ERKNet
The European
Rare Kidney Disease
Reference Network

WGIKD
Working Group on
Inherited Kidney Disorders

WELCOME TO

ERKNet
Advanced Webinars on Rare Kidney Disorders

Date: 21 December 2021

Topic: Monogenic forms of hypertension

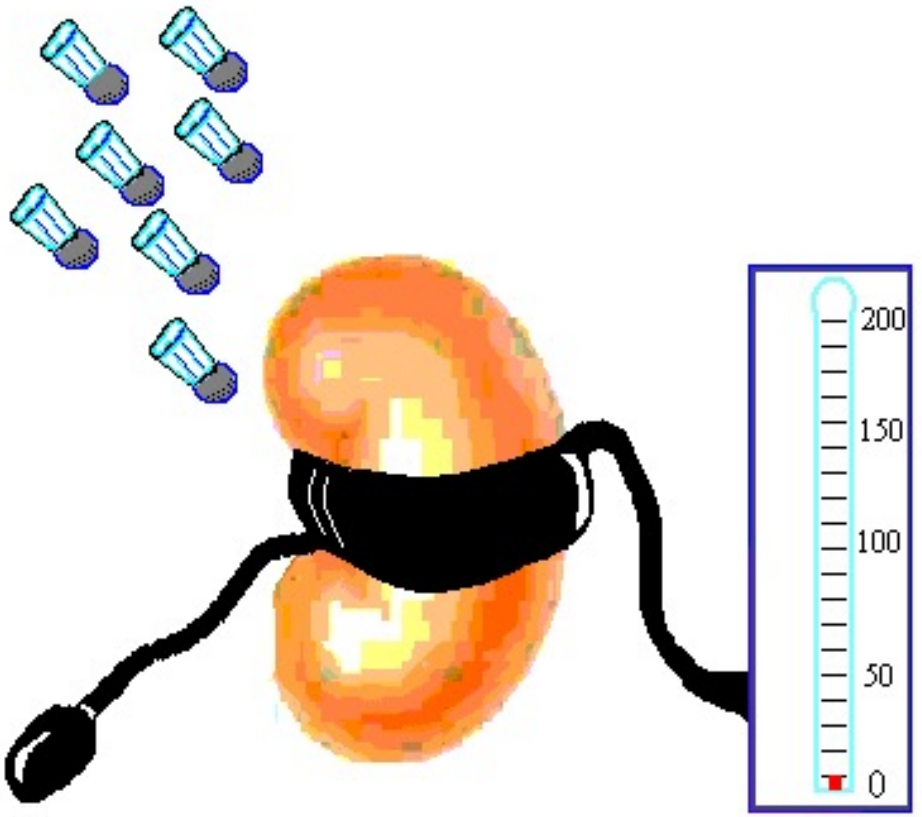
Speaker: Francesco Trepicione (Naples, Italy)

Moderator: Tom Nijenhuis (Nijmegen, Netherlands)

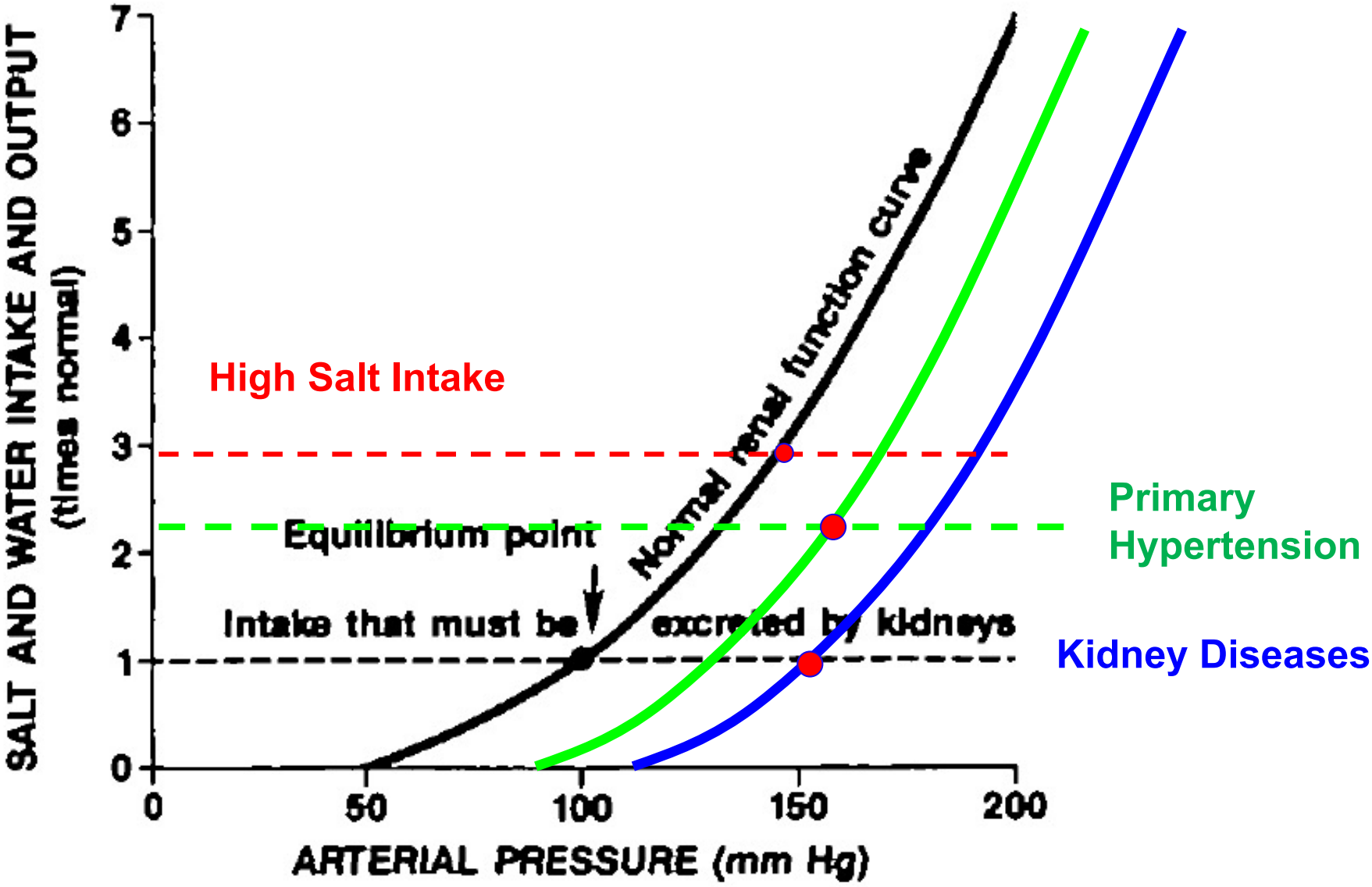
Agenda

- Why the kidney is involved in blood pressure regulation?
- Monogenic form of hypertension
  - Case reports introducing physiopathology

The Kidney – Salt – Blood Pressure

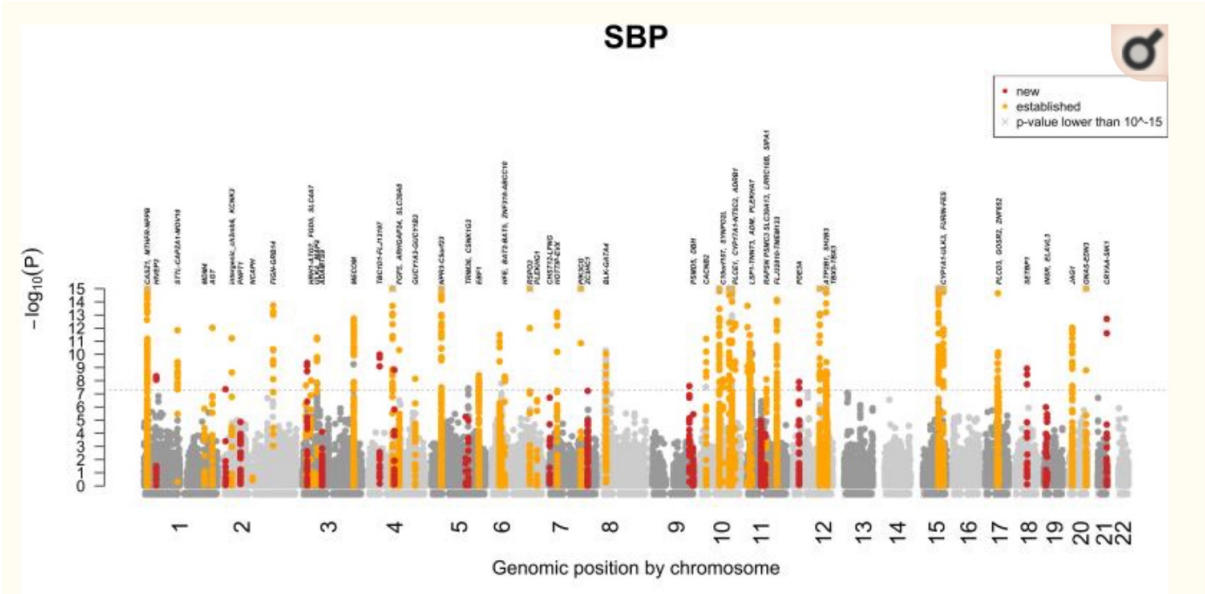


Infinite feedback gain system



Guyton AC Hypertension 1990

Genetic causes of Hypertension

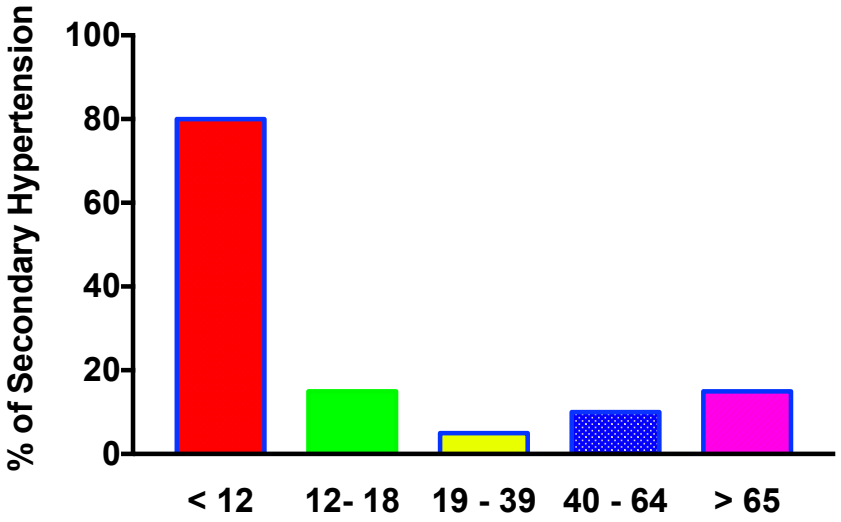


Genome wide association studies for primary hypertension

- 280 gene variants

Strict Genetic
Enviroment - interaction

Frequency of Secondary Hypertension/age



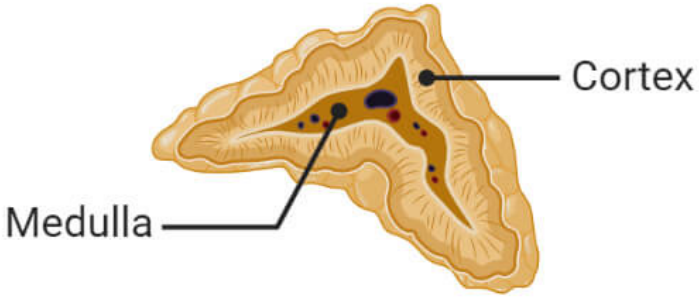
In Hypertensive Chinese Han population (n: 1179) with Hypertension onset < 35y/o **2.4%** were diagnosed affected by one of the known Monogenic Form of Hypertension

Viera AJ *et al.* Am Fam Physician 2010

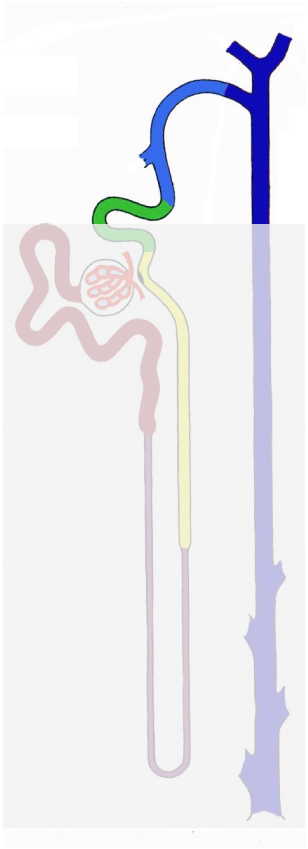
Bao M *et al.* J Med Genet 2019

Target organ for monogenic form of Hypertension

Mineral-active steroids overproduction & Aldosterone-sensitive distal nephron



- Hypertension
- Normo/Hypo-kaelemia
- Genital and/or puberal abnormalities
- Lab Steorids Abnormalities



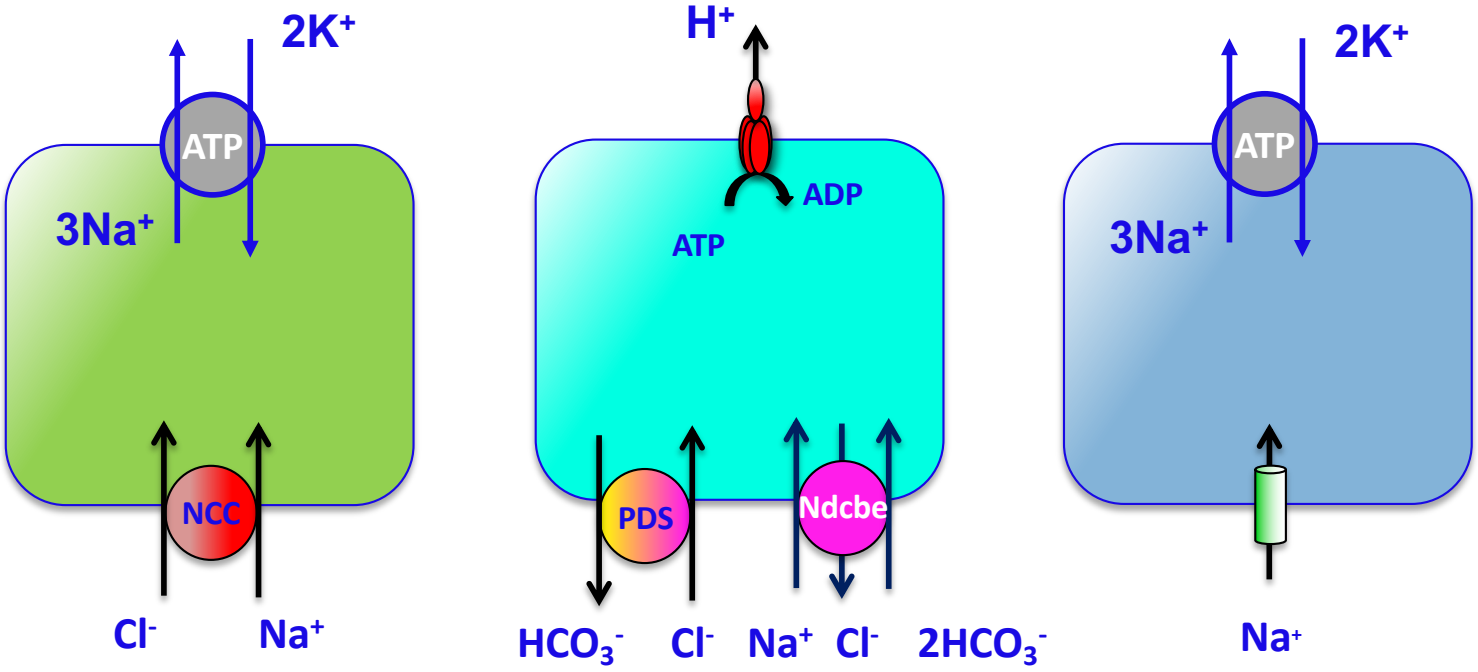
Hypertension Exacerbated by Pregnancy:
- *NR3C2*

