30 Smith–Lemli–Opitz Syndrome

MIM 270400

Major Clinical Findings

Smith–Lemli–Opitz syndrome (SLOS) is a multiple congenital malformation and intellectual disability syndrome with a broad clinical spectrum and phenotypes ranging from mild to severe. SLOS occurs in approximately 1 in 20,000–30,000 births in populations of northern and central European background. SLOS is mainly characterized by growth retardation, microcephaly, psychomotor delay, soft tissue syndactyly of the 2nd and 3rd toes, and genital abnormalities. In males, genital findings range from mild anomalies to sex reversal. Severely affected individuals exhibit multiple malformations in the central nervous system (including the eye), heart, kidney, and bowel. Individuals with a severe phenotype may die in the neonatal period because of failure to thrive and hepatic dysfunction. More mildly affected patients show a better prognosis. Characteristic facial features include ptosis, strabismus, a flat nasal bridge, anteverted nares, and micrognathia. Cleft palate has been observed in about 50%.

Postaxial polydactyly of the hands and feet is observed in 25% of mildly affected individuals and in 75% of those severely affected. Soft tissue syndactyly of the 2nd and 3rd toes has been documented in about 80%. Because of a short 1st metacarpal, the thumb appears to be short; a short 1st metatarsal is a frequent radiographic feature. Dislocated hips occur in about 50% of the affected individuals. Positional foot abnormalities are frequent.

Individuals with SLOS show a characteristic behavioral profile of psychomotor delay, language impairment, sleep disturbance, self-injurious behavior, and autism spectrum of behavior. Cholesterol supplementation may improve the clinical course.

Occasional Findings

Clinodactyly of fingers, holoprosencephaly, partial agenesis of the cerebellar vermis, agenesis of the corpus callosum, seizures, lung abnormalities, hypoplastic labia majora, upper urinary tract anomalies, renal cysts, hypoplasia of the kidneys, various congenital heart defects, broad maxillary alveolar ridges, and increased photosensitivity.

Genetic Transmission

Autosomal recessive.

Differential Diagnosis

Pallister–Hall syndrome can be distinguished by the presence of a hypothalamic hamartoblastoma.

Molecular Pathology

SLOS is caused by homozygous or compound heterozygous mutations in the *DHCR7* gene encoding sterol delta-7-reductase, the penultimate enzyme of mammalian sterol biosynthesis that converts 7-dehydrocholesterol (7-DHC) to cholesterol. Deficiency of 7-dehydrocholesterol reductase is the causative factor of SLOS. The mutation spectrum of *DHCR7* varies significantly among populations.

References

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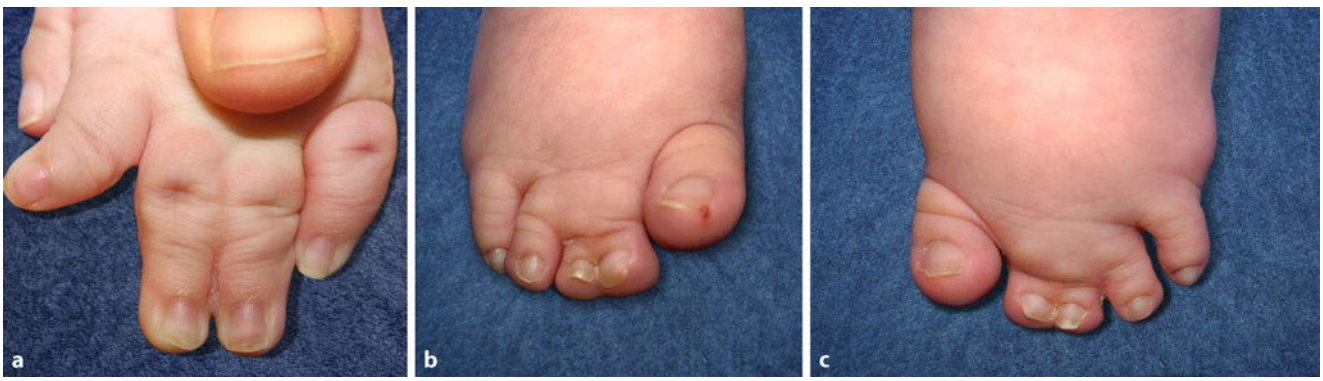

Fig. 30.1 **a** Syndactyly of digits III/IV, radial deviation of digit II. **b, c** Feet of the same individual showing typical syndactyly of toes II/III as well as partial syndactyly with toe IV

S. Mundlos, D. Horn, *Limb Malformations*,
DOI 10.1007/978-3-540-95928-1_30, © Springer-Verlag Berlin Heidelberg 2014