ERKNet

The European
Rare Kidney Disease
Reference Network

Monogenic Hypertension

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MARHEA
Maladies Rénales Héréditaires de l'Enfant et de l'Adulte

Hyperkalemia

hypokalemia

↑Na^+ reabsorption → ↑Volemia → ↑Blood pressure

Renin

Geller syndrome (hypertension during pregnancy)

MR

Aldosterone

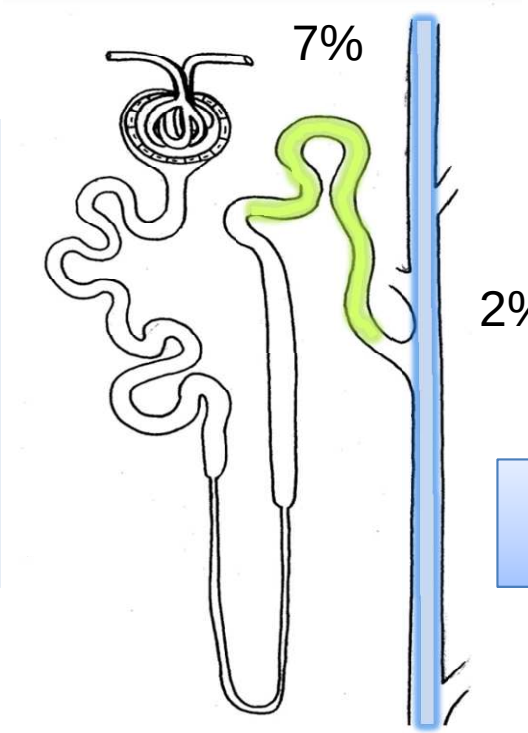
Cortisol → Cortisone

Apparent mineralocorticoid excess (AME)

Familial Hyperkalemic Hypertension

Gordon syndrome

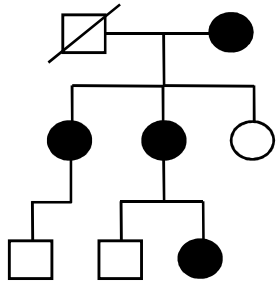
Type 2 Pseudo-hypoaldosteonism

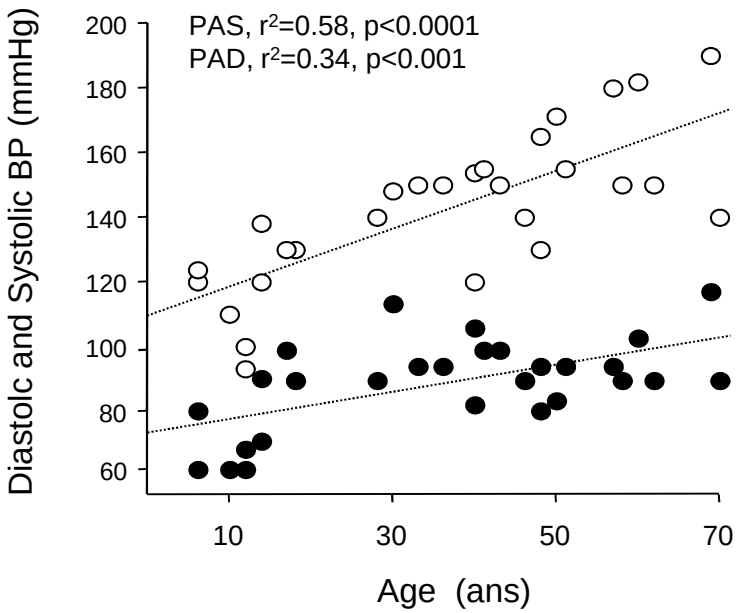


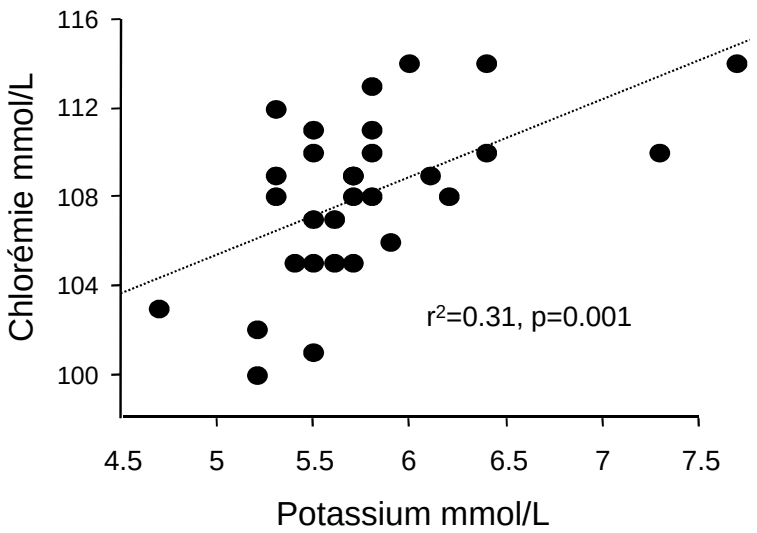
Liddle syndrome

Gordon Syndrome
Familial Hyperkaliemic Hypertension
PseudoHypoaldosteronism type 2

- First description 1960
- Hypertension, normal renal function
- Autosomal dominant transmission
- Hyperkalaemia, hypochloraemia, metab. acidosis
- Low plasma renin, +/- low aldosterone
- High sensitivity to thiazide diuretics

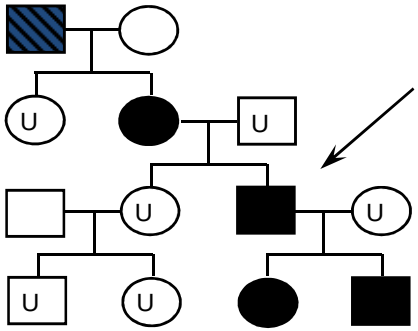






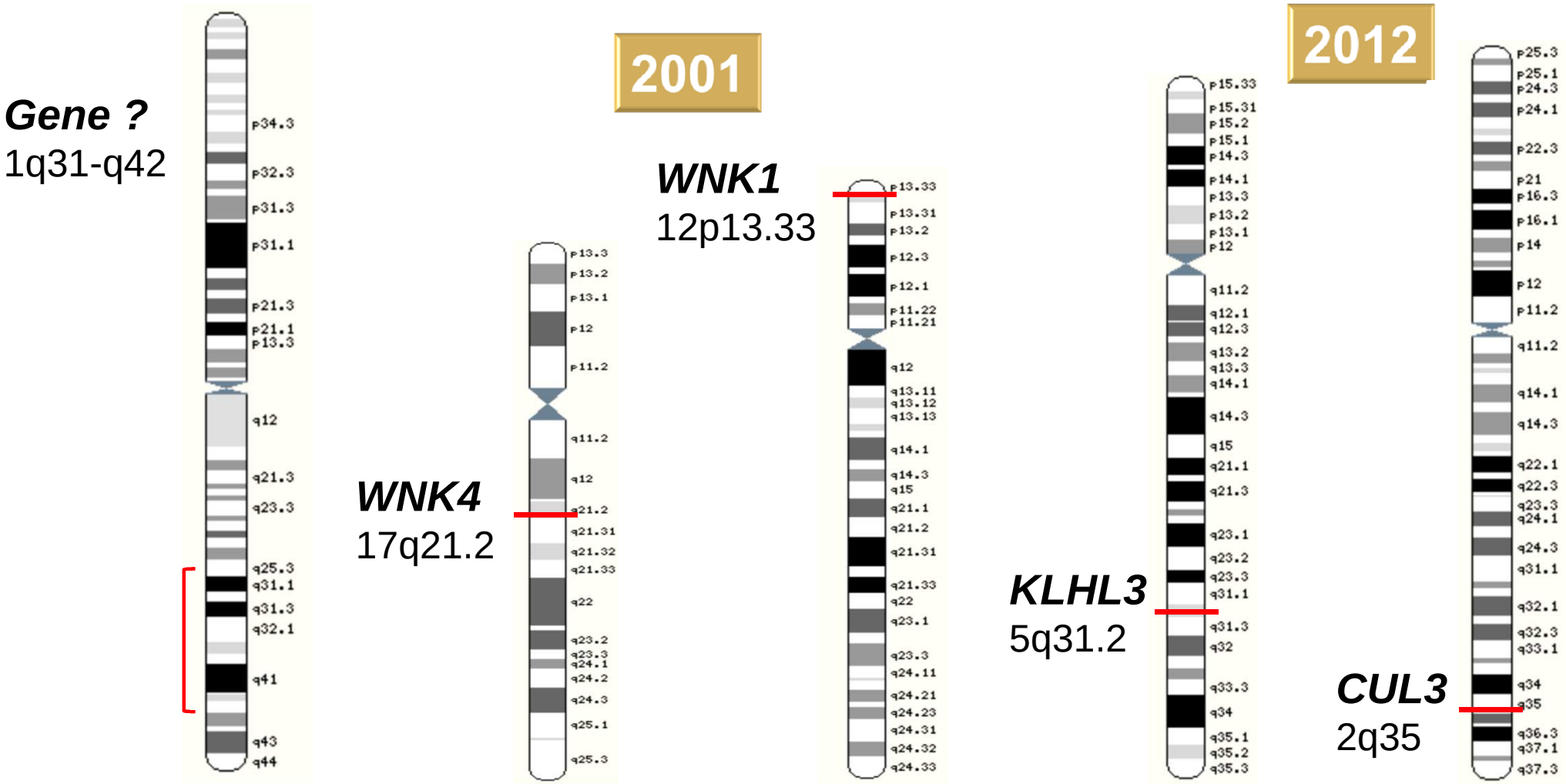
Achard, *Clin Exp Pharmacol Physiol.* 2001, *Am J Med* 2003

Clinical Presentation



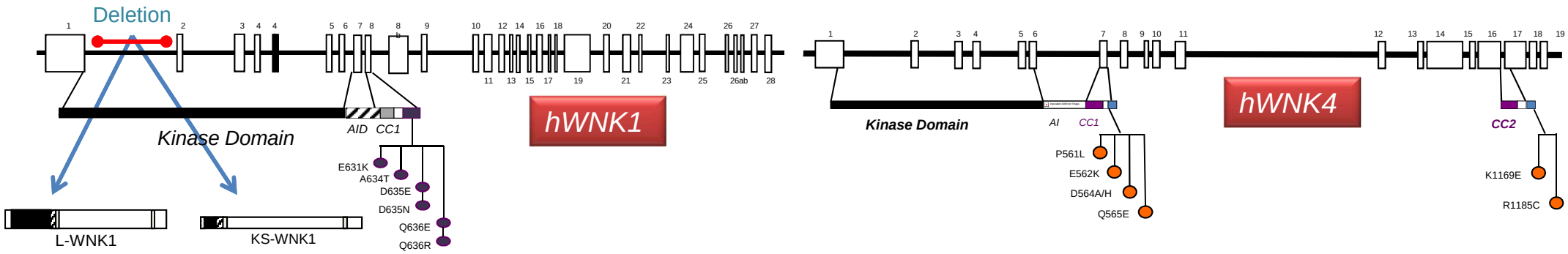
	Age (years)	Sex (M/F)	BMI (Kg/m2)	BP (mmHg)	K^+ (mmol/L)	Creatinine (µmol/L)
Father	36	M	26.2	160/100	5.6-6.4	74
Grandmother	58	F	25.4	170/95	5.2-5.7	65
Daughter	10	F	17.8	120/80	5.3-5.5	42
Son	6	M	15.2	110/70	5.5-5.8	37

