Normal Portal Tract & Duct Plate Malformation Associated with Developmental Syndromes and Congenital Hepatic Fibrosis

Ductal Plate Malformation & Syndromes

- Meckel-Gruber
- Jeune
- Ivemark
- Bardet-Biedel
- Tuberous Sclerosis
- Smith-Lemli-Opitz
- Ellis-van Creveld
- Elejalde
- Trisomy 9 & 13
<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Locus Name</th>
<th>Gene Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive</td>
<td>PKHD1</td>
<td>PKHD1</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>NPHP1</td>
<td>NPHP1</td>
</tr>
<tr>
<td></td>
<td>NPHP2</td>
<td>NPHP2</td>
</tr>
<tr>
<td></td>
<td>NPHP3</td>
<td>NPHP3</td>
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<td></td>
<td>NPHP4</td>
<td>NPHP4</td>
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<tr>
<td></td>
<td>NPHP5</td>
<td>NPHP5</td>
</tr>
<tr>
<td></td>
<td>NPHP5 (SLSN)</td>
<td>NPHP5</td>
</tr>
<tr>
<td></td>
<td>NPHP7</td>
<td>NPHP7</td>
</tr>
<tr>
<td></td>
<td>NPHP8</td>
<td>NPHP8</td>
</tr>
<tr>
<td></td>
<td>NPHP9</td>
<td>NPHP9</td>
</tr>
<tr>
<td>X-linked syndrome and disorders</td>
<td>JBT51</td>
<td>JBT51</td>
</tr>
<tr>
<td></td>
<td>JBT52</td>
<td>JBT52</td>
</tr>
<tr>
<td></td>
<td>JBT53</td>
<td>JBT53</td>
</tr>
<tr>
<td></td>
<td>JBT54</td>
<td>JBT54</td>
</tr>
</tbody>
</table>

| X-linked syndromes and disorders | JBT55      | CEP90       |
|                                  | JBT56      | THAEM67     |
|                                  | JBT57      | AR1238      |
|                                  | JBT58      | AR1238      |
| BBS1                              | BBS2       | BBS2        |
| BBS2                              | BBS2       | BBS2        |
| BBS3                              | AR26       | AR26        |
| BBS4                              | AR1238     | AR1238      |
| BBS5                              | BBS5       | BBS5        |
| BBS6                              | NPH2       | NPH2        |
| BBS7                              | BBS7       | BBS7        |
| BBS8                              | TTC1       | TTC1        |
| BBS9                              | BBS9       | BBS9        |
| BBS10                             | BBS10      | BBS10       |
| BBS11                             | THAEM67    | THAEM67     |
| BBS12                             | BBS2       | BBS2        |
| BBS13                              | AR1238     | AR1238      |
| BBS14                              | NPH2       | NPH2        |
| BBS15                              | NPH2       | NPH2        |
| BBS16                              | CEP90      | CEP90       |
| Meckel syndrome                   | MKS1       | MKS1        |
|                                  | MKS2       | MKS2        |
|                                  | MKS3       | MKS3        |
| Craniectodermal dysplasia         | Unknown    | Unknown     |
| Ellis-van Creveld syndrome        | EVC        | EVC         |
|                                  | EVC        | EVC         |
| Jeune asphyxiating thoracic dysplasia | JATD   | JATD       |
| X-linked                           | OTC1       | OTC1        |
| Autosomal Dominant                | PKD1       | PKD1        |
|                                  | PKD2       | PKD2        |
| ADPKD                             | PKD1       | PKD1        |
|                                  | PKD2       | PKD2        |
Cholestatic Disorders

- Neonatal Cholestasis
- Idiopathic Neonatal Cholestasis (15%)
- Viral Neonatal Cholestasis (CMV 3-5%)
- Bacterial & Parasitic
- Bile Duct Obstruction & Cholangiopathies
  - EHBA (25-30%)
  - Choledochal Cysts
  - Caroli Disease
  - Congenital Hepatic Fibrosis
  - Sclerosing Cholangitis
  - Bile Duct Stenosis

Cholestatic Disorders

- Cholestatic Syndromes (20%)
  - Alagille
  - PFIC
  - Dubin Johnson
  - Rotor
- Metabolic
  - Alpha-1-Antitrypsin (7-10%)
  - Cystic Fibrosis
  - Iron Storage Disease
  - Endocrinopathies
  - Amino Acid Disorders
  - Lipid Disorders
Cholestatic Disorders

