Smith-Lemli-Opitz Syndrome 101

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Outline

- Review the discovery of Smith-Lemli-Opitz syndrome (SLOS) and its underlying cause
- Describe the clinical features of SLOS and recommended medical care
- Discuss the rationale behind various treatment approaches for SLOS

Origins

A newly recognized syndrome of multiple congenital anomalies

David W. Smith, M.D.,* Luc Lemli, M.D., and John M. Opitz, M.D.

MADISON, WIS.

Smith *et al*., 1964. *The Journal of Pediatrics*. 64(2):210-217

Origins

Originally described as “RSH syndrome”

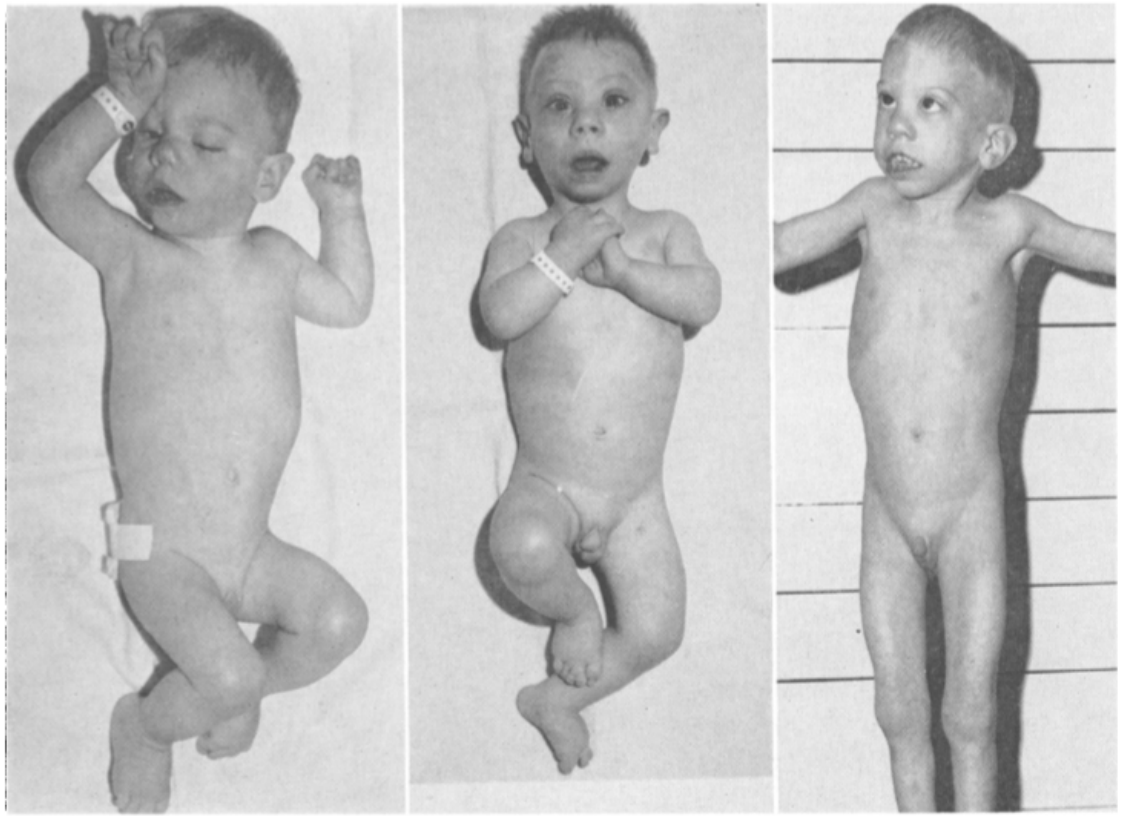


Fig. 2. From left to right: W. S. at 10 months, P. R. at 9½ months, and S. H. at 5$\frac{3}{12}$ years of age.

“The syndrome is presented with the hope that other cases will be recognized, allowing for the further definition of the condition and its etiology.”

Smith *et al.*, 1964. *The Journal of Pediatrics*. 64(2):210-217

Early Observations

- None of the individual characteristics were pathognomonic of the disorders
- None of the individual characteristics were obligatory
- The condition varied enormously in expressivity
- The occurrence in many races from unrelated parents indicated this was a relatively “common” disorder

