



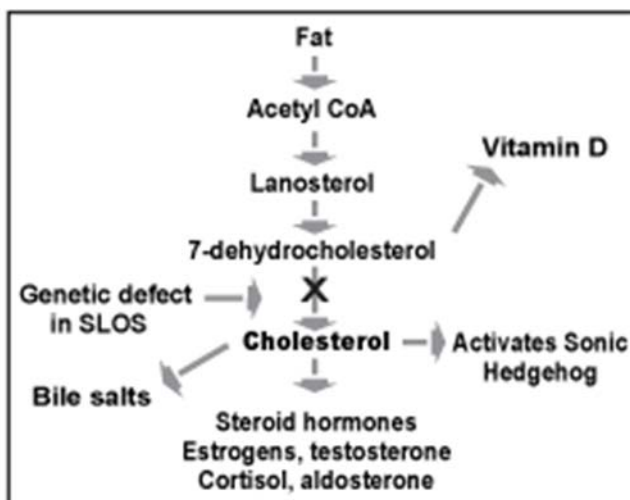
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## Smith Lemli Opitz Syndrome Colleen Lentz, MS

### Introduction:

Smith-Lemli-Opitz Syndrome (SLOS) is a genetic condition resulting from errors in the way the body produces cholesterol. SLOS is caused by mutations in the DHCR7 gene, which is responsible for the conversion of a chemical called 7-dehydrocholesterol (7-DHC) to cholesterol in our bodies. Our bodies require cholesterol for embryonic growth and development and for the production of hormones, vitamin D, and substances that help to digest food. Cholesterol also plays a very important role in brain functioning. This is because cholesterol activates a protein called Sonic Hedgehog (SHH), which plays roles in embryonic development, neural patterning, and mood regulation. When the body is unable to convert 7-DHC to cholesterol, two things occur: (1) the body will accumulate high concentrations of 7-DHC and its isomer, or chemical relative, 8-DHC, both of which are toxic to the body, and (2) the body will be deprived of the cholesterol needed for normal growth and development.

Figure 1: Formation of cholesterol



For children with SLOS, the combination of high 7-DHC/8-DHC and low cholesterol result in a combination of physical features that can include:

- Intellectual disability (90%)
- Heart defect (50%)
- Kidney defect (25%)
- Cleft palate (40-50%) or high palate
- Midline brain anomaly (microcephaly, corpus callosum malformations)
- Genital malformations
- Liver cholestasis
- Syndactyly
- Polydactyly
- Feeding problems, often failure to thrive
- Low or extremely low muscle tone; delaying or inhibiting development and speech
- Constipation; sometimes with a secondary diagnosis of Hirshsprungs Disease
- Reflux, sometimes severe requiring surgery
- Hearing loss
- Cataracts
- Sensitivity to the sun
- Weak immune system
- Scoliosis; brittle bones
- Osteoporosis
- Allergies

Many of the physical malformations associated with SLOS including the limb, genital, brain, and heart defects, are thought to be due to altered functioning of Sonic Hedgehog Protein (SHH), which is normally activated by cholesterol. SHH is a signaling protein that functions in the patterning and growth of embryonic structures including the CNS, facial structures, and limbs. When activated, SHH initiates and sustains a cascade of other proteins that are critical for normal growth and development. Two of these proteins, BMP2 and BMP7, are expressed in the distal portion of our limb buds. These proteins play important roles in the formation of finger and toe development. Without initiation of these proteins, limb

malformations such as 2-3 syndactyly of the toes and pre-axial polydactyly can be seen.

Genital malformations such as undescended testicles and hypospadias are seen in 50% of boys with Smith-Lemli-Opitz. Hypospadias is a congenital condition in which the opening of the urethra is on the underside of the penis. Girls with SLOS have been reported to have genital abnormalities that include a bicornuate uterus and septate vagina. The genital abnormalities observed in children with SLOS are thought to be due to the abnormal regulation of SHH, which is responsible for activating a protein called WNT4, which plays a role in sexual differentiation of male and female genitalia.

Congenital heart defects are reported in half of all children with SLOS. The majority of these heart defects are atrioventricular heart canal defects and septal defects as well as anomalous pulmonary venous return problems. It has been determined that SHH plays a role in development of the left-right axis of the heart. Thus, altered function of the SHH pathway is a probable cause of the heart defects seen in children with SLO.

### Behavior:

In addition to the physical manifestations listed above, behavioral issues can be very challenging in children with Smith-Lemli-Opitz Syndrome. Behavioral issues such as irritability, hyperactivity, and outbursts are common, as are sleep difficulties and self injurious behavior. Autism-like features are seen in ~50-80% of children with SLOS. In fact, autism is so prevalent, it has been proposed that the incidence of Autism Spectrum Disorder may be higher in SLOS than in any other single gene disorder (Sikora et al, 2006). This has researchers exploring the possible link between cholesterol deficiency and autism in the general population.

