Non-cystinotic Fanconi syndrome

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De Toni – Debre - Fanconi Syndrome

- **Fanconi G.** Die nicht diabetischen Glykosurien und Hyperglykaemien des alteren Kindes. *Jahrbuch fuer Kinderheilkunde* 1931; 133: 257–300
  - Renal glycosuria

  - Rickets & glycosuria

  - Rickets & glycosuria & nephropathy

- **Fanconi G.** Der nephrotisch-glykosurische Zwergwuchs mit hypophosphataemischer Rachitis. *Deutsche Medizinische Wochenschrift* 1936; 62: 1169–1171
  - Rickets & glycosuria & nephropathy
Proximal tubular cell and Fanconi syndrome

- Isolated apical transporter defects
  - Rarely Fanconi sd

- Mutations of transcription factors
  - Rarely Fanconi sd

- Isolated baso-lateral transporter defects
  - Possible Fanconi sd

- Energy depletion / metabolic failure
  - Frequent Fanconi sd

- Impaired receptor-mediated endocytosis
  - Receptor mutations
    - No / mild Fanconi sd
  - Intracellular trafficking defects
    - Frequent Fanconi sd
### Genetic forms of Fanconi Syndrome

**Metabolic Diseases**
- **Galactosemia** *(GALT)*: cataract, liver disease, vomiting, diarrhea, encephalopathy
- **Fructose Intolerance** *(ALDOB)*: hypoglycaemia, vomiting, liver disease
- **Thyrosinemia** *(FAH)*: liver disease, poor growth
- **Wilson disease** *(ATP7B)*: liver disease, encephalopathy, Kayser-Fleischer rings
- **Mitochondrial cytopathies**

**Membrane Transporters & Transcription Factors**
- **Fanconi-Bickel** *(GLUT2)*: hypoglycemia, liver disease, rickets, failure to thrive
- **Lysinuric protein intolerance** *(SLC7A7)*: failure to thrive, hepatosplenomegaly, respiratory failure, immunological disorders
- **AD Fanconi Syndrome** *(R76W HNF4α)*: neonatal hyperinsulinism, MODY1, macrosomia

**Receptor-Mediated Endocytosis**
- **Imerslund-Gräsbeck syndrome** *(CUB, AMN)*
- **Donnai-Barrow syndrome** *(LPR2)*
- **Cystinosis** *(CTNS)*
- **Lowe syndrome** *(OCRL1)*
- **Dent disease** *(CLCN5, OCRL1)*
- **ARC syndrome** *(VPS33B, VIPAR)*: joint contractures, cholestasis, ichthyosis, CNS malformation, platelet anomalies

**Unknown cause:** "idiopathic Fanconi syndrome"
Renal tubular disorders in mitochondrial disorders

- Renal Fanconi syndrome
  - Renal tubular acidosis
  - Isolated hyperaminoaciduria
  - Isolated hypomagnesemia
  - Bartter-like phenotype
Autosomal dominant renal Fanconi syndrome

- Heterozygous missense mutation in the EHHADH gene
- Peroxisomal enzyme expressed in the proximal tubule involved in fatty acid oxidation
- The mutation introduces a new mitochondrial targeting motif
- Impaired mitochondrial oxidative phosphorylation with a dominant-negative effect
Organic aciduria in renal mitochondrial disease

NB: may also be observed in the absence of hyperlactacidemia
Electron microscopy in renal tubular mitochondrial diseases
Hereditary tyrosinemia type I

- **Acute form (0-6 months)**
  most frequent hepatic and systemic failure

- **Sub-acute form (6-24 months)**
  hepatosplenomegaly coagulopathy failure to thrive
  Fanconi syndrome, often rickets neurologic crises (if untreated)

- **Chronic form (>2 years)**
  subclinical liver and/or renal tubular dysfunction
Hereditary tyrosinemia type I

- **Blood:**
  - ↑↑↑ tyrosine, methionine, and phenylalanine
  - ↑↑↑ alpha-fetoprotein
  NB: LFT’s are often normal or only slightly elevated

- **Urine:**
  - tyrosine metabolites
  - (p-hydroxyphenylpyruvate, p-hydroxyphenyllactate, and p-hydroxyphenylacetate)
Toxic compounds in hereditary tyrosinemia type I

- L-tyrosine
- 4-hydroxyphenylpyruvate
- homogentisate
- maleylacetoacetate
- succinylacetoacetate
- succinylacetone

Fah-/-

Lethal

TAT - tyrosine aminotransferase
HPPD - hydroxyphenylpyruvate dioxygenase
HGD - homogentisate 1,2-dioxygenase
MAAI - maleylacetoacetate isomerase
FAA - fumarylacetoacetase

