ERKNet
The European
Rare Kidney Disease
Reference Network

european
society for
paediatric
nephrology

WELCOME TO

ESPN/ERKNet
Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: 15 June 2021

Topic: Dent‘s Disease

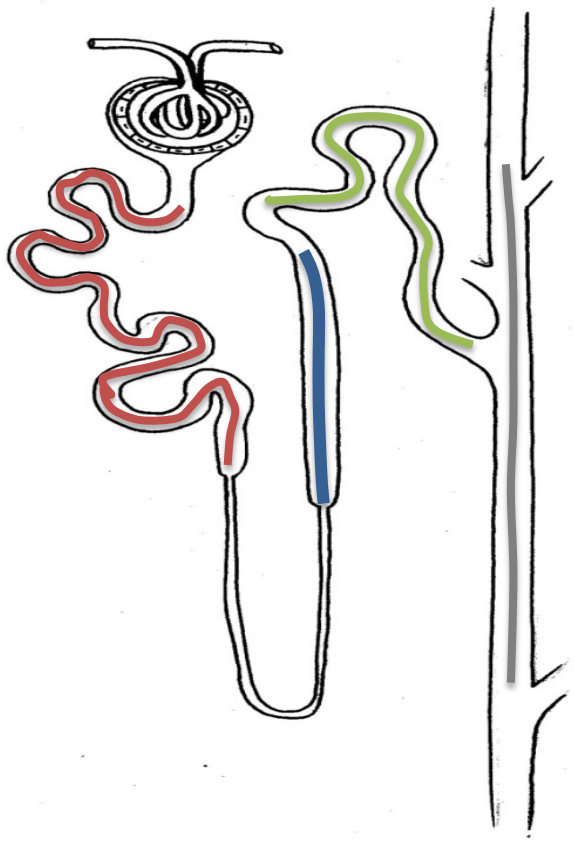
Speaker: Rosa Vargas Poussou

Moderator: Tom Nijenhuis

Dent Disease – Proximal Tubulopathy

Proximal Tubule
Reabsorption:
H_20 60-70%
Na^+ 60-70%
Ca^{2+} 60%
$HCO3^-$ 80%
$PO4^-$ 80%
Amino acids
Glucose
Low molecular weight proteins (LMWP)
Urate and citrate

TAL Loop of Henle
Reabsorption:
Mg^{2+} 70%
Na^+ 20-25%
Ca^{2+} 25-30%

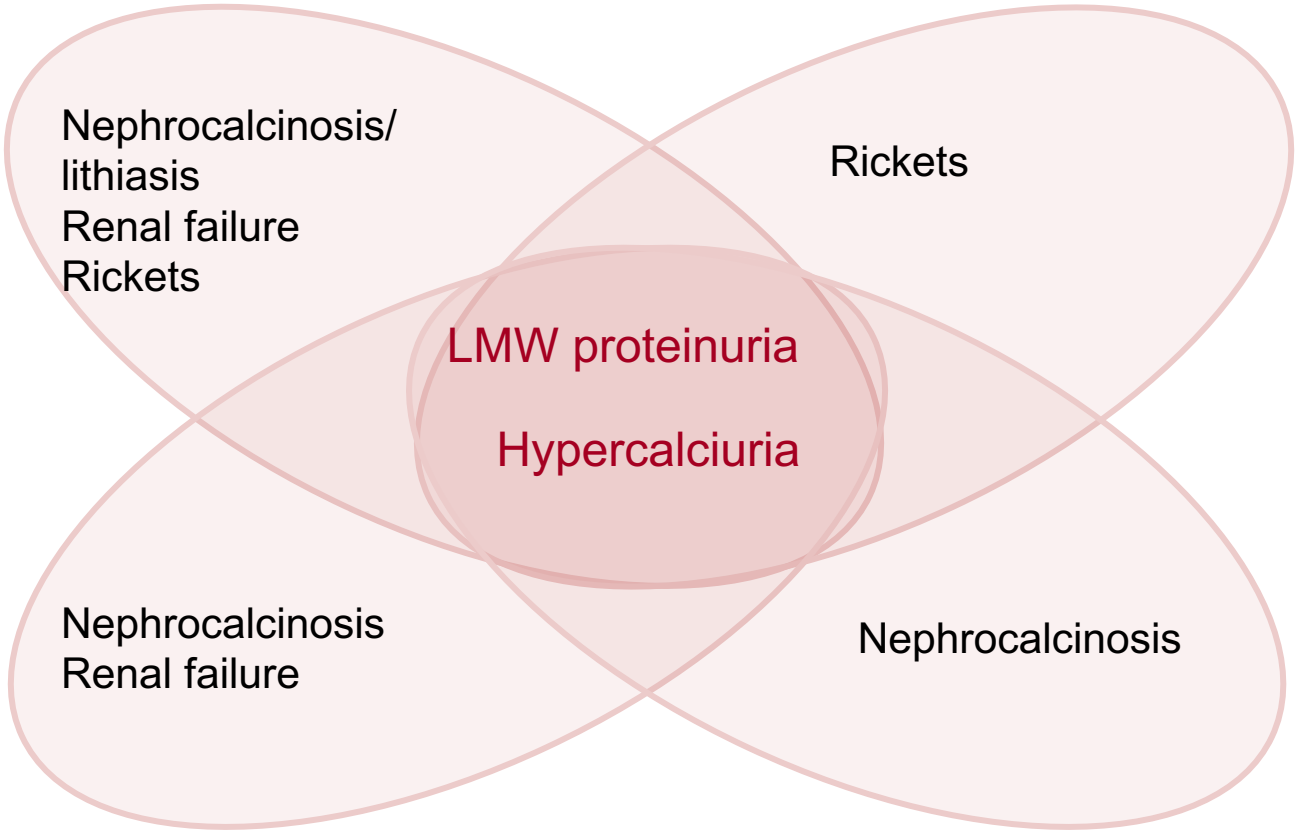


Distal convoluted tubule
Reabsorption:
Na^+ 7%
Ca^{2+} and Mg^{2+} 10%

Collecting duct
Reabsorption:
Na^+ 2%
H_2O
Secretion:
H^+ and K^+

Dent disease

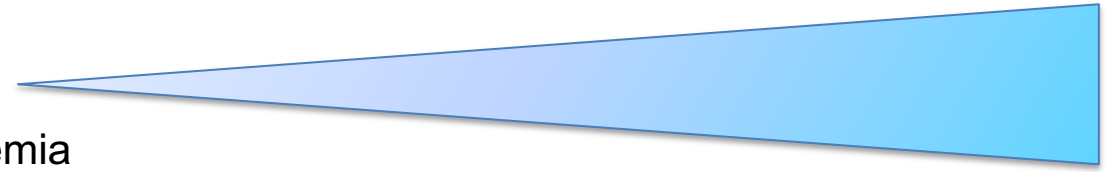
X-linked recessive nephrolithiasis



X-linked hypophosphataemic rickets

Idiopathic tubular proteinuria

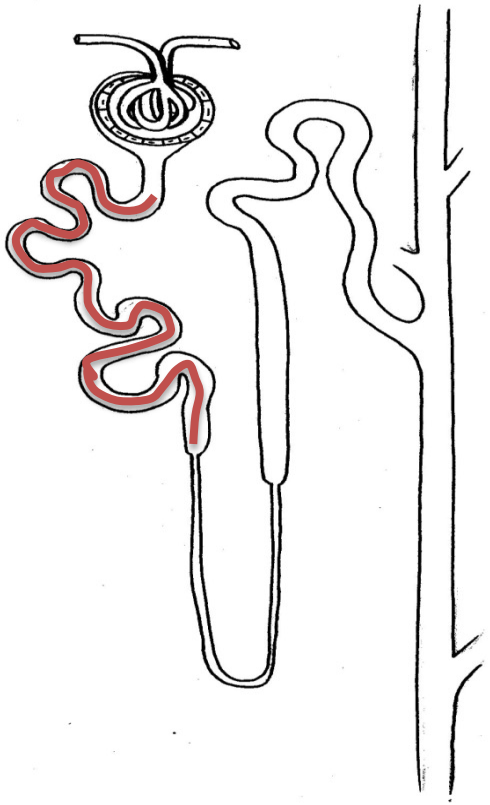
Glycosuria
Aminoaciduria
Proximal acidosis
Renal hypophosphataemia

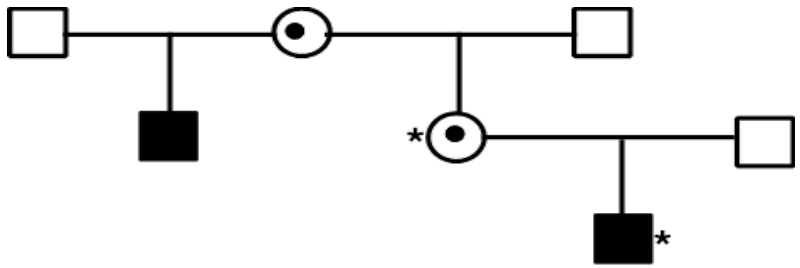


Partial Fanconi 70%

De de Toni Debré Fanconi Syndrome 10%

Dent disease – Genetically heterogeneous





Recessive X-linked

Dent disease – 1
Molecular bases: 1996
CLCN5 gene, Xp11.22
Protein ClC-5

50 – 60%

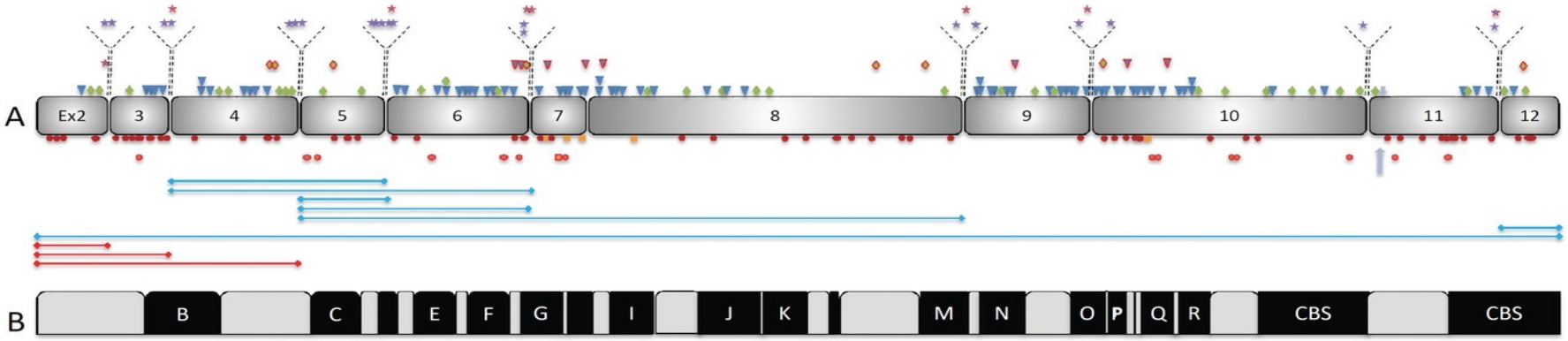
Dent disease – 2
Molecular bases: 2005
OCRL gene, Xq24.26
Protein OCRL

15%

?

