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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

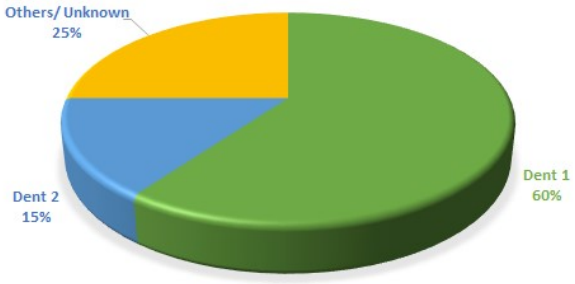
Let's talk about Dent disease 1 and 2
⚡Prevalence is unknown
⚡So far we know of ~250 families (Dent-1) & ~50 patients (Dent-2) disease

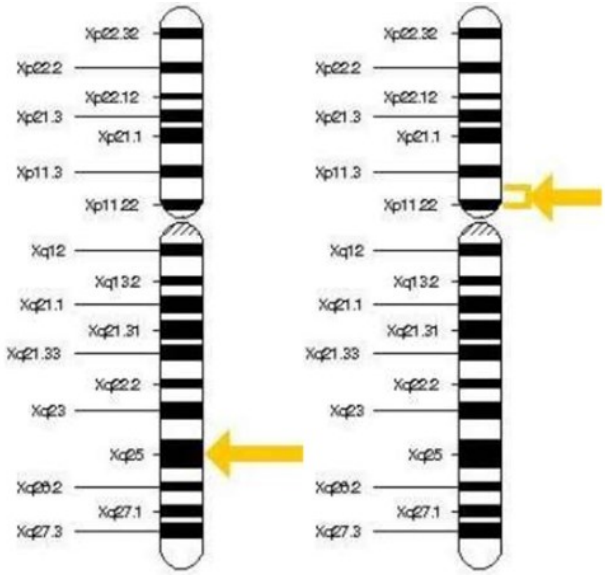
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964617/

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

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	TG**G** → TG**A**	Trp → Stop	*Mae*III	Loss of 469 amino acids from D6 to C terminus
6/94*	648	**C**GA → **T**GA	Arg → Stop	*Taq*I	Loss of 100 amino acids from cytoplasmic domain
12/95†	704	**C**GA → **T**GA	Arg → Stop	*Bsl*I	Loss of 42 amino acids from cytoplasmic domain
Missense mutations					
13/94*	200	C**T**G → C**G**G	Leu → Arg	*Aci*I	Disruption of charge distribution within D3
9/95‡	244	T**C**G → T**T**G	Ser → Leu	SSO	Disruption of helix in D5
10/92†	506	GGG → GAG	Gly → Glu	*Mnl*I	Disruption of charge distribution within D11
2/92*	520	**T**CT → **C**CT	Ser → Pro	*Mnl*I	Disruption of helix in D11
Splice site mutations					
4/94*	Intron 5 132–172 deleted	g**t** → g**g**		*Hph*I	Loss of D2
19/94*	Intron 5 132–172 deleted	g**t** → a**t**		*Hph*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