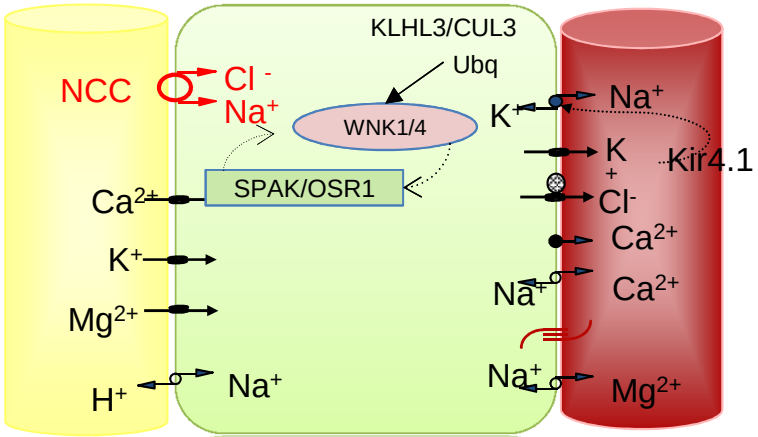
	CO_2T (mmol/L)	Cl- (mmol/L)	Renin act. (ngAI/ml/h)	Aldost. (pg/ml)	Response to HCTZ
Father	18-26	111	0.08	152	++
Grandmother	22	112	-	-	+
Daughter	17-21	111	0.5	144	++
Son	16-20	113	0.4	91	++

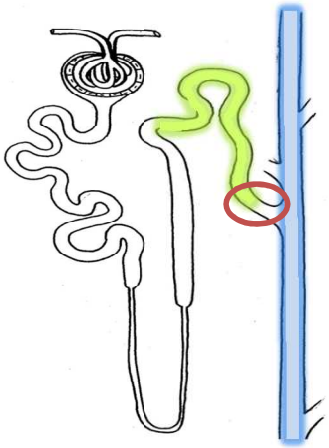


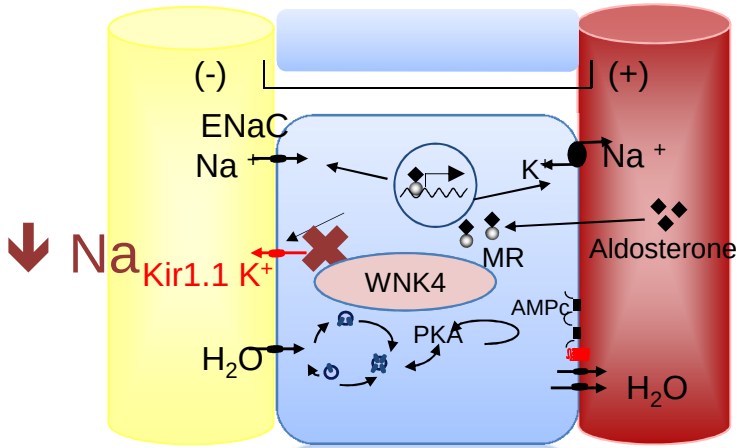
Wilson FH et al Science 2001

Boyden LM et al Nature 2012
Louis-Dit-Picard H et al. Nat Genet 2012





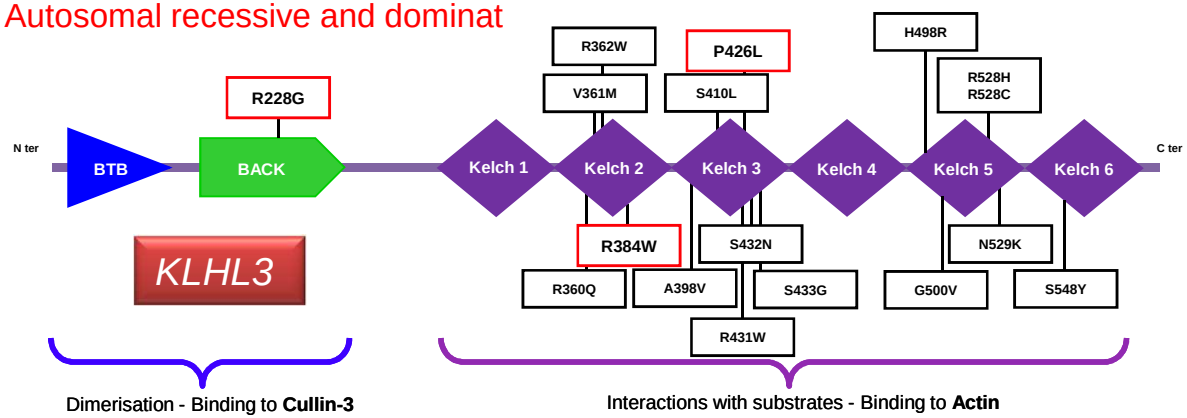


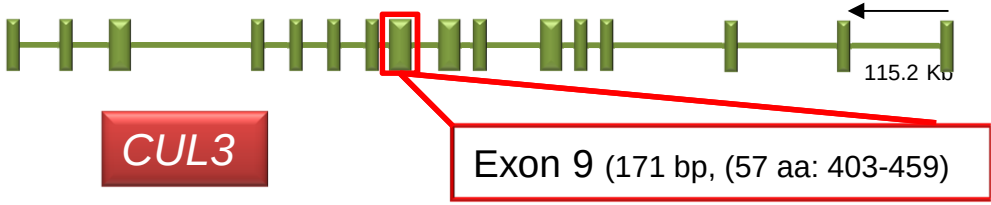


Up-regulation of the NCC
Increased Na^+ reabsorption

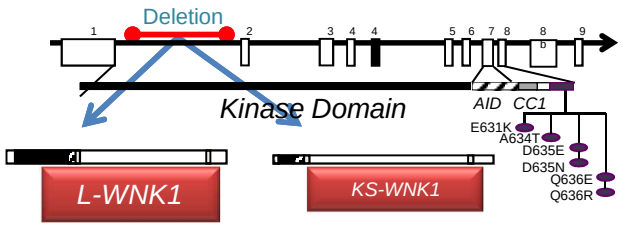
Reduced K^+ secretion by Kir 1.1 (ROMK) channel

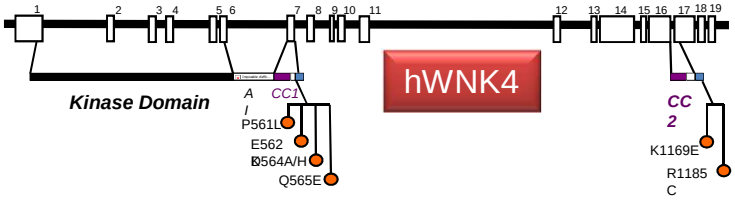
Autosomal recessive and dominat

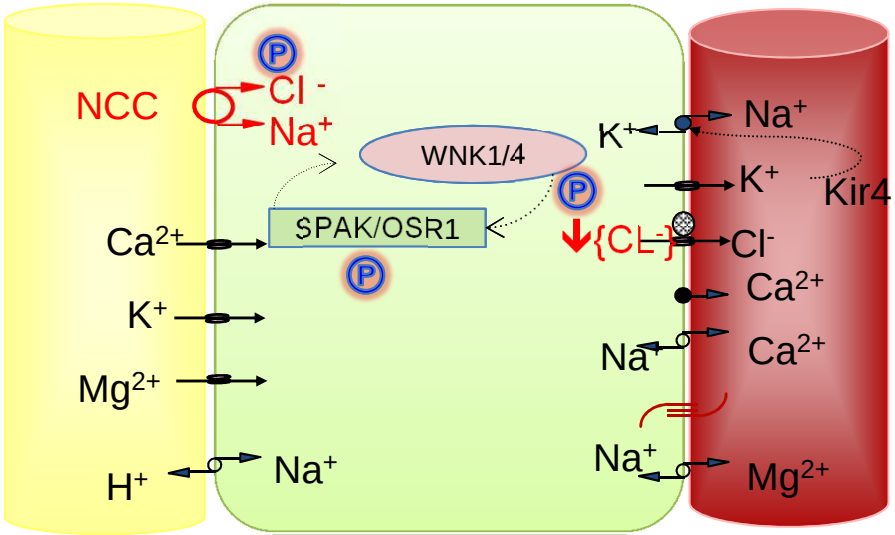


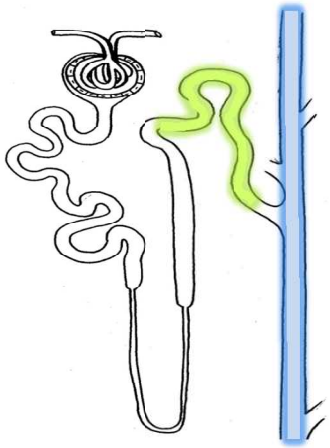


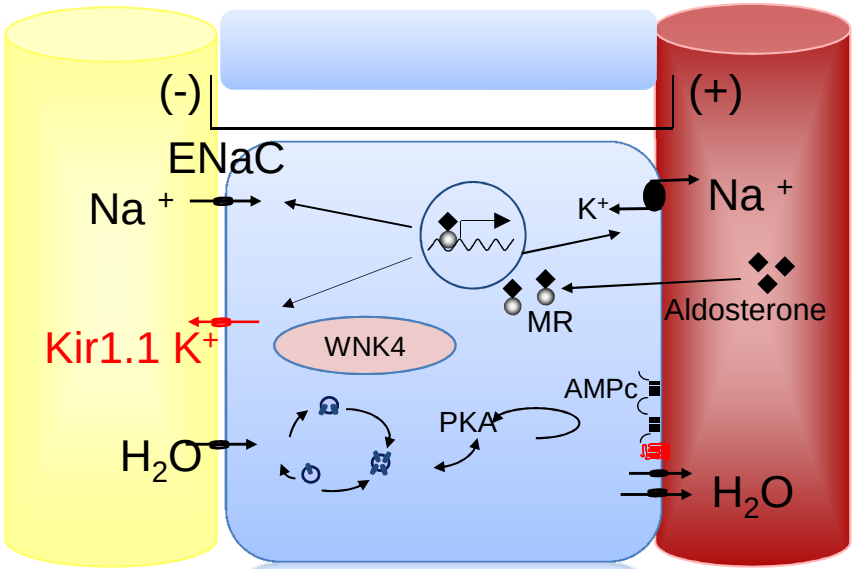
De novo

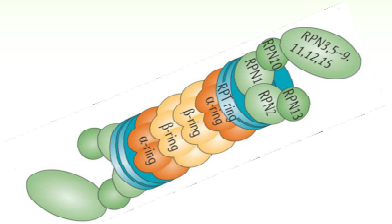

Deletion
Kinase Domain
AID
CC1
E631K
A634T
D635E
D635N
Q636E
Q636R
L-WNK1
KS-WNK1

