X-linked Intellectual Disability Panel: Sequencing and CNV Analysis

Test Code: MXL1
Turnaround time: 6 weeks
CPT Codes: 81302 x1, 81401 x1, 81404 x1, 81405 x1, 81406 x1, 81407 x1, 81408 x1, 81243 x1

Condition Description

Intellectual disability (ID) is a nonprogressive cognitive impairment affecting 1-3% of the Western population. It is estimated that up to 50% of moderate-severe cases have genetic causes and approximately 10% are due to X-linked intellectual disability disorders (XLID). XLID can be syndromic or nonsyndromic and is observed in all ethnic groups. More than 100 XLID syndromes have been described in the literature to date. Fragile X is the most common XLID syndrome (~1 in 4000 males) while others can be quite rare with only a few patients reported in the literature. Males can have moderate to severe intellectual disability depending on a syndrome, and carrier females can also be affected, but typically have milder clinical symptoms.

A majority of individuals with XLID are non-syndromic with no other features to assist in diagnosis. Because of the number of genes involved, it is very difficult to identify which X-linked gene may be responsible for the phenotype in any given patient. Simultaneous testing of all known XLID genes in a single study provides a significant diagnostic advantage over single gene sequencing. Additional benefits for the patient and families include:

- Providing information for recurrence risk and family planning and allowing for presymptomatic support
- Helping physicians determine appropriate follow-up testing and develop a health maintenance plan
- Predicting better patient prognostic value
- Assisting researchers in the understanding of the molecular basis of disease in the hope for treatments and cures
- Assessing the possibility of therapy for some forms of XLID

Testing includes trinucleotide repeat analysis for the FMR1 (test code: MFRAX) gene.

Genes

ACSL4, AFF2, AP1S2, ARHGEF8, ARX, ATP6AP2, ATP7A, ATRX, BCR, BRWD3, CASK, CCDC22, CDK16, CDKL5, CLCN2, CNKSR2, CUL4B, DDX3X, DDX11, DMD, FANCB, FGD1, FLNA, FMR1, FRMD4, FTSJ1, GDI1, GKC3, GRIK3, HCCS, HCF1, HPRT1, HSD17B10, HUWE1, IDS, IGBP1, IL1RAPL1, IQSEC2, KDM5C, KLF8, L1CAM, LAMP2, MAOA, MBTPS2, MECP2, MED12, MED15, MGI1, NAA10, NDP, NDUF3, NEXMIF, NLSN3, NLGN4X, NSDHL, OQRFL, OFD1, OPHN1, OTC, PAK3, PCDH19, PDHAI, PGK1, PHF6, PHF8, PLP1, PORCN, PQBP1, PRPS1, PTCH1, RAB39B, RBM10, RPL10, RPS6KA3, SHROOM4, SLC16A2, SLC9A6, SMC1A, SMS, SOX3, SYN1, SYNGAP1, SYS, TIMM8A, TSPAN7, UBE2A, URF3B, ZDHHC15, ZDHHC3, ZNF711

Indications

This test is indicated for:

- Individuals with a clinical and family history consistent with an X-linked intellectual disability disorder after fragile X testing and genomic array testing are normal.
- Carrier testing in adult females with a family history of X-linked intellectual disability.

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.

Copy Number Number Analysis: Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

Detection

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. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

Copy Number Analysis: The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (~< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

MFRA:
Normal: Approximately 5-44 CGG repeats.
Intermediate: Approximately 54-45 unmethylated CGG repeats.
Premutation: Approximately 55-200 CGG repeats and methylation of expanded allele.
Affected: Over 200 CGG repeats and methylation of expanded allele.

### Reference Range

**Next Generation Sequencing:** N/A.

**FRAX:**
Normal: Approximately 5-44 CGG repeats.
Intermediate: Approximately 54-45 unmethylated CGG repeats.
Premutation: Approximately 55-200 CGG repeats and methylation of expanded allele.
Affected: Over 200 CGG repeats and methylation of expanded allele.

### 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 72 hours of collection. Do not freeze.

### Related Tests

- The Autism Panel is available to detect the most common known genetic causes of autism/ID. The autism panel includes testing for fragile X syndrome and chromosome microarray analysis (using oligonucleotide array) and is recommended before XLID gene sequencing panel testing.
- Testing is also available for individual XLID genes that have specific phenotypes.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- X-linked Intellectual Disability: Deletion/Duplication Panel.