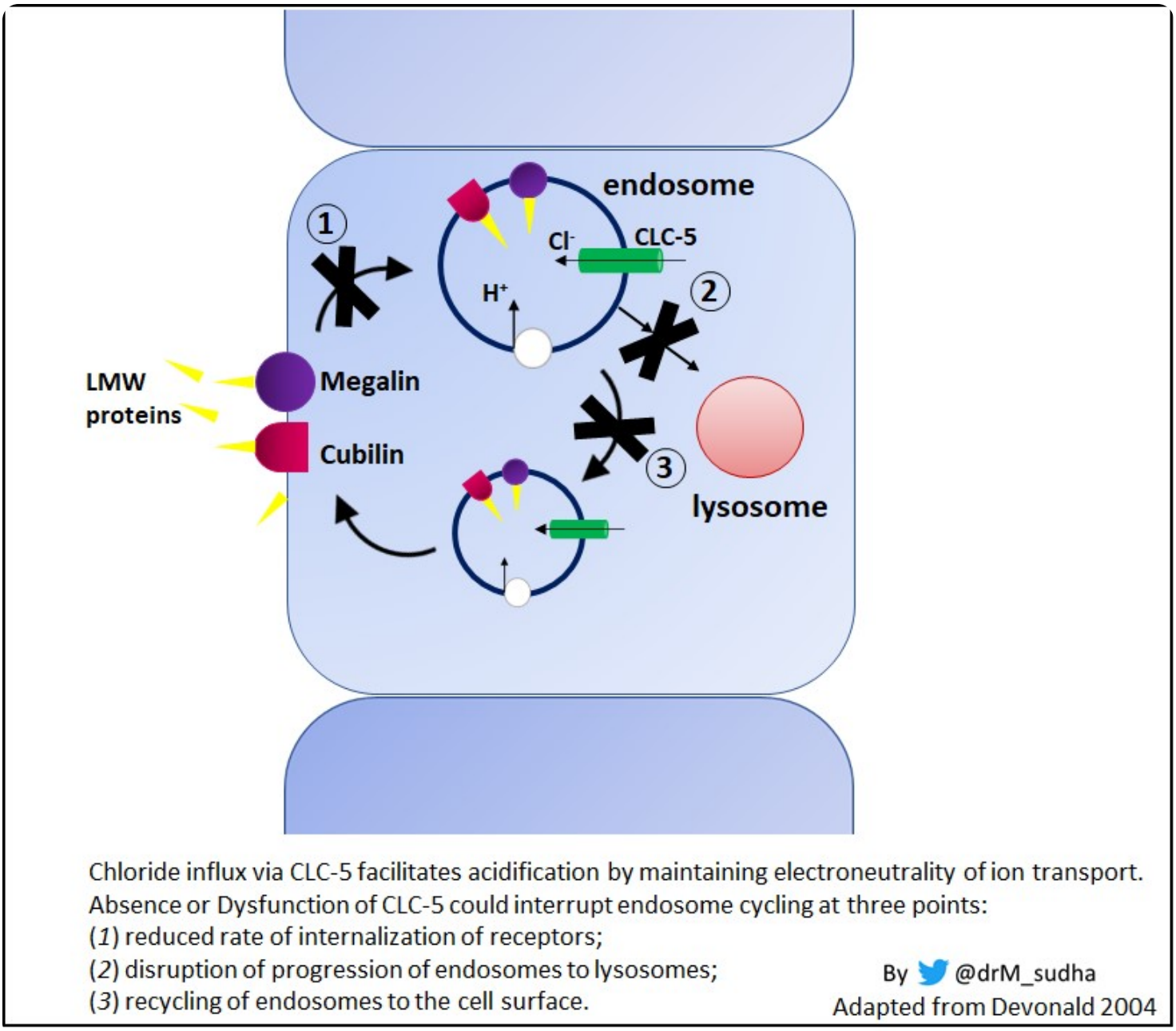
* Eight British families (26 affected, 33 unaffected members) with Dent's disease, † two North American families (29 affected, 75 unaffected members) with XRN, and ‡ one Italian family (9 affected, 10 unaffected members) with XLRH were studied. The clinical details of 7 of the 8 kindreds with Dent's disease, designated families 2/92, 4/94, 6/94, 7.2/94, 12/89, 13/94 and 19/94 have been previously reported[3] 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/



