



# Case #139

NAME Educational Activities Committee

Case provided by:

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A liveborn male fetus at 37 weeks' gestation expired after approximately two weeks of life due to a complicated post-natal course. He was born to a G2P0010 mother in her late twenties. Prenatal ultrasound showed multiple congenital anomalies and amniocentesis revealed a clinically significant variant with otherwise normal male karyotype. Additionally, the newborn screen was positive for elevated 7-dehydrocholesterol levels.

Based on this history and the external findings shown in the photos, which chromosome is most likely involved?

- A. Chromosome 7
- B. Chromosome 11
- C. Chromosome 13
- D. Chromosome 21

Answer...

## B. Chromosome 11 (correct – 47.74%)

**Smith–Lemli–Opitz syndrome (SLOS)** is an **autosomal recessive metabolic disorder** caused by a **deficiency of 7-dehydrocholesterol reductase (*DHCR7* gene on **chromosome 11**)**, the final enzyme in the cholesterol biosynthesis pathway. Impaired conversion of 7-dehydrocholesterol (7-DHC) to cholesterol leads to **low serum and tissue cholesterol levels with marked accumulation of 7-DHC**, producing a characteristic pattern of **congenital malformations and multisystem dysfunction**. Reported incidence varies by population, but **estimates range from 1:20,000 to 1:60,000 live births**, with a higher carrier frequency (approximately 1% in individuals of Northern European ancestry). The most common pathogenic variant is **c.964-1G>C**, which was found in this case.

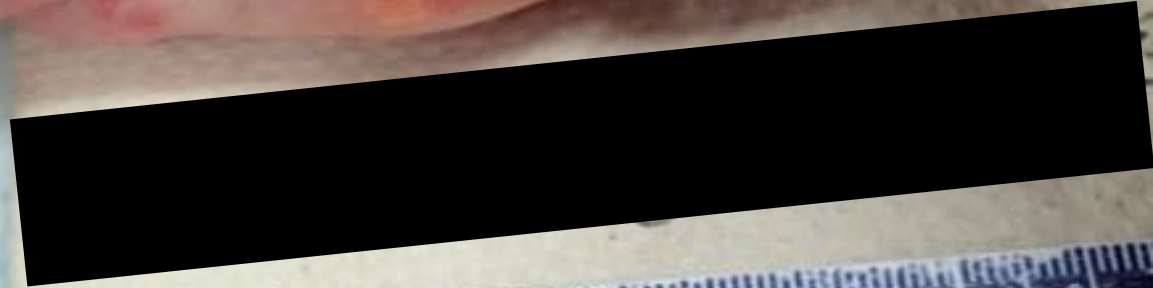
SLOS manifests along a broad severity spectrum, from mild behavioral or neurodevelopmental abnormalities to severe, lethal malformations. Common external exam features include **microcephaly, micrognathia, depressed nasal bridge, low-set ears, post-axial polydactyly, 2-3 toe syndactyly (present in this case but not shown), cryptorchidism, and genital anomalies (e.g., small phallus, hypospadias)**. See next slides for annotations.



Small phallus with hypospadias



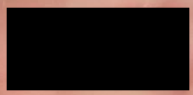
Undescended left testicle



Depressed nasal bridge; micrognathia



Low-set ears



Positive 7-DHC on newborn SLO screen  
(highlighted by red boxes).

 Dehydrocholesterol, 7

Component

Ref Range & Units (hover)

Smith-Lemli-Opitz Screen	Positive <sup>VC</sup>
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Internal congenital anomalies frequently involve the **cardiac, renal, and gastrointestinal systems**, including **atrioventricular canal defects (bicuspid aortic valve and patent foramen ovale was noted in this case, not shown), patent ductus arteriosus (also present in this case but not shown)**, renal dysplasia, pyloric stenosis, and Hirschsprung disease. **Central nervous system malformations are common**—e.g., holoprosencephaly, agenesis or hypoplasia of the corpus callosum, ventriculomegaly, and cerebellar hypoplasia—and contribute significantly to morbidity and mortality. The brain, unfortunately, was markedly macerated in this case.

Neonatal and postnatal complications typically include feeding difficulties, failure to thrive, **respiratory insufficiency, recurrent infections (diffuse bilateral acute bronchopneumonia was present in this case)**, and severe cholestatic liver disease. **Many severely affected infants die in the neonatal period or early infancy (as in this case)**. Diagnostic confirmation is achieved through **elevated serum or tissue 7-DHC levels and/or *DHCR7* gene testing**, both of which were positive in this case.

*To summarize, we present a case of an approximately two-week-old liveborn male fetus (born at 37 weeks' gestation) to a female in her late twenties. Prenatal ultrasound showed multiple congenital anomalies, and amniocentesis revealed the most common clinically significant variant of DHCR7 on chromosome 11 (c.964-1G>C), confirming a diagnosis of SLOS. In addition, the newborn screen was positive for elevated 7-DHC, further supporting this diagnosis.*

*At autopsy, we confirmed the presence of multiple congenital anomalies, including post-axial polydactyly, cryptorchidism, genital anomalies (e.g., small phallus, hypospadias), depressed nasal bridge, microcephaly, micrognathia, and low-set ears, which are shown in the represented photographs. Additional anomalies such as 2-3 toe syndactyly, bicuspid aortic valve, patent foramen ovale, and patent ductus arteriosus, were also identified but not shown. **The biochemical findings of elevated 7-dehydrocholesterol and DHCR7 variant, with the observed phenotypic anomalies described above, confirm SLOS.***

***For pathologists, recognition of a pattern of anomalies such as this should raise suspicion for SLOS versus other enzymopathy/metabolic disease, and prompt biochemical or genetic testing should be pursued if not already performed ante-mortem.***

Other responses...

