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Smith-Lemli-Opitz Syndrome

Synonym: SLOS

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Summary

Clinical characteristics

Smith-Lemli-Opitz syndrome (SLOS) is a congenital multiple-anomaly / cognitive impairment syndrome caused by an abnormality in cholesterol metabolism resulting from deficiency of the enzyme 7-dehydrocholesterol (7-DHC) reductase. It is characterized by prenatal and postnatal growth restriction, microcephaly, moderate-to-severe intellectual disability, and multiple major and minor malformations. The malformations include distinctive facial features, cleft palate, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly, and 2-3 syndactyly of the toes. The clinical spectrum is wide; individuals with normal development and only minor malformations have been described.

Diagnosis/testing

The diagnosis of SLOS is established in a proband with suggestive clinical features and elevated 7-dehydrocholesterol level and/or by identification of biallelic pathogenic variants in *DHCR7* by molecular genetic testing. Although serum concentration of cholesterol is usually low, it may be in the normal range in approximately 10% of affected individuals, making it an unreliable test for screening and diagnosis.

Management

Treatment of manifestations: While no long-term dietary studies on cholesterol supplementation have been conducted in a randomized fashion, cholesterol supplementation may result in clinical improvement. Early intervention and physical/occupational/speech therapies are indicated for identified disabilities. Consultation with a nutritionist and consideration of hypoallergenic or elemental formulas in infants; gastrostomy as needed for feeding; neonatal cholestatic liver disease often resolves with cholesterol and/or bile acid therapy. A trial of melatonin or another hypnotic may be considered for those with sleep disturbance. Orthotics, tendon release surgery, or Botox® as needed. Proper clothing and sunscreen with UVA and UBV protection for photosensitivity. Routine treatment for gastroesophageal reflux, pyloric stenosis, Hirschsprung disease,

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constipation, recurrent otitis media, hearing loss, cataracts, ptosis, strabismus, psychiatric disturbance/behavioral issues, seizures, cleft palate, dental anomalies, congenital heart defects, hearing loss, limb defects, and adrenal insufficiency, including stress-related doses of steroids during illness and other physical stress.

Surveillance: Routine health supervision including monitoring of growth parameters, nutritional status, developmental progress, behavior, stooling pattern, changes in tone, seizures (if present), and movement disorders at each visit; monitoring of cholesterol, serum concentration of 7-DHC, and serum amino transferases (ALT and AST) every three to four months in the first few years of life and twice yearly thereafter; screening for vision problems and hearing loss annually in childhood; dental evaluations twice yearly starting at age three years; assessment for signs of puberty and rate of pubertal progression starting at age ten years; monitor for gonadal location and signs/symptoms of urinary tract infection as clinically indicated.

Agents/circumstances to avoid: Treatment with haloperidol or other drugs in the same class. Psychotropic drugs (trazodone, aripirazole) that elevate 7-DHC should be used with caution; extended sun exposure should be avoided.

Evaluation of relatives at risk: Testing of all sibs so that cholesterol supplementation can begin as soon as possible after birth.

Other: For severely affected infants, consider surgical management of congenital anomalies (e.g., cleft palate, congenital heart disease, genital anomalies) as for any other severe, usually lethal disorder.

Genetic counseling

SLOS is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier detection is possible if the pathogenic variants in the family are known. Prenatal testing for a pregnancy at increased risk is possible using biochemical testing or molecular genetic testing if the pathogenic variants in the family are known.

Diagnosis

Clinical diagnostic criteria for Smith-Lemli-Opitz syndrome (SLOS) have not been established.

Suggestive Findings

Smith-Lemli-Opitz syndrome **should be suspected** in individuals with the following clinical features and laboratory findings.

Clinical features

- Characteristic facial features (narrow forehead, epicanthal folds, ptosis, short mandible with preservation of jaw width, short nose, anteverted nares, and low-set ears)
- 2-3 syndactyly of the toes (minimal to Y-shaped)
- Microcephaly
- Growth restriction / short stature
- Intellectual disability
- Hypospadias in males
- Cleft palate
- Postaxial polydactyly

Laboratory findings

- Elevated serum concentration of 7-dehydrocholesterol (7-DHC) as defined by the laboratory

  Note: (1) 7-DHC concentration is usually measured in blood samples, but can be measured in other tissues. In rare instances, serum concentrations of 7-DHC and cholesterol can be in the normal ranges and a strong clinical suspicion of SLOS may require sterol analysis from cultured fibroblasts or confirmatory genetic testing [Koo et al 2010]. (2) Some individuals on psychotropic medications can have elevated 7-DHC levels secondary to the medication, giving rise to false positive test results. Such individuals typically do not have the physical features of SLOS, but may be tested for SLOS because of neurocognitive issues. (3) Different laboratories may report results in different units. Laboratories in the US report results as milligrams per deciliter (mg/dL) or micrograms per milliliter (µg/mL); European laboratories most often report results as millimoles per liter (mmol/L). Thus, direct comparison of values between laboratories requires caution.

