

Metachromatic Leukodystrophy via PSAP Gene Sequencing --Test #511

Brief Description of Clinical Features: Metachromatic Leukodystrophy (MLD, OMIM 250100) is a lysosomal storage disorder due to the abnormal degradation of sulfatide and its subsequent accumulation, mainly in the nervous system. The lysosomal degradation of sulfatide requires both the enzyme arylsulfatase A (ARSA) and the sphingolipid-activator protein 1 (SAP-1). While most patients with MLD have deficiency in the ARSA enzyme, some patients have deficiency in SAP-1. MLD is a progressive neurodegenerative disease. Three clinical subtypes are distinguished on the basis of the age of onset: **1) Late Infantile MLD** is characterized by onset before the age of two years and death by the age of five. Symptoms begin with a decline of physical and mental abilities after a few months of normal development and progress to blindness, deafness, paralysis and difficulty in swallowing (Masters et al. Arch Dis Child 39:345-355, 1964). **2) Juvenile MLD** is characterized by onset between five and ten years of age and death by the age of twenty. Symptoms include slow deterioration of speech, gait and posture, spasticity, and dystonia (Schutta et al. J Med Genet 3:86-91, 1966). **3) Adult MLD** is characterized by onset after the age of sixteen, unsteady gait and slow neurological progression with cognitive loss (Müller et al. J Neurol Sci 9:567-584, 1969). See also the MLD Foundation at <http://www.mldfoundation.org/>.

Genetics: All forms of MLD are inherited with an autosomal recessive manner; they are caused by mutations in the *ARSA* gene (Gieselmann et al. Proc Natl Acad Sci USA 86:9436-9440, 1989) or the *PSAP* gene (Kretz et al. Proc Natl Acad Sci USA 87:2541-2544, 1990). To date, 17 *PSAP* mutations have been reported. They are distributed along the entire coding region of the gene, and occurred in patients from various ethnic groups. Mutations include missense, nonsense, splicing and small insertions. In addition to MLD, mutations in the *PSAP* gene were reported in patients with Gaucher disease (Schnabel et al. FEBS Lett 284:57-59, 1991; Diaz-Font et al. Hum Genet 117:275-277, 2005), patients with Krabbe disease (Spiegel et al. Mol Genet Metab 84:160-166, 2005) and patients with Combined Saposin Deficiency (Schnabel et al. J Biol Chem 267:3312-3315, 1992).

Description of This Particular Test: The *PSAP* gene encodes the Sphingolipid Activator Protein 1 (SAP-1). This test involves bidirectional DNA sequencing of all 14 coding exons and splice sites of the *PSAP* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. We will sequence any single or double exons in family members of patients with known mutation or to confirm previous results.

Reference Sequences: Genomic: **NC_000010.10** mRNA and protein: **CCDS 7311.1**

Indications for Test: Candidates for this test are patients with MLD and no mutations in the *ARSA* gene (Test #620), and also patients with atypical forms of Gaucher disease (OMIM 610539), Krabbe disease (OMIM 611722), and Combined Saposin Deficiency (OMIM 611721).

Sensitivity of Test: Currently not known.

Turn Around Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the *PSAP* Gene: \$ 790

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x14	83898 \$ 230	Sequencing x14	83904 \$ 350
Separation x1	83894 \$ 60	Interpretation/Report x1	83912 \$ 80

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

Contact for info: Dr. Khemissa Bejaoui, khemissa@preventiongenetics.com, www.preventiongenetics.com