Sun et al, JASN 2000
Toxic compounds in hereditary tyrosinemia type I

Sun et al, JASN 2000
Toxic compounds in hereditary tyrosinemia type I

- L-tyrosine
- 4-hydroxyphenylpyruvate
- Homogentisate
- Maleylacetoacetate
- Fumarylacetoacetate
- Acetoacetate
- Fumarate

Type II tyrosinemia

Type III tyrosinemia

Fah-/-

Lethal

Fah-/Hppd-/-

No liver or renal disease

Fah-/Hppd-/-

Fanconi syndrome

+ Homogentisate

Sun et al, JASN 2000

TAT - tyrosine aminotransferase
HPPD - hydroxyphenylpyruvate dioxygenase
HGD - homogentisate 1,2-dioxygenase
MAAI - maleylacetoacetate isomerase
FAA - fumarylacetoacetase
Toxic effects of succinylacetone on renal tubular cells

- **In vitro:**
  1. direct inhibition of brush border transporters
  2. altered plasma membrane fluidity
  3. reduced O2 consumptions by tubular mitochondria (reversible)
     (Spencer Kidney International 1988)

- **In vivo - experimental:**
  injection in rats induces renal Fanconi syndrome
  (Spencer Biochem Med Metab Biol 1987)

- **In vivo - humans:**
  normalization of succinylacetone after liver transplantation corrects renal tubular acidosis
  (Herzog Transplantation 2006; Pierik JIMD 2005)
Toxic compounds in hereditary tyrosinemia type I

NTBC

[(2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione), nitisinone]

Patient n°5

TAT - tyrosine aminotransferase
HPPD - hydroxyphenylpyruvate dioxygenase
HGD - homogentisate 1,2-dioxygenase
MAAI - maleylacetoacetate isomerase
FAA - fumarylacetoacetase

Maiorana et al, Mol Genet Metabol 2014
Receptor mediated endocytosis in proximal tubular cells

D'Amico, Kidney Int 2003

Nielsen et al, Kidney Int 2016

Christensen and Birn, Am J Physiol Renal 2001
Low molecular proteinuria

Carrier females of Dent’s disease

AD Fanconi syndrome
Dent’s disease
Lowe syndrome

Normal subjects
Glomerulonephritis

Genetic forms of Fanconi syndrome with overt low molecular proteinuria

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>LOCUS</th>
<th>PROTEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystinosis</td>
<td>CTNS</td>
<td>Cystinosin</td>
</tr>
<tr>
<td>Dent 1</td>
<td>CLCN5</td>
<td>CLC-5</td>
</tr>
<tr>
<td>Dent 2</td>
<td>OCRL1</td>
<td>PI-4,5-biphosphate-phosphatase</td>
</tr>
<tr>
<td>Lowe syndrome</td>
<td>OCRL1</td>
<td>PI-4,5-biphosphate-phosphatase</td>
</tr>
<tr>
<td>ARC syndrome</td>
<td>VPS33B, VIPAR</td>
<td>Vacuolar sorting proteins</td>
</tr>
<tr>
<td>Imerslund-Gräsbeck syndrome</td>
<td>CUBN, AMN</td>
<td>Cubilin, Amnionless</td>
</tr>
<tr>
<td>Donnai-Barrow syndrome</td>
<td>LRP2</td>
<td>Megalin</td>
</tr>
<tr>
<td>Severe PTC cytopathies</td>
<td>~</td>
<td>~</td>
</tr>
<tr>
<td>Idiopathic Fanconi Syndrome</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Willow et al, Kidney Int 2017
Imerslund-Gräsbeck syndrome

- Selective Vit. B12 malabsorption with LMWP
- AR disorder, first described in Finland and Norway (prevalence 1:200,000)
- Megaloblastic anemia, responsive to parenteral Vit. B12 therapy
- Other reported manifestations (infrequent):
  - failure to thrive
  - frequent infections
  - neurological symptoms

Mutations in the CUBN or AMN genes

amnionless is required for the expression of cubilin in the brush-border

Intestinal receptor for the Vit B12 - intrinsic factor complex

Storm et al. BMC Medical Genetics 2013

Andersen et, Nature 2010
Imerslund-Gräsbeck syndrome: CUBN mutation

- 20 year old male born from consanguineous parents
- At 17 months: anorexia and megaloblastic anemia (Hb 5.3 g/dl; MCV 97 fl)
- Homozygous CUBN exon 23 (c.3329+1G>T)
- Renal biopsy for IgA nephropathy

Storm et al, NEJM 2011
Imerslund-Gräsbeck syndrome: CUBN mutation

Storm et al, NEJM 2011
Donnai-Barrow syndrome (facio-oculo-acustico-renal syndrome)

- **Face:**
  - wide-set eyes - outer corners pointing downward
  - short bulbous nose - flat nasal bridge
  - back-rotated ears
  - widow's peak hairline

- **Eye:**
  - severe myopia
  - retinal detachment
  - iris coloboma

- **Ear:**
  - sensorineural hearing loss

- **Kidneys:**
  - low molecular weight proteinuria
  - FSGS?