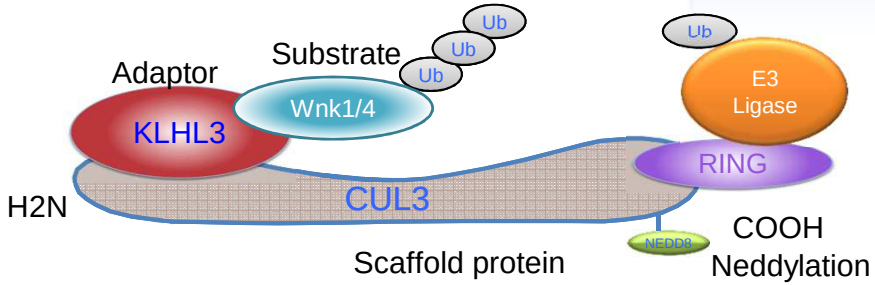

Kinase Domain
hWNK4
CC1
P561L
E562
Q565E
CC2
K1169E
R1185C

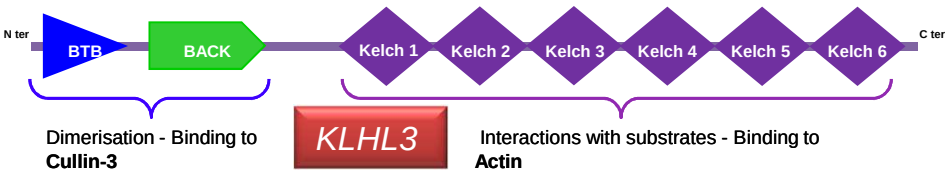

NCC
Cl -
Na+
WNK1/4
SPAK/OSR1
Ca2+
K+
Mg2+
H+
Na+
K+
Na+
K+
Kir4.1
Cl-
Ca2+
Na+
Ca2+
Na+
Mg2+

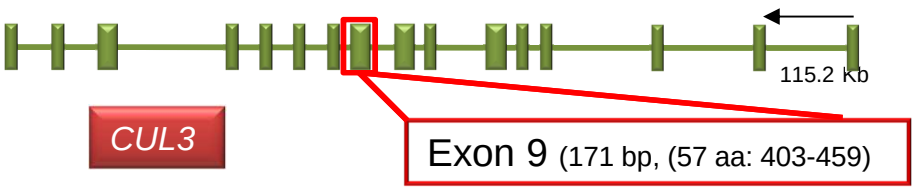


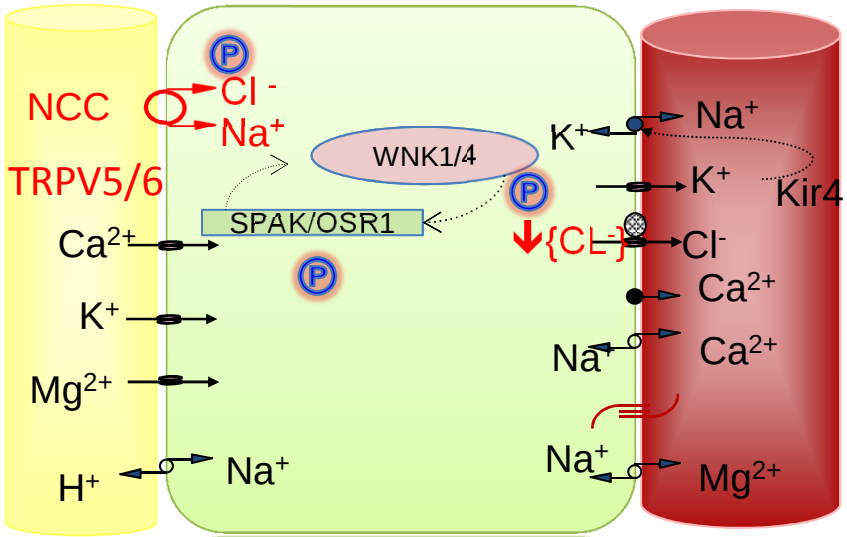

(-)
(+)
ENaC
Na +
K+
Na +
Aldosterone
MR
Kir1.1 K+
WNK4
AMPc
PKA
H2O
H2O

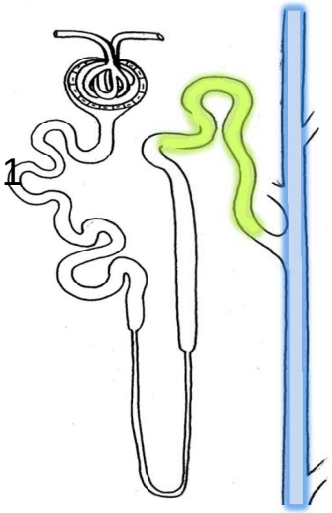

Proteasome

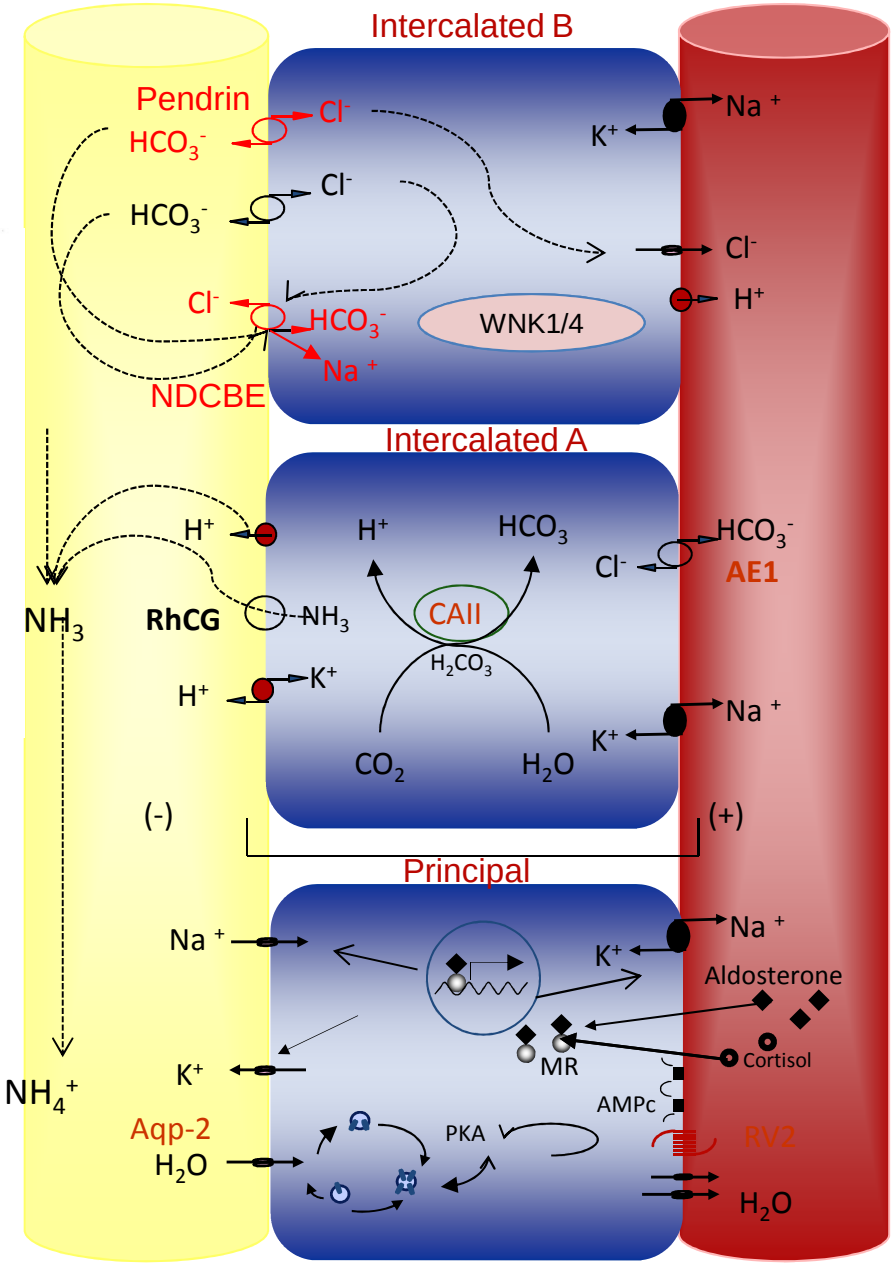

Adaptor
Substrate
Ub
Ub
Ub
Ub
E3
Ligase
KLHL3
Wnk1/4
RING
H2N
CUL3
NEDD8
COOH
Scaffold protein
Neddylation


N ter
BTB
BACK
Kelch 1
Kelch 2
Kelch 3
Kelch 4
Kelch 5
Kelch 6
C ter
Dimerisation - Binding to
Cullin-3
KLHL3
Interactions with substrates - Binding to
Actin


115.2 Kb
CUL3
Exon 9 (171 bp, (57 aa: 403-459)







Hypercalciuria

Jiang Y *et al*.
AJP Renal Physyology 2007
Yang SS et al.
Endocrinology 2010
TRPV5/6 ??

Acidosis

López-Cayuqueo KI, *et al*.
A mouse model of PHAII reveals a novel mechanism of renal tubular acidosis.
Kidney Int. 2018

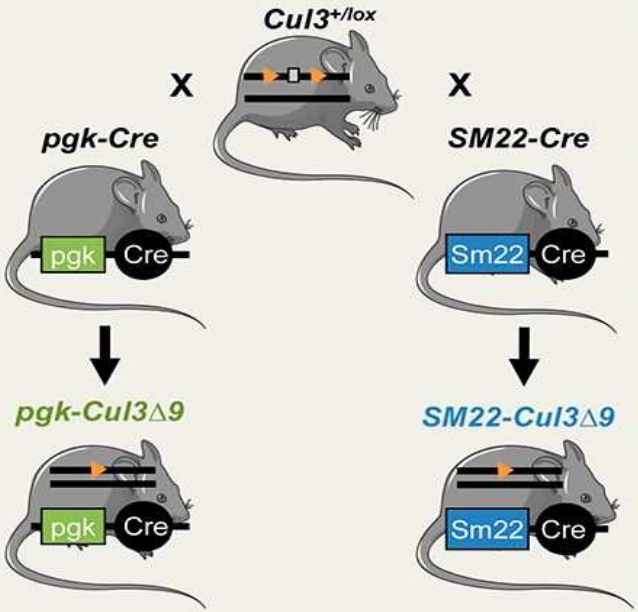
Gordon syndrome : Phenotype/Genotype

Patients	*CUL3*	*KLHL3*	*KLHL3*	*WNK4*	*WNK1*	*WNK1*
	HeteroZ Δex9	HomoZ	HeteroZ	HeteroZ (ex 7-17)	HeteroZ Δintron-1	HeteroZ acidic motif (ex7)
	n = 14	n = 4	n = 16	n = 6	n = 3	n = 26
Age (years)	6,6 [1,3-28]	8.4 [0,3-17]	35,9 [15-56]	31 [5-45]	39 [13-71]	23 [0,1-59]
SBP (mmHg)	160 [124-190]	153 [130-170]	148 [103-190]	147 [107-180]	146 [126-166]	117 [90-148]
DBP (mmHg)	98 [80-115]	90 [71-110]	92 [53-115]	88 [59-110]	89 [76-102]	75 [43-116]
K+ (mmol/L)	7,1 [5,8-9,6]	6.0 [5,1-7,3]	5,9 [5,3-6,7]	5,7 [5,5-6,4]	5,7 [5,3-6,1]	5,6 [5,0-7,1]
Cl- (mmol/L)	112 [104-120]	109 [71-110]	107 [103-112]	113 [109-119]	107 [104-110]	108 [102-112]

