

30.1 Introduction

Cholesterol has several essential functions in normal cell physiology. Not only is cholesterol a major component of cellular membranes, but it is also the precursor of bile acids and steroid hormones and plays an important role in embryonic and postnatal development. For many years, mevalonate kinase deficiency (MKD) was the only known genetic disorder of the cholesterol biosynthetic pathway [1, 2]. However, the discovery of increased levels of 7-dehydrocholesterol and hypocholesterolemia in patients with Smith-Lemli-Opitz syndrome (SLOS) in 1993 [3, 4] opened the way for the emergence of a new group of metabolic disorders – inborn errors of post-squalene cholesterol. At first glance, these disorders appear to be very heterogeneous: one disorder with profound physical and neurologic disease (MKD), two disorders classified as multiple malformation syndromes (SLOS and desmosterolosis [5]), and two others as skeletal dysplasias (Conradi-Hünemann syndrome (CDPX2) [6] and CHILD syndrome [7, 8]). However, there are several features shared by these disorders. For example, a distinctive facial dysmorphism is a major characteristic of SLOS, but similar facial features have also been reported in some patients with MKD and CDPX2. Moreover, whereas marked skeletal abnormalities are hallmarks of CDPX2 and CHILD syndrome, rhizomelic shortness has been described in MKD, SLOS, and desmosterolosis as well. In addition, congenital cataracts have been reported in all of the known cholesterol biosynthetic disorders except the form of CHILD syndrome caused by a deficiency of the 4-methylsterol demethylase complex. The recent discovery of the biochemical bases of these rare but well-known genetic disorders has not only provided accurate biochemical methods for their diagnosis, but has also allowed better delineation of the spectrum of their complex clinical phenotypes [9].

■ Mevalonate Kinase Deficiency

Mevalonate kinase deficiency (MKD) is a rare, autosomal recessive disorder with an incidence of less than 1 in 100,000 births and highly variable clinical expression [2]. Important characteristics of MKD include febrile crises

associated with arthralgia, edema, increased erythrocyte sedimentation rate, and a morbilliform rash; developmental delays; hepatosplenomegaly; diarrhea; and mevalonic aciduria. The inflammatory spells occur every 3 to 6 weeks, usually without a specific precipitating event. More severely affected patients may have dysmorphic features, severe failure-to-thrive, rhizomelic dwarfism, cataracts, or anemia. Biochemically more mildly affected patients may have only minimal psychomotor retardation, hypotonia, myopathy, or ataxia. Recently, a third group of patients with mevalonate kinase deficiency has been identified. These patients have recurrent episodes of fever and hyperimmunoglobulinemia D [10], but only minimally increased mevalonic acid excretion and none of the developmental or physical abnormalities associated with classical MKD [11, 12]. The diagnosis of all forms of MKD is based on increased urinary excretion of mevalonic acid and deficient activity of mevalonate kinase activity in fibroblasts, lymphocytes, or lymphoblasts, or, more recently, mutation analysis. Despite many attempts at treatment, there is no proven effective therapy for any form of MKD.

■ 3 β -Hydroxysteroid Dehydrogenase (NSDHL) Deficiency

3 β -Hydroxysteroid dehydrogenase, encoded by *NSDHL* (NAD(P)H steroid dehydrogenase-like) functions in the heteromultimeric enzyme complex, 4 α -methylsterol-4-demethylase. Recently, several patients with Congenital Hemidysplasia, Ichthyosis, and Limb Defects (CHILD syndrome) were found to have increased levels of 4-methylsterols and/or mutations in the *NSDHL* gene [8]. CHILD syndrome is a rare (fewer than 50 patients reported), X-linked dominant disorder characterized by unilateral ichthyosiform skin lesions and ipsilateral reduction deformities of the limbs [13]. Concomitant anomalies on the affected side include punctate calcifications of the epiphyses of the vertebrae and long bones, abnormal calcification of the laryngeal and tracheal cartilages, and hypoplasia of internal organs, especially the kidney. The ichthyosiform skin lesions cover large segments of the body, sparing the face, and there is characteristically a sharp line of demarcation between normal and abnormal skin at the midline of the trunk. A deficiency of *NSDHL* can be identified by sterol analysis of plasma, tissue, cultured lymphoblasts or fibroblasts, or by mutation analysis.