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

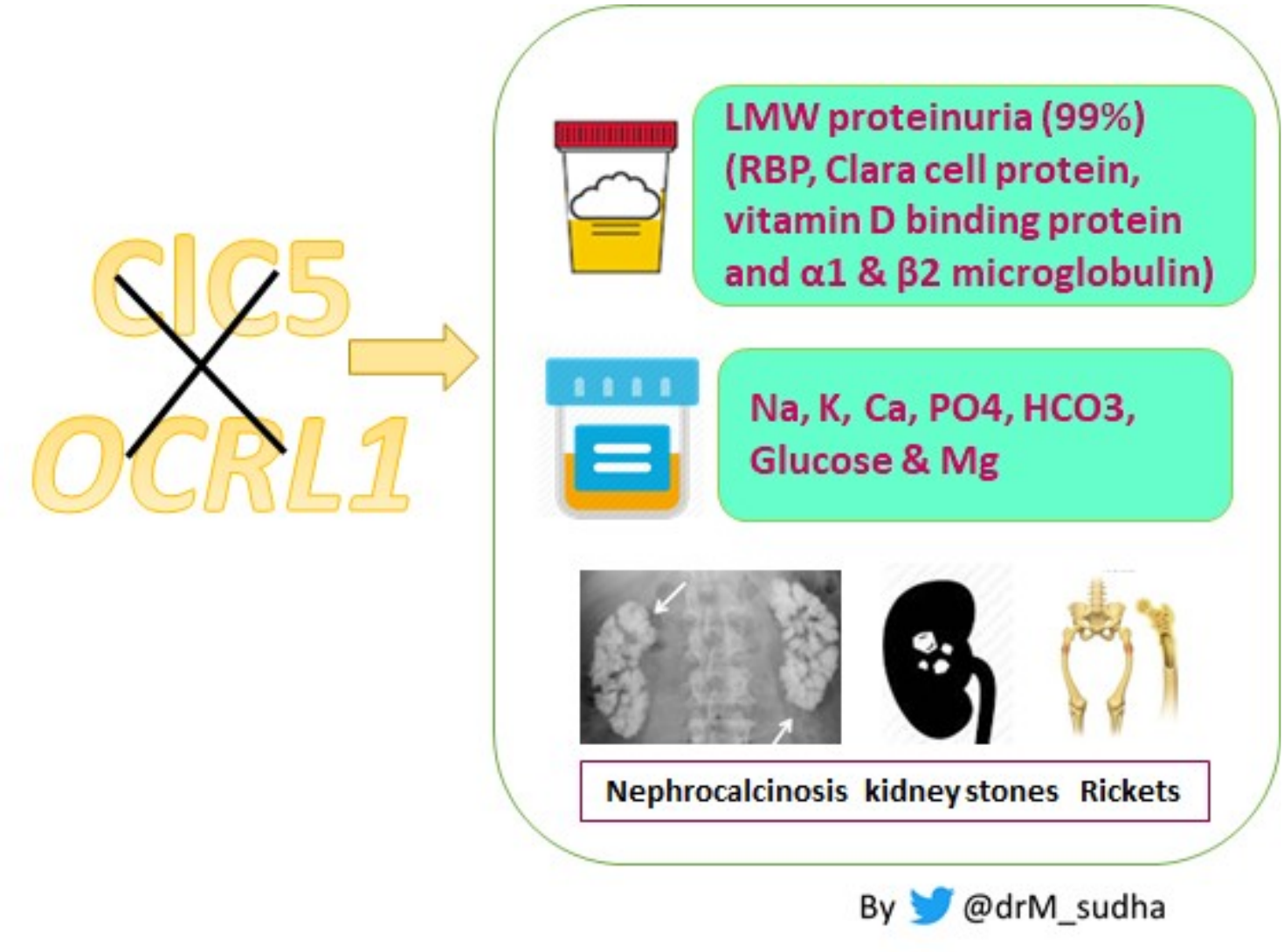
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964617/

