GENEReviews

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Smith-Lemli-Opitz Syndrome

[*RSH Syndrome, SLO Syndrome, SLOS*]

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Summary

Disease characteristics. Smith-Lemli-Opitz syndrome (SLOS) is a congenital multiple anomaly 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 retardation, microcephaly, moderate to severe mental retardation, 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 and individuals have been described with normal development and only minor malformations.

Diagnosis/testing. The diagnosis of SLOS relies on clinical suspicion and detection of elevated serum concentration of 7-DHC. 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. *DHCR7* is the only gene known to be associated with SLOS. Sequence analysis of *DHCR7* detects approximately 96% of known mutations.

Management. *Treatment of manifestations:* Cholesterol supplementation may result in clinical improvement; early intervention and physical/occupational/speech therapies for identified disabilities; consultation with a nutritionist; gastrostomy as needed for feeding; routine treatment for pyloric stenosis, gastroesophageal reflux, constipation, recurrent otitis media, cataracts, ptosis, and/or strabismus; orthotics, tendon release surgery, or Botox® as needed; proper clothing and sunscreen with UVA and UBV protection for photosensitivity. *Prevention of secondary complications:* treatment with stress-related doses of steroids during illness and other stress; attention to airway management and other potential complications during anesthesia; close monitoring during use of psychotropic medications. *Surveillance:* routine health supervision including history, physical examination, monitoring of growth parameters, age-appropriate developmental assessment, nutritional assessment. *Agents/circumstances to avoid:* treatment with haloperidol; sun exposure. *Testing 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 disease-causing mutations in the family are known. Prenatal testing for pregnancies at risk is possible using biochemical testing or molecular genetic testing if the disease-causing mutations in the family are known.

Diagnosis

Clinical Diagnosis

Clinical diagnostic criteria have not been established for Smith-Lemli-Opitz syndrome (SLOS). A pattern of congenital anomalies suggests the diagnosis. The following are the most commonly observed features:

- Characteristic facial features
- Microcephaly
- Postaxial polydactyly
- 2-3 syndactyly of the toes
- Growth and mental retardation
- Cleft palate
- Hypospadias in males

Testing

For laboratories offering biochemical testing, see Testing.

Decreased activity of the enzyme 7-dehydrocholesterol (7-DHC) reductase results in failure to convert 7-DHC to cholesterol [Irons et al 1993, Irons et al 1994, Tint et al 1994, Elias & Irons 1995]:

- **Serum concentration of 7-DHC.** The diagnostic test is an elevation of serum concentration of 7-DHC as defined by the laboratory for a given patient.

  Note: (1) 7-DHC concentration is usually measured in blood samples, but can be measured in other tissues. (2) Some individuals on psychotropic medications can have elevated 7-DHC levels secondary to the medication, giving rise to true false-positive test results. Such individuals rarely have the physical features of SLOS, but may be tested for SLOS because of neurocognitive issues; molecular genetic testing and/or fibroblast testing is needed to clarify the diagnosis. (3) Different laboratories may report results in different units. Laboratories in the US report results as milligrams per deciliter or micrograms per milliliter; European laboratories most often report results as millimoles per liter. Thus, direct comparison of values between laboratories requires caution.

- **Serum concentration of cholesterol.** Although most affected individuals have hypocholesterolemia, serum concentration of cholesterol values in normal and affected individuals can overlap, particularly when the affected individuals are older or have a milder phenotype [Kelley 1995]. 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.

Carrier detection

- 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.

- However, biochemical testing of fibroblasts has been successful in carrier detection [Shefer et al 1997].
- Carrier testing is also possible by molecular genetic analysis if the disease-causing mutations in the family are known.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. The *DHCR7* gene encoding 7-DHC reductase [Fitzky et al 1998, Wassif et al 1998, Waterham et al 1998] is the only gene associated with SLOS.

