APCN x TSN 2025
23rd Asian Pacific Congress of Nephrology
Gene, Immunology, Vast, MEtabolism at its Finest!

Update in Dyskalemia

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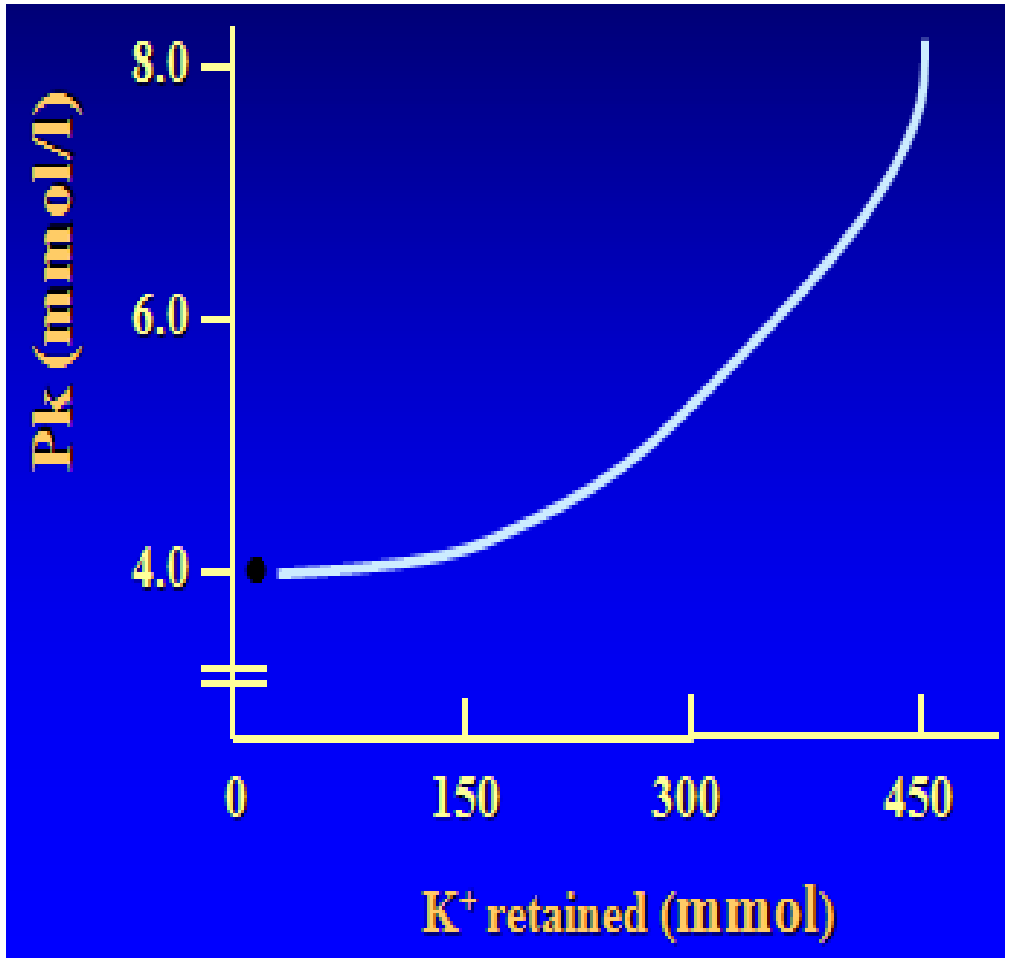
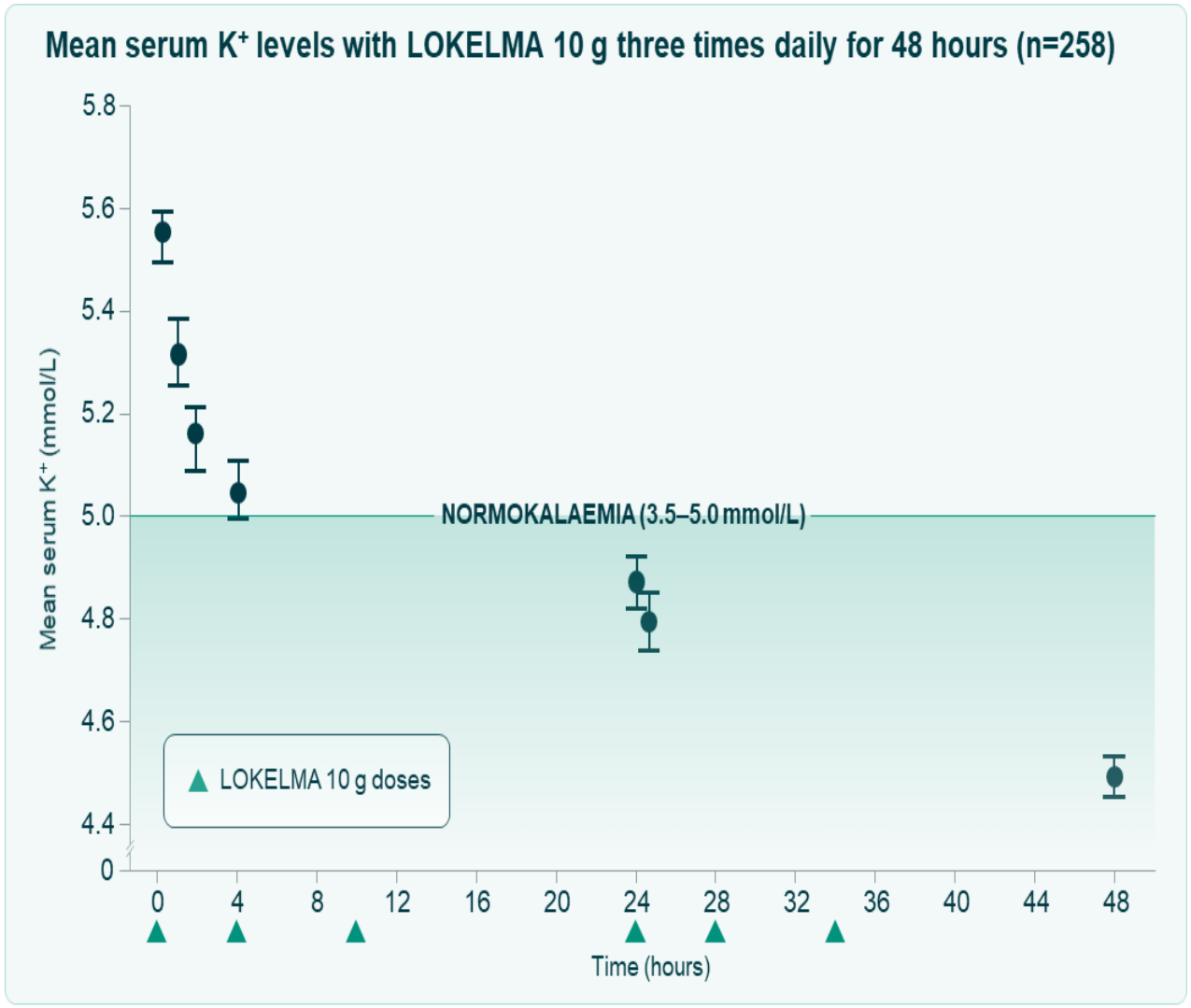
Acute therapy for hyperkalemia

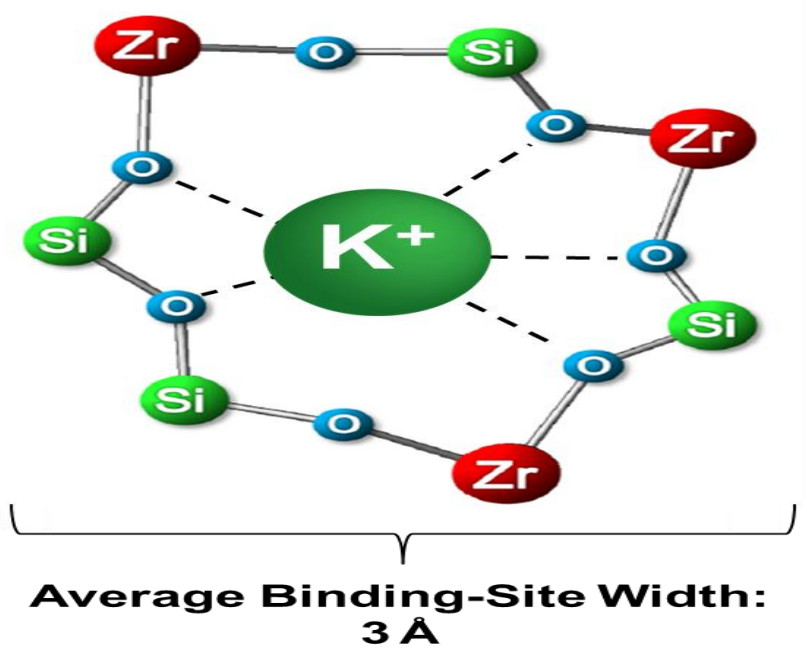
- Stabilization of myocardium
  - Ca^{+2} gluconate or chloride
  - Hypertonic saline, NaCl, $NaHCO_3$
  - Correct acidosis
- Extra-renal K disposal
  - Insulin
  - β2 agonist
  - Alkali
- Potassium removal
  - GI
    - Oral K-resins (CPS, SPS) (X)
  - Kidney
    - Loop diuretic and/or florinef
  - Hemodialysis

K^+ Retention and PK^+ Value



Can SZC as a novel potassium chelating resin be used in the acute treatment of severe hyperkalemia?





In the open-label phase, serum potassium levels declined from 5.6mmol/L at baseline to 4.5mmol/L at 48 hours.

- Median time to normalization was **2.2 hours**.
- **84%** of patients achieving normokalemia by **24 hours**.
- **98%** of patients achieving normokalemia by **48 hours**.

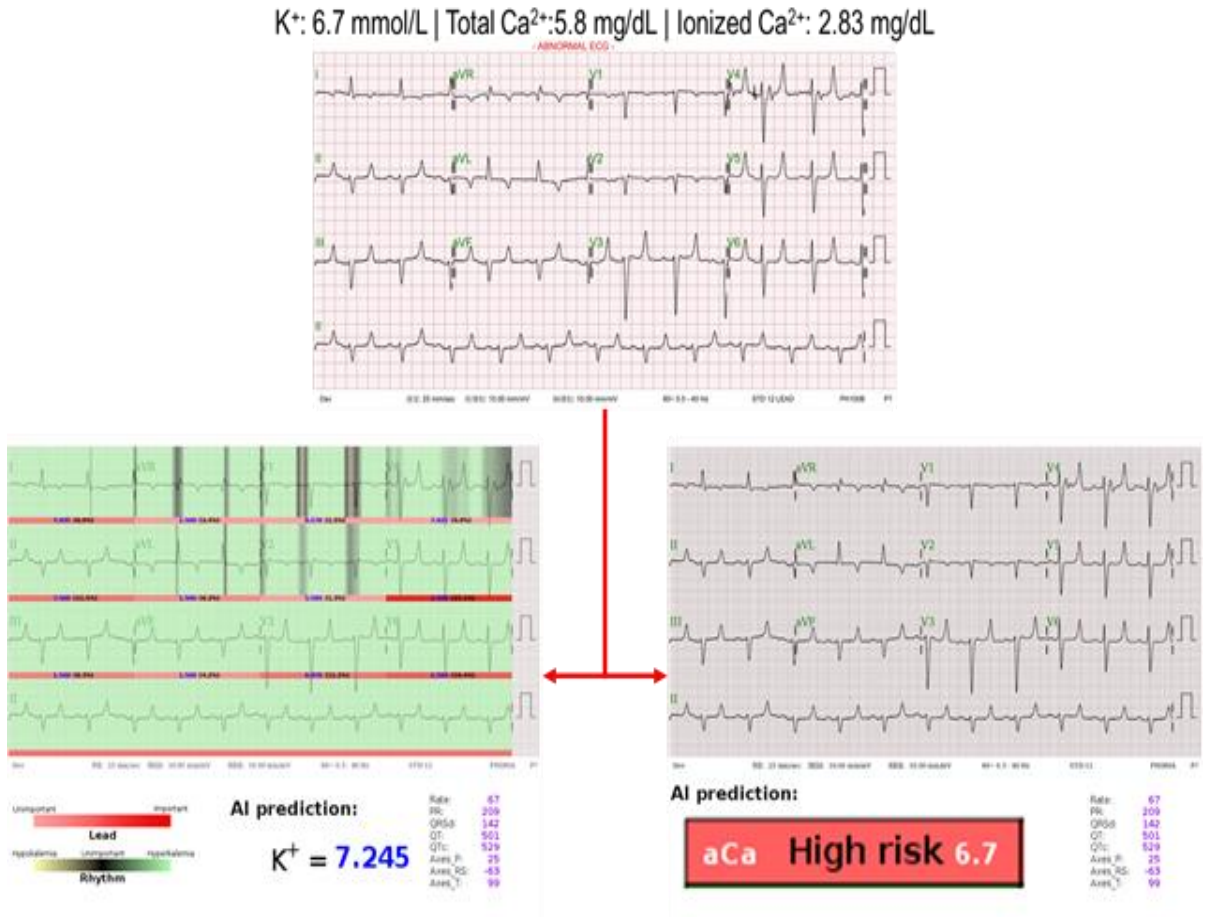
SZC: 2.5-2.8 K⁺/gm, **25-28 K⁺/10 gm**

Its onset of action is faster than older resins. SZC may be a valuable adjunct for rapid K reduction in severe hyperkalemia.

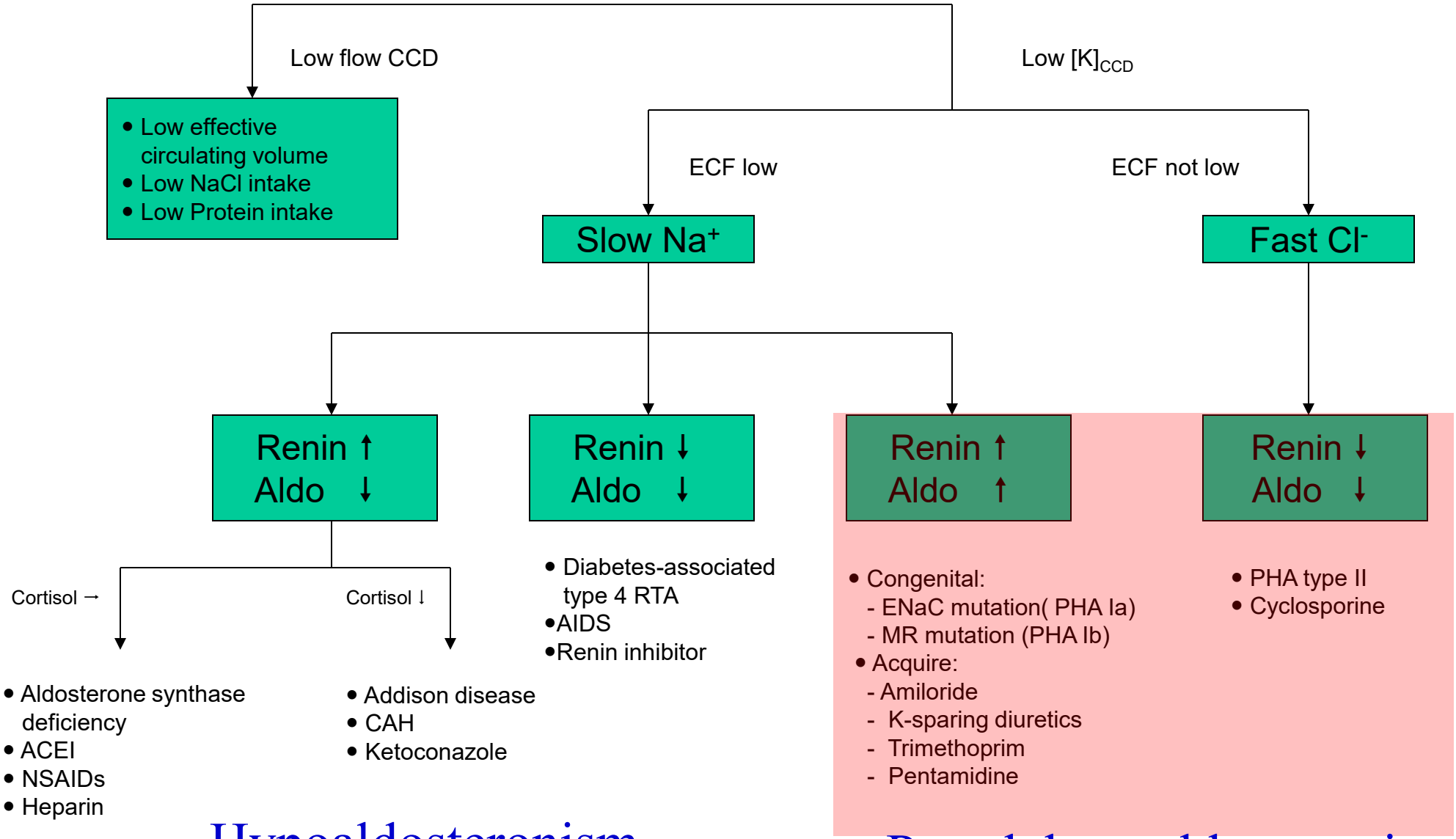
Hyperkalemia in HBS: A Less-Appreciated K^+ shift aberration

- After PTX, PK increased from average 4.4 to 6.2 mmol/L within 10-12 hours
- Of note, 15% of them had PK >6.0 mmol/L
- It has been reported that one die of hyperkalemia after PTX
- Without evidence of higher K load, K shift is the major cause.
- The most relevant factor appears to be **acute** hypocalcemia
- The more profound hypocalcemia may cause severe hyperkalemia.
- Correct hyperkalcemia with IV calcium and glucose with insulin
- Arrange HD with high Ca but low K dialysate after the operation
- Pre-PTX higher ALP is related to PTX acute hypocalcemia and hyperkalemia

