Childhood Ataxia with Central Nervous System Hypomyelination: **EIF2B4** Gene Deletion/Duplication

**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 <1 year), an early childhood-onset form (onset age 1-5 years), a late childhood-/juvenile-onset form (onset age 5-15 years), and an adolescent-onset form. The prenatal/congenital form is characterized by severe encephalopathy. In the later-onset forms initial motor and mental development is normal or mildly delayed followed by neurologic deterioration with a chronic progressive or subacute course. Chronic progressive decline can be exacerbated by rapid deterioration during febrile illnesses or following head trauma or major surgical procedures, or by acute psychological stresses such as extreme fright.

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**

EIF2B4

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of CACH/VWM in individuals who have tested negative for sequence analysis
- Carrier testing in adults with a family history of CACH/VWM who have tested negative for sequence analysis

**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 causative 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.

**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**

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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.

**Special Instructions**

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

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the *EIF2B4* gene is available and is required before deletion/duplication analysis (WR).
- Sequence and deletion/duplication 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.
- 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.