- Metabolic Disorders
  - Urea Cycle
  - Carbohydrate (Galactosemia 1%, GSD Type IV)
  - Mitochondrial Disorders
  - Peroxisomal Disorders
- Bile Acid Synthetic Disorders (2%)
- Cholelithiasis
- Insipissated Bile/Mucus
- Tumors/Masses
- Toxic
- Miscellaneous

Choledochal Cyst

- Segmental Dilatation of Bile Duct System
- 1:15,000 Live Births
- Gender Ratio 4F:1M
- Present with Jaundice, Abdominal Mass, & Vomiting in Infancy
- Distinguishing From EHBA Difficult
- Caroli’s Disease (Type V)
- Cholangiocarcinoma Risk (10%, > over 20 yrs of age)
Neonatal Cholestasis

| Extrahepatic biliary atresia | Bile ductule proliferation  
|                             | Portal fibrosis  
|                             | Ductular and canalicular cholestasis  
| Paucity of intrahepatic bile ducts | Loss of interlobular bile ducts  
|                             | (bile duct to hepatic artery ratio <0.8)  
| Neonatal hepatitis | Portal and acinar lymphocyte inflammation; Apoptotic bodies  
| Parenteral nutrition | Bile ductule proliferation  
|                             | Portal fibrosis or cirrhosis  
| Metabolic disorders | Steatosis, fibrosis or cirrhosis;  
|                             | Storage products in liver cells and/or Kupffer cells  

Neonatal Hepatitis

- Distinction From Obstruction Based Upon Clinical, Laboratory and Radiologic Findings
- Obstruction
  - Intralobular Ducts Bile Plugs
  - Bile Duct Proliferation
  - Portal Inflammation
- Neonatal Hepatitis
  - Inflammation, Increased Hematopoiesis
  - Hepatocyte Ballooning, Giant Cell Transformation, Necrosis
  - Variable Degree of Cholestasis
- Overlap with Obstruction
- Idiopathic Hepatitis – Higher Morbidity and Mortality
Extra-Hepatic Biliary Atresia

- Obliterative Cholangiopathy
- Progressive Cirrhosis with Death by Age 2 Years if Not Treated
- 1-8 per 15,000 Live Births in USA
- Perinatal Form (most common)
- Embryonic/Fetal Form (10-35%) with Congenital Anomalies
- Other Associations: Maternal Diabetes, Trisomy 21 & 18, Primary Ciliary Dyskinesia (Situs) Syndrome

Panel: Clinical findings of biliary atresia at presentation

- Jaundice
- Presenting sign.
- Pale stool
- Variable colour from white to beige.
- Dark urine
- Caused by excretion of water-soluble bilirubin conjugates; urine might stain the nappy and coat the stool, leading to false identification of coloured stool.
- Coagulopathy (responsive to intravenous vitamin K)
- Common in infants who are breastfed and those who have received oral vitamin K or no vitamin K in the postnatal period. 

Failure to thrive

- Results from poor absorption of long-chain fats and the catabolic state; excessive feeding is a characteristic clinical sign of failure to thrive.

Hepatosplenomegaly and ascites

- Late (>3 months of age) signs suggestive of cirrhosis.
Biliary Atresia & Splenic Malformation Syndrome (BASM)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenic malformation (eg, polysplenia, asplenia, double spleen)</td>
<td>100%</td>
</tr>
<tr>
<td>Situs inversus</td>
<td>37%</td>
</tr>
<tr>
<td>Preduodenal portal vein</td>
<td>40%</td>
</tr>
<tr>
<td>Intestinal malrotation</td>
<td>60%</td>
</tr>
<tr>
<td>Absent inferior vena cava</td>
<td>70%</td>
</tr>
<tr>
<td>Cardiac anomalies (eg, ventricular septal defect, atrial septal defect, hypoplastic left heart)</td>
<td>45%</td>
</tr>
<tr>
<td>Pancreatic anomalies (eg, annular pancreas)</td>
<td>11%</td>
</tr>
</tbody>
</table>