### **A. Chromosome 7 (incorrect – 9.06%)**

**Williams syndrome** results from a microdeletion at 7q11.23 and is associated with characteristic “elfin” facies, supraaortic stenosis, hypercalcemia, and neurodevelopmental features. It is not associated with elevated 7-dehydrocholesterol, disorders of cholesterol biosynthesis, or the pattern of limb and genital anomalies seen in this case.

### **C. Chromosome 13 (incorrect – 30.51%)**

**Patau syndrome (trisomy 13)** classically presents with severe midline defects, including holoprosencephaly, cleft lip/palate, scalp defects, and polydactyly. While polydactyly may overlap, trisomy 13 is a numerical chromosomal abnormality, not an enzymatic defect, and would not produce elevated 7-DHC or a normal karyotype on amniocentesis.

### **D. Chromosome 21 (incorrect – 12.69%)**

**Down syndrome (trisomy 21)** is associated with characteristic facial features, single palmar crease, hypotonia, and atrioventricular septal defects. It does not involve abnormalities of cholesterol metabolism, elevated 7-DHC, or the genital and limb anomaly pattern characteristic of Smith–Lemli–Opitz syndrome.

*A differential diagnosis summary table for syndromes that may have features like SLOS at time of autopsy are provided in the next two slides. Note: this table is not completely comprehensive or exhaustive of all possible differentials, but rather a primer for consideration and further exploration.*

# Differential Diagnosis of SLOS

Syndrome	Key External Exam Features	Key Internal Exam Features	Chromosome / Gene(s)	Newborn Screen / Measurable Abnormalities
<b>Smith–Lemli–Opitz syndrome (SLOS)</b>	Microcephaly, micrognathia, depressed nasal bridge, <b>low-set ears</b> , post-axial <b>polydactyly</b> , <b>2–3 toe syndactyly</b> , ambiguous genitalia, <b>hypospadias</b> , <b>cryptorchidism</b>	<b>Congenital heart disease</b> (AV canal defects, PDA), renal dysplasia, GI anomalies (Hirschsprung disease, pyloric stenosis), CNS malformations (holoprosencephaly, corpus callosum anomalies)	<b>DHCR7 gene, chromosome 11</b> (autosomal recessive)	<b>Elevated 7-dehydrocholesterol (7-DHC)</b> with low cholesterol
<b>Williams syndrome</b>	“ <b>Elfin</b> ” facies (periorbital fullness, wide mouth, full lips), stellate iris pattern, short stature	<b>Supravalvular aortic stenosis</b> , other elastin-related vascular abnormalities, hypercalcemia-related nephrocalcinosis	<b>7q11.23 microdeletion</b> (ELN gene)	Typically <b>normal</b> ; may show hypercalcemia (not a primary NBS marker)
<b>Patau syndrome (Trisomy 13)</b>	Severe craniofacial anomalies, cleft lip/ <b>palate</b> , scalp defects ( <b>cutis aplasia</b> ), post-axial <b>polydactyly</b>	<b>Holoprosencephaly</b> , congenital heart disease, renal anomalies (cystic kidneys)	<b>Trisomy 13</b>	<b>Abnormal aneuploidy</b> screening prenatally; <b>no specific metabolic marker</b> on NBS

# Differential Diagnosis of SLOS

Syndrome	Key External Exam Features	Key Internal Exam Features	Chromosome / Gene(s)	Newborn Screen / Measurable Abnormalities
<b>Down syndrome (Trisomy 21)</b>	Up-slanting <b>palpebral fissures</b> , <b>epicanthal folds</b> , flat nasal bridge, <b>single palmar crease</b> , hypotonia	<b>Atrioventricular septal defects</b> , duodenal atresia, Hirschsprung disease	<b>Trisomy 21</b>	May have elevated TSH on NBS (congenital hypothyroidism); otherwise nonspecific
<b>Meckel-Gruber syndrome</b>	<b>Occipital encephalocele</b> , post-axial polydactyly, facial clefts	<b>Bilateral cystic renal dysplasia</b> , hepatic fibrosis, CNS malformations	Multiple genes (e.g., <b>TMEM67</b> , <b>CC2D2A</b> ); <b>MKS1</b> ciliopathy (autosomal recessive)	<b>No specific NBS marker</b> ; lethal structural anomalies dominate
<b>Turner syndrome</b>	<b>Lymphedema</b> of hands/feet, <b>webbed neck</b> , low posterior hairline, <b>shield chest</b>	<b>Coarctation of the aorta</b> , bicuspid aortic valve, streak gonads	<b>45,X</b> (or mosaic variants)	Possible abnormal sex chromosome screening; no metabolic marker
<b>Cystic fibrosis</b>	Often subtle externally; may show <b>meconium ileus</b> in neonates	<b>Pancreatic duct obstruction and fibrosis</b> , bronchiectasis, intestinal obstruction	<b>CFTR gene, chromosome 7</b> (autosomal recessive)	<b>Elevated immunoreactive trypsinogen (IRT) ± CFTR mutation analysis</b>

# REFERENCES

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