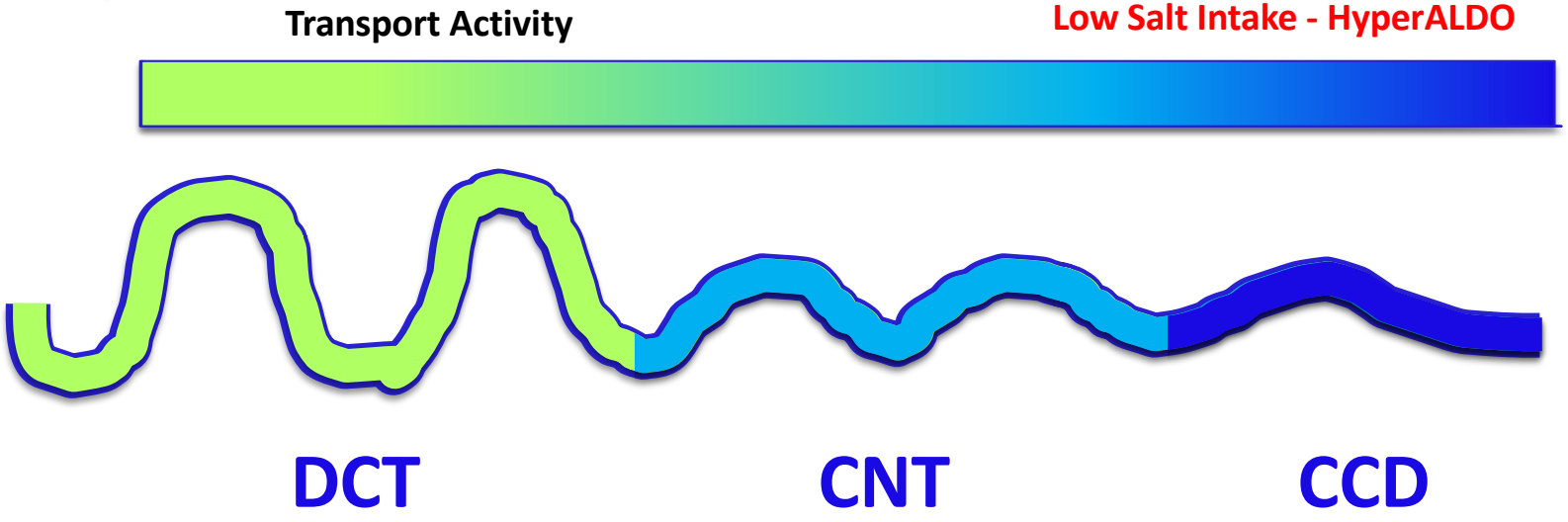
Gordon Syndrome:
- *WNK1 - WNK4 - KLHL3 - CUL3*

Apparent Mineraloc. Excess:
- *HSD11B2*

Liddle syndrome:
- *SCNN1B - SCNN1C - SCNN1A*

Sodium transport along the distal nephron





Case Report 1: unexpected hyperkalemia

A 17 y/o male presented with:

- High Blood Pressure (138–142 /90–92 mmHg)
- hyperkalemia (6.1 mM)
- hyperchloremic metabolic acidosis (HCO_3^- 19 mM)

Anglani F. *et al* J. Nephrol 2021

Pool question 1:
What would you ask for?

1. Serum creatinine and glucose
2. Pharmacological Anamnesis
3. CT scan of the kidneys
4. Doppler ultrasound of renal arteries

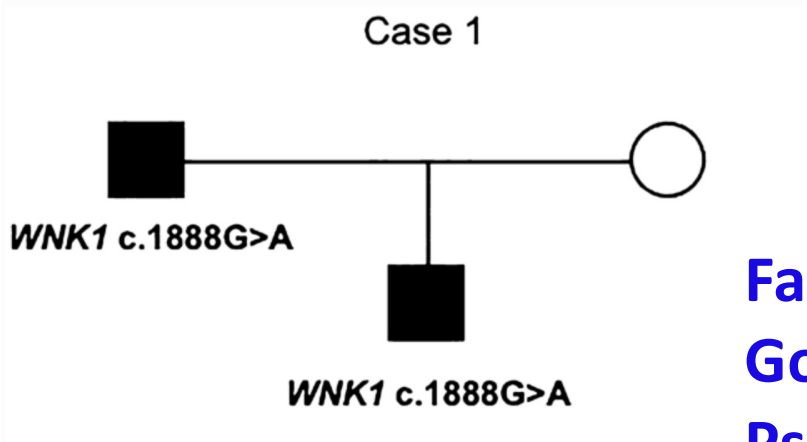
Case Report 1: unexpected hyperkalemia

- eGFR normal
- Renin and aldosterone were at lower normal range (4.2 mIU/L and 220 pmol/L)
- Renal ultrasound was normal and the patient was asymptomatic.

Anglani F. *et al* J. Nephrol 2021

Case Report 1: Familial Hypertension with Hyperkalemia and metabolic acidosis

After 1 month of treatment with HCTZ, complete recovery to normal blood K and HCO_3^-



Familial Hyperkalemic Hypertension
Gordon Syndrome
Pseudo-Hypoaldosteronism type-2