ExtraHepatic Biliary Atresia
### Table 2. Reported Frequency of Selected Histopathologic Features Distinguishing Biliary Atresia From Nonobstructive Etiologies of Neonatal Cholestasis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Biliary Atresia, %</th>
<th>Nonobstructive Diseases, %</th>
<th>Source, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductular reaction immoderate to severe</td>
<td>76–100</td>
<td>13.4–22</td>
<td>Russo et al., 2011; Lee et al., 2009; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Fibrosis (at least fibrosis)</td>
<td>53.6–100</td>
<td>6.7–87.8</td>
<td>Russo et al., 2011; Lee et al., 2009; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Expansion of portal tracts</td>
<td>4.9–70</td>
<td>0–14</td>
<td>Russo et al., 2011; Lee et al., 2009; Rastogi et al., 2009; Torbenson et al., 2010; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Advanced fibrosis (bridging fibrosis or cirrhosis)</td>
<td></td>
<td></td>
<td>Russo et al., 2011; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Ductal/ductular bile plugs</td>
<td>42.9–69</td>
<td>0–23</td>
<td>Russo et al., 2011; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Sinusoidal fibrosis (zone 3)</td>
<td>20</td>
<td>32</td>
<td>Russo et al., 2011; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Hepatocyte swelling</td>
<td>30</td>
<td>23</td>
<td>Russo et al., 2011; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Giant cell transformation of hepatocytes (&gt; mild/local)</td>
<td>14–43</td>
<td>23–80</td>
<td>Davenport et al., 1993; Russo et al., 2011; Lee et al., 2009; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Extramedullary hematopoeisis</td>
<td>47–56</td>
<td>36–68.2</td>
<td>Russo et al., 2011; Lee et al., 2009</td>
</tr>
<tr>
<td>Acute cholangitis</td>
<td>17–9–37</td>
<td>14–20</td>
<td>Russo et al., 2011; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Portal inflammation (at least moderate)</td>
<td>28</td>
<td>20</td>
<td>Russo et al., 2011</td>
</tr>
<tr>
<td>Hepatocellular necrosis</td>
<td>35</td>
<td>37</td>
<td>Russo et al., 2011</td>
</tr>
<tr>
<td>Duct plate malformation</td>
<td>10–48.8</td>
<td>0–0.5</td>
<td>Davenport et al., 1993; Russo et al., 2011; Rawley et al., 1992; Yamaguti &amp; Patricio, 2011; Fuchs et al., 2009; Shimmura et al., 2008; Low et al., 2001; Paddar et al., 2009; Rastogi et al., 2009</td>
</tr>
<tr>
<td>Bile duct inflammation</td>
<td>31</td>
<td>18.5</td>
<td>Russo et al., 2011</td>
</tr>
<tr>
<td>Bile duct loss</td>
<td>7.3–8.5</td>
<td>0–25.5</td>
<td>Lee et al., 2009; Rawley et al., 1992; Yamaguti &amp; Patricio, 2011; Torbenson et al., 2010</td>
</tr>
</tbody>
</table>

### Histopathologic Diagnostic Pitfalls in Biliary Atresia

- **False-positive interpretation**
  - Total parenteral nutrition–associated liver disease
  - α1-Antitrypsin deficiency

- **False-negative interpretation**
  - Early age at diagnosis (usually <4–6 weeks)
  - Small/inadequate sample (<5–6 portal tracts)
Ductal Plate Malformation-Like in Several Portal Tracts in BA

No Proliferation in 4 week old with later proven BA
Figure 5: Outcomes of patients with biliary atresia
Alagille Syndrome
(arteriohepatic dysplasia, syndromic bile duct paucity)

- Autosomal Dominant Complex Multisystem Disorder (liver, heart, eyes, face, skeleton)
- Diagnostic Features (3 of 5)
  - Cholestasis
  - Cardiac Defect (Pulmonary Artery & Branches Stenosis - Common)
  - Skeletal (Butterfly Vertebra)
  - Characteristic Facial Features
  - Eye (Posterior Embryotoxon)
- Bile Duct Paucity (<0.8 ratio)
  - Develops Over Time
  - Bile Duct Paucity in 90%