25 – 35%

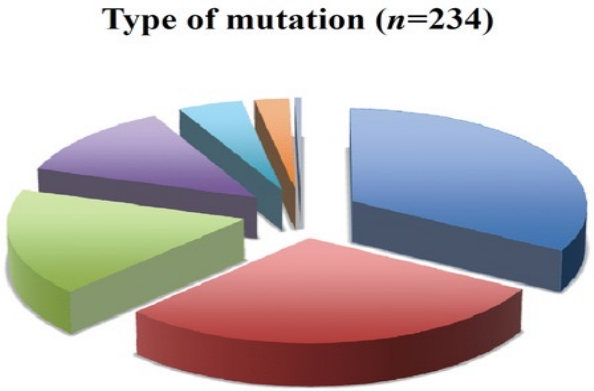
Mutation Update of the *CLCN5* Gene Responsible for Dent Disease 1

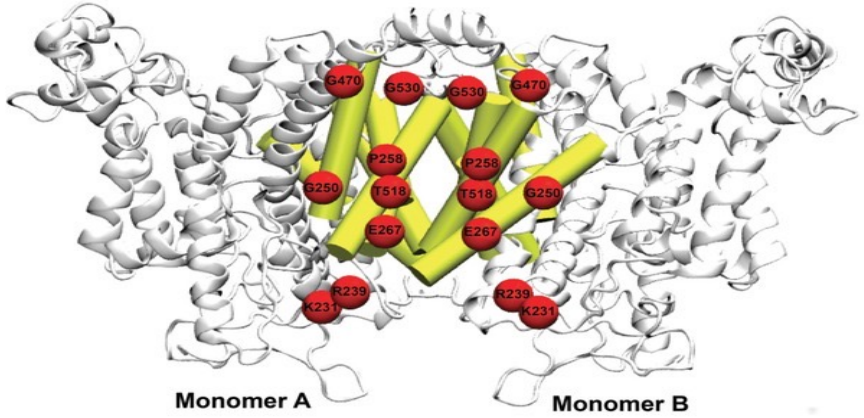


Protein: ClC-5
746-amino acid
electrogenic $2Cl^-/H^+$
exchanger

C

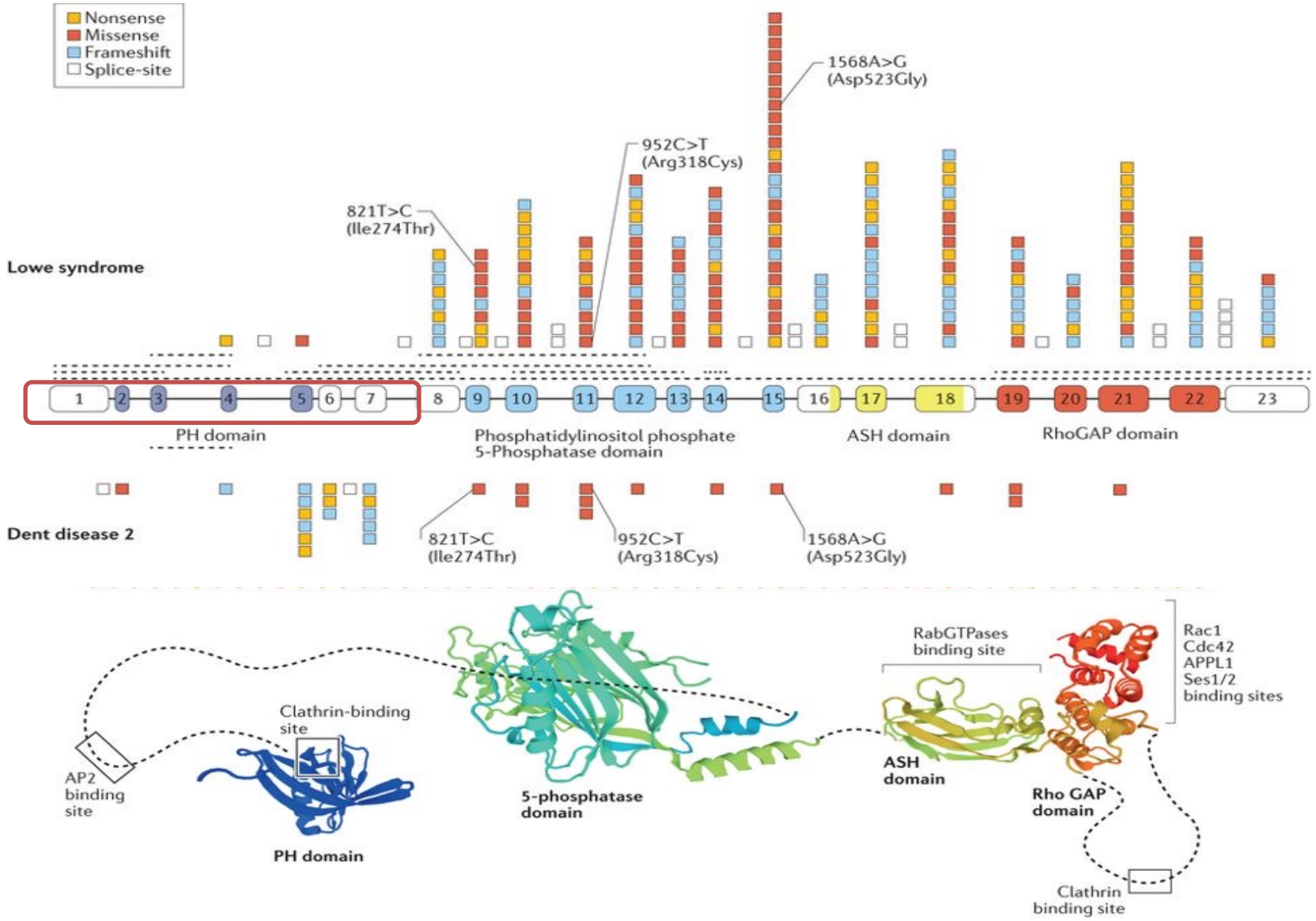
- Missense (33.33%)
- Frameshift (29.05%)
- Nonsense (17.52%)
- Splicing (12.39%)
- Large deletion (4.70%)
- Inframe (2.56%)
- Other (Alu insertion) (0.42%)
- Novel mutations





Mansour-Hendili et al. *Human Mutation* 2015

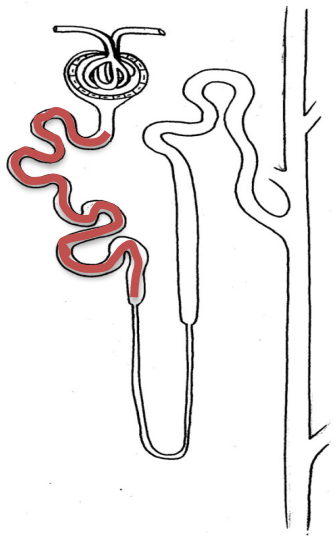
OCRL gene and protein

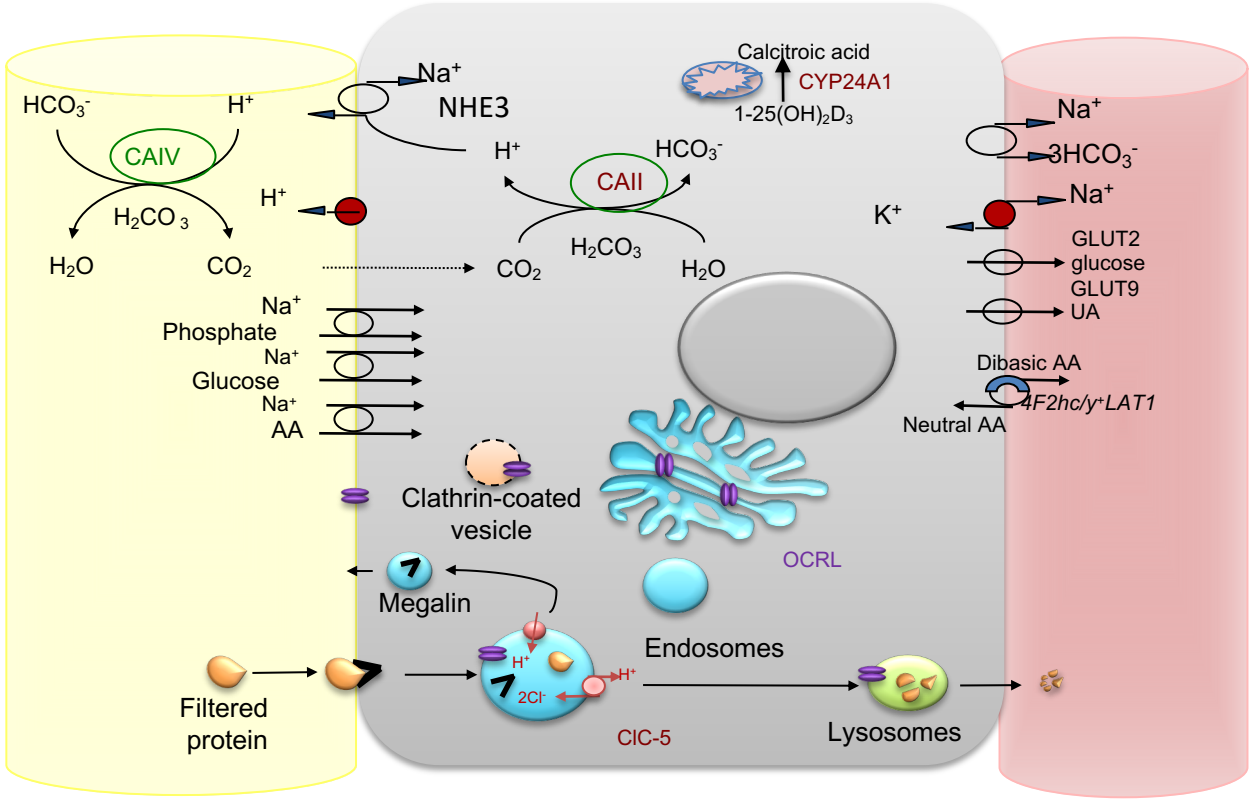


inositol polyphosphate-5-phosphatase

De Matteis MA et al. The 5-phosphatase OCRL in Lowe syndrome and Dent disease 2. *Nat Rev Nephrol* 2017

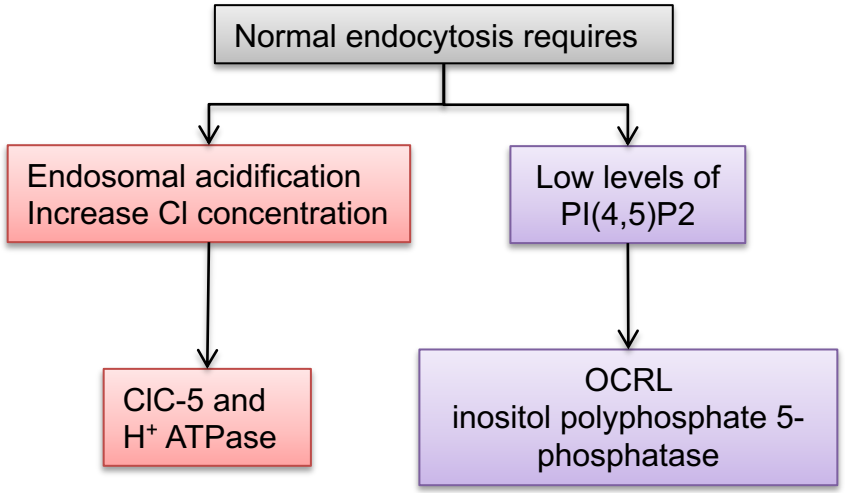
Proximal Cell

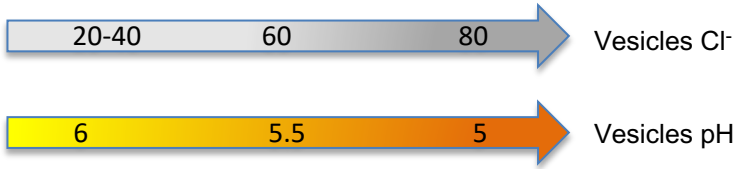


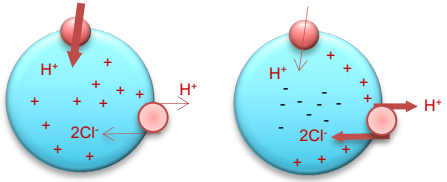


Reabsorption

Na^+ 60-70 %
Ca^{2+} 60%
HCO_3^- 80%
PO_4^- 80%
Glucose
Amino acids
LMWP
Uric acid and citrate
Ammonia production