- **Low serum concentration of cholesterol.** Serum concentration of cholesterol in unaffected and affected individuals can overlap, particularly when the affected individuals are older or have a milder phenotype.

  Because normal serum concentrations of cholesterol change with age, values must be considered in the context of the individual.

  Note: Serum concentration of cholesterol determined by the method employed in most hospital laboratories, which measures total cholesterol (cholesterol plus the precursors), does not identify all individuals with SLOS because total cholesterol levels can be in the normal range.

Establishing the Diagnosis

The diagnosis of Smith-Lemli-Opitz syndrome **is established** in a proband with suggestive clinical features and elevated 7-dehydrocholesterol level AND/OR biallelic pathogenic (or likely pathogenic) variants in *DHCR7* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *DHCR7* variants of uncertain significance (or of one known *DHCR7* pathogenic variant and one *DHCR7* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Smith-Lemli-Opitz syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Smith-Lemli-Opitz syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Smith-Lemli-Opitz syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *DHCR7* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not

detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **An intellectual disability multigene panel** that includes *DHCR7* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of Smith-Lemli-Opitz syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Smith-Lemli-Opitz Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DHCR7	Sequence analysis [3]	96% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	<4% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Waterham & Hennekam [2012]
5. Most of the affected individuals studied have two detectable pathogenic variants; rare individuals had only one detectable pathogenic variant [Waterham & Hennekam 2012].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Weaver et al [2010], Aradhya et al [2012]

Clinical Characteristics

Clinical Description

Severe Smith-Lemli-Opitz syndrome (SLOS) is characterized by prenatal and postnatal growth restriction, microcephaly, moderate-to-severe intellectual disability, and multiple major and minor malformations including

characteristic facial features, cleft palate, abnormal gingivae, cardiac defects, hypospadias, ambiguous genitalia (failure of masculinization of male genitalia), postaxial polydactyly, and 2-3 toe syndactyly [Nowaczyk & Irons 2012]. Individuals with milder forms may have only subtle facial characteristics, hypotonia, 2-3 toe syndactyly, and mild to no intellectual disability. Clinical variability is noted even within families, as sibs with SLOS have been reported with medical and developmental problems of different degrees.

Table 2. Features of Smith-Lemli-Opitz Syndrome

Feature	% of Persons w/Feature	Comment
2-3 toe syndactyly	>99%	
Growth restriction	>90%	
Microcephaly	80%-84%	
Photosensitivity	Common [1]	UVA mediated
Congenital heart defect	50%	
Hypospadias &/or bilateral cryptorchidism	50%	In males
Cleft palate	40%-50%	
Hypotonia	40%-50%	
Postaxial polydactyly	25%-50%	
Renal anomalies	25%	
External female genitalia w/a 46,XY karyotype	20%-25%	
Cataract	20%	May be congenital or develop acutely

1. Exact frequency unknown

Growth

- Prematurity and breech presentation are common. Neonates frequently have poor suck, irritability, and failure to thrive.
- Children and adults with SLOS are generally smaller than average with severe failure to thrive.
  - Growth parameters are typically 2 SD or more below the mean for age or, in less affected children, for family background.
  - Congenital, static microcephaly is also common.

Feeding difficulties/gastrointestinal issues. Infants with SLOS frequently have feeding problems secondary to a combination of hypotonia, oral-motor incoordination, gastrointestinal problems and formula intolerance.

- In general, infants with more severe congenital anomalies have more feeding problems.
- Constipation is a common problem and may be related to hypotonia, dysmotility, and/or hypomotility.
- Gastroesophageal reflux is also common in infancy and improves with age in some individuals.
- Liver disease is variable and can range from severe cholestasis (generally in those who are more severely affected) to mild/moderate stable elevation of serum amino transferases [Rossi et al 2005].
- Pyloric stenosis and Hirschsprung disease are rare findings.

Development and behavior

- Cognitive function ranges from borderline intellectual capability to severe intellectual disability. Low normal intellectual function can be seen in individuals with mild forms of SLOS [Mueller et al 2003, Eroglu et al 2017].
- Behavior signs/symptoms include the following:

- Sensory hyperreactivity
- Irritability
- Sleep cycle disturbance
  Many individuals require very little sleep, often only a few hours per night [Zarowski et al 2011].
- Self-injurious behavior (hand biting and/or head banging)
- Autism spectrum behaviors (46%-53%)
- Temperament dysregulation
- Social and communication deficits [Diaz-Stransky & Tierney 2012, Thurm et al 2016]

- Depression and other psychiatric problems have been reported in older individuals.

