Smith-Lemli-Opitz syndrome and cholesterol biosynthesis related disorders

Generoso Andria (Naples)
Inborn errors of metabolism associated with dysmorphic features and malformation syndromes

Congenital malformations and malformation syndromes associated with a metabolic defect
Malformation syndromes caused by disorders of cholesterol synthesis

Journal of Lipid Research  Volume 52, 2011

Forbes D. Porter\textsuperscript{1,*} and Gail E. Herman\textsuperscript{†}
Presqualene cholesterol synthetic pathway.

from Porter & Herman, 2011
Presqualene metabolic pathway

Mevalonic aciduria

Glucose
\[ \Downarrow \]
Acetyl-CoA
\[ \Downarrow \]
3-hydroxy-3-methyl glutaryl CoA
\[ \Downarrow \]  \textit{HMG reductase}
Mevalonic acid
\[ \Downarrow \]  \textit{Mevalonate kinase}
5-phosphomevalonic acid
\[ \Downarrow \]
Isopentenyl-PP
\[ \Downarrow \]
Geranyl-PP
\[ \Downarrow \]
Farnesyl-PP
\[ \Rightarrow \] Squalene

Cholesterol

Lanosterol
# Mevalonic aciduria / Hyper IgD periodic fever syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>MVA</th>
<th>HIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental retardation</td>
<td>+++++</td>
<td>-</td>
</tr>
<tr>
<td>Hypotonia/myopathy</td>
<td>-/++</td>
<td>-</td>
</tr>
<tr>
<td>Ataxia/cerebellar atrophy</td>
<td>-/++++</td>
<td>-</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>+++++</td>
<td>-</td>
</tr>
<tr>
<td>Dysmorphisms</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Visceromegaly</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Cataract</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Periodic fever</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Limphoadenopathy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Skin rash</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Abdominal pain, diarrhea</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
**Thematic Review Series: Genetics of Human Lipid Diseases**

**Malformation syndromes caused by disorders of cholesterol synthesis**

*Journal of Lipid Research  Volume 52, 2011*

Forbes D. Porter and Gail E. Herman

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**TABLE 1. Malformation syndromes associated with inborn errors of cholesterol synthesis**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>MIM number</th>
<th>Inheritance pattern</th>
<th>Gene</th>
<th>Human chromosome</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLOS</td>
<td>270400</td>
<td>Autosomal recessive</td>
<td>DHCR7</td>
<td>11q12.13</td>
<td>7DHC reductase</td>
</tr>
<tr>
<td>Lathosterolosis</td>
<td>607830</td>
<td>Autosomal recessive</td>
<td>SC5D</td>
<td>11q23.3</td>
<td>SC5D</td>
</tr>
<tr>
<td>Desmosterolosis</td>
<td>602398</td>
<td>Autosomal recessive</td>
<td>DHCR24</td>
<td>1p31.1-p33</td>
<td>DHCR24</td>
</tr>
<tr>
<td>CDPX2</td>
<td>302960</td>
<td>X-Linked dominant</td>
<td>EBP</td>
<td>Xp11.22-11.23</td>
<td>3β-Hydroxysteroid Δ8,Δ7-sterol isomerase</td>
</tr>
<tr>
<td>CHILD Syndrome</td>
<td>308050</td>
<td>X-Linked dominant</td>
<td>NSDHL</td>
<td>Xq28</td>
<td>3β-Hydroxysteroid dehydrogenase</td>
</tr>
<tr>
<td>SC4MOL</td>
<td>607545</td>
<td>Autosomal recessive</td>
<td>SC4MOL</td>
<td>4q32-q34</td>
<td>Sterol C-4 methyl oxidase</td>
</tr>
<tr>
<td>Antley-Bixler</td>
<td>207410</td>
<td>Autosomal recessive</td>
<td>POR</td>
<td>1q11.2</td>
<td>Cytochrome P450 oxidoreductase</td>
</tr>
<tr>
<td>HEM dysplasia*</td>
<td>215140</td>
<td>Autosomal recessive</td>
<td>LBR</td>
<td>1q42.1</td>
<td>Lamin B receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DHCR14 (TM7SF2)</td>
<td>11q13</td>
<td>Sterol Δ14-reductase</td>
</tr>
</tbody>
</table>

\* As discussed in the text, the HEM dysplasia phenotype is likely due to a laminopathy rather than an inborn error of cholesterol synthesis.