Clinical testing. Most affected individuals are compound heterozygotes for two different abnormal alleles, with an overall mutation detection rate of 96% in one series of 133 individuals [Witsch-Baumgartner et al 2001]. Most of the affected individuals studied have two detectable mutations; rare individuals had only one detectable mutation [Yu & Patel 2005]. It has been hypothesized that mutations that are not found by routine testing methods are regulatory mutations that affect either transcription or stability of the *DHCR7* mRNA [Correa-Cerro & Porter 2005]:

- **Sequence analysis.** Sequence analysis of all exons and all intron-exon boundaries detects mutations in approximately 96% of affected individuals [Witsch-Baumgartner et al 2001].
- **Targeted mutation analysis.** In addition to offering sequence analysis of the coding region, some laboratories offer targeted mutation analysis of common mutation(s). The mutations included in testing panels vary among laboratories.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	Point mutations in *DHCR7*	>80%	Clinical Testing
Targeted mutation analysis	Mutations in testing panels (variable by laboratory)	Variable	

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm the diagnosis in a proband with equivocal biochemical test results. Molecular genetic testing of the *DHCR7* gene is generally considered a second-tier test and may be useful in instances in which serum concentration of 7-DHC is difficult to interpret, or in which only DNA from the affected individual is available.

Carrier testing for at-risk relatives requires molecular genetic testing; prior identification of the disease-causing mutations in the family is necessary.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require molecular genetic testing; prior identification of the disease-causing mutations in the family is necessary.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in the *DHCR7* gene.

Clinical Description

Natural History

Classic Smith-Lemli-Opitz syndrome (SLOS) is characterized by prenatal and postnatal growth retardation, microcephaly, moderate to severe mental retardation, 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 [Cunniff et al 1997, Ryan et al 1998, Krajewska-Walasek et al 1999, Kelley & Hennekam 2000]. Individuals with milder forms may have only subtle facial characteristics, hypotonia, 2-3 toe syndactyly, and mild developmental delay. Clinical variability is noted even within families as sibs with SLOS have been reported with medical and developmental problems of different degrees.

Prematurity and breech presentation are common. Neonates frequently have poor suck, irritability, and failure to thrive [Pinsky & DiGeorge 1965].

Infants with SLOS frequently have feeding problems secondary to a combination of hypotonia, oral-motor incoordination, and gastrointestinal problems that include dysmotility, hypomotility, gastrointestinal reflux, constipation, and formula intolerance. In general, infants with the more severe phenotype have more feeding problems. Children and adults with SLOS are generally smaller than average.

Pyloric stenosis and Hirschsprung disease have been reported [Dallaire & Fraser 1966, Patterson et al 1983, Lipson & Hayes 1984]. Constipation is a common problem. 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].

Cognitive function ranges from borderline intellectual capability to severe mental retardation. Low normal intellectual function can be seen in individuals with mild or variant forms of SLOS [Mueller et al 2003].

Behavioral signs/symptoms include sensory hyperreactivity, irritability, sleep cycle disturbance, self-injurious behavior (hand biting and/or head banging), autism spectrum behaviors (46%-53%), temperament dysregulation, and social and communication deficits [Tierney et al 2000, Tierney et al 2001]. Many individuals require very little sleep, often only a few hours per night.

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

Developmental abnormalities of the central nervous system include microcephaly (80%-84%), abnormalities of myelination, ventricular dilatation, malformations of the corpus callosum and/or cerebellum, Dandy-Walker malformation and its variants, and holoprosencephaly (5%) [Ryan et al 1998, Kelley & Hennekam 2000, Caruso et al 2004]. Hypotonia, which is common in young children, affects feeding and delays motor development. Older children often exhibit hypertonia.

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 children 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.

Hypospadias and/or bilateral cryptorchidism occur 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]. 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 [Pinsky & DiGeorge 1965, Dallaire & Fraser 1966, Gorlin et al 1990]. Other findings include persistent urogenital sinus and posterior labial fusion without clitoromegaly in a female with an XX karyotype [Chemaitilly et al 2003] and precocious puberty in girls with SLOS [Starck et al 1999; Irons, unpublished].

Since the report of Curry et al (1987), it has been recognized that many 46,XY individuals with severe manifestations of SLOS have extreme undermasculinization of the external genitalia, resulting in female external genitalia (termed "sex reversal"). Lin et al (1997) reported that 20%-25% of individuals with SLOS described in the literature have a 46,XY karyotype with a female phenotype.

