PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

CLIA #: 52D1027685 ● CAP #: 7185561
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Cabezas X-Linked Mental Retardation Syndrome via *CUL4B* Gene Sequencing (Test #561)

Brief Description of Clinical Features: Mutations in the *CUL4B* gene cause a form of X-linked mental retardation (XLMR) with short stature, small testes, muscle wasting, and tremor (OMIM 300354) (Cabezas et al. *J Med Genet* 37:663-668, 2000). Other clinical features include prominent lower lip, kyphosis, joint hyperextensibility, abnormal gait, decreased fine motor coordination, relative macrocephaly, central obesity, unprovoked aggressive outbursts, and small high arched feet with wide sandal-gap toes (Tarpey et al. *Am J Hum Genet* 80:345-352, 2007). Speech delay may also be evident beginning in childhood, and adults may have absent or very limited speech.

Genetics: Cabezas Syndrome is inherited in an X-linked recessive manner. The *CUL4B* gene encodes cullin 4B, a scaffold protein which forms a complex that functions as an E3 ubiquitin ligase. Affected males have the common feature of mental retardation in addition to variable presentation of the features listed above. In obligate carrier females, Zou et al. (*Am J Hum Genet* 80:561-566, 2007) found a strong selection against cells expressing the mutant allele, resulting in an extremely skewed X inactivation pattern. Consistent with this observation, obligate carriers have been found to be essentially normal (Tarpey et al. *Am J Hum Genet* 80:345-352, 2007).

Description of This Particular Test: The cullin 4B protein is encoded by exons 2-22 of the *CUL4B* gene located on chromosome Xq24. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.
Reference Sequences: Genomic: NC_000023.9 mRNA and Protein: CCDS 35379.1

Indication for Testing: Males with MR and speech delay with family histories consistent with X-linked recessive inheritance. Adult males with MR and absent or very limited speech.

Sensitivity of test: A systematic mutation screening strategy found *CUL4B* mutations in eight of 250 families with X-linked MR in which chromosomal and *FMR1* abnormalities had been ruled-out (Tarpey et al. *Am J Hum Genet* 80:345-352, 2007). These authors suggest *CUL4B* mutations may account for 3% of all XLMR, thus making it the second most frequent cause of this heterogeneous and common disorder.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *CUL4B* Exons 2-22 $ 1090

CPT Codes:

Sample Ascertainment	83890	$ 30	DNA Isolation	83891	$ 40
Amplification x 22	83898	$ 350	Sequencing x22	83904	$ 530
Separation	83894	$ 60	Interpretation/Report	83912	$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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