Marzukiewicz, in preparation

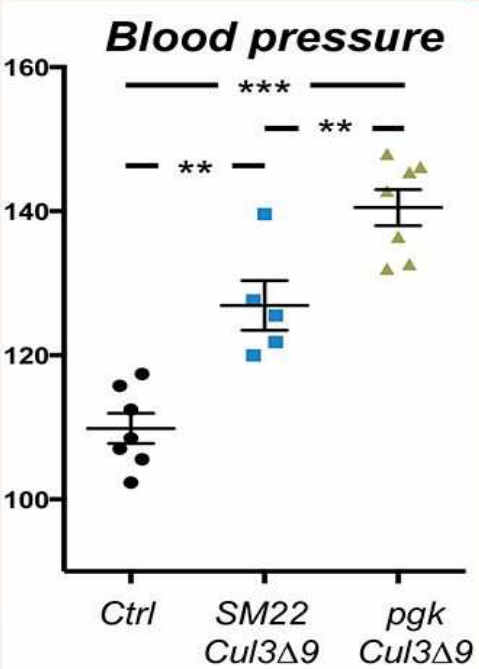
Severe arterial hypertension from Cullin-3 mutations is caused by both renal and vascular effects

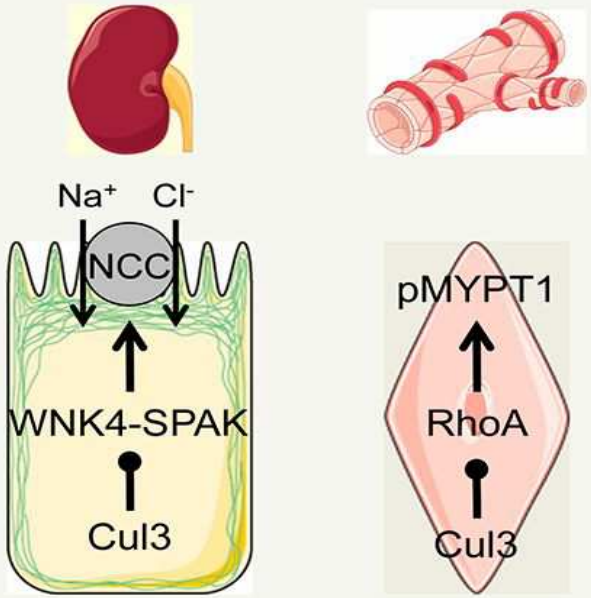
METHODS



We compared two mouse models, expressing the mutant Cul3 protein ubiquitously (*Cul3-Δ9*) or specifically in vascular smooth muscle cells (*Sm22-Cul3Δ9*).

OUTCOME





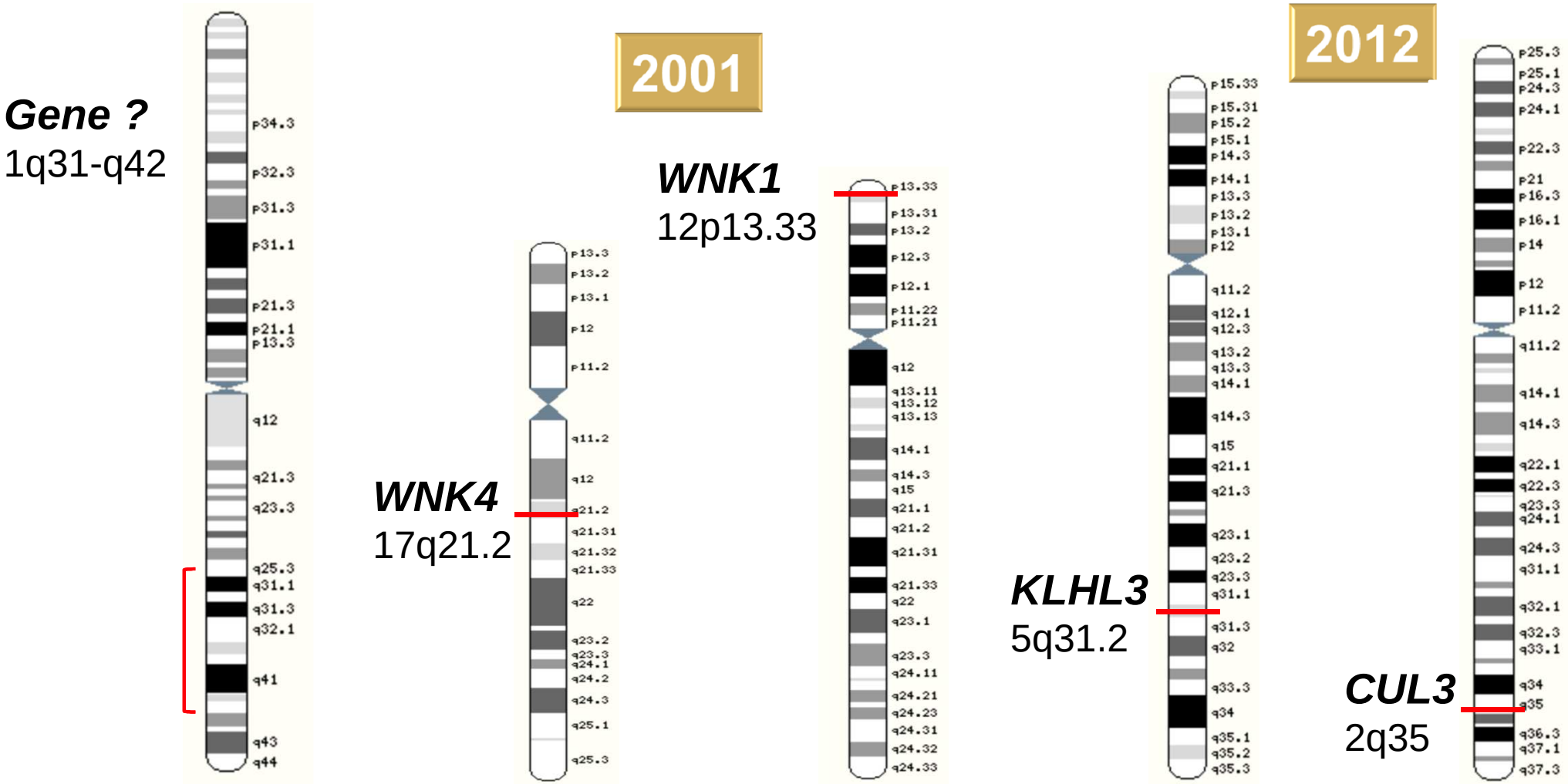
CONCLUSION

CUL3-related hypertension is caused by an alteration of both renal and vascular functions, the latter being associated with an activation of the RhoA signalling pathway and thus a decreased vasorelaxation.

doi:10.1681/ASN.2017121307

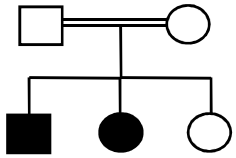
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Waed Abdel Khalek et al. JASN 2019;30:811-823



	PHA IIA	PHA IIB	PHA IIC	PHA IID	PHA IIE
Affected	36% (?)	5%	4%	40%	15%
Inheritance	AD	AD	AD	AD, AR	AD
Type of mutations	?	Intron 1 del. Missense Ex 7	Missense Ex 7 and 17	Missense Others	Splice Ex 9

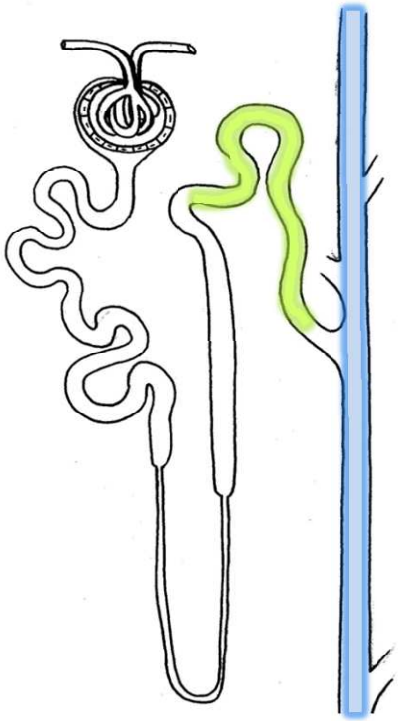
Apparent mineralocorticoid excess (AME)
Ulick syndrome



- Autosomal recessive transmission
- Severe Hypertension (insidious end-organ damage)
- Low plasma renin and aldosterone
- Hypokalaemia
- Low birth weight and failure to thrive
- Polyuria and polydipsia
- Nephrocalcinosis
- Urinary elevated ratio of cortisol (F) to cortisone (E) metabolites
- Cases with mild phenotype (AME type 2)

Apparent mineralocorticoid excess (AME)