Neurologic issues. Hypotonia, which is common in young children, affects feeding and delays motor development.

- Older children often exhibit hypertonia.
- Seizures can occur, but are not more common than in the general population.

Neuroimaging. Individuals with SLOS commonly have anomalies involving the midline and para-midline structures of the brain [Lee et al 2013]. Developmental abnormalities of the central nervous system include the following [Nowaczyk & Irons 2012, Lee et al 2013]:

- Abnormalities of myelination
- Ventricular dilatation
- Malformations of the corpus callosum and/or cerebellum
- Dandy-Walker malformation and its variants
- Holoprosencephaly (5%) [Weaver et al 2010]

Skin. Photosensitivity, which is commonly seen in SLOS, appears to be UVA mediated [Anstey 2001].

- Photosensitivity can be severe and can result from even brief exposure to sunlight.
- Many individuals cannot tolerate any exposure to sunlight; others can tolerate varying periods of exposure if properly clothed and protected with a UVA- and UVB-protection sunscreen.

Anomalies of the genitalia. Many 46,XY individuals with severe manifestations of SLOS have extreme undervirilization of the external genitalia, resulting in female external genitalia (termed "sex reversal"). Approximately 20%-25% of individuals with SLOS described in the literature have a 46,XY karyotype with a female phenotype [Lin et al 1997].

Because genital abnormalities are easier to recognize in males than females, males are more likely than females to be evaluated for a diagnosis of SLOS.

- Hypospadias and/or bilateral cryptorchidism occurs in 50% of reported males with SLOS [Gorlin et al 1990, Lin et al 1997].
- Bicornuate uterus and septate vagina have been noted in 46,XX females [Lowry et al 1968].
- Other findings include:
  - Persistent urogenital sinus and posterior labial fusion without clitoromegaly in a female with an XX karyotype [Chemaitilly et al 2003];
  - Precocious puberty in affected girls [Irons, unpublished].

Renal anomalies. Approximately 25% of affected individuals have renal anomalies, most commonly renal hypoplasia or agenesis, renal cortical cysts, hydronephrosis, and structural anomalies of the collecting system.

Oral

- Cleft palate is present in 40%-50% of affected individuals and may contribute to feeding and growth problems.
- Dental anomalies include oligo- and polydontia, enamel hypoplasia, tooth crowding, agenesis of teeth, marked curve of Spee (occlusal curvature), and widely spaced incisors [Muzzin & Harper 2003, Rojare et al 2019].

Characteristic facial features include narrow forehead, epicanthal folds, ptosis, short nose with anteverted nares, short mandible with preservation of jaw width, and nevus simplex (sometimes also referred to as capillary hemangioma or nevus flammeus) over the nasal root that extends onto the glabella [Nowaczyk et al 2012].

- The ears are low set and posteriorly rotated, but can be otherwise normal [Nowaczyk et al 2012].
- The neck is often short with redundant skin at the nape.

The characteristic facial appearance may be subtle in some individuals, but when assessed objectively, is present even in the least severely affected individuals; the severity of the dysmorphic features correlates with the severity of both the biochemical and physical abnormalities [Nowaczyk et al 2012].

Ophthalmologic findings. Congenital cataracts are present in approximately 20% of affected individuals [Cunniff et al 1997, Lin et al 1997]. Cataracts may also develop acutely [Goodwin et al 2008]. Other ophthalmologic manifestations [Atchaneeyasakul et al 1998]:

- Ptosis
- Strabismus
- Optic atrophy
- Optic nerve hypoplasia

Cardiac anomalies. Up to 50% of affected individuals have an identified cardiac defect with an increased incidence of atrioventricular canal defects and anomalous pulmonary venous return. Pulmonary stenosis has also been reported [Prosnitz et al 2017, Nasr et al 2019]

Respiratory. Cardiorespiratory problems can occur secondary to malformations of the heart or respiratory tract, including the trachea or larynx.

- Abnormal pulmonary lobation and pulmonary hypoplasia are common in more severely affected individuals [Quélin et al 2012].
- An increased frequency of upper- and/or lower-respiratory infections is seen, particularly in infancy and early childhood.

Musculoskeletal findings. Y-shaped syndactyly of the second and third toes is the most common (though not universal) finding.