*from Porter & Herman, 2011*
from Porter & Herman, 2011
Smith-Lemli-Opitz syndrome (SLOS)

Described in 1964

OMIM: 270400
Autosomal recessive
Incidence: 1:40000-60000

Elevated levels of 7-DHC and 8-DHC in physiological fluids and tissues (1993) due to the deficiency of 7-DHC reductase

The first true metabolic syndrome of multiple congenital malformations
Smith-Lemli-Opitz syndrome

Dysmorphic features
- Developmental delay
- Failure to thrive
- Cataract
- Internal organs malformations

Genital anomalies

Limb anomalies

Brain malformations
Is there a “typical” SLOS facies? Yes, but…

(Nowaczyk et al., 1998; Prasad et al., 2002)
Frequency of DHCR7 mutations in Europe

De Brasi et al, 1999; Witsch-Baumgartner et al, 2005
Treatment of SLOS

1997  Irons et al  dietary cholesterol supplementation

2000  Jira et al  Simvastatin, new therapeutic approach

COMMENTS

- Since cholesterol does not cross the BBB an indirect effect is plausible, mediated through sterol metabolites (neurosteroids or oxysteroids) that can cross the BBB

- Therapeutic efficacy of combined simvastatin and dietary cholesterol supplementation has not yet been substantiated, for example by a placebo-controlled trial
• Cholesterol plays a structural role in cellular membranes and lipid rafts

• Cholesterol is a precursor for the synthesis of steroids, neuroactive steroids, oxysteroids, and bile acids

• Impaired sonic hedgehog function (SHH) due to cholesterol deficiency or to accumulation of 7DCH and derived oxysterols

• Studies in pharmacological or genetic animal models suggest the involvement of various biological pathways in the SLOS phenotype
Desmosterolosis

FitzPatrick et al, 1997

Andersson et al, 2002

Perinatal lethality
IUGR
Cranio-facial dysmorphisms
Ambiguous genitalia
Internal malformations
Skeletal anomalies
Osteosclerosis
Agenesis of the corpus callosum

+ 3 unpublished patients
Lathosterolosis, a Novel Multiple-Malformation/Mental Retardation Syndrome Due to Deficiency of 3β-Hydroxysteroid-Δ⁵-Desaturase

Nicola Brunetti-Pierri,¹,³,* Gaetano Corso,²,* Massimiliano Rossi,¹ Paola Ferrari,⁵ Fiorella Balli,⁵ Francesco Rivasi,⁶ Ida Annunziata,⁴ Andrea Ballabio,³,⁴ Antonio Dello Russo,² Generoso Andria,¹ and Giancarlo Parenti¹

Departments of ¹Pediatrics and ²Biochemistry and Medical Biotechnology, Federico II University, ³Telethon Institute of Genetics and Medicine, and ⁴Medical Genetics, Second University of Naples, Naples; and Departments of ⁵Pediatrics and ⁶Pathology, University of Modena, Modena, Italy
Case referred to our Dept in 2001

Healthy parents, no consanguinity

II-1 Microcephaly, myelomeningocele, polydactyly, clubfeet
# Lathosterolosis

| CNS        | Developmental delay  
<table>
<thead>
<tr>
<th></th>
<th>Hypotonia</th>
</tr>
</thead>
</table>
| Cranio-facial anomalies | Microcephaly        
|            | Dysmorphic features |
| Skeleton   | Polydactyly         
|            | Syndactyly 2-3-4 toes |
|            | Vertebral anomalies |
| Other      | Bilobed gallbladder |
|            | Horseshoe kidney    |
|            | Conductive hearing loss |

<table>
<thead>
<tr>
<th>AST 262-310 U/l</th>
<th>ALT 188-218 U/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-GT 539-639 U/l</td>
<td>ALP 1362-1731 U/l</td>
</tr>
<tr>
<td>Total bil 2.47 mg/dl</td>
<td>Direct bil 1.73 mg/dl</td>
</tr>
<tr>
<td>Cholesterol: 130 mg/dl</td>
<td>Brain MRI: normal</td>
</tr>
</tbody>
</table>
Lathosterolosis

Poor growth
Cranio-facial dysmorphic features
Gum hypertrophy
Corneal opacity
Syndactyly
Post-axial Polydactyly
Hepatosplenomegaly
Lipid and MPS storage macrophages parenchyma
Hypospadias
Developmental delay
Demyelination
Cerebral calcifications