Recurrent hyperkalemia following PTX (ALP 3-4 fold)



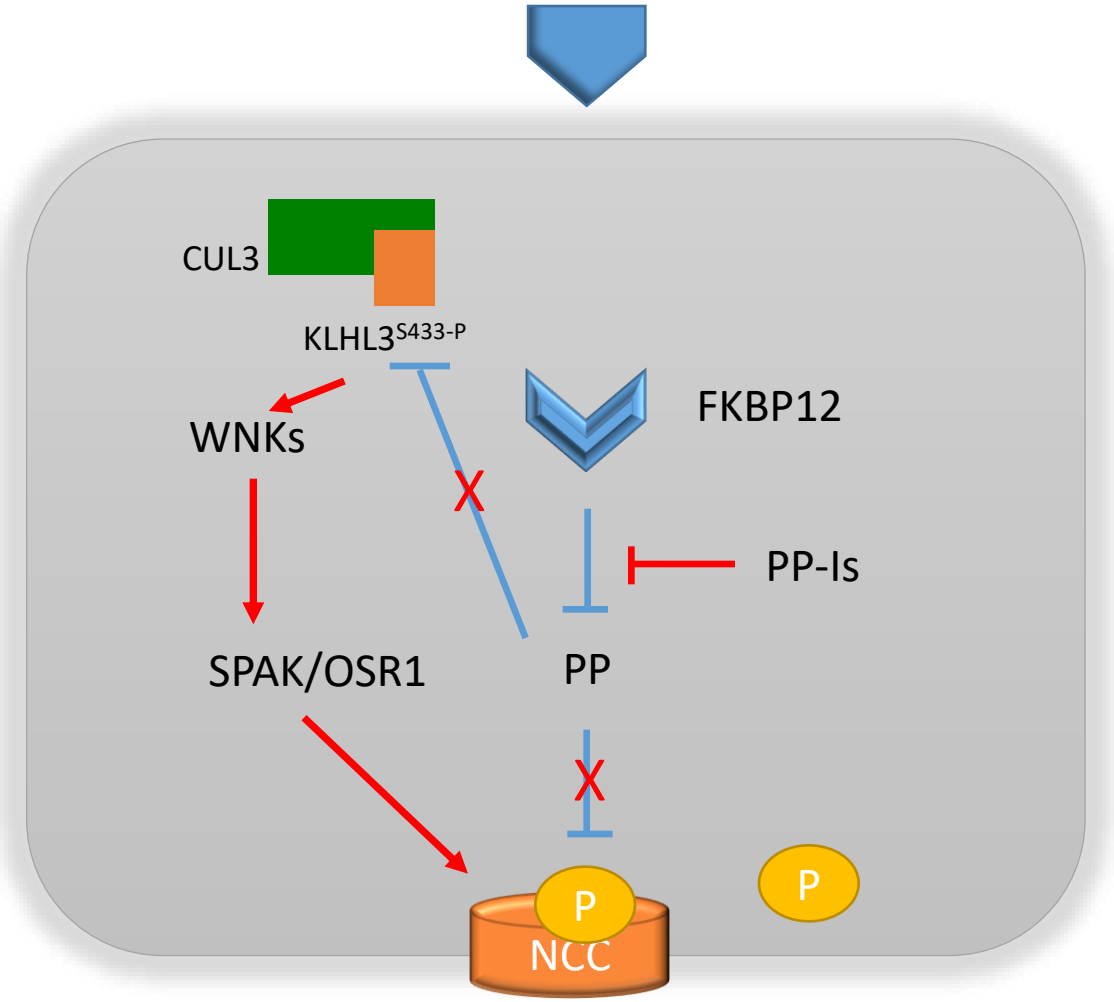
Hyperkalemia with low K^+ excretion



Hypoaldosteronism

Pseudohypoaldosteronism

The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension



Ewout J. Hoorn and David Ellison.
Nat Med 2011;17(10): 1304–1309

Cullin/RING E3 ligase complexes (CRL) bind with WNK1/4 as upstream stimulator of SPAK-NCC

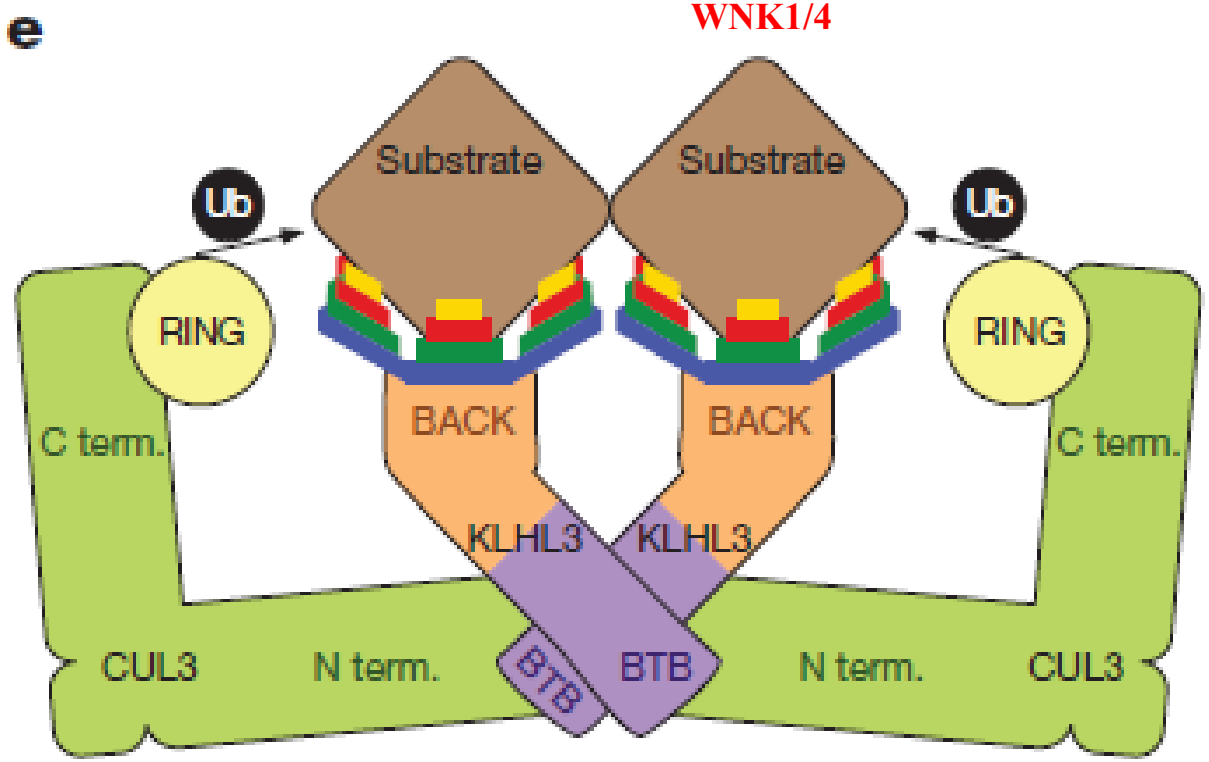


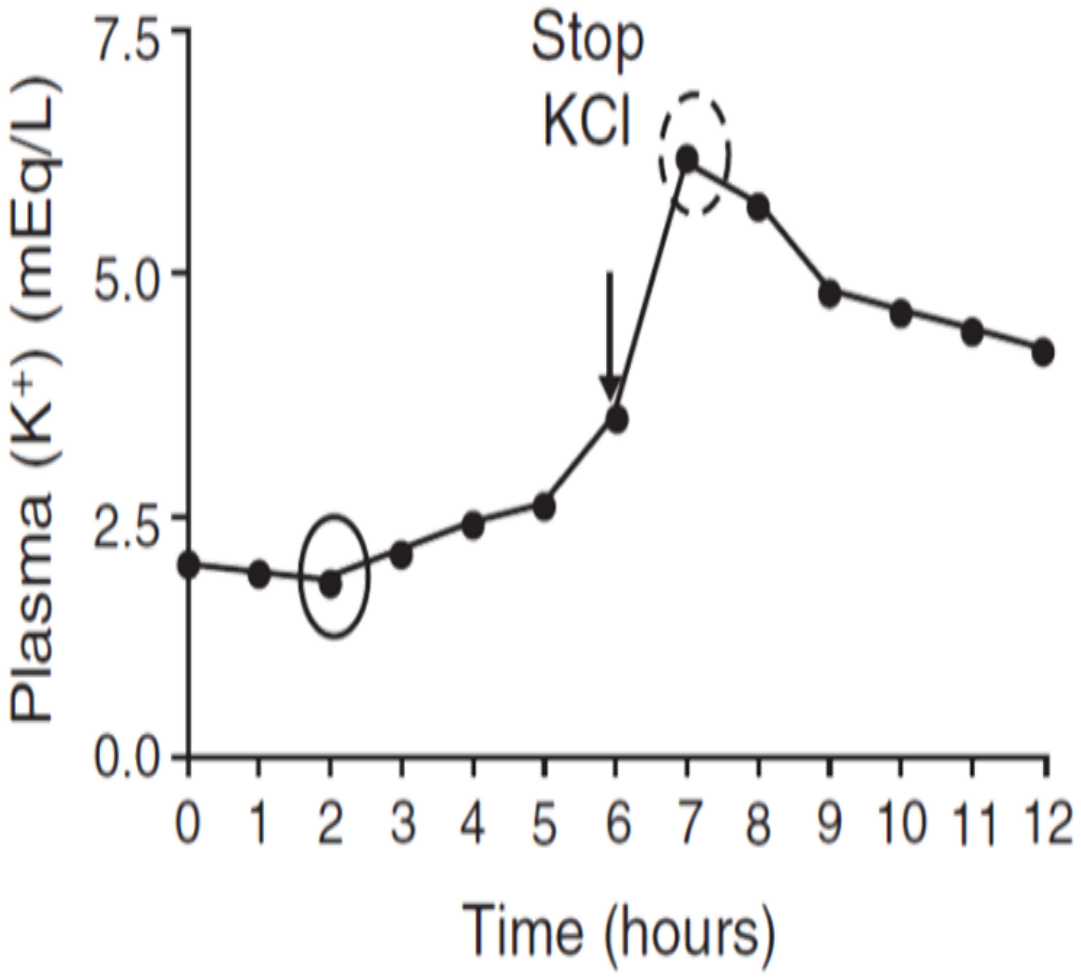
Table 1 | PHAII phenotypes, stratified by genotype.

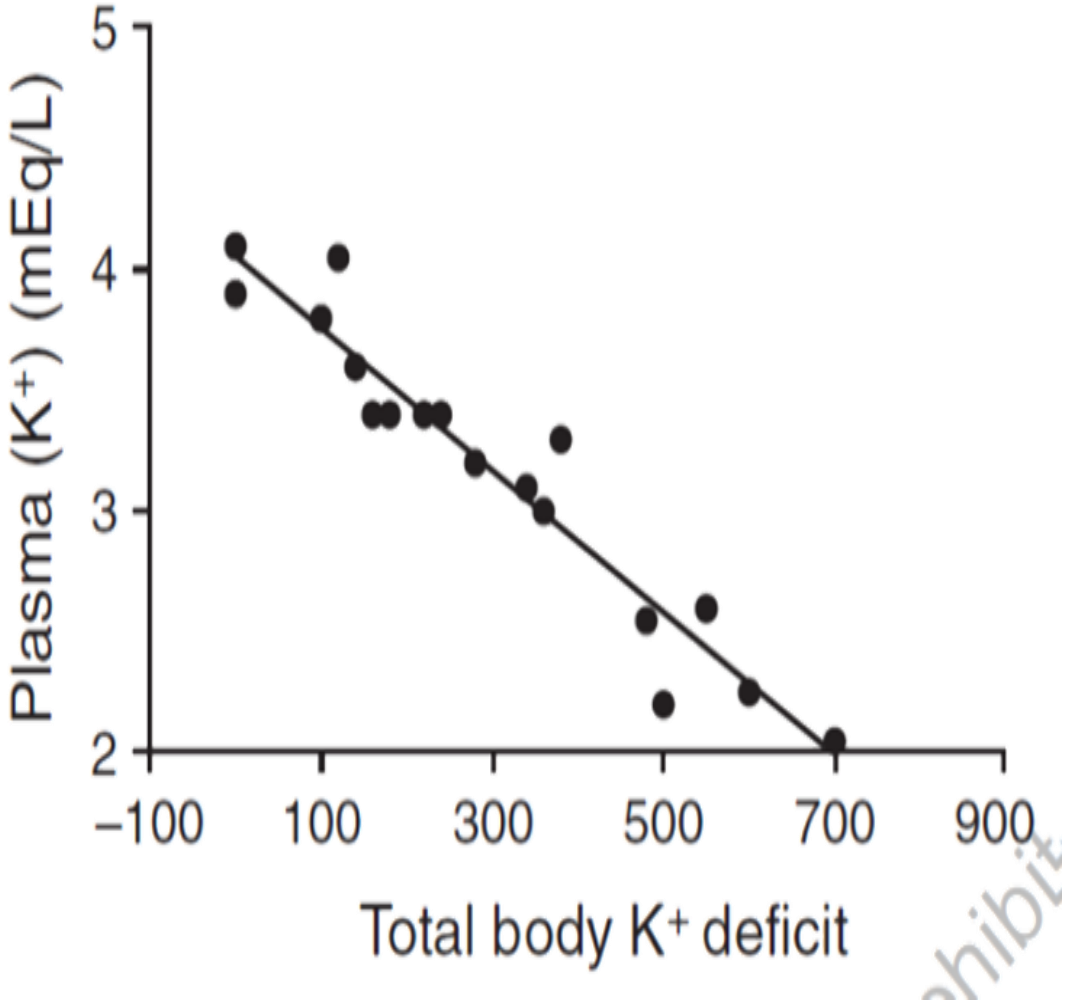
Mutant gene	No. of kindreds	No. of affecteds	Dx/Ref age*	K^+ (mM) (nl 3.5–5.0 mM)†	HCO_3^- (mM) (nl 22–28 mM)†	Hypertension at ≤age 18 (%)†
CUL3	17	21	9 ± 6	7.5 ± 0.9	15.5 ± 2.0	94
KLHL3 recessive	8	14	26 ± 14	6.8 ± 0.5	17.6 ± 1.5	14
KLHL3 dominant	16	40	24 ± 18	6.2 ± 0.6	17.2 ± 2.5	17
WNK4	5	15	28 ± 18	6.4 ± 0.7	20.8 ± 2.3	10
WNK1	2	23	36 ± 20	5.8 ± 0.8	22.4 ± 4.6	13