■ 3 β -Hydroxysteroid- Δ^8, Δ^7 -Isomerase Deficiency

3 β -Hydroxysteroid- Δ^8, Δ^7 -isomerase (sterol- Δ^8 -isomerase, emopamil-binding protein) immediately follows the 4 α -methylsterol-4-demethylase complex in the cholesterol biosynthetic pathway. In 1999, Kelley et al. reported an abnormal sterol pattern in patients with Conradi-Hünemann syndrome (CDPX2) [6]. The neutral sterol fraction of plasma, tissues, and cultured fibroblasts from these patients contained increased levels of cholest-8(9)-en-

3β -ol (8(9)-cholestenol) and cholesta-5,8-dien- 3β -ol (8-dehydrocholesterol; 8DHC), indicating a block in cholesterol synthesis at the level of sterol- Δ^8 -isomerase. Subsequent molecular studies demonstrated mutations in the gene, *EBP*, encoding this enzyme [14, 15]). CDPX2 is a rare (incidence less than 1 in 100,000 births), X-linked dominant disorder characterized in females by a variable combination of bilateral and asymmetric shortening of long bones; punctate calcifications of epiphyses, trachea, and larynx; segmental cataracts, and patches of ichthyotic skin that mostly follow the lines of Blaschko [16, 17]. Other abnormalities in some CDPX2 patients include polydactyly, dysmorphic facies, peripheral pulmonic stenosis and related vascular abnormalities, optic hypoplasia, and cervical compressive myelopathy. Although CDPX2 is thought to be lethal in males early in gestation, several 46, XY males with CDPX2-like chondrodysplasia punctata or skin lesions have had an abnormal sterol pattern in plasma consistent with sterol- Δ^8 -isomerase deficiency. The diagnosis of CDPX2 can be made by biochemical or molecular methods. It should be noted that, in several instances, a mutation in the gene encoding sterol- Δ^8 -isomerase was found not only in a clinically affected daughter, but also in the apparently clinically unaffected mother. Thus, diagnostic studies should be pursued in all women with affected offspring. Sterol- Δ^8 -isomerase deficiency has also been found in several patients with the clinical diagnosis of CHILD syndrome.

■ Desmosterolosis

The third defect in cholesterol biosynthesis to be identified was Desmosterolosis. In 1998, FitzPatrick et al. described a 46, XX female infant with multiple malformations including macrocephaly, cleft palate, ambiguous genitalia, and limb abnormalities. At autopsy, this infant was found to have markedly increased tissue levels of cholesta-5,24-dien- 3β -ol (desmosterol) [5]. To date, only one other patient with this disorder has been identified, a 2-year-old male with microcephaly, short stature, speech and psychomotor delays, and increased levels of desmosterol in plasma and cultured lymphoblasts (H. Andersson and R. Kelley, unpublished observations). Although quite different in their clinical presentations, both patients were found to have mutations in the gene encoding 3β -hydroxysteroid- Δ^{24} -reductase (desmosterol reductase), the enzyme that converts desmosterol to cholesterol (H. Waterham, personal communication).

■ Smith-Lemli-Opitz Syndrome

The most common disorder of cholesterol biosynthesis, with an estimated incidence of 1 in 40,000 births, is Smith-Lemli-Opitz (RSH) syndrome [18, 19]. This autosomal recessive disorder is characterized clinically by distinctive facial anomalies, limb and genital malformations, and mental retardation.

tion. Internal structural and functional abnormalities involving the lung, kidney, brain, heart, and gastrointestinal system are also common in more severely affected patients. In 1993, Irons et al. found that patients with SLOS have increased levels of cholesta-5,7-dien-3 β -ol (7-dehydrocholesterol, 7DHC), suggesting a deficiency of 3 β -hydroxysteroid- Δ^7 -reductase (7-dehydrocholesterol reductase), the terminal enzyme of the Kandutsch-Russell pathway for cholesterol biosynthesis [20]. Subsequently, most patients with a clinical diagnosis of SLOS have been found to have increased levels of 7DHC and, in most cases, low levels of cholesterol in blood and tissues [21, 22]. With the identification of a biochemical marker for SLOS, the clinical spectrum for this disorder has expanded to include mildly affected patients with no discrete malformations and normal intelligence as well as severely affected fetuses who die in utero from multiple internal anomalies. In addition to this extreme clinical variability, there is also a wide range of biochemical severity among patients with SLOS. Whereas some patients have plasma levels of cholesterol less than 0.25 mmol/l at the time of diagnosis, others, approximately 10%, have normal plasma levels of cholesterol, despite even 100-fold increased levels of 7DHC [9, 23]. Furthermore, there is a subset of SLOS patients who have normal cholesterol levels and only minimally increased levels of 7DHC, similar to the sterol pattern in some SLOS obligate heterozygotes. However, studies in cultured fibroblasts or lymphoblasts from these patients show a sterol pattern unequivocally diagnostic of SLOS (R. Kelley, unpublished observations). Thus, whereas SLOS can be diagnosed by analysis of plasma sterols in the majority of patients, a small percentage may require more detailed analysis of sterol biosynthesis in cultured cells. At present, SLOS is the only disorder of cholesterol biosynthesis that improves with metabolic therapy, specifically, dietary supplementation with cholesterol [23, 24].