Characteristic facial features include temporal narrowing, epicanthal folds, blepharoptosis, a broad nasal bridge and short nasal root, anteverted nares, cleft palate, often low-set and posteriorly rotated ears, and micrognathia [Lowry et al 1968, Fierro et al 1977]. Cleft palate is present in 40%-50% of affected individuals reported [Johnson 1975, Cunniff et al 1997] and may contribute to feeding and growth problems. The neck is often short with redundant skin at the nape.

Congenital cataracts are present in approximately 20% of affected individuals [Finley et al 1969, Cunniff et al 1997, Lin et al 1997]. Other ophthalmologic manifestations include ptosis, strabismus, optic atrophy, and optic nerve hypoplasia [Atchaneeyasakul et al 1998].

Cunniff et al (1997) and Lin et al (1997) reported that up to 50% of their patients had an identified cardiac defect. They also reported an increased incidence of atrioventricular canal defects and anomalous pulmonary venous return when compared with an unselected series of individuals with SLOS [Park et al 1968, Lin et al 1997].

Cardiorespiratory problems can occur secondary to malformations of the heart or respiratory tract, including the trachea or larynx. An increased frequency of upper- and/or lower-respiratory infections is seen particularly in infancy and early childhood.

Renal hypoplasia and cystic kidneys have been reported [Thompson & Baraitser 1986].

Syndactyly of the second and third toes is a common, but not universal, finding. Postaxial 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]. Less common findings include hypoplastic or short thumbs, clinodactyly, hammer toes, and dorsiflexed halluces [Pinsky & DiGeorge 1965, Opitz 1969].

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

Other medical/dental issues include recurrent otitis media, splenomegaly, and hearing loss (both conductive and sensorineural). Seizures can occur but are not common.

Genotype-Phenotype Correlations

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 clinical severity [Tint et al 1995, Cunniff et al 1997, Yu et al 2000b]. Mortality is particularly high in the group of individuals with the lowest cholesterol concentrations (~10 mg/dL).

Molecular genetic. A strict genotype-phenotype correlation is difficult because most affected individuals are compound heterozygotes. However, a severe phenotype has been described in homozygotes for the two functional null alleles c.1237-1G>C (IVS8-1G>C, the intron 8 splice acceptor) and p.Trp151X, and for the missense mutation p.Arg404Cys [Witsch-Baumgartner et al 2000].

Witsch-Baumgartner et al (2000) found a general correlation in severity, depending on whether the mutation was a putative null mutation, a mutation in the large cytoplasmic domain, a transmembrane domain mutation, or a C-terminal mutation. However, the significant variation seen in severity, even among individuals with similar mutations, suggests significant influences on phenotype other than the *DHCR7* mutation [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

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

The birth prevalence of SLOS is estimated to be approximately 1:20,000 to 1:40,000 live births [Tint et al 1994]; in individuals of northern or central European ancestry, it has also been variably estimated to range from 1:10,000 to 1:60,000 [Porter 2000]. SLOS is less common in those of Asian or African ancestry.

Affected females, who lack the genital abnormalities seen in affected males, are underascertained.

In an investigation of 1503 random blood samples from newborn screening blood spots, 16 samples had the intron 8 splice acceptor mutation. This information was used to calculate a carrier frequency of approximately 1:30, with a predicted prevalence of SLOS between 1:1,590 and 1:13,500 [Battaile et al 2001]. A higher figure for affected individuals than what is observed clinically may be explained by an increased incidence of intrauterine fetal demise or neonatal death in severely affected individuals or under-reporting of more mildly affected individuals who lack physical findings suggestive of SLOS.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Although many malformation syndromes share at least some of the clinical features of SLOS (e.g., polydactyly, hypospadias, cleft palate), 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. The biochemical findings (Clinical Diagnosis) should allow for ready differentiation between individuals with SLOS and those with conditions that are clinically and biochemically similar.