Opitz, 1994. *American Journal of Medical Genetics*. 50(4):344-346

Mechanism

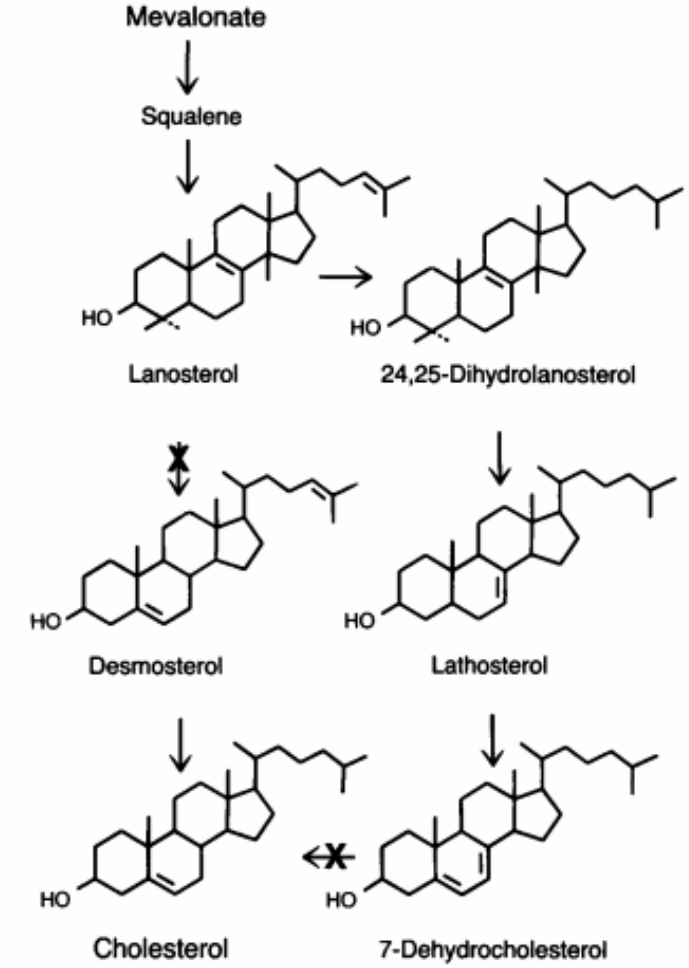


Figure 4. Steps in Cholesterol Biosynthesis.
Cholesterol is synthesized from C-24(25) saturated and C-24(25) unsaturated intermediates (structures at left and right, respectively). The symbol X denotes the proposed block in cholesterol biosynthesis in the Smith–Lemli–Opitz syndrome — defective reduction of the C-7 double bond of 7-dehydrocholesterol or of any other intermediate with a C-7 double bond.

Tint *et al*., 1994. *New England Journal of Medicine*. 330;107-113

SLOS Today: Demographics

Prevalence:

- 1 out of every 20,000-60,000 live births
  - More common in individuals of northern or central European ancestry
  - Less common in individuals with Asian or African ancestry

Carrier frequency:

- Approximately 1 in 30 individuals

Battaile, *et al*., 2001. *Molecular Genetics and Metabolism*. 72:67-71.
Nowaczyk *et al*., 2006. *American Journal of Medical Genetics*. 140A:2057-2062.

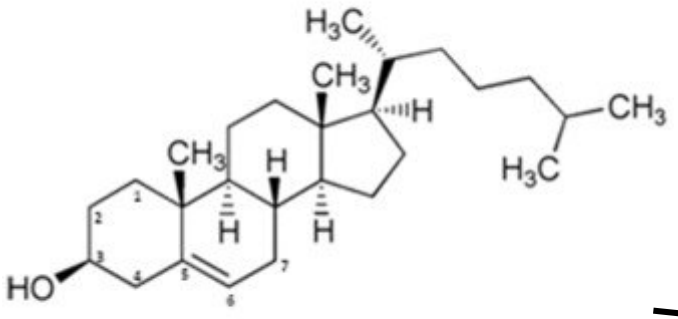
SLOS Today: Clinical Features

General	Slow growth, developmental delay, intellectual disability, low muscle tone, sleep issues, aggressive behaviors, autistic features
Skin	Sensitivity to light, eczema
Head	Small head size, small jaw, arched palate, cleft palate, holoproscencephaly
Eyes	Eyelid drooping, lazy eye, cataracts, underdeveloped optic nerve
Heart	Various heart malformations (septal defects, patent ductus arteriosis, AV canal), high blood pressure
Gastrointestinal Tract	Pyloric stenosis, Hirschsprung's disease, intestinal malrotation, constipation, reflux, feeding issues, cholestatic liver disease
Kidney and Genitals	Underdeveloped genitals, undescended testicles, kidney malformations
Extremities	Shortened arms, 2,3 toe syndactyly, extra fingers or toes, short thumbs

DeBarber *et al*., 2011. *Expert Reviews in Molecular Medicine*. Jul 22;13:e24.

