Metachromatic Leukodystrophy: ARSA Gene Deletion/Duplication

**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 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**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. 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:

Oragene™ 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.
- 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.

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