### Link between ASD and cholesterol:

The association between cholesterol and behavior has been well studied. In fact, low serum cholesterol has been linked in numerous scientific papers to suicide, accidents, and violence (Engelberg, 1992; Virkkunen, 1979; Zureik et al, 1996). This is because cholesterol plays a vital role in neuron signaling and development of the brain structure. The association between cholesterol and autism is less studied but has become a huge area of interest among researchers including Dr. Richard Kelly and Dr. Tierney from Johns Hopkins University. Kelly and Tierney have dedicated their careers to investigating the behavioral effects of cholesterol deficiency in individuals with SLOS. They are especially interested in the association between cholesterol deficiency and autism and wonder if non-syndromic autism is caused by low levels of cholesterol. To test this idea, Kelly and Tierney recruited 150 children with autism and collected blood samples from which cholesterol levels were measured. In nearly 20% of children, the levels of cholesterol were lower than the 5th % of normal age-comparable children. This is significant enough to suggest a correlation between cholesterol and autism (Tierney et al, 2006). Further studies are needed to investigate the

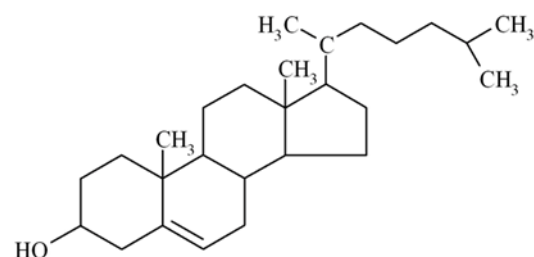
relationship between hypocholesteremia and autism.

### Management:

There is no cure for SLOS, however there is medical treatment and/or management for some of its features. Management of physical features can include specialized care by: cardiology, ophthalmology, GI, genitourinary, musculoskeletal, and audiology specialists. Nutritional assessments every 3-4 months in the first few years of life is important to monitor 7-DHC and amino transferase levels. Finally, given the wide variability in cognitive function, a developmental assessment should be arranged. An early developmental assessment is important because it can help identify the need for early intervention therapies including physical, occupational, and speech therapy. Age-appropriate developmental assessments should be performed at least twice a year until age three years old and annually thereafter (Genereviews, SLOS).

Management for children with SLOS should also include cholesterol therapy, which has been proven to improve nutritional status, muscle tone, growth, and photosensitivity in children with SLOS (Azurdia et al, 2001; Irons et al, 2007; Tierney et al, 2000,2001). The degree to which cholesterol therapy improves behavior is still unknown. Anecdotal evidence based on medical and parental observational studies supports the idea that cholesterol therapy modulates adverse behavior, but this has been difficult to confirm in clinical trials. Furthermore, there is debate as to whether cholesterol can cross the blood brain barrier (BBB) in children with SLOS. In unaffected children, cholesterol is unable to cross the blood brain barrier. However, given that cholesterol is needed to form the membranes of cells that create the BBB, it is plausible that children with SLOS might have a more permeable brain barrier that is capable of allowing absorption of cholesterol into the brain tissue. In addition to cholesterol therapy, the use of Simvastatin has been used to decrease the high levels of 7-DHC and 8-DHC in children with SLOS. Current research studies include looking at the effects of antioxidants, prenatal cholesterol supplementation, and gene therapy on the physical and behavioral profiles of children with SLOS.

Figure 2: Cholesterol chemical composition

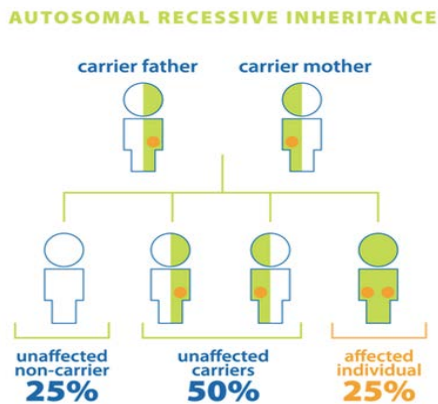


### Incidence/Inheritance:

Smith-Lemli-Opitz Syndrome is inherited in an autosomal recessive manner. This means that a child must inherit two

mutations, or changes, in the DHCR7 gene in order to have SLOS. Assuming that both parents carry a DHCR7 mutation, the chance of a child inheriting both copies is 25%. Children who inherit just one mutation are clinically unaffected themselves, but will be carriers for the condition. As a carrier, individuals carry a 50% risk of passing on the gene with the genetic change to future offspring. The prevalence of this condition is 1 in 20,000-40,000 births/year. It is estimated that the average person has a 1 in 30 chance of being a carrier for this condition. This is much higher than expected, given the rarity of the condition. This can be explained by the loss of SLOS-affected pregnancies before they reach full term.

**Figure 3: Autosomal recessive inheritance**



### Diagnosis/Testing:

Although there is no established clinical diagnostic criteria for individuals with SLOS, if suspected, a blood test will be used to identify an elevated concentration of 7-dehydrocholesterol or an elevated 7-DHC:cholesterol ratio. Molecular confirmation of SLOS can then be performed by genetic analysis of the DHCR7 gene.

Prenatal diagnosis of SLOS can be performed with the biochemical analysis of amniotic fluid. Molecular prenatal diagnosis of SLOS is also available for families with known mutations (Porter & Herman, 2011).

### Family Support Group Contacts:

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education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of intellectual disabilities. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

#### **ABOUT THE RCPU:**

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate intellectual disabilities through medical evaluations,

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