

Wolman Disease and Cholesteryl Ester Storage Disease via *LIPA* Gene Sequencing -- Test #482

Brief Description of Disorders: Wolman disease (WD, OMIM 278000) and cholesteryl ester storage disease (CESD, OMIM 278000) are rare storage disorders due to the deficiency of the lysosomal acid lipase (LAL). This deficiency leads to the progressive accumulation of triglycerides and cholesteryl esters in lysosomes of affected tissues (Patrick and Lake, Nature 222:1067-1068, 1969). Although both WD and CESD present with divergent phenotypes, the two disorders can be distinguished on the basis of the age of onset, disease course and severity. WD is characterized by onset of symptoms during the first or second month of life and death by the end of the first year from hepatic and adrenal failure. Typical symptoms include hepatosplenomegaly, steatorrhea, bilateral adrenal calcification, and failure to thrive (Dincsoy et al. Am J Clin Pathol 81:263-269, 1984). CESD is diagnosed within the first or second decade of life and follows milder course, with survival beyond middle age. Clinical features include hepatomegaly, hypercholesterolemia, and premature atherosclerosis (Burke and Schubert, Science 176:309-310, 1972; Sloan and Fredrickson, J Clin Invest 51:1923-1926, 1972). Biochemically, WD is characterized by a complete absence of LAL activity, while CESD patients maintain a residual enzyme activity.

Genetics: WD and CESD both exhibit autosomal recessive inheritance. Mutations in the *LIPA* gene are responsible for LAL deficiency and subsequent development of both disorders (Anderson et al. Proc Natl Acad Sci USA 91:2718-2722, 1994; Klima et al. J Clin Invest 92:2713-2718, 1993). At least 15 and 25 mutations have been reported, worldwide, in patients with CESD and WD respectively (<http://www.biobase-international.com>). Mutations causing WD produce an enzyme with no activity or no enzyme at all; while at least one CESD mutant allele produces enough residual enzymatic function to ameliorate the phenotype (Anderson et al. Mol Genet Metab 68:333-345, 1999).

Description of This Particular Test: The *LIPA* gene encodes lysosomal acid lipase, which catalyzes the hydrolysis of cholesteryl esters and triglycerides. This test involves bidirectional DNA sequencing of all 9 coding exons and splice sites of the *LIPA* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will sequence any single or double exons in family members of patients with known mutations or to confirm previous results.

Reference Sequences: Genomic: **NC_000010.9** mRNA: **NM_000235.2**
 Protein: **NP_000226.2** mRNA and Protein: **CCDS 7401.1**

Indications for Test: Patients with features suggestive of WD or CESD and their biological relatives are candidates.

Sensitivity of Test: Unknown at this time.

Turnaround Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the *LIPA* Gene: **\$ 620**

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x9	83898	\$ 170	Sequencing x9	83904	\$ 250
Separation x1	83894	\$ 45	Interpretation/Report x1	83912	\$ 85

Accreditation Info. CLIA ID #: **52D1027685** (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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