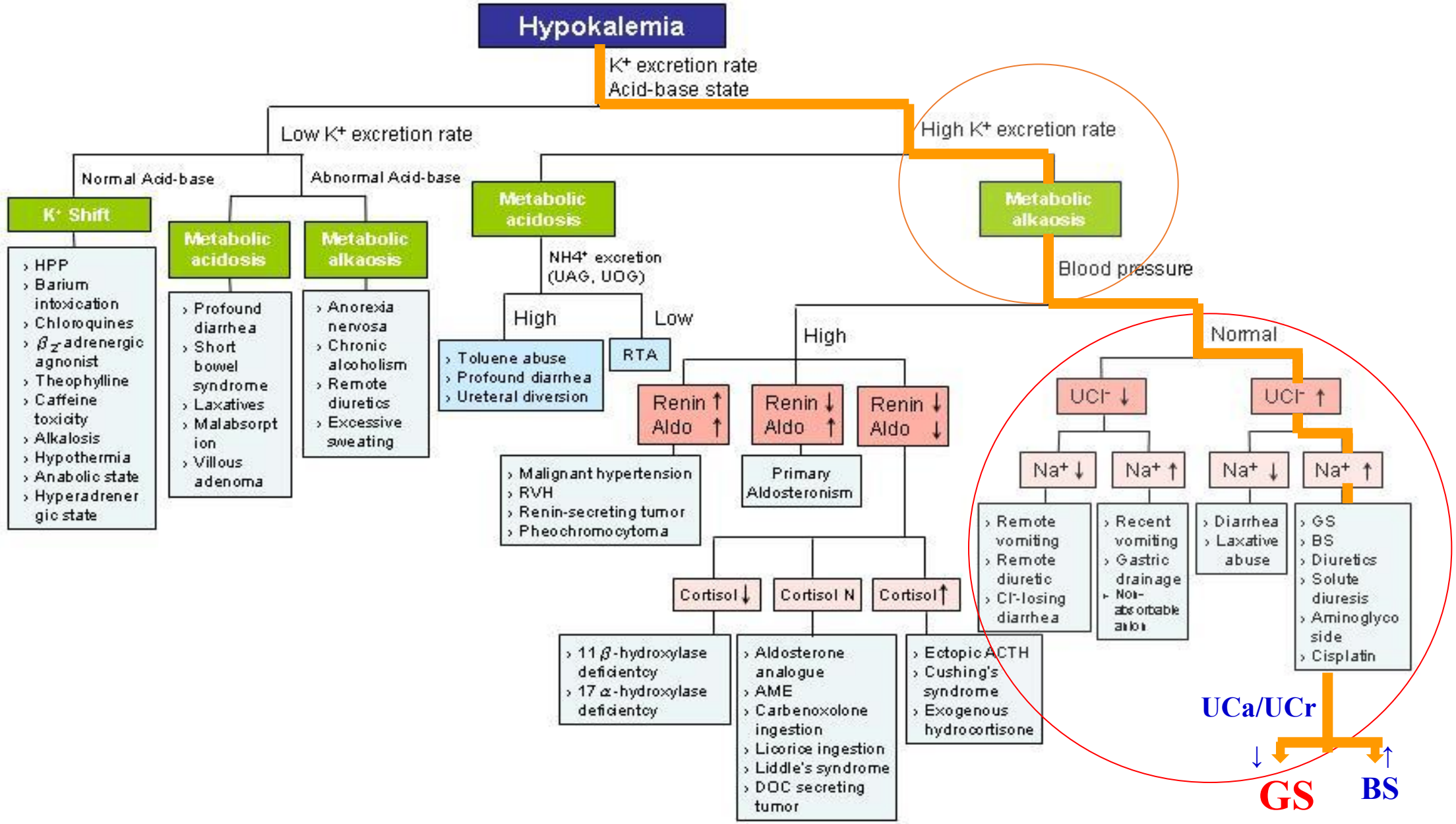
13%

Nature. 2012;482(7383):98-102

K^+ given: **acute K^+ shift** **vs** **chronic K^+ deficit**

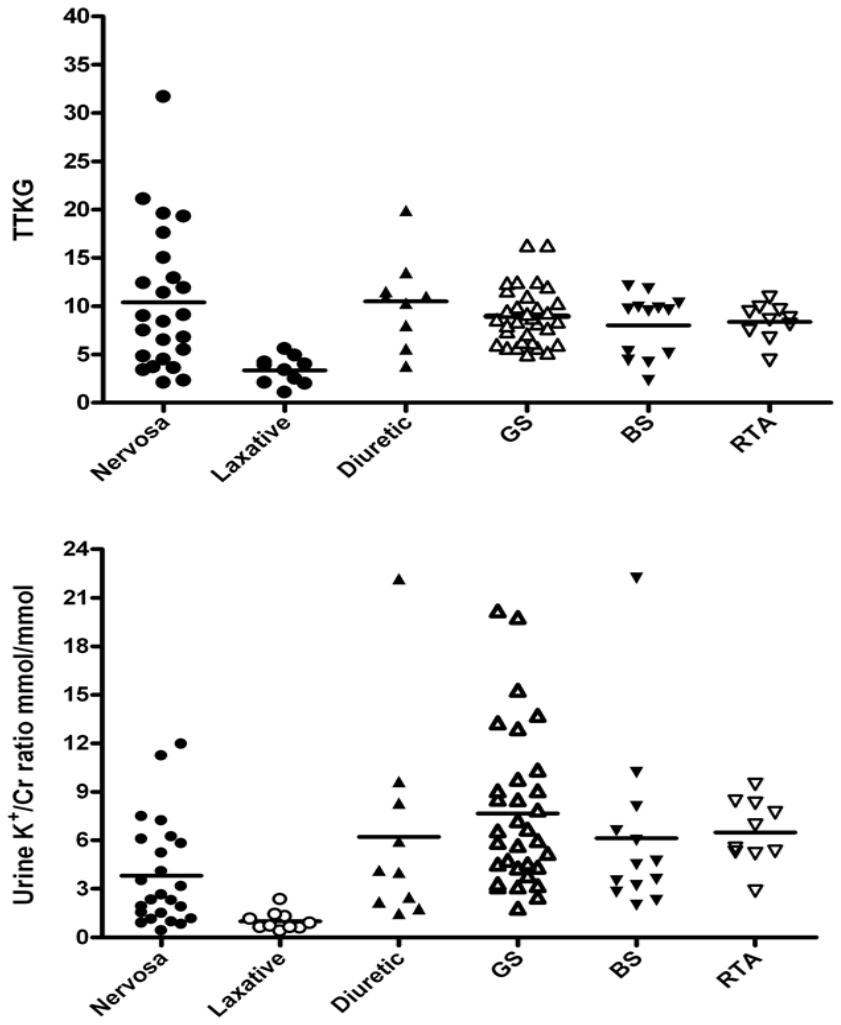


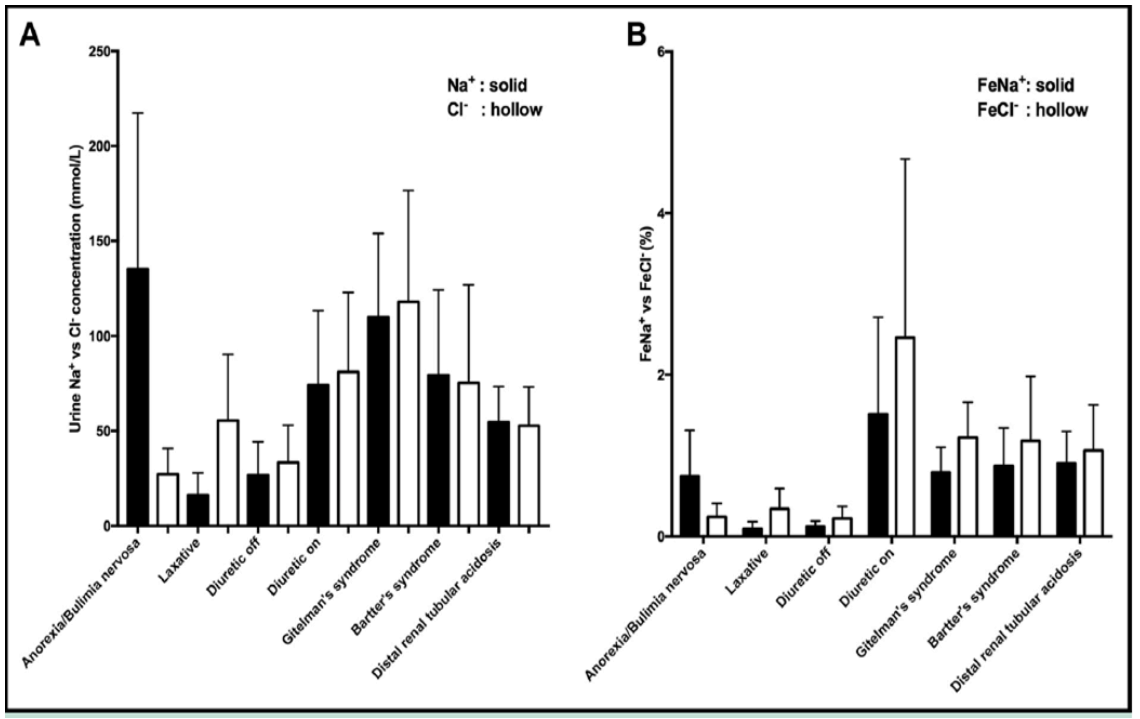




Lin SH Curr Medicinal Chem 2007; 14: 1551-1565.

Etiologies and Urine K^+ and **Na^+ vs Cl^-** excretion rate for Pseudo and true GS/BS



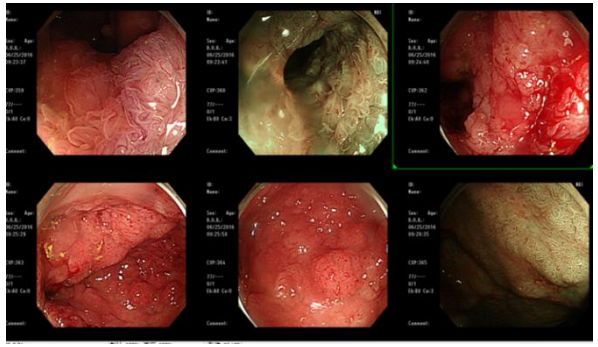


- High and coupled urine Na^+ and Cl^- : in RTD, “on” diuretics use
- Uncoupled urine Na^+ and Cl^- excretions: Cutoff value
- Laxative use with low urine **Na^+/Cl^- ratio < 0.6**
- A/B nervosa with high urine **Na+/Cl- ratio > 1.7**
- Low and fixed Na^+/Cl^- ratio : “off ” diuretics. (0.9 +/- 0.2)

Wu KL and Lin SH et al. Am J Med. 2017;130(7):846-855

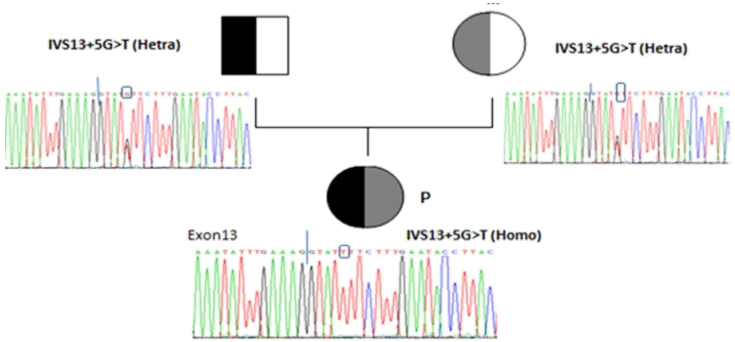
Examples with High urine K excretion but low Na and Cl excretion: Not renal disorders

- 68 y/o female with diarrhea and severe hypokalemia and metabolic alkalosis
- PK 2.4, pH 7.54 HCO3: 37.4 mmol/L
- **UNa (mmol/L) 11**
- **UK (mmol/L) 50.7**
- **UCl (mmol/L) <15**
- **UCr (mg/dL)** 77.5
- **UOsm** (mOsm/kg H_2O) 327

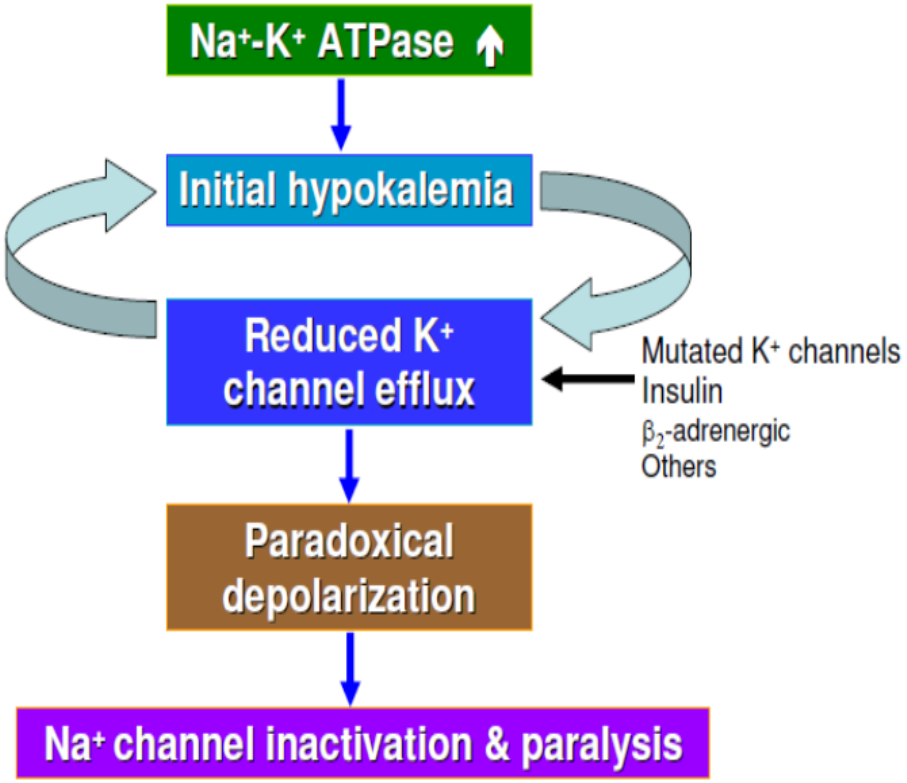


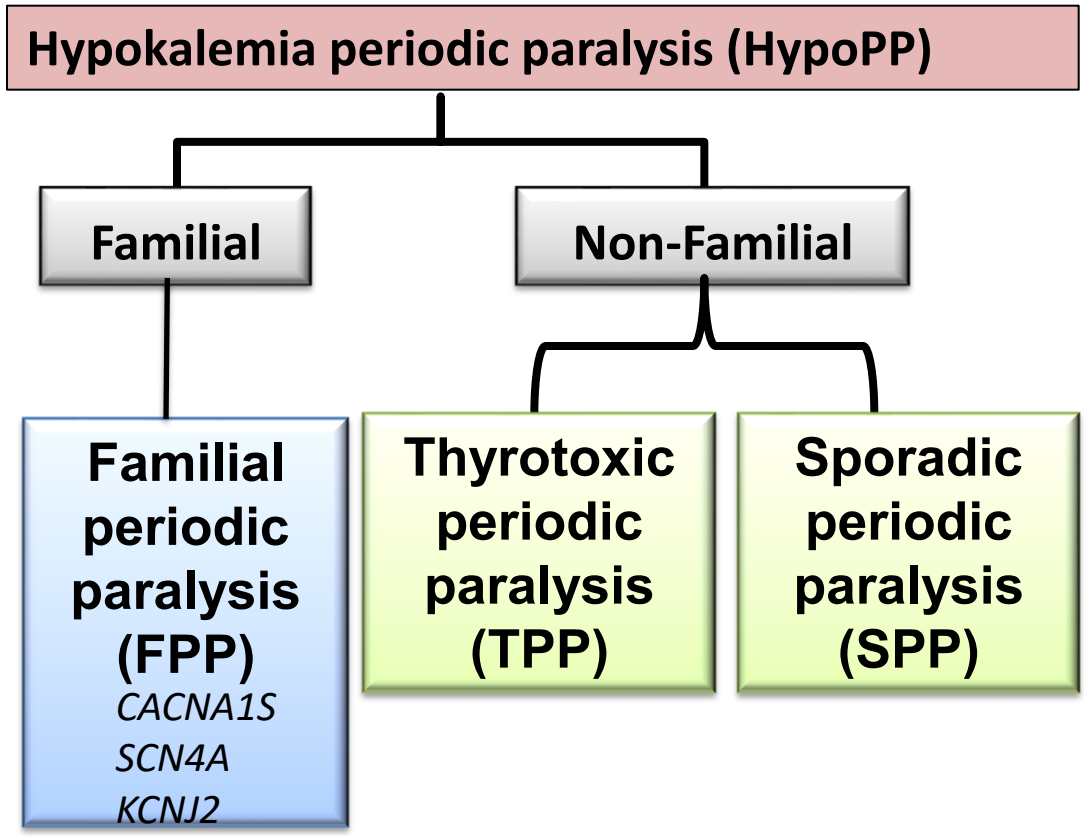
- 2 y/o was referred for the chronic hypokalemia with BS (very high TTKG), very high PRA and aldosterone
- PK 2.8-3.2, pH 7.44 HCO3: 28.4 mmol/L

UNa (mmol/L)	**28**	**32**
UK (mmol/L)	**136**	**121**
UCl (mmol/L)	**16**	**14**
UCr (mg/dL)	**27.5**	**31**
UOsm (mOsm/kg H_2O)	302	340



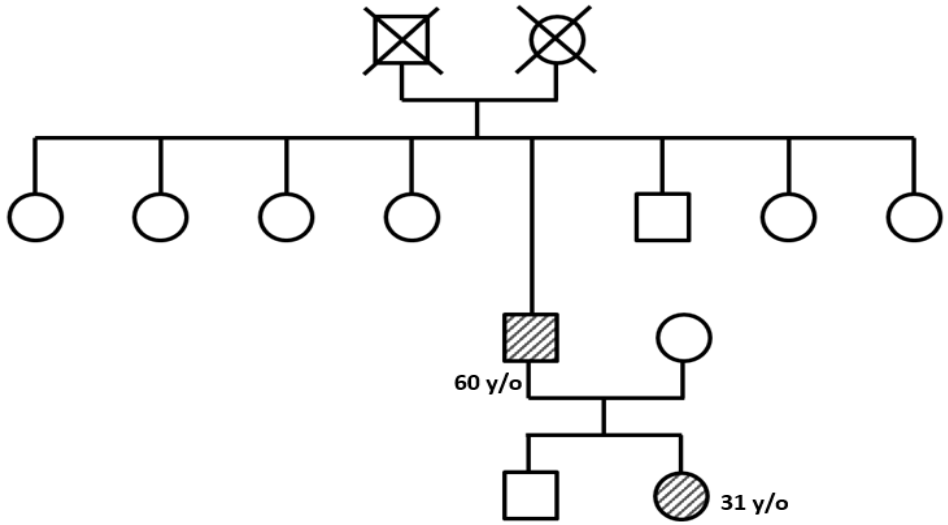
K^+ Shift





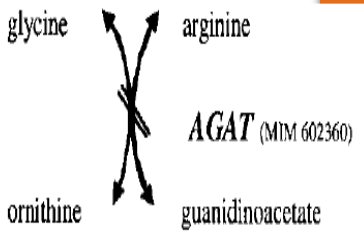
(Lin SH, MCP 2005 and JASN 2012, JBC 2013, Neurology 2018)

Autosomal Dominant Renal Fanconi's Syndrome with Progressive Renal Failure



		Patient 1 (Father)	Patient 2 (Daughter)
Age (year-old)		60	31
Age of onset		20	15
Serum	Reference		
Creatinine	0.5-0.9 mg/dl	3.6	1.1
Uric acid	2.3-7.0 mg/dl	2.9	<1.5
Phosphate	2.7 to 4.5 mg/dl	2.1	2.3
Sodium	136-145 mmol/L	141	135
Potassium	3.5-5.1 mmol/L	3.1	3.4
Chloride	98-107 mmol/L	108	106
CO2 content	21-31 mmol/L	18	19
Urine			
Glucose		3+	4+
Protein		2+	+
Acetone		+	2+
FEP		61.3%	32.5%
FEUA		57.9%	37 %
Osteomalacia		Present	Present

