FRAXE Syndrome: **AFF2** Gene Sequencing

**Test Code:** T1  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81479 x1

### Condition Description

In patients who have the cytogenetic changes of fragile X syndrome but lack the molecular changes characteristic of that disorder (i.e., are FMR1-mutation negative), a second site of fragility, symbolized FRAXE, has been demonstrated to be expanded. Data suggests that an etiologic relationship may exist between FRAXE and nonspecific X-linked intellectual disability. Loss of expression of the gene **AFF2** has been correlated with FRAXE expansion. Sequence analysis and deletion/duplication analysis are also available to identify mutations in the **AFF2** gene.

For patients with suspected FRAXE syndrome, repeat expansion testing and methylation analysis are recommended as the first step in mutation identification. For patients in whom mutations are not identified, full gene sequencing and deletion/duplication analysis are also available.

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

Please note that **AFF2** and **FMR2** are the same gene. This test is therefore a single-gene test.

### Genes

**AFF2, FMR2**

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of FRAXE syndrome
- Carrier testing in adult females with a family history of FRAXE syndrome

### Methodology

**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

**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 will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

**Analytical Sensitivity:** ~99%

### Specimen Requirements

**Submit only 1 of the following specimen types**

**Type: Saliva**

**Specimen Requirements:**
Oragene™ Saliva Collection Kit  
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**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 unclocted cord or cardiac blood

**Specimen Collection and Shipping:**
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 8µg

Isolation using the Perkin Elmer™ 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.

**Special Instructions**
Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.
Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**
- Repeat expansion testing and methylation analysis are available and are strongly recommended as the first step in mutation identification.
- **Deletion/duplication analysis of the AFF2 gene** by CGH array is available for those individuals in whom sequence analysis is negative.
- A CGH array-based test for deletion/duplication analysis of 109 different X-linked intellectual disability genes is available.
- Testing for fragile X syndrome at the FRAXA site is available by repeat expansion/methylation analysis, *FMR1* sequencing, and *FMR1* deletion/duplication analysis.
- Custom diagnostic mutation analysis is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.