XLMR with Short Stature, Small Testes, Muscle Wasting, and Tremor: CUL4B Gene Sequencing

Test Code: SCUL4
Turnaround time: 6 weeks
CPT Codes: 81479 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 the syndrome, and carrier females can also be affected, but typically have milder clinical symptoms.

Mutations in the *CUL4B* gene (Xq24) have been associated with syndromic X-linked intellectual disability (XLID). In a study of 250 families with multiple members having XLID, all of whom had a normal karyotype and negative fragile X testing, mutations in *CUL4B* were identified in eight families. Phenotypic features common in these affected family members included moderate ID with some variability, severe speech delay, short outbursts of aggression, an intention tremors of the hands, seizures (common in childhood but not common in adults), ataxia, short stature, central obesity, macrocephaly, undescended and/or small testes, small feet with abnormal toes and a wide sandal gap.

Carrier females are typically unaffected, however, some mild phenotypic features have been reported.

For patients with suspected XLMR with Short Stature, Small Testes, Muscle Wasting, and Tremor, 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:
- OMIM #300354: XLMR with Short Stature, Small Testes, Muscle Wasting, and Tremor
- OMIM #300304: CUL4B gene

### Genes

**CUL4B**

### Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of XLMR with Short Stature, Small Testes, Muscle Wasting, and Tremor.
- Carrier testing in adults with a family history of XLMR with Short Stature, Small Testes, Muscle Wasting, and Tremor.

### 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:** In a study of 250 families with multiple members having XLID, all of whom had a normal karyotype and negative fragile X testing, mutations in *CUL4B* were identified in eight families. 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 clinical and/or biochemical phenotype.

**Analytical Sensitivity:** ~99%

### Specimen Requirements

Submit only 1 of the following specimen types
- * Preferred specimen type: Whole Blood

**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.

**Related Tests**

- Deletion/duplication analysis of the CUL4B 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 only for known familial mutations to individuals 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 panels are available for 30, 60, and 90 genes.