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/



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

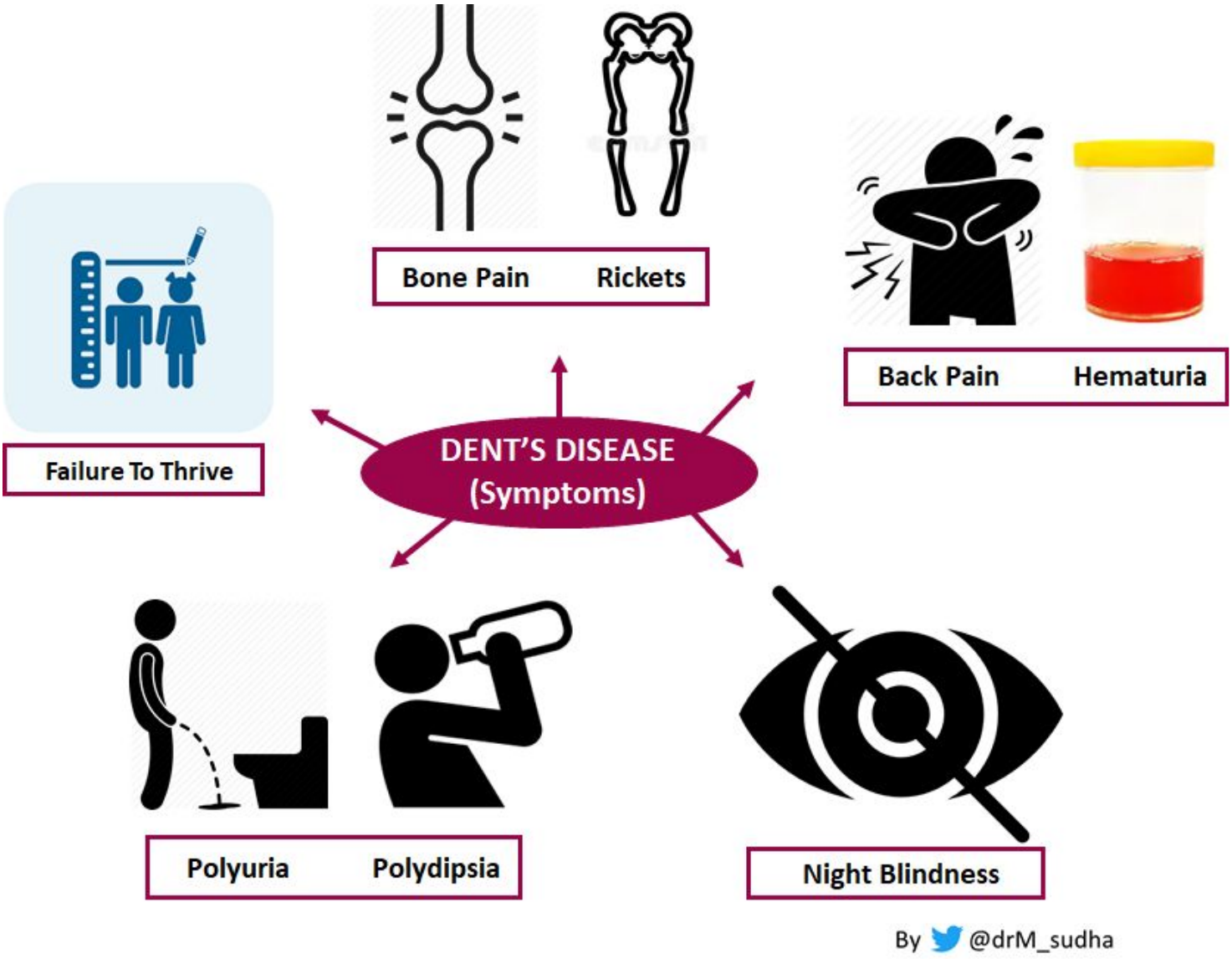
⚡Failure to thrive-early childhood

⚡Polyuria & polydipsia

⚡bone pain & difficulty in walking (rickets)

⚡abdominal pain and hematuria (kidney stones)

