In 2007, Tarpey et al. conducted a study of individuals with mental retardation (MR) from 250 families compatible with X linkage. None of these individuals had mutations in any of the XLMR-linked genes identified at the time. Three different mutations in the \textit{UPF3B} gene (Xq25-q26) were identified in three families. One of these families had a clinical diagnosis of FG syndrome (FGS), while the other two families had clinical diagnoses of Lujan-Fryns syndrome (LFS). They then analyzed 118 affected individuals from a cohort of families with putative XLMR and found a \textit{UPF3B} mutation in a family with nonsyndromic XLMR. Mental retardation in these families was mild to severe.

Features present in more than half of affected males in the first three families included a slender build with poor musculature, a long and thin face, high arched palate, high nasal bridge, and pectus. Half of the affected individuals had autistic features or behavioral problems. While the clinical phenotype is variable, many of these clinical features are suggestive of LFS and FGS. The affected males from the fourth family had normal physical examinations, and were hence classified as nonsyndromic XLMR.

Carrier females had normal intelligence and normal physical examinations.

For patients with suspected XLMR 14, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

References:

\textbf{Genes}

\textit{UPF3B}

\textbf{Indications}

This test is indicated for:

- Confirmation of a clinical diagnosis of XLMR 14
- Carrier testing in adults with a family history of XLMR 14

\textbf{Methodology}

PCR amplification of 11 exons contained in the \textit{UPF3B} gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

\textbf{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%

\textbf{Specimen Requirements}

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

\textbf{Type: Whole Blood}

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml
Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection 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**

- Deletion/duplication analysis of the *UPF3B* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Custom diagnostic mutation analysis (KM) 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.