Clinical symptoms

- Growth failure, failure to thrive, weight loss
- Ambiguous genitalia, delayed puberty, precocious puberty
- Developmental delay, seizures, dementia, encephalopathy, stroke
- Deafness, blindness, pain agnosia
- Skin rash, abnormal pigmentation, lack of pigmentation, excessive hair growth, lumps and bumps
- Dental abnormalities
- Immunodeficiency, thrombocytopenia, anemia, enlarged spleen, enlarged lymph nodes
- Many forms of cancer
<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Amino acid metabolism</td>
<td>phenylketonuria, maple syrup urine disease, glutaric acidemia type 1, homocystinuria</td>
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<tr>
<td>Carbohydrate metabolism</td>
<td>glycogen storage disease, galactosaemia</td>
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<tr>
<td>Urea cycle disorder</td>
<td>OTC deficiency, carbamoyl phosphate synthetase I deficiency</td>
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<tr>
<td>Disorders of organic acid metabolism (organic acidurias)</td>
<td>alkaptonuria, propionic acidemia, methyl malonic aciduria, isovaleric acidemia</td>
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<tr>
<td>Lysosomal storage disorders</td>
<td>Gaucher's disease, Niemann Pick disease, Fabry disease mucopolysaccharidoses</td>
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<td>Transport protein defects</td>
<td>cystic fibrosis, cystinuria, cystinosis</td>
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<tr>
<td>Disorders of fatty acid oxidation and mitochondrial metabolism</td>
<td>Medium-chain acyl-coenzyme A dehydrogenase deficiency (often shortened to MCADD.)</td>
</tr>
<tr>
<td>Porphyrin metabolism</td>
<td>Acute intermittent porphyria</td>
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<td>Disorders of purine or pyrimidine metabolism</td>
<td>Lesch-Nyhan syndrome</td>
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<td>Steroid metabolism</td>
<td>Lipoid congenital adrenal hyperplasia, congenital adrenal hyperplasia</td>
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<tr>
<td>Mitochondrial function</td>
<td>Kearns-Sayre syndrome, Pearson syndrome</td>
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<td>Peroxisomal function</td>
<td>Zellweger syndrome, adrenoleukodystrophy</td>
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<td>Metals metabolism</td>
<td>Wilson disease</td>
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<td>Connective tissue defects</td>
<td>Hypophosphatasia</td>
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<tr>
<td>Hereditary hyperbilirubinemia</td>
<td>Crigler-Najjar syndrome</td>
</tr>
</tbody>
</table>
I. Amino acid metabolism

Phenylketonuria (PKU)

• Definition:
  PKU is a metabolic disorder caused by a deficiency of the liver enzyme phenylalanine hydroxylase.

• Inheritance:
  Autosomal recessive
Diagnosis of HPA

- **Biochemical testing**
  - quantitative plasma amino acid analysis
  - urine pterin studies
  - dihydropterin reductase measurement

Note: Enzyme analysis is not usually indicated for PAH, because it is a hepatic enzyme.

- **Genetic diagnosis**
  - Targeted mutation analysis - sequence analysis of select exons
  - Sequence analysis /mutation scanning
  - Duplication/deletion analysis
  - Linkage analysis
Good sample

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Galactosemia

- **Definition:**
  Galactosemia is a rare genetic metabolic disorder that affects an individual's ability to metabolize the sugar galactose properly.

- **Inheritance:**
  Autosomal recessive
Galactose metabolism

Galactose is converted into glucose by the action of three enzymes:

- galactose-1-phosphate uridyl transferase
- galactokinase
- UDP galactose epimerase
Type III galactosemia
(UDP galactose epimerase)

• **Gene:** *GALE* gene
• **Location:** 1p36-p35
• **Gene product:** UDP-galactose-4-epimerase
• **Function:** conversion of UDP-glucose to UDP-galactose
Clinical characteristics

- Hypotonia
- Poor feeding
- Vomiting
- Weight loss
- Jaundice
- Hepatomegaly
- Liver dysfunction
- Aminoaciduria
- Cataracts.
Prevention of Galactosemia

• Prenatal Testing
  – chorionic villus sampling – 10-12 weeks’ gestation
  – amniocentesis – 15-18 weeks’ gestation

• Preimplantation genetic diagnosis (PGD)
Diagnosis and treatment of alkaptonuria

• **Diagnosis**
  – gas chromatography-mass spectrometry analysis (detection of a significant amount of HGA in the urine by gas chromatography-mass spectrometry analysis)
  – molecular genetic testing
    o Targeted mutation analysis
    o Sequence analysis

• **Treatment**
  symptomatic
Diagnosis and treatment of Gaucher’s disease

• Diagnosis
  – Clinical
  – Enzyme testing
  – Genetic (sequencing)

• Treatment
  – Enzyme replacement with i.v. recombinant glucocerebrosidase – 200 000$ annually
Diagnosis and treatment of adrenoleukodystrophy

• Diagnosis
  – Clinical
  – Plasma very long chain fatty acid (VLCFA) determination by gas chromatography-mass spectrometry
  – Molecular genetic analysis
  – Newborn screening

• Treatment
  – Dietary therapy
  – Transplant
  – Gene therapy
  – Treatment of the adrenal insufficiency