Mutations in the *HSD11B2* gene

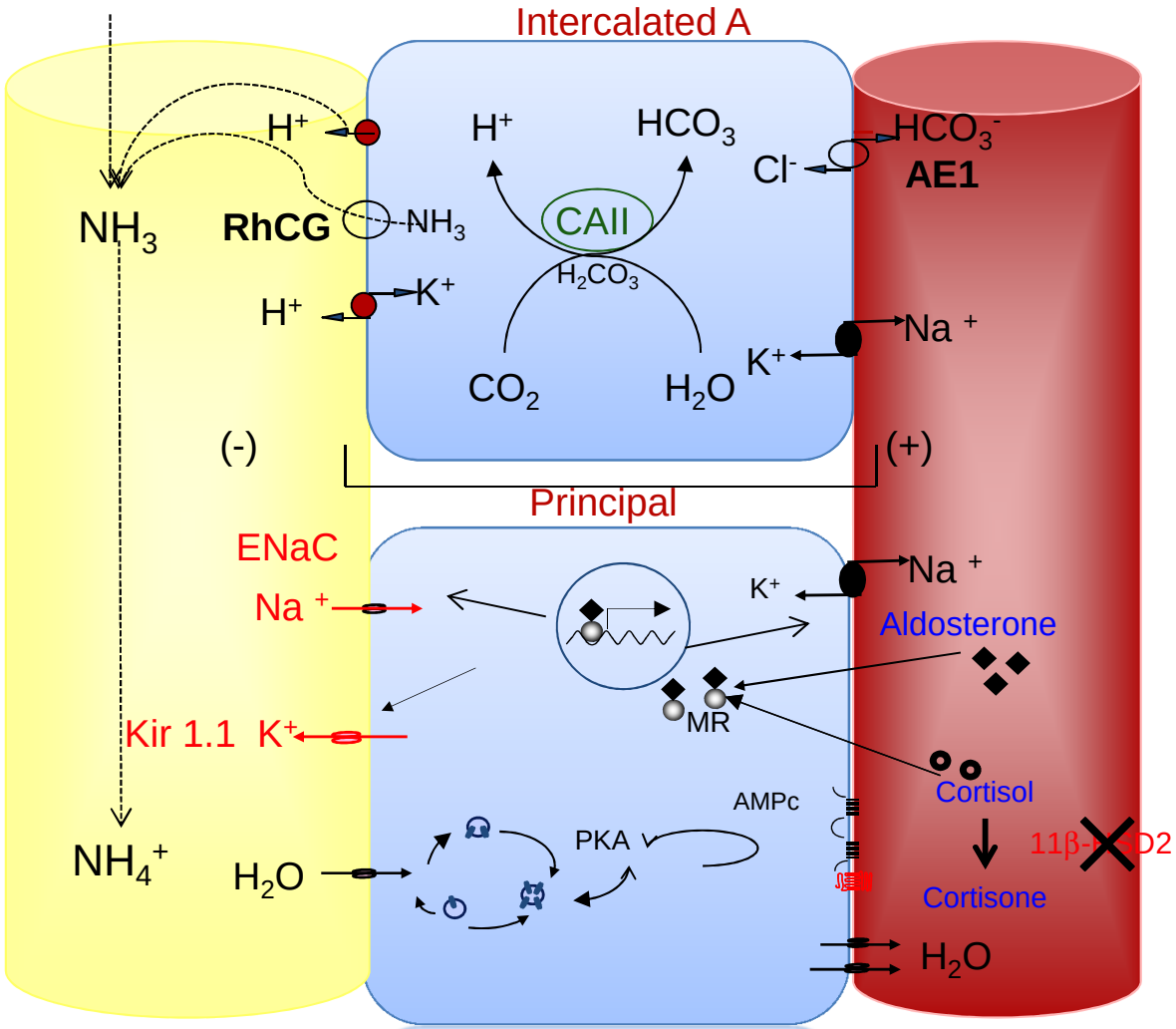


↑Na^+ reabsorption

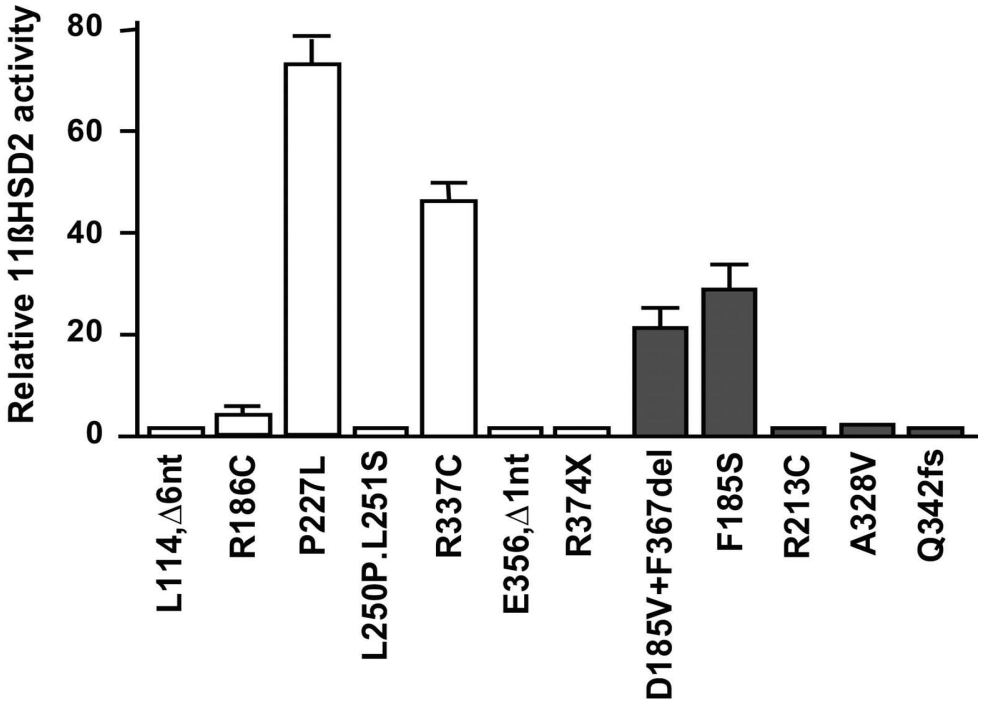
↑Volemia

↑Blood pressure

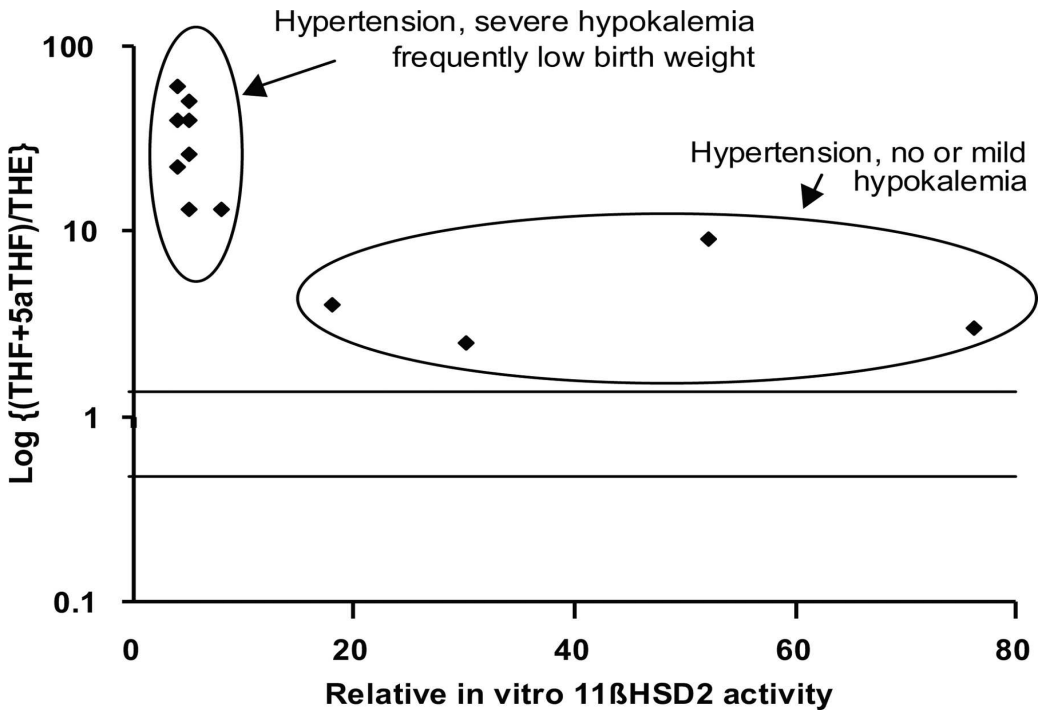
↓Renin ↓Aldosterone



Genotype–phenotype correlations in apparent mineralocorticoid excess (AME).

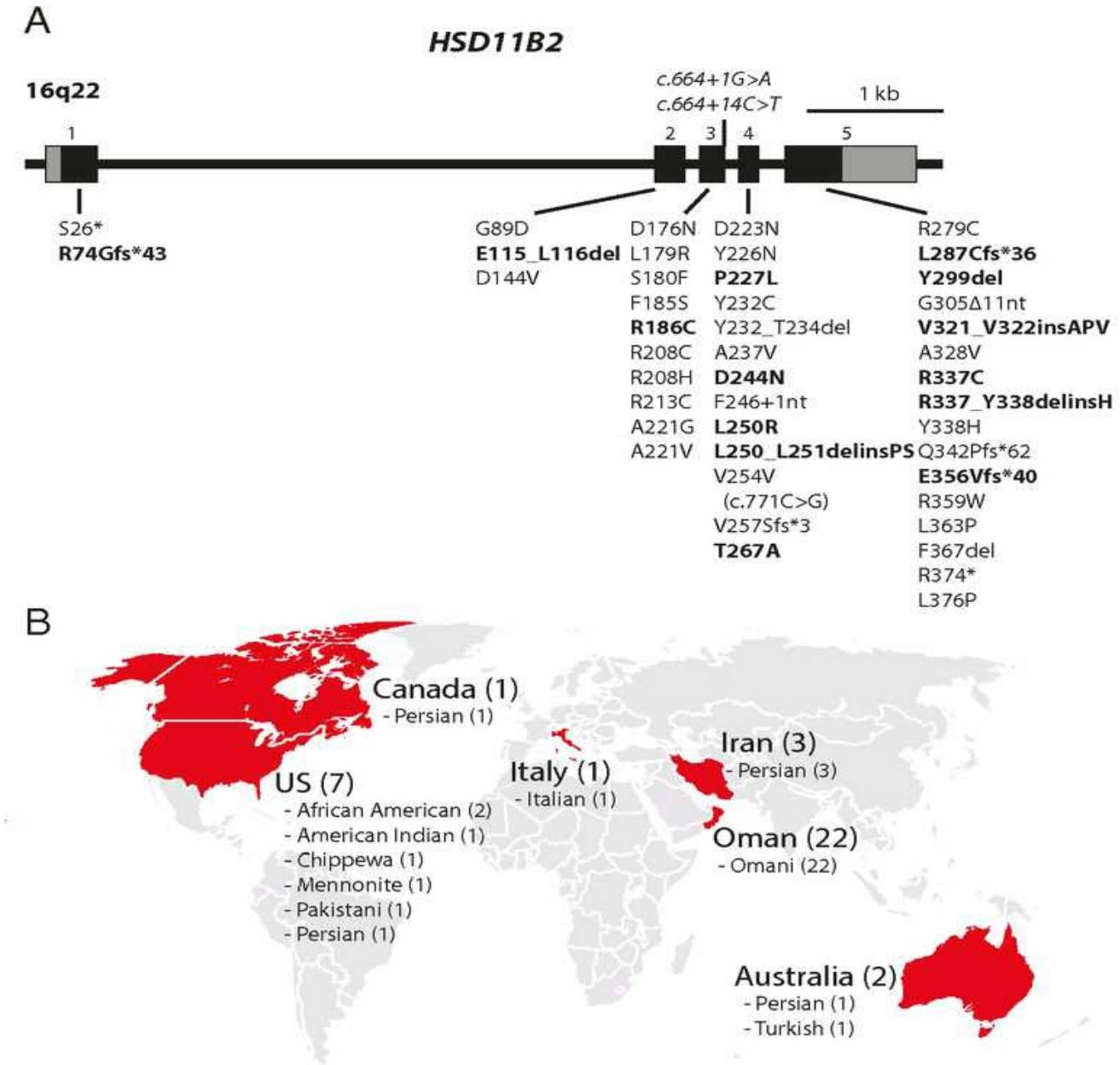


	L114,Δ6nt	R186C	P227L	L250P.L251S	R337C	E356,Δ1nt	R374X	D185V+F367del	F185S	R213C	A328V	Q342fs
Low birth weight	+	+	-	+	-	+	+	-	+	+	-	-
Hypokalemia	++	+	-	++	(+)	++	++	(+)	-	++	+	++
Hypertension	++	++	+	++	++	++	++	++	++	++	++	++
(THF+5αTHF)/THE	40	13	3	40	9	60	50	4	2.5	13	22	26



