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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

<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

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

[https://rarediseases.org/rare-diseases/dent-](https://rarediseases.org/rare-diseases/dent-disease/#:~:text=The%20exact%20incidence%20and%20prevalence,reported%20in%20a)

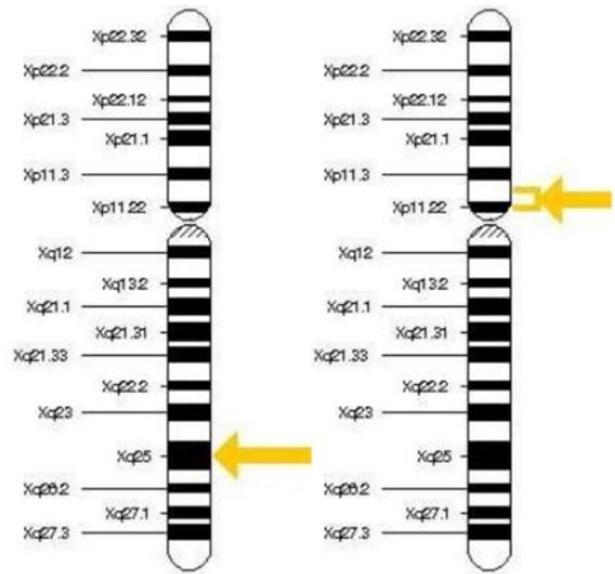
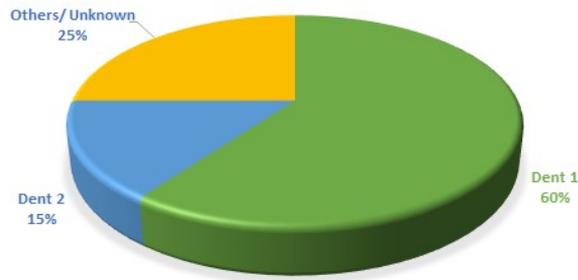
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What are the associated genetic mutations?

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)



Zhang et al 2017

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5451742/>

<https://www.ukessays.com/essays/biology/dents-disease-symptoms-genetics-5245.php>

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

TABLE 1 CLCN5 mutations found in families with X-linked hypercalciuric nephrolithiasis

Family	Codon	Base change	Amino acid change	Restriction enzyme change/SSO	Predicted effect
Nonsense mutations					
7.2/94*	279	TGG → TGA	Trp → Stop	<i>Maelll</i>	Loss of 469 amino acids from D6 to C terminus
6/94*	648	CGA → TGA	Arg → Stop	<i>TaqI</i>	Loss of 100 amino acids from cytoplasmic domain
12/95†	704	CGA → TGA	Arg → Stop	<i>Bsll</i>	Loss of 42 amino acids from cytoplasmic domain
Missense mutations					
13/94*	200	CTG → CGG	Leu → Arg	<i>AccI</i>	Disruption of charge distribution within D3
9/95‡	244	TCG → TTG	Ser → Leu	SSO	Disruption of helix in D5
10/92†	506	GGG → GAG	Gly → Glu	<i>MnlI</i>	Disruption of charge distribution within D11
2/92*	520	TCT → CCT	Ser → Pro	<i>MnlI</i>	Disruption of helix in D11
Splice site mutations					
4/94*	Intron 5 132–172 deleted	gt → gg		<i>HphI</i>	Loss of D2
19/94*	Intron 5 132–172 deleted	gt → at		<i>HphI</i>	Loss of D2
Deletions					
7.1/94*	2-kb deletion 132–241 deleted				Loss of D2–D4
12/89*§	515-kb deletion				Absence of protein

* Eight British families (26 affected, 33 unaffected members) with Dent's disease, † two North American families (29 affected, 75 unaffected members) with XRN, and ‡ one Italian family (9 affected, 10 unaffected members) with XLRH were studied. The clinical details of 7 of the 8 kindreds with Dent's disease, designated families 2/92, 4/94, 6/94, 7.2/94, 12/89, 13/94 and 19/94 have been previously reported³ and referred to as families A, E, D, F, H, C and G, respectively.

