

## Leukoencephalopathy with Vanishing White Matter and Ovarioleukodystrophy via Sequential *EIF2B1-EIF2B2-EIF2B3-EIF2B4-EIF2B5* Gene Sequencing (Test #610)

**Brief Description of Clinical Features:** Mutations in the genes that encode the five subunits of the eukaryotic translation initiation factor 2B (*EIF2B1-B5*) cause a heterogeneous spectrum of white matter disorders in which MRI studies show a symmetric pattern of white matter rarefaction, cystic degeneration, and loss of oligodendrocytes by apoptosis (van der Knaap et al. *Neurology* 51:540-547, 1998; Bugiani et al. *J Neuropath Exp Neurol* 69:987-996, 2010). Over the course of the disease, white matter gradually vanishes and is replaced by cerebrospinal fluid. Age at onset varies from prenatal to adulthood, with childhood onset being the most common. The earliest onset cases are associated with oligohydramnios, IUGR, microcephaly, contractures and severe encephalopathy. In later onset cases development is normal initially, followed by a progressive course with features of ataxia, spasticity, optic atrophy, and diminished mental ability. Periods of acute deterioration can be provoked by stresses such as febrile illness, minor head injury or extreme fright (Vermeulen et al. *Ann Neurol* 57:560-563, 2005). A severe and early onset form of the disease, called Cree leukoencephalopathy, is found among Natives of northern Quebec and Manitoba (Black et al. *Ann Neurol* 24:490-496, 1988). The mild juvenile and adult forms are often associated with primary ovarian failure, a syndrome referred to as ovarioleukodystrophy (Schiffmann et al. *Ann Neurol* 41:654-661, 1997; Fogli et al. *Am J Hum Genet* 72:1544-1550, 2003).

**Genetics:** The eukaryotic initiation factor, 2B, is a GTP exchange factor that regulates the rate of protein synthesis. EIF2B is a heteropentameric protein encoded by the five genes *EIF2B1 – B5*. The *EIF2B* related leukodystrophies (OMIM #603896) are inherited in an autosomal recessive manner. Thus far, only *EIF2B2*, *EIF2B4* and *EIF2B5* have been implicated in ovarioleukodystrophy (Fogli et al. 2003). Approximately 90% of all pathogenic variants are missense mutations (Fogli et al. *Neurology* 62:1509–517, 2004).

**Description of This Particular Test:** Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence of each gene, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. Unless otherwise requested, the order of testing will be *EIF2B5*, followed by *EIF2B2* and *EIF2B4*, and finally *EIF2B1* and *EIF2B3*.

**Reference Sequences:**

Gene:	Genomic: NC_	mRNA and Protein: CCDS_	mRNA: NM_	Protein: NP_
<i>EIF2B1</i>	000012.11	31924.1	001414.3	001405.1
<i>EIF2B2</i>	000014.8	9836.1	014239.3	055054.1
<i>EIF2B3</i>	000001.10	517.1	020365.3	065098.1
<i>EIF2B4</i>	000002.11	33164.1	001034116.1	001029288.1
<i>EIF2B5</i>	000003.11	3252.1	003907.2	003898.2

**Indications for Testing:** Individuals with MRI findings demonstrating diffusely abnormal cerebral white matter.

**Sensitivity of test:** Sensitivity among individuals with characteristic MRI findings is ~90% (Schiffmann et al. GeneReview, 2010). Over 60% of all molecularly diagnosed patients have mutations in *EIF2B5* and another ~20% have mutations in *EIF2B2* or *EIF2B4* (Schiffmann et al. 2010). Mutations in *EIF2B3* and *EIF2B1* account for ~9% and ~2% of patients, respectively.

**Turnaround Time:** Maximum of 60 days, although many tests are completed in 2-3 weeks.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price: Sequential Sequencing of: *EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5***

CPT Code	<i>EIF2B1</i>	<i>EIF2B2</i>	<i>EIF2B3</i>	<i>EIF2B4</i>	<i>EIF2B5</i>	Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$ 140 (x8)	\$ 140 (x7)	\$ 180 (x11)	\$ 160 (x10)	\$ 200 (x12)	\$ 810 (x48)
83904	\$ 220 (x8)	\$ 220 (x7)	\$ 280 (x11)	\$ 250 (x10)	\$ 310 (x12)	\$ 1210 (x48)
83894	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 120 (x1)
83912	\$ 80 (x1)	\$ 80 (x1)	\$ 80 (x1)	\$ 80 (x1)	\$ 80 (x1)	\$ 180 (x1)
<b>Totals:</b>	<b>\$ 540</b>	<b>\$ 540</b>	<b>\$ 640</b>	<b>\$ 590</b>	<b>\$ 690</b>	<b>\$ 2390*</b>

\*When three or more of the genes on this panel are sequentially tested, a 15% discount will apply to the total cost.

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

**Contact:** Thomas L. Winder, PhD, FACMG, [tom.winder@preventiongenetics.com](mailto:tom.winder@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)