30.2 Nomenclature

No.	Disorder – affected component	Tissue distribution	Chromosomal localisation	MIM
30.1	Mevalonate kinase deficiency Mevalonic aciduria Hyper IgD syndrome	All tissues	12q24.1	251170
30.2	3 β -Hydroxysteroid dehydrogenase deficiency CHILD syndrome	All tissues	Xq28	308050
30.3	3 β -Hydroxysteroid- Δ^8, Δ^7 -isomerase deficiency Conradi-Hünemann syndrome (CDPX2)	All tissues	Xp11.22–23	302960
30.4	3 β -Hydroxysteroid- Δ^{24} -reductase deficiency Desmosterolosis	All tissues	1p31.1–33	125650
30.5	3 β -Hydroxysteroid- Δ^7 -reductase deficiency Smith-Lemli-Opitz syndrome	All tissues	11q12–13	270400

30.3 Metabolic Pathways

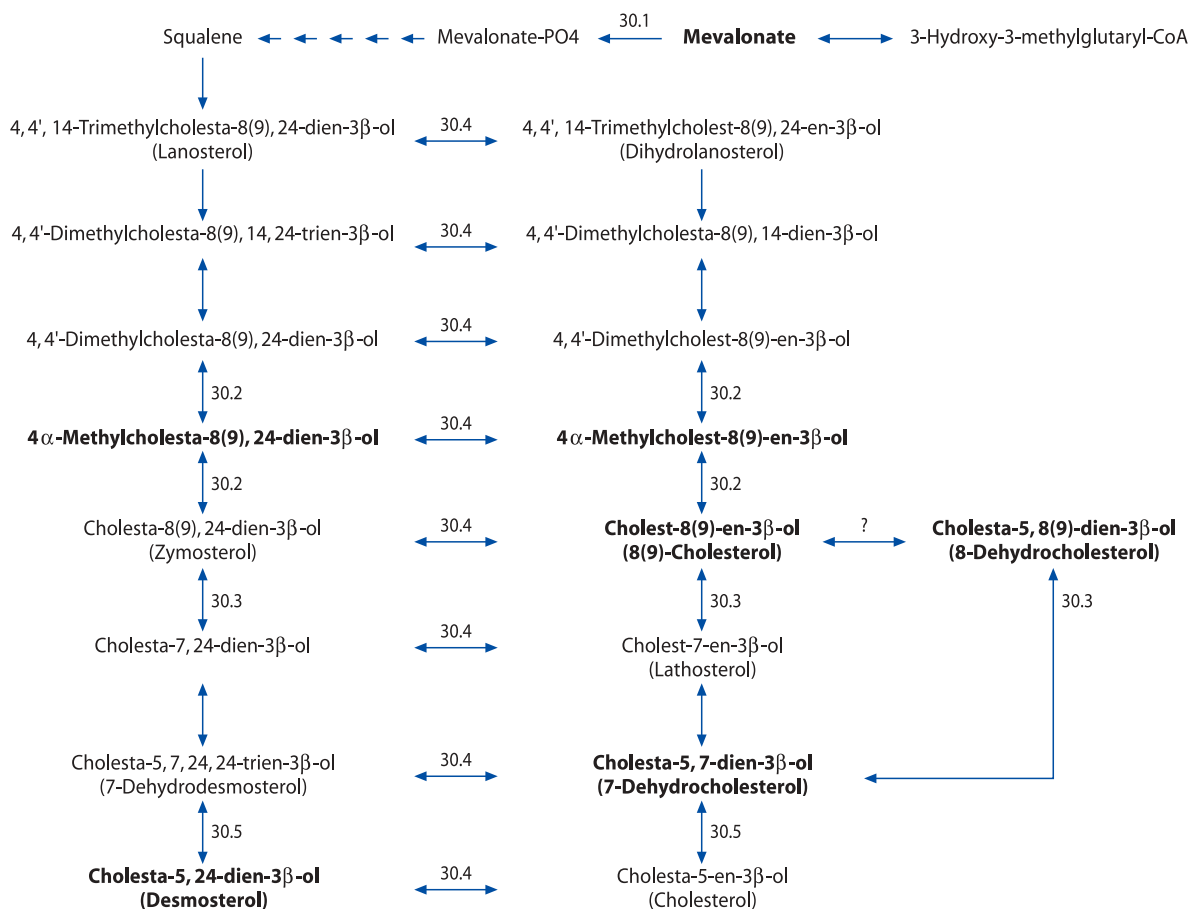


Fig. 30.1. The pathway of cholesterol biosynthesis. 30.1, Mevalonate kinase; 30.2, 3 β -hydroxysteroid dehydrogenase of the 4 α -methylsterol-4-demethylase complex; 30.3, 3 β -hydroxysteroid- Δ^8, Δ^7 -isomerase (sterol- Δ^8 -isomerase); 30.4, 3 β -hydroxysteroid- Δ^{24} -reductase (desmosterol reductase); 30.5, 3 β -hydroxysteroid- Δ^7 -reductase (7-dehydrocholesterol reductase)