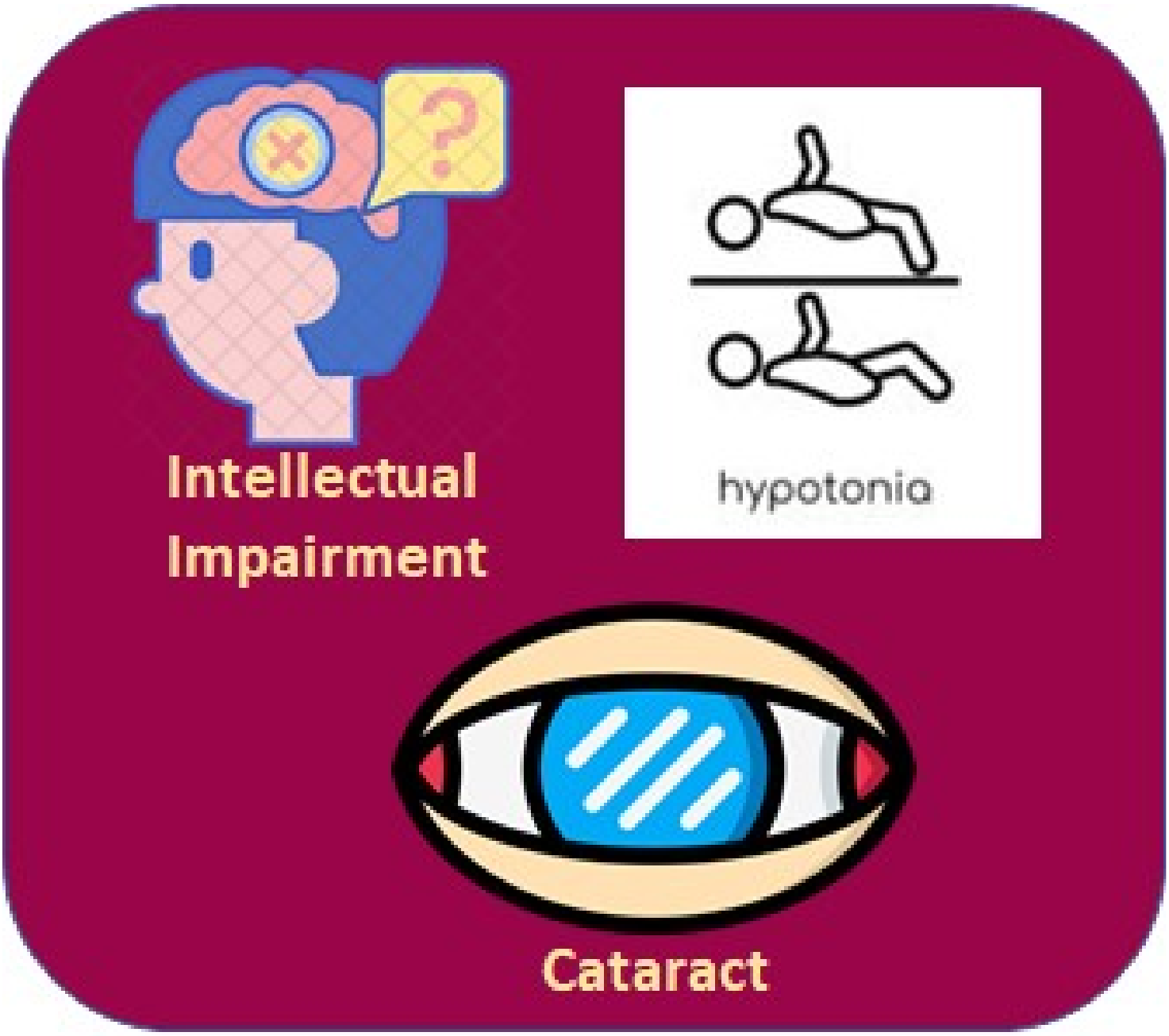
⚡episodic night blindness (loss of RBP)