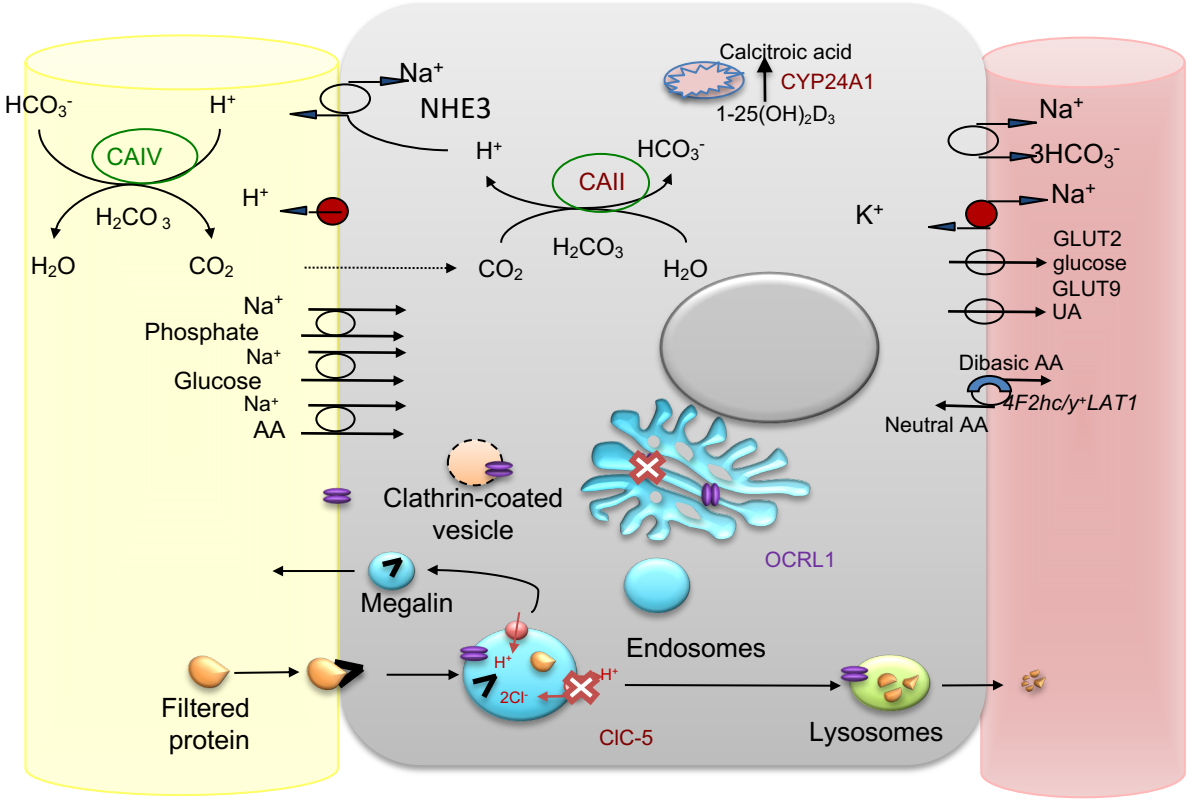


$PI(4,5)P_2$

↓

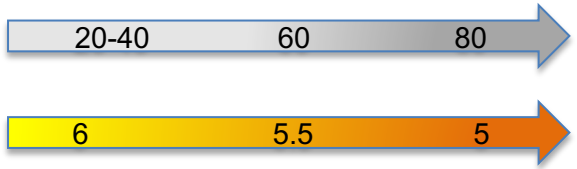
PI(4)P

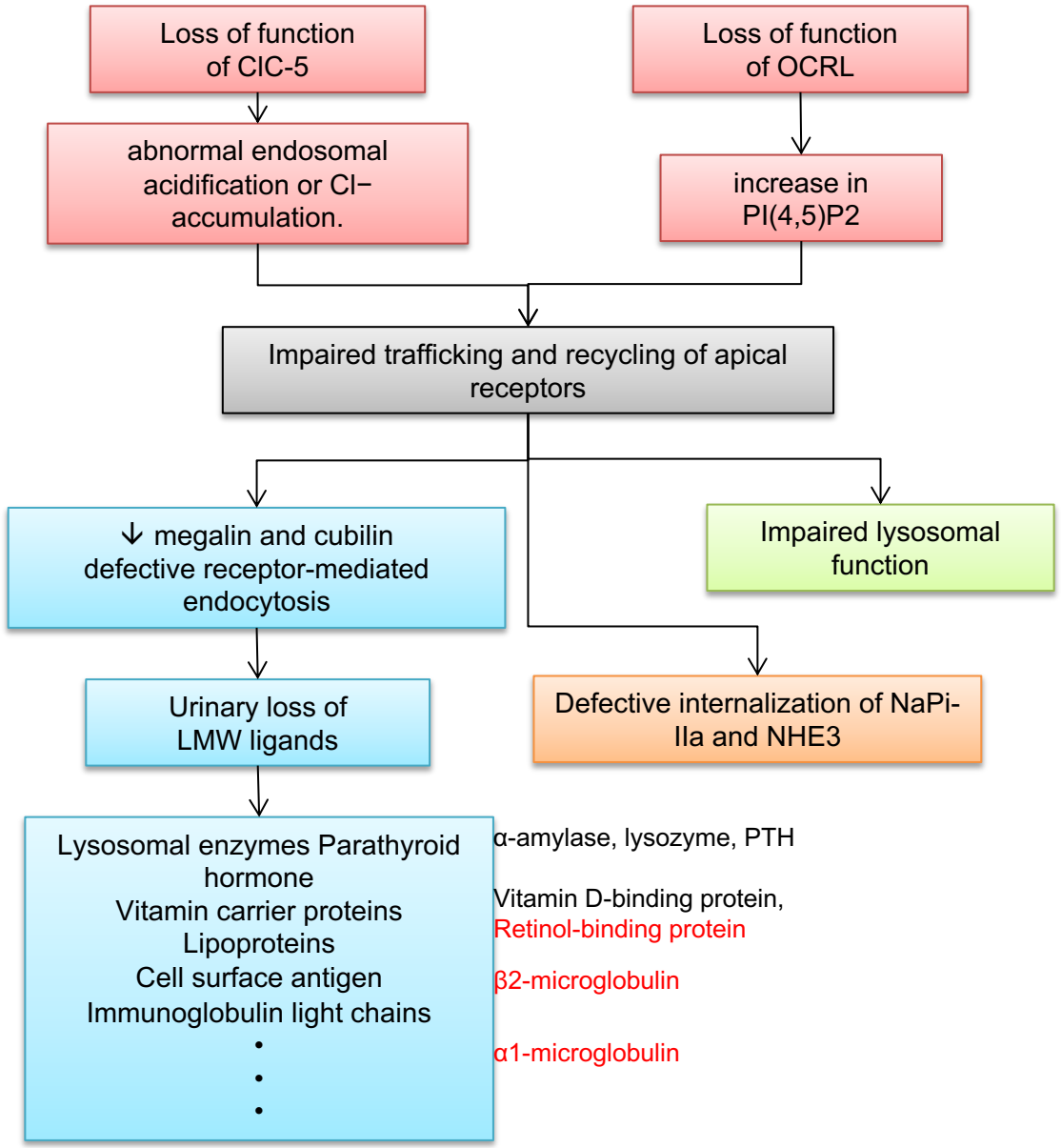
Dent disease - Pathophysiology



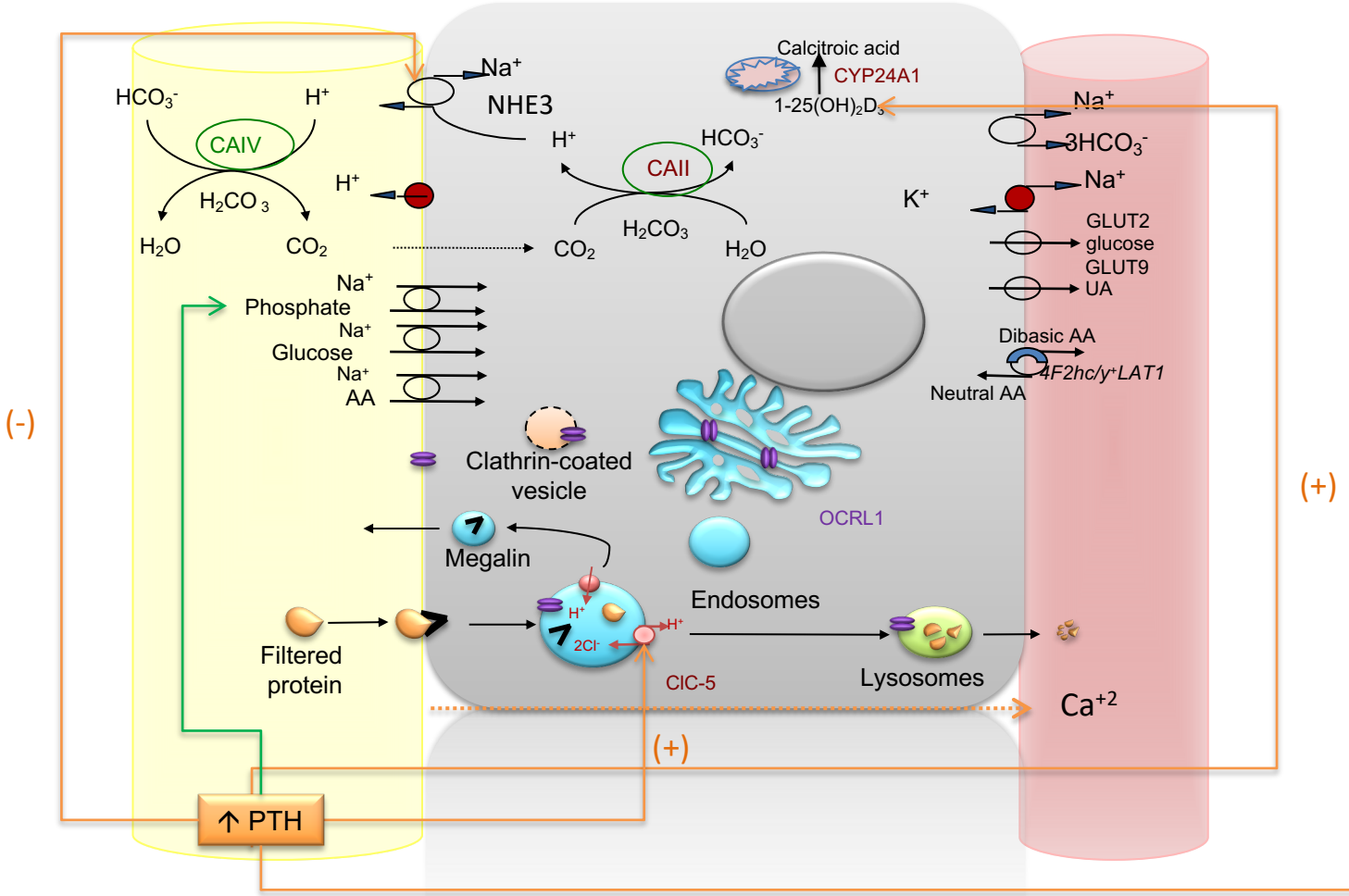
Reabsorption

Na$^+$ 60-70 %
Ca^{2+} 60%
HCO$_3^-$ 80%
PO$_4^-$ 80%
Glucose
Amino acids
LMWP
Uric acid and citrate
Ammonia production