The Many Faces of SLOS

Underlying Cause



Cholesterol

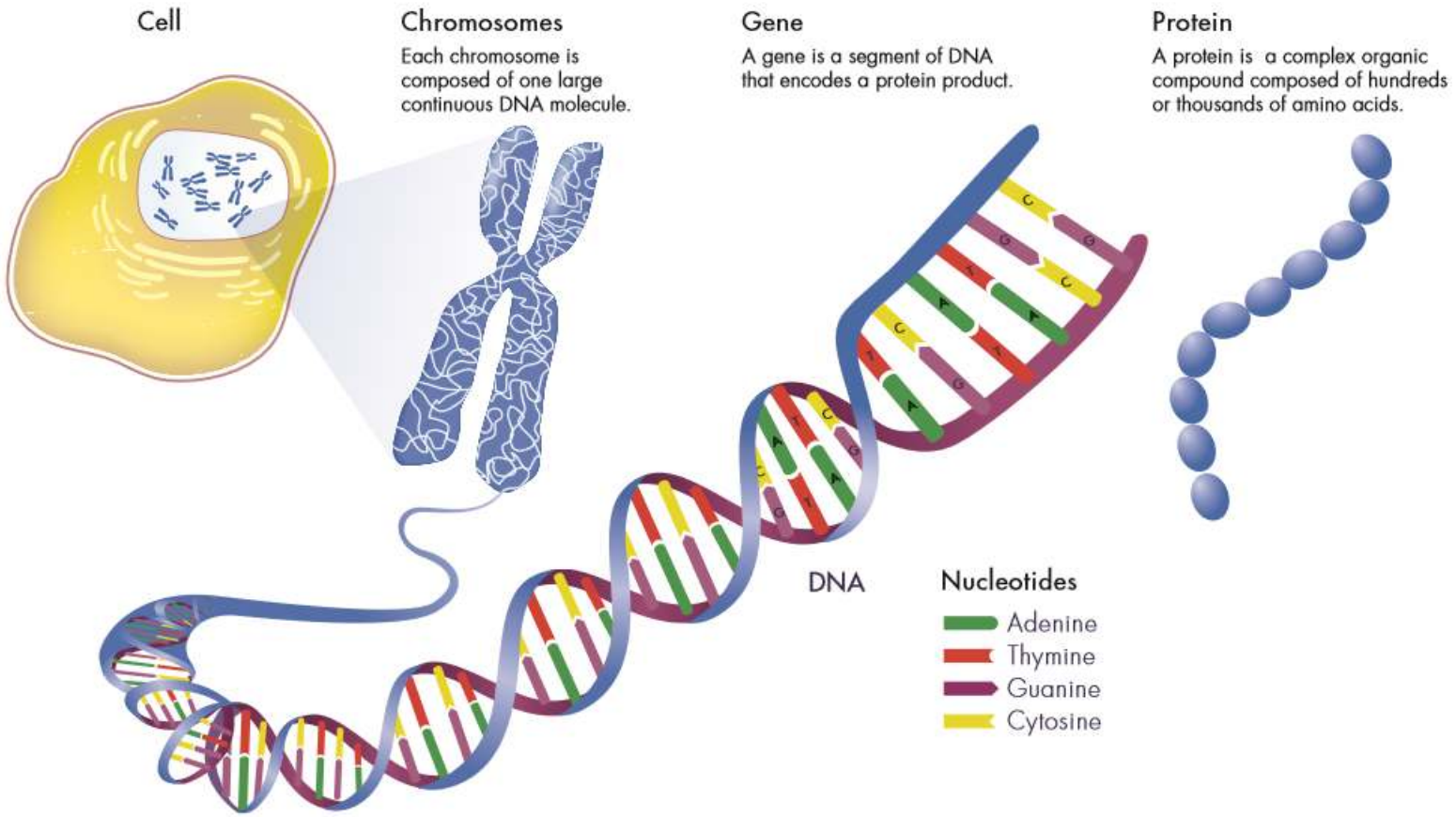
Steroid Hormones

Bile Acids

Embryonic Development

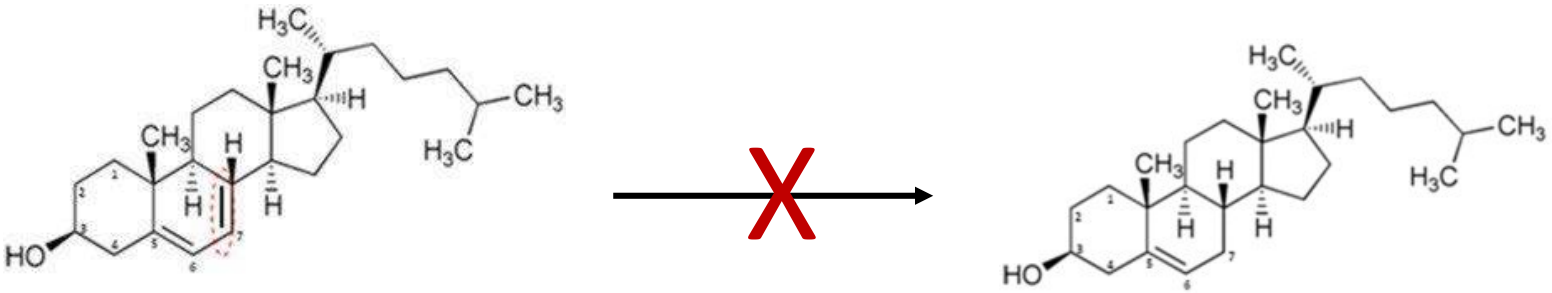
Cellular Membranes

Genetic Cause



