

## Childhood Ataxia with Central Nervous System Hypomyelination Panel: Sequencing and CNV Analysis

**Test Code:** WJ

**Turnaround time:** 6 weeks

**CPT Codes:** 81479 x1

### Condition Description

Childhood ataxia with central nervous system hypomyelination/vanishing white matter disease (CACH/VWM) is characterized by ataxia, spasticity, and variable optic atrophy. The phenotypes range from a prenatal/congenital form to a subacute infantile form (onset age

The diagnosis of CACH/VWM can be made with confidence in individuals with typical clinical findings, characteristic abnormalities on cranial MRI (cerebral hemispheric white matter that is symmetrically and diffusely abnormal with a signal intensity close to or the same as cerebrospinal fluid), and identifiable mutations in one of five causative genes (*EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*) encoding the five subunits of the eucaryotic translation initiation factor, eIF2B. Mutations have been found in approximately 90% of individuals with CACH/VWM using sequence analysis or mutation scanning. Affected individuals are homozygotes or compound heterozygotes for mutations within the same gene. The percentage of mutations found in each gene is as follows: *EIF2B1* 4%, *EIF2B2* 15%, *EIF2B3* 7%, *EIF2B4* 17%, *EIF2B5* 57%. Intrafamilial variability exists. Heterozygotes (carriers) are asymptomatic. No clinical or MRI abnormalities have been found in carriers for mutations in *EIF2B1-5*.

The prevalence of CACH/VWM is not known; it is considered one of the most common leukodystrophies. In a study of unclassified leukodystrophies in childhood, CACH/VWM was the most common. "Cree leukoencephalopathy," described in the native North American Cree and Chippewayan indigenous population, is now recognized to be the same as the infantile form of CACH/VWM.

Testing is available for each gene individually or as a panel.

[Click here](#) for the GeneTests summary on this condition.

### Genes

[EIF2B1](#), [EIF2B2](#), [EIF2B3](#), [EIF2B4](#), [EIF2B5](#)

### Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of CACH/VWM
- Carrier testing in adults with a family history of CACH/VWM

### 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 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

**Clinical Sensitivity:** Approximately 90%. 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 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.

### Specimen Requirements

**Submit only 1 of the following specimen types**

**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.

**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.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

**Related Tests**

- Sequence analysis of each of the *EIF2B1-5* genes is available individually for carrier testing in those individuals with a partner who is a known carrier.
- [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 to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.