

## Megalencephalic Leukoencephalopathy with Subcortical Cysts via *MLC1* Gene Sequencing (Test #601)

**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](http://www.genetests.org)) and the United Leukodystrophy Foundation ([www.ulf.org](http://www.ulf.org)).

**Genetics:** MLC is usually inherited in an autosomal recessive manner. 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). Mutations in *MLC1* account for ~ 75% of patients with a clinical diagnosis and MRI findings of MLC (Boor et al. *Hum Mutat* 27:505-512, 2006). Over 80 different pathogenic mutations have been reported to date, and include most types. Gross deletions account for ~ 6% of all *MLC1* mutations; while nonsense mutations appear to be rare. Mutations have been reported in patients from various ethnic populations. Several mutations are prevalent in specific populations. These include two missense mutations, p.Gly59Glu and p.Ser93Leu, that are common in the Libyan Jewish and Japanese populations, respectively. A founder mutation, c.135insC (p.Cys46LeufsX34), has been documented in East-Indian populations. However, no genotype-phenotype correlations have been established because of the clinical variability among patients with the same *MLC1* mutations. The *MLC1* protein is expressed mainly in the brain and leukocytes and has a putative transport function (Boor et al. *J Neuropathol Exp Neurol* 64:412-419, 2005).

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *MLC1* 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\_000022.10** mRNA: **NM\_015166.3**  
 Protein: **NP\_055981.1** mRNA and Protein: **CCDS 14083.1**

**Indications for Test:** Patients with clinical diagnosis and MRI findings of MLC and potential heterozygous carriers.

**Sensitivity of Test:** This test detects mutations in ~ 75% of individuals with MLC.

**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 *MLC1* Gene: \$ 740**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 12	83898 \$ 220	Sequencing x 12	83904 \$ 330
Separation x1	83894 \$ 40	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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