Dent disease - Pathophysiology



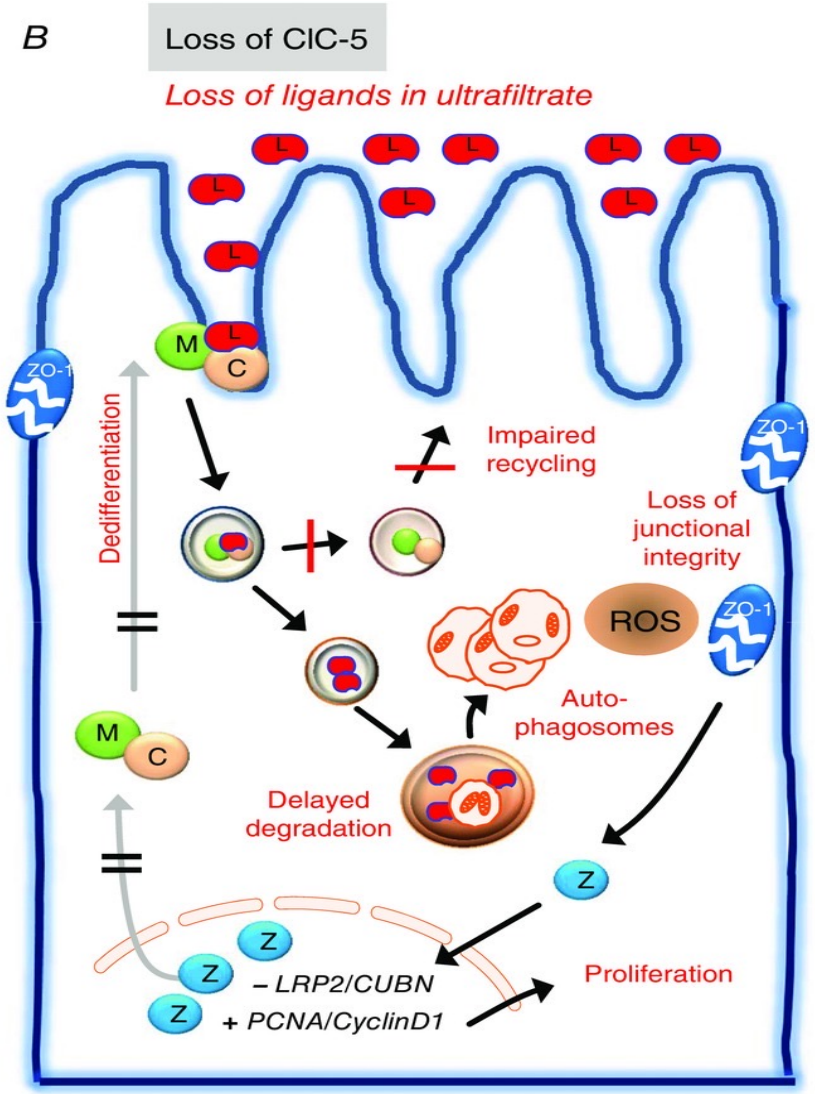
↑ 1-α-hydroxylase mRNA
↑ 1,25(OH)2D levels
↑ intestinal calcium absorption

↓ apical uptake of 25(OH)D

↑ calcium transcellular reabsorption in DCT

Gene expression in KO models
Urinary proteome of patients
with Dent disease 1

Increased expression:
proliferation markers
oxidative scavengers
interstitial matrix remodeling



Wright J, et al., Physiol Genomics 2008
Gailly P, Luciani A, Kidney Int 2008
Santucci L, et al., J Proteome 2016

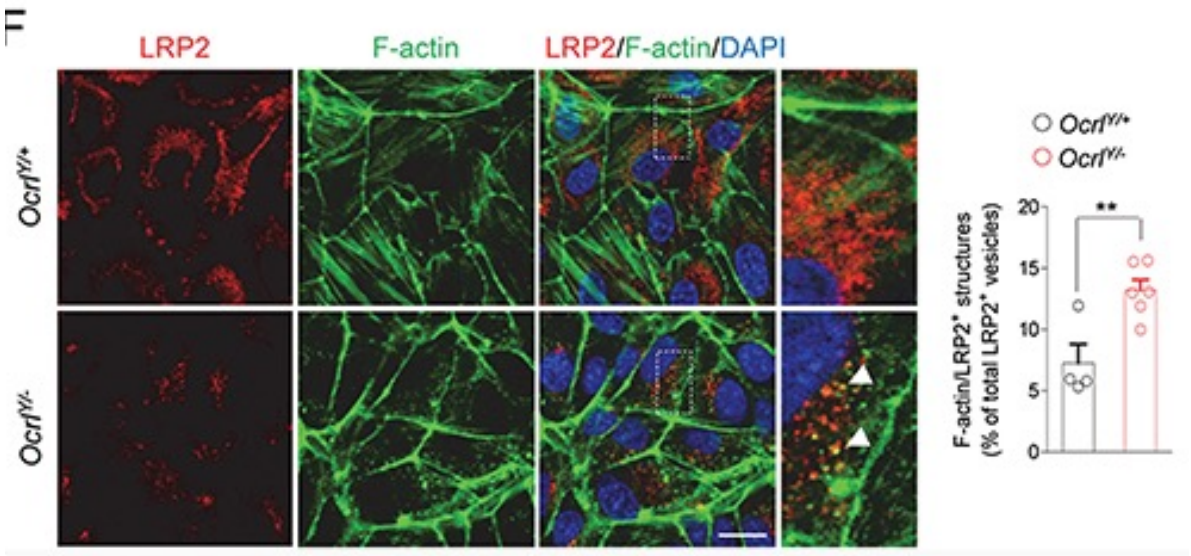
Devuyst O, Luciani A, J Physiol 2015

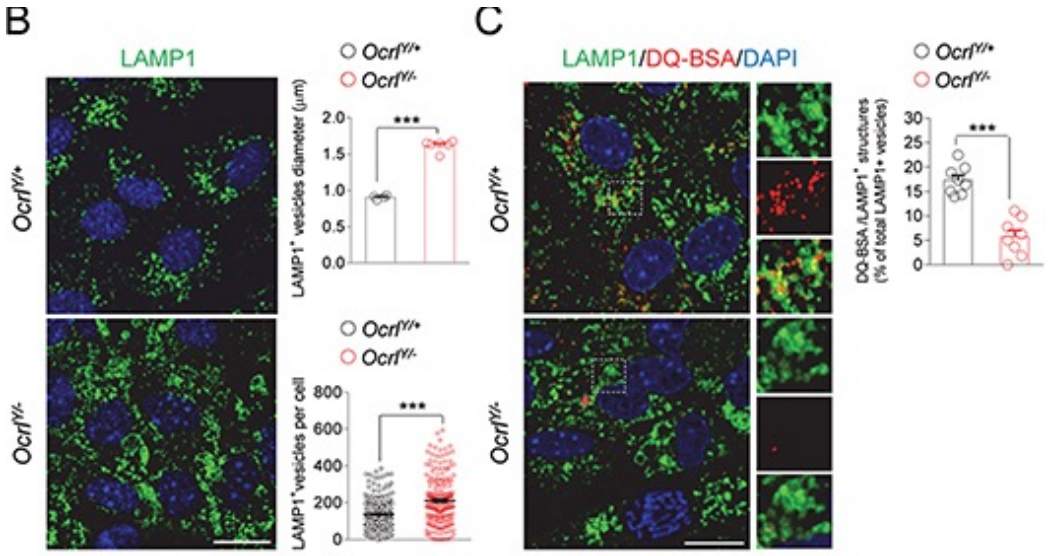
Dent 2 and Lowe
Humanized mouse model

Accumulation of PI(4,5)P2
in endolysosomes

Local hyper-polymerization of F-actin;
impaired trafficking of the endocytic
LRP2 receptor

Disruption of the
lysosomal dynamic





Festa BP et al., Human Mol Genet 2019

Dent disease – Clinical presentation

	Dent 1	Dent 2
	(n=108)	(n=9)
Age at diagnosis median [IQR].	11 [5; 21]	6 [3; 8]
LMWP	93/93 (100%)	7/7 (100%)
Hypercalciuria	81/88 (92%)	3/3 (100%)
Nephrolithiasis	24/74 (32%)	1/6 (17%)
Nephrocalcinosis	44/104 (42%)	1/9 (11%)
Aminoaciduria	16/32 (50%)	4/5 (80%)
Renal hypouricemia	19/30 (63%)	1/1
Hypokalemia	31/70 (44%)	1/4 (25%)
Glycosuria	26/58 (45%)	0/6 (0%)
Acidosis	9/54 (17%)	2/8 (25%)
Incomplete Fanconi*	51/70 (73%)	5/9 (55%)
Complete Fanconi**	8/70 (11%)	1/9 (11%)
Rickets	14/75 (19%)	1/7 (14%)
Failure to thrive	12/40 (30%)	4/6 (67%)

Blanchard A et al. Observations of a large Dent disease cohort Kidney Int 2016

Dent 1	Dent 2
(n = 377) global literature	(n=17)
9 [5-16] (n=311)	5.95 [5; 10]
365/365 (100%)	17/17 (100%)
287/359 (80%)	12/17 (67%)
232/354 (65.5%)	6/17 (33%)
	9/17 (50%)
45/93 (48%)	4/17 (22%)
--	- -
22/60 (37%)	1/17 (5.5%)
27/105 (26%)	4/17 (22%)
6/66 (9%)	3/17 (17%)
--	--
--	0
53/247 (21%)	0
--	9/17 (50%)

Mansour-Hendili Muman Mut 2015 - Zaniew M et al. NDT 2016

Dent disease – Clinical presentation - Asia

	Sekine T. et al. *NDT* 2014		Sakakibara N et al. *PN* 2020		Ye Q et al. *Clin Genet* 2019	
	Dent 1	Dent 2	Dent 1	Dent 2	Dent 1	Dent 2
	(n=61)	(n=11)	(n=72)	(n=13)	(n=32)	(n=13)
Age at diagnosis median [IQR].			5 [3; 9]	3 [1.5; 5.5]	4 (0.58 - 12)	2 (0.17 - 10)
LMWP	61/61 (100%)	11/11 (100%)	72/72 (100%)	13/13(100%)	32/32 (100%)	13/13(100%)
Hypercalciuria	25/54 (46%)	7/10 (70%)	24/62 (39%)	7/10 (70%)	21/32 (66%)	12/13 (92%)
Nephrolithiasis					3/32 (9.4%)	2/13 (15%)
Nephrocalcinosis	20/53 (38%)	1/10 (10%)	14/63 (22%)	1/9 (11%)	14/32 (44%)	3/13 (23%)
Aminoaciduria	No	No				
Hypokalemia			No	No		
Glycosuria	No	No	2/68 (3%)	0/13 (0%)		
Acidosis	No	No	0/65 (0%)	0/13 (0%)		
Incomplete Fanconi*	No	No	No	No		
Complete Fanconi**	No	No	No	No		
Rickets	0/61 (0%)	1/11 (2%)	No	No	3/32 (9.4%)	2/13 (15%)

Dent disease – Clinical presentation- Global 1

Phenotype	DD1 (*n* = 772)	DD2[a] (*n* = 143)	Chi-squared test (*p* value)
Age at diagnosis (years, range)	0.2–66	0.1–30.5	
Proteinuria	136/148 (92)	39/39 (100)	0.141
LMWP	719/720 (100)	134/134 (100)	1.000
Nephrotic range proteinuria	55/149 (37)	20/42 (48)	0.282
Hypercalciuria	556/686 (81)	104/122 (85)	0.323
Hematuria	88/145 (61)	16/32 (50)	0.361
Aminoaciduria	84/178 (47)	30/72 (42)	0.513
Hyperuricosuria	10/26 (38)	–	
Glycosuria	84/376 (22)	11/113 (10)	0.005
Hyperphosphaturia	62/228 (27)	9/46 (20)	0.372
Hypouricemia	25/62 (40)	3/5 (60)	0.699
Hypophosphatemia	78/240 (33)	5/49 (10)	0.003
Hypokalemia	80/257 (31)	6/56 (11)	0.003
Hypomagnesemia	7/36 (19)	1/19 (5)	0.309
Incomplete Fanconi syndrome	62/93 (67)	10/14 (71)	0.961
Complete Fanconi syndrome	8/154 (5)	1/38 (3)	0.810
Renal failure	159/565 (28)	39/89 (44)	0.004