Other sterol metabolic disorders include the following (although the pattern of sterol abnormalities is distinct from that seen in SLOS):

- Beta-sitosterolemia (abnormal sterol biosynthesis, normal to elevated cholesterol levels, episodic hemolysis, tuberous xanthomatosis, early atherosclerosis).
- CHILD syndrome (**c**ongenital **h**emidysplasia, **i**chthyosiform nevus, **l**imb **d**efects)
- Desmosterolosis (macrocephaly, hypoplastic nasal bridge, thick alveolar ridges, gingival nodules, cleft palate, total anomalous pulmonary venous drainage, ambiguous genitalia, short limbs, generalized osteosclerosis)
- Mevalonic aciduria (normal to slightly reduced cholesterol levels, developmental delay, dysmorphic facial features, central cataracts, anemia, hepatosplenomegaly).
- X-linked dominant chondrodysplasia punctata (alopecia, cataracts, ichthyosis, punctate calcification of bones, rhizomelic limb shortening)

Disorders with similar clinical findings include the following:

- Trisomy 13 syndrome (holoprosencephaly, cleft lip and cleft palate, cardiac defects, polydactyly)
- Trisomy 18 syndrome (growth retardation, characteristic facial appearance, short sternum, cardiac defects, camptodactyly, early lethality)
- Dubowitz syndrome (growth retardation, blepharophimosis, toe syndactyly, eczema, immune deficiency)
- Meckel-Gruber syndrome (encephalocele, cystic renal disease, polydactyly)
- Noonan syndrome (growth retardation, downslanting palpebral fissures, broad posterior neck, pulmonic stenosis, hypospadias)
- Russell-Silver syndrome (intrauterine growth retardation, limb asymmetry, fifth finger clinodactyly)
- Simpson-Golabi-Behmel syndrome (macrosomia, facial clefts, polydactyly)
- Pseudotrisomy 13 syndrome (holoprosencephaly, polydactyly)
- Pallister-Hall syndrome (hypothalamic hamartoblastoma, polydactyly)
- Nguyen syndrome [Nakane et al 2005]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Smith-Lemli-Opitz syndrome (SLOS), the following evaluations are recommended:

- Physical examination with special attention to growth parameters, congenital anomalies, and neurologic findings (hypotonia/hypertonia, seizures)
- Developmental assessment
- Ophthalmologic evaluation for strabismus, cataracts, and functional eye problems
- Cardiac evaluation (ECG and echocardiogram) for congenital defects
- Musculoskeletal evaluation for delineation of syndactyly, polydactyly, abnormalities of tone, and need for ankle-foot orthoses (AFOs) or other orthotics
- Genitourinary examination for anomalies of external genitalia in males and females
- Evaluation for functional problems of the gastrointestinal system by history and, if indicated, studies for pyloric stenosis and gastroesophageal reflux. Particular attention should also be given to stooling pattern, abdominal distention, or other signs of possible bowel obstruction, particularly in children with a more severe phenotype, because of their risk for Hirschsprung disease.
- Nutritional assessment for feeding problems and poor weight gain
- Possible MRI or other cranial imaging to evaluate for holoprosencephaly and/or other brain anomalies
- Renal ultrasound evaluation for renal anomalies
- Hearing evaluation for either sensorineural or conductive hearing loss
- Laboratory evaluation including glucose and electrolytes (for adrenal insufficiency), serum concentrations of amino transferases and bilirubin (for cholestatic liver disease), and testosterone in males

Treatment of Manifestations

Cholesterol supplementation. Devising a treatment strategy for SLOS has been difficult as all factors contributing to the clinical phenotype are not yet known with certainty. It is likely that both low cholesterol levels and elevation of the cholesterol precursors 7-DHC and 8-DHC contribute to many of the clinical findings in affected individuals. Therefore, treatment strategies to date have focused on supplying exogenous cholesterol (either as egg yolks or as crystalline cholesterol in either an oil-based or aqueous suspension) in an attempt to raise cholesterol levels and secondarily decrease the levels of the precursors 7-DHC and 8-DHC. In general, patients with a more severe biochemical defect require larger doses of cholesterol.