30.4 Signs and Symptoms

Table 30.1. Mevalonate kinase deficiency (MKD)

System	Symptoms/markers	Classic MKD	Hyper IgD syndrome
Characteristic clinical findings	Recurrent systemic crises (fever, lymphadenopathy, rash, arthropathy, diarrhea, edema)	+	+
	Psychomotor retardation	+	–
	Failure-to-thrive	+	–
	Hypotonia/myopathy	+	±
	Anemia, leukocytosis, thrombocytopenia	±	±
Routine laboratory	Cholesterol (P)	n↓	n
	Serum transaminases (AST, ALT) (S)	n↑	unk
	Creatine kinase (S, P)	n↑	unk
	Immunoglobulin D	n↑	↑
	Immunoglobulin A	n↑	n–↑
Special laboratory	Erythrocyte sedimentation rate	n–↑	n–↑
	Mevalonic acid (U)	↑ ↑ ↑	↑
	Ubiquinone-50 (P)	n–↓	unk
	Bile acids (U)	n–↓	unk
	Leukotriene E4 (U)	↑	unk
CNS	Cerebellar hypoplasia/atrophy	+	–
	Ataxia	+	–
Eye	Cataracts	±	–
Other	Dysmorphic facies	±	–
	Hepatosplenomegaly	±	±
	Diarrhea and malabsorption	±	±

unk, unknown.

Table 30.2. 3 β -Hydroxysteroid dehydrogenase (NSDHL) deficiency

System	Symptoms/markers	Infancy	Older child/adult
Characteristic clinical findings	CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform erythroderma and Limb Defects)	+	+
	Unilateral limb defects	+	+
	Ichthyosiform skin lesions demarcated at the midline	+	+
	Minor contralateral bone and skin abnormalities	\pm	\pm
Routine laboratory	X-ray: punctate calcification of skeletal and nonskeletal cartilage	\pm	–
Special laboratory	Sterol analysis (P, tissue, lymphoblasts): 4-methylsterols, 4,4'-dimethylsterols, 4-carboxysterols	\uparrow	\uparrow
Skin	Erythematous psoriasiform skin lesions:		
	Large diffuse lesions on limbs and trunk to the midline	+	+
	Linear streaks or swirls	+	+
	Predilection for skin folds (Ptychotrophism)	–	+
CNS	Unilateral brain hypoplasia	\pm	\pm
	Hydrocephalus	\pm	\pm
Skeletal	Absent or hypoplastic long bones and/or phalanges	+	+
	Vertebral anomalies (hemivertebrae, clefts, fusions)	\pm	\pm
Genitourinary	Unilateral renal agenesis	\pm	\pm
	Hydronephrosis or hydroureter	\pm	\pm
Cardiovascular	Cardiac malformations	\pm	\pm
Pulmonary	Unilateral pulmonary hypoplasia	\pm	\pm
Other	Dystrophic nails	\pm	\pm
	Alopecia	\pm	\pm

Table 30.3. 3β -Hydroxysteroid- Δ^8, Δ^7 -isomerase (CDPX2) deficiency

System	Symptoms/marker	Infancy	Older child/adult
Characteristic clinical findings	Congenital or neonatal ichthyosiform erythroderma	+	–
	Ichthyosis (nonerythematous)	–	+
	Whorled, thick, adherent hyperkeratosis	+	±
	Follicular atrophoderma	+	+
	Striate hypermelanosis	+	±
	Dystrophic nails	±	±
Routine laboratory	Alopecia	+	+
	X-ray: Punctate calcifications of epiphyses, trachea, and larynx	+	±
Special laboratory	Sterol analysis (P, FB, LYM):		
	8(9)-cholestenol	↑–↑↑	↑–↑↑
	8-dehydrocholesterol	↑	↑
CNS	Mental retardation	Rare	Rare
Eye	Cataracts, typically segmental	±	±
	Microphthalmos	±	±
	Optic hypoplasia	±	±
Skeletal	Bilateral and asymmetrical shortening of long bones	+	+
	Scoliosis	±	±
	Rib and vertebral anomalies	±	±
	Polydactyly	Rare	Rare
	Cervical compressive myelopathy	Rare	Rare
	Contractures	±	±
Genitourinary	Renal dysgenesis (mostly hypoplasia)	±	±
Other	CHILD syndrome (Congenital hemidysplasia with ichthyosiform erythroderma and limb defects)	±	±
	Frontal bossing	±	±
	Midface hypoplasia	±	±
	Micrognathia	±	±
	Hypertelorism	±	±