- **Other features:**
  - ipoplasia of the corpus callosum
  - mild to moderate intellectual disability
  - congenital diaphragmatic hernia
  - omphalocele

- **Very rare**

- **LRP2 gene mutations**
Megalin and cubilin expression in genetic and acquired PT diseases

Cystinosis

Control

Disease

Lowe

Dent

Sjogren

Control

Disease

Human
Gaide Chevronnay et al, JASN 2014

Zebrafish
Otrabella et al, Plos Genet 2015

Mouse
Christensen et al, PNAS 2003

Human
Wang et al, Arthritis Res Ther 2017
Overlapping phenotypes between Dent disease and Lowe syndrome

CLCN5

Dent1

vs.

Dent2

OCRL1

Lowe

vs.
Dent 1 vs. Dent 2

- urinary concentration defect
- increased LDH and CPK in Dent 2

Table 1 | Presentation at clinical diagnosis of patients with Dent type 1 and type 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dent-1</th>
<th>Dent-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>11 (5-21)</td>
<td>6 (3-8)</td>
</tr>
<tr>
<td>LMWP</td>
<td>93 of 93 (100%)</td>
<td>7 of 7 (100%)</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>81 of 88 (92%)</td>
<td>3 of 3 (100%)</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>24 of 74 (32%)</td>
<td>1 of 6 (17%)</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>44 of 104 (42%)</td>
<td>1 of 9 (11%)</td>
</tr>
<tr>
<td>Aminoaciduria</td>
<td>16 of 32 (50%)</td>
<td>4 of 5 (80%)</td>
</tr>
<tr>
<td>Renal hypouricemia</td>
<td>19 of 30 (63%)</td>
<td>1 of 1 (100%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>31 of 70 (44%)</td>
<td>1 of 4 (25%)</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>26 of 58 (45%)</td>
<td>0 of 6 (0%)</td>
</tr>
<tr>
<td>Acidosis</td>
<td>9 of 54 (17%)</td>
<td>2 of 8 (25%)</td>
</tr>
<tr>
<td>Incomplete Fanconi syndrome *</td>
<td>51 of 70 (73%)</td>
<td>5 of 9 (55%)</td>
</tr>
<tr>
<td>Complete Fanconi syndrome *</td>
<td>8 of 70 (11%)</td>
<td>1 of 9 (11%)</td>
</tr>
<tr>
<td>Rickets</td>
<td>14 of 75 (19%)</td>
<td>1 of 7 (14%)</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>12 of 40 (30%)</td>
<td>4 of 6 (67%)</td>
</tr>
</tbody>
</table>

Blanchard et al, Kidney Int 2016
Chronic renal failure: Dent 1 vs. Dent 2 vs. Lowe

Data extrapolated from Blanchard et al, Kidney Int 2016 and from Zaniew et al, Nephrol Dial Transpl 2016
# Dent 2 vs. Lowe

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Lowe</th>
<th>Dent disease 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extrarenal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract$^6$</td>
<td>100%</td>
<td>7%</td>
</tr>
<tr>
<td>Intellectual impairment$^3$</td>
<td>100%</td>
<td>27%</td>
</tr>
<tr>
<td>Growth retardation (mean height SDS)</td>
<td>100%(-3.7)</td>
<td>Frequent (-2.1)</td>
</tr>
<tr>
<td>Arthropathy$^1$</td>
<td>Frequent</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Elevated CPK and/or LDH$^9$</td>
<td>98%</td>
<td>97%</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>45%</td>
<td>28%</td>
</tr>
<tr>
<td>LMWP</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Albuminuria$^8$</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>Lysosomal enzymuria</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>Aminoaciduria</td>
<td>79%</td>
<td>41%</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>82%</td>
<td>78%</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>57%</td>
<td>4%</td>
</tr>
<tr>
<td>Phosphate wasting</td>
<td>51%</td>
<td>15%</td>
</tr>
<tr>
<td>Potassium wasting</td>
<td>23%</td>
<td>4%</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>10%</td>
<td>15%</td>
</tr>
</tbody>
</table>

De Matteis et al, Nat Rev Nephrol 2017
Mutations in Lowe syndrome and Dent 2 disease

De Matteis et al, Nat Rev Nephrol 2017
Thank you

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