Gilles Morineau et al. JASN 2006;17:3176-3184

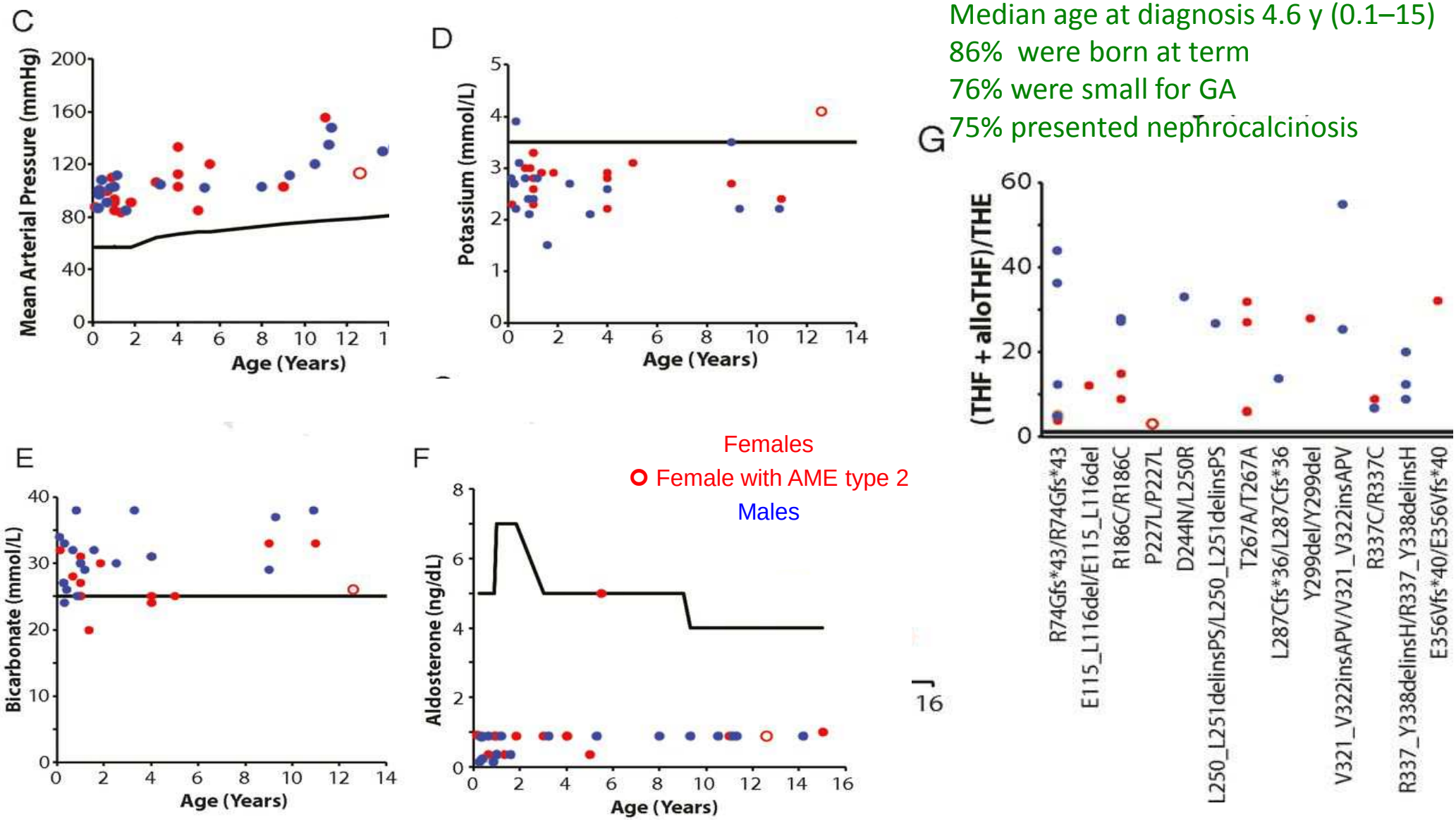
Clinical profile for patients with AME due to HSD11B2 deficiency from seven nations of the International Consortium for Rare Steroid Disorders.



Mabel Yau et al. PNAS 2017;114:52:E11248-E11256

Clinical profile for patients with AME due to HSD11B2 deficiency from seven nations of the International Consortium for Rare Steroid Disorders.

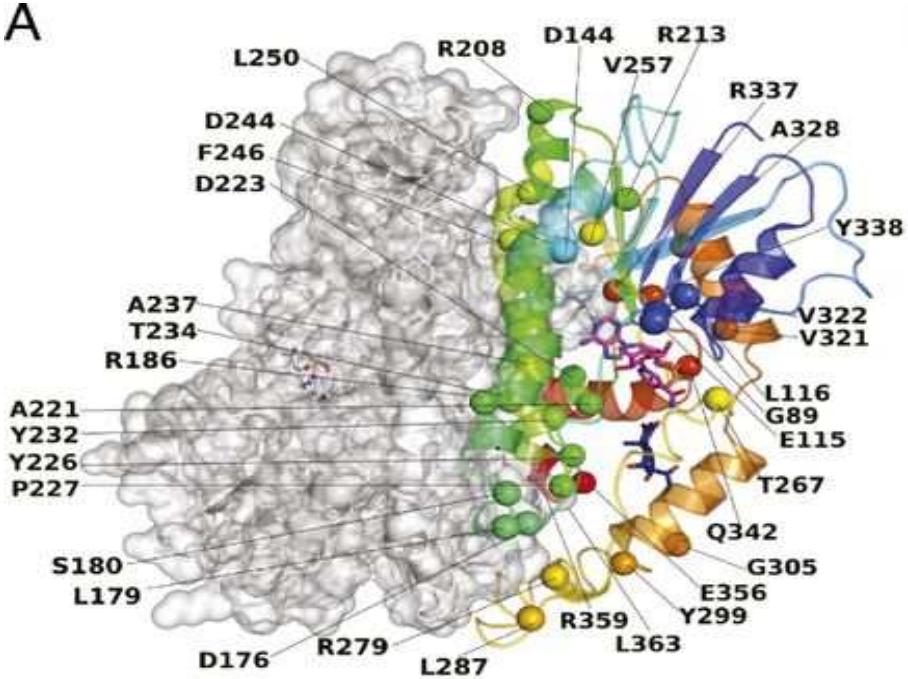
Median age at diagnosis 4.6 y (0.1–15)
86% were born at term
76% were small for GA
75% presented nephrocalcinosis



Mabel Yau et al. PNAS 2017;114:52:E11248-E11256

Disruptive mutations affecting the dimer interface of HSD11B2.

A



B

Disease				Engineered			
Mutant	ΔΔG (kcal/mol)	Mutant	ΔΔG (kcal/mol)	Mutant	ΔΔG (kcal/mol)	Mutant	ΔΔG (kcal/mol)
G89D	0.5	P227L	0.3	D91N	1.6	Y338H	1.8
D144V	1.7	Y232C	3.8	E115G	3.3	Y338A	2.7
D176N	2.1	A237V	0.8	E115K	2.6	Y338F	0.6
L179R	0.5	D244N	1.1	Y232F	1.0	Y339A	3.3
S180F	1.2	L250R	2.3	K236R	0.3	Y339H	1.8
F185S	1.5	L250P	3.2	R335K	2.2	Y339F	0.8
R186C	4.2	L251S	0.4	R335Q	1.6		
R208H	1.7	T267A	0.4	R335A	2.6		
R208C	4.8	R279C	4.1	R336K	1.2		
R213C	4.8	A328V	0.7	R336A	1.3		
A221V	0.4	R337C	2.8	R336Q	2.4		
A221G	1.3	Y338H	2.9	R337K	4.1		
D223N	1.0	R359W	4.0	R337A	2.8		
Y226N	2.0			R337Q	3.0		

Not studied: L363P, L376P

Severe AME:
mutants that enhance dimerization
Disrupt the substrate- or coenzyme-binding site, or severely impair structural stability.

Mild AME (type 2): P227L, R279C, and R359W indirectly disrupting substrate binding or causing mild alterations in protein structure.
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Mabel Yau et al. PNAS 2017;114:52:E11248-E11256

PNAS

Apparent mineralocorticoid excess (AME)

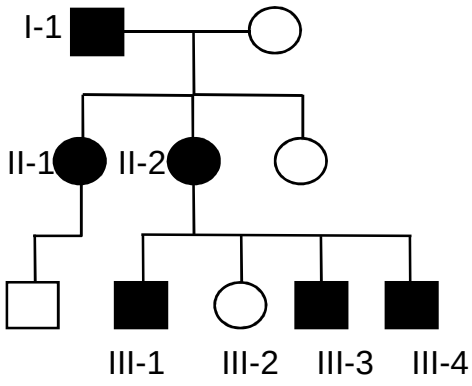
Follow-up data – n = 16

- Cardiovascular complications
  - 3 patients died from cardiac arrest at 16, 16, and 17 yr.
  - Left ventricular hypertrophy :12/16
  - Hypertensive retinopathy: 10/16
  - For the 13 surviving patients:
    - 12 had persistent left ventricular hypertrophy,
    - 3 showed aortic root dilation,
    - 2 had aortic insufficiency.
- Other complications
- Nephrocalcinosis: present in 8/9 patients after 4.1–14.5 y.
- CKD: 4 patients developed 10 y after diagnosis.
- Renal transplantation: 2 patients. Remission of the low-renin hypertension and hypokalemic

Liddle Syndrome

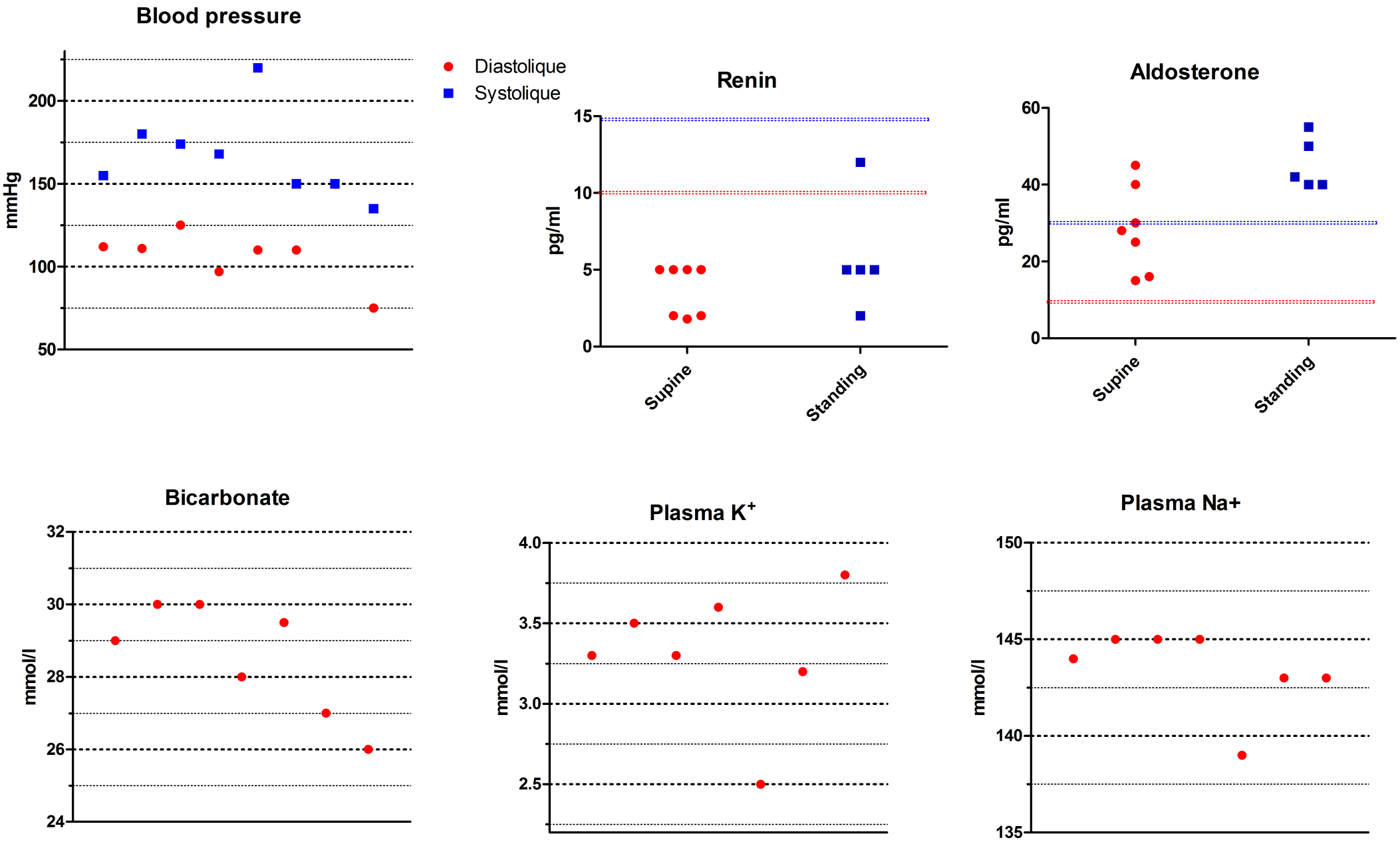
First description in 1963

- Autosomal dominant transmission
- Severe or moderate Hypertension
- Hypokalaemia
- Metabolic alkalosis
- Low plasma renin and aldosterone



