DHCR7 Gene Analysis in Smith-Lemli-Opitz Syndrome

Disorder also known as: SLO syndrome; 7-dehydrocholestorol reductase deficiency

Clinical Features:
Smith-Lemli-Opitz syndrome (SLOS) is a severe developmental disorder. The clinical spectrum is wide and includes both pre- and post-natal growth retardation, mild to severe mental retardation, multiple congenital malformations (both major and minor), and characteristic facies. Frequent additionally observed findings include: microcephaly, micrognathia, cleft palate, cardiac defects, abnormal external genitalia, post-axial polydactyly, and 2-3 toe syndactyly. Infants are often hypotonic with poor suck, and have failure to thrive. Older children commonly have behavioral concerns including autism, hyperactivity, aggression, and self-injurious behavior.[1-3]

Genetics:
Pathogenic variants in the *DHCR7* gene underlie SLOS. Children with SLOS have elevated serum 7-dehydrocholesterol (7-DHC) levels and low levels of serum cholesterol. In cholesterol biosynthesis, 7-DHC is converted to cholesterol by the enzyme 3β-hydroxysterol Δ^7-reductase (sterol delta-7-reductase), which is encoded by the gene *DHCR7*. *DHCR7* is also required to reduce 7-dehydrodesmosterol to desmosterol.[1-3] The *DHCR7* gene is located on chromosome 11q13.4.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *DHCR7* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons (3-9) and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *DHCR7* 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:
According to a large study of individuals with clinically and biochemically characterized SLOS, sequence analysis of the coding exons and corresponding splice junctions detected one or both variants in 96% of patients.[1] There have been several reports of patients with SLOS in whom only a single heterozygous variant was identified in the coding sequence of the *DHCR7*

gene. Although variants in the promoter region of the gene have not thus far been identified, it is possible that the second variant in these rare patients affects the regulatory mechanism of the gene.[2] The sensitivity of *DHCR7* analysis in prenatal cases ascertained based on fetal ultrasound abnormalities is currently unknown. The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

More than 200 variants in the *DHCR7* gene have been described. A single splice-site variant accounts for approximately 1/3 of mutant alleles in identified patients, denoted IVS8-1G→C. However, variants can occur most anywhere else within the coding region of the gene. Variants include missense, nonsense, splice-site, small deletions/insertions, and gross deletions.[4,5]

References:

1. Witsch-Baumgartner et al. (2000) Am. J. Hum. Genet. 66 (2):402-12 (PMID: 10677299)
2. Correa-Cerro et al. (2005) Molecular Genetics And Metabolism 84 (2):112-26 (PMID: 15670717)
3. Yu et al. (2005) Clin. Genet. 68 (5):383-91 (PMID: 16207203)
4. Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)
5. Lanthaler et al. (2015) Clin. Genet. 88 (2):149-54 (PMID: 25040602)