ARSB Gene Analysis in Maroteaux-Lamy Syndrome/ Mucopolysaccharidosis VI (MPSVI)

CLINICAL FEATURES

Mucopolysaccharidosis VI (MPSVI) or Maroteaux-Lamy syndrome is a lysosomal storage disorder with a wide spectrum of features ranging from a severe, rapidly progressing form to a relatively mild, slowly progressing form. Symptoms can include short stature, skeletal deformities, stiff and contracted joints, hepatosplenomegaly, coarse facial features, respiratory difficulties, hearing loss, corneal clouding, and cardiac abnormalities. Neurological development is generally normal. The rapidly progressing form is characterized by onset before 2 or 3 years, impaired mobility by 10 years, delayed puberty, an adult height less than 120 cm, cervical spinal cord compression, respiratory insufficiency, surgical complications and frequently death in the 2nd or 3rd decade due to heart failure.[1] The slowly progressing form is characterized by later onset of symptoms with a diagnosis being made after 5 years of age; however, some patients are not diagnosed until the 2nd or 3rd decades. These patients may also develop skeletal complications including carpal tunnel syndrome, joint disease and a decrease in their overall functional status, and most will develop more serious complications of MPSVI at some point including joint degeneration, cardiac valve disease, sleep apnea, decreases in pulmonary function and reduced endurance.[1] Birth prevalence estimates for MPS VI range from 0.5 to 4.3 per million live births, with the exception of a very high rate in Turkish immigrants in Germany (2.3 per 105 live births).[1]

GENETICS

MPSVI is caused by pathogenic variants in the *ARSB* gene encoding the arylsulfatase B (ASB) or *N*-acetylgalactosamine 4-sulfatase enzyme that hydrolyzes the C4 sulfate ester from the glycosaminoglycans (GAG) dermatan sulfate and chondroitin sulfate during their lysosomal degradation. Patients with MPSVI generally have ASB activity that is 10% or less than controls in leukocytes or cultured fibroblasts, leading to their intralysosomal storage and excretion in the urine. The *ARSB* gene is located on chromosome 5q13-5q14 and has 8 exons.

INHERITANCE PATTERN

Autosomal Recessive

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *ARSB* gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations.

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Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

REFERENCES:

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