- Postaxial, bilateral foot polydactyly is present in one quarter to one half of all affected individuals [Gorlin et al 1990, Cunniff et al 1997, Lin et al 1997]. Some individuals with a more severe phenotype also have postaxial bilateral polydactyly of the hands.
- Less common findings include hypoplastic or short thumbs and thenar hypoplasia.
- The index finger often has a subtle "zig-zag" appearance secondary to misalignment of the phalanges [Nowaczyk & Irons 2012].
- Less common are clinodactyly, hammer toes, and dorsiflexed halluces.

Ears and hearing. Recurrent otitis media and conductive hearing loss have been reported in a majority of infants and children with SLOS.

Endocrinologic issues. Because cholesterol is a precursor of steroid hormones (including cortisol, aldosterone, and testosterone), endocrine problems (including electrolyte abnormalities, hypoglycemia, and hypertension) can be seen.

- Adrenal insufficiency can result in severe electrolyte abnormalities [Chemaitilly et al 2003].
- Low serum concentrations of testosterone have been seen in severely affected males [Chasalow et al 1985].

Biochemical. Although strict correlations between the serum concentration of cholesterol and clinical outcome are not possible, most studies have identified an inverse correlation between serum concentration of cholesterol and number and severity of congenital anomalies [Tint et al 1995, Yu et al 2000, Waterham & Hennekam 2012]. Mortality is particularly high in the group of individuals with the lowest cholesterol concentrations (~10 mg/dL).

Genotype-Phenotype Correlations

A strict genotype-phenotype correlation is difficult because most affected individuals are compound heterozygotes.

- In general, individuals who are homozygous for two null alleles, such as the common c.964-1G>C or p.Trp151Ter variants, have a severe phenotype.
- A detailed evaluation of 207 individuals with SLOS showed that the most severe phenotypes were observed in individuals with two null variants or with two variants in loop 8-9 (amino acids 352-411), while those with one or two pathogenic variants in loop 1-2 (amino acids 59-94 and amino acids 119-151 respectively) or one pathogenic variant in the N-terminus (amino acids 1-37) have milder phenotypes [Waterham & Hennekam 2012].

However, the significant variation seen in severity, even among individuals with similar pathogenic variants, suggests influences on phenotype other than the *DHCR7* pathogenic variant [Porter 2000]. One important factor may include transport of cholesterol from the mother to the fetus early in pregnancy. A more severe phenotype has been seen in offspring of women who have an *APOE* E2 allele [Witsch-Baumgartner et al 2004, Woollett 2005], which may interfere with binding of apo E-containing maternal lipoproteins in the placenta.

Nomenclature

SLOS may also be referred to as RSH syndrome or SLO syndrome.

Curry et al [1987] described 19 infants with a severe form of SLOS that included cleft palate, cardiac defects, and early lethality. This disorder was termed Smith-Lemli-Opitz syndrome type II. With the advent of laboratory testing for SLOS, it has become apparent that SLOS type II is not biochemically distinct, but rather represents the more severe end of the spectrum of the SLOS phenotype.

Prevalence

In North America, the birth prevalence of SLOS is estimated at 1:40,000 live births [Cross et al 2015], although it should be noted that affected females, who lack the genital abnormalities seen in affected males, are underascertained. The carrier frequency in North America is estimated at 1% [Cross et al 2015]. SLOS is less common in individuals of Asian or African ancestry [Wright et al 2003].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *DHCR7*.

Differential Diagnosis

Clinical features. Although many malformation syndromes share at least some of the clinical features of Smith-Lemli-Opitz syndrome (SLOS) (e.g., polydactyly, hypospadias, cleft palate), with the exception of squalene synthase deficiency they rarely have more than two of these features in common. In particular, the Y-shaped 2-3 toe syndactyly, present in most individuals with SLOS, is rarely seen in other disorders.

Biochemical findings. The biochemical findings (Diagnosis) should allow for ready differentiation between individuals with SLOS and those with conditions that are clinically and biochemically similar. Biochemically, only SLOS presents with elevated 7DHC and low or low-normal plasma cholesterol. Other sterol metabolic disorders present with distinct patterns of sterol abnormalities and are unlikely to be confused with SLOS.

See Table 3 for genes associated with disorders that share some clinical features of SLOS.

Table 3. Genes and Disorders of Interest in the Differential Diagnosis of Smith-Lemli-Opitz Syndrome

Gene(s)	Differential Diagnosis Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/SLOS	Distinguishing from SLOS
B9D1 *B9D2* *CC2D2A* *CEP290* *KIF14* *MKS1* *NPHP3* *RPGRIP1L* *TCTN2* *TMEM107* *TMEM216* *TMEM231* *TMEM67*	Meckel syndrome (OMIM PS249000)	AR	Polydactyly	• Cystic renal disease • Encephalocele
BRAF *KRAS* *LZTR1* *MAP2K1* *NRAS* *PTPN11* *RAF1* *RIT1* *SOS1*	Noonan syndrome	AD AR [1]	• Broad posterior neck • Growth restriction • Hypospadias	• Downslanting palpebral fissures • Pulmonic stenosis
DHCR24	Desmosterolosis (OMIM 602398)	AR	• Sterol metabolic disorder • Ambiguous genitalia • Cleft palate • Microcephaly • Total anomalous pulmonary venous drainage	• Generalized osteosclerosis • Gingival nodules • Hypoplastic nasal bridge • Macrocephaly [2] • Short limbs • Thick alveolar ridges

Table 3. continued from previous page.

