

## 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
- Cabezas et al. (2000) J Med Genet. 37:663-668.
- Tarpey et al. (2007) Am J Med Genet. 80:345-352.

### 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**

**Type:** DNA, Isolated

**Specimen Requirements:**  
Microtainer

8µg

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.

**Type: Saliva**

**Specimen Requirements:**

Oragene™ Saliva Collection Kit

Oragene™ 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.

## 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.