Whole exome/genomic sequencing



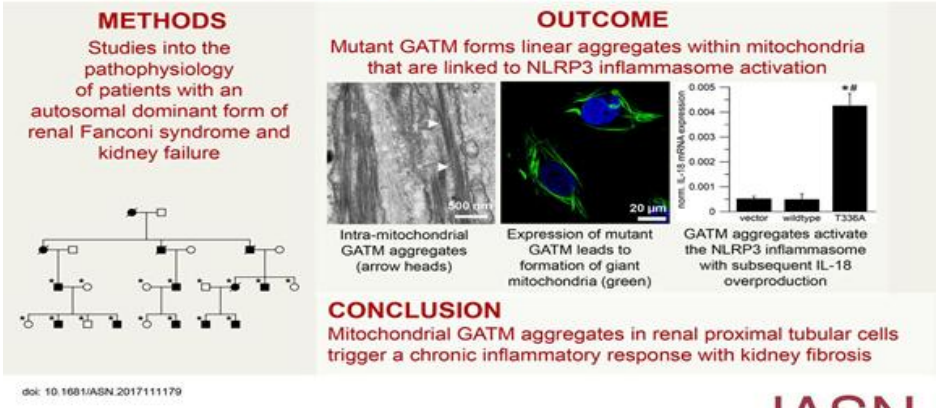
"GATM"

one of the potential culprit gene

T336I

Glycine Amidinotransferase (GATM), Renal Fanconi Syndrome, and Kidney Failure

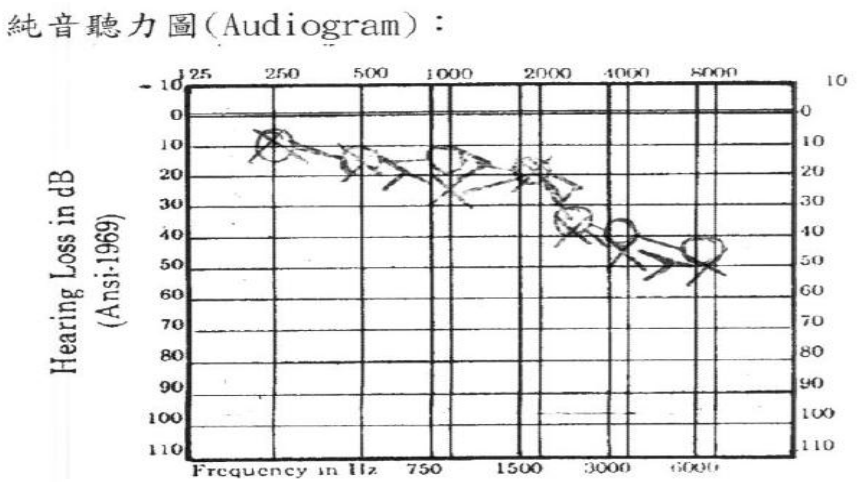
GATM, renal Fanconi syndrome and kidney failure

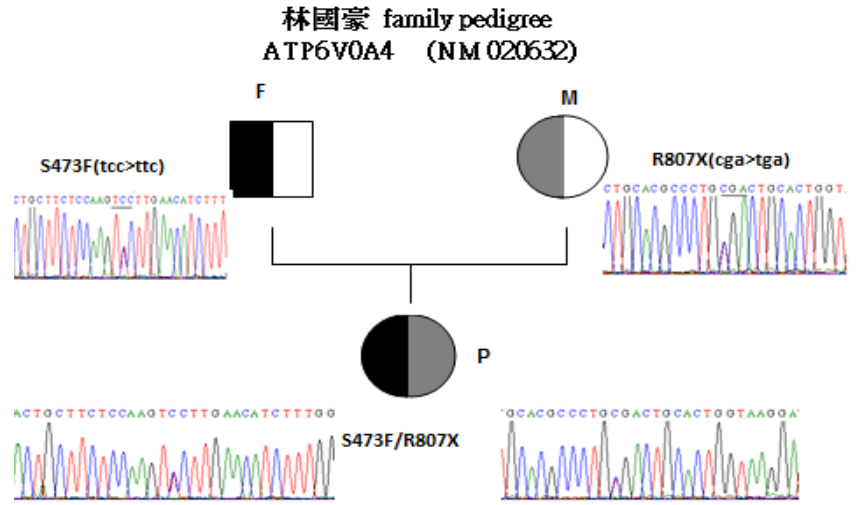


A 20 Y/O Male with dRTA and nephrocalcinosis

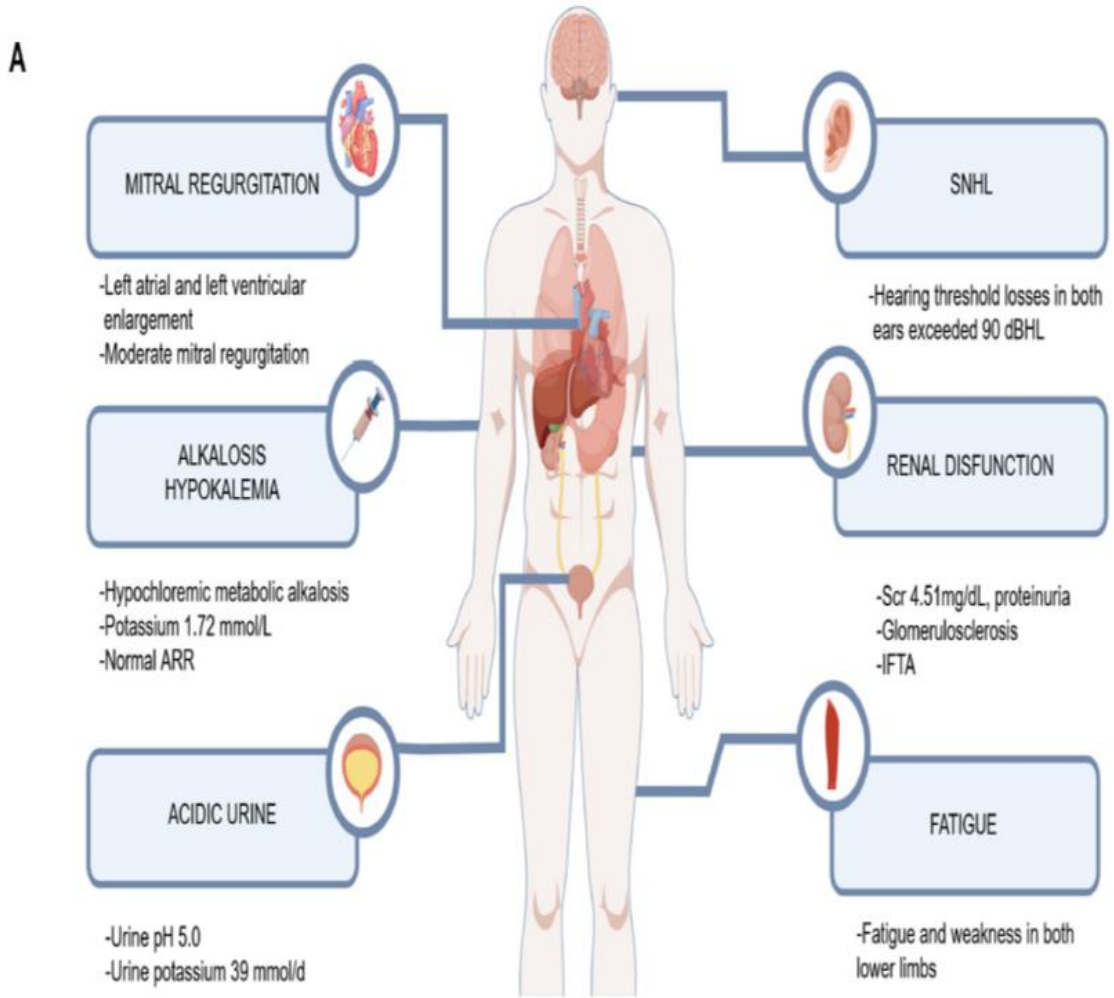
Gene	Protein	Function	Inheritance	OMIM[a]
SLC4A1	Anion exchange protein 1 (AE1)	Cl^-/HCO_3^- anion exchanger	AD or AR	#611590
ATP6V1B1	V-type proton ATPase subunit B1	H^+-ATPase subunit	AR SNHL	#267300
ATP6V0A4	V-type proton ATPase 116 kDa subunit a4	H^+-ATPase subunit	AR SNHL	#602722
FOXI1	Forkhead box I1 (FOXI1)	Transcription factor	AR SNHL	#60079[b]
WDR72	WD repeat-containing protein 72 (WDR72)	Unknown	AR	#613211

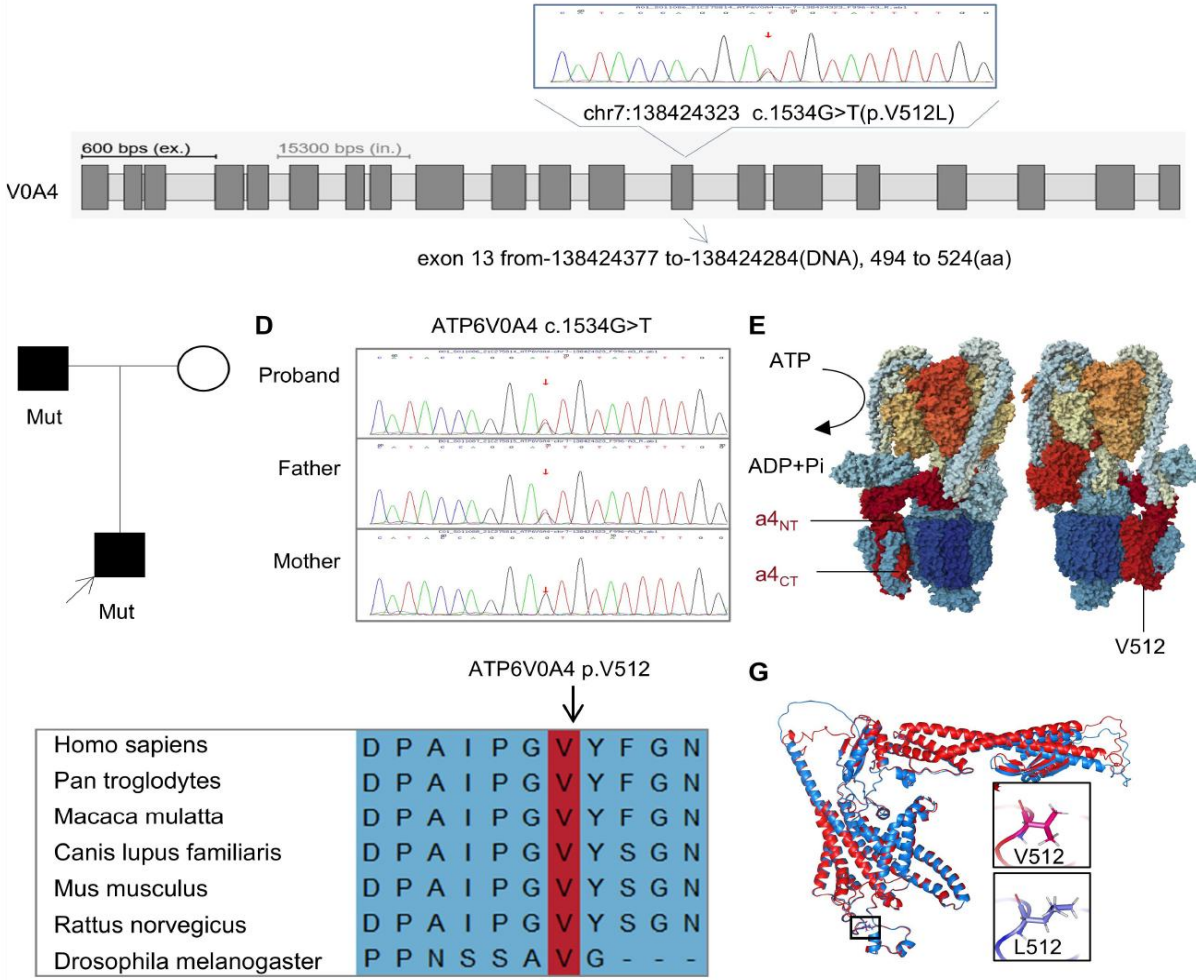
Extrarenal pathological conditions in the inner ear, red blood cells or teeth.





AD ATP6V0A4 Gain of Function (V512L) Drives Primary Distal Renal Tubular Alkalosis with Enhanced V-ATPase activity





JCI 2025

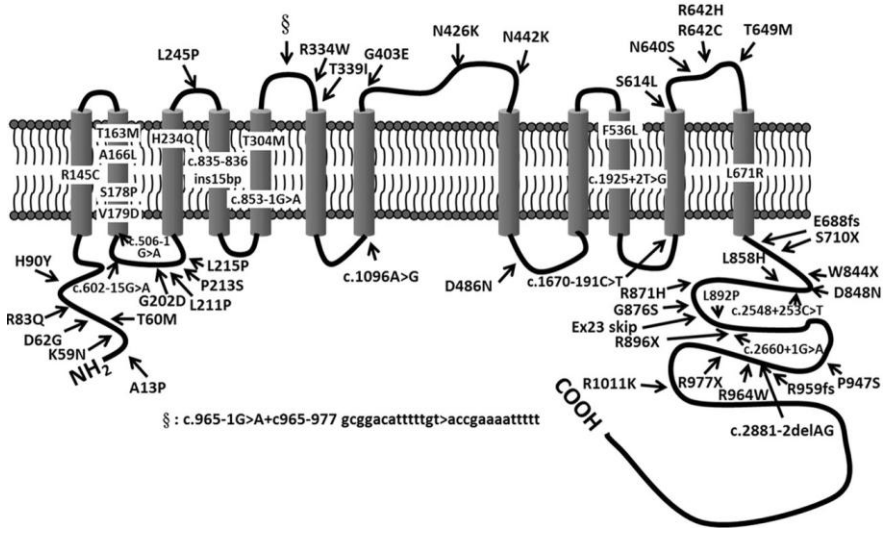
Salt-losing Tubulopathy with Hypokalemia: BS vs GS

	Bartter's Syndrome		Gitelman's Syndrome		
	Case 1	Case 2	Case 1	Case 2	Case 3
Age/sex	5/ M	25/ M	57/ F	41/ F	22/ F
Ccr (ml/min/1.73m²)	68	105	84	112	93
Na^+ (mEq/l)	130	132	143	139	137
K^+ (mEq/l)	**2.2**	**2.0**	**3.0**	**2.8**	**2.2**
Cl^- (mEq/l)	75	77	99	106	81
CO_2 content (mEq/l)	34	37	29.5	33.2	42.5
Ca^{2+} (mEq/l)	3.8	4.0	4.7	4.85	4.9
Mg^{2+} (mEq/l)	–	–	**0.93**	**1.1**	**1.22**
PO_4^{3-} (mg/dl)	–	–	3.9	3.9	–
Renin (ng/ml)	–	–	**39**	**43.2**	**48.8**
Aldosterone excretion (µg/day)	38	40	25	13	8

Frederic C. Bartter, et al. Am J Med 1962
Gitelman HJ, et al. Trans Assoc Am Physicians. 1966

GS: the most common tubulopathy

- NaCl wasting (ECF↓)
- Renal K^+ wasting with Hypokalemia
- LOH OK (Uosm)
- Divalents UCa, PMg
- Hypocalciuria
- Hypomagnesemia



- **Genotype analysis:**
- 57 different SLC12A3 mutations with compound heterozygosity being the most common from 130 unrelated families with 161 probands.
- Approximately 12-13% of patients had triple independent mutations.
- Autosomal pseudo-dominant inheritance with the affected parents and siblings.
- 22 mutations were recurrent (87.1% vs 41.5% 7 recurrent mut in French cohort vs 78% 47 recurrent mut in Europe survey (164 families)
- Two deep intron mutations: 14%.
- **Phenotype analysis:**
- Hypocalciuria or hypomagnesemia were **not found in 10%** of patients, respectively.
- Male patients had an earlier age of onset, more severe hypokalemia and symptoms.
- **Correlation between genotype and phenotype:**
- Patients with homozygous and deep mutation in intron 13 (c.1670-191C>T) had more severe phenotype.
- **Follow-up:**
- Approximately 5-6% patients developed CKD (III-V) or type 2 DM, respectively.

Allele-specific RT-PCR for the early detection of recurrent *SLC12A3* mutations for GS

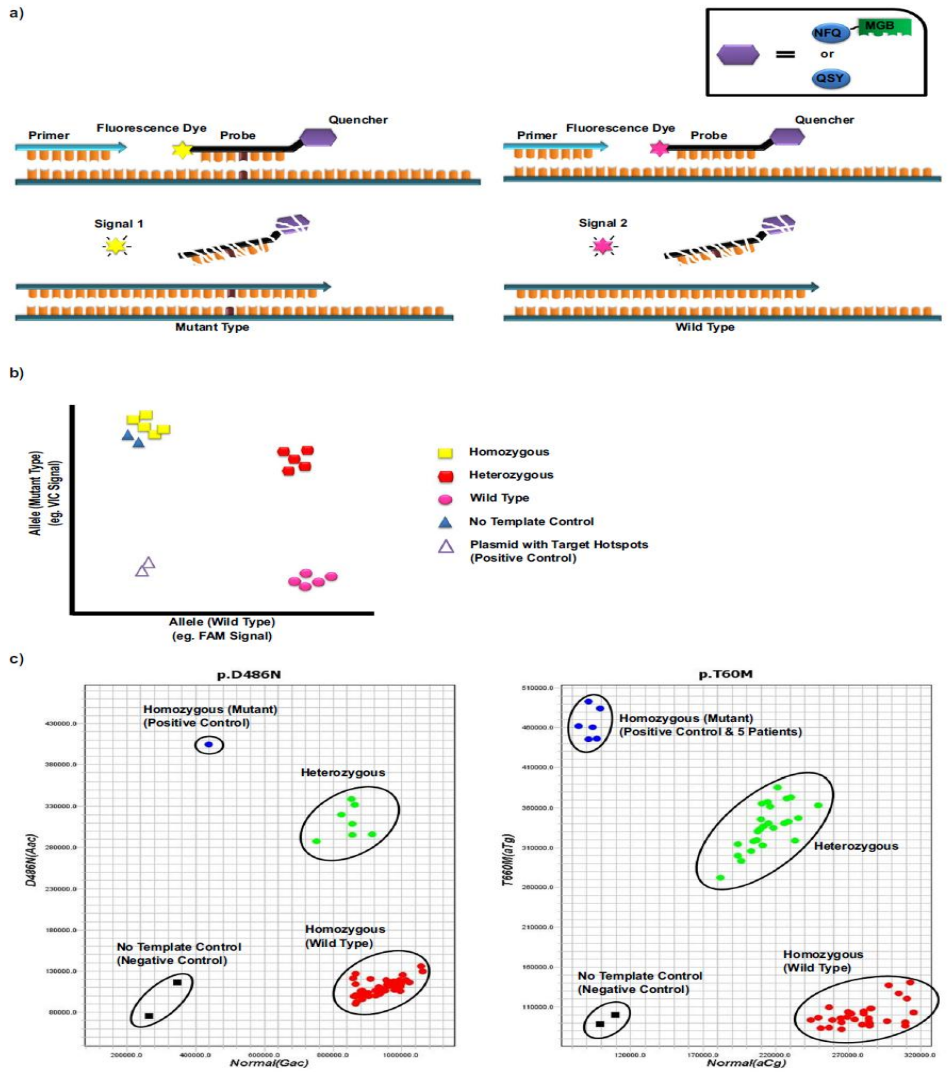


Table 2. Recurrent mutation-based detection in clinically diagnosed GS patients.