Gianesello L, et al. Hum Genet. 2021

Dent disease – Clinical presentation- Global 2

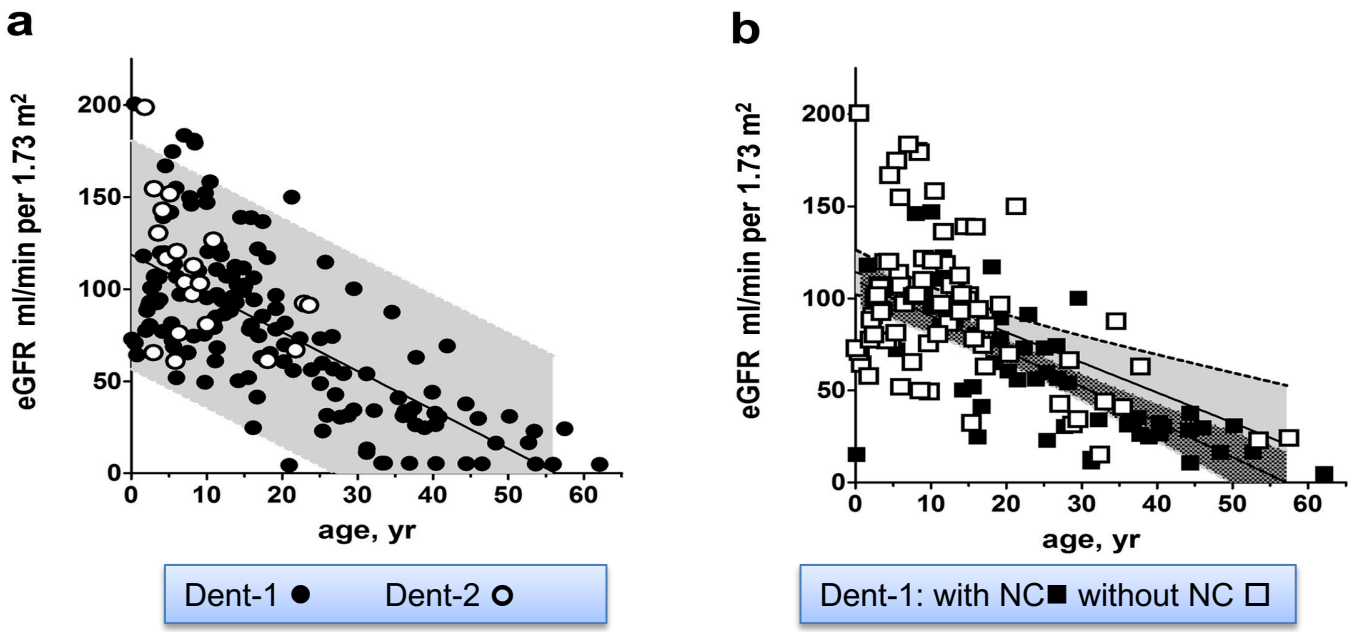
Phenotype	DD1 (*n* = 772)	DD2[a] (*n* = 143)	Chi-squared test (*p* value)
Metabolic alkalosis	3/24 (13)	1/10 (10)	1.000
Metabolic acidosis	25/321 (8)	6/87 (7)	0.960
Nephrocalcinosis	366/664 (55)	32/127 (25)	0.000
Failure to thrive	33/122 (27)	27/50 (54)	0.001
Nephrolithiasis	95/388 (24)	9/66 (14)	0.000
Bone disorders	85/449 (19)	8/67 (12)	0.223
Neurological symptoms	–	4/16 (25)	
Intellectual disability	7/76 (9)	13/53 (25)	0.037
Cataract	1/9 (11)	8/87 (9)	1.000
Hypotonia	–	1/18 (5)	
Behavioral alterations	–	0/20(0)	

Gianesello L, et al. Hum Genet. 2021

Park et al. 2014; Sakakibara et al. 2020		↑ serum CPK and LDH	
Sethi et al. 2009; Becker-Cohen et al. 2012	Night blindness		

Dent disease – Evolution

Progression to ESRF: 3rd and 5th decades of life in 30–80% of affected males

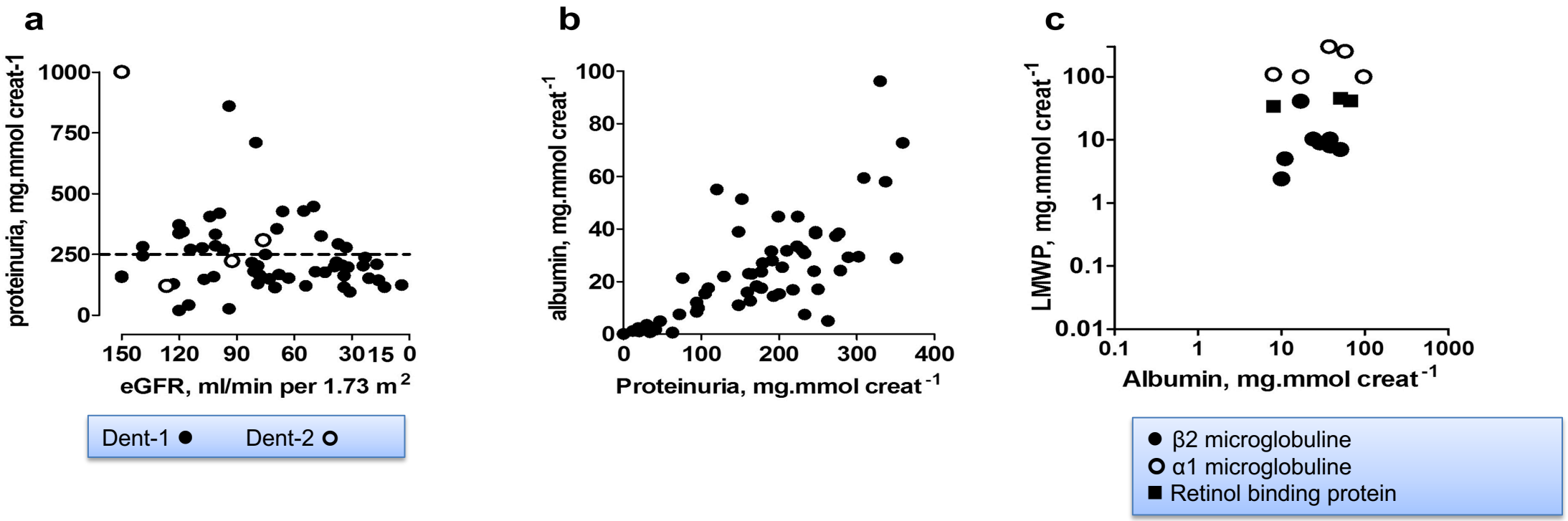


	Predicted age to reach the stage (mean [95% confidence interval]	
	Linear mixed effect model (eGFR)	Continuous-time hidden Markov model
CKD2 (60<eGFR ≤ 90 mL/min/1,73 m²)	18.4 [17.4;19.3]	14.3 [9.4;21.8]
CKD3 (30<eGFR ≤ 60 mL/min/1,73 m²)	32.8 [31.5;34.1]	25.0 [19.5 ; 33.2]
CKD4 (15<eGFR ≤ 30 mL/min/1,73 m²)	47.2 [45.2; 49.4]	47.0 [35.7; 65.6]
CKD5 (eGFR ≤ 15 mL/min/1,73 m²)	54.4 [52.0;57.0]	53.1 [41.0;72.5]

Blanchard A et al. Observations of a large Dent disease cohort Kidney Int 2016

Dent disease – Evolution 2

Proteinuria



Blanchard A et al. Observations of a large Dent disease cohort Kidney Int 2016

Renal Biopsy - Dent disease

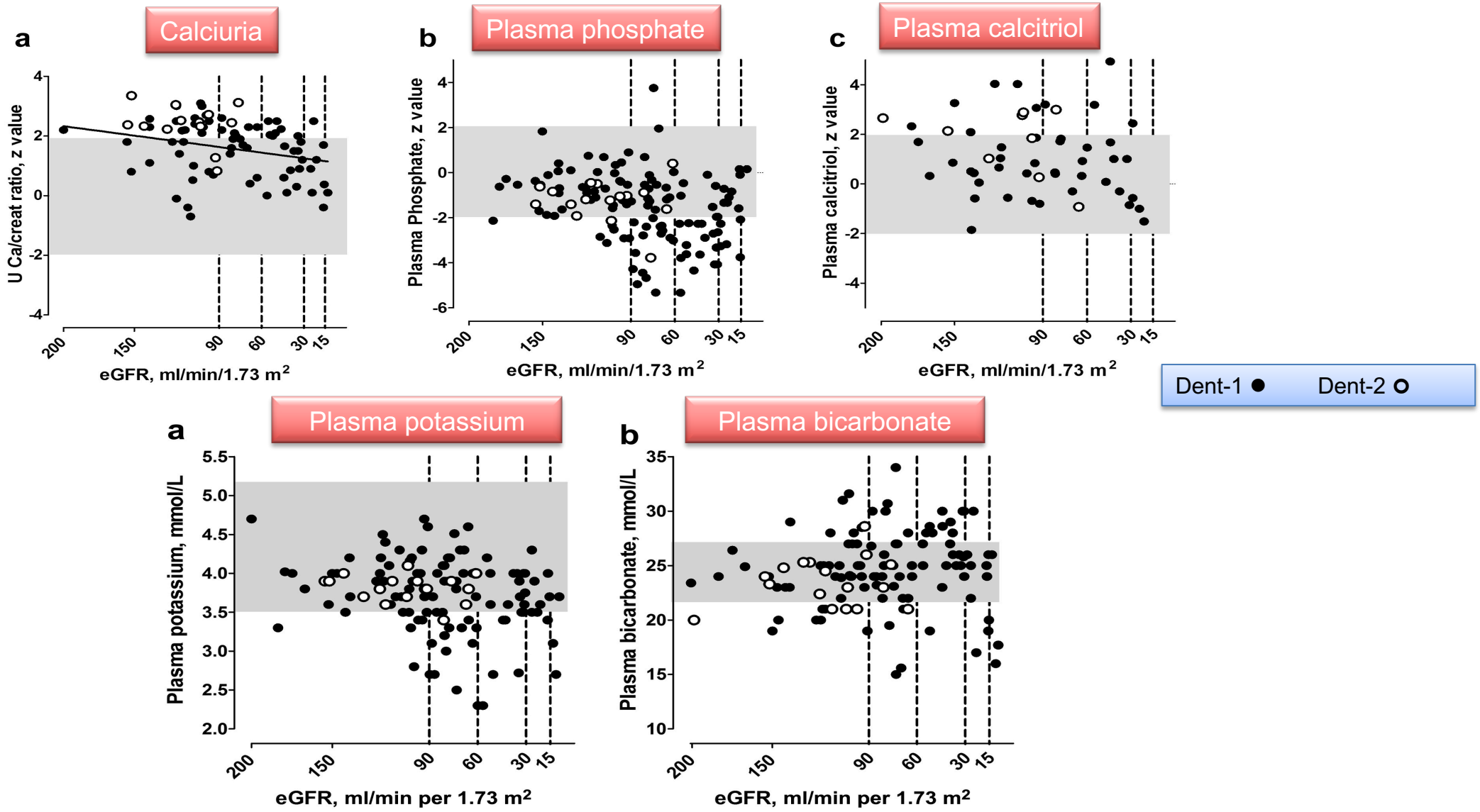
	DD1	DD2
Glomerular histology		
Normal	12/76 (16)	4/17 (24)
Unspecified sclerosis	18/76 (24)	–
FGGS	16/76 (21)	1/17 (6)
FSGS	15/76 (20)	3/17 (18)
Mesangial proliferation	17/76 (22)	7/17 (41)
Minor glomerular abnormalities	7/76 (9)	4/17 (24)
Periglomerular fibrosis	5/76 (7)	–
Expansion of mesangial matrix	3/76 (4)	1/17 (6)
Immature glomeruli	2/76 (3)	–
Adherence to Bowman capsule	1/76 (1)	1/17 (6)
Other (perihyliar hyalinosis, ECM hyperplasia, collapsed tuft, podocytes' hypertrophy)	4/76 (5)	–

