

## Metachromatic Leukodystrophy Panel via ARSA and PSAP Gene Sequencing --Test #621

**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 or ARSA (encoded by the *ARSA* gene) and the sphingolipid-activator protein 1 or SAP-1 (encoded by the *PSAP* gene). 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).

**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, ~150 and ~10 mutations have been reported in the *ARSA* and *PSAP* genes, respectively. They are distributed along the entire coding regions of the genes, and occurred in patients from various ethnic groups.

**Description of This Particular Test:** PreventionGenetics offers sequencing of each gene individually, or the combined Panel described here. For the Panel test, *ARSA* will be sequenced first. Sequencing of *PSAP* will not be performed if two likely causative mutations are found in *ARSA*. The Panel involves bidirectional DNA sequencing of all coding exons of the *ARSA* and *PSAP* genes. The full coding sequence of each exon plus ~50 bp of flanking DNA on either side are sequenced. This Panel provides cost savings compared to sequencing the genes individually. As indicated, we will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

**Reference Sequences:**

Gene	Genomic	mRNA	Protein	CCDS
<i>ARSA</i>	NC_000022.9	NM_000487.4	NP_000478.2	14100.1
<i>PSAP</i>	NC_000010.10	NM_002778.2	NP_002769.1	7311.1

**Indications for Test:** Candidates for this test are patients with MLD.

**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: Sequential Testing of the ARSA and PSAP Genes: \$1140**

**CPT Codes:**

Gene	83890	83891	83898	83904	83894	83912	Total
<i>ARSA</i>	\$ 30 x1	\$ 40 x1	\$ 110 x6	\$ 170 x6	\$ 60 x1	\$ 80 x1	<b>\$ 490</b>
<i>PSAP</i>	\$ 30 x1	\$ 40 x1	\$ 210 x14	\$ 330 x14	\$ 90 x1	\$ 90 x1	<b>\$ 790</b>
<b>Panel</b>	\$ 30 x1	\$ 40 x1	\$ 330 x20	\$ 490 x20	\$130 x1	\$120 x1	<b>\$ 1140</b>

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

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