Gene(s)	Differential Diagnosis Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/SLOS	Distinguishing from SLOS
EBP	MEND syndrome (OMIM 300960) or chondrodysplasia punctata-2 (CDPX2)	XL	• Sterol metabolic disorder • Midface hypoplasia • Narrow forehead • Ptosis • 2-3 toe syndactyly • Postaxial polydactyly	• 4-5 finger syndactyly • Camptodactyly • Scoliosis • Hypopigmentation of the skin
FDFT1	Squalene synthase deficiency [3]	AR	• 2-3 toe syndactyly • DD & ID • Facial dysmorphism • Genital abnormalities • Structural brain malformations • Congenital heart defects • Autism	• Normal 7-DHC • ↑ plasma farnesol • Urine organic acids profile w/↑s in: methylsuccinate; mevalonate lactone; saturated & unsaturated branched-chain dicarboxylic acids
GLI3	Pallister-Hall syndrome	AD	Polydactyly	Hypothalamic hamartoblastoma
SC5D	Lathosterolosis	AR	• Sterol metabolic disorder • Cleft palate • 2-3 toe syndactyly • Hepatic steatosis • Microcephaly • Narrow forehead	Hematologic anomalies

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; GC-MS = gas chromatograph-mass spectroscopy; ID = intellectual disability; MOI = mode of inheritance; SLOS = Smith-Lemli-Opitz syndrome; XL = X-linked

1. Noonan syndrome is most often inherited in an autosomal dominant manner. Noonan syndrome caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

2. Desmosterolosis may be associated with macrocephaly or microcephaly.

3. Squalene synthase deficiency is a rare inborn error of cholesterol biosynthesis with multisystem clinical manifestations similar to Smith-Lemli-Optiz syndrome.

Other disorders to consider in the differential diagnosis of SLOS include the following (shared clinical findings are indicated in parentheses):

- Trisomy 13 syndrome (holoprosencephaly, cleft lip and cleft palate, cardiac defects, polydactyly)
- Pseudotrisomy 13 syndrome (OMIM 264480; holoprosencephaly, polydactyly)
- Dubowitz syndrome (OMIM 223370; growth restriction, blepharophimosis, toe syndactyly, eczema, and immune deficiency)
- Nguyen syndrome (OMIM 609643; facial dysmorphism, 2-3 toe syndactyly, failure to thrive, low plasma cholesterol)

Management

No consensus clinical management guidelines have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Smith-Lemli-Opitz syndrome (SLOS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Smith-Lemli-Opitz Syndrome

System/Concern	Evaluation	Comment
Constitutional	Assessment of growth, incl weight, length/height, & head circumference	
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• Consider assessment for pyloric stenosis or gastroesophageal reflux in those w/suggestive symptoms. • Particular attention should be given to stooling pattern, abdominal distention, or other signs of possible bowel obstruction because of risk for Hirschsprung disease.
	AST, ALT, and bilirubin concentrations	To assess for cholestatic liver disease
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language evaluation • Evaluation for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Neurologic	Neurologic eval	To incl brain MRI & EEG if seizures are a concern
Genitourinary	Physical exam of external genitalia	• To assess for genital anomalies • If external genital anomalies are present, consider pelvic imaging to evaluate for internal structures (e.g., undescended gonads, müllerian structure).
	Renal ultrasound	To evaluate for structural renal anomalies
Craniofacial	Clinical assessment for cleft palate	Referral to a multidisciplinary craniofacial team, if possible
Dental	Routine dental assessment & follow up	May require sedation for dental work
Eyes	Ophthalmologic eval	To assess for strabismus, cataracts, & functional eye problems
Cardiovascular	Consider EKG & echocardiogram.	• To assess for congenital heart defect • Consider referral to cardiologist.
Musculoskeletal	Orthopedics / physical medicine & rehabilitation / PT / OT eval	To incl assessment of: • Syndactyly, polydactyly, & abnormalities of the toes • Gross motor & fine motor skills • Need for ankle-foot orthoses or other orthotics • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Hearing	Audiologic eval	Assess for hearing loss.
Endocrine [1]	Consider glucose & electrolyte levels in infants.	To assess for adrenal insufficiency
	Testosterone level in males	In adolescents/adults w/signs of delayed or incomplete puberty

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy
1. In severely affected individuals, treatment with stress steroids in doses customarily used for children with congenital adrenal hyperplasia (see 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia) is recommended during periods of illness, stress, or prolonged decrease in oral intake [Bianconi et al 2011].