Krakowiak e coll, 2003
CHILD Syndrome
(Congenital Hemidysplasia Ichthyosiform Erythroderma Limb Defects)

Variable hypomelia
Joint limitations
Monolateral ichthyosiform erythroderma and alopecy (R>L)
Chondrodysplasia punctata
Congenital heart defects
Visceral involvement (kidney, lung)
Cleft palate
Additional phenotypes associated with genes of the C-4 sterol demethylase complex

Mutations in the human SC4MOL gene encoding a methyl sterol oxidase cause psoriasiform dermatitis, microcephaly, and developmental delay

Miao He,1,2 Lisa E. Kratz,3 Joshua J. Michel,2,4 Abbe N. Vallejo,2,4 Laura Ferris,5 Richard I. Kelley,3 Jacqueline J. Hoover,2 Drazen Jukic,6 K. Michael Gibson,2,7 Lynne A. Wolfe,2 Dhanya Ramachandran,1 Michael E. Zwick,1 and Jerry Vockley2,8

JCI, 121:976, 2011

Hypomorph Temperature-Sensitive Alleles of NSDHL Cause CK Syndrome

Keith W. McLaren,1,2,3,21 Tesa M. Severson,4,21 Christèle du Souch,1,2,3,21 David W. Stockton,5 Lisa E. Kratz,6 David Cunningham,7 Glenda Henderson,8 Ryan D. Morin,4 Diane Wu,4 Jessica E. Paul,4 Jianghong An,4 Tanya N. Nelson,8 Athena Chou,1,2 Andrea E. DeBarber,9 Louise S. Merkens,10 Jacques L. Michaud,11 Paula J. Waters,8 Jingyi Yin,1 Barbara McGillivray,1,2,3 Michelle Demos,12 Guy A. Rouleau,11 Karl-Heinz Grzeschik,13 Raffaella Smith,14 Patrick S. Tarpey,14 Debbie Shears,15 Charles E. Schwartz,16 Jozef Gecz,17 Michael R. Stratton,14 Laura Arbou,1 Jane Hurlburt,1 Margot I. Van Allen,1,2 Gail E. Herman,7 Yongjun Zhao,4 Richard Moore,4 Richard I. Kelley,6 Steven J.M. Jones,4,18 Robert D. Steiner,19 F. Lucy Raymond,20 Marco A. Marra,4 and Cornelius F. Boerkoel1,2,3,*
Greenberg Dysplasia
Hydroops-Ectopic CalcificationsMoth-eaten skeletal dysplasia (HEM)

- Intrauterine/neonatal lethality
- Fetal hydrops
- Short limbs (rhizomelic and mesomelic)
- Moth-eaten appearance of bones
- Ectopic calcifications
- Platyspondyly
- Post-axial polydactyly
- Pulmonary hypoplasia
- Extramedullary hematopoeisis
Elevated levels of cholesta-8,14-dien 3-β-ol in fibroblasts cultured in delipidated medium

Sterol Δ14- reductase deficiency

LBR 1q42
TM7SF2 11q13

Mutations in LBR gene found in patients with Greenberg dysplasia

Greenberg Dysplasia (HEM)
Craniosynostosis
Mid-face hypoplasia
Proptosis
Choanal atresia

Radio-humeral synostosis
Bowed femur
Fractures

Ambiguous genitalia

Heart and renal malformations
FGFR2 mutations (autosomal dominant)

Teratogens (Fluconazole)

21-hydroxylase deficiency + “?”

Sporadic (autosomal recessive)

Antley-Bixler S.

14-α-demethylase P450 oxidoreductase (CYP51)

Defect of cholesterol metabolism?
<table>
<thead>
<tr>
<th></th>
<th>MVA</th>
<th>SLOS</th>
<th>Desmosterolosis</th>
<th>CDPX2 CHILD</th>
<th>Lathosterolosis</th>
<th>HEM</th>
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<tbody>
<tr>
<td><strong>Mental Retardation</strong></td>
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<tr>
<td><strong>Brain anomalies</strong></td>
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<td>(midline defects)</td>
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<td><strong>Limb anomalies</strong></td>
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<td>(syn/polydactyly)</td>
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<tr>
<td><strong>Abnormal bone</strong></td>
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<tr>
<td>calcification</td>
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<td><strong>Internal organs</strong></td>
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<tr>
<td>malformations</td>
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</table>