

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 Wolman disease is extremely rare.³

Genetics:

LAL deficiency has an autosomal recessive inheritance pattern. 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.

Test Methods:

Variant analysis of the LIPA gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the LIPA 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.

Test Sensitivity:

In a series of small studies each including between 2 and 11 patients with LAL deficiency, analysis of the LIPA gene identified variants on 96% of alleles (65/68).^{1, 2, 3, 4, 5, 6, 7, 8}

Variant Spectrum:

At this time, greater than 40 variants in the LIPA gene have been reported including 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 In almost all reported cases, patients with Wolman disease have been born to consanguineous parents.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.¹ It 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:

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3. Pisciotta et al., (2000) Mol Genet Metab 97 :143-148.
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7. Aslanidis et al., (1996) Genomics 33 :85-93.
8. Fasano et al., (2012) Mol Genet Metab 105 :450-456.