Treatment of Manifestations

Table 5. Targeted Treatment of Manifestations in Individuals with Smith-Lemli-Opitz Syndrome

Manifestation	Goal	Treatment	Considerations/Other
Low cholesterol & ↑ cholesterol precursors [1]	To ↑ cholesterol levels & ↓ 7-DHC & 8-DHC	Cholesterol supplementation [2, 3, 4, 5]	Those w/a more severe biochemical defect require larger doses of cholesterol.

1. Including 7-dehydrocholesterol (7-DHC) and 8-DHC
2. Egg yolk or crystalline cholesterol in an oil-based or aqueous suspension
3. Dietary studies on cholesterol supplementation have not been conducted in a randomized fashion.
4. Dietary therapy does not appear to increase the levels of cholesterol in CSF [van Rooij et al 1997].
5. Cholesterol supplementation should be considered in all individuals with SLOS because it may result in clinical improvement and has minimal side effects [Svoboda et al 2012, Thurm et al 2016].

Documented improvements after institution of cholesterol supplementation include the following:

- Improved growth
- Reduced photosensitivity
- Increased nerve conduction velocity
- Improved tone
- Achievement of ambulation
- Developmental cognitive and behavioral changes

Note: A placebo-controlled trial of simvastatin [Wassif et al 2017] noted an improvement in the levels of 7-DHC and the 7-DHC/cholesterol ratio and improvement on the irritability subtest of the Aberrant Behavior Checklist-C. While simvastatin appears to be safe in individuals with SLOS, the authors refrain from recommending it as a therapy.

Table 6. Supportive Treatment of Manifestations in Individuals with Smith-Lemli-Opitz Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues. [1]	Low threshold for clinical feeding evaluation &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
	Consider use of hypoallergenic or elemental formulas in infants.	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Bowel dysfunction	Standard treatment for gastroesophageal reflux	
	Standard treatment for Hirschsprung disease & pyloric stenosis [1]	Referral to gastroenterologist
	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	For constipation
Neonatal cholestatic liver disease	Cholesterol &/or bile acid therapy	Consider referral to hepatologist.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Psychiatric disturbance & behavioral issues	Standard treatment per psychiatrist	• Haloperidol [2] • Trazodone & apripiprazole (Abilify®) ↑ 7-DHC levels. [3]
Sleep disturbance	A trial of melatonin; if insufficient, other hypnotic may be considered.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [4]
Hypotonia & later hypertonia	Orthopedics / physical medicine & rehab / PT & OT incl AFOs & other orthotics, stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
	Tendon release surgery [1] or Botox® therapy	In older children w/significant hypertonia
Photosensitivity	Skin protection through proper clothing, avoidance of sun exposure, & UVA- & UVB-protection sunscreen	
Genital anomalies	Standard treatment per urologist &/or gynecologist [1]	
Cleft palate	Standard treatment [1]	
Dental anomalies	Proper positioning, choice of dental devices, & sedation techniques need to be considered. [1]	Muzzin & Harper [2003]
Cataracts, ptosis, &/or strabismus	Standard treatment(s) per ophthalmologist [1]	
Congenital heart defects	Standard treatment per cardiologist [1]	
Limb defects	Syndactyly of hands &/or feet &/or polydactyly may require surgical repair. [1]	
Recurrent otitis media	Standard treatment	Incl consideration of tympanostomy tube placement. [1]
Hearing loss	Hearing aids may be helpful as per otolaryngologist.	Community hearing services through early intervention or school district
Adrenal insufficiency	Standard treatment per endocrinologist [5]	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family/Community	Ensure appropriate social work involvement to connect families w/local resources, respite, & support.	Ongoing assessment of need for palliative care involvement &/or home nursing
	Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy; AFO = ankle-foot orthosis
1. Anesthetic problems including muscular rigidity and malignant hyperthermia have been reported [Choi & Nowaczyk 2000]. Airway management during anesthesia may be challenging; use of a laryngeal mask airway has been successful [Leal-Pavey 2004, Matveevskii et al 2006].
2. Treatment with haloperidol may exacerbate the biochemical sterol abnormalities in individuals with SLOS and cause an increase in symptoms; see Agents/Circumstances to Avoid.
3. One must weigh the benefit of such medications against the potential negative side effects; see Agents/Circumstances to Avoid.
4. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
5. In severely affected individuals, treatment with stress steroids in doses customarily used for children with congenital adrenal hyperplasia (see 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia) is recommended during periods of illness, stress, or prolonged decrease in oral intake [Bianconi et al 2011].