No Unit	Sex	Age Yeard	$[K^+]$ mmol/L	$[Mg^{2+}]$ mg/dl	$U_{Ca/Cr}$ mmol/mmol	Allele 1	Allele 2
01	F	63	2.9	1.3	0.03	p.R959fs	p.R959fs
02	F	35	2.1	1.6	0.08	p.R642C	p.T649M
03	F	24	3.0	1.7	0.02	p.T60M	p.N442K
04	M	36	1.7	1.6	0.06	p.W844X	p.R959fs
05	M	24	3.2	1.7	0.08	p.R83Q	p.R871H
06	M	19	1.7	1.9	0.03	p.T60M	p.T60M
07	F	32	2.8	1.4	0.02	p.R83Q	**c.2285 +2T>C**[a]
08	M	60	1.8	1.1	0.10	p.R83Q	p.R83Q
09	M	22	2.8	1.3	0.07	c.1670-191C>T	p.D486N
10	F	26	2.7	1.2	0.03	p.N442K	p.R959fs
11	F	28	2.4	1.3	0.14	p.R959fs	**p.D62G**[a]
12.	M	18	1.9	1.5	0.02	p.T163M/p.R871H	p.D486N

[a]The mutations detected by direct sequencing.
The two bold values represent mutations which were initially not detected by recurrent mutation-based mutation detection plate because both of them were not included in the recurrent mutations defined in this study. Since only monoallelic mutation was identified in the two patients, other genetic tests were conducted and the two SLC12A3 mutations were identified.

Yan MT, et al. NPG Genomic Medicine 2021;6:68

GS without NCC and CLCNKB mutations

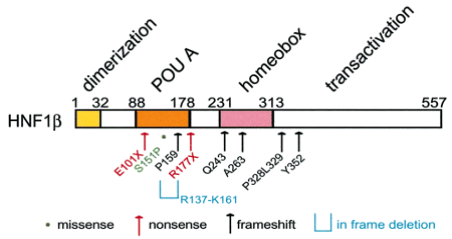
- A 38-year-old female had chronic hypokalemia and severe hypomagnsemia accompanied by severe neuromuscular symptoms for more than 10 years.
-

Plasma	Normal range	Data
Hgb	(13-16 gm/dl)	13.8
Na^+	(135-142 mmol/l)	141
K^+	(3.5-5.0 mmol/l)	3.1
Cl^-	(96-108 mmol/l)	96
Total Ca^{2+}	(8.6-10.2 mg/dl)	9.8
IP	(2.7-4.5 mg/dl)	4.2
Mg	(1.6-2.5 mg/dl)	1.4
BUN	(6-20 mg/dl)	18
Creatinine	(0.7-0.9 mg/dl)	1.3
Total Protein	(6.6-8.7 mg/dl)	7.6
Albumin	(3.9-4.9 mg/dl)	4.2

Urine		Data
Na^+	(mmol/l)	60
K^+	(mmol/l)	45
Cl^-	(mmol/l)	76
P	(mg/dL)	48.3
Ca	(mg/dL)	1.1
Mg	(mg/dL)	8.6
Protein	(mg/dL)	45
Osmolality	mos/kg H2O	432
UUN	(mg/dL)	501
UA	(mg/dL)	59.5
Cr	(mg/dL)	82

SLC12A3 and *CLCNKB* mutations sequencing with different methods: negative

MLPA for HNF-β mutation: heterozyous **large deletion of HNF-1β.**



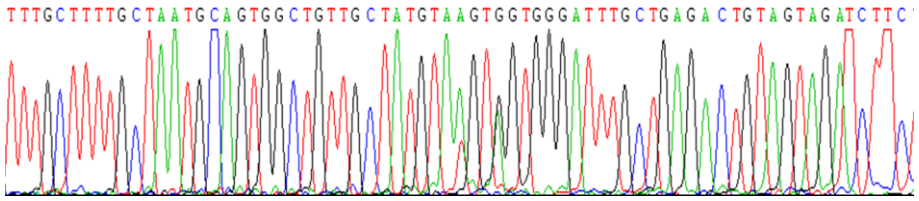
Late Onset of BS

A 32 y/o female was referred due to chronic hypokalemia, nephrocalcinosis and CKD, stage III
Hx: nocturia for more than 1o years
BP 120/70 mmHg, HR 78/min
Lab: K 2.8 mmol/L HCO_3 29 mmol/L Tca 10.1 Mg 2.1 mg/dl, Cr: 1.1 mg/dl, UA: 9.3 mg/dl
Urine: Na 63 K 20 Cl 73 Ca 8.2 Mg 3.0 Cr 23 mg/dl , Osm 234
Hormone: high PRA and aldosterone
Immune study and malignancy: negative

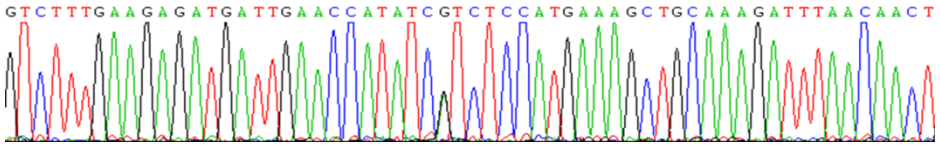
A 36 y/o female was referred due to chronic hypokalemia, hypocalcemia, and nephrocalcinosis for more than 10 years
Lab:
Na: 142 mmol/L K 3.0 mmol/L HCO_3 34 mmol/L Tca 6.98 Mg 1.76 mg/dl, Cr: 0.8 mg/dl, albumin: 4.0 g/dl,
Urine:
Na 17 K 3.6 Cl 14 Ca 2.2 Mg 0.4 Cr 15.5 mg/dl , Osm 89.4
Hormone: high PRA and aldosterone
Immune study and malignancy: negative

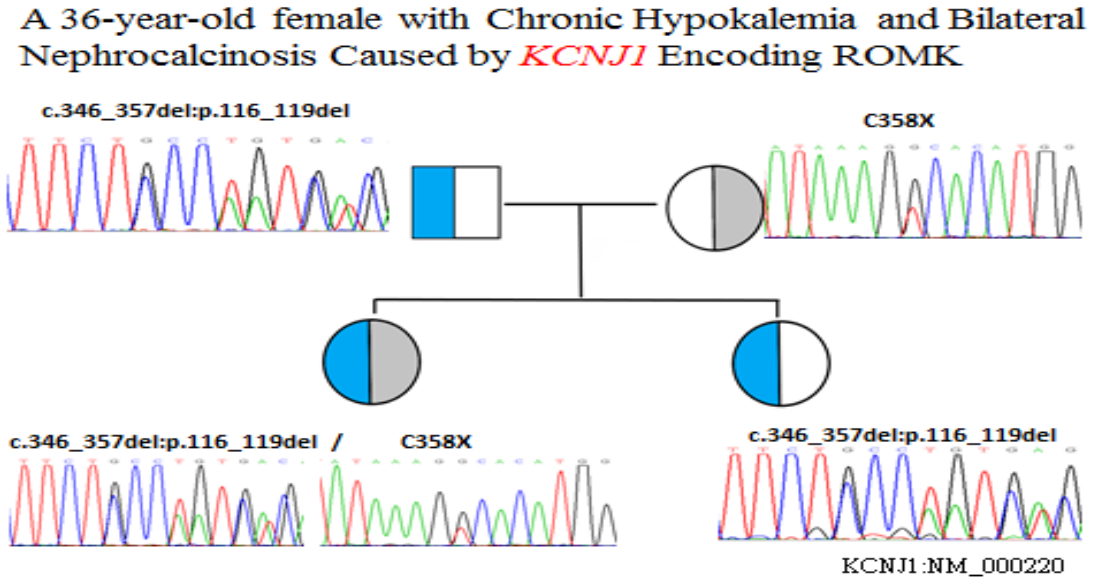
***SLC12A1* encoding NKCC2 mutation**

Y275X(taT>taA)

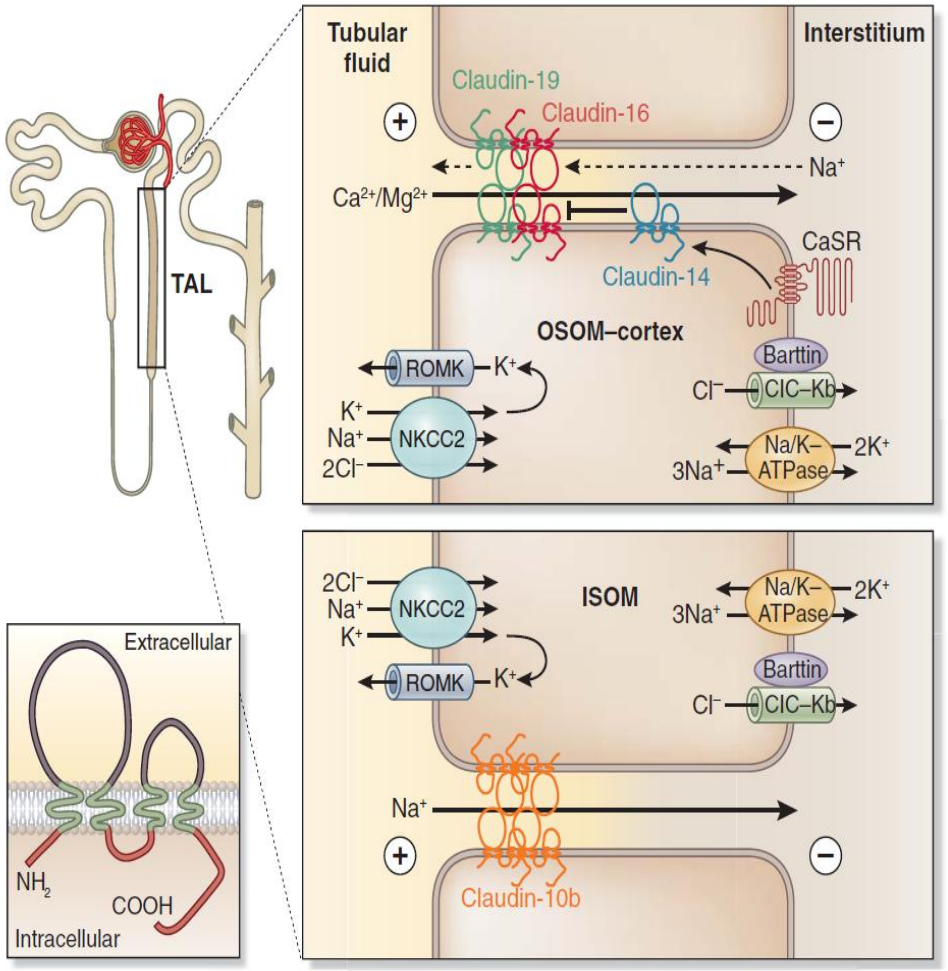


R999H(cGt>cAt)





A Novel Hypokalemic-Alkalotic Salt-Losing Tubulopathy in patients with *CLDN* 10 Mutation



- Hypokalemic metabolic alkalosis with hypomagnesuric hypermagnesemia and severe hypocalciuria: A new syndrome?

Table 2. Simultaneous Urine Indices and Serum Values

Date	FE_{Na} (%)	Serum Potassium (mEq/L)	FE_K (%)	U_{osm}	TTKG	Serum Magnesium (mEq/L)	FE_{Mg} (%)	FE_{Ca} (%)	TPR (%)
1/3/94	1.6	2.8	33.6	—	—	2.4	—	—	—
3/15/95	3.0	4.5	40.5	—	—	2.5	5.2	—	77.2
8/8/95	1.8	2.4	31.5	345	7.3	2.3	3.8	—	72.5
8/11/95	0.5	2.9	39.8	325	12.7	2.7	3.2	0.08	74.2
10/25/95	1.6	3.4	48.4	372	10.5	2.6	3.6	0.09	88.9

Abbreviations: FE, fractional excretion; TTKG, transtubular potassium gradient; TPR, tubular phosphate reabsorption.

Mehrotra R, et al. AJKD 1997

- Two patients (M 15 and F 21) were initially diagnosed to have GS, but without biallelic *SLC12A3* mutations
- Hypocalciuria and hypomagnesuria with increased serum Mg
- Impaired urine concentration
- Pathogenic claudin 10 mutations affect TAL paracellular ion transport and cause a novel tight junction disease characterized by a non-BS, non-GS, AR hypokalemic salt-losing tubulopathy phenotype.

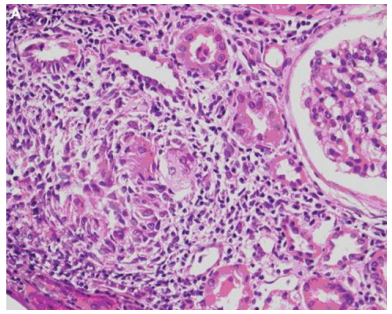
Bonger EMGH, et al. JASN 2017

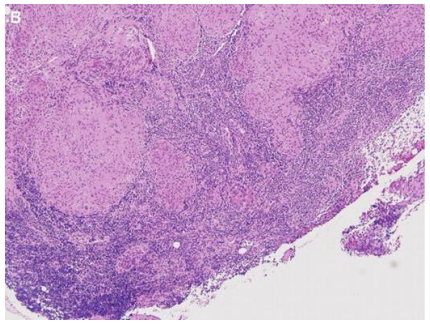
Persistent and high Urine NaCl excretion and exclusion of acquired or secondary causes

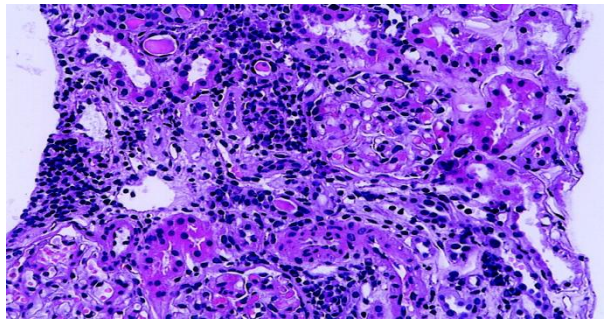
- Acquired BS
  - **Drugs:**
    Diuretics: surreptitious use of loop
    Diuretics: on and off effect
    Antibiotics: aminoglycosides, colistin
    Chemotherapy: cisplatin
  - **Autoimmune diseases**: SLE, SS, others
  - Infection: TB
  - Others: sarcoidosis

Acquired GS

- **Drugs:**
  Diuretics: thiazides
  Antibiotics: kanamycin
  Chemotherapy: cisplatin, bendamustine
- **Autoimmune diseases**: SS, pSS, others
- Others: GU tract obstruction, paraneoplasms





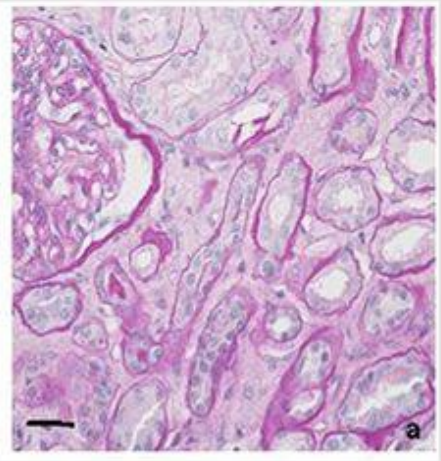


Hypomagnesemia, Hypocalcemia and Tubulointerstitial Nephropathy Due to Claudin-16 Autoantibodies.

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

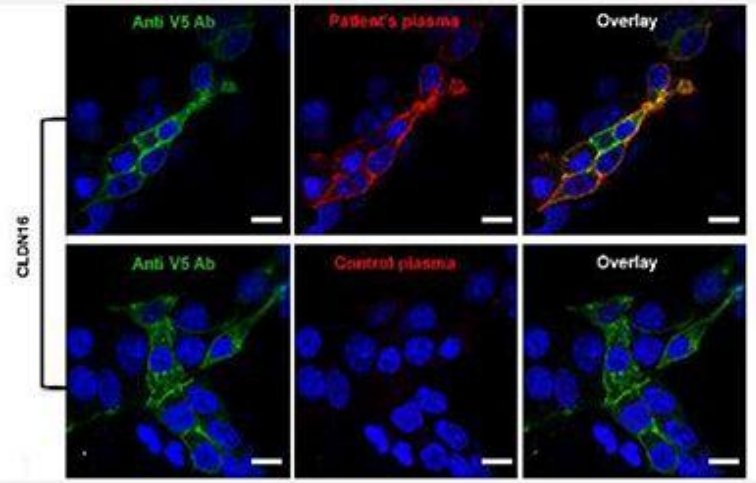
METHODS

An adult patient with acquired severe hypomagnesemia, hypocalcemia and tubulointerstitial nephropathy with rapidly progressing kidney injury was investigated using *in vitro* and *in vivo* experiments.



