**Molecular Diagnostic Laboratory**
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# Fragile X Syndrome

CGG triplet repeats on *FMR1* gene

## Indications for Molecular Testing

- Individuals of either sex with mental retardation, developmental delay, or autism, especially if they have physical or behavioral characteristics of Fragile X Syndrome [long faces, large ears, prominent jaws, post-pubertal macroorchidism], a family history of Fragile X Syndrome, or male or female relatives with undiagnosed mental retardation.
- Individuals seeking reproductive counseling who have a family history of Fragile X Syndrome or a family history of undiagnosed mental retardation.
- Fetuses of known carrier mothers.

## Testing Methodology

Screening procedure utilizes Polymerase Chain Reaction (PCR). If unable to determine fragment sizes by PCR, then direct mutation testing is performed by Southern analysis (Methylation). Southern analysis involves determination of restriction endonuclease DNA fragment sizes and methylation status with the StB12.3 *FMR1* probe.

## Interpretation of DNA analysis

Identification of CGG triplet repeat expansion mutations in the *FMR1* gene is associated with X-linked, pseudo-dominant inheritance of mental retardation. Normal individuals have between 6 and 52 (median 30) repeats of CGG per *FMR1* allele. Repeat numbers from 52 to about 150 characterize individuals with **premutation** alleles, i.e. they are carriers of an unstable repeat region. A new clinical phenotype, Fragile X- Associated Tremor Ataxia syndrome (FXTAS) has been observed in some males with a premutation allele and premature ovarian failure (POF) in some females. Further expansion occurs in the meiosis of germ cells of carrier females who may, in turn, pass on larger, expanded (>200) copies or **full mutation** alleles to their offspring. Individuals with full mutation-size alleles have the highest risk of mental retardation and associated phenotypic features. Individuals with full mutation alleles that are unmethylated may have milder clinical features and intermediate mental function.

## Specimen Requirements

**Peripheral blood**--1 lavender-top (EDTA) tube. Invert several times to mix blood.
**Prenatal Diagnosis**--1 x $10^6$ nucleated cells in cell medium (amniocytes nor chorionic villi sampling (CVS) is not available) Do not freeze. Forward promptly at ambient temperature to the following address:

**Molecular Diagnostic Laboratory**
**Barnes-Jewish Hospital, Institute of Health**
**Mail Stop 90-28-344**
**425 South Euclid Avenue, Room 5970**
**St. Louis, MO 63110**

Clinical information must be provided with specimen referral in order to correctly interpret test results.

## Current Pricing

Contact Lab Customer Service for current pricing 314 362-1470.
CPT codes: PCR 81243, Southern analysis (additional) 81244

OSHU DNA Diagnostic Lab, Version 4 protocol
Tassone F, Pan R, Amiri K, Taylor AK, Hagerman PJ. A rapid polymerase chain reaction-based screening method for identification of all expanded alleles of the fragile X (FMR1) gene in newborn and high-risk populations. J Mol Diagn. 2008;10:43-9.
Spector EB, Kronquist K, et al. Technical Standards and Guidelines for Fragile X Testing by the American College of Medical Genetics. 2006. Electronic publication available at: http://www.acmg.net/pages/acmg_activities/stds-2002/fx.htm
Hamdan H, Tynan J, Fenwick R, Leo J. Automated detection of trinucleotide repeats in Fragile X syndrome. Molecular Diagnosis 4 December 1997;2(4):259-269.
Warren ST, Nelson DL. Advances in Molecular Analysis of Fragile X syndrome. JAMA 16 February 1994;271(7):536-542.
Jacquemont S., Hagerman R., Leehey M., Hall D., Levine R. Penetrance of the Fragile X-Associated Tremor/Ataxia Syndrome in a Premutation Carrier Population. JAMA, January 28, 2004, 291 (4): 460-469.