	DD1	DD2
Tubular histology		
Normal	11/58 (19)	4/8 (50)
Tubular atrophy	17/58 (29)	1/8 (13)
Interstitial fibrosis	13/58 (22)	1/8 (13)
Calcification	10/58 (17)	–
Tubulointerstitial lesions	9/58 (16)	1/8 (13)
Calcium deposits	7/58 (12)	–
Intratubular proteinaceous casts	6/58 (10)	1/8 (13)
Interstitial inflammation	5/58 (9)	0/8 (0)
Nephrocalcinosis	4/58 (7)	
Vascular degeneration	3/58 (5)	–
Interstitial mononuclear cells infiltrate	2/58 (3)	–
Interstitial lymphocytes infiltrate	1/58 (2)	1/8 (13)
Acute tubular necrosis	–	1/8 (13)
Other (cortical fibrosis, interstitial chronic inflammation, chronic tubulointerstitial nephropathy with ischemic renal damage)	3/58 (5)	–

	DD1	DD2
Immunofluorescence		
Negative	16/19 (84)	2/2 (100)
IgM deposits	3/19 (16)	–
C3 deposits	1/19 (5)	–
Transmission electron microscopy		
Normal	5/27 (19)	–
Foot process effacement	18/27 (67)	2/2 (100)
Electrondense deposits	1/27 (4)	–
Irregular GBM folding	–	1/2 (50)
Other (mesangial proliferation, collapsed glomeruli, GBM thickness, global sclerosis)	4/27 (15)	–

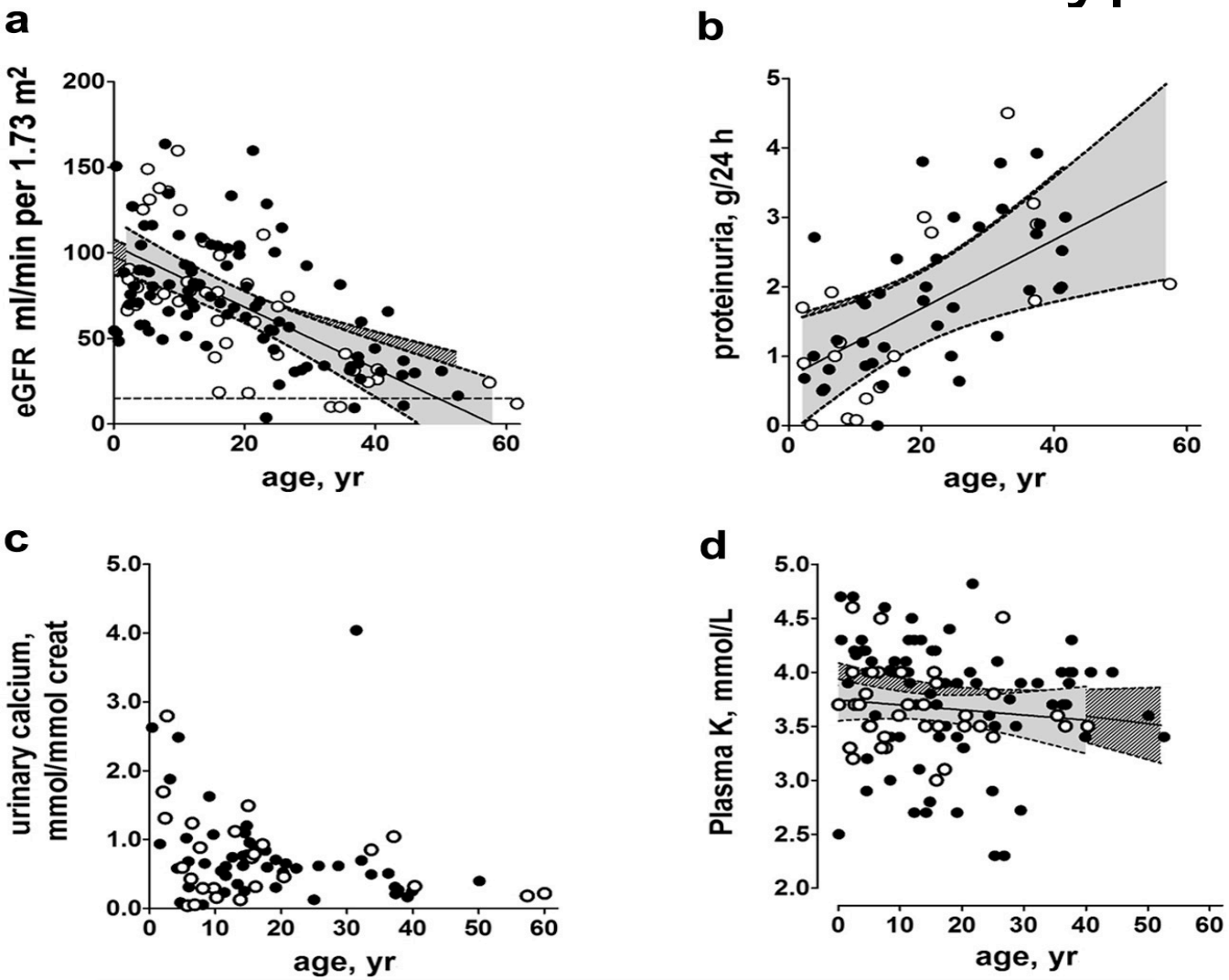
Gianesello G et al. Genetics and phenotypic heterogeneity of Dent disease: the dark side of the moon. *Human Genetics* 2020

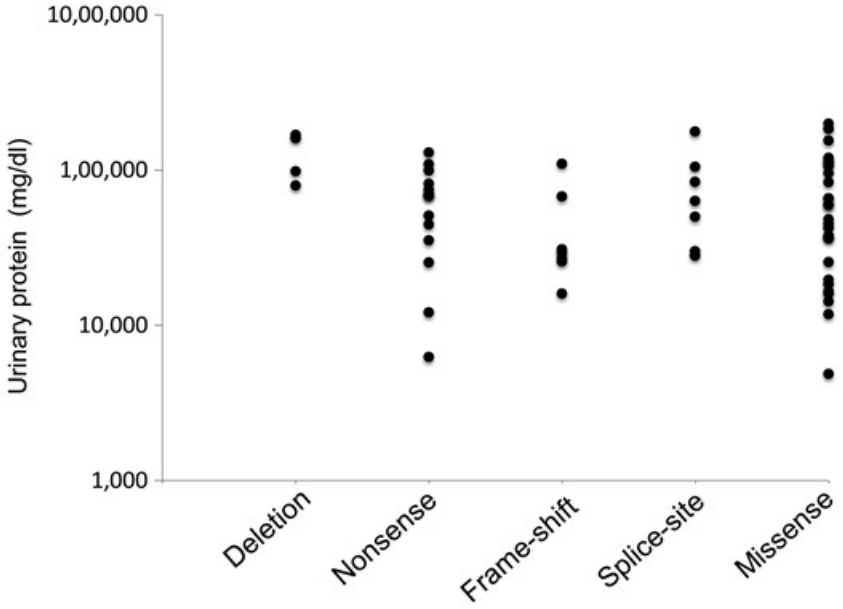
Dent disease – Evolution 3



Blanchard A et al. Observations of a large Dent disease cohort Kidney Int 2016

Dent-1 Phenotype/Genotype



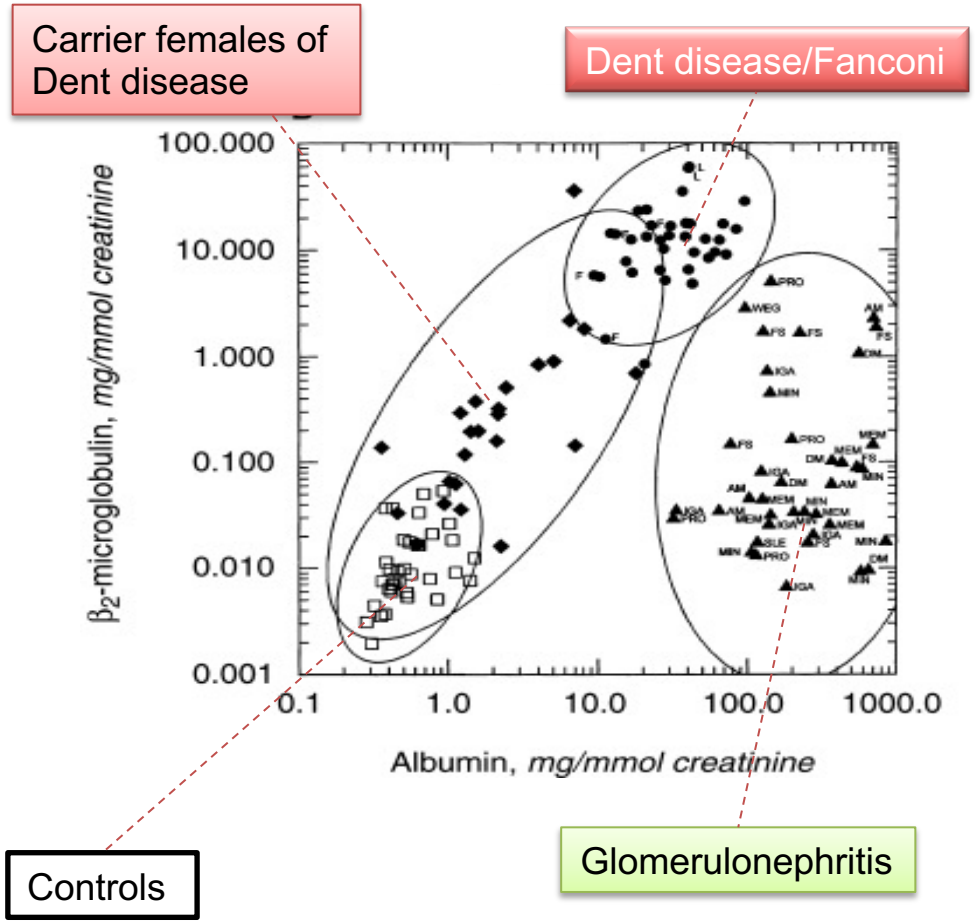


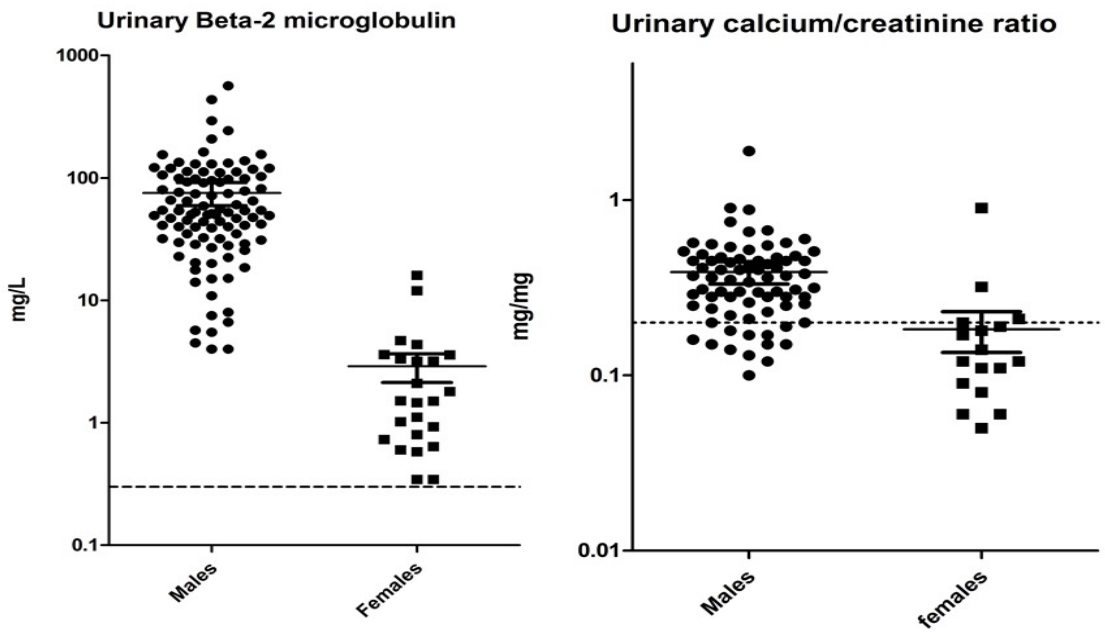
●Severe mutations (nonsense, frameshift, deletion, or splice-site)
○Moderate mutations (missense and in-frame)