§ Previously described^{6,8}.

Lloyd 1996

<https://pubmed.ncbi.nlm.nih.gov/8559248/>

Very well, what is ClC-5?

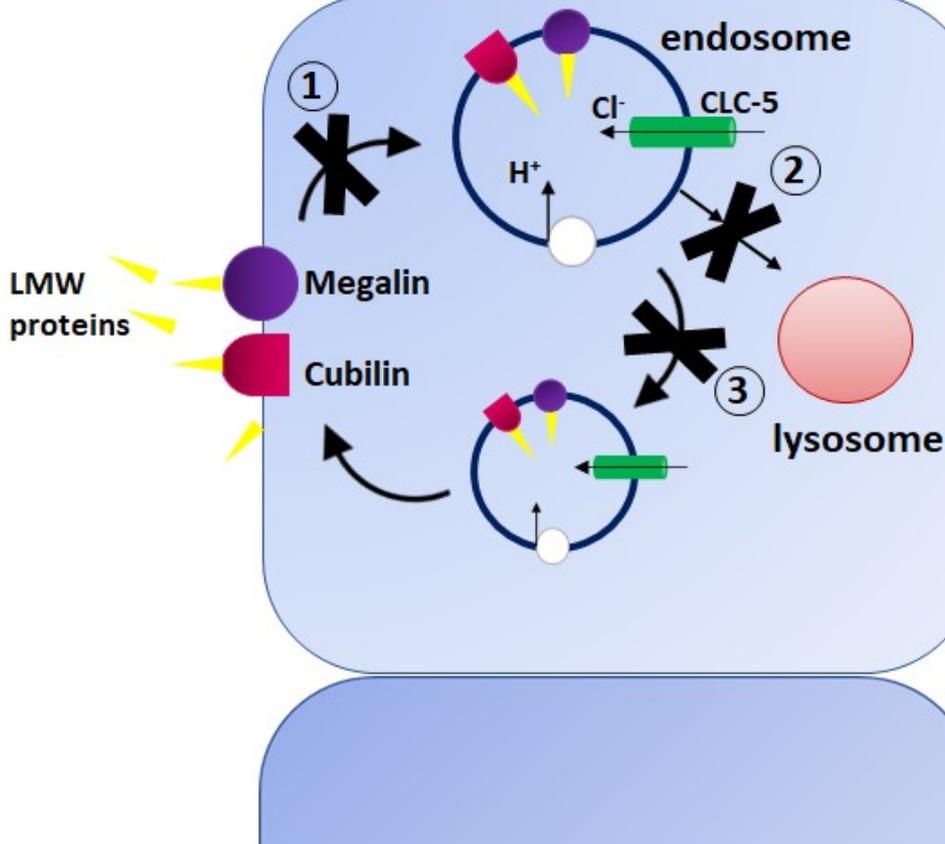
⚡ Cl⁻ H exchanger in cells of PCT & CD (intercalated cells)

⚡ important for:

📌 receptor-mediated endocytosis of LMW proteins

📌 electrical shunt for H⁺-ATPase which allows vesicle acidification in the endocytic pathway

<https://pubmed.ncbi.nlm.nih.gov/12815097/>



Chloride influx via CLC-5 facilitates acidification by maintaining electroneutrality of ion transport. Absence or Dysfunction of CLC-5 could interrupt endosome cycling at three points:

- (1) reduced rate of internalization of receptors;
- (2) disruption of progression of endosomes to lysosomes;
- (3) recycling of endosomes to the cell surface.

