Kidney epithelial cells are highly polarized with vectorial transport of ions, proteins, & molecules across apical and basolateral membranes via various channels. What happens if one of the channels is disrupted or lost?

#Dents #ClC5 #OCRL1 #NSMC #Nephtwitter #ASPNeph

What is Dent's disease?

a heterogeneous group of X-linked recessive (XLR) disorders

- Dent 1
- XLR nephrolithiasis (XRN)
- XLR hypercalciuric hypophosphatemic rickets (XLRH)
- LMW proteinuria with hypercalciuria and nephrocalcinosis
- Dent 2

[Article](https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-5-28)

Let's talk about Dent disease 1 and 2

- Prevalence is unknown
- So far we know of ~250 families (Dent-1) & ~50 patients (Dent-2) disease

[Article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964617/)
[Article](https://rarediseases.org/rare-diseases/dent-disease/#:~:text=The%20exact%20incidence%20and%20prevalence%2C%20reported%20in%20approximately%2025%20individuals)

What are the associated genetic mutations?

All the above

- Dent 1 - Xp11.22 - CLCN5 - Cl-/H+ exchanger ClC-5 (CLC family of Cl-channels/transporters) - Also XRN, XLRH
- Dent 2 - Xq25 - OCRL1 - (PIP2) 5-phosphatase (also Lowe Syndrome)
In addition, various other types of mutations are seen:

- 36%: nonsense mutations
- 33%: missense mutations
- 14%: frameshift deletion
- 5%: frameshift insertions
- 3% each: donor & acceptor splice site mutation
Very well, what is ClC-5?

- Cl- H exchanger in cells of PCT & CD (intercalated cells)

- Important for:
  - Receptor-mediated endocytosis of LMW proteins
  - Electrical shunt for H+-ATPase which allows vesicle acidification in the endocytic pathway

Lloyd 1996


Let's talk about OCRL1-

- OCRL1 helps lysosomes in renal PT cells & trans-Golgi network in fibroblasts with endosomal/lysosomal trafficking by
  - inactivating PIP2
  - interaction with clathrin
  - interaction with Rab5 effector APPL1

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964617/

Disruption of ClC5 or OCRL1 ➡️

- LMW proteinuria (RBP, Clara cell protein, vitamin D binding protein & α1 & β2 microglobulin) - 99%
- Loss of Na, K, Ca, PO4, HCO3, Glucose & Mg

This leads to symptoms (appear in early childhood and worsen over time)

- Failure to thrive - early childhood
- Polyuria & polydipsia
- Bone pain & difficulty in walking (rickets)
- Abdominal pain and hematuria (kidney stones)
- Episodic night blindness (loss of RBP)
How are the symptoms of Dent 2 different from Dent 1?

Dent 2 has intellectual impairment, hypotonia, & cataract (subclinical) in addition to the symptoms seen in Dent 1.

Fun fact👇👇👇

🌟 mutations in OCRL1 is also associated with the oculo-Cerebro-renal syndrome of Lowe 🌟
P/E & Labs:

- Growth chart: dropping percentiles
- Urinalysis: Hyposthenuria, glucosuria, aminoaciduria, phosphaturia, uricosuria, kaliuresis, hematuria, impaired acidification
- Hypercalciuria (≥ 4 mg/kg (24-hr) or spot UCCR: ≥0.25 mg/mg) ~95% ♂
- Nephrocalcinosis ~75% ♂
Diagnosis: requires all 3 of the following

- LMW proteinuria,
- hypercalciuria and
- at least one of the following: nephrocalcinosis, kidney stones, hematuria, hypophosphatemia or renal insufficiency

(or)

When CLCN5 mutation is present, only one of the above
Confirmation:
- Molecular genetic testing-mutational analysis of CLCN5 and/or OCRL1
- 10% of patients (de novo mutations) - transmitted X-linked
- No genotype-phenotype correlation
- intra-familial variability
- Antenatal diagnosis & pre-implantation testing - not advised

Kidney biopsy (not needed for diagnosis)
- LM: progressive & non-specific
- Glomerular hyalinosis, tubular degeneration, Ca pyro-PO4 crystal deposition & mild IF
- Hyaline casts +/- calcifications (outer medulla) - 1st sign of nephrocalcinosis
- Rarely FSGS

IF/EM: normal usually

differential diagnosis

**Differential Diagnosis of Dent’s Disease**

**Inherited disorders**
- Lowe syndrome
- Cystinosis
- Galactosemia
- Hereditary fructose intolerance
- Glycogen storage disease (von Gierke disease)
- Fanconi-Bickel syndrome
- Tyrosinemia type I
- Wilson disease
- Mitochondrial diseases (cytochrome-c oxidase deficiency)
- Idiopathic/Sporadic Fanconi syndrome

**Acquired disorders**
- Glomerular proteinuria (nephrotic syndrome)
- Light chain nephropathy (multiple myeloma)
- Sjogren syndrome
- Auto-immune interstitial nephritis
- Acute tubulo-interstitial nephritis with uveitis (TINU)
- Renal transplantation
- Anorexia nervosa

**Exogenous Substances**
- Drugs
- Aminoglycosides, outdated tetracycline
- Valproate, salicylate
- Adefovir, cidofovir, tenofovir
- Ifosfamide, cisplatin, Imatinib
- Chinese herbs (aristolochic acid)
- Chemical compounds (paraquat, diachrome, 6-mercaptopyrine, toluene, maleate)
- Heavy metals (Lead, cadmium, chromium, platinum, uranium, mercury)
Let's talk a little more about female carriers:

- milder LMW proteinuria (70%)
- hypercalciuria (50%) in females carriers
- Rarely, nephrolithiasis & ESKD

# Lyonization

Management:

- supportive, Rx of hypercalciuria & nephrolithiasis
- thiazide diuretics (cautious) hypovolemia & hypo K (primary tubulopathy)
- Vit D (cautious) hypercalciuria

Prognosis: good in the majority

- Progression to ESKD - 3rd and 5th decades of life in 30-80% of affected males
**DENT’S DISEASE**

<table>
<thead>
<tr>
<th>Group of X-linked disorders</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dent disease 1</td>
<td>1. <strong>CLCN5</strong> - CLC-5 - Cl/H+ exchanger (CLC family of Cl-channels/transporters) - Xp11.22 - (Dent disease 1 (60%), XLRH, XLRH)</td>
</tr>
<tr>
<td>2. X-linked recessive nephrolithiasis (XRN)</td>
<td></td>
</tr>
<tr>
<td>3. X-linked recessive hypercalciuric hypophosphatemic rickets (XLH)</td>
<td>2. <strong>OCRL1</strong> - (PHP2) S - Xq25 - phosphatase (Dent disease 2 (19%), Lowe Syndrome)</td>
</tr>
<tr>
<td>4. Low-molecular-weight proteinuria with hypercalcuria and nephrocalcinosis</td>
<td>3. Various mutations - 25%</td>
</tr>
<tr>
<td>5. Dent disease 2</td>
<td></td>
</tr>
</tbody>
</table>

**My favorite Part - The Summary**

Until Next time...#ASPNeph #NSMC #podkopiluwak

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