Anglani F. *et al* J. Nephrol 2021

Gordon Syndrome

Familial Hyperkaliemic Hypertension

PseudoHypoAldosteronism type II

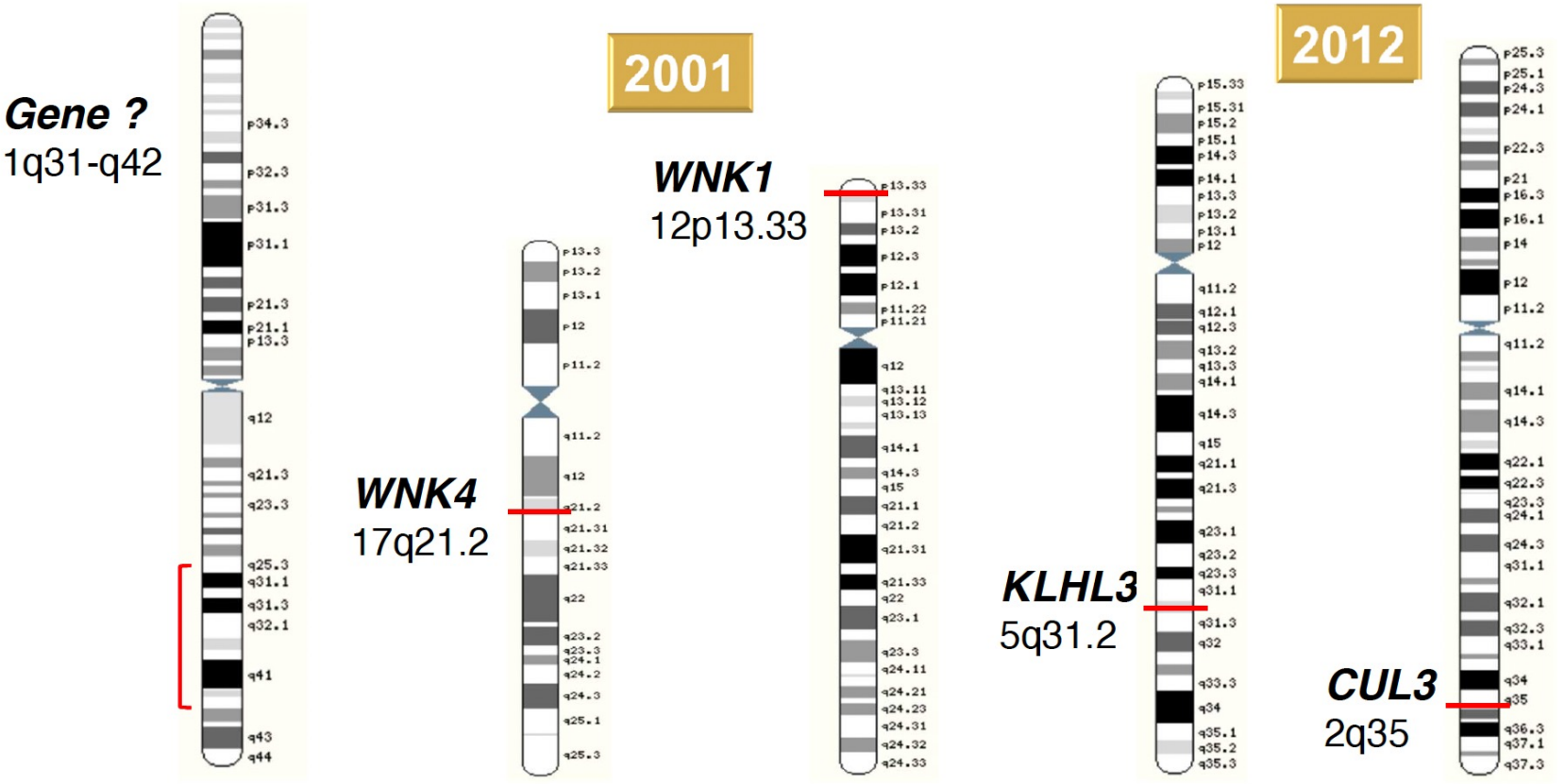
Gordon

- Hyperkalaemia
- Met. Acidosis
- Hypercalciuria
- Low Renin
- Hypertension

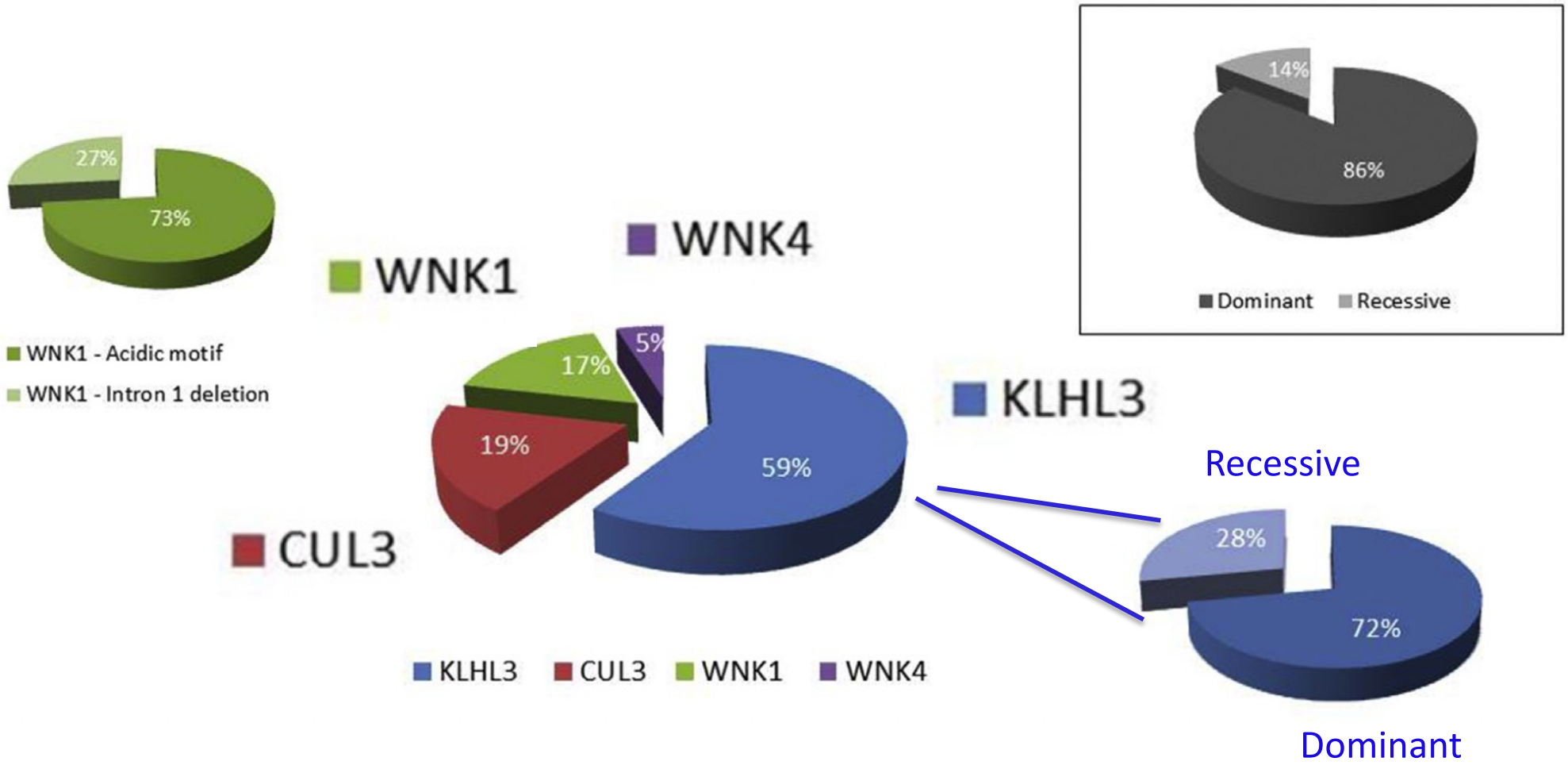
Gitelman

- Hypokalaemia
- Met. Alkalosis
- Hypocalciuria
- High Renin
- Hypotension

Gene involvement

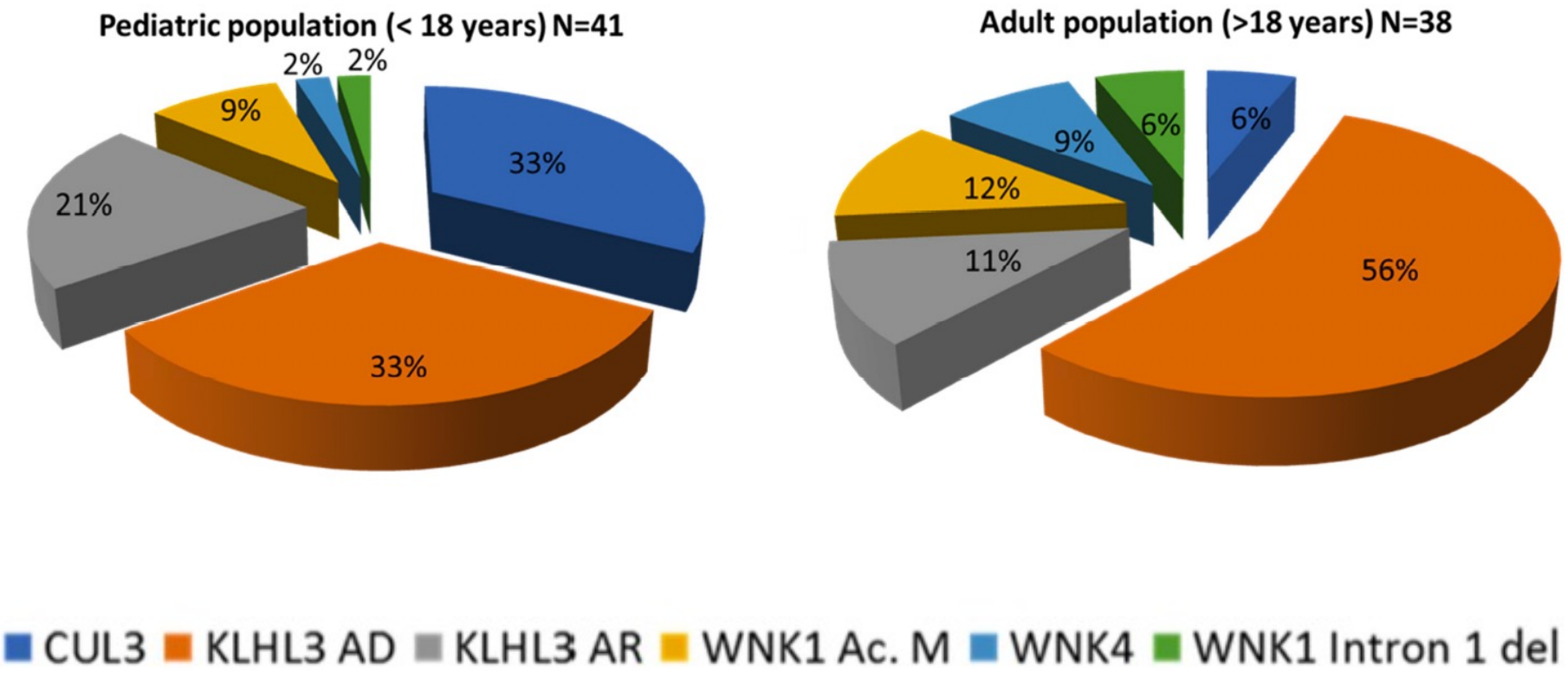


Causative genes and inheritance



Hureaux M et al. Kid Int Reports 2021

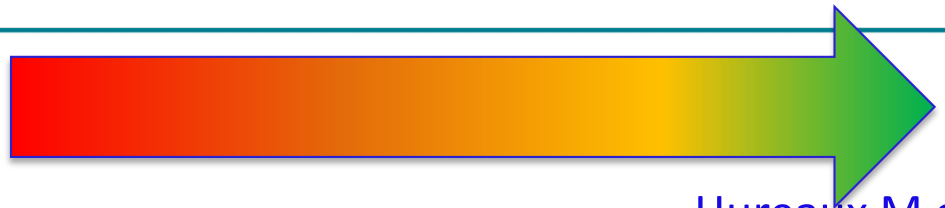
Gene frequency by age



Hureaux M et al. Kid Int Reports 2021

Genotype to phenotype correlation

All patients (N = 153)	Normal values (when applicable)	*CUL3* n = 19	*KLHL3* AR n = 16	*KLHL3* AD n = 56	*WNK4* n = 10	*WNK1* intron 1 del. n = 23	*WNK1* acidic motif n = 29	*P* (Kruskal-Wallis test)
Sex M/F		9/10	13/3	23/33	5/5	9/14	13/16	
age at work-up, years		7 [2-16][Hν]	9 [4-26]	33 [19-52] [ν]	38 [13-43]	36 [17-49] [H]	27 [6-45]	<0.0001
age at discovery*		5.5 [2.0-14.3][N]	5.5 [2.5-31.7]	24.0 [11.0-44.0][N]	19.0 [15.8 -27.5]	36.0 [8.0-37.0]	16.5 [4.8-24.25]	0.0308
Na^+, mmol/l	136-145	138 [136-140][7]	138 [136-139][3]	139 [137-140][7]	139 [137-141]	139 [139-140][1]	140 [139-141][7]	0.04
K^+, mmol/l	3.5-5.1	7.1 [6.8-7.6][4€Hν]	6.9 [5.8-8.0][1Δθμ]	5.5 [5.2-6.0][9μν]	5.9 [5.4-6.4]	5.5 [5.3-5.8][1θH]	5.7 [5.1-6.1][4Δ€]	<0.0001
Cl^-, mmol/l	95-105	113 [111-116][4Eην]	111 [109-113][3M]	107 [105-110][11Mν]	112 [108-114][1]	108 [106-111][1η]	108 [106-110][7E]	<0.0001
HCO3-, mmol/l	22.0-27.0	16.0 [15.1-17.0][6Hνλ]	18.2 [15.0-19.5][3Θμ]	22.0 [19.4-23.5][13μν]	22.1 [18.8-23.8][λ]	23.8 [22.0-27.0][1ΘΗλ]	19.7 [18.2-21.1][7λ]	<0.0001
eGFR, ml/min per 1.73 m^2**	>90	117 [100-131][10]	108 [104-193][8]	94 [82-108][21]	96 [84-138][1]	88 [58-139][4]	94 [73-124][11]	nd
Protides, g/l	63-78	70 [60-73][12]	72 [66-83][12]	70 [65-73][11]	69 [67-70]	69 [65-71][2]	66 [64-73][10]	nd
Uric acid, µmol/l	137-393	225 [170-369][13]	291 [291-316][12]	279 [166-320][47]	222 [177-311][5]	182 [182-182][22]	178 [160-193][14]	nd
Total calcium, mmol/l	2.09-2.52	2.38 [2.30-2.50][13]	2.31 [2.20-2.40][11]	2.32 [2.21-2.44][34]	2.31 [2.27-2.40]	2.48 [2.48-2.48][22]	2.32 [2.21-2.40][8]	nd
Magnesium, mmol/l	0.64-0.90	0.86 [0.84-0.89][17]	0.73 [0.70-0.90][12]	0.82 [0.75-0.86][49]	0.86 [0.86-0.86][9]	0.69 [0.66-0.79][19]	0.79 [0.76-0.81][22]	nd
Renin lying, pg/ml ***	1.5-17.0	2.5 [0.6-2.9][12]	2.7 [1.5-4.4][9]	3.3 [1.4-5.0][35]	6.1 [3.4-10.0][3]	5 [2.8-9.0][13]	2.3 [0.8-5.1][16]	nd
Aldosterone lying, pg/ml (RIA)***	40-200	102 [28-514][9]	50 [21-148][7]	56 [37-127][30]	190 [41-258][2]	105 [60-207][12]	188 [69-242][12]	nd

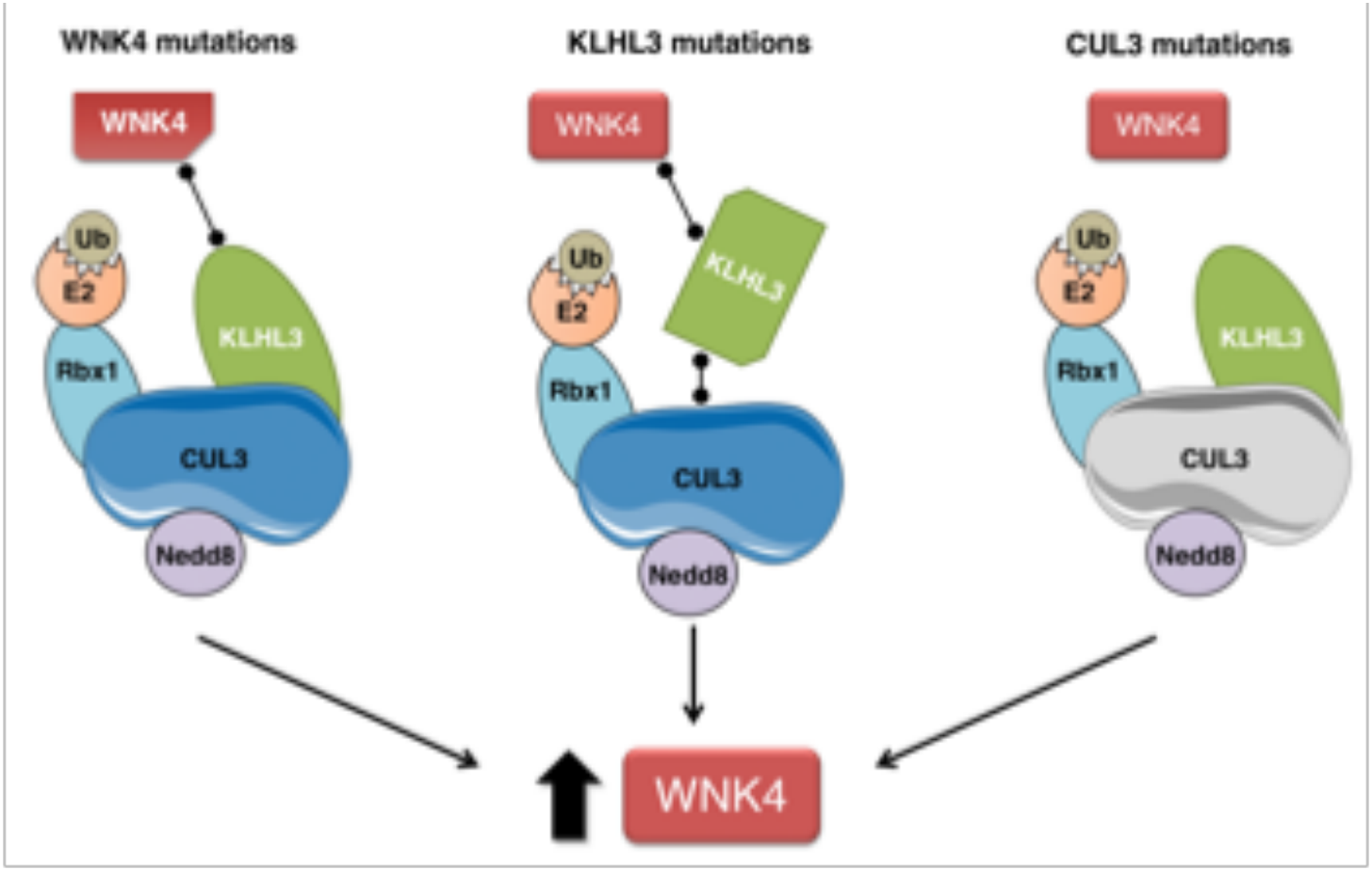


Hureaux M et al. Kid Int Reports 2021

Additional clinical features

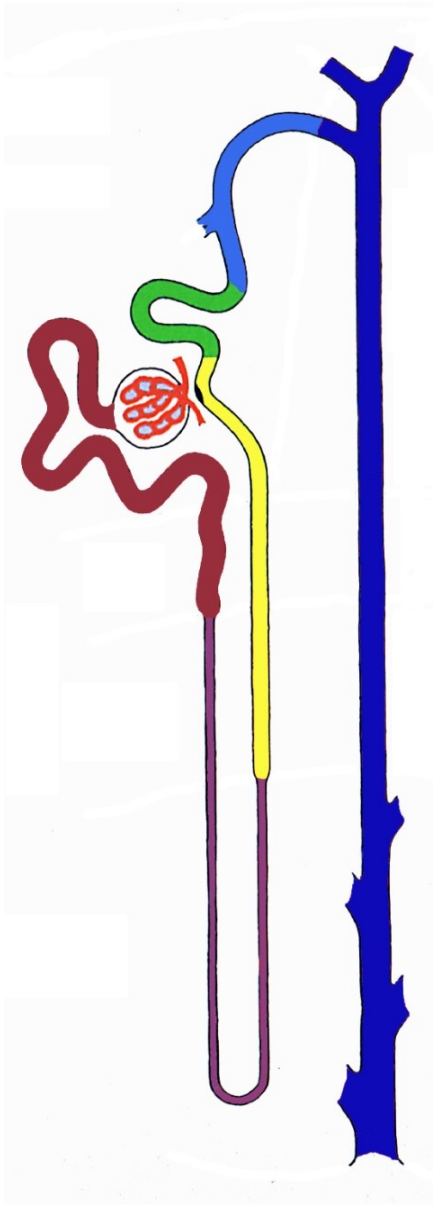
	WNK1	*WNK4*	*KLHL3*	*CUL3*
Hypertension	Least severe phenotype and metabolic disorder often precedes hypertension	Metabolic disorder often precedes hypertension	Recessive mutations are more severe and diagnosed at an earlier age than dominant mutations	Most severe phenotype. Presents at youngest age (>90% had hypertension <age 18.
Hyperkalaemia	Least severe	Yes	Dominant mutations had significantly higher serum K^+ than recessive mutations	Most severe Presents at youngest age
Metabolic Acidosis	Least severe	Yes	Yes	Most severe
Other features		Hypercalciuria Hypocalcaemia Decreased bone mineral density Renal calcium stones		Fertility likely affected in de novo mutations. Growth impairment most likely

