



## Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) and Premature Ovarian Failure (POF): Two Distinct Phenotypes Caused by Premutation in the Fragile X Syndrome Gene (*FMRI*)

By A.L. Rosa, M.D., Ph.D.; B.A. Bejjani, M.D., F.A.C.M.G.; and M.L. Hoffmann, Ph.D.

Mutations in the X-linked Fragile X mental retardation gene 1 (*FMRI*) cause fragile X syndrome, a relatively common form of inherited mental retardation. The most common mutation in *FMRI* is an expansion of the polymorphic repeated sequence (CGG)<sub>n</sub>, which is located in the 5' untranslated region of the gene. (Test Update "Fragile X Syndrome: Molecular Diagnosis and Carrier Testing" By ML Hoffmann, Ph.D.; A.L. Rosa, M.D., Ph.D.; and B.A. Bejjani, M.D., F.A.C.M.G., November 2003.)

Variation in the number of CGG repeats at the *FMRI* locus (or the *allele size* of the *FMRI* gene) defines four categories of individuals: 1) *normal*, carrying alleles with 5 to 44 repeats; 2) *gray zone*, with 45-54 repeats; 3) *premutation*, with 55-200 repeats; and 4) *full mutation*, with more than 230 repeats.

Prevalence estimates in the general population indicate that 1 in 250 females and 1 in 800 males are carriers of *premutation alleles* (i.e., 55 to 200 CGG repeats). Carrier individuals have been largely considered to be normal. Recent data, however, established two distinctive clinical phenotypes in individuals carrying premutations: fragile X-associated tremor/ataxia syndrome (FXTAS) and premature ovarian failure (POF).

### Fragile X-associated tremor/ataxia syndrome (FXTAS)

This is a new syndrome recognized in adult males and characterized by progressive cerebellar ataxia and intention tremor with associated radiological signs. Additional FXTAS symptoms may include cognitive decline, psychological symptoms, parkinsonism, peripheral neuropathy or lower-limb proximal muscle weakness, and autonomic dysfunction. MRI may show mild to moderate brain atrophy. A definite diagnosis of FXTAS is important for appropriate genetic counseling and because ataxia, action tremor or autonomic dysfunction are also signs for other neurological diseases. Provisional diagnostic criteria for "definite" FXTAS have been proposed (Jacquemont et al. 2003 Am J Hum Genet 72, 869-878). Testing the *FMRI* gene should be considered in adult males with clinical features consistent with FXTAS.

### Premature ovarian failure (POF)

POF affects 16-24% of female premutation carriers. The syndrome is defined as the spontaneous cessation of menses before the age of 40. It may also be caused by viral infections, radiation exposure, anti-ovarian antibodies, and genetic defects including numerical chromosomal abnormalities (aneuploidy). The risk of POF in the general population is about 1%.

The pathogenic mechanism underlying FXTAS and POF appears to be distinct from the gene-silencing events that leads to fragile X syndrome and is the subject of intense research.

### Quick Facts

- ▶ Females carrying a *premutation* are at risk of having children affected with fragile X syndrome.
- ▶ Females carrying a *premutation* may develop premature ovarian failure (POF).
- ▶ Adult males carrying a *premutation* may develop fragile X-associated tremor/ataxia syndrome (FXTAS).
- ▶ FXTAS primarily consists of ataxia and/or intention tremor.
- ▶ Additional FXTAS symptoms may include cognitive decline, psychological symptoms, parkinsonism, and autonomic dysfunction. MRI may show mild to moderate brain atrophy.
- ▶ Polymerase chain reaction (PCR) and Southern blotting are used to detect *premutation alleles* for the *FMRI* gene.
- ▶ Testing the *FMRI* gene should be considered in individuals with clinical features of fragile X syndrome, females with POF, and adult males with definite FXTAS.
- ▶ PAML/SHMC has been offering fragile X analysis since December 2, 2003.

For more information, please contact Client Services or see us on the Web at



## Test Information

DESCRIPTION **FRAGILE X SYNDROME ANALYSIS**

METHOD PCR and Southern blot

ORDER CODE FRAGX

CPT CODE 83891, 83894 × 2, 83898, 83912, 83892 × 2, 83896, 83897

SPECIMEN 7 mL EDTA, sodium citrate or ACD whole blood (lavender, blue or yellow top tube).  
Submit original and unopened tube only. Store and transport at room temperature or refrigerated. Include patient's family history and clinical indication.

**This test must be ordered on a paper requisition that accompanies the specimen. It is not orderable on the PAML computer system.**

COMMENTS *Minimum amount:* 5 mL.

*Unacceptable conditions:* plasma, serum, heparinized whole blood, severely hemolyzed specimens, specimens in leaking containers or more than 5 days old, specimens not received in the original collection tubes.

*Stability:* 72 hours at room temperature, 5 days refrigerated, unacceptable frozen.

SCHEDULE Weekly

TURNAROUND 2-3 weeks

RANGES "See separate report."

*Provided for the clients of*

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PACLAB NETWORK LABORATORIES  
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