

Prenatal Testing for DHCR7 Gene Variants: Smith-Lemli-Opitz Syndrome

Disorder also known as: SLO syndrome; RSH syndrome; Rutledge lethal multiple congenital anomaly syndrome; Polydactyly, sex reversal, renal hypoplasia, and unilobar lung; Lethal acrodysgenital syndrome

Clinical Features in Newborns and Children:

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 fail to thrive. Older children commonly have behavioral concerns including autism, hyperactivity, aggression, and self-injurious behavior.

Children with SLOS have elevated serum 7-dehydrocholesterol (7-DHC) levels and low levels of serum cholesterol. In affected pregnancies, abnormal concentration of 7-DHC occur in amniotic fluid obtained between 15-18 week's gestation or in tissue from chorionic villus sampling (CVS). In cholesterol biosynthesis, 7-DHC is converted to cholesterol by the enzyme 3 β -hydroxysterol Δ 7-reductase (sterol delta-7-reductase), which is encoded by the gene DHCR7. DHCR7 is also required to reduce 7-dehydridesmosterol to desmosterol. Pathogenic variants in the DHCR7 gene are the cause of SLOS.

Prenatal Ultrasound and Biochemical Findings:

Ultrasound evaluation in affected pregnancies may identify intrauterine growth restriction (IUGR), major brain, heart, renal or limb malformations and ambiguous genitalia, with female-appearing genitalia or severe hypospadias seen in an XY fetus. IUGR is the predominant ultrasound finding⁴. Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk for SLOS due to a positive family history can be offered molecular testing regardless of ultrasound findings, if desired. Maternal serum screening at 15-20 week's gestation that identifies low concentrations of unconjugated estriol, HCG and alpha-fetoprotein or isolated low unconjugated estriol may warrant further testing for SLOS in the fetus.⁵ However, data are currently insufficient to make specific recommendations about which pregnancies to investigate for SLOS when results of maternal serum screening tests are abnormal.⁶ For pregnancies with no family history of SLOS, where SLOS is suspected due to ultrasound findings, abnormal maternal serum screening or both, measurement of 7-DHC

levels in amniotic fluid or in tissue obtained from chorionic villus samples (CVS) is recommended prior to sequence analysis of the DHCR7 gene.

Genetics:

Autosomal recessive

Test Methods:

Using genomic DNA, analysis is performed by bidirectional sequencing of coding exons (3-9) and flanking splice sites of the DHCR7 gene. If sequencing identifies a variant on only one allele of the DHCR7 gene, 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. For known familial variants, the relevant portion of the DHCR7 gene will be analyzed in duplicate. Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

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% 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 and/or abnormal maternal serum screening result is currently unknown.

References:

1. Witsch-Baumgartner et al., (2000) *Am J Hum Genet* 66:402-412;
2. Correa-Cerro et al., (2005) *Mol Gen Metab* 84:112-26;
3. Yu, H. and Patel, S.B., (2005) *Clin Genet* 68:383-91.
4. Goldenberg A, et al., *Am J Med Genet A*. 2004; 124: 423–6.
5. Rossiter et al., (1995) *Am J Med Genet* 56:272-5.
6. Irons, M. (Updated [Oct. 24, 2007]). *Smith-Lemli-Opitz Syndrome* In: *GeneReviews at Genetests: Medical Genetics Information Resource* (database online). Copyright, University of Washington, Seattle. 1997- 2010. Available at <http://www.genetests.org>