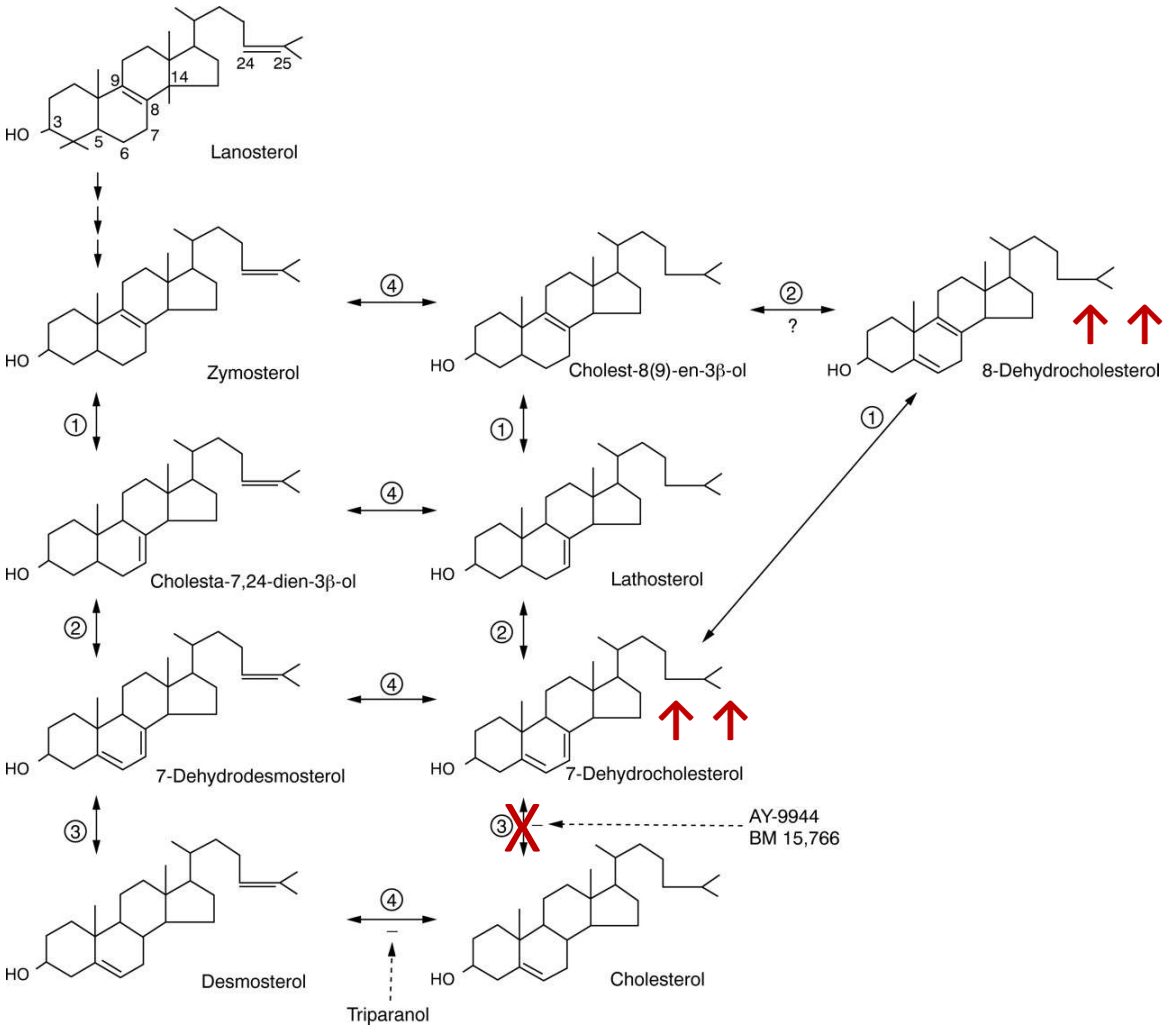
Greenwood Genetic Center

Underlying Cause



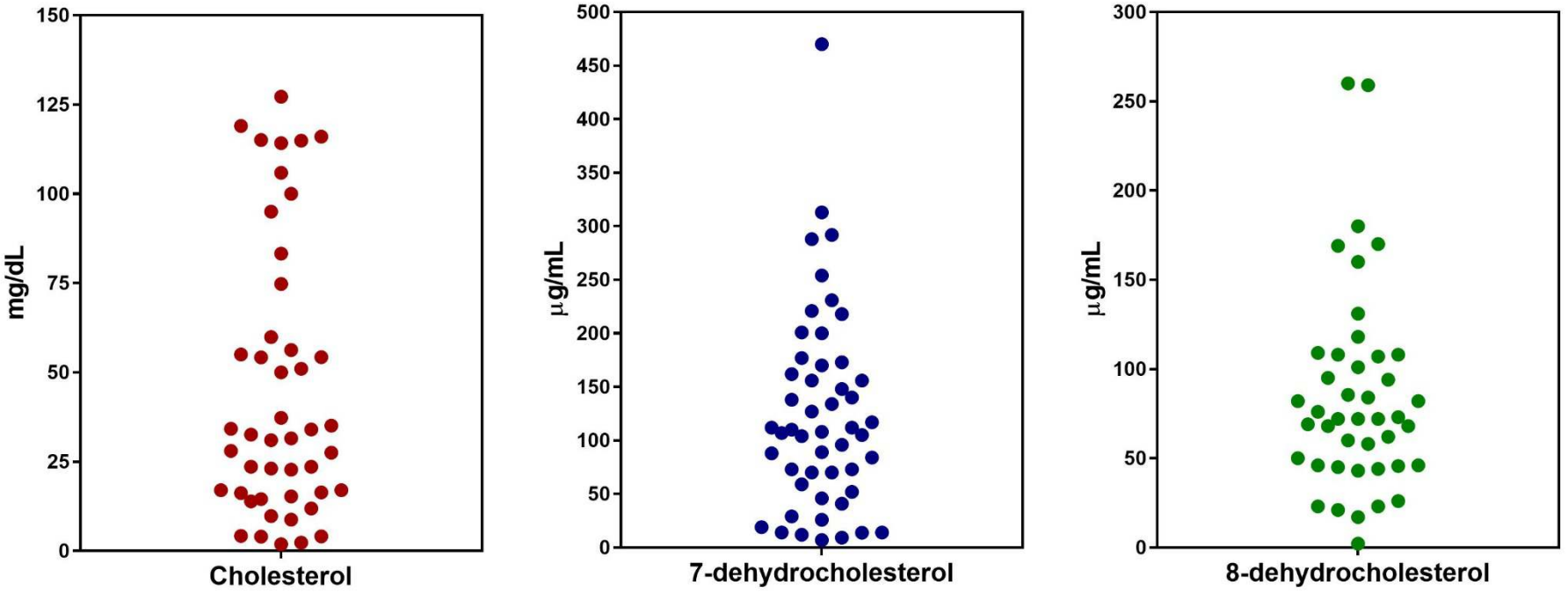
***DHCR7* Gene:** Provides instructions for the enzyme 7-dehydrocholesterol reductase