By @drM_sudha
Adapted from Devonald 2004

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/>

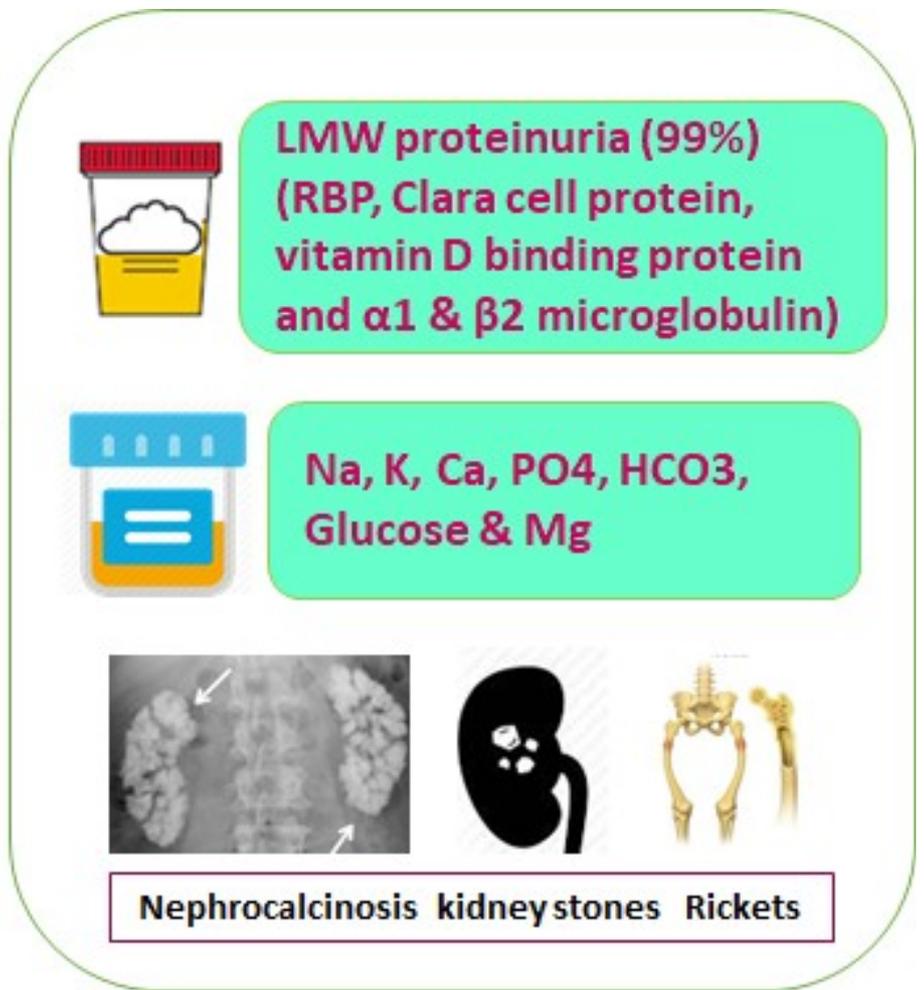
Disruption of CLC5 or OCRL1

⚡ LMW proteinuria (RBP, Clara cell protein, vitamin D binding protein & α1 & β2 microglobulin) - 99%

⚡ Loss of Na, K, Ca, PO₄, HCO₃, Glucose & Mg

<https://pubmed.ncbi.nlm.nih.gov/12548389/>

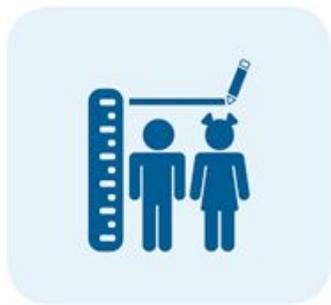
~~CIC5~~
~~OCRL1~~



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

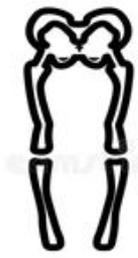
- ⚡ Failure to thrive-early childhood
- ⚡ Polyuria & polydipsia
- ⚡ bone pain & difficulty in walking (rickets)
- ⚡ abdominal pain and hematuria (kidney stones)
- ⚡ episodic night blindness (loss of RBP)