Table 1. Putative Factors Involved in the Pathogenesis of Biliary Atresia

<table>
<thead>
<tr>
<th>Immunologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overexpression of adhesion molecules in biliary epithelium</td>
</tr>
<tr>
<td>Aberrant expression of class I and II HLA</td>
</tr>
<tr>
<td>Expression of Fas ligand and increased apoptosis of bile duct epithelial cells</td>
</tr>
<tr>
<td>Maternal microchimerism (inflammatory and biliary epithelial cells)</td>
</tr>
<tr>
<td>Th1 and Th2 response</td>
</tr>
<tr>
<td>Innate immune response (natural killer cells and Toll-like receptors)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reovirus type 3</td>
</tr>
<tr>
<td>Rotavirus</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Papillomavirus</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic/metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFCC gene/CRYPTIC protein</td>
</tr>
<tr>
<td>VEGF gene</td>
</tr>
<tr>
<td>Jagged-1/Notch signaling</td>
</tr>
<tr>
<td>Inversin gene (sm)</td>
</tr>
<tr>
<td>a1-Antitrypsin deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular insult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial hypertrophy of hepatic artery branches by histopathology and imaging studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Environmental/miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational use of drugs (amphetamines, alcohol)</td>
</tr>
<tr>
<td>Phytoxins, mycotoxins</td>
</tr>
<tr>
<td>Industrial toxins</td>
</tr>
<tr>
<td>Gestational diabetes, maternal age</td>
</tr>
</tbody>
</table>

Clinical Finding | Frequency | % of Individuals |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile duct paucity</td>
<td>69/81</td>
<td>85%</td>
</tr>
<tr>
<td>Chronic cholestasis</td>
<td>88/92</td>
<td>96%</td>
</tr>
<tr>
<td>Cardiac murmur</td>
<td>90/92</td>
<td>97%</td>
</tr>
<tr>
<td>Eye findings</td>
<td>65/83</td>
<td>78%</td>
</tr>
<tr>
<td>Vertebral anomalies</td>
<td>37/71</td>
<td>51%</td>
</tr>
<tr>
<td>Characteristic facies</td>
<td>36/92</td>
<td>96%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>29/69</td>
<td>40%</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>7/17</td>
<td>41%</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>27/31</td>
<td>87%</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>2/92</td>
<td>2%</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>15/92</td>
<td>16%</td>
</tr>
</tbody>
</table>
Alagille Syndrome

- Skeletal Manifestations: Asymptomatic Butterfly Vertebrae (Vertebral Body Clefting) in 33-87%
- Facial Features (All): Prominent Forehead, Deep-Set Eyes, Moderate Hypertelorism, Pointed Chin, Saddle or Straight Nose with Bulbous Tip, Inverted Triangle Form to Face
- Renal Abnormalities (23-74%): Small Hyperechoic Kidney, UPJ Obstruction, Renal Cysts, Renal Tubular Acidosis
- Pancreatic Insufficiency
- Growth Failure (50-90%)
- Gross Motor Skill Delays (2%) & Cognitive Delay (16%)
- Vascular Anomalies: Renovascular, Middle Aortic Syndrome, Moyamoya Syndrome, CVA (15%, basilar, carotid, middle cerebral): Accounts for 34% Mortality
- Delayed Puberty with High-Pitched Voice
- Extra Digital Flexion Crease
- Craniosynostosis
- Lower Extremity Fractures

Bile Duct Paucity

Cytokeratin
Alagille Syndrome: End-Stage
Alagille Syndrome

- **Autosomal Dominant Inheritance**
  - Incidence 1: 70,000 Live Births (under estimated)
- **JAG1 Mutation (20p12)** in 89% with Jagged 1 Protein
- **NOTCH2 (1p13-p11)** in 1% with Neurogenic Locus Notch Homolog Protein 2
- Inherited Mutation in 30-50%
- De Novo Mutation in 50-70%
- Phenotype in JAG1 and NOTCH2 Mutations Indistinguishable

Alagille Syndrome: Treatment

- **Pruritus and Xanthoma**: Ursodeoxycholic Acid, Partial External Biliary Diversion, Cholestyramine, Rifampin & Naltrexone
- **Liver Transplantation for End-Stage Disease (20-50%)**
  - 80% 5-Yr Survival
- **Growth & Development**: Optimize Nutrition, Fat Soluble Vitamin Supplements
- **Cardiac, Renal & Neurologic Involvement**: Standard Treatment of Disease
- **Avoid Contact Sports if Splenomegaly (Spleen Guard)**
- **Avoid Alcohol**
- **Risk for Hepatocellular Carcinoma**
Disorders With Bile Duct Paucity