Underlying Cause



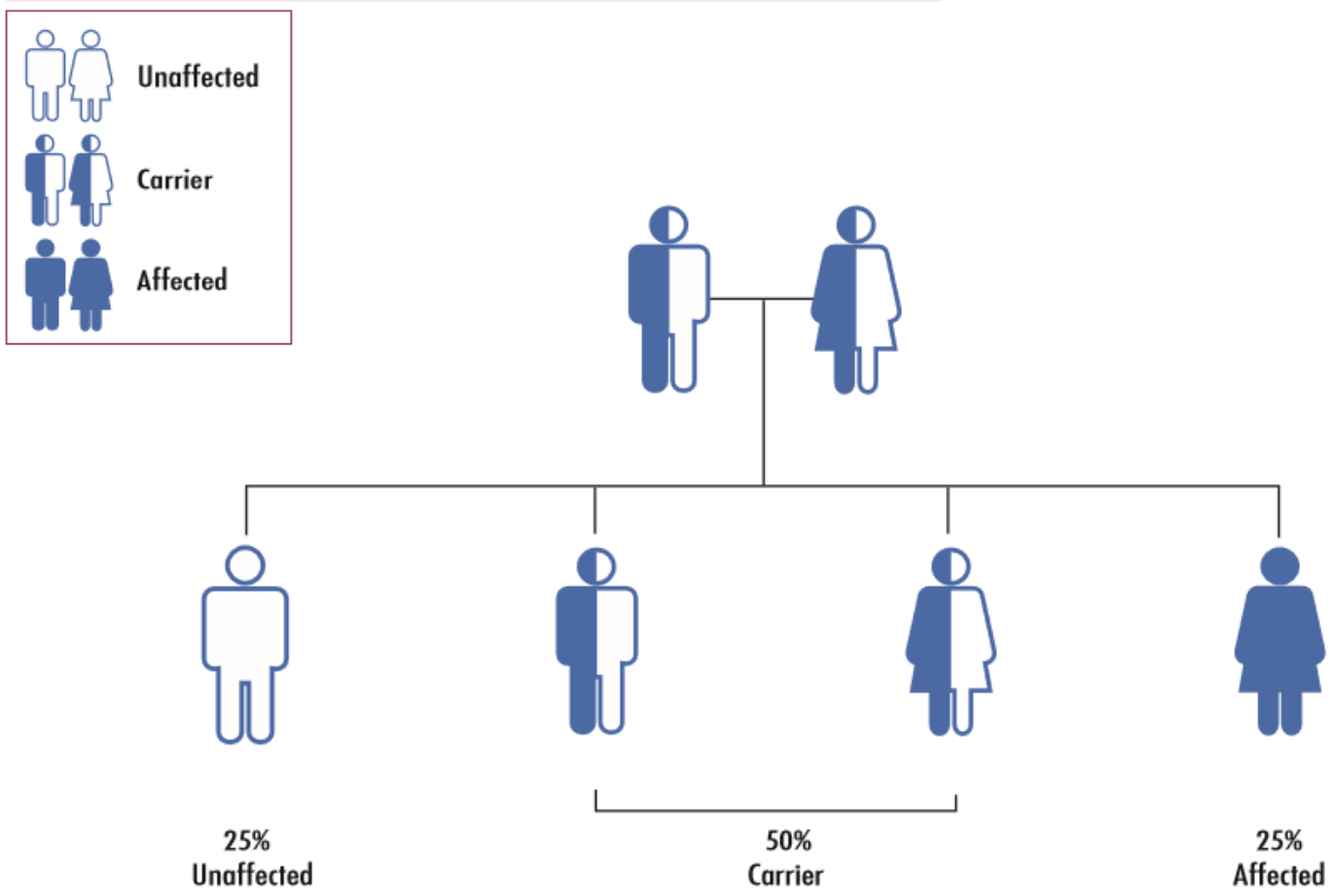
Kelley and Hennekam, 2000. *Journal of Medical Genetics*. 37:321-335

Cholesterol and Its Precursors



Adapted from Witsch-Baumgartner et al., 2000. *American Journal of Human Genetics*. 66:402-412.