How WNK1, WNK4, KLHL3 and CUL3 gene regulate NCC activity



… courtesy from Juliette Hadchouel

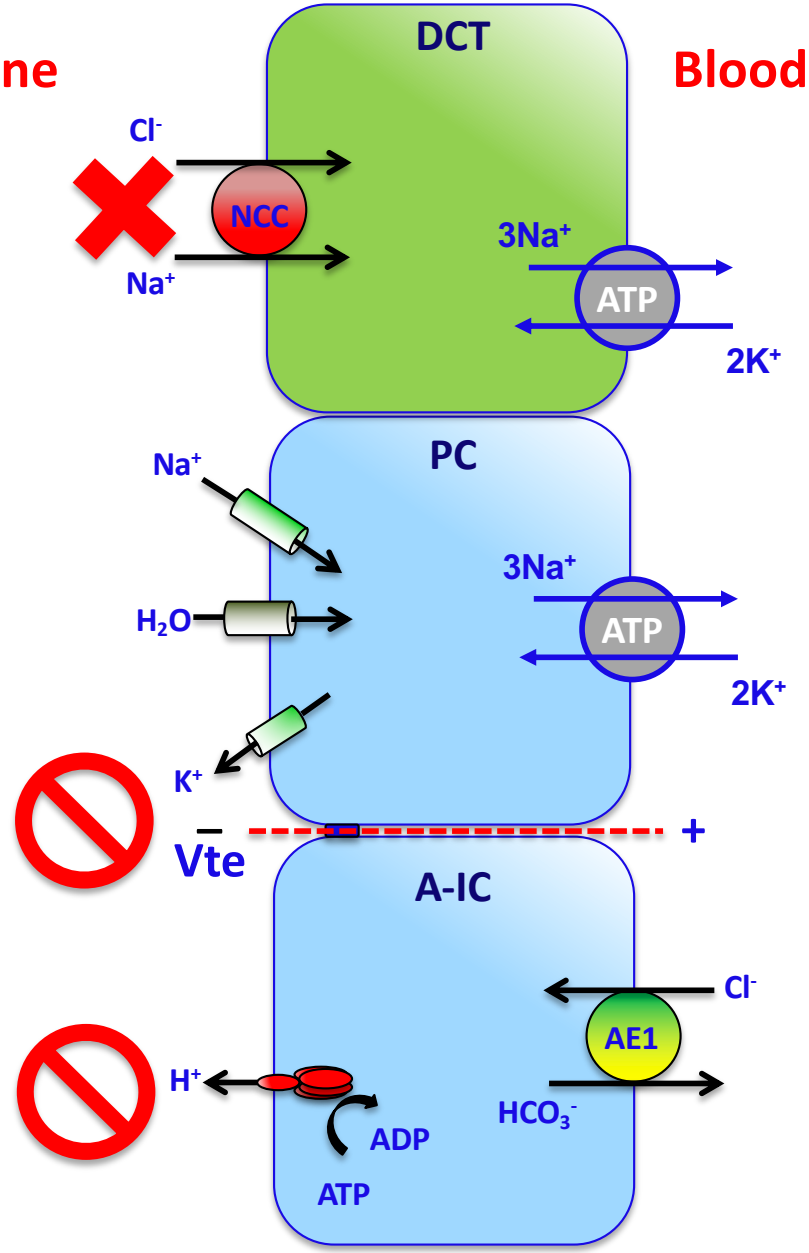
Gordon Syndrome pathogenesis



Hypertension

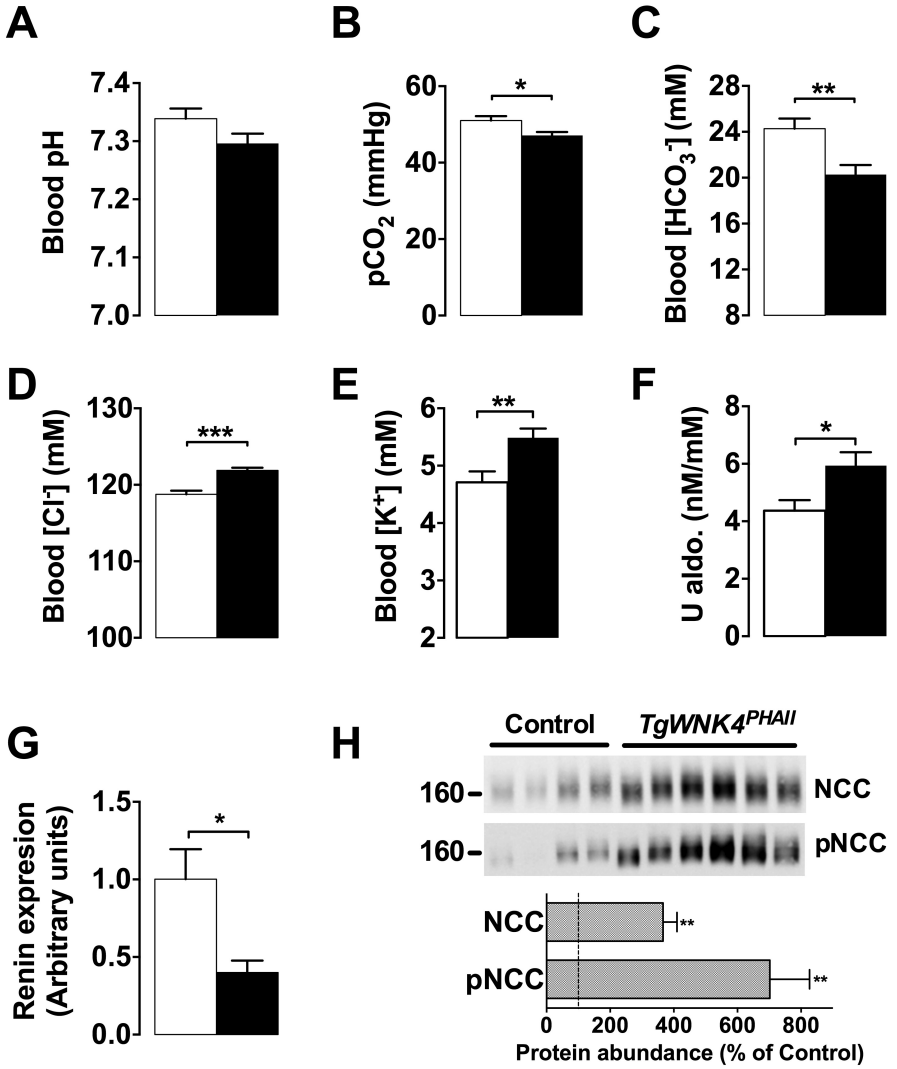
Hyperkalemia

Met. Acidosis



Tg(Wnk_4^{PHA2}) mice recapitulates FHH

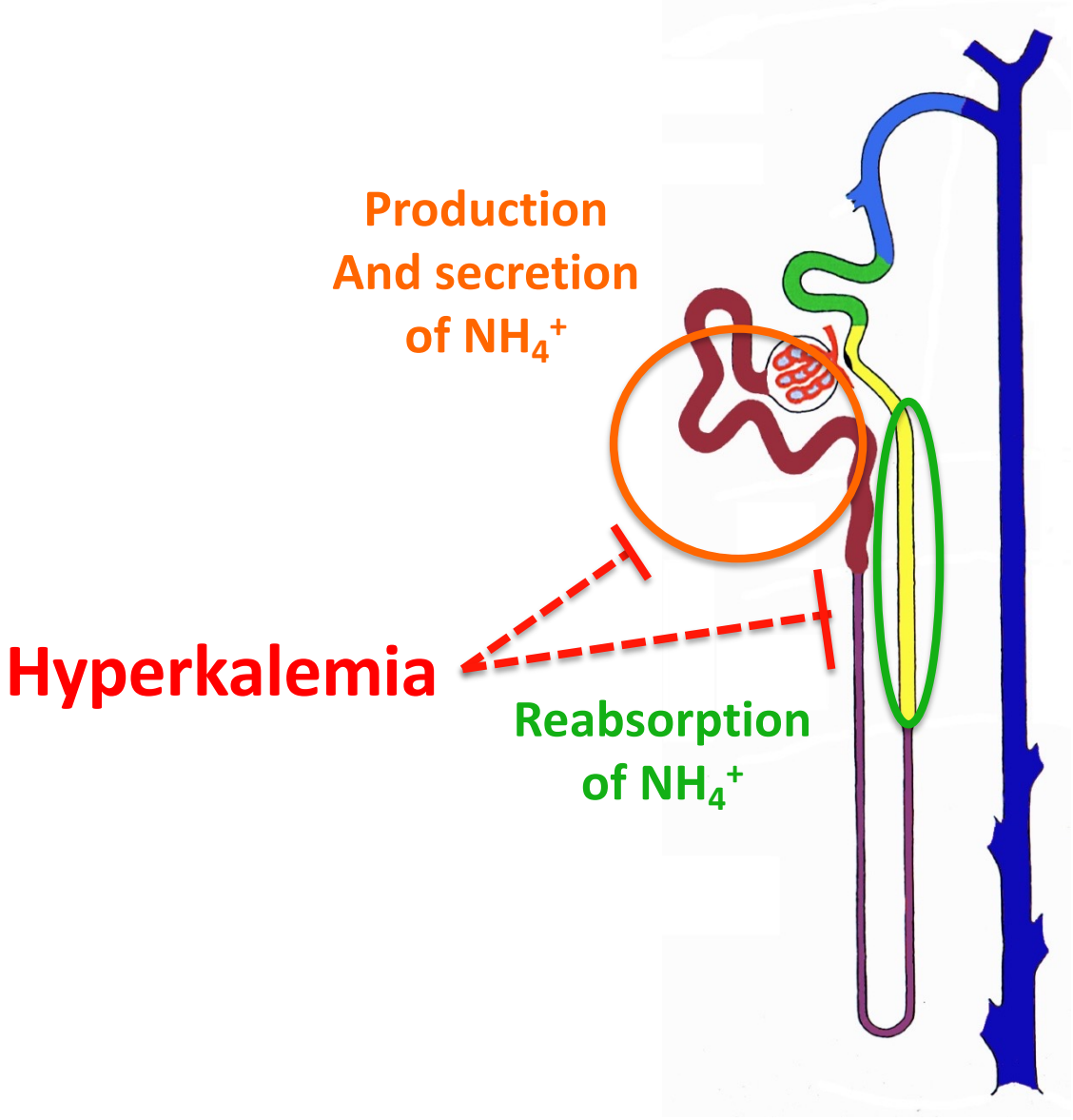
Wnk4 Q562E carrying mutation from Lifton's lab



López-Cayuqueo KI, et al. Kid Int 2018

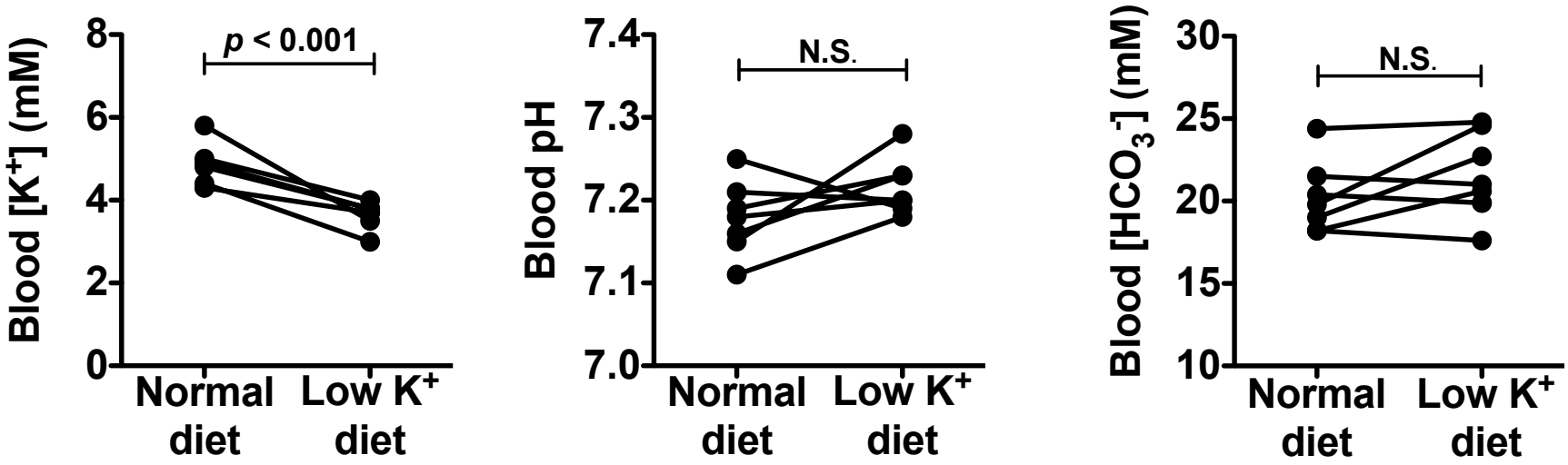
Could Acidosis be caused by hyperkalemia?

HypeK$^+$ interfers with ammonium metabolism



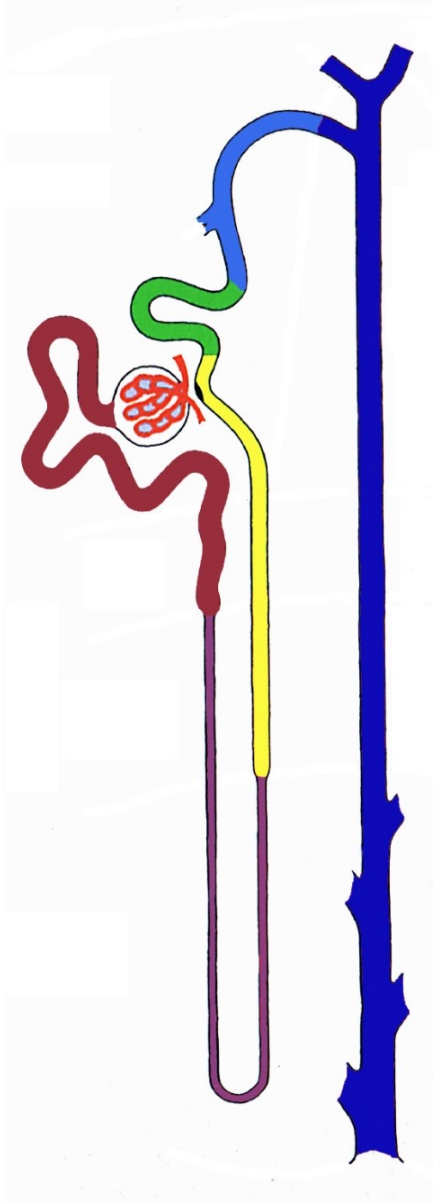
Normalizing blood [K] does not correct metabolic acidosis

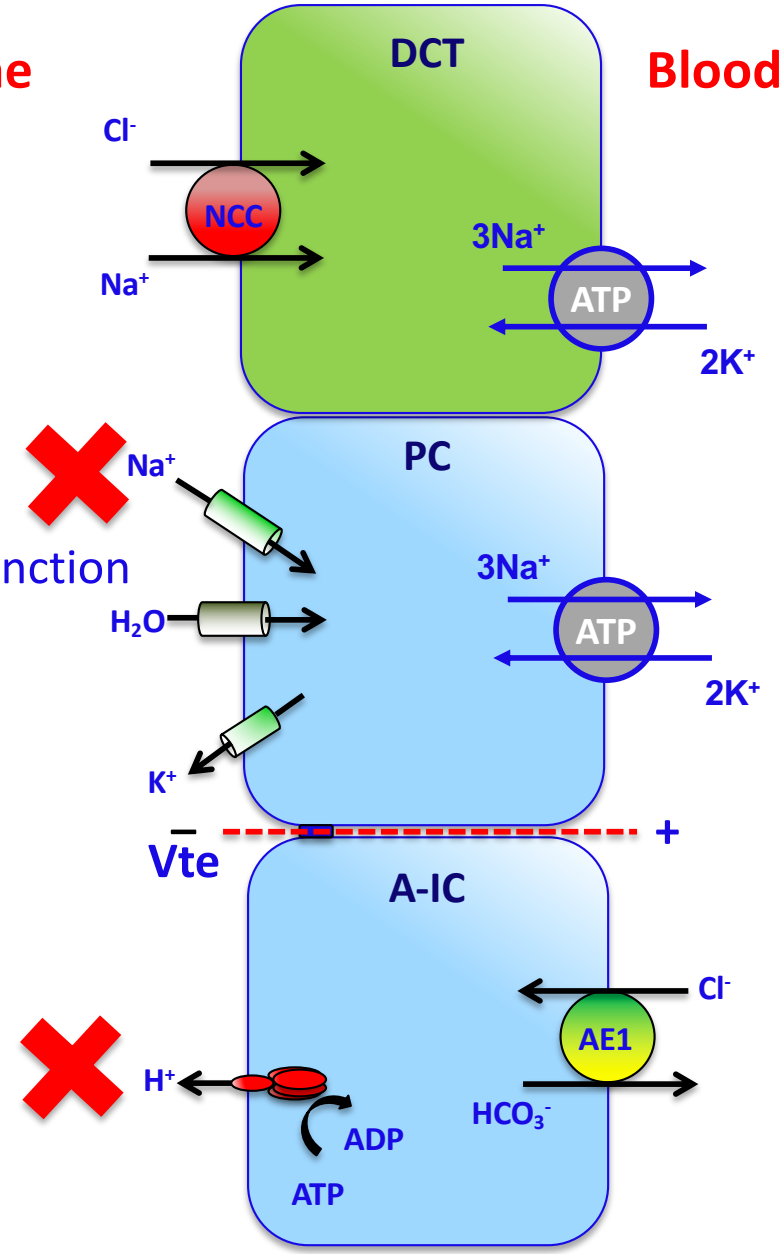
Tg(Wnk4^{PHA2}) were kept 4 days on a Low K diet



López-Cayuqueo KI, et al. Kid Int 2018

Could FHH be associated to a form of dRTA?