- Syndromic: Alagille
- Metabolic & Genetic
  - AIAT
  - Cystic Fibrosis
  - Peroxisomal Disorders
  - Trisomy 21
  - Prune Belly Syndrome
- Congenital Infections
  - CMV
  - Rubella
  - Syphilis

- Inflammatory & Immune
  - Graft vs Host Disease
  - Chronic Rejection
  - Sclerosing Cholangitis
  - Sarcoidosis
- Other
  - Drugs/Antibiotics Associated with Vanishing Bile Duct Syndrome
    - EHBA (late)
    - Panhypopituitarism
  - Idiopathic

Familial Intrahepatic Cholestatic Disorders

- PFIC 1 (18q21, Bylers): Low GGT - Presents as Hepatitis
- Benign Recurrent Cholestasis (BRIC, 18q21):
  - Episodes of Cholestasis with Pruritus and Fibrosis
- PFIC 2 (2q24): Low GGT - Presents as Hepatitis
- PFIC 3 (7q21): High GGT - Presents as Hepatitis
- Dubin-Johnson (10q24): Pigment Accumulation in Hepatocytes
- Intrahepatic Cholestasis of Pregnancy (7q21):
  - 3rd Trimester Cholestasis with High Fetal Loss
- Aagenaes Syndrome (15q): Cholestasis & Lymphedema
- North American Indian Childhood Cirrhosis (16q22):
  - Progressive Cholestasis, Mimics EHBA, Cirrhin Mutation
Progressive Familial Intrahepatic Cholestasis

- Autosomal Recessive Disorders – Disrupt Bile Formation & Presents with Cholestasis in Childhood
- 3 Types (PFIC1, PFIC2, PFIC3) with Mutations in Hepatocellular Transport System Genes
- PFIC1 & PFIC2 Present in 1st Few Months of Life
- PFIC3 – Later in Infancy, Childhood or Young Adult
- Cholestasis, Jaundice & Pruritus
- Develop End-Stage Liver Disease Before Adulthood
- Diagnosis: Clinical Phenotype, Liver Ultrasound, Cholangiogram, Liver Biopsy & Genetic Testing
Figure 3
Schematic approach to the diagnosis of PFIC excluding the neonatal period, during which biliary atresia is the main cause of cholestasis.
PFIC: Features

- PFIC1: Canalicular Cholestasis, Absence of Bile Ductular Proliferation, Cholangiole Increase
- PFIC2: Lobular Architecture Disruption, Lobular and Portal Fibrosis and Inflammation, Canalicular Cholestasis, Absence of Bile Ductular Proliferation, Cholangiole Increase
- PFIC3: Portal Fibrosis, Bile Duct Proliferation, Inflammation, Possible Giant Cell Transformation, Occasional Cholestasis with Bile Plugs, Progresses to Biliary Cirrhosis
PFIC Management

- Pruritus: Ursodeoxycholic Acid, Nasobiliary Drainage, Partial External Biliary Diversion
- Liver Transplantation for End-Stage Disease (portal hypertension, cirrhosis, liver failure)
- Extrahepatic Complications (diarrhea, liver steatosis, short stature) Do Not Improve & May be Aggravated with Biliary Diversion or Liver Transplantation
- Chronic Diarrhea May Become Intractable When Bile Salt Secretions Restored with Liver Transplantation
  - Associated with Severe Steatosis & Steatohepatitis Leading to Cirrhosis and Re-Transplantation (may recur with new transplant)
- Risk for Hepatocellular Carcinoma & Cholangiocarcinoma (Especially PFIC2 - 15%)
Alpha-1-Antitrypsin Deficiency

- Autosomal Recessive Metabolic Disorder (serpine protease inhibitor [AIAT], 14q31-3) with Codominant Expression by Each Allele
- Prevalence of 1 in 2,500 to 5,000 live births
- Normal Allele: PiM
- Most Common Alleles (Caucasians): 95% M, 2-3% S & 1% Z

AIAT Expression:

