Metachromatic Leukodystrophy: ARSA Gene Sequencing

Test Code: AV  
Turnaround time: 4 weeks  
CPT Codes: 81479 x1

**Condition Description**

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by an insufficiency of the enzyme arylsulfatase A. Patients with decreased arylsulfatase A activity have elevated urinary sulfatides and metachromatic sulfatide containing lipid deposits in their brain and nervous tissue. Development is normal until the onset of symptoms, which include progressive loss of motor function, neurological deterioration, behavioral changes, seizures, and MRI changes. The age of onset varies between forms and ranges from early childhood (late infantile MLD, approximately 50-60% of cases), to childhood (juvenile MLD, approximately 20-30% of cases), to adulthood (adult MLD, approximately 15-20% of cases). The age of onset is usually similar within a family, though exceptions have been reported.

All three forms of MLD are caused by mutations in the ARSA gene. Mutations that result in no enzyme activity are called I alleles while mutations that result in some residual enzyme activity are called A alleles. Pseudodeficiency mutations, called Pd alleles, which result in lower enzyme activity but are not disease-causing have been described. Diagnostic sequencing analysis of the ARSA gene coding region is available for patients with metachromatic leukodystrophy and their at-risk relatives on a clinical basis.

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array.

For questions about testing for MLD, call EGL Genetics at (470) 378-2200 or (855) 831-7447. For further clinical information about lysosomal storage diseases, including management and treatment, call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524.

**References:**


**Genes**

**ARSA**

**Indications**

- Confirmation of a clinical diagnosis of metachromatic leukodystrophy.
- Prenatal testing for known familial mutation.
- Assessment of carrier status in high risk family members known mutation analysis.

**Methodology**

PCR amplification of 8 exons contained in the ARSA gene coding region will be performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variants of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions are not detected by this analysis.

**Detection**

Clinical Sensitivity: 16/16 mutations found in 8 Italian families [1]. 18/18 mutations found in 9 Czech and Slovak families [2]. 32/32 mutations found in 18 Spanish families [3].

Analytical Sensitivity: ~99%

Prevalence: ~ 1 / 2,500 of western Navajo Nation [4]. The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of MLD is not specifically known, but is likely to be rare and may vary by ethnicity.

Results of molecular analysis must be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**
Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragené™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside EGL Genetics, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

**Related Tests**

- Arylsulfatase A Enzyme Assay is available for diagnosis.
- Lysosomal Enzyme Screening Panel is available to assess for 13 lysosomal storage diseases.
- Mutation Analysis for Pseudodeficiency Allele may be available upon request.
- Known Mutation Analysis (KM) is available to test family members.
- Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor for specific requirements for prenatal testing before collecting a fetal sample.