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected

individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Routine health supervision by a physician familiar with SLOS, its complications, and its treatment includes the following.

Table 7. Recommended Surveillance for Individuals with Smith-Lemli-Opitz Syndrome

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters [1] • Evaluation of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation	
	Assessment of cholesterol, serum concentration of 7-DHC, and serum amino transferases (ALT & AST)	Every 3-4 mos in1st few yrs of life; 2x/yr thereafter
Development	Monitor developmental progress & educational needs.	Age-appropriate developmental assessment ≥2x/yr until age 3 yrs; annually thereafter
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior [2]	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, movement disorders.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Eyes	Pediatric vision screening	Annually in childhood
Hearing	Pediatric hearing screening	
Genitourinary	Monitor for urinary tract infections & gonadal location.	As clinically indicated
Dental	Evaluation by a dentist	≥2x/yr starting at age 3 yrs
Endocrine	Assessment for signs of puberty & progression through puberty	Starting at age ~10 yrs until adulthood
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/ respite care, home nursing, other local resources) & care coordination.	At each visit

1. Because children with SLOS have low muscle mass, careful monitoring of weight gain and growth is necessary so that overconsumption of calories does not lead to obesity.
2. In individuals who are on psychotropic drugs, close monitoring of clinical signs/symptoms and consideration of monitoring serum concentration of 7-DHC (depending on the drug that is prescribed) is recommended; see Agents/Circumstances to Avoid.

Agents/Circumstances to Avoid

Treatment with haloperidol, which has a high affinity for the DHCR7 substrate binding site, may exacerbate the biochemical sterol abnormalities in individuals with SLOS and cause an increase in symptoms. It is likely that other drugs in this class will cause the same change in sterol levels [Kelley & Hennekam 2000].

Other psychotropic drugs shown to elevate 7-DHC are trazodone and aripiprazole (Abilify®) [Hall et al 2013]. Thus, one must weigh the benefit of such medications against the potential negative side effects. As many

individuals with SLOS do require psychotropic medications, close monitoring of clinical signs/symptoms and serum concentration of 7-DHC is recommended.

Photosensitivity can be severe and extended periods of sun exposure should be avoided, as severe sunburn can occur with only limited exposure; however, limited sun exposure is possible for some affected individuals as long as protective clothing is worn and a sunscreen with UVA and UVB properties is used.

Evaluation of Relatives at Risk

It is appropriate to clarify the status of all sibs in order to identify as early as possible those who would benefit from prompt initiation of cholesterol supplementation. Evaluations include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Measurement of 7-DHC concentration in plasma or amniotic fluid (prenatally) if the pathogenic variants in the family are not known. In cases of borderline 7-DHC concentration, molecular genetic testing is indicated. Caution must be exercised in interpreting elevated 7-DHC concentration in individuals treated with haloperidol, aripiprazole, and trazodone [Hall et al 2013].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

No current guidelines exist for the management of pregnant women with SLOS, as to date only one affected woman with a successful pregnancy has been identified [Ellingson et al 2014].

Therapies Under Investigation

A study assessing the safety and therapeutic benefits of cholesterol supplementation and antioxidant medications is underway in Colorado (see Cholesterol and Antioxidant Treatment in Patients with Smith-Lemli-Opitz Syndrome).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

For more severely affected infants with SLOS, the issues of surgical management of congenital anomalies such as cleft palate, congenital heart disease, and genital anomalies need to be considered as they would be in any other infant with a severe, usually lethal disorder.

Reassignment of sex of rearing for infants with a 46,XY karyotype and female genitalia may not always be appropriate because most will have early death, and the process of sex reassignment can be highly disruptive to a family already coping with the difficult issues of having a child with a genetic disorder characterized by life-threatening medical complications.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Smith-Lemli-Opitz syndrome (SLOS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *DHCR7* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing SLOS.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Intrafamilial variability has been observed in SLOS but, in general, the severity of manifestations in the proband can be used to predict the clinical outcome in a sib with the same pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing SLOS.

Offspring of a proband

- Individuals with severe SLOS have not been reported to reproduce.
- Fertility does not appear to be reduced in mildly affected individuals with SLOS. A woman with SLOS who was not diagnosed until her pregnancy as having SLOS gave birth to a normal child [Ellingson et al 2014].

Other family members. Each sib of a proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *DHCR7* pathogenic variants in the family.

