Review
Bartter Syndrome

