnormally expanded CGG trinucleotide repeat in one *FMRI* allele is present in affected and carrier males and females. Greater than 200 CGG repeats is a full mutation allele; 55-200 repeats is a premutation allele; 45-54 repeats is an intermediate allele which may expand upon transmission; 44 or fewer repeats is a normal allele (ref. 1). Full mutation alleles with >200 repeats also show hypermethylation. Less than 1% of patients with fragile X syndrome do not have an CGG expanded allele but carry an *FMRI* deletion or point mutation, which is not detectable by this test.

### Two tests are available for the following indications:

#### 1. Fragile X DNA test:

- Differential diagnosis of nonspecific X-linked mental retardation, autism, pervasive developmental delay (PDD), and FRAXE mental retardation.
- Evaluation of a male or female child with developmental delay of unknown etiology.
- Carrier testing for the mother of a child with an *FMRI* full mutation. She is an obligate carrier and genetic counseling is recommended.
- Males and females who have a family member with a diagnosis of fragile X mental retardation or a documented *FMRI* full mutation or premutation.
- Males or females seeking reproductive counseling who have a family member with unexplained mental retardation
- Females with premature ovarian failure
- Adult males and females with cerebellar ataxia and/or intention tremor, who may also have short-term memory loss, executive function deficits, cognitive decline, parkinsonism, peripheral neuropathy, lower limb proximal muscle weakness, or autonomic dysfunction.
- Confirmation of a diagnosis in a patient diagnosed previously by cytogenetic analysis.

#### 2. Fragile X DNA test in conjunction with a routine karyotype:

- Males or females with unexplained developmental delay, autism-like disorders, or mental retardation, especially if other features are present, such as autistic-like behavior, large ears, macroorchidism, or family history of mental retardation. This combined test detects *FMRI* gene abnormalities and constitutional cytogenetic abnormalities and is recommended for evaluating the first symptomatic case ascertained in a family. The University of Washington Cytogenetics Laboratory performs the routine karyotype and a separate report is issued.

### Genetic Counseling

Genetic counseling can be useful to patients and families considering genetic testing. The laboratory can provide referrals to genetics clinics in the patient's locale or a listing can be found at [www.genetests.org](http://www.genetests.org)

### Ordering

1. Obtain blood sample.
2. Fill out a Clinical Lab Request - Genetics for each patient.  
(Available at <http://depts.washington.edu/labweb/Divisions/MolDiag/MolDiagGen/index.htm>).  
-Request: "Fragile X, DNA test" or "Fragile X, DNA test + karyotype"
3. Provide items needed for test interpretation:
  - Reason for ordering test (e.g., confirm diagnosis; R/O)
  - Clinical history (e.g., developmental delay, autistic-features, mental retardation, macroorchidism)
  - Pedigree / family history

4. Call Laboratory Medicine Community Services (206)598-6066 to arrange the best method of shipment.  
NOTE: For Fragile X DNA test and routine karyotype tests: Call (206)598-4488 Cytogenetics Laboratory (after hours page 206-598-6190) before overnight shipment to: Cytogenetics Laboratory, Room NW-125, University of Washington Medical Center, 1959 NE Pacific Street, Seattle, WA 98195 (Requisition and information available at <http://www.pathology.washington.edu/clinical/cytogenetics/>)

### Sample Requirements and Specimen Handling

\*For the DNA test only: Whole blood: 5 mL in EDTA (purple top).

\*For the combined DNA test and routine karyotype two blood samples are required:

1. Whole blood: 5 mL in EDTA (purple top) for DNA test
2. Whole blood: 2-10 mL in Heparin (green top) for cytogenetics  
Sample should be received within 24 hours of collection.  
Sample must be kept at room temperature. Do not refrigerate, do not freeze.

\*For prenatal diagnosis specimens, call the Genetics Lab with information on fetal sample and expected date of receipt (blood sample of affected/carrier parent may also be required). Consult Genetics Laboratory.

### Test Frequency and Reporting

Test results usually within 2-3 weeks of specimen receipt; prenatal samples are expedited. A written interpretative report is issued.

### References

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2. Bardoni B, Mandel JL. Advances in understanding of fragile X pathogenesis and FMRP function, and in identification of X linked mental retardation genes. *Curr Opin Genet Dev.* 12:284-93, 2002.
3. Saul RA, Tarleton J. Fragile X Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2003. Available at <http://www.genetests.org>.
4. Sherman SL. Premature ovarian failure in the fragile X syndrome. *Am J Med Genet* 97:189-194, 2000.
5. Jacquemont S, Hagerman RJ, Leehey M, et al. Fragile X premutation tremor/ataxia syndrome: molecular, clinical and neuroimaging correlates. *Am J Hum Genet* 72:869-878, 2003.
6. Hagerman PJ, Hagerman RJ. The Fragile-X premutation: A maturing perspective. (review article). *Am J Hum Genet* 74:805-816, 2004.
7. Viancalana V, Beldjord C, Taillandier A, et al. Five years of molecular diagnosis of fragile X syndrome (1997-2001): A collaborative study reporting 95% of the activity in France. *Am J Med Genet* 129A:218-224, 2004.