LIPA Gene Analysis in Lysosomal Acid Lipase Deficiency

CLINICAL FEATURES

Lysosomal acid lipase (LAL) is a lysosomal enzyme that is involved in intracellular lipid metabolism. Complete deficiency of the LAL enzyme causes Wolman disease, while reduced but residual LAL activity (approximately 2%-8% of controls in blood leukocytes) causes cholesteryl ester storage disease (CESD). Wolman disease is fatal within the first year of life due to severe hepatomegaly, persistent diarrhea and failure to thrive. CESD is a milder disease that is characterized by hyperlipidemia and hepatomegaly that can be observed in childhood or develop in adulthood. Several CESD patients with no typical clinical symptoms or with only mild liver enlargement even at an advanced age have also been reported.[1] In general, CESD is not associated with a reduced life span although atherosclerosis and chronic liver disease have been identified as a premature cause of death.[2] The incidence of CESD in the general population is not known but has been estimated at approximately 2.5 per 100,000, while Woman disease is extremely rare.[3]

GENETICS

LAL deficiency is caused by variants in the *LIPA* gene that encodes the LAL enzyme that hydrolyzes cholesteryl esters and triglycerides internalized via receptor-mediated endocytosis of plasma lipoprotein particles. Deficiency of the LAL enzyme results in accumulation of cholesteryl esters and triglycerides in most tissues of the body, which is higher in patients with Wolman disease than in patients with CESD. The *LIPA* gene is located on chromosome 10q23.31 and has 10 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 *LIPA* 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. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

VARIANT SPECTRUM

Variants reported in the *LIPA* gene include missense, nonsense, splice site, small deletions/insertions and large deletions .Variants that cause Wolman disease result in the production of catalytically inactive LAL enzyme and are typically deletions/insertions, splice site and nonsense variants. Missense variants which almost completely

abolish enzyme function are rare but have also been associated with Wolman disease.[1] A c.894-1 G>A (IVS8-1 G>A) splice site variant accounts for approximately 70% of *LIPA* alleles in patients with CESD and is estimated to be found with a frequency of 1 in 200 in the general population.[1, 3] The c.894-1 G>A variant allows for approximately 3% of normal splicing to occur.[5] With the exception of the c.894-1 G>A splice site variant, variants associated with CESD are heterogeneous missense variants that retain some residual LAL activity.1It is not uncommon for a patient with CESD to harbor a Wolman variant on one *LIPA* allele and a CESD variant on the opposite allele.[1]

REFERENCES:

1. Lohse et al., (2000) J Lipid Res 41:23-31.
2.Pagani et al., (1998) J Lipid Res 39 :1382-1388.
3.Pisciotta et al., (2000) Mol Genet Metab 97 :143-148.
4.Anderson et al., (1999) Mol Genet Metab 68 :333-345.
5.Lohse et al., (1999) J Lipid Res 40 :221-228.
6.Pagani et al., (1996) Hum Mol Genet 5 :1611-1617.
7.Aslanidis et al., (1996) Genomics 33 :85-93.
8.Fasano et al., (2012) Mol Genet Metab 105 :450-456