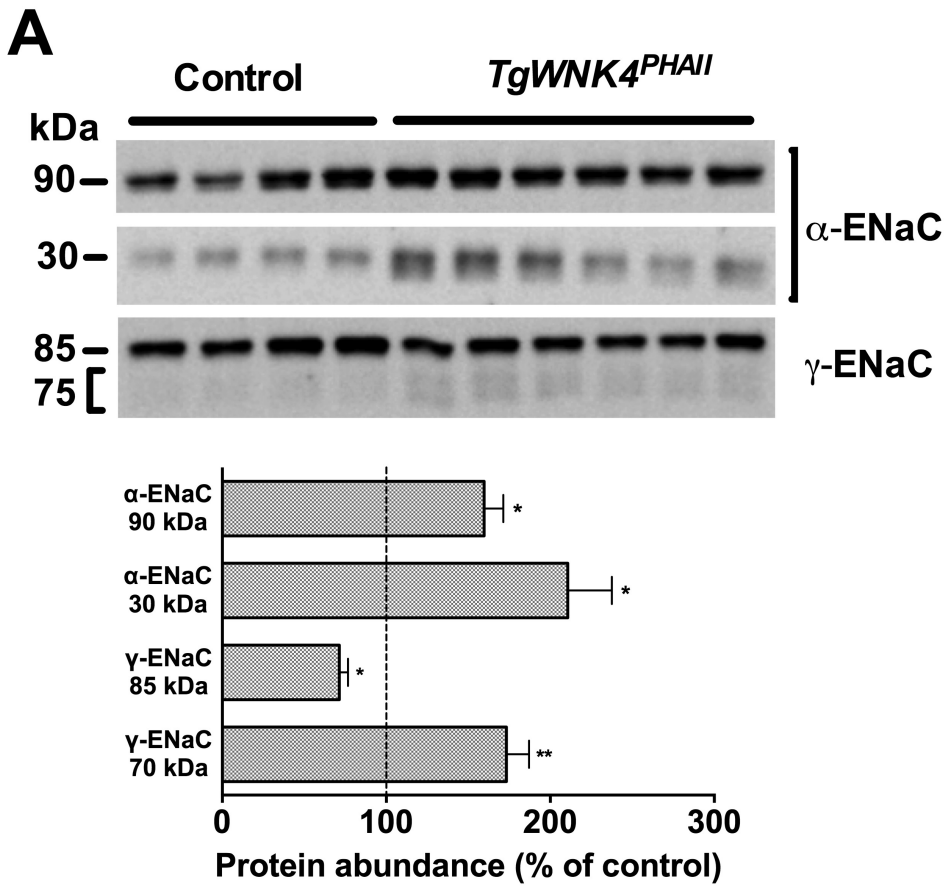


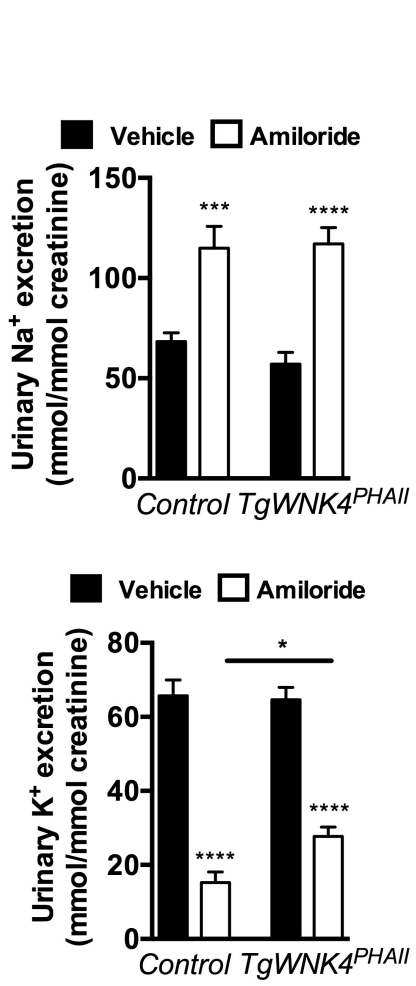


Secondary to ENaC dysfunction

Primary impairment

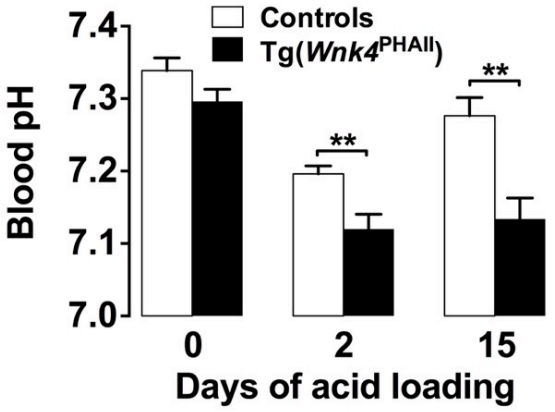
ENaC is responsive to amiloride as in control mice

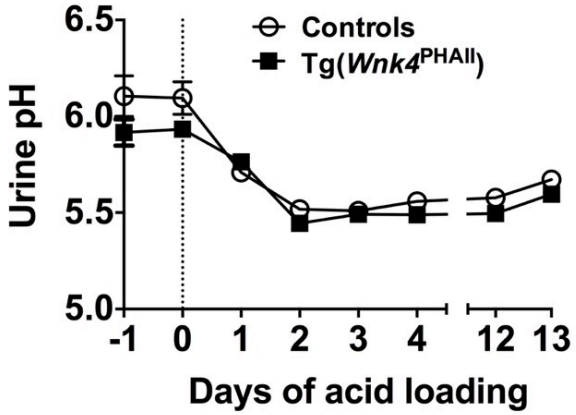


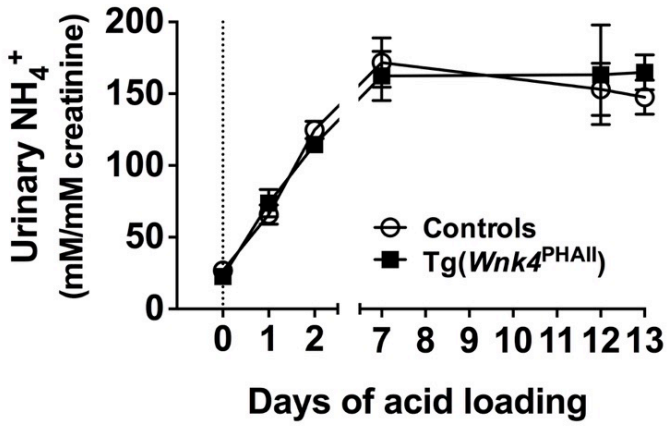


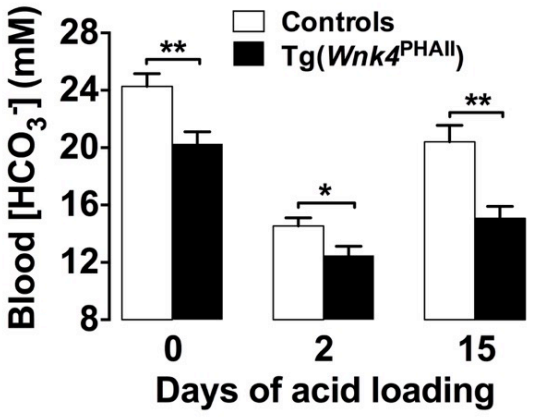
López-Cayuqueo KI, et al. Kid Int 2018

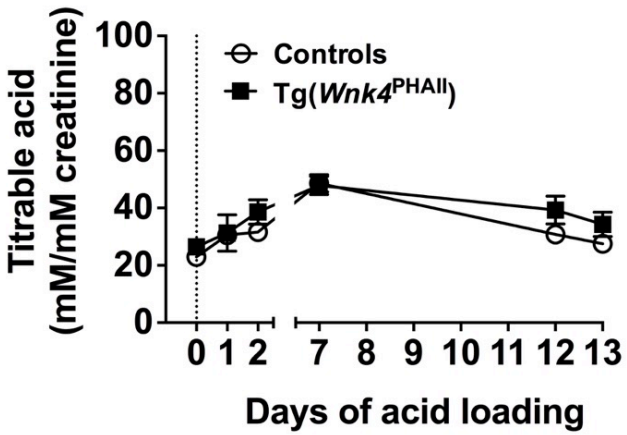
Tg(Wnk_4^{PHA2}) mice properly respond to acid load