It should be emphasized that dietary studies on cholesterol supplementation have not been conducted in a randomized fashion. Although improved growth [Elias et al 1997, Irons et al 1997], reduced photosensitivity [Azurdia et al 2001, Starck et al 2002a], and increased nerve conduction velocity [Starck et al 2002a] have been objectively documented, evidence for other benefits such as behavioral and developmental improvement is largely anecdotal [Elias et al 1997, Nwokoro & Mulvihill 1997]. Nonetheless, cholesterol supplementation should be considered in all individuals with SLOS because it may result in clinical improvement and has minimal side effects [Elias et al 1997, Nwokoro & Mulvihill 1997, Battaile & Steiner 2000].

Other treatments

Referral to appropriate early intervention and physical/occupational/speech therapies is often required for identified disabilities.

Many infants have difficulty with suck and/or swallow and may require gastrostomy for feeding and support of a nutritionist to help monitor caloric intake and growth. Infants with severe feeding problems generally require the insertion of gastrostomy tubes and/or the use of hypoallergenic, elemental formulas. 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.

For those with frequent vomiting or apparent gastroesophageal reflux, a diagnosis of pyloric stenosis should be considered and treated as in the general population. Gastrointestinal reflux and/or constipation require treatment by a gastroenterologist.

Neonatal cholestatic liver disease often resolves with cholesterol and/or bile acid therapy.

Surgical repair may be required for cataracts, ptosis, and/or strabismus.

Syndactyly of hands and/or feet and/or polydactyly may require surgical repair.

Orthopedic management of the early hypotonia and later hypertonia includes the use of AFOs and other orthotics, as well as physical and occupational therapy.

Tendon release surgery or Botox® therapy may be indicated in older children with significant hypertonia.

Dental management can be challenging. Proper positioning, choice of dental devices, and sedation techniques need to be considered [Muzzin & Harper 2003].

Recurrent otitis media may require tympanostomy tube placement.

Photosensitivity can be severe and many children 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.

Prevention of Secondary Complications

In moderately to more severely affected patients, 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.

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].

Surveillance

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

- History, physical examination, and monitoring of growth parameters, with the frequency to be determined by the severity of the child's condition
- Age-appropriate developmental assessment at least twice a year until age three years and annually thereafter
- Nutritional assessment at least every three to four months until age two years and twice yearly thereafter

- Monitoring of cholesterol and 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

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 patients 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].

Thus, one must weigh the benefit of such medications fagainst the potential negative side effects. As many patients 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.

Testing of Relatives at Risk

All sibs should be tested either prenatally or shortly after birth.

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

Therapies Under Investigation

Jira et al (2000) used the HMG-CoA reductase inhibitor simvastatin to treat two affected individuals for 14 and 23 months, resulting in normalization of cholesterol levels and a decrease of plasma precursors by 28% and 33%. Improvement in the precursor/cholesterol ratio in the cerebrospinal fluid was also found. Morphometric parameters improved in both individuals, and no adverse side effects were observed.

Starck et al (2002b) treated two affected individuals with simvastatin, cholesterol supplementation, and bile acids and found reduction in absolute and relative serum concentration of 7-DHC. However, in one of these individuals, simvastatin was discontinued after hepatotoxic side effects and increased photosensitivity were observed.

Search ClinicalTrials.gov 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 gender 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.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as

information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 a proband are obligate carriers, and, therefore, carry one mutant allele.
- Carriers are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Individuals with SLOS have not been reported to reproduce.

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

Carrier Detection

- Carriers for SLOS cannot be identified using serum biochemical testing.
- Carrier detection is possible in at-risk relatives when both *DHCR7* disease-causing mutations have been identified in an affected family member.

Related Genetic Counseling Issues

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.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant

in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

High-risk pregnancies. 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 15-18 weeks' gestation [Abuelo et al 1995, Dallaire et al 1995, Rossiter et al 1995] 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.

If the two disease-causing mutations in the *DHCR7* gene have been identified in the proband, molecular genetic testing may be used in place of biochemical testing or to clarify indeterminate results [Loeffler et al 2002].

