

Smith-Lemli-Opitz Syndrome via *DHCR7* Gene Sequencing (Test #410)

Brief Description of Clinical Features: Smith-Lemli-Opitz Syndrome (SLOS) (OMIM 270400) is a deficiency in the enzyme 7-dehydrocholesterol reductase which catalyzes the last step in the biosynthesis of cholesterol. Affected children have high plasma 7-dehydrocholesterol/cholesterol ratios. The enzyme deficiency leads to a variety of developmental problems including growth and mental retardation, 2-3 toe syndactyly, microcephaly, anteverted nares, ptosis, genital abnormalities, heart defects, polydactyly, and photosensitivity. The most severe cases are usually diagnosed in infancy, with milder cases diagnosed in childhood or even adult life. The great majority of SLOS patients have some clinical features of autism (Sikora et al. Am J Med Genet, Part A 140A:1511-1518, 2006). For more information see Cunniff GeneReviews (www.genetests.org) 2004; Correa-Cerro and Porter Mol Genet Metab 84:112-126, 2005; and Yu and Patel Clin Genet 68:383-391, 2005.

Genetics: SLOS exhibits autosomal recessive inheritance. Mutations in the *DHCR7* gene encoding 7-dehydrocholesterol reductase are the only known cause of SLOS. About 125 causative *DHCR7* mutations have been reported to date (Witsch-Baumgartner et al. Hum Mut 17:172-182, 2001; Correa-Cerro and Porter 2005). About 90% of these mutations are missense, although “gene knockout” mutations (splicing, nonsense, and frameshift) are also known. Among those with European ancestry, the most common mutations appear to be IVS8-1 G>C, Thr93Met, Trp151Stop, Arg404Cys, and Val326Leu. Carrier rates for SLOS in some populations may be as high as 1/30. Missed diagnoses and especially spontaneous miscarriages may explain the difference between the expected incidence based on carrier rates and the actual incidence of roughly 1/30,000 (Nowaczyk et al. Am J Med Genet, Part A 140A:2057-2062, 2006).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 7 coding exons of the *DHCR7* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. We will sequence any single exon or pair of exons in family members of patients with known mutations, and to confirm research results (\$190-340).

Reference Sequences: Genomic: NC_000011.8 mRNA: NM_001360.1 protein: NP_001351.1

Indications for Test: All patients with biochemical and clinical features of SLOS are candidates for this test. We will also sequence the *DHCR7* gene in relatives of patients to determine carrier status.

Sensitivity of Test: Using DNA sequencing and characterizing patients by plasma sterol concentrations and clinical features, Witsch-Baumgartner et al. (Am J Hum Genet 66:402-412, 2000) detected two likely causative mutations in 78 out of 84 (93%) SLOS patients and one likely causative mutation in the remaining 6 (7%).

Turn Around 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 complete coding regions of *DHCR7* Gene **\$ 440**

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x7	83898	\$ 100	Sequencing x7	83904	\$ 140
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 80

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

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