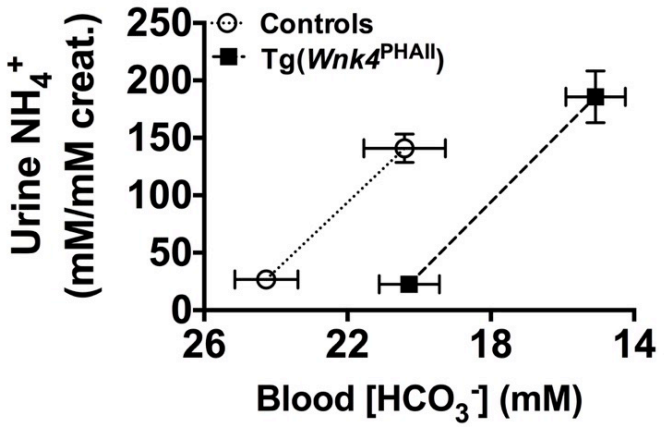












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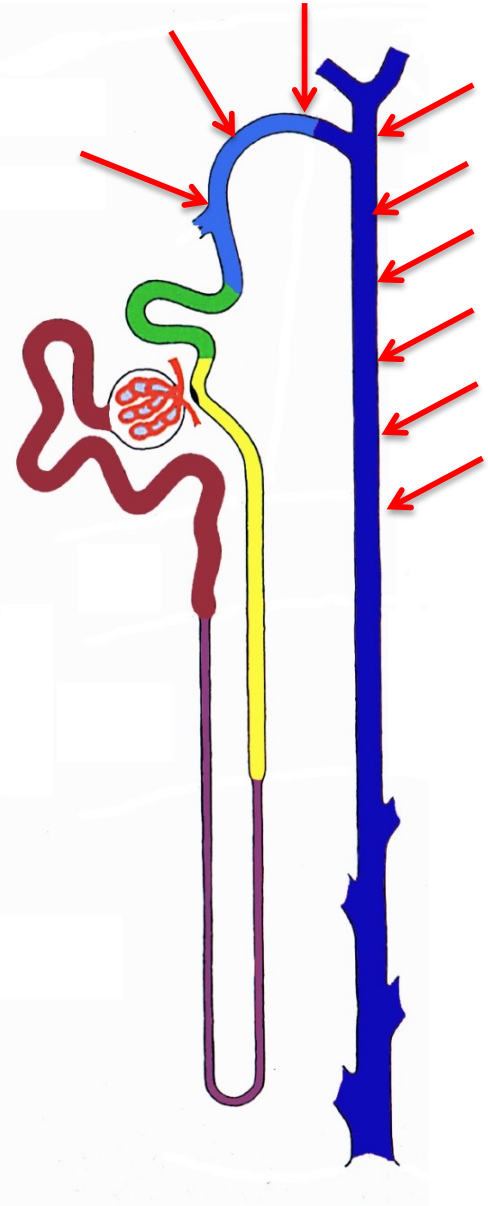
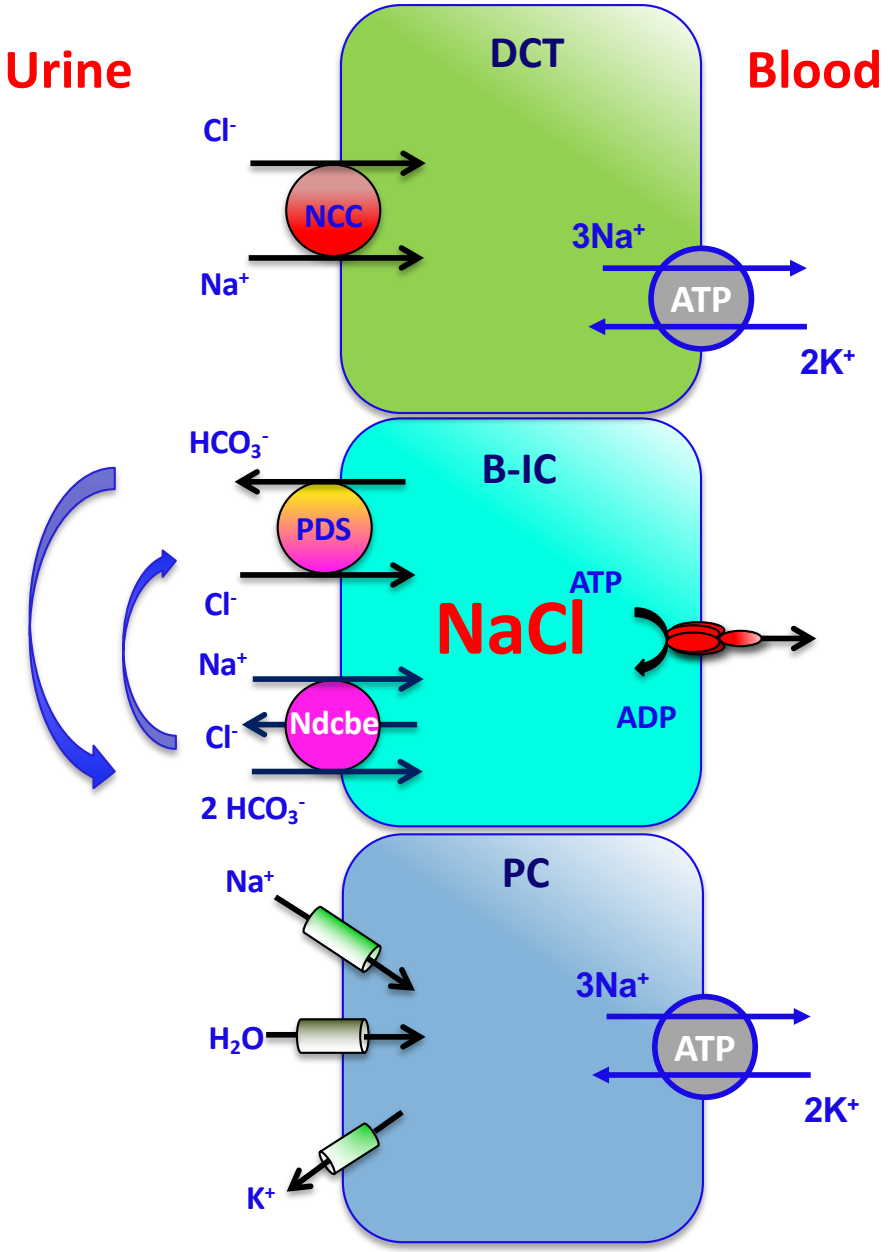
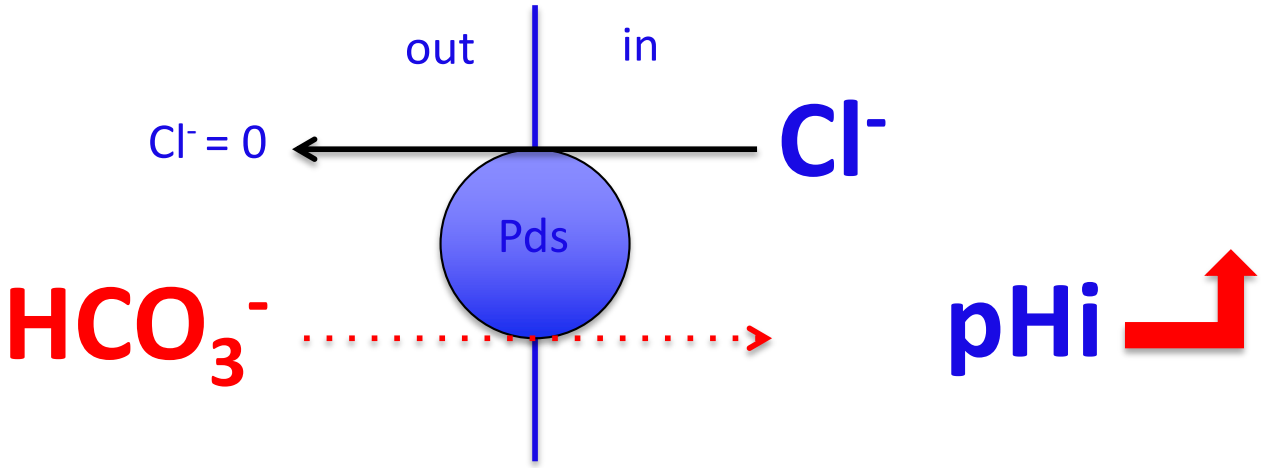
Could bicarbonate leak play a role?

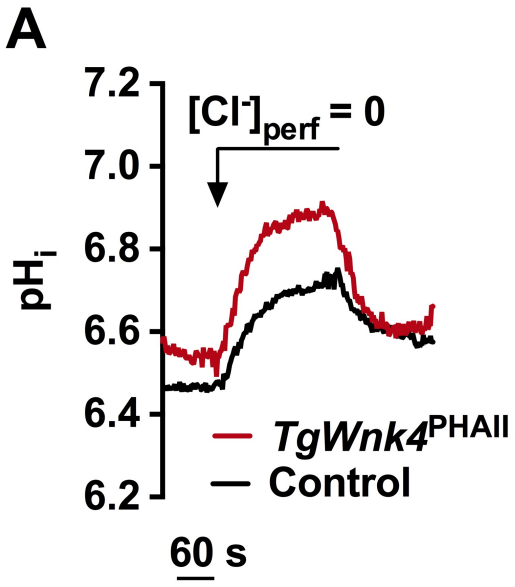


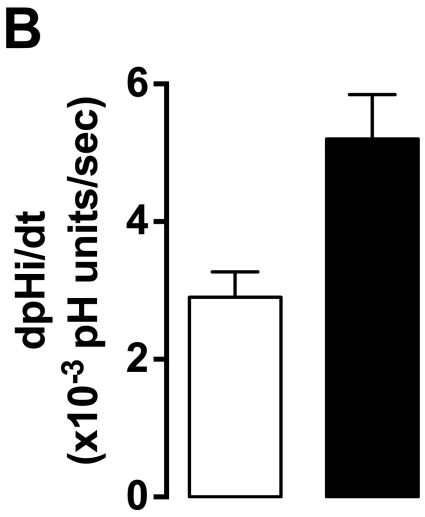
HCO_3^- secretion

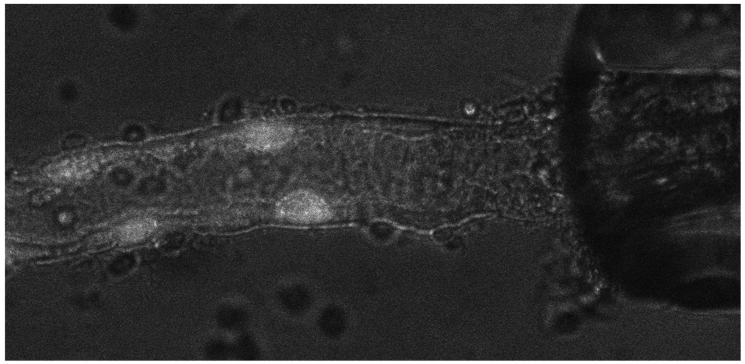


Pds activity is increased in Tg(Wnk_4^{PHA2})



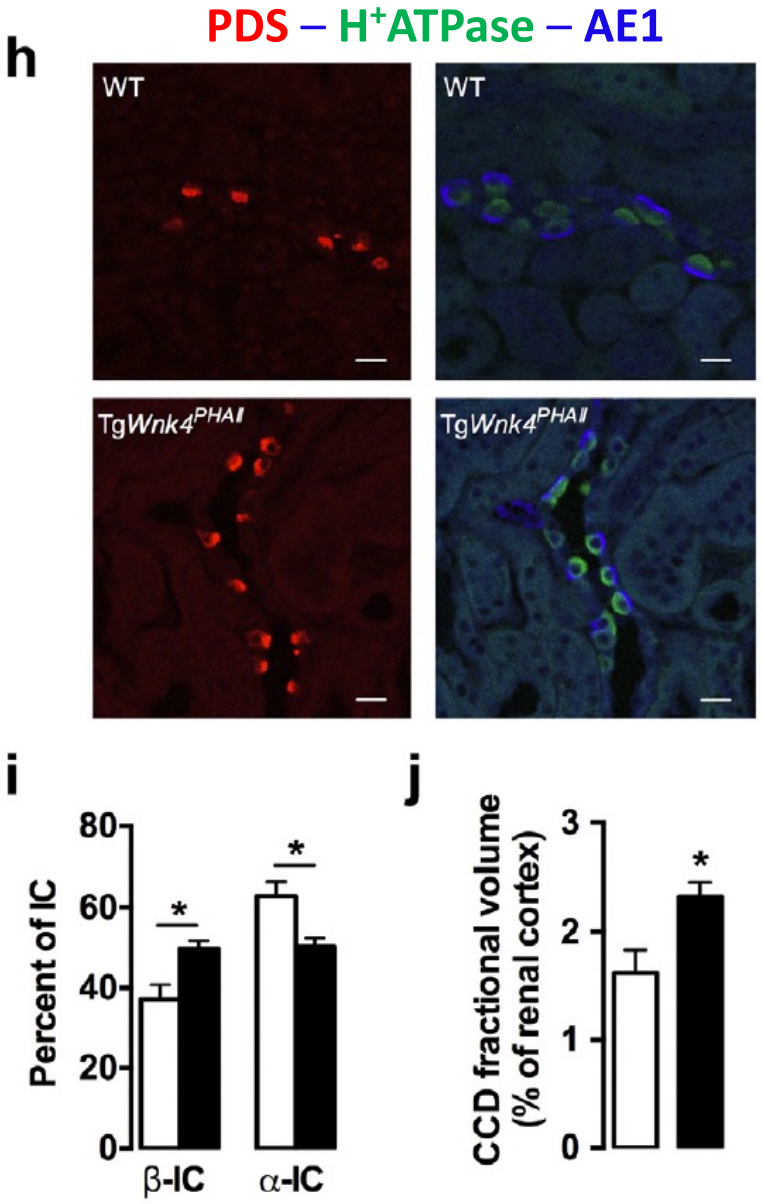






López-Cayuqueo KI, et al. Kid Int 2018

B-IC number is increased in Tg(Wnk_4^{PHA2})



López-Cayuqueo KI, et al. Kid Int 2018

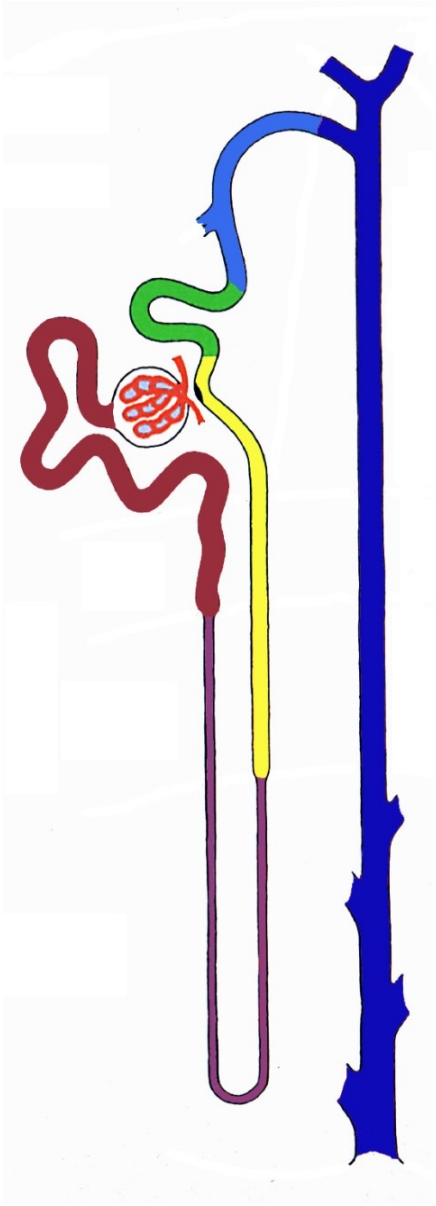
Ablation of pendrin in Tg(Wnk_4^{PHA2}) restores acid-base and potassium homeostasis

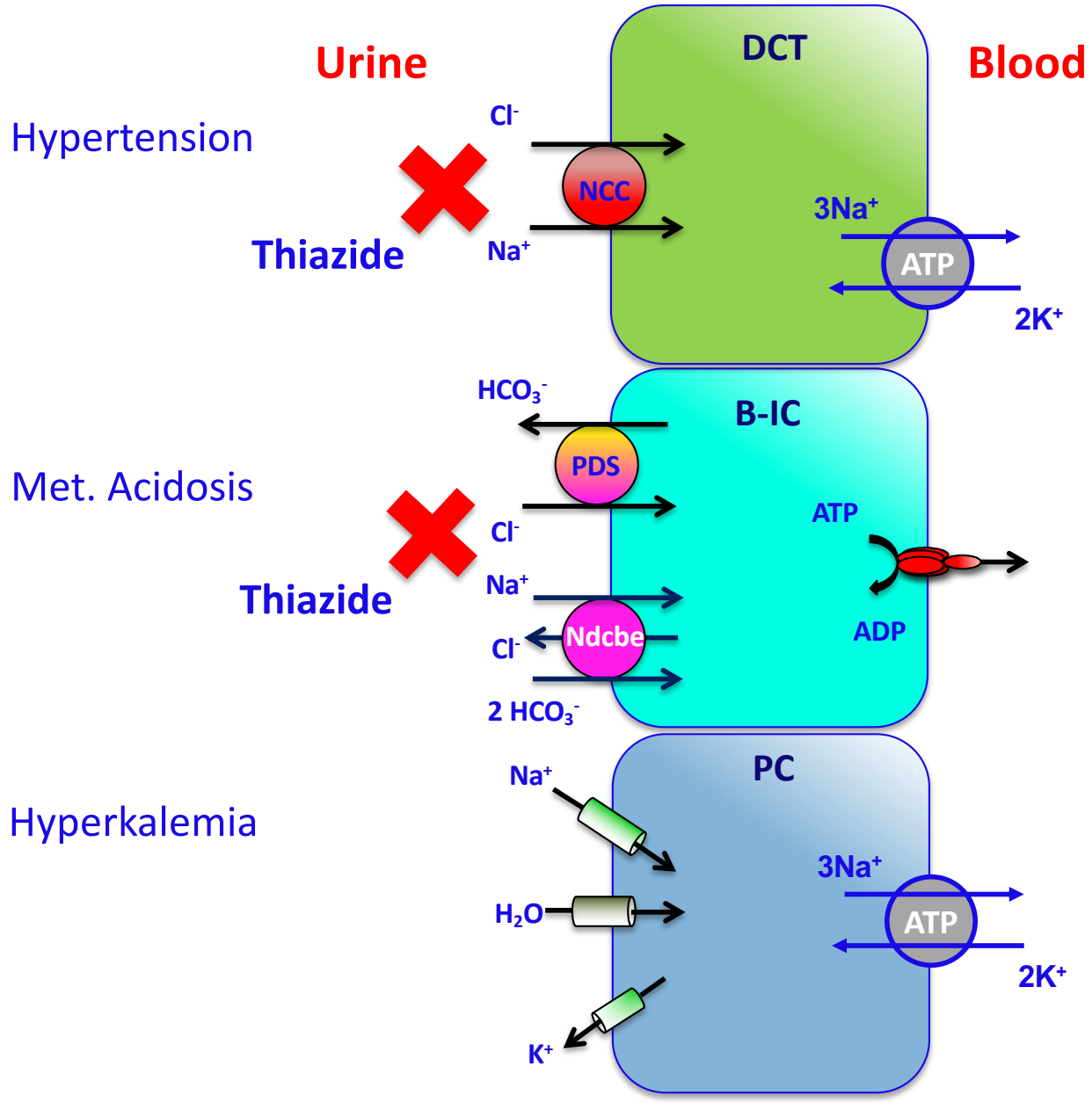
Table 1 | Blood parameters of control, Tg*Wnk4*^{PHAII};*Pds*$^{+/+}$, and Tg*Wnk4*^{PHAII};*Pds*$^{-/-}$ mice

