

Premature Ovarian Failure: Sequencing Panel and *FMR1* CGG Repeat Analysis

Test Code: MM660

Turnaround time: 6 weeks

CPT Codes: 81243 x1, 81405 x1, 81406 x1

Condition Description

FMR1-related disorders include fragile X syndrome, fragile X-associated tremor/ataxia syndrome (FXTAS), and *FMR1*-related premature ovarian insufficiency (POI). *FMR1*-related premature ovarian insufficiency (POI) is the onset of ovarian dysfunction or menopause before the age of 40 years. Women who are carriers of *FMR1* premutation range expansions are at increased risk for POI (estimated as high as 21%), though penetrance of POI is not complete. Recent reports indicate that women who carry a premutation size expansion may have a slight increased risk for developing fragile X-associated tremor/ataxia syndrome (FXTAS), a disorder that causes tremors, balance problems, difficulty walking, and memory difficulty.

The *FMR1* gene is located on the X chromosome. *FMR1*-related disorders are associated with the presence of a triplet (CGG) repeat expansion in the promoter of *FMR1* leading to methylation and subsequent inactivation of the *FMR1* gene. The normal range of CGG repeats is approximately 5-44. Repeats in this range are considered stable when passed from parent to child. Repeats in the 45-54 range are considered intermediate (or grey-zone), for which the risk of expansion to a full mutation of 200 repeats or more when passed to children is low but not well defined at this time. Individuals with approximately 55-200 CGG repeats are premutation carriers. Females with expansions in this range are at risk for POI. The number of repeats in this range is unstable and may expand when passed to children. Individuals with fragile X have over 200 CGG repeats. Males with over 200 repeats are almost always affected, while females may be more mildly affected. Women who are carriers of a full size expansion are not at increased risk of POI. Mosaicism has also been reported in some individuals with *FMR1* mutations, indicating the presence of two different repeat sizes or variation in the extent of methylation.

All other genes on this panel have been associated with premature ovarian failure.

[Click here](#) for the GeneReviews summary on this condition.

Genes

[BMP15](#), [CYP17A1](#), [CYP19A1](#), [DIAPH2](#), [EIF2B2](#), [EIF2B3](#), [EIF2B5](#), [FIGLA](#), [FMR1](#), [FOXL2](#), [FSHR](#), [GALT](#), [GDF9](#), [HEM1](#), [LHCGR](#), [LMNA](#), [NOBOX](#), [NR5A1](#), [POF1B](#), [POR](#), [PSMC3IP](#)

Indications

This test is indicated for adult females with premature ovarian failure.

Methodology

The DNA surrounding the CGG repeat in the *FMR1* gene is amplified by PCR and the size of the repeat is determined by capillary electrophoresis.

For all remaining genes:

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

Detection

All cases of premutation expansion mutations for *FMR1* will be detected by this assay.

For all remaining genes:

Next Generation Sequencing: Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical Sensitivity: ~99%.

Reference Range

Normal for *FMR1*: < 44 CGG repeats, Intermediate: 45-55 CGG repeats, Premutation: 55--200 repeats, Full mutation: >200 CGG repeats

Specimen Requirements

Submit only 1 of the following specimen types

Type: DNA, Isolated**Specimen Requirements:**

Microtainer

20µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene™ kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.

Related Tests

- [EXTAS \(EJ\)](#) is indicated for older men with late-onset, progressive ataxia and intention tremor or for fathers of women who are premutation range carriers of an *FMR1* expansion.
- [Testing for fragile X syndrome \(MFRAX\)](#) is indicated for males and females with symptoms of Fragile X.
- The [female infertility panel \(MEMR1\)](#) is available for women experiencing infertility due to ovarian dysfunction or menopause.