Blanchard A et al. Observations of a large Dent disease cohort Kidney Int 2016

Sekine T et al. NDT 2014

Dent disease – Heterozygous females

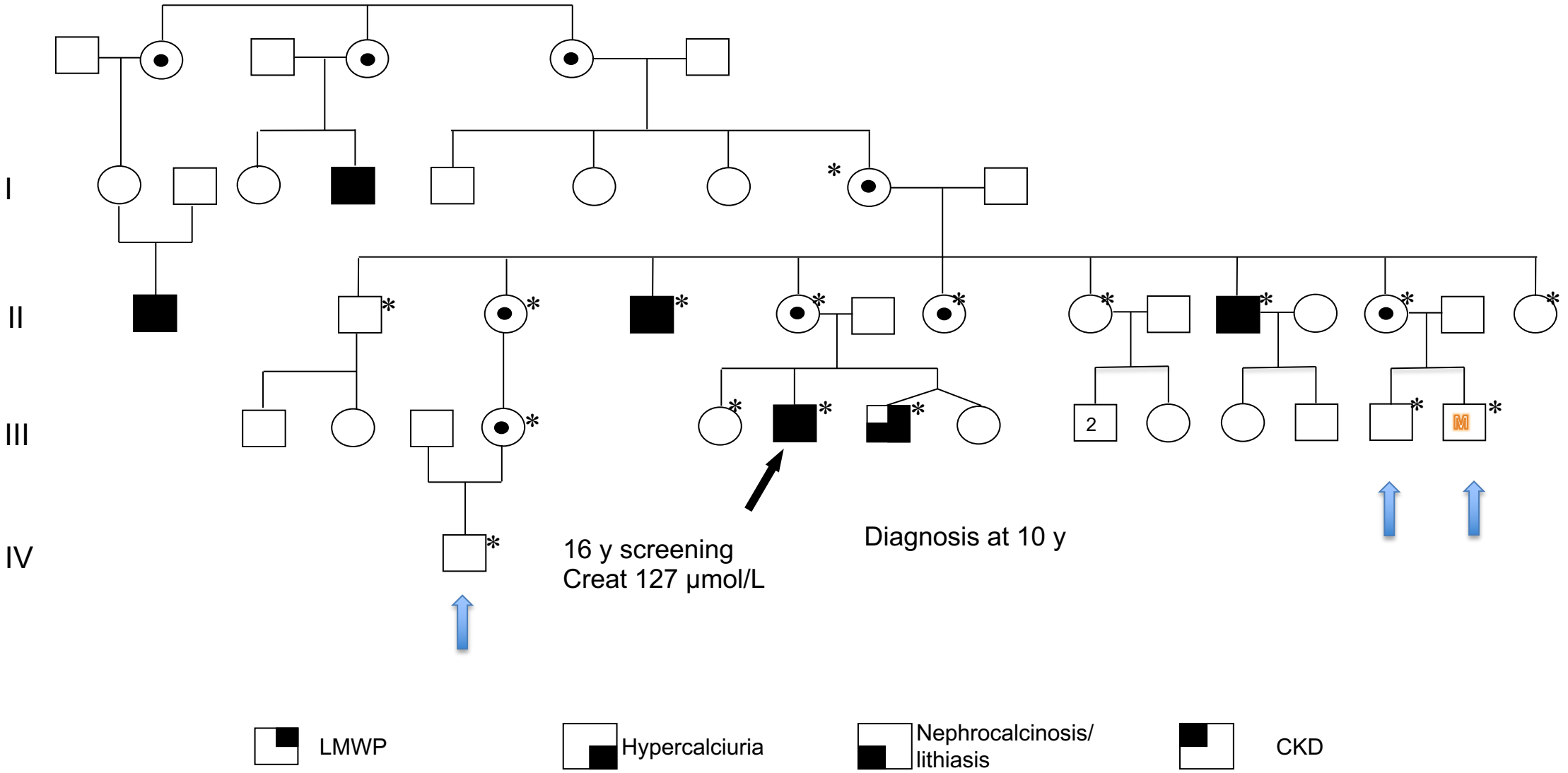




Norden A. et al. Kidney Int 2000

Mansour-Hendili L et al. Hum Mut 2015

CLCN5 mutation:
c.2079_2080insG, p.Thr694AspfsX48 htz



Mansour-Hendili et al. *Hum Mutat.* 2015;36:742-752

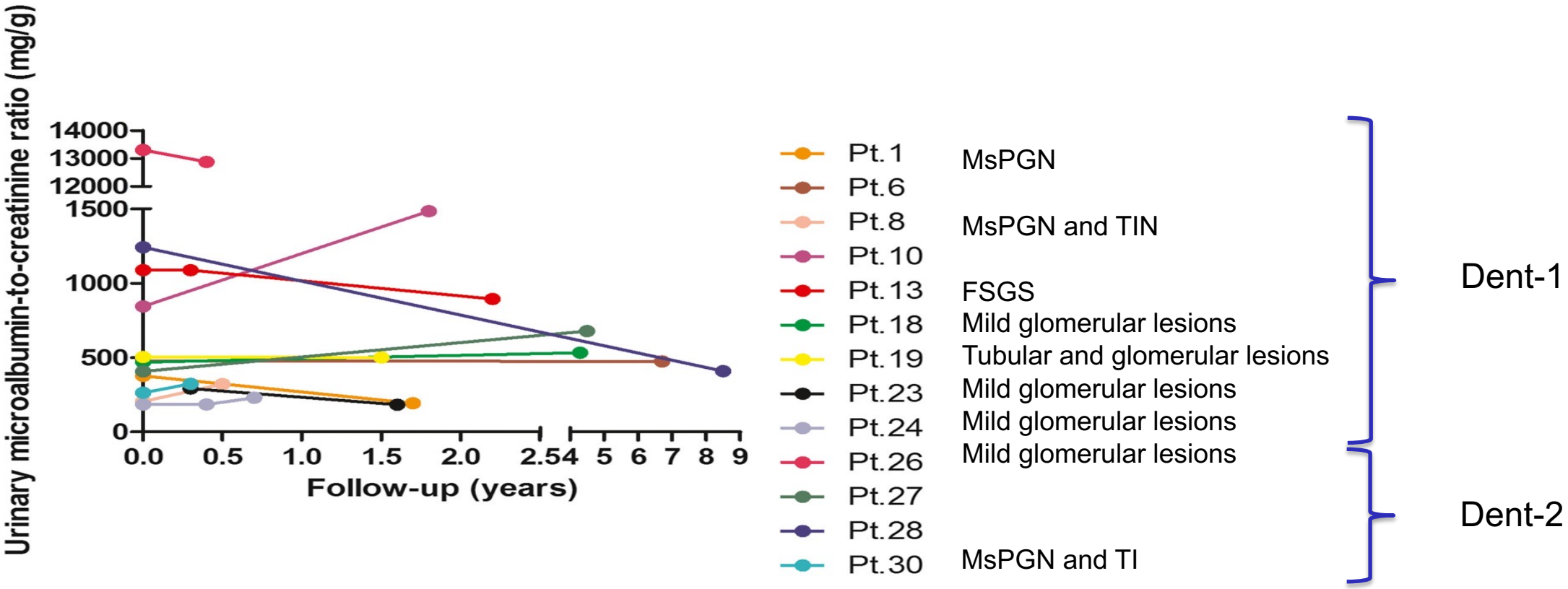
Differential diagnosis

- Genetic diseases
  - Other causes of Renal Fanconi syndrome
  - Distal renal tubular acidosis (transient proximal tubular anomalies)
  - Other causes of nephrocalcinosis (Bartter syndrome, Infantile hypercalcemia, Hypophosphatemic rickets with hypercalciuria,)
  - Other causes of mixed proteinuria and FSGF
- Drugs and toxics

Treatment

- ✓ Symptomatic
- ✓ Supplements (Na, K , Pi, water…)
- ✓ Drugs
  - ✓ Hydrochlorothiazide
  - ✓ Indomethacin
  - ✓ Potassium citrate
  - ✓ Angiotensin-converting enzyme inhibitors
  - ✓ Angiotensin receptor blockers
  - ✓ Calcitriol: not always indicated in patients with CKD

Phenotypic spectrum and antialbuminuric response to angiotensin converting enzyme inhibitor and angiotensin receptor blocker therapy in pediatric Dent disease



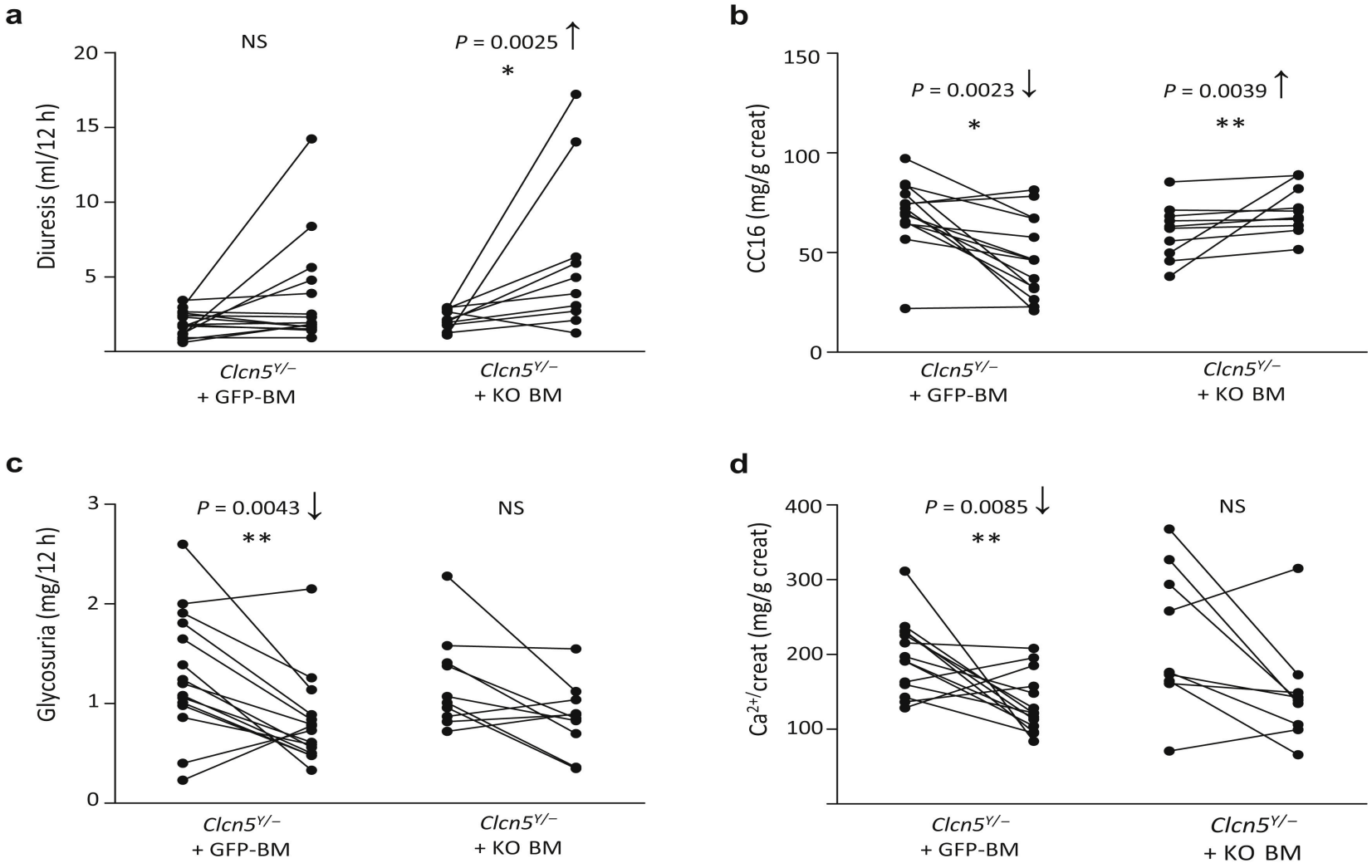
Age at onset of treatment was 5.4 (1.6–15.4) years
Duration of treatment: 1.7 (0.3–8.5) years
Reduction in urinary ACR in 54% (7/13)