Blood	Control	*TgWnk4*^{PHA2};*Pds*$^{+/+}$	*TgWnk4*^{PHA2};*Pds*$^{-/-}$
pH	7.26 ± 0.01	7.26 ± 0.01	7.30 ± 0.01$^{\#\#}$
PCO_2	56 ± 1	51 ± 1*	54 ± 2
HCO_3^-, mM	22.9 ± 0.7	20.8 ± 0.3*	23.7 ± 0.6$^{\#\#\#\#}$
Na^+, mM	148.5 ± 1.0	148.6 ± 0.6	149.9 ± 0.4
Cl^-, mM	109.1 ± 0.4	114.0 ± 0.4****	112.0 ± 0.5$^{\#\#}$
K^+, mM	4.40 ± 0.07	5.08 ± 0.08****	4.39 ± 0.06$^{\#\#\#\#}$
Hematocrit, %	42.5 ± 0.8	39.8 ± 0.4**	41.8 ± 0.5$^{\#\#}$

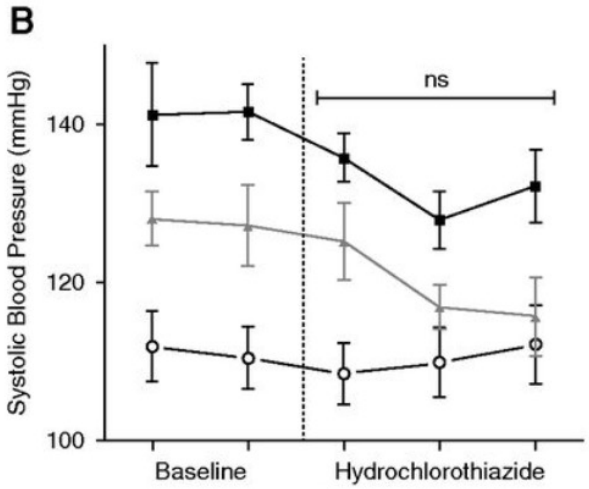
López-Cayuqueo KI, et al. Kid Int 2018

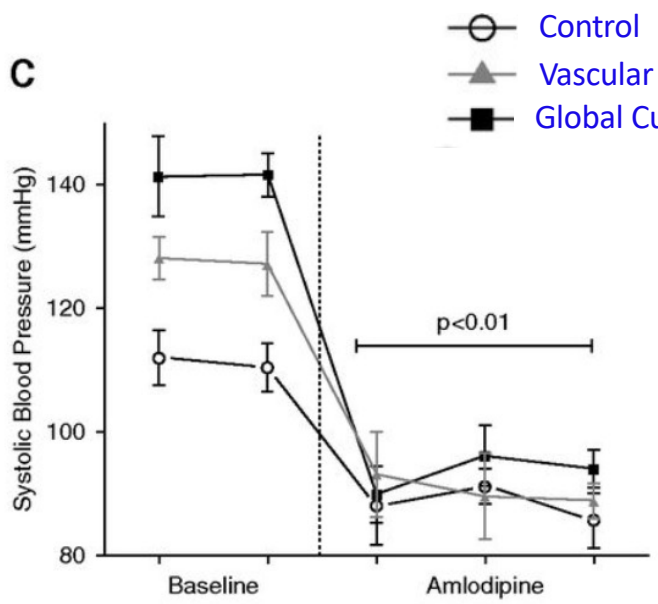
New model for pathogenesis of FHH



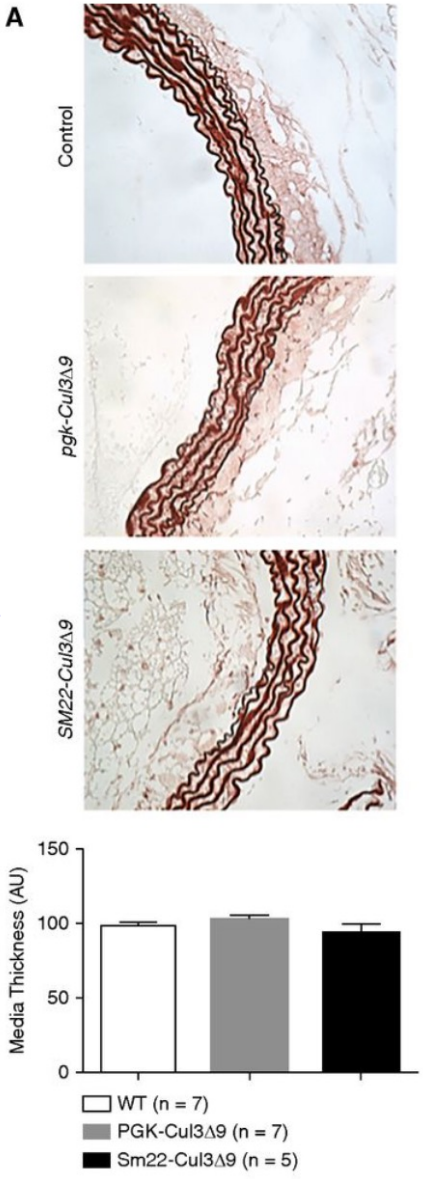


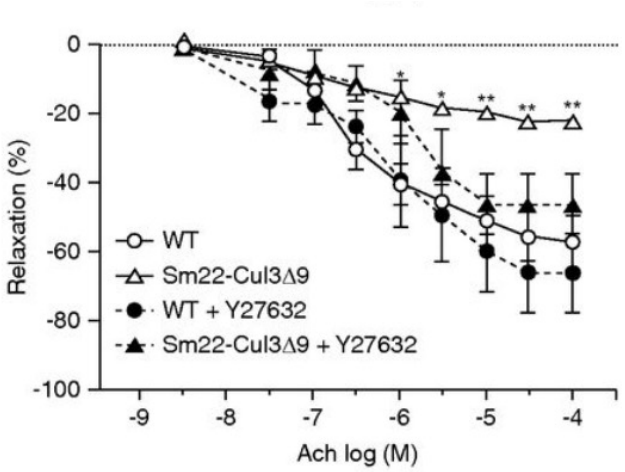
Additional extra-renal pro-hypertensive mechanisms from Cul$^{\Delta 9}$ mice





Control
Vascular Cul3 var
Global Cul3 var





Aortas from *SM22-Cul3Δ9* mice showed increased expression of RhoA, a key molecule involved in regulation of vascular tone,

Abdel Khalek W et al. JASN 2019

Case Report 2: a baby with hypokalaemia and metabolic alkalosis

- 1 y/o baby admitted for failure to thrive

- K^+: 2.1 mM <
- Na^+: 143 mM =
- Cl^-: 94 mM <
- Mg^{2+}: 0.91 mM =
- UCa^{2+}/Creat: 0.31 mg/mg >

Pool question 2:
What is the most likely diagnosis?

1. Gordon Syndrome
2. Gitelman Syndrome
3. Bartter Syndrome
4. Apparent Mineralocorticoids Excess
5. Liddle Syndrome

Differential diagnosis require evaluation of volemia

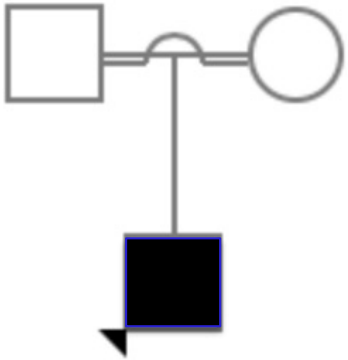
AME

- Hyporkalaemia
- Met. Alkalosis
- Hypercalciuria
- Polyuria
- Low Renin & Aldo
- Hypertension
- CKD

Bartter

- Hyporkalaemia
- Met. Alkalosis
- Hypercalciuria
- Polyuria
- High Renin & Aldo
- Hypotension
- Rare CKD

Case Report 2: a baby with hypokalaemia and metabolic alkalosis

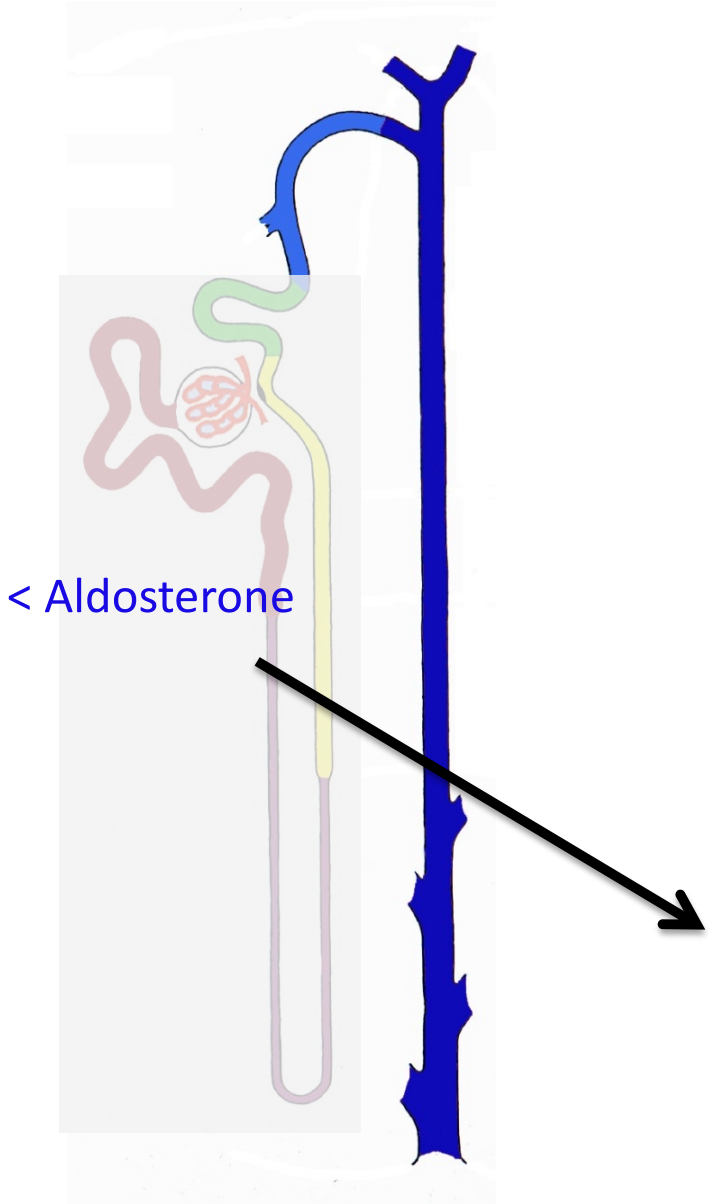


- Born pre-term by consanguineous parents
- Aldosterone & Renin <<
- By 4 y/o Hypertension more evident
- Nephrocalcinosis
- Progressive CKD since 11 y/o, currently CKD IV at 30 y/o
- Genetic Analysis revealed p.Arg208His *HSD11B2* mutation

Apparent Mineralcorticoid Excess Syndrome

- Autosomal Recessive Inheritance
- Failure to thrive and low stature
- Hypertension
- Low renin and aldosterone levels
- Hypokalaemia with metabolic alkalosis
- Polyuria and polydipsia
- Nephrocalcinosis
- High serum cortisol to cortisone (or their metabolites) ratio
- Increased cardiovascular risk