RESULTS

Hypomagnesemia in the patient was causally linked to autoantibodies directed against claudin-16, a transmembrane protein that controls paracellular magnesium reabsorption in the thick ascending limb of Henle's loop.



OUTCOME

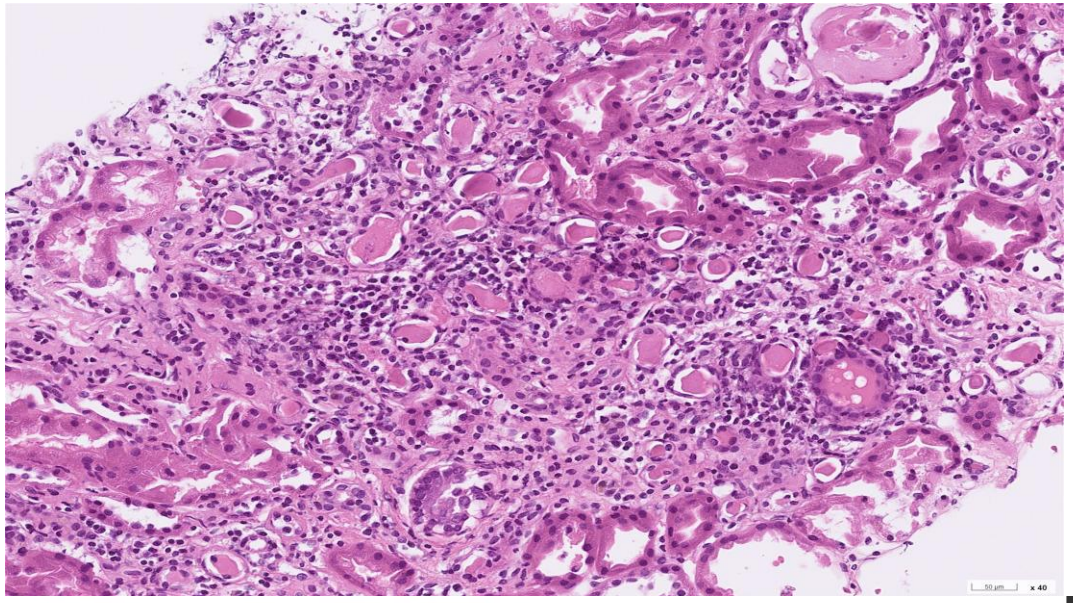
Plasma exchange and rituximab use was associated with improvement in the patient's glomerular filtration rate but hypomagnesemia persisted. The patient was subsequently diagnosed with a renal carcinoma, which expressed high level of claudin-16 mRNA.

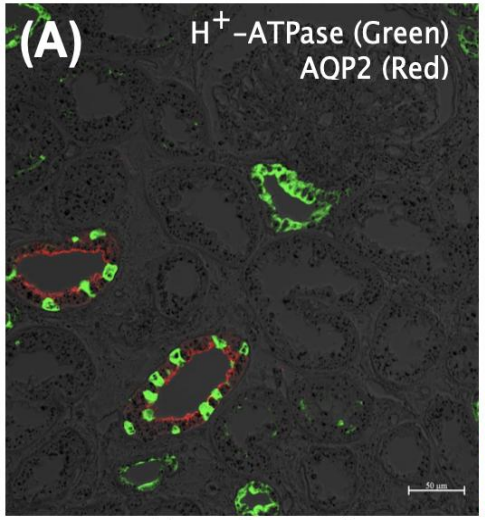
CONCLUSIONS

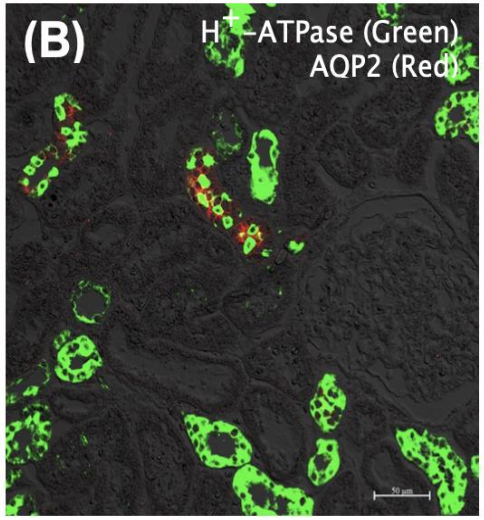
Pathogenic claudin-16 autoantibodies represent a novel autoimmune cause of specific renal tubular transport disturbances and tubulointerstitial nephropathy.

doi: 10.1681/ASN.2022010060

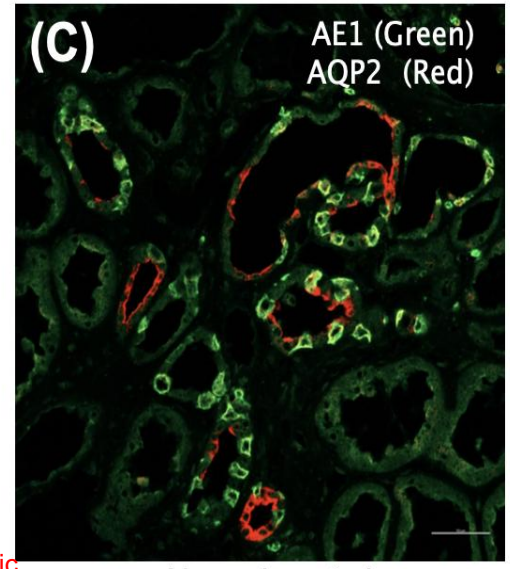
Autoimmune Tubulopathy: A 16 y/o girl with distal RTA and hypokalemia but negative genetic diagnosis by NGS

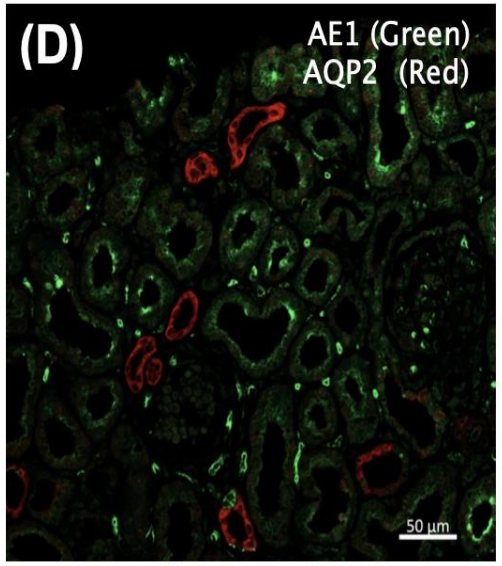




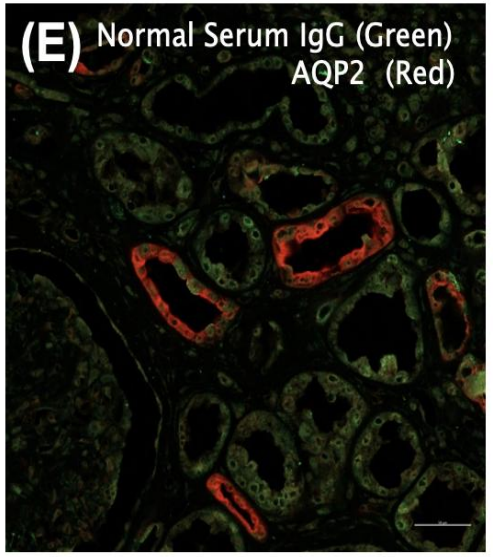


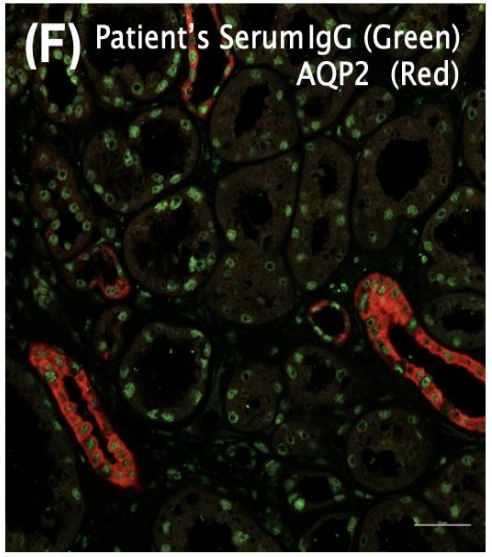
Normal control | Our patient





Normal control | Our patient





Normal control | Normal control

Tesng MH Pediatric Nephrol 2025

SGH NEP

How Rapid is “Rapid” to Detect Severe Dyskalemia

- Detection of dyskalemia relies on laboratory tests.
- Since cardiac tissue is sensitive to dyskalemias, electrocardiography (ECG) may be able to uncover clinically important dyskalemias before laboratory.
- Even experienced clinicians frequently do not recognize the ECG morphologic changes associated with dyskalemias.
- Using ECG-based DLM with large annotated data, we successfully developed ECG-12Net to help predict severe dyskalemia in seconds.

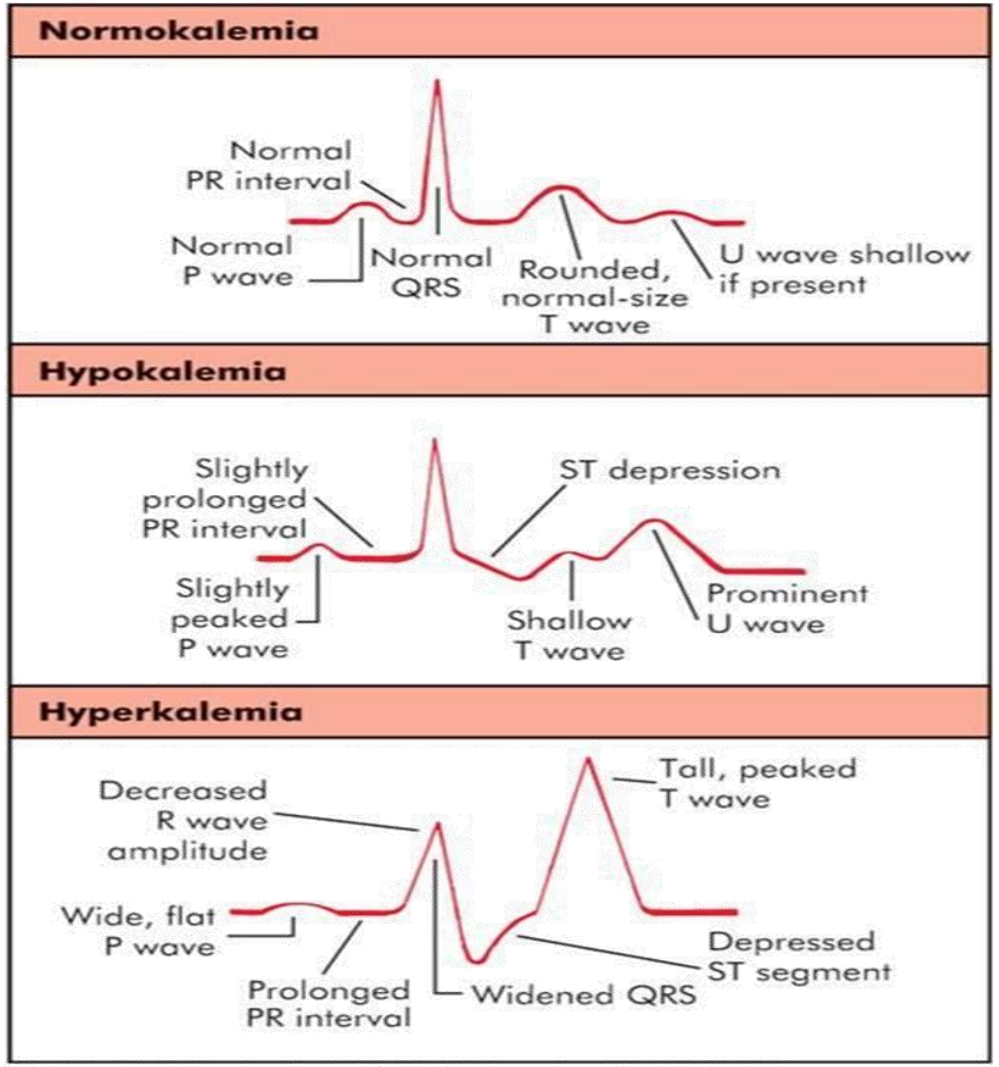
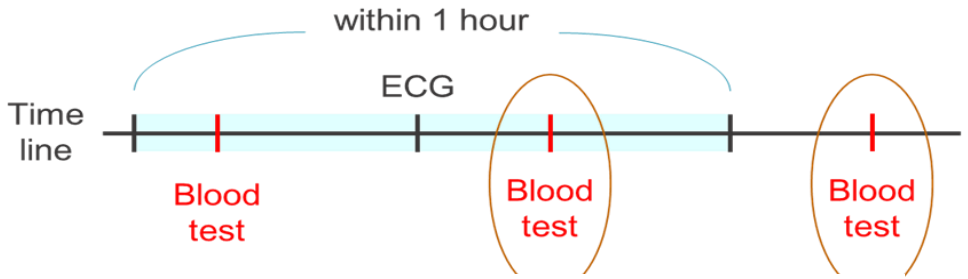
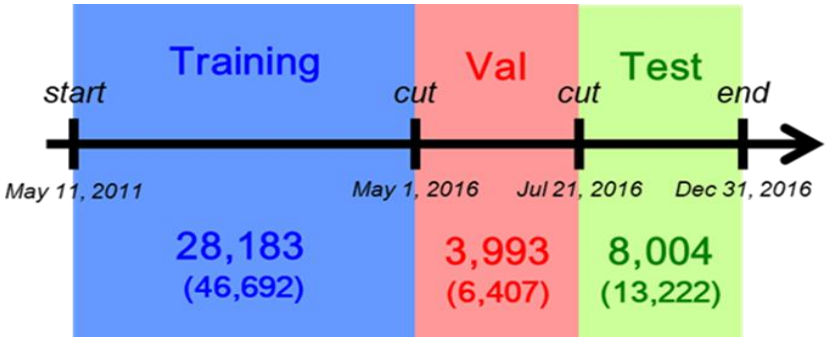
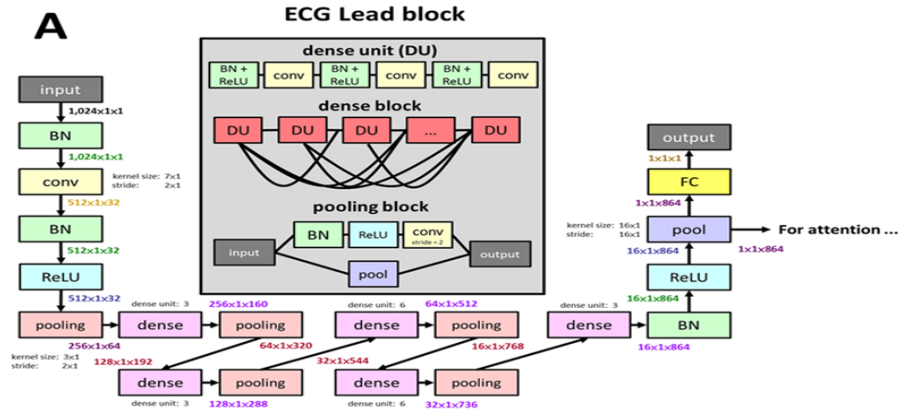


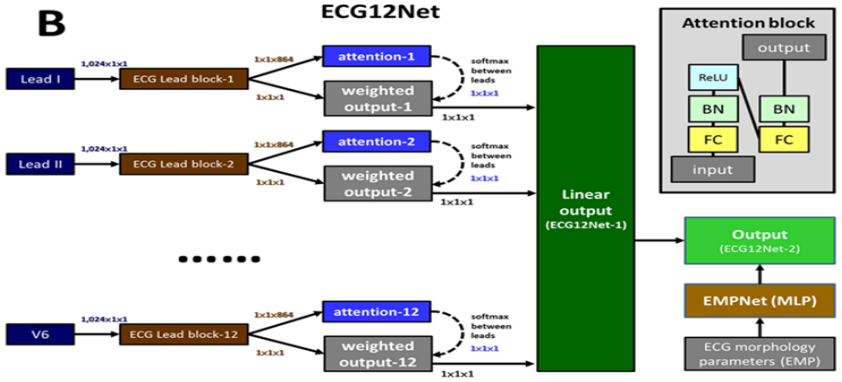
Fig. 4-7. Electrocardiogram Changes with Potassium Imbalance