- PiMM 100%
- PiSS 50-60%
- PiZZ 10-20%

Table 2  α₁-AT Phenotypes and Corresponding Typical α₁-AT Serum Levels

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Level (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiMM</td>
<td>20-48</td>
</tr>
<tr>
<td>PiMZ</td>
<td>12-35</td>
</tr>
<tr>
<td>PiSS</td>
<td>15-33</td>
</tr>
<tr>
<td>PiSZ</td>
<td>8-19</td>
</tr>
<tr>
<td>PiZZ</td>
<td>2.5-7.0</td>
</tr>
<tr>
<td>Null/Null</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Convert micromolar to milligrams per deciliter by multiplying by conversion factor of 5.2.
AIAT in Infancy

- Neonatal Cholestasis (hepatitis)
  - Jaundice, Pruritus, Abdominal Distention
  - Poor Feeding and Weight Gain
  - Hepatomegaly and Splenomegaly
  - Elevated Total and Conjugated Bilirubin
  - Elevated AST, ALT, Hypoalbuminemia, Coagulopathy (Vitamin K Deficiency)

- Liver Biopsy: Highly Variable Findings in Infancy – Mimics Neonatal Cholestasis, Neonatal Hepatitis, Biliary Atresia & Metabolic Diseases of Infancy
Metabolic Diseases with Cytoplasmic Inclusions

- Globular Inclusions
  - Alpha-1-Antitrypsin
  - Fibrinogen Storage Disease
- Granular Inclusions
  - Alpha-1-Antichymotrypsin Deficiency
- Mallory Bodies
  - Wilson Disease
  - Endemic Tyrolean Cirrhosis
- Striations
  - Gaucher Disease
- Ground Glass Inclusions
  - GSD, Type IV
  - LaFora Disease
- Crystals
  - Cystinosis
  - Wolman Disease
  - Cholesterol Storage Disease
  - Protoporphyria
- Pigment
  - NPC Type C – lipofuscin
  - Dubin-Johnson – lipomelanin
  - Hemochromatosis – iron
  - Wilson Disease - copper
Cystic Fibrosis

- Autosomal Recessive (cyclic AMP dependent chloride channel defect)
- Mutation in CFTR Gene (7q31.2) in Cholangiolar Epithelium
- Steatosis (60%) & Focal Biliary Cirrhosis (10% Infants, 27% 1st Yr, 70% Adults)
- Multilobular Cirrhosis in 4-10%
- Rarely, Neonatal Cholestasis
Limy Bile Syndrome
By Carol L. Fowler, Humberto Solano, George D. Ferry, Linda R. Maagraf, and Franklin J. Harberg
Lexington, Kentucky and Houston, Texas

Calcium carbonate gallstones in children
Mark D. Stringer⁎, Roger D. Soloway, Donald R. Taylor.
### Table 1  Demographic and etiologic factors in 63 consecutive children undergoing cholecystectomy for choledocholithiasis, grouped by dominant gallstone constituent