Deng H et al Molecular Genetics & Genomic Medicine, 2020

Perspectives

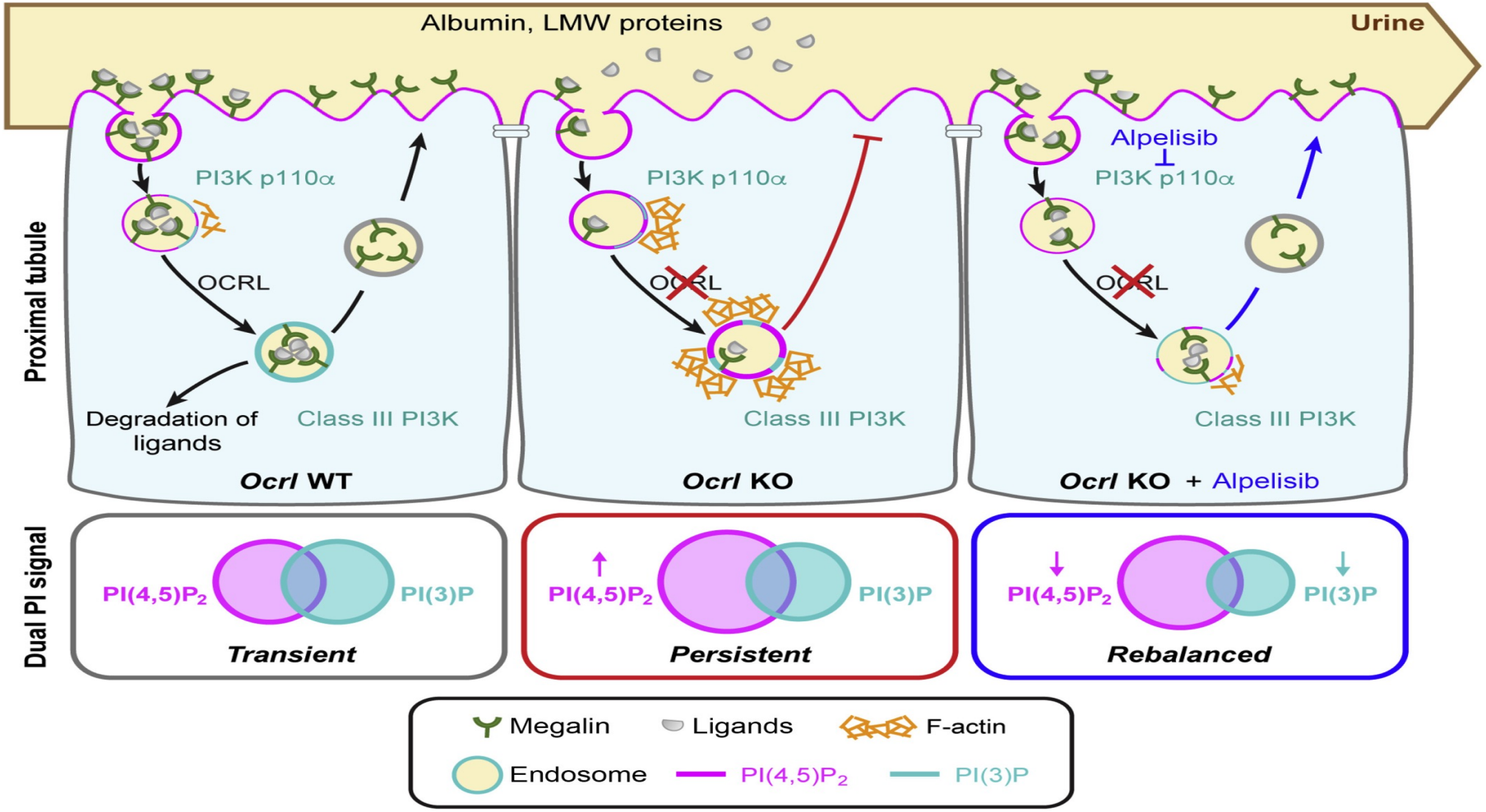
- Proximal cells dysfunction and progression to CKD.
- Role of tubular proteinuria?
- Phenotypic variability ?
- Randomized studies in large cohorts of patients to assess treatment efficacy
- New therapies

Perspectives – Treatment 1



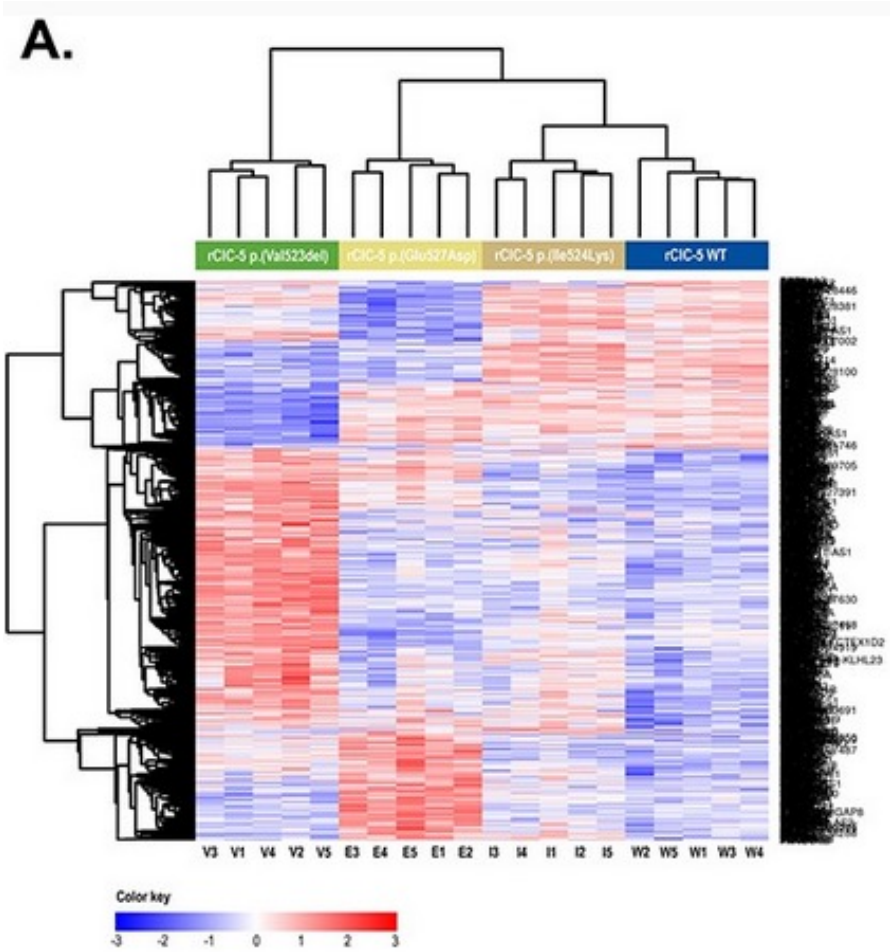
Gabriel et al.. Bone marrow transplantation improves proximal tubule dysfunction in a mouse model of Dent disease. Kidney Int. 2017

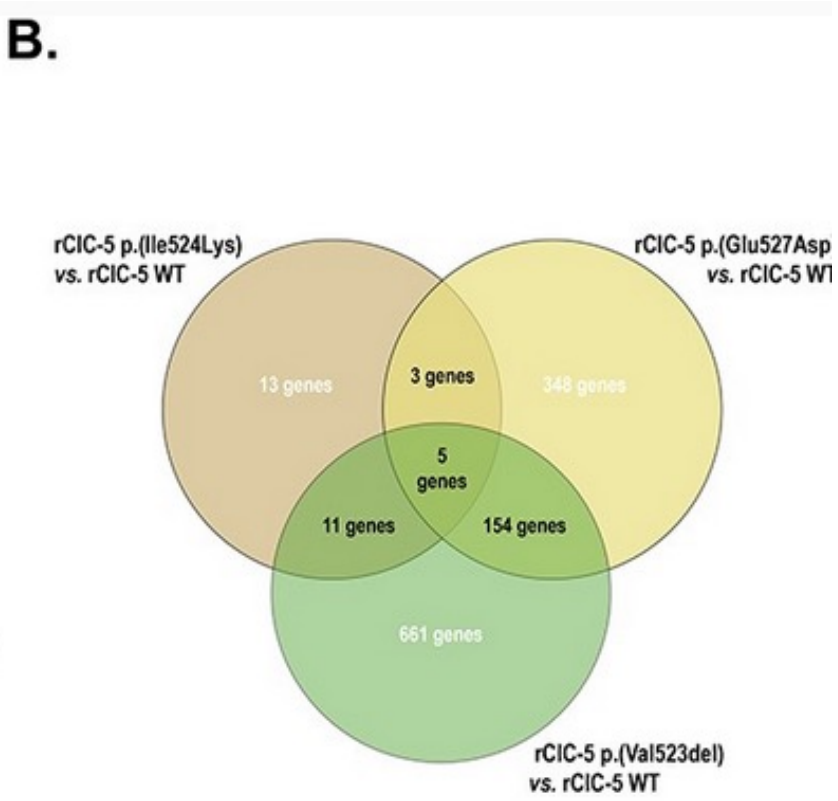
Perspectives- Treatment 2



Berquez M, et al. The phosphoinositide 3-kinase inhibitor alpelisib restores actin organization and improves proximal tubule dysfunction in vitro and in a mouse model of Lowe syndrome and Dent disease. Kidney Int. 2020

Perspectives – Genotypic Variability





Biological processes:

- kidney development,
- anion homeostasis,
- organic acid transport,
- extracellular matrix organization
- cell-migration

Duran M, et al. Novel Dent disease 1 cellular models reveal biological processes underlying ClC-5 loss-of-function. Human Mol Genet. 2021

Next Webinars

ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **29 June 2021**

Speaker: **Jürgen Floege**

Topic**: Update on KDIGO on Immune Glomerulopathies**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **07 September 2021**

Speaker: **Dieter Haffner**

Topic: **Renal hypophosphatemia**

ERKNet/ERA-EDTA Advanced Webinars on Rare Kidney Disorders

Date: **21 September 2021**

Speaker: **Aude Servais**

Topic**: Cystinosis- adult view**

Subscribe the ERKNet and IPNA Newsletter and don‘t miss Webinars!