Failure To Thrive



Bone Pain



Rickets



Back Pain



Hematuria



Polyuria



Polydipsia



Night Blindness

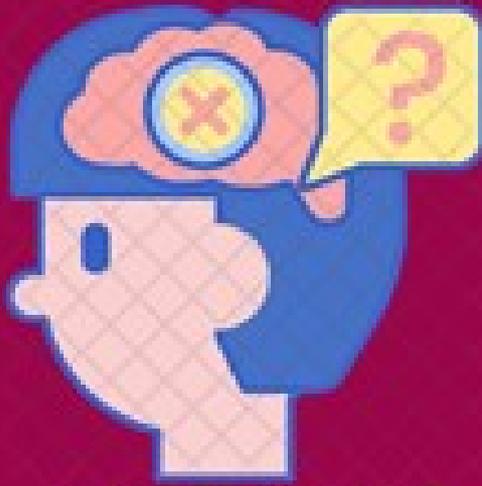
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How are the symptoms of Dent 2 different from Dent 1?

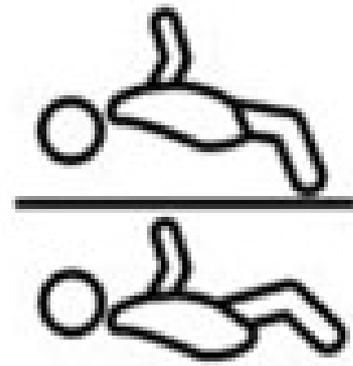
Dent 2 has intellectual impairment, hypotonia, & cataract (subclinical) in addition to the symptoms seen in Dent 1

Fun fact 🙌🙌🙌

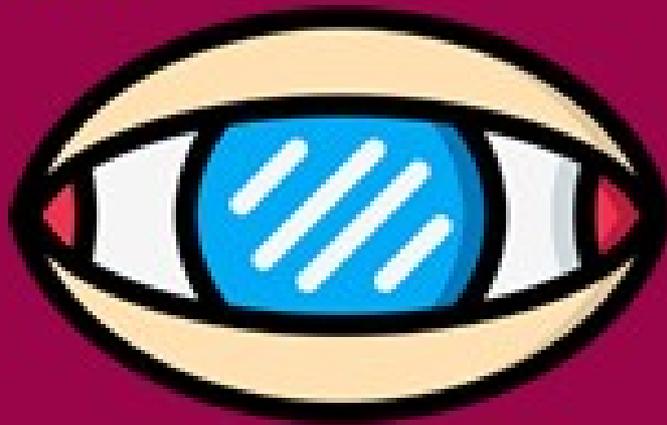
★ mutations in OCRL1 is also associated with the oculo-Cerebro-renal syndrome of Lowe ★



