EGL Genetics | Eurofins Clinical Diagnostics
2460 Mountain Industrial Boulevard | Tucker, Georgia 30084
Phone: 470-378-2200 or 855-831-7447 | Fax: 470-378-2250
eglgenetics.com

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:
1). Bertelli, M., S. Gallo, A. Buda, S. Cecchin, A. Fabbri, C. Lapucci, G. Andrighetto, V. Sidoti, L. Lorusso, and M. Pandolfo, Novel mutations in the arylsulfatase A gene in eight Italian families with metachromatic leukodystrophy. *J Clin Neurosci*, 2006. 13(4): p. 443-8.
2). Berna, L., V. Gieselmann, H. Poupetova, M. Hrebicek, M. Elleder, and J. Ledvinova, Novel mutations associated with metachromatic leukodystrophy: phenotype and expression studies in nine Czech and Slovak patients. *Am J Med Genet A*, 2004. 129(3): p. 277-81.
3). Gort, L., M.J. Coll, and A. Chabas, Identification of 12 novel mutations and two new polymorphisms in the arylsulfatase A gene: haplotype and genotype-phenotype correlation studies in Spanish metachromatic leukodystrophy patients. *Hum Mutat,* 1999. 14(3): p. 240-8.
4). Holve, S., D. Hu, and S.E. McCandless, Metachromatic leukodystrophy in the Navajo: fallout of the American-Indian wars of the nineteenth century. *Am J Med Genet,* 2001. 101(3): p. 203-8.

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 variations 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

Type: DNA, Isolated

Specimen Requirements:
Microtainer
8µg
Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is

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recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:
EDTA (Purple Top)
Infants and Young Children (2 years of age to 10 years old: 3-5 ml
Older Children & Adults: 5-10 ml
Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: Saliva

Specimen Requirements:
Oragene™ Saliva Collection Kit
Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

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.