XLMR with Short Stature, Small Testes, Muscle Wasting, and Tremor: \textit{CUL4B} Gene Deletion/Duplication

\textbf{Test Code:} DCUL4  
\textbf{Turnaround time:} 2 weeks  
\textbf{CPT Codes:} 81228 x1

\textbf{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 \textit{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.

Mutations in the \textit{CUL4B} gene (Xq24) have been associated with syndromic \textit{X}-linked intellectual disability (XLID). In a study of 250 families with multiple members having XLID, all of whom had normal karyotype and negative fragile X testing, mutations in \textit{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: \textit{CUL4B} gene

\textbf{Genes}

\textit{CUL4B}

\textbf{Indications}

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

\textbf{Methodology}

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causing of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

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Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow 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

- Sequence analysis of the CUL4B gene is available and is required before deletion/duplication analysis.
- 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.