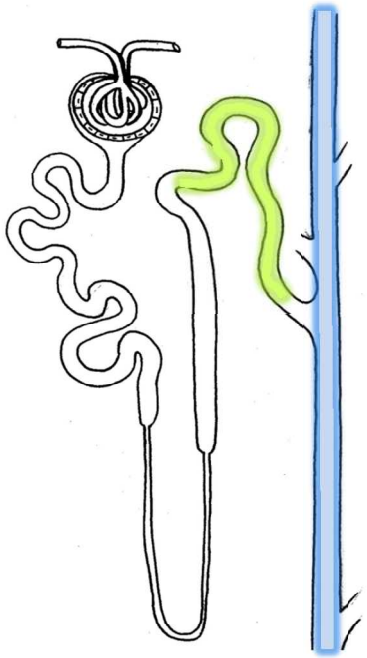
	Mother	Children			
	II-1	III-1	III-2	III-3	III-4
Age	43	23	21	19	15
Sex	F	M	F	M	M
BMI (kg/m$^{2)}$	20.4	19.6	23.3	23.2	18.1
Age at diagnosis	28	21	-	19	14
BP (no treatment)	192/96	174/125	124/72	180/111	155/112
BP (amiloride)	134/83	138/74	-	127/80	129/81

Liddle Syndrome – Data at diagnosis



Liddle Syndrome

Gain-of-function subunits of ENaC

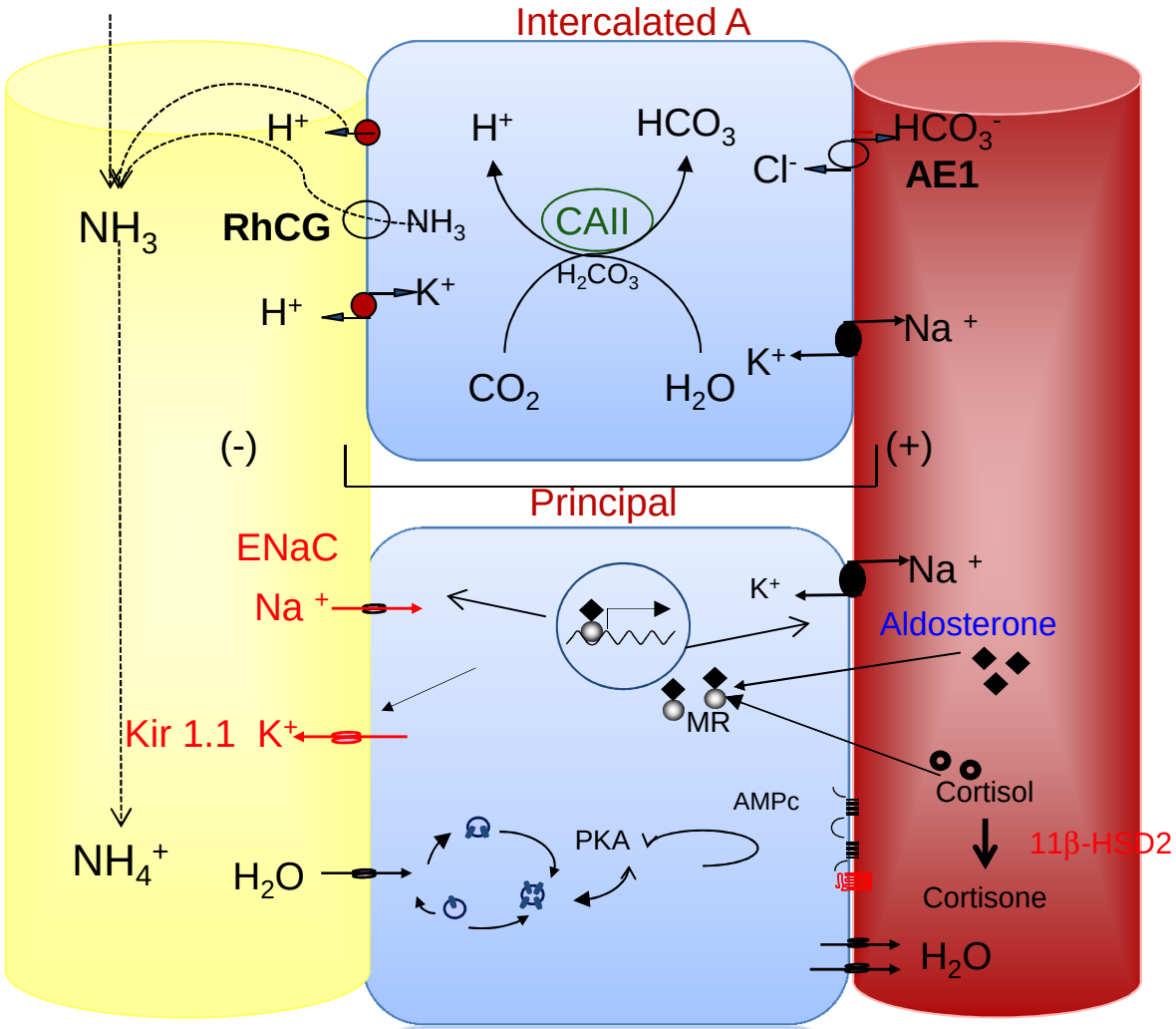


↑Na^+ Reabsorption and K+ secretion

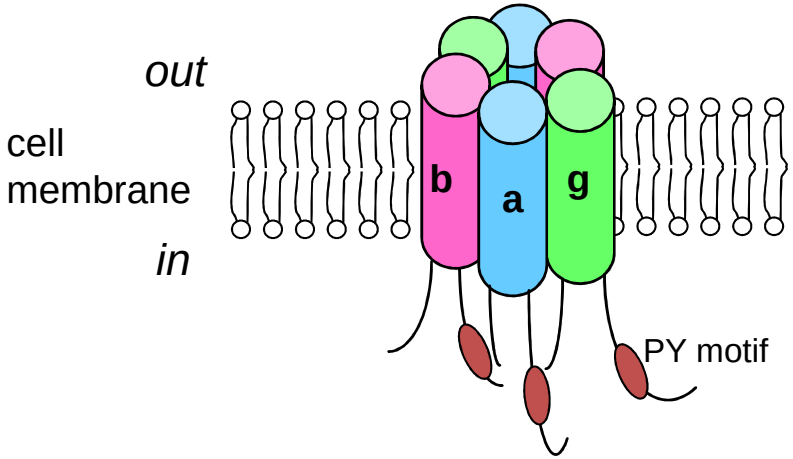
↑Volemia

↑Blood pressure

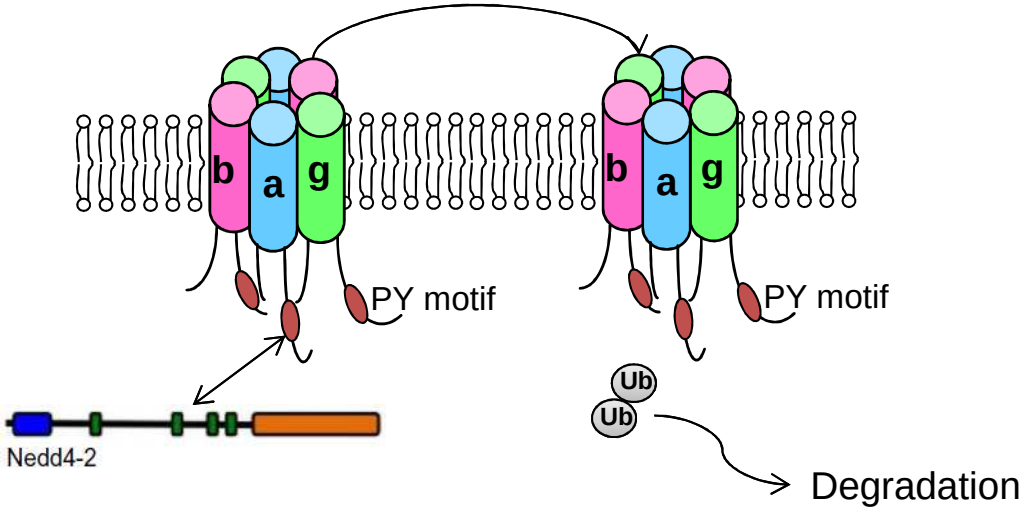
↓Renin ↓Aldosterone



ENaC



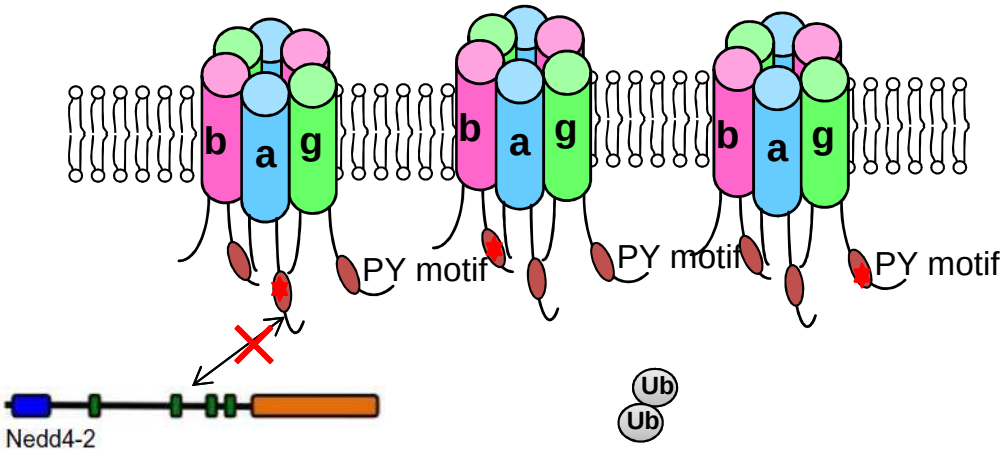
Ubiquitination



PY motif

```
a  --ALTAPPPAYATLGPRP--
b  --IPGTPPPNYDSLRLQP--
g  --VPGTPPPKYNTLRLER--
```

Liddle syndrome



Cell surface accumulation

A Missense Mutation in the Extracellular Domain of Alpha ENaC Causes Liddle Syndrome

METHODS

Phenotypic, genetic, and electro-physiological characterization of a novel Liddle family (resistant hypokalemic hypertension) without mutations in β- or γ-ENaC

- Hypertension
- Suppressed renin & aldosterone
- Active ENaC (amiloride sensitivity)
- Mutation (Cys479 to Arg)

OUTCOME

The C479R mutation increased amiloride-sensitive ENaC current in oocytes ~2-fold due to higher open probability

CONCLUSION

Novel mutation in extracellular domain αENaC causes Liddle syndrome by increasing channel activity