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 findings in the fetus might prompt consideration of SLOS. For example:

The combination of low concentrations of unconjugated estriol, HCG, and alpha-fetoprotein on routine maternal serum testing at 15-20 weeks' gestation could suggest the possible diagnosis of SLOS [Rossiter et al 1995]. 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. Palomaki et al (2002) examined a prenatal screening model based on second trimester maternal serum concentration of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol. They found that a cutoff risk level of one in 50 would result in the detection of 62% of affected pregnancies, while 0.34% of normal pregnancies would screen positive. The positive predictive value of such a screening test is approximately 1% (1 in 90).

Low maternal serum concentrations of unconjugated estriol alone may warrant further investigation, especially when associated with abnormal ultrasonographic findings suggestive of SLOS.

Fetal ultrasound examination. Prenatal findings of SLOS may include intrauterine growth retardation, 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 intrauterine growth restriction (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 only noted in 10% [Goldenberg et al 2004].

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Smith-Lemli-Opitz Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
DHCR7	11q12-q13	7-dehydrocholesterol reductase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Smith-Lemli-Opitz Syndrome

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

Table C. Genomic Databases for Smith-Lemli-Opitz Syndrome

Gene Symbol	Entrez Gene	HGMD
DHCR7	1717 (MIM No. 602858)	DHCR7

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *DHCR7* gene contains nine exons and eight introns and spans 14,100 base pairs; exons 3-9 encode the protein 7-dehydrocholesterol reductase [Witsch-Baumgartner et al 2001]. The gene has an open reading frame of 1425 nucleotides.

Pathologic allelic variants: More than 120 mutations have been described [Correa-Cerro & Porter 2005, Yu & Patel 2005] (see Table 2).

The most frequently found abnormal allele (28.2%) is c.1237-1G>C (IVS8-1G>C), a splice site acceptor mutation in the last base of intron 8 that leads to an alternative upstream cryptic splice acceptor site. This results in the insertion of 134 base pairs of intronic sequence into the *DHCR7* mRNA, resulting in a frameshift and premature stop codon.

Other common abnormal alleles and their estimated frequencies include p.Thr93Met (10.4%), p.Trp151X (6.0%), p.Arg404Cys (5.2%), p.Val326Leu (5.0%), p.Arg352Trp (3.2%), p.Glu448Lys (3.2%), p.Gly410Ser (2.2%), p.Arg242Cys (1.8%), p.Ser169Leu (1.7%), p.Phe302Leu (1.3%), and p.Arg242His (1.0%). The 12 mutations account for 69.2% of reported alleles [Correa-Cerro & Porter 2005].

Approximately 90% of mutations are missense mutations distributed among all coding exons, in addition to a relatively few nonsense mutations, splicing defects, insertions, and deletions, which presumably result in loss of enzymatic activity and represent functional null alleles [Witsch-Baumgartner et al 2001].

Table 2. *DHCR7* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias) [1]	Protein Amino Acid Change	Reference Sequence
c.278C>T	p.Thr93Met	NM_001360.2
c.452G>A	p.Trp151X	
c.506C>T	p.Ser169Leu	
c.724C>T	p. Arg242Cys	
c.725G>A	p.Arg242His	
c.906C>G	p.Phe302Leu	
c.976G>T	p.Val326Leu	
c.1054C>T	p.Arg352Trp	
c.1210C>T	p.Arg404Cys	
c.1228G>A	p.Gly410Ser	
c.1237-1G>C (IVS8-1G>C)	--	
c.1342G>A	p.Glu448Lys	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

Normal gene product: The gene has an open reading frame of 1425 nucleotides and encodes a 475-amino acid polypeptide with a predicted molecular weight of 54.5 kd [Porter 2000]. The normal gene product is 7-dehydrocholesterol (7-DHC) reductase (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.

Abnormal gene product: Decreased function of 7-DHC reductase fails to convert 7-DHC to cholesterol, resulting in elevation of the cholesterol precursors 7-DHC and 8-DHC and generally decreased levels of cholesterol.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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

Smith-Lemli-Opitz/RSH Foundation
P.O. Box 212
Georgetown MA 01833
Phone: 978-352-5885
Email: sloinfo@smithlemliopitz.org
www.smithlemliopitz.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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