Table 30.4. 3β -Hydroxysteroid- Δ^{24} -reductase deficiency (desmosterolosis)

System	Symptoms/marker	Patient 1 (age 34 w gestation)	Patient 2 (age 2 y)
Characteristic clinical findings	Macrocephaly	+	–
	Microcephaly	–	+++
	Gingival nodules	+	–
	Cleft palate (posterior midline)	+	+
	Micrognathia	+	+
	Facial dysmorphism	+	+
	Mental retardation	NA	+
Routine laboratory	X-ray: Osteosclerosis	+	–
Special laboratory	Sterol analysis (tissue, P): desmosterol	↑↑↑	↑
CNS	Agenesis of the corpus callosum	+	+
	Cerebral gyral abnormalities	+	–
	Ventriculomegaly	+	–
Skeletal	Rhizomesomelia	+	–
	Club foot	–	+
Genitourinary	Ambiguous genitalia	+	–
	Renal hypoplasia	+	–
Cardiovascular	Patent ductus arteriosus	–	+
	Anomalous pulmonary venus return	+	–
GI	Short, malrotated small bowel	+	–
Pulmonary	Pulmonary hypoplasia	+	–

Table 30.5. 3β -Hydroxysteroid- Δ^7 -reductase deficiency (Smith-Lemli-Opitz syndrome)

System	Symptoms/marker	Percentage of patients with abnormality			
		<10%	10–50%	50–90%	>90%
Characteristic clinical findings	Microcephaly				+
	Broad alveolar ridges			+	
	Micrognathia			+	
	Anteverted nares			+	
	Cleft palate			+	
	Excess digital whorls			+	
	Growth retardation				+
	Mental retardation				+
	Infantile hypotonia				+
Routine laboratory	Cholesterol (P)		n	↓	
Special laboratory	Sterol analysis (P, FB, LYM):				
	7-dehydrocholesterol	n (<1%)	↑		↑↑–↑↑↑
	8-dehydrocholesterol	n (<1%)	↑		↑↑–↑↑↑
CNS	Agenesis of the corpus callosum	+			
	Cerebellar hypoplasia		+		
	Holoprosencephaly	+			
	Behavioral problems				+
Eye	Cataract		+		
	Epicanthal folds		+		
	Ptosis			+	
	Strabismus		+		
Skeletal	2–3 toe syndactyly				+
	Postaxial polydactyly		+		
	Club foot	+			
	Shortened limbs	+			
	Epiphyseal stippling	+			
Genitourinary	Hypospadias			+	
	Cryptorchidism			+	
	Ambiguous or female genitalia in 46 XY		+		
	Renal hypoplasia or unilateral agenesis		+		
Cardiovascular	Bilateral renal agenesis (Potter sequence)		+		
	Heart malformations (AV canal, secundum ASD, patent ductus arteriosus, VSD)			+	
GI	Pyloric stenosis		+		
	Hirschsprung disease		+		
	Intestinal dysmotility			+	
	Feeding disorder				+
Pulmonary	Abnormal pulmonary lobation		+		
	Pulmonary hypoplasia		+		
	Anomalies of laryngeal and tracheal cartilages		+		
Liver	Chronic hepatic disease	+			
	Coagulopathy (vitamin K responsive)	+			
Auditory	Sensorineural hearing defect		+		

30.5 Reference Values

■ Organic acids – Urine (SID GC-MS)

Age	Mevalonic Acid (mmol/mol creat)
All ages	0.06–0.21 ^a

^a Hoffmann, 1991.

■ Sterols – Plasma (GC-MS)

Age	Cholesterol (mmol/l)	7-Dehydrocholesterol (μmol/l)	8-Dehydrocholesterol (μmol/l)	Cholest-8(9)-en-3β-ol (μmol/l)	Desmosterol (μmol/l)	4-Methylcholest-8(9)en-3β-ol (μmol/l)	4-Methylcholesta-8,24-dien-3β-ol (μmol/l)
Birth–1 w	1.86 (0.96–3.00)	0.10 (<0.02–0.31)	<0.02	0.07 (<0.03–0.77)	1.79 (0.52–4.16)	<0.05	<0.05
1–3 m	3.15 (2.38–4.12)	0.16 (0.03–0.49)	<0.02	<0.02	2.85 (1.04–6.50)	<0.05	<0.05
3–18 m	3.81 (2.96–4.43)	0.19 (<0.02–0.57)	<0.02	<0.02	2.57 (0.26–5.98)	<0.05	<0.05
18 m–3 y	3.86 (2.91–4.96)	0.16 (<0.02–0.52)	<0.02	<0.02	2.04 (0.52–5.46)	<0.05	<0.05
3–16 y	3.83 (2.89–4.74)	0.19 (0.03–0.52)	<0.02	<0.02	1.60 (0.26–3.64)	<0.05	<0.05
>16 y	4.36 (2.66–6.02)	0.28 (0.10–0.52)	<0.02	<0.02	1.95 (0.21–4.42)	<0.05	<0.05