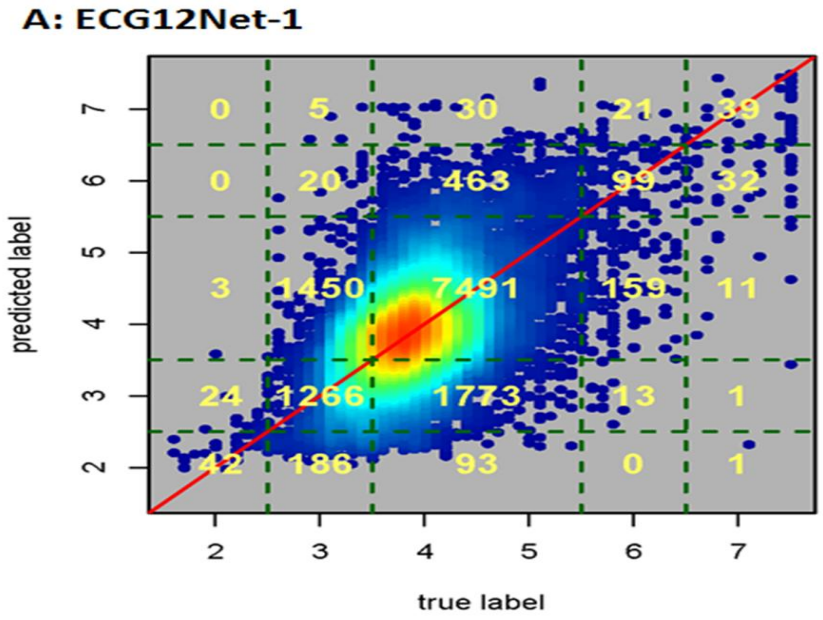
Bloodless AI-ECG for the detection of Dyskalemia using large annotated serum K^+









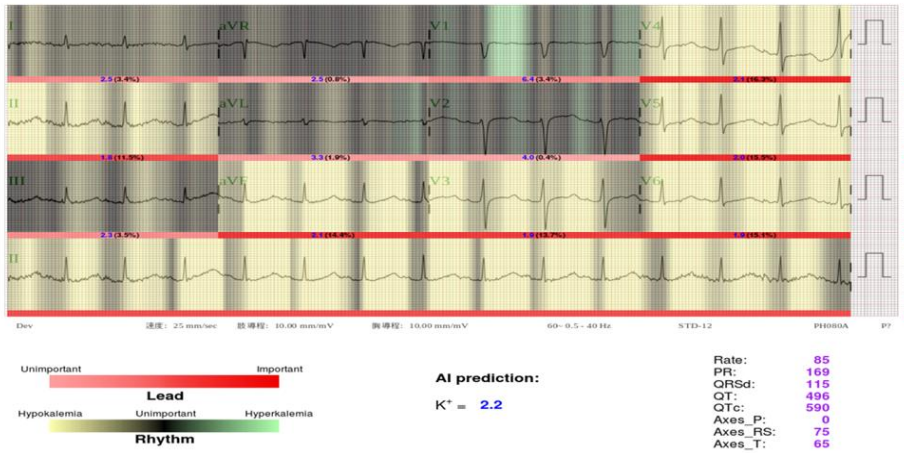


Sens (severe-hypoK): 95.6%
(severe hyperK): 84.5%

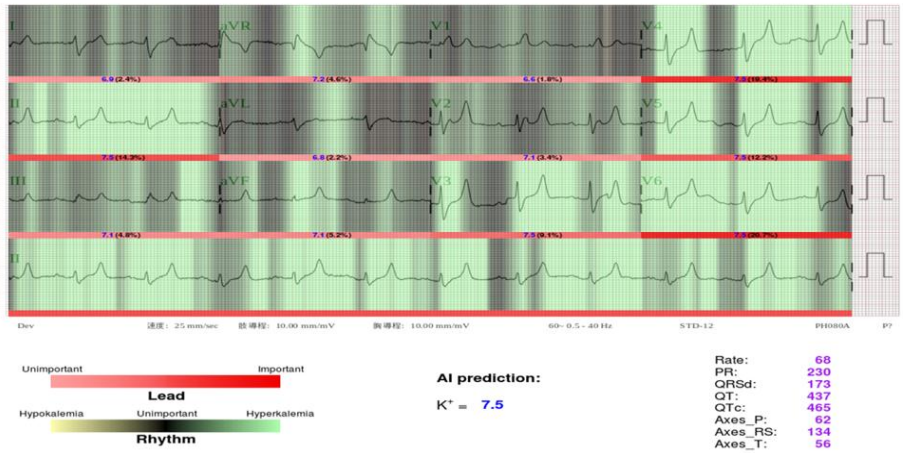
Lin CS et al, JMIR Med Inform 2020

Visualization analysis for ECG12Net in selected severe hypokalemia and hyperkalemia.

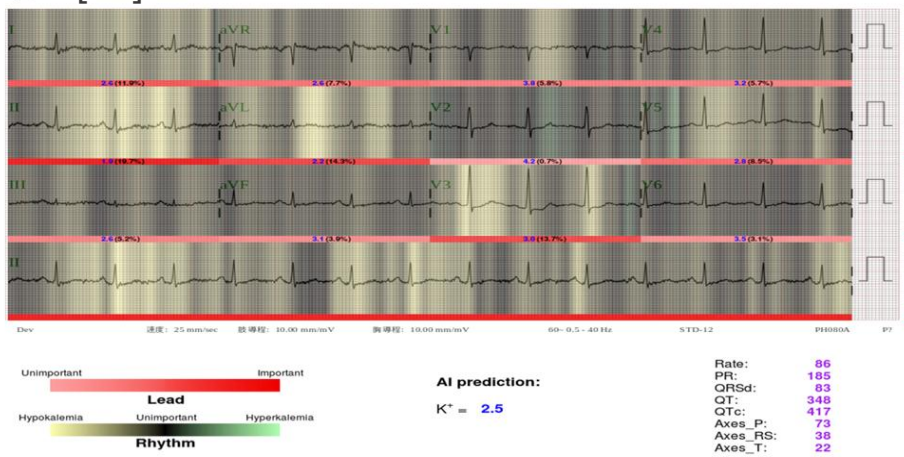
A [K+] 2.3



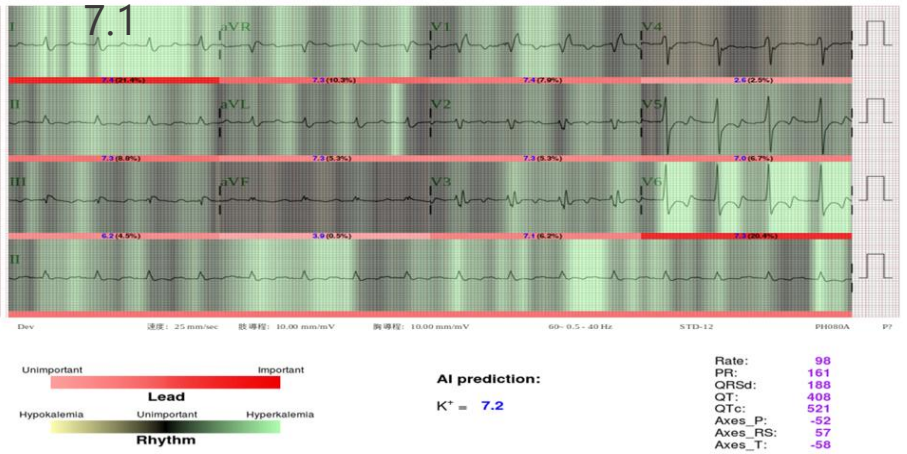
C [K+] 9.1



B [K+] 2.5



D [K+] 7.1

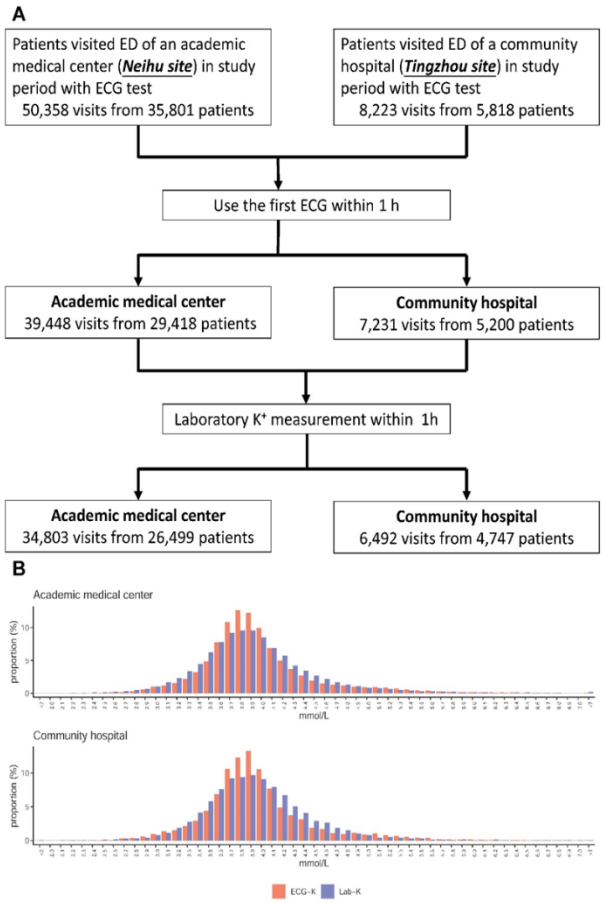


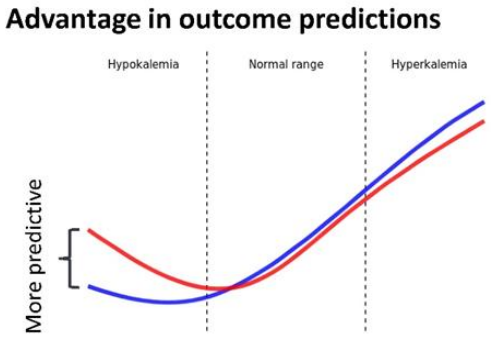
Comparison with Previous Studies

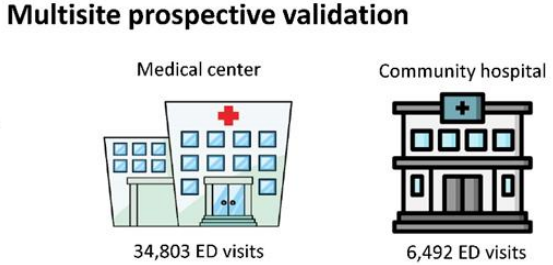
	This study	Galloway et al.
Sample size	66,321	1,576,581
Patients	**ED**	**CKD, stage ≥III**
Blood K^+	**Dyskalemia**	**Hyperkalemia**
Blood K^+ and ECG recording	**1hr < ECG < 1hr**	**<12 hrs**
Prediction type	**Continuous**	Binary
ECG lead	**12 leads**	**2 (I,II) or 4 leads**
Hyperkalemia ($K^+ \geq 5.5$)		
AUCs	0.911	0.853-0.883
Sensitivity	41.1-**84.5%**	81.3-84.0%
Specificity	**96.0%**	77.0-84.2%
Positive predictive value	26.9%	11.9-15.4%
Negative predictive value	98.5%	99.0-99.4%
Hypokalemia ($K^+ \leq 3.5$)		
AUCs	0.750	NA
Sensitivity	49.6-**95.6%**	NA
Specificity	**81.6%**	NA
Positive predictive value	44.7%	NA
Negative predictive value	85.0%	NA
Human-Machine Competition	Yes	No

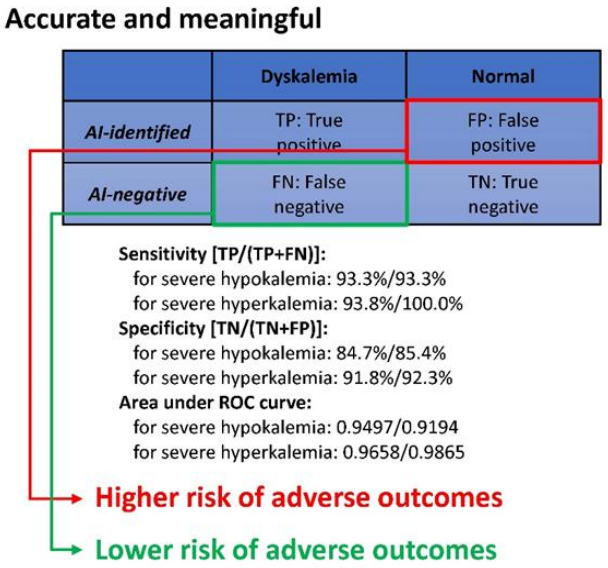
Bloodless AI-ECG K^+ Helps Predict the Outcome

Black-Box Validation with outcome prediction after May, 2019





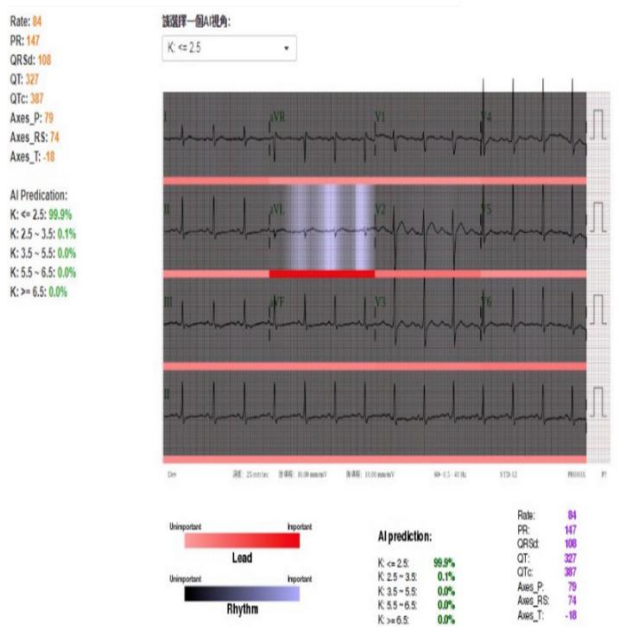




NPJ Digital Med 2022; 5: 8 (1-12)

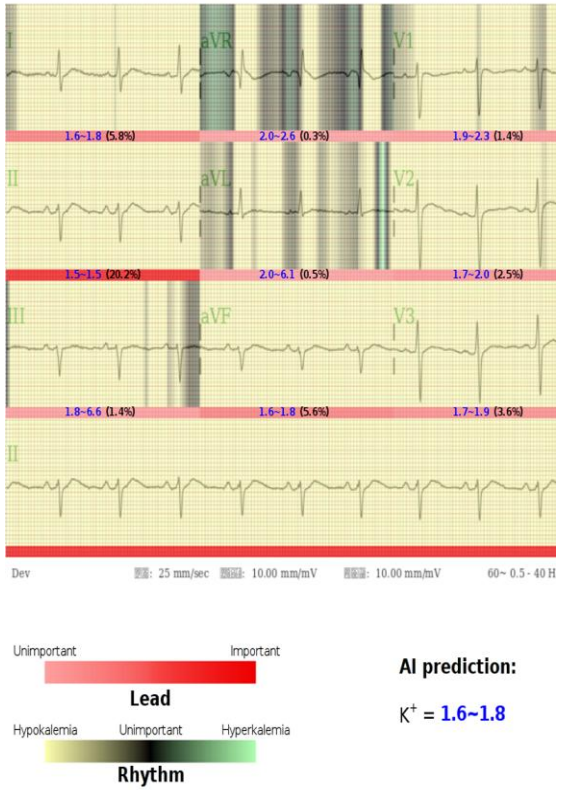
Early Detection of Severe Dyskalemia and Laboratory Error

Case : **A Young Male with Muscle Paralysis**



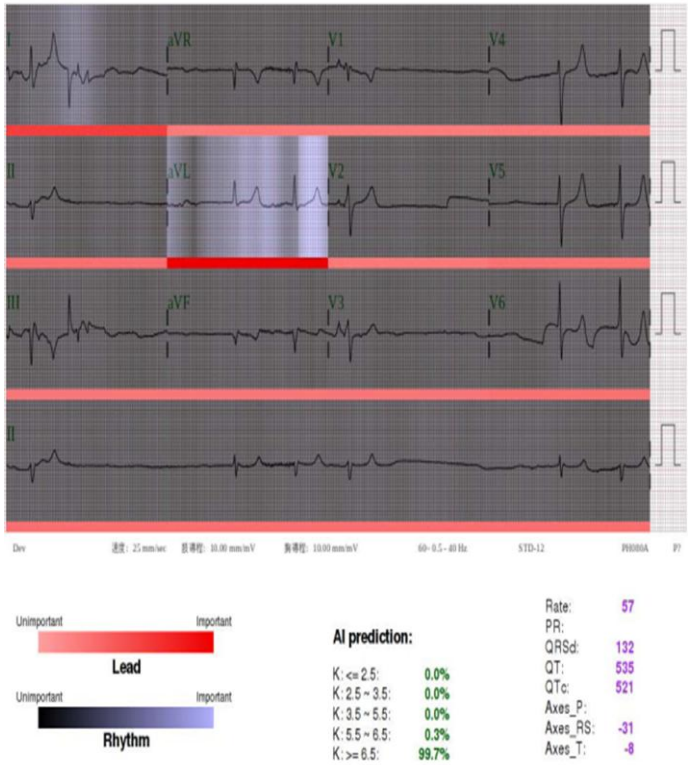
K^+: 2.2

A 24 Y/O Male with Chronic Hypokalemia (GS) at OPD



檢驗代碼	檢驗結果	檢驗結果單位	最小/最大安全值
GLU(ER)	H 120	mg/dL	74 - 100
BUN	15	mg/dL	7 - 25
eGFR	86.7 Stage2		
Creatinine	1.1	mg/dL	0.7 - 1.2
Uric Acid	4.7	mg/dL	2.3 - 7.0
Total Calcium	9.6	mg/dL	8.6 - 10.2
AST	31	U/L	- 40
ALT	37	U/L	- 41
Total Protein	8.2	g/dL	6.6 - 8.7
Albumin	4.5	g/dL	3.5 - 5.7
A/G Ratio	1.2		1.2 - 2.4
Na	L 135	mmol/L	136 - 145
K	L 1.6	mmol/L	3.5 - 5.1
Cl	100	mmol/L	98 - 107
Magnesium	1.9	mg/dL	1.7 - 2.55
PANIC INFORM			
通知日期	20/08/01		
通知時間	11h03m		
通知電話	12501		
被通知人	DR.林		
通知者	申慧人		

