

Megalencephalic Leukoencephalopathy with Subcortical Cysts, Autosomal Dominant and Recessive, *via HEPACAM* Gene Sequencing (Test #602)

Brief Description of Clinical Features: Megalencephalic leukoencephalopathy with subcortical cysts (MLC, OMIM 604004), also known as Van der Knaap disease is a slowly progressive myelinopathy characterized by macrocephaly, delay in walking, early-onset ataxia, seizure, and spasticity. Motor dysfunction, mild mental retardation, and behavioral problems may occur later in life. Additional late-onset symptoms include cerebellar ataxia, hypertonia, dysarthria, and dysphagia. Hallmark magnetic resonance imaging (MRI) findings include subcortical cysts in the tips of the temporal lobes and in frontoparietal subcortical areas and swollen cerebral white matter. Onset of symptoms usually occurs during the first year of life (Van der Knaap et al. *Ann Neurol* 37:324-334, 1995). MLC is clinically heterogeneous with regards to age of onset, degree of macrocephaly and mental impairment, severity, and disease progression. MLC is a rare disease that affects patients worldwide. Incidence is higher than expected within consanguineous populations (Topcu et al. *Brain Dev* 20:142-153, 1998). See also Van der Knaap and Scheper (GeneReviews, 2008, www.genetests.org) and the United Leukodystrophy Foundation (www.ulf.org).

Genetics: Defects in two genes, *MLC1* and *HEPACAM*, have been reported in patients with MLC (Leegwater et al. *Am J Hum Genet* 68:831-838, 2001; López-Hernández et al. *Am J Hum Genet* 88:422-32, 2011). About 75% of MLC patients have mutations in the *MLC1* gene. In these patients, the disease is inherited with an autosomal recessive pattern. Mutations in the *HEPACAM* gene have been reported in the majority of patients without *MLC1* mutations. In about 45% of these patients, the clinical symptoms and MRI findings recover significantly over time, while the macrocephaly is maintained. In this group, patients have only one heterozygous *HEPACAM* mutation, and the parents with the mutations have macrocephaly, indicating a dominant mode of inheritance. About 25% of the patients without *MLC1* mutations have the typical MLC phenotype. This group of patients have two recessive *HEPACAM* mutations, while their asymptomatic parents are heterozygous for the mutations, indicating a recessive mode of inheritance. To date, fifteen different pathogenic *HEPACAM* mutations, mostly missense, have been reported. The *HEPACAM* gene encodes GlialCAM, an IgG-like cell adhesion molecule that binds directly to the *MLC1* protein (López-Hernández et al. 2011).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *HEPACAM* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will also sequence one (Test #100, \$190) or two (Test #200, \$340) exons in family members of patients with known mutations or to confirm research results.

Reference Sequences: **Genomic:** NC_000011.9 **mRNA:** NM_152722.4
 Protein: NP_689935.2 **mRNA and Protein:** CCDS 8456.1

Indications for Test: Patients with clinical diagnosis and MRI findings of MLC, without *MLC1* mutations.

Sensitivity of Test: This test detects mutations in ~ 75% of individuals with MLC and no *MLC1* mutations.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 20-30 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of all coding exons of the *HEPACAM* Gene:** **\$ 590**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 8	83898 \$ 170	Sequencing x 8	83904 \$ 240
Separation x1	83894 \$ 30	Interpretation/Report x1	83912 \$ 80

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

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