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% ♂

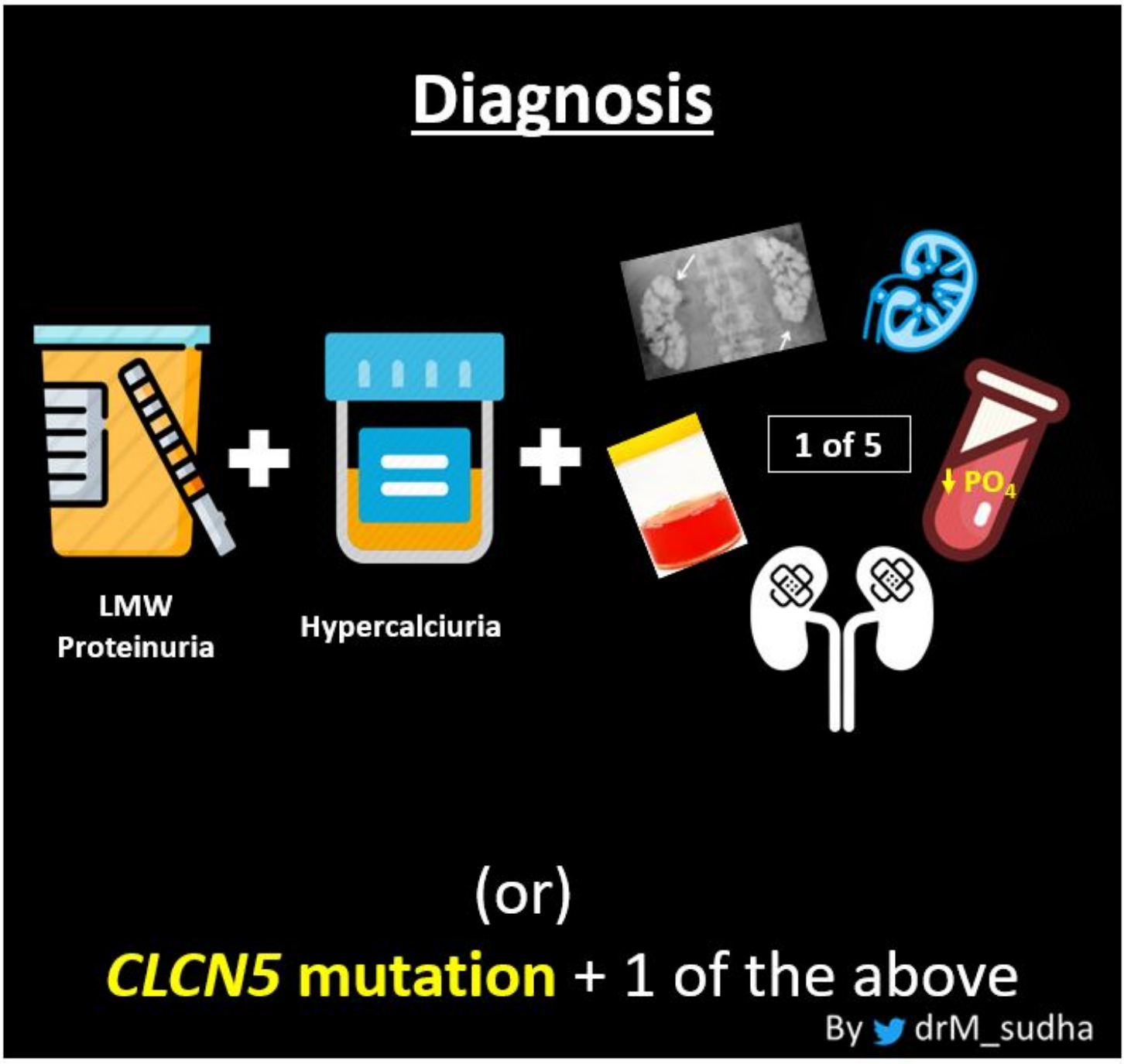
⚡nephrocalcinosis ~75% ♂

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



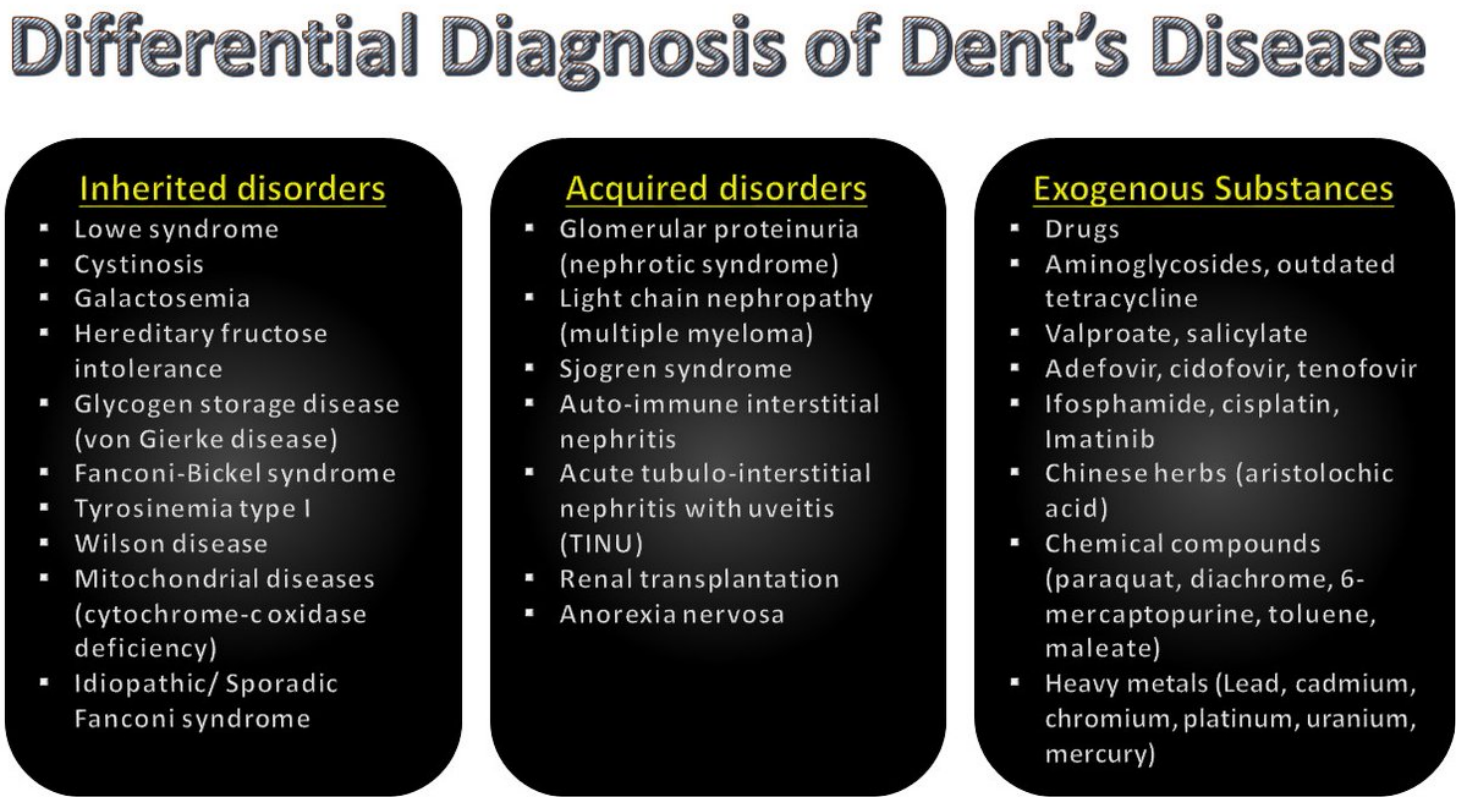
Confirmation:
⚡Molecular genetic testing-mutational analysis of CLCN5 and/or OCRL1

👇
📌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



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♂️⚡

My favorite Part- The Summary

Until Next time…#ASPNeph #NSMC #podkopiluwak