Autosomal Recessive Inheritance Pattern



Diagnosis

Prenatal Ultrasound Findings:

- Poor growth
- Brain, heart, kidney, or limb malformations
- Underdeveloped male genitalia

Prenatal Laboratories:

- Low estriol
- Low hCG
- Low alpha fetoprotein
- Elevated equine sterols

Rossiter *et al.*, 1995. *American Journal of Medical Genetics*. 56:272-275.
Shackleton, *et al.*, 1999. *The Journal of Clinical Endocrinology and Metabolism*. 84(3):1157-1159

Diagnosis

Clinical Features:

- Characteristic facial features
- 2,3 toe syndactyly
- Small head size
- Feeding and growth issues
- Developmental delays
- Underdeveloped genitals in males
- Cleft palate
- Extra fingers or toes

Laboratories:

- Serum 7-dehydrocholesterol
  - Typically elevated
- Serum cholesterol
  - Sometimes low, but may be normal
- Molecular testing of *DHCR7* gene

Medical Care

At Diagnosis:

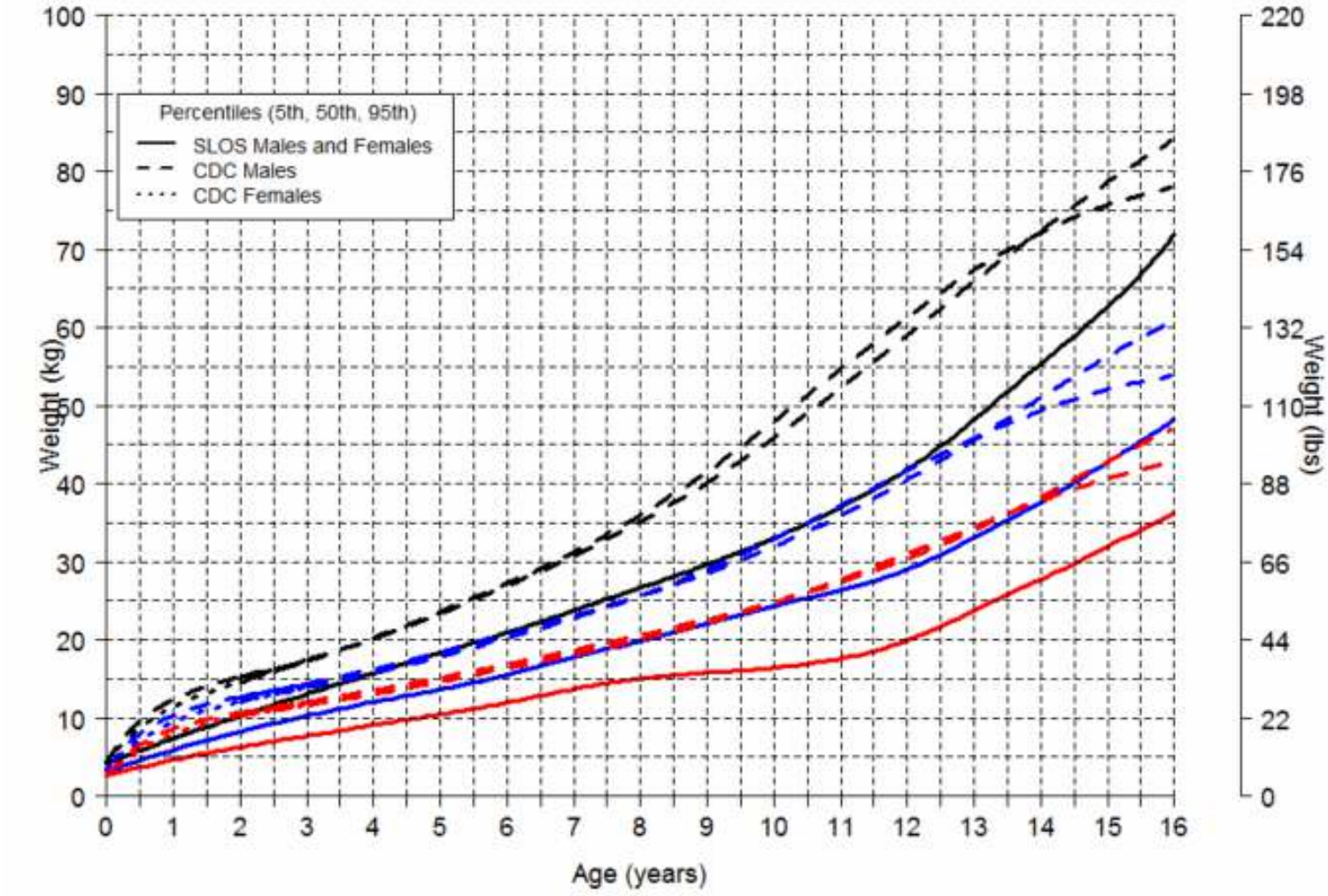
- Detailed history and physical examination
- Developmental assessment
- Ophthalmology exam
- Echocardiogram and ECG
- Brain imaging
- Kidney ultrasound
- Hearing evaluation
- Laboratories to look for signs of adrenal or liver issues
- Consultation with clinical geneticist