<table>
<thead>
<tr>
<th>Type of stone</th>
<th>Composition</th>
<th>n</th>
<th>Age (y), mean ± SD</th>
<th>Sex ratio</th>
<th>Recognized etiologic factors</th>
</tr>
</thead>
</table>
| Cholesterol   | 97% cholesterol (78%-90%) | 13 | 11.0 ± 4.0       | 10 F, 3 M | Obesity (4 with BMI ≥50, 8 with BMI ≥25)  
Positive FH 5  
Ileal disease/resection 1  
Cystic fibrosis 1  
Congenital enteropathy 1  
Congenital hemolytic disorders 12  
Previous malaria 1  
Neonatal abdominal surgery 4 (+ PN in 3)  
Neonatal PN 1  
Chemotherapy + PN 1  
Down syndrome 2 (+ cardiac surgery in infancy)  
Progressive familial intrahepatic cholestasis 1  
Choledochal cyst 1  
No recognized factors 7  
Neonatal intensive care 7 (prematurity 6,  
blood transfusions 7, PN 6, neonatal abdominal  
surgery 5)  
Down syndrome 2  
Hemolytic disorder 1 (spherocytosis with no FH)  
Gilbert disease 1  
No recognized factors 3  
Choledochal cyst + biliary sepsis 1  
Evan syndrome 1  
Erythromelalgia 1  
Heredity spherocytosis 1  
Positive FH 1 |
| Black pigment | 72% calcium bilirubinate (18%-93%) | 30 | 7.3 ± 4.4       | 16 F, 14 M |  
Congenital hemolytic disorders 12  
Previous malaria 1  
Neonatal abdominal surgery 4 (+ PN in 3)  
Neonatal PN 1  
Chemotherapy + PN 1  
Down syndrome 2 (+ cardiac surgery in infancy)  
Progressive familial intrahepatic cholestasis 1  
Choledochal cyst 1  
No recognized factors 7  
Neonatal intensive care 7 (prematurity 6,  
blood transfusions 7, PN 6, neonatal abdominal  
surgery 5)  
Down syndrome 2  
Hemolytic disorder 1 (spherocytosis with no FH)  
Gilbert disease 1  
No recognized factors 3  
Choledochal cyst + biliary sepsis 1  
Evan syndrome 1  
Erythromelalgia 1  
Heredity spherocytosis 1  
Positive FH 1 |
| Calcium carbonate | 92% calcium carbonate (78%-90%) | 15 | 6.6 ± 4.0       | 3 F, 12 M |  
Neonatal intensive care 7 (prematurity 6,  
blood transfusions 7, PN 6, neonatal abdominal  
surgery 5)  
Down syndrome 2  
Hemolytic disorder 1 (spherocytosis with no FH)  
Gilbert disease 1  
No recognized factors 3  
Choledochal cyst + biliary sepsis 1  
Evan syndrome 1  
Erythromelalgia 1  
Heredity spherocytosis 1  
Positive FH 1 |
| Brown pigment | fatty acids and calcium bilirubinate | 2  | 4.8 & 12.8 | 1 F, 1 M |  
Neonatal intensive care 7 (prematurity 6,  
blood transfusions 7, PN 6, neonatal abdominal  
surgery 5)  
Down syndrome 2  
Hemolytic disorder 1 (spherocytosis with no FH)  
Gilbert disease 1  
No recognized factors 3  
Choledochal cyst + biliary sepsis 1  
Evan syndrome 1  
Erythromelalgia 1  
Heredity spherocytosis 1  
Positive FH 1 |
| Protein dominant | 70% protein (65%-80%) | 3  | 10.3 ± 2.4 | 1 F, 2 M |  
Neonatal intensive care 7 (prematurity 6,  
blood transfusions 7, PN 6, neonatal abdominal  
surgery 5)  
Down syndrome 2  
Hemolytic disorder 1 (spherocytosis with no FH)  
Gilbert disease 1  
No recognized factors 3  
Choledochal cyst + biliary sepsis 1  
Evan syndrome 1  
Erythromelalgia 1  
Heredity spherocytosis 1  
Positive FH 1 |

FH indicates family history; PN, parenteral nutrition.

### Table 2  Adult gallstone types and patient demographics based on composition (n = 50)

<table>
<thead>
<tr>
<th>Stone type</th>
<th>Composition</th>
<th>n</th>
<th>Sex</th>
<th>Age (y), mean ± SD</th>
<th>BMI, mean ± SD</th>
<th>Other clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>97% cholesterol (73%-99%)</td>
<td>39</td>
<td>34 F, 5 M</td>
<td>48.5 ± 13.4</td>
<td>28.28 ± 6.61</td>
<td>Positive FH 4, hypercholesterolemia 6, hypothyroidism 1, hormone replacement therapy 3</td>
</tr>
<tr>
<td>Black pigment</td>
<td>85% calcium bilirubinate (81%-97%)</td>
<td>7</td>
<td>6 F, 1 M</td>
<td>73.4 ± 8.77</td>
<td>26.79 ± 2.97</td>
<td>Positive FH 2, hypercholesterolemia 3, hypothyroidism 1, hormone replacement therapy 1, cirrhosis 1</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Calcium carbonate (75% and 88%)</td>
<td>2</td>
<td>2 F</td>
<td>75, 76</td>
<td>25.3, 26.0</td>
<td>Nil</td>
</tr>
<tr>
<td>Brown pigment</td>
<td>Fatty acid dominant (54%)</td>
<td>1</td>
<td>F</td>
<td>54</td>
<td>22.8</td>
<td>Nil</td>
</tr>
<tr>
<td>Protein</td>
<td>Protein dominant (75%)</td>
<td>1</td>
<td>F</td>
<td>41</td>
<td>21.8</td>
<td>Nil</td>
</tr>
</tbody>
</table>