■ Sterols – Cultured Cells (GC-MS)

7-Dehydrocholesterol (% ratio to chol)	7-Dehydrocholesterol (% ratio to chol)	Cholest-8(9)-en-3β-ol (% ratio to chol)	Cholest-8(9)-en-3β-ol (% ratio to chol)	Desmosterol (% ratio to chol)	4-Methylcholest-8(9)en-3β-ol (% ratio to chol)	4-Methylcholesta-8,24-dien-3β-ol (% ratio to chol)
LYM 0.17 (0.06–0.35)	FB 0.21 (0.02–0.85)	LYM 0.07 (<0.01–0.14)	FB 0.16 (0.04–0.63)	LYM 0.27 (0.07–0.69)	LYM 0.12 (0.01–0.39)	LYM 0.08 (0.01–0.26)

chol, cholesterol.

30.6 Pathological Values

■ Mevalonate Kinase Deficiency

Type	Mevalonic acid (mmol/mol creat) (U)
Classic MKD ^a	3165–51433
Hyper IgD syndrome ^b	
Acute	21–143
Well	4.4–10.3

^a Hoffmann, 1991.

^b Kelley, unpublished data.

■ 3 β -Hydroxysteroid Dehydrogenase Deficiency

	4-Methylcholest- 8(9)en-3 β -ol (μ mol/l) P	4-Methylcholesta- 8,24-dien-3 β -ol (μ mol/l) P	4-Methylcholest- 8(9)en-3 β -ol (% ratio to chol) LYM	4-Methylcholesta- 8,24-dien-3 β -ol (% ratio to chol) LYM
Patient 1	14.7	8.8	1.2	0.8
Patient 2	19.8	8.9	NA	NA

chol, cholesterol.

■ 3 β -Hydroxysteroid- Δ^8, Δ^7 -Isomerase Deficiency

	8(9)-Cholestenol (μ mol/l) P	8-Dehydrocho- lesterol (μ mol/l) P	8(9)-Cholestenol (% ratio to chol) LYM	8(9)-Cholestenol (% ratio to chol) FB
All ages	23.3 (0.5–106.8)	9.2 (0.8–38.7)	23.5 (1.6–73.5)	13.3 (1.8–37.3)

chol, cholesterol.

■ 3 β -Hydroxysteroid- Δ^{24} -Reductase Deficiency (Desmosterolosis)

	Desmosterol (μ mol/l) P	Desmosterol (% ratio to chol) LYM
Patient (age 2 y)	138	55

■ 3β-Hydroxysteroid-Δ⁷-Reductase Deficiency (Smith-Lemli-Opitz Syndrome)

Age	Cholesterol (mmol/l) P	7-Dehydrocholesterol (μmol/l) P	8-Dehydrocholesterol (μmol/l) P	7-Dehydrocholesterol (% ratio to chol) LYM	7-Dehydrocholesterol (% ratio to chol) FB
Birth–1 w	0.49 (0.07–2.43)	263 (109–1292)	195 (62–725)		
1–3 m	0.84 (0.09–2.97)	355 (7.8–746)	239 (23–439)		
3–18 m	1.16 (0.11–2.30)	411 (70–1222)	240 (78–614)		
18 m–3 y	2.57 (1.12–4.50)	184 (0.4–426)	137 (<0.02–348)		
3–16 y	2.66 (0.42–4.91)	197 (1.9–759)	130 (<0.02–434)		
>16 y	2.51 (1.06–5.06)	271 (5.0–959)	157 (12–553)		
All ages				25.6 (2.2–98.2)	25.9 (1.6–128.0)

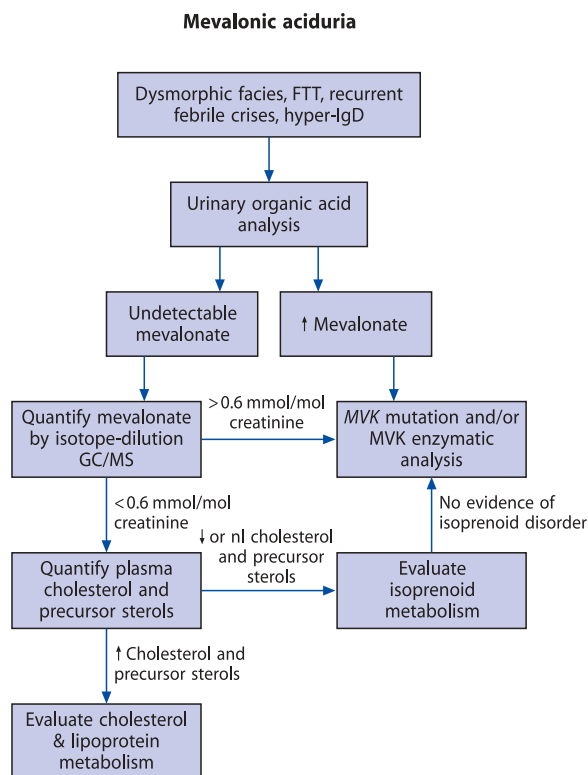
chol, cholesterol.