Medical Care

Ongoing:

- Detailed history and physical examination
- Developmental assessment
- Nutrition assessment with SLOS growth curves
- Laboratories (cholesterol, 7-dehydrocholesterol, 8-dehydrocholesterol, liver transaminases)

Smith-Lemli-Optiz Syndrome, Weight vs. Age (0-16 Years) with CDC Curves

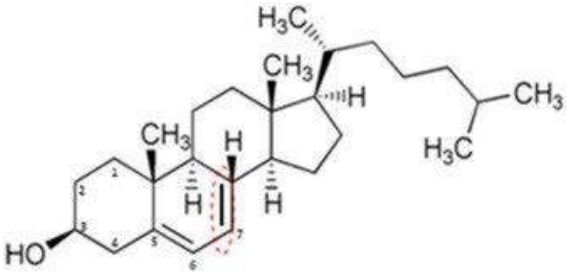


Lee *et al*., 2012. *American Journal of Medical Genetics*. 158(11):2707-2713.

Treatment

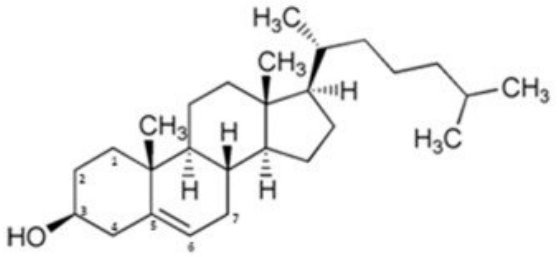
- Therapy services
- Feeding tubes
- Cholesterol and/or bile acid therapy for liver disease
- Surgical repair for eye issues
- Polydactyly repair
- Tympanostomy tubes for frequent ear infections
- UV protective clothes and sunscreen