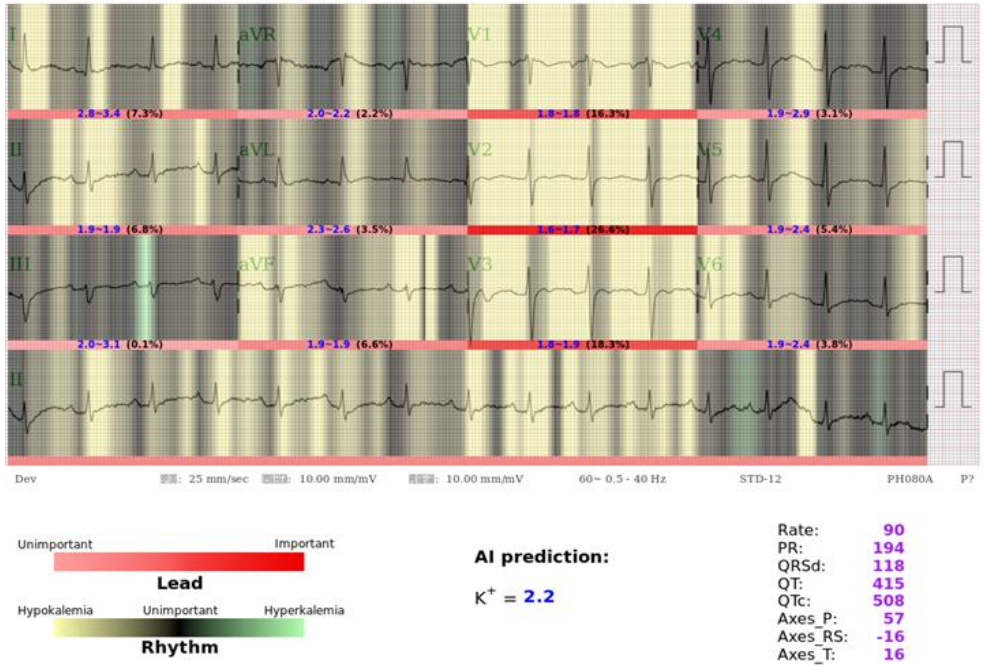
A 52-year-old: DM and CKD stage IV female with laboratory hypokalemia (2.6 mmol/L)



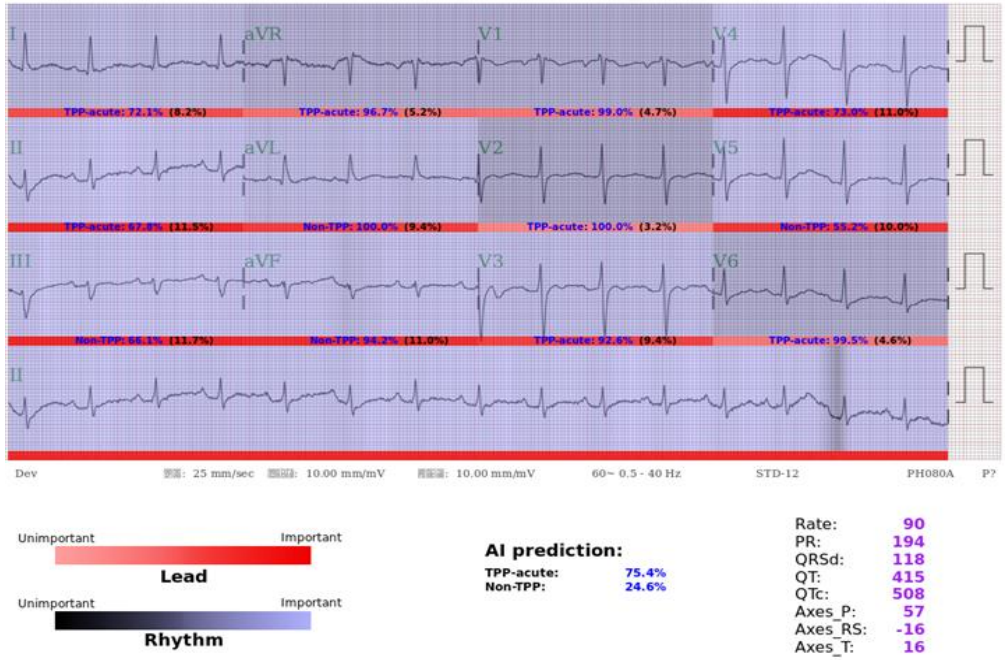
Lab K: 7.1 mmol/L

TPP: ECG
Hyperthyroidism on heart
Hypokalemia on heart
K Shift into cells

AI-ECG for Help Diagnose the causes of Hypokalemic Paralysis: TPP vs non-TPP



Hypokalemic paralysis

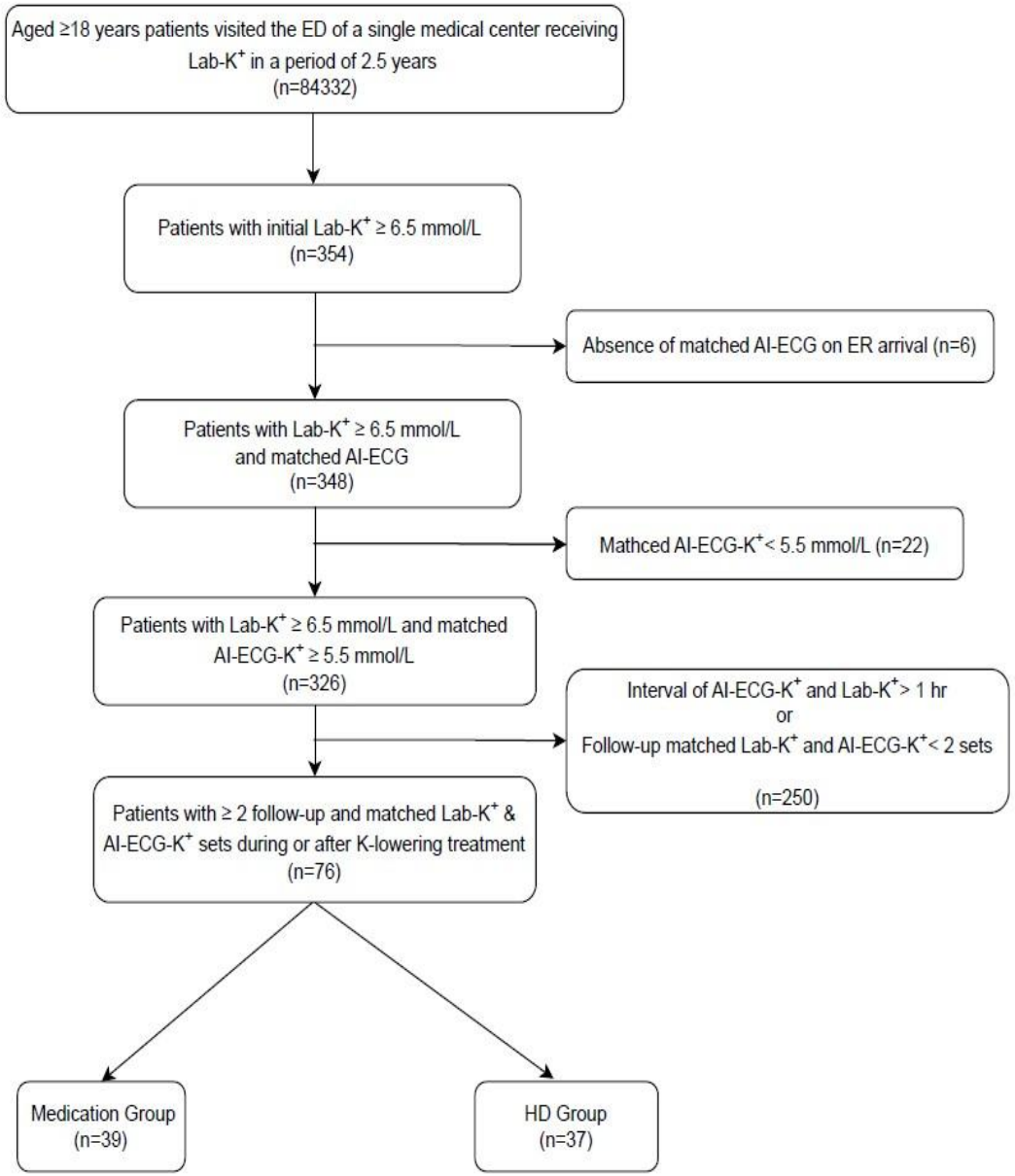


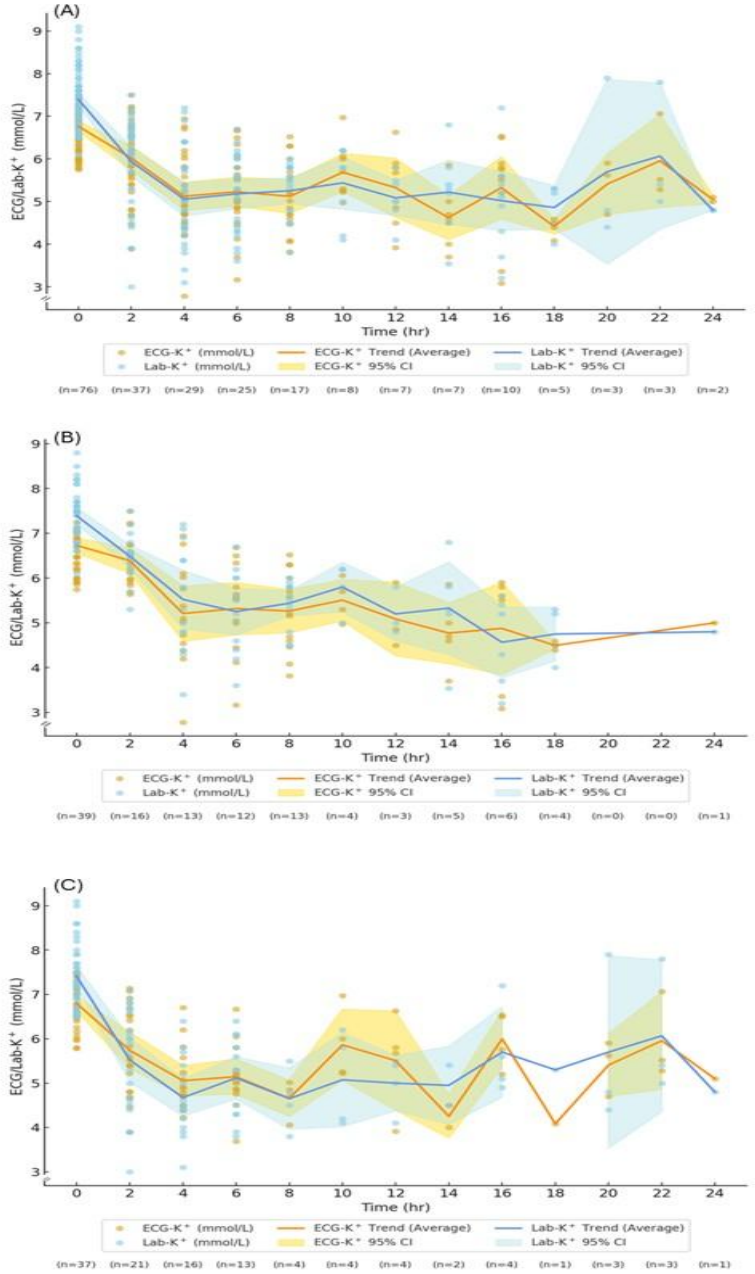
The ECG-TPP score defined as the similarity of ECG of typical TPP by DLM had the value of probability >50.0% with a sensitivity of 87.5% and a specificity of 69.2%.

60 mmol K^+ supplement

Lin C et al. J Endocrinol Soc 2021 **Featured article and high-cited paper**

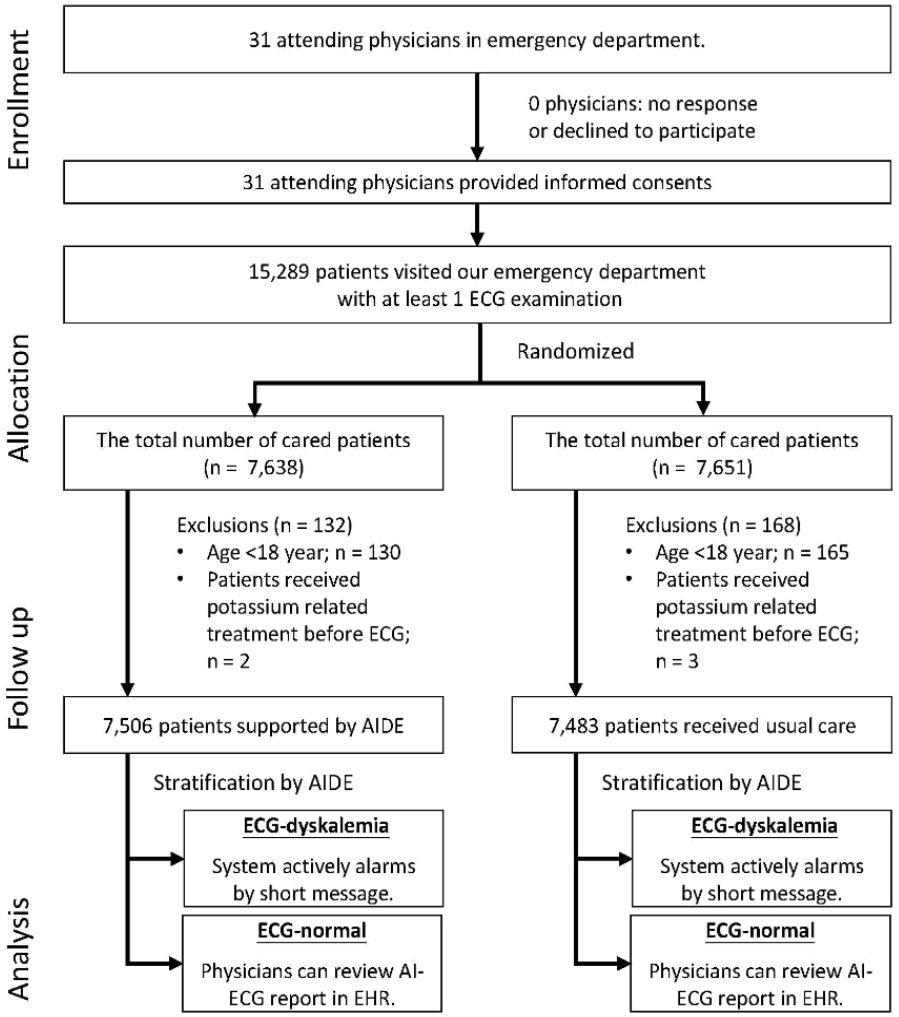
Monitoring Serum Potassium Concentration in Patients with Severe Hyperkalemia: the Role of Bloodless AI-Assisted Electrocardiography





Chen CC, et al. CKJ, 2025

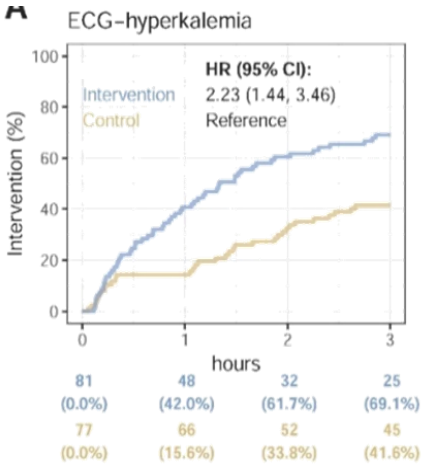
Artificial Intelligence enabled Dyskalemia using Electrocardiogram (AIDE) alert on potassium imbalance treatment: a pragmatic randomized controlled trial

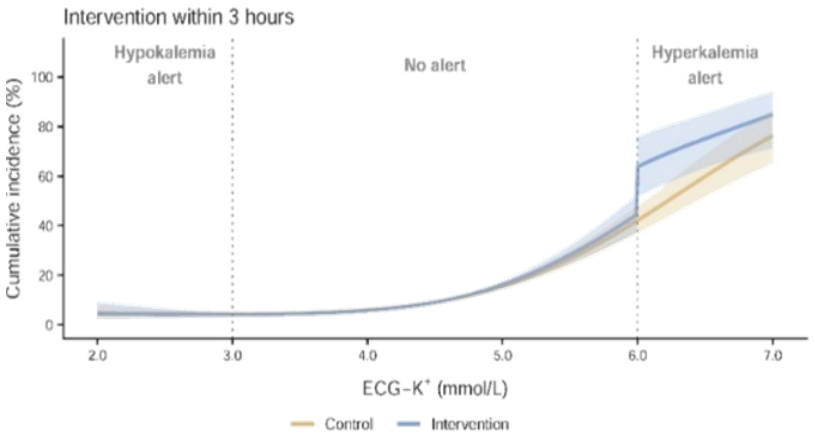


RCT settings

- **Emergency department in TSGH (~6 months)**
- **AI alert vs. usual care for physicians**
- **Primary endpoint: early treatment**

ClinicalTrial.gov: NCT05118022





Nature Comm 2025 Lin C and Lin SH

Summary

- High urine K^+ excretion rate did not indicate renal tubular disorders
- Diagnostic pearl: spot urine electrolytes (Na^+ vs Cl^-, divalents), PH, Osm
- To make genetic diagnosis after the exclusion of secondary causes.
- AI-ECG for early detection and monitoring of severe dyskalemia and previvor prediction.
- AIDE alerts facilitate physicians for early intervention of hyperkalemia.