30.7 Loading Tests

None.

30.8 Diagnostic Flow Charts

Fig. 30.2. Diagnostic flow chart for mevalonic aciduria.
FTT, failure-to-thrive; *MVK*, mevalonate kinase



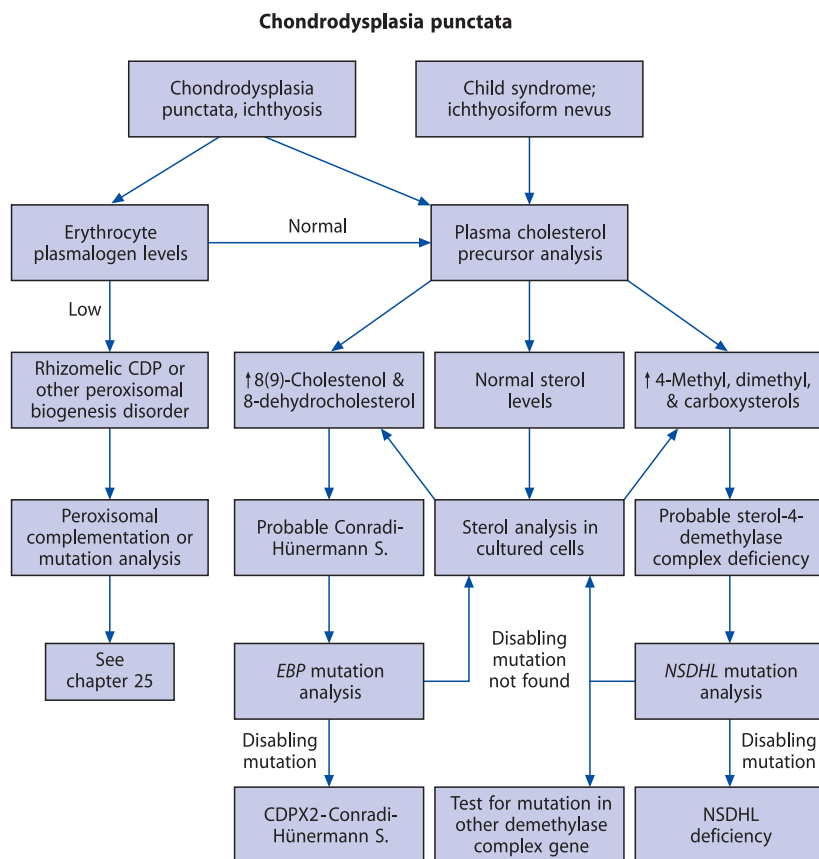


Fig. 30.3. Diagnostic flow chart for the evaluation of chondrodysplasia punctata. *NSDHL*, NAD(P)H steroid dehydrogenase-like; *EBP*, emopamil-binding protein