Cholesterol or Bile Acid Supplementation



7-dehydrocholesterol

7-dehydrocholesterol reductase



Cholesterol

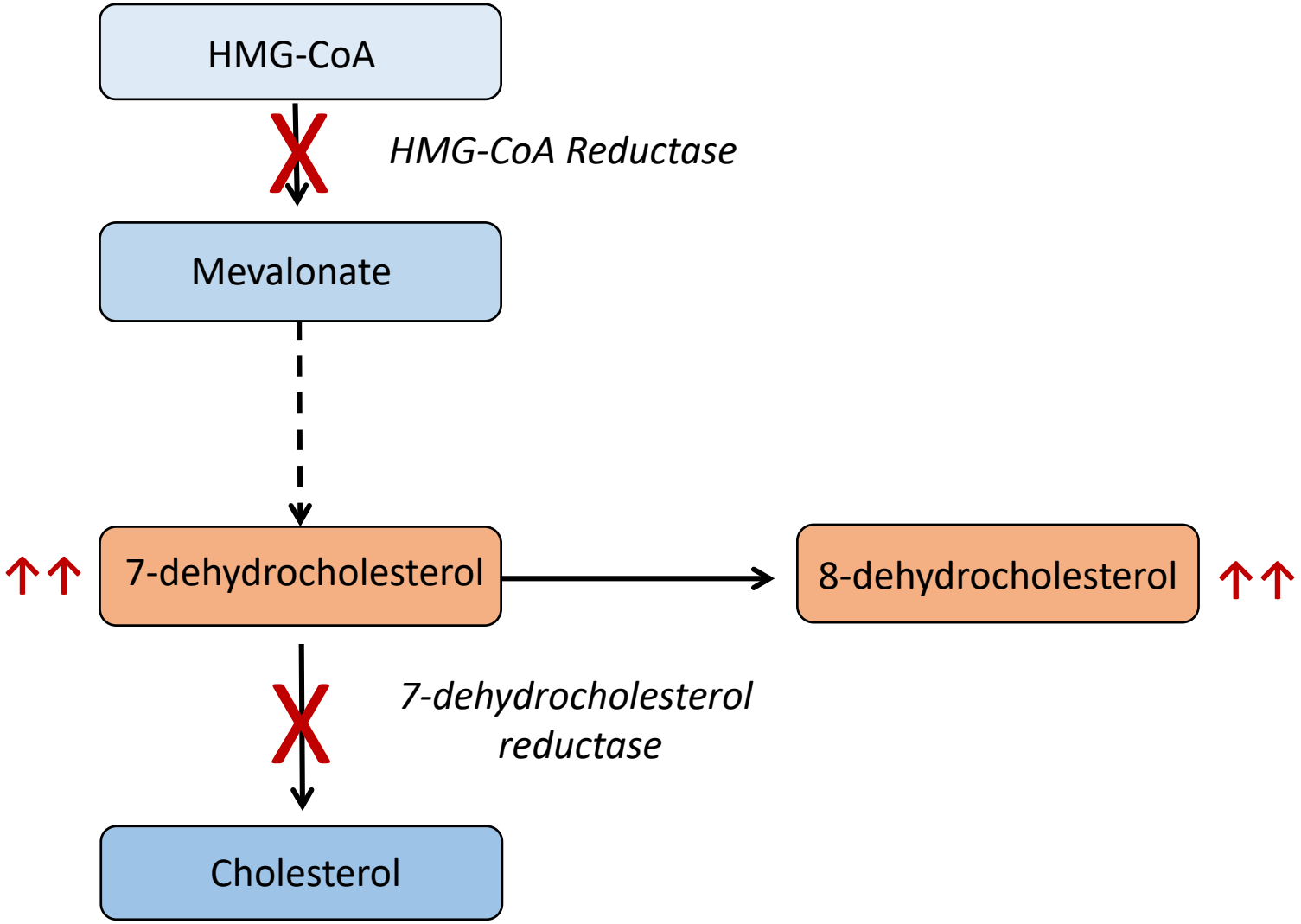
Steroid Hormones

Bile Acids

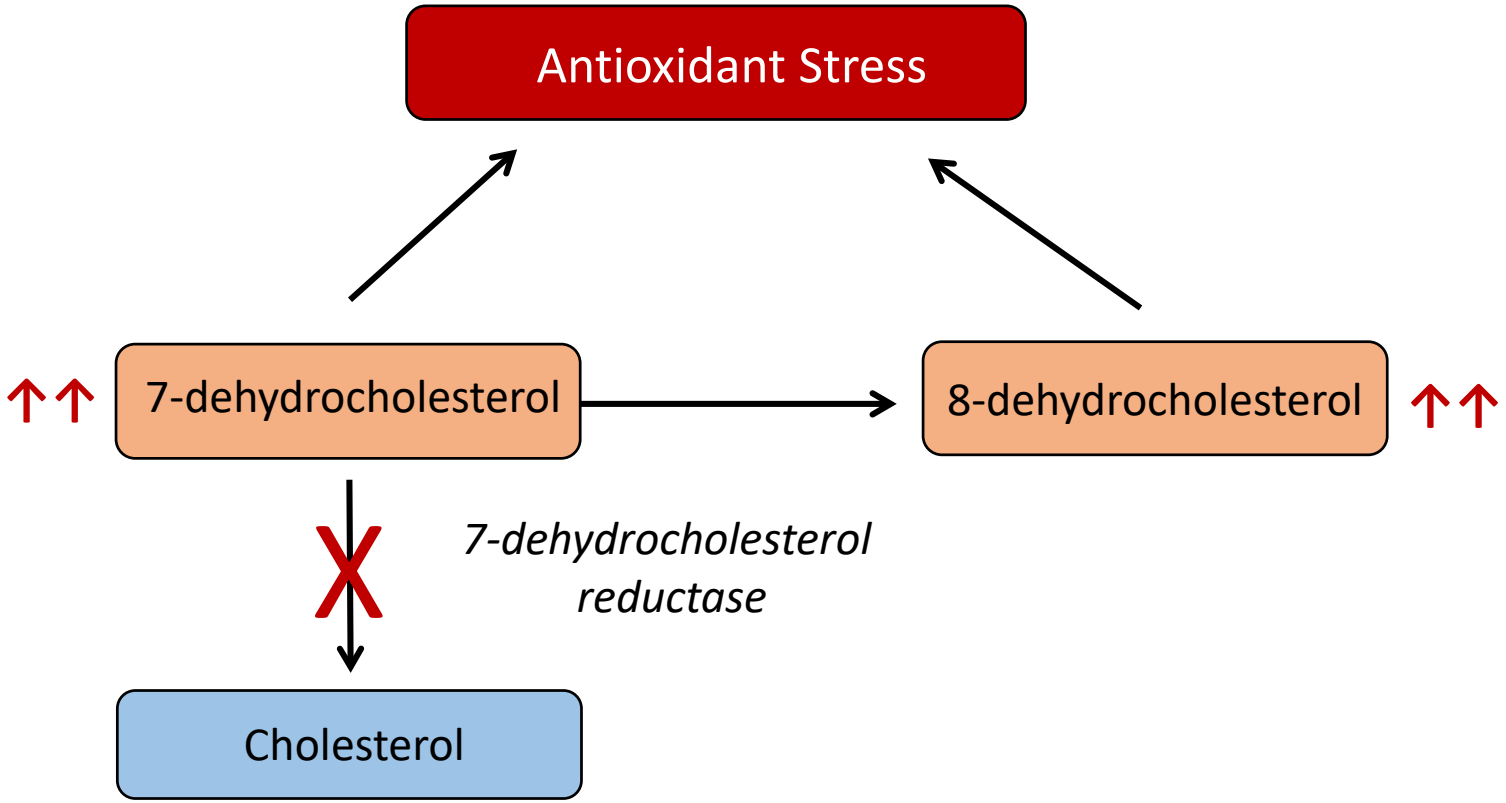
Embryonic Development

Cellular Membranes

HMC-CoA Reductase Inhibitors



Antioxidant Supplementation



Additional Therapies

- Prenatal cholesterol supplementation
- Stem cell therapy
- Gene therapy

Resources

- Smith-Lemli-Opitz Foundation
- Rare Disease Clinical Research Network (STAIR)
- Clinicaltrials.gov