MCOLN1 Variant Analysis in Mucolipidosis IV

Clinical Features:
Mucolipidosis IV (MLIV) is a progressive neurological lysosomal storage disease that usually is evident during the first year of life, and presents with mental retardation, corneal opacities, and delayed developmental milestones. Ocular findings also include retinal degeneration, myopia, strabismus, and photophobia. Neurological symptoms include hypotonia and pyramidal tract signs. There are cytoplasmic inclusions ("storage bodies") in almost every cell type of the patients. Most affected individuals reach a maximal developmental age of 12-15 months. Mucolipidosis IV is due to pathogenic variants in the *MCOLN1* gene and more than 80% of reported patients are of Ashkenazi Jewish descent. Two common variants (IVS3-2 A>G and a 6,450 bp deletion) account for 95% of cases in the Ashkenazi Jewish population. MLIV is rare in the general population.

Inheritance Pattern:
Autosomal recessive

Test Methods:
Two tests are available for the *MCOLN1* gene. Sequence analysis of the *MCOLN1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the coding exons, and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *MCOLN1* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. Exon-leveldeletion/duplication testing can also be ordered separately for the *MCOLN1* gene. Of note, this deletion/duplication test will detect the common 6.45 kb deletion, that is not identifiable by sequence analysis.

Test Sensitivity:
Full sequence analysis of *MCOLN1* is expected to identify the common IVS3-2 A>G variant, which is present on up to 72-78% of mutant MCOLN1 alleles in Ashkenazi Jewish carriers, and other variant(s) if they exist in the coding regions and intron/exon boundaries in persons with MLIV from Ashkenazi Jewish, non Ashkenazi Jewish and mixed ancestry backgrounds. The 6.45 kb deletion, which is found in approximately 23-30% of Ashkenazi Jewish carriers would not be identified by sequence analysis, but would be detected by exon-level deletion/duplication analysis of the *MCOLN1* gene and can be ordered separately. The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

Over 80% of patients with MLIV are Ashkenazi Jews, and two variants account for 95% of these cases. The remaining 5% of Jewish patients with MLIV are expected to have variants elsewhere in the *MCOLN1* gene. The most common variant occurring in 72%-78% of Ashkenazi Jewish carriers is a splice site defect (IVS3-2 A→G). Less frequent is a 6,450 bp deletion that spans from the 5'UTR into exon 7 of the *MCOLN1* gene, which is found in about 23-30% of Ashkenazi Jewish carriers.

References:

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