Smith-Lemli-Opitz syndrome and related disorders

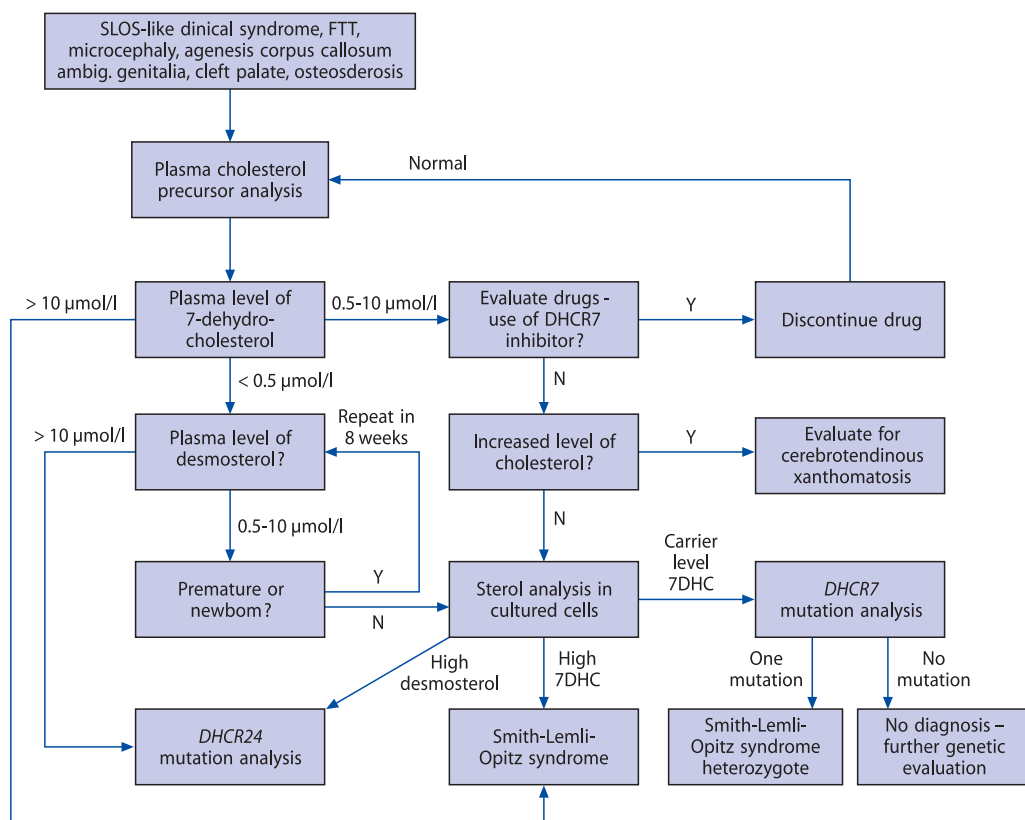


Fig. 30.4. Diagnostic flow chart for Smith-Lemli-Opitz syndrome and related disorders. *FTT*, failure-to-thrive; *DHCR7*, 3β -hydroxysteroid- Δ^7 -reductase; *7DHC*, 7-dehydrocholesterol; *DHCR24*, 3β -hydroxysteroid- Δ^{24} -reductase

30.9 Specimen Collection

Disorder	Test	Preconditions	Material	Handling	Pitfalls
30.1	Organic acid analysis	None	U (random)	Keep frozen (−20 °C)	^a
30.2	Sterol analysis	None	P, LYM	Keep frozen (−20 °C)	^b
30.3	Sterol analysis	None	P, FB, LYM	Keep frozen (−20 °C)	^b
30.4	Sterol analysis	None	P, LYM, FB	Keep frozen (−20 °C)	None
30.5	Sterol analysis	None	P, LYM, FB	Keep frozen (−20 °C)	^c

^a Quantification of MVA by stable isotope GC-MS necessary for certain diagnosis of hyper IgD syndrome in non-acute samples.

^b Skewed X-inactivation in favor of normal allele.

^c Haloperidol and other “sigma” ligands may increase the level of 7DHC; 7DHC and 8DHC are subject to degradation over time in plasma at room temperature.

30.10 Prenatal Diagnosis

Disorder	Material	Timing, trimester
30.1	AF, cultured AFC, CV	I, II
30.5	AF, cultured AFC, CV, CCVS	I, II

30.2–30.4: No experience with prenatal diagnosis thus far.

30.11 DNA Analysis

Disorder	Specimen	Methodology
30.1	Any DNA source	PCR, SSCP, sequence analysis
30.2	Any DNA source	PCR, SSCP, sequence analysis
30.3	Any DNA source	PCR, SSCP, sequence analysis
30.4	Any DNA source	PCR, SSCP, sequence analysis
30.5	Any DNA source	PCR, SSCP, sequence analysis

30.12 Initial Treatment

There is no required emergent metabolic management for disorders of cholesterol biosynthesis, although serious or life-threatening physical anomalies requiring acute medical intervention are common. However, because an occasional patient with severe SLOS – usually with a cholesterol level less than 0.5 mM – has developed signs of glucocorticoid and/or mineralocorti-

coid deficiency under stress, steroid replacement therapy may sometimes be needed. In addition, when there is an acute life-threatening condition, such as pneumonia, and oral cholesterol replacement therapy is not possible, intravenous banked plasma ("fresh-frozen" plasma) can be a valuable parenteral source of cholesterol.

30.13 Summary/Comments

Inborn errors of cholesterol biosynthesis represent a relatively new group of disorders with considerable clinical and biochemical heterogeneity. However, because all of the critical diagnostic metabolites are small molecules amenable to analysis by gas chromatography, diagnosis of these conditions is possible in most biochemical genetics laboratories. Nevertheless, because of the extreme variability of these conditions, clinicians must carry a high index of suspicion for disorders of cholesterol biosynthesis, especially for mild variants, and biochemical geneticists should select analytical methods that provide the highest accuracy and sensitivity. Furthermore, because the biosynthesis of cholesterol is achieved through a complex sequence of more than 20 enzymatic steps, evaluation of biochemically undiagnosed syndromes that share characteristics with the known sterol disorders may lead to the discovery of new inborn errors of cholesterol biosynthesis.

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