Pathogenesis of AME



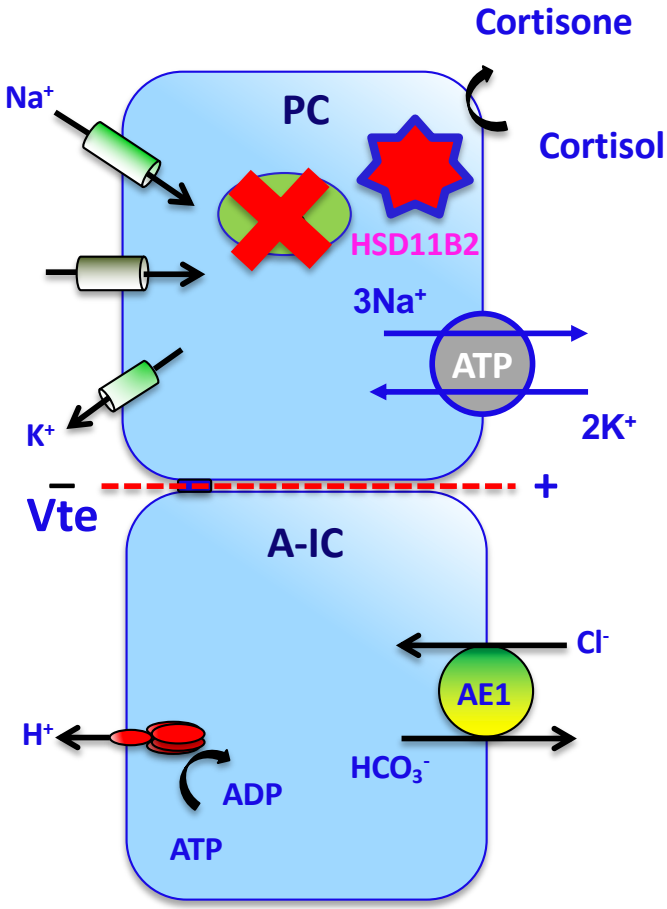
< Aldosterone

Hypertension

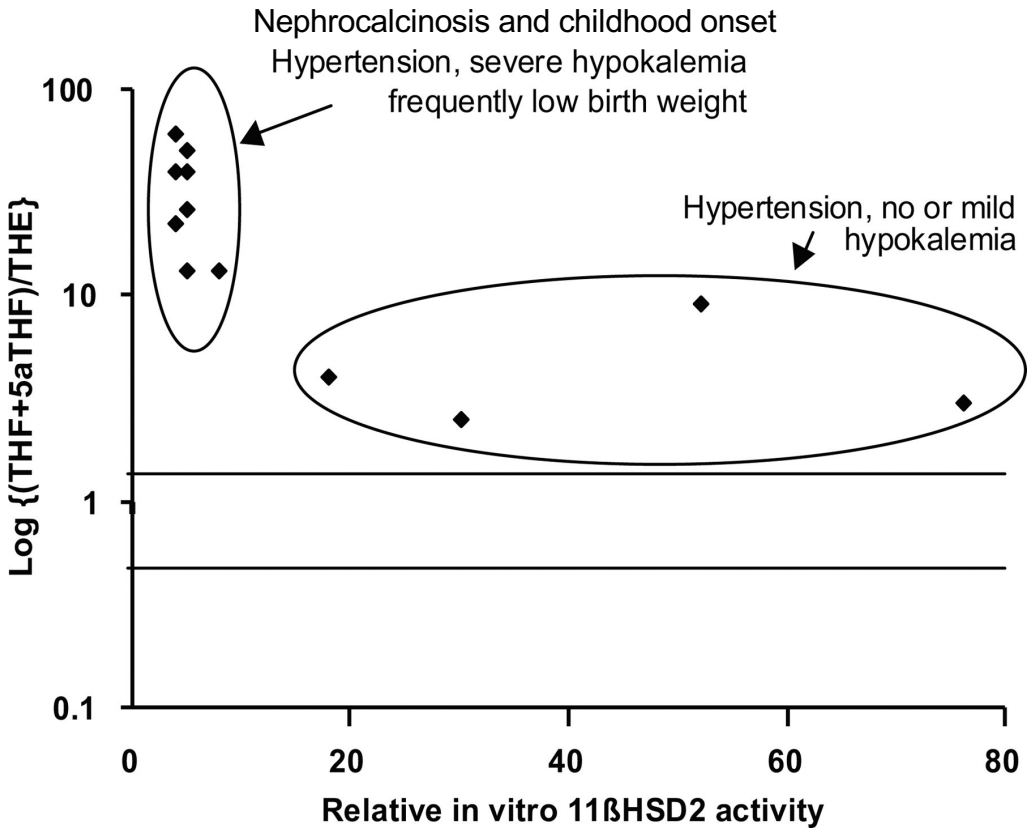
Hypokalaemia

Met Alkalosis

Hypercalciuria & Polyuria



Residual HSD11B2's activity correlates with phenotype severity



AME type I

AME type II

Morineau G. *et al.* JASN 2006

Case Report 3: severe hypertension

- 13 y/o boy presented with:
- BP:185/105 mmHg
- K^+ : 3.2 mM
- Metabolic Alkalosis
- Low Renin Acitivity
- Low serum aldosterone

Tetti M *et al.* Int J Mol Sci 2018

Pool question 3:
What would you consider as differential diagnosis?

1. Gordon Syndrome
2. Renovascular Hypertension
3. Familial Hyperaldosteronism I or II or CAH
4. Apparent Mineralocorticoids Excess
5. Liddle Syndrome

Case Report 3: severe hypertension

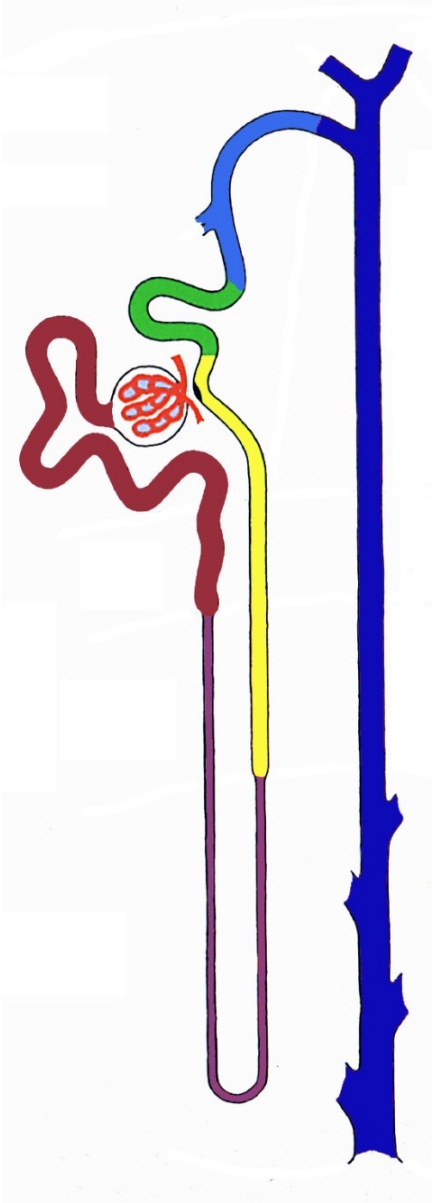
- Steroid profile normal
- 3 months on spironolactone had not clinical and biochemical response

Tetti M *et al.* Int J Mol Sci 2018

Liddle Syndrome

- Autosomal Dominant Inheritance
- Hypertension
- Low renin and aldosterone levels
- Hypokalaemia (*may be absent or very mild*)
- Metabolic alkalosis
- Mineralocorticoid Receptor Antagonist resistant
- Increased cardiovascular risk

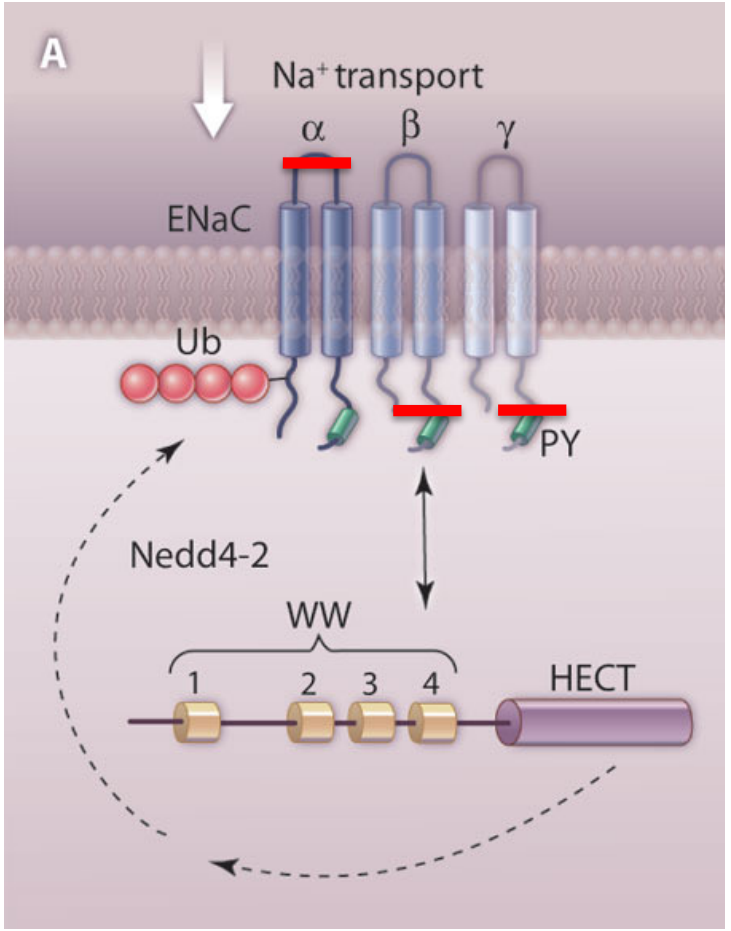
Pathogenesis of Liddle Syndrome



Hypertension

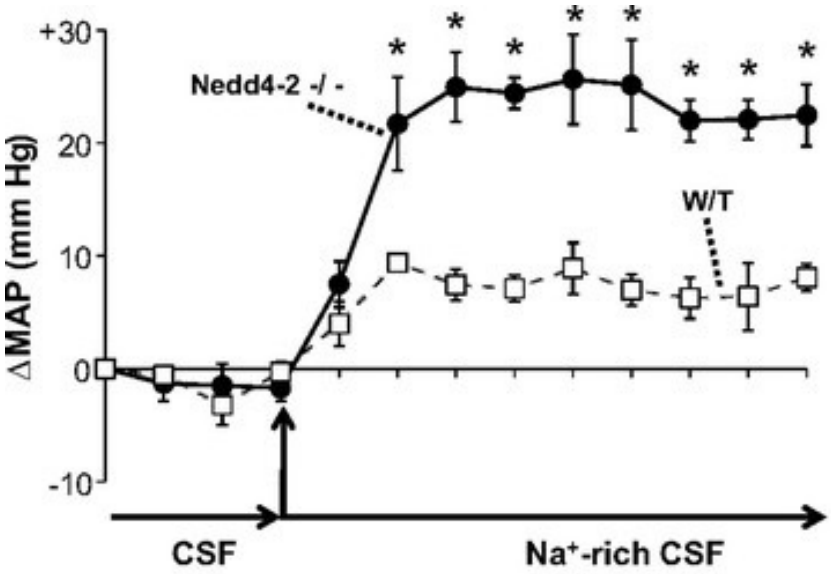
Hypokalaemia

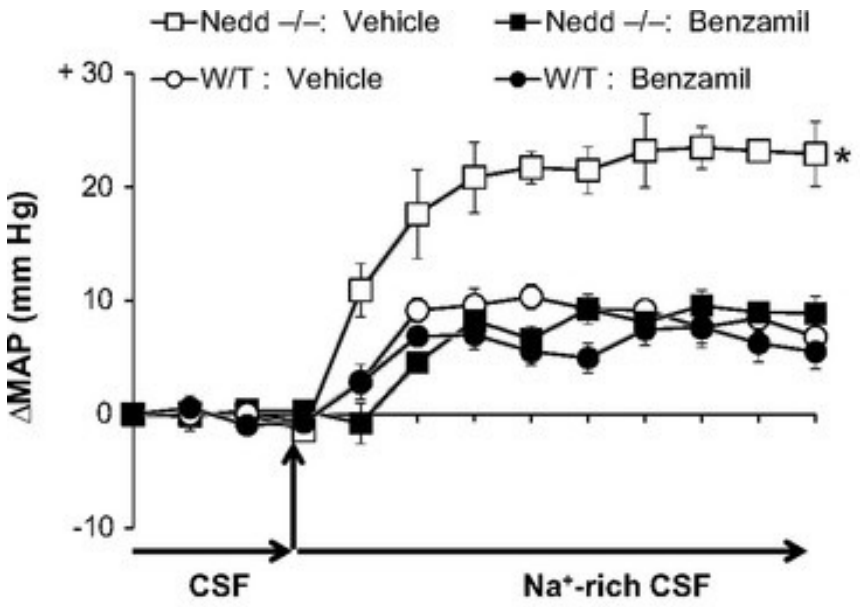
Met Alkalosis



Snyder P et al. Sci. Signal 2009

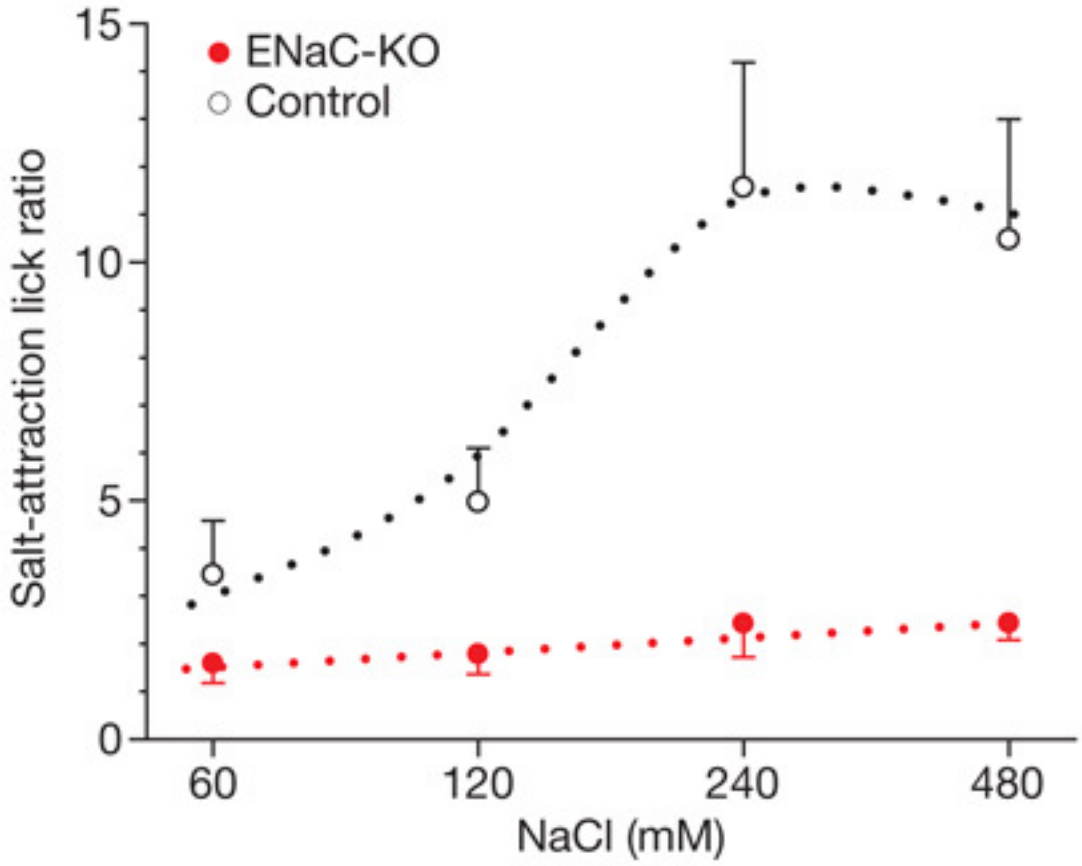
Systemic role of ENaC for BP control





Van Huysse J et al. Hypertension. 2012

ENaC expression on tongue control salt - taste



J Chandrashekar *et al.* Nature 2010

Conclusion

Table 1 Characteristics of and treatments for monogenic forms of low-renin hypertension.

Disorder	Age of onset	Pattern of inheritance	Aldosterone level	Serum potassium level	Genetic test (reference)	Treatment[h]
FH-I (GRA)[a]	Second or third decade	Autosomal dominant	High	Decreased in 50% of cases; marked decrease with thiazides	Commercial	Glucocorticoids
FH-II[a]	Middle	Autosomal dominant	High	Low to normal	Research (11)	Spironolactone, eplerenone
DOC oversecretion due to CAH[b,c]	Childhood	Autosomal recessive	Low	Low to normal	Research (25)	Glucocorticoids
Activating MCR mutation exacerbated by pregnancy[d]	Second or third decade	Unknown	Low	Low to normal	Research (14,15)	Delivery of fetus
AME[b,e]	Childhood	Autosomal recessive	Low	Low to normal	Commercial	Spironolactone, dexamethasone
Liddle syndrome[f]	Third decade	Autosomal dominant	Low	Low to normal	Commercial	Amiloride, triamterene
Gordon's syndrome[g]	Second or third decade	Autosomal dominant	Low	High	Research (22)	Thiazide diuretic, low-sodium diet

Garovic V *et al.* Nat Clin Pract Nephrol 2006

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