**Intellectual
Impairment**



hypotonia



Cataract

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% ♂

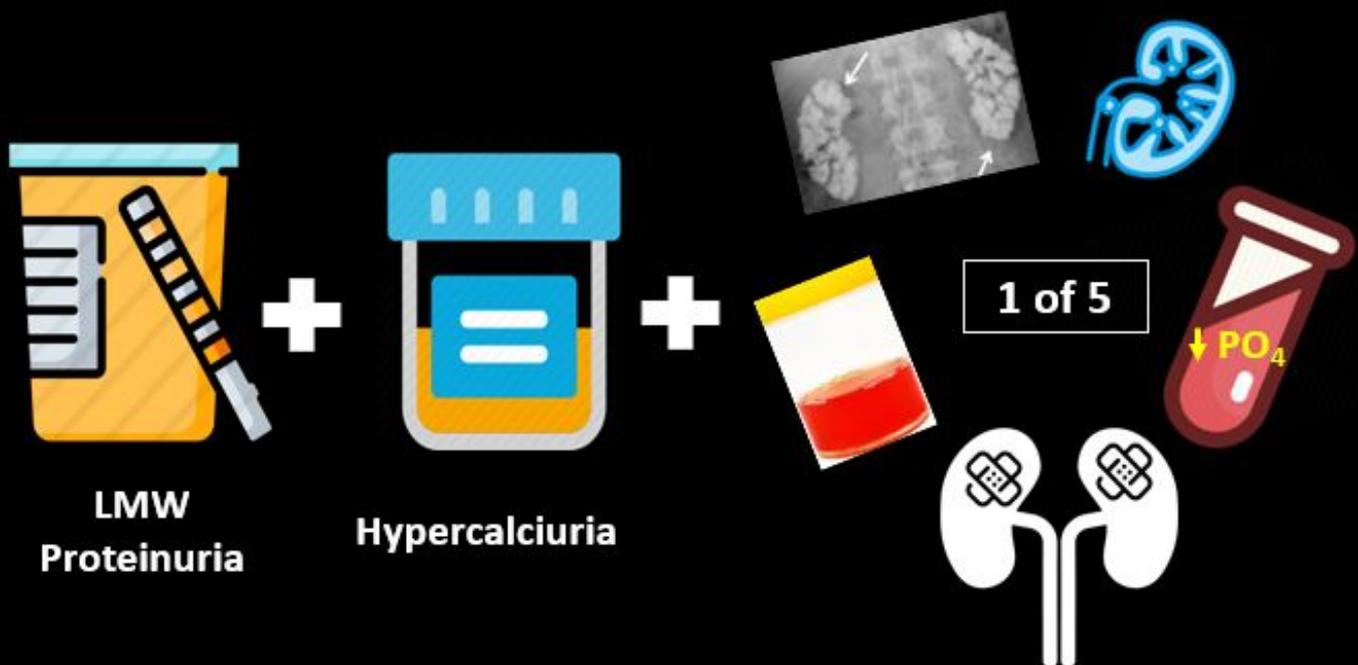
Diagnosis: requires all 3 of the following

- ✦ 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

Diagnosis



(or)

***CLCN5* mutation** + 1 of the above

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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-mercaptopurine, 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

Management



Supportive



Prognosis: good in the majority

- ⚡ Progression to ESKD - 3rd and 5th decades of life in 30-80% of affected males ♂ ⚡

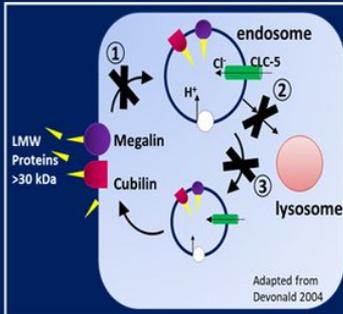
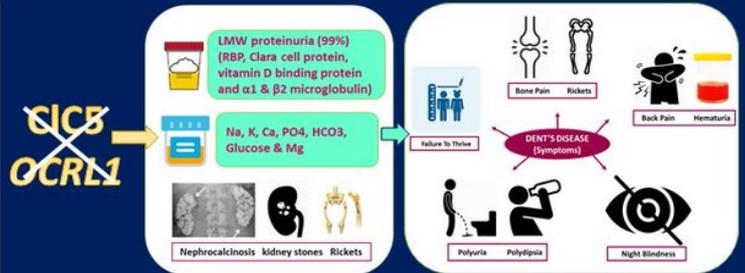
DENT'S DISEASE

Group of X-linked disorders

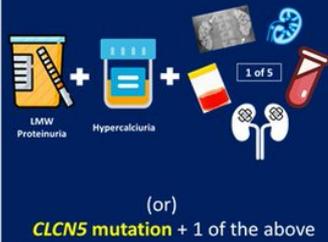
1. Dent disease 1
2. X-linked recessive nephrolithiasis (XRN)
3. X-linked recessive hypercalciuric hypophosphatemic rickets (XLRH)
4. Low-molecular-weight proteinuria with hypercalciuria and nephrocalcinosis
5. Dent disease 2

Associated Genes

1. *CLCN5* - ClC-5 - Cl-/H+ exchanger (CLC family of Cl-channels/transporters) - Xp11.22 - (Dent disease 1 (60%), XRN, XLRH)
2. *OCRL1* - (PIP2) 5 - Xq25 - phosphatase (Dent disease 2 (15%), Lowe Syndrome)
3. Various mutations -25%



Diagnosis



Confirmatory Test



Management



Prognosis

good in majority
ESKD - 3rd and 5th decades of life (30-80%)

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