Note: Because of considerable overlap between the ranges of serum concentration of cholesterol and 7-DHC in carriers and non-carriers, carrier status cannot be determined by measuring the serum concentration of either compound.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown)..

Prenatal Testing and Preimplantation Genetic Testing

High-Risk Pregnancies

Molecular genetic testing. Once the *DHCR7* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Molecular genetic testing may be used in place of biochemical testing or to clarify indeterminate biochemical results [Loeffler et al 2002, Waye et al 2007].

Biochemical testing. For pregnancies known to be at 25% risk for SLOS based on family history, the finding of abnormal concentration of 7-DHC levels in amniotic fluid obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation [Abuelo et al 1995, Dallaire et al 1995, Rossiter et al 1995, Griffiths et al 2008] or in tissue obtained from chorionic villus samples (CVS) at approximately ten to 12 weeks' gestation [Mills et al 1996, Sharp et al 1997] is diagnostic. Caution should be exercised in diagnosing individuals with a family history of a mild variant form of SLOS. In this situation, demonstration of the enzyme deficiency in cultured amniocytes will be required.

Ultrasound prenatal detection of SLOS is possible in affected fetuses with multiple congenital anomalies. Intrauterine growth restriction (IUGR) is common in fetuses with SLOS. Facial features of SLOS can be observed as early as 18 weeks' gestation [Nowaczyk & Irons 2012, Quélin et al 2012]. However, ultrasound examination may be normal, especially in cases with mild SLOS [Goldenberg et al 2004].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Low-Risk Pregnancies

In pregnancies in which no family history of SLOS exists, certain fetal ultrasound findings could prompt consideration of SLOS. Prenatal findings of SLOS may include IUGR; major malformations of the brain, heart, kidneys, or limbs; and ambiguous genitalia, especially female-appearing genitalia or severe hypospadias in an XY fetus. Other nonspecific findings may include increased nuchal translucency, cystic hygroma, nonimmune hydrops, and cleft palate. However, although abnormal findings on ultrasound examination can be seen in fetuses with SLOS, no pattern is pathognomonic. Furthermore, ultrasound examination may be normal. Goldenberg et al [2004] found that IUGR, the most frequent ultrasound finding, was detected in 67% of affected fetuses; IUGR was an isolated finding in 45% and associated with at least one other anomaly in 55%. Ultrasound examinations were considered normal in 17%; early detection of multiple malformations was noted in only 10% [Goldenberg et al 2004]. Quélin et al [2012] found that the pattern of anomalies in fetuses diagnosed with SLOS differed from that in the individuals diagnosed postnatally.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Smith-Lemli-Opitz syndrome

- **Smith-Lemli-Opitz/RSH Foundation**
  PO Box 212
  Georgetown MA 01833
  Phone: 978-352-5885
  Fax: 978-352-5885
  Email: sloinfo@smithlemliopitz.org
  www.smithlemliopitz.org
- **RDCRN Contact Registry for Sterol and Isoprenoid Research (STAIR) Consortium**
  RDCRN Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Smith-Lemli-Opitz Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DHCR7	11q13.4	7-dehydrocholesterol reductase	DHCR7 database	DHCR7	DHCR7

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Smith-Lemli-Opitz Syndrome (View All in OMIM)

270400	SMITH-LEMLI-OPITZ SYNDROME; SLOS
602858	7-@DEHYDROCHOLESTEROL REDUCTASE; DHCR7

Molecular Pathogenesis

DHCR7 encodes the protein 7-dehydrocholesterol reductase [Witsch-Baumgartner et al 2001] (3β-hydroxysteroid-Δ7-reductase), the last enzymatic step in cholesterol biosynthesis [Irons et al 1993, Irons et al 1994, Tint et al 1994, Elias & Irons 1995], which catalyzes the conversion of 7-DHC to cholesterol. Failure of 7-DHC reductase to convert 7-DHC to cholesterol results in elevation of the cholesterol precursors 7-DHC and 8-DHC and generally decreased levels of cholesterol. The pathophysiology of the clinical features of SLOS remains unknown.

Mechanism of disease causation. SLO occurs through a loss-of-function mechanism.

Table 8. Notable *DHCR7* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_001360.2 NP_001351.2	c.964-1G>C (IVS8-1G>C)		Most common pathogenic variant; accounts for ~28% of disease alleles; assoc w/a severe phenotype [Correa-Cerro & Porter 2005]
	c.452G>A	p.Trp151Ter	Common variants assoc w/a severe phenotype
	c.1210C>T	p.Arg404Cys	
	c.278C>T	p.Thr93Met	Assoc w/a milder phenotype; common in individuals of Mediterranean or Cuban ancestry [Nowaczyk et al 2004]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

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