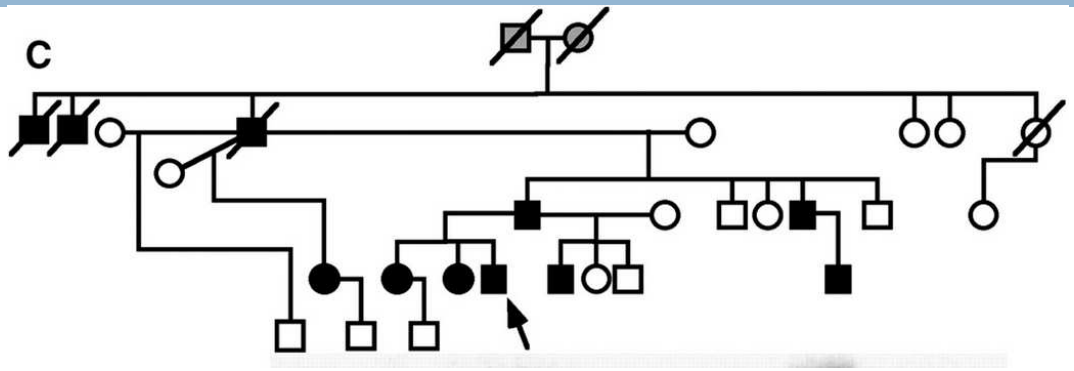
Mahdi Salih, Ivan Gautschi, Miguel X. van Bemmelen, Michael Di Benedetto, Alice S. Brooks, Dorien Lugtenberg, Laurent Schild, Ewout J. Hoorn. **A Missense Mutation in the Extracellular Domain of Alpha ENaC Causes Liddle Syndrome.** JASN ASN201611163
doi:10/1681/ASN.2016111163

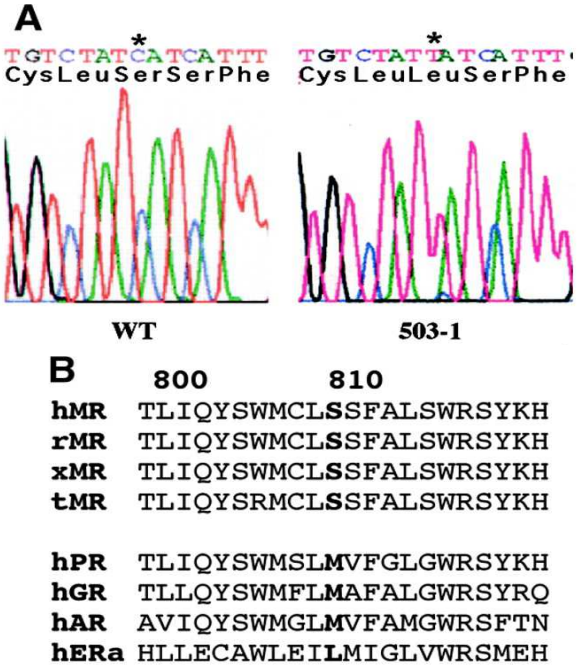
JASN

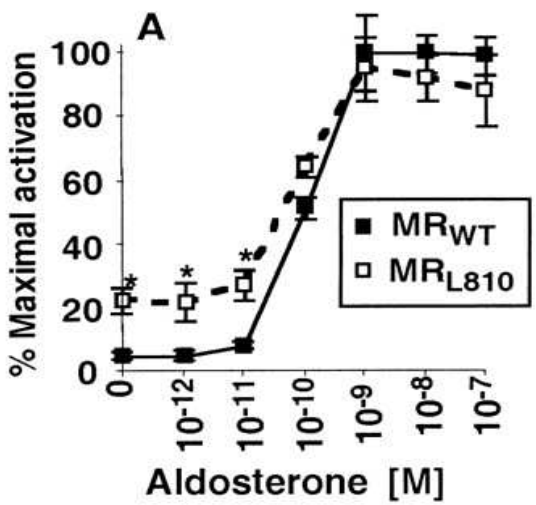
Mahdi Salih et al. JASN 2017;28:3291-3299

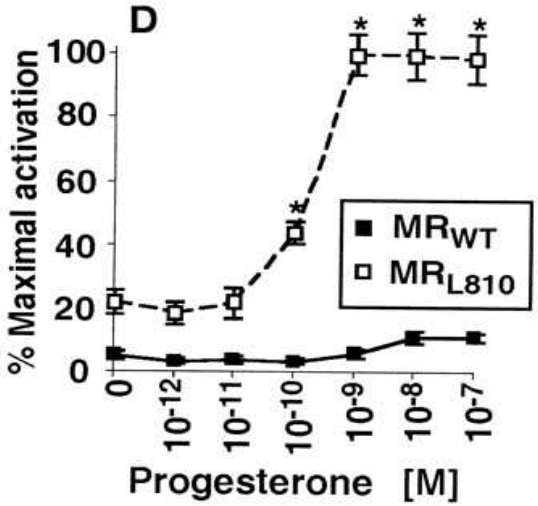
Hypertension Exacerbated by Pregnancy
Geller Syndrome

- Autosomal dominant transmission
- Low-renin and low-aldosterone hypertension
- Hypokalaemia
- Early onset
- Worsening during pregnancy









NR3C2 gene – Mineralocorticoid receptor (MR)

Geller et al. Science 2000; 289: 119

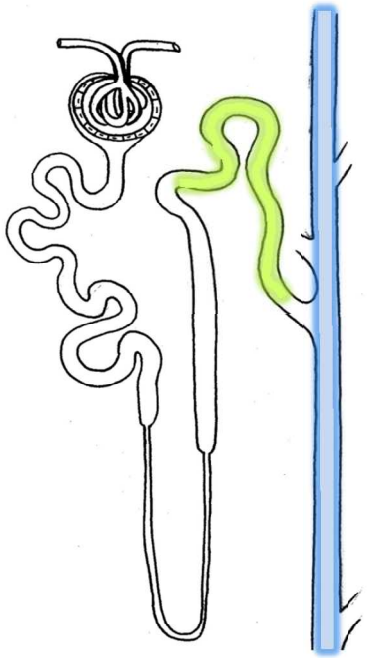
Activating Mineralocorticoid Receptor Mutation

Clinical parameter	MR_{L810}^{+} (=8)	MR_{L810}^{-} (n=11)	P
Age	29.1 ± 6.3	32.9 ± 8.1	0.88
HTN < age 20	100 %	0 %	<0.0001
anti-HTN medication	1.5 ± 0.27	0.2 ± 0.12	0.0001
SBP (mmHg)	167 ± 11	126 ± 10	0.014
DBP (mmHg)	110 ± 6	78 ± 6	0.002
Serum K^+ (mM)	3.91 ± 0.18	4.36 ± 0.11	0.08
Serum HCO_3^- (mM)	27.1 ± 0.87	26.4 ± 0.83	0.59
Serum aldosterone (ng/dl)	2.48 ± 0.68	12.1 ± 2.96	0.008
Urinary aldosterone (µg/24 hrs)	<2	7.75 ± 1.55	0.03

Geller et al. Science 2000; 289: 119

Hypertension Exacerbated by Pregnancy

Gain of fonction mutation of mineralocorticoid receptor



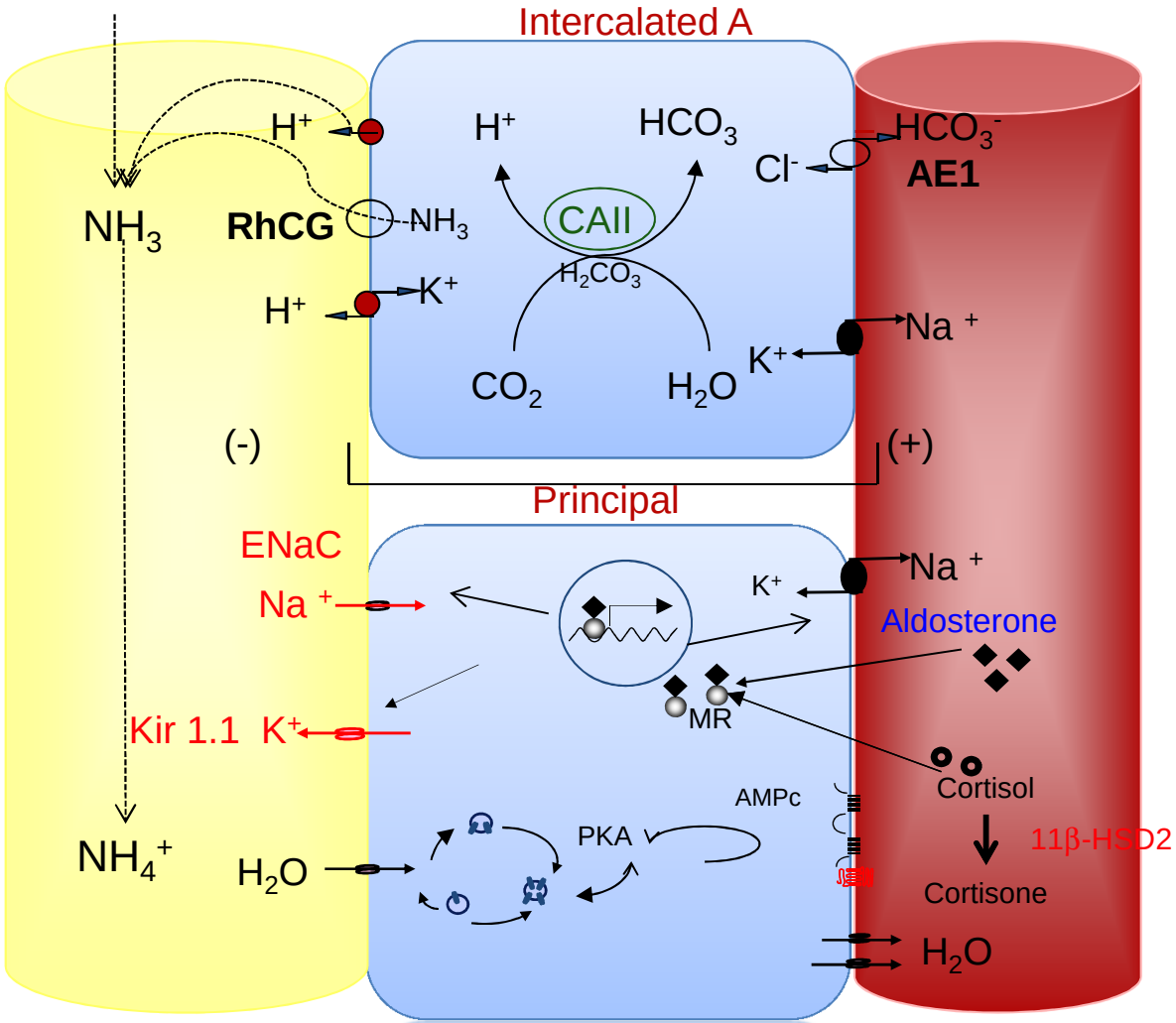
↑Na^+ reabsorption

↑Volemia

↑Blood pressure

↓Renin

↓Aldosterone



Treatment

	Gordon syndrome	Apparent mineralocorticoid excess	Liddle syndrome	Hypertension exacerbated by pregnancy
Main treatment	Thiazides diuretics	MR Antagonists: spironolactone or eplerenone Dexamethasone	ENaC Blockers Amiloride Triamterene	Amiloride
Other treatments	Amlodipine (for CUL3 patients)	Amiloride		

Conclusion - Monogenic hypertension

- ✓ Diseases associated with increase of Na reabsorption in the DCT and CD
- ✓ Low renin hypertension
- ✓ Abnormal plasma potassium
- ✓ Precise diagnosis is important for:
  - ✓ Genetic counselling
  - ✓ Specific and early treatment
  - ✓ Prevention of complications

ERKNet

The European
Rare Kidney Disease
Reference Network

Next webinar: June 25, ” XLH Recommendations"

Dieter Haffner

Hannover (Germany)