

Metachromatic Leukodystrophy via ARSA Gene Sequencing (Test #620)

Brief Description of Clinical Features: Metachromatic Leukodystrophy (MLD; OMIM 250100) is caused by deficiency of Arylsulfatase A, a lysosomal enzyme involved in the metabolism of sulfated glycolipids found in myelin sheaths. In the absence of adequate Arylsulfatase A activity, cerebroside sulfate accumulates resulting in lethal progressive demyelination (von Figura et al. *in* Scriver et al. *Metabolic and Molecular Basis of Human Disease*. 3695-3724, 2001). Patients with late infantile onset MLD begin to lose acquired skills between 1 and 2 years of age. Initial signs may follow a febrile illness, and later signs include blindness, seizures, peripheral neuropathy and weakness. Juvenile onset MLD occurs between 4 years of age and puberty. Presenting signs may include a decline in school performance and changes in behavior. Progression is slower than the late infantile form and life expectancy is 10 to 20 years. Adult onset MLD patients present after sexual maturity, sometimes as late as the fifth decade of life. Declining work or school performance and changes in behavior suggestive of psychosis or dementia are sometimes the presenting features (eg Walz et al. *Arch Neurol* 44:225-7, 1987; Marcao et al. *Arch. Neurol* 62:309-313, 2005). In other adults, however, peripheral neuropathy is the presenting feature (Felice et al. *Neurology* 55:1036-1039, 2000). The disease course in adult onset cases may be two to three decades (Fluharty, Arylsulfatase Deficiency, *GeneReviews*, 2006).

Genetics: Metachromatic leukodystrophy is inherited in an autosomal recessive manner. Within families, age of onset is similar. Over 100 ARSA mutations, mostly missense, have been reported and four mutations (c.459+1G>A, c.1204+1G>A, p.Ile179Ser, p.Pro426Leu) account for approximately 25%-50% of all ARSA mutations in patients of central and western European decent (Fluharty, 2006). A pseudodeficiency allele consisting of two polymorphisms in *cis* [c.1049A>G (p.Asn305Ser); c.*96A>G] encodes diminished amount of a poorly localized ARSA protein (Ott et al. *Hum Genet* 101:135-140, 1997). This allele is associated with decreased enzyme activity but normal clinical phenotype.

Description of This Particular Test: Arylsulfatase A is coded by exons 1-8 of the ARSA gene on chromosome 22q13. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. Our test also covers the c.*96A>G SNP.

Reference Sequences: **Genomic: NC_000022.9** **mRNA and Protein: CCDS 14100.1**

Indications for Testing: Arylsulfatase A enzyme activity in patient leukocytes that is <10% of normal values; progressive neurological deterioration; or leukodystrophy on MRI studies.

Sensitivity of test: Diminished Arylsulfatase A activity is the most common cause of Metachromatic Leukodystrophy. Rarely, mutations in the prosaposin gene (*PSAP*) cause Metachromatic Leukodystrophy (Gieselmann et al. *Hum Mutat* 4:233-242, 1994). Test sensitivity should be high in cases with demonstrated enzyme deficiency. For example, Gort et al. (*Hum Mutat* 14:240-248, 1999) identified 100% of the mutations in 18 unrelated Spanish MLD patients.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of ARSA Gene** **Exons 1-8** **\$ 490**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x6	83898	\$ 110	Sequencing x6	83904	\$ 170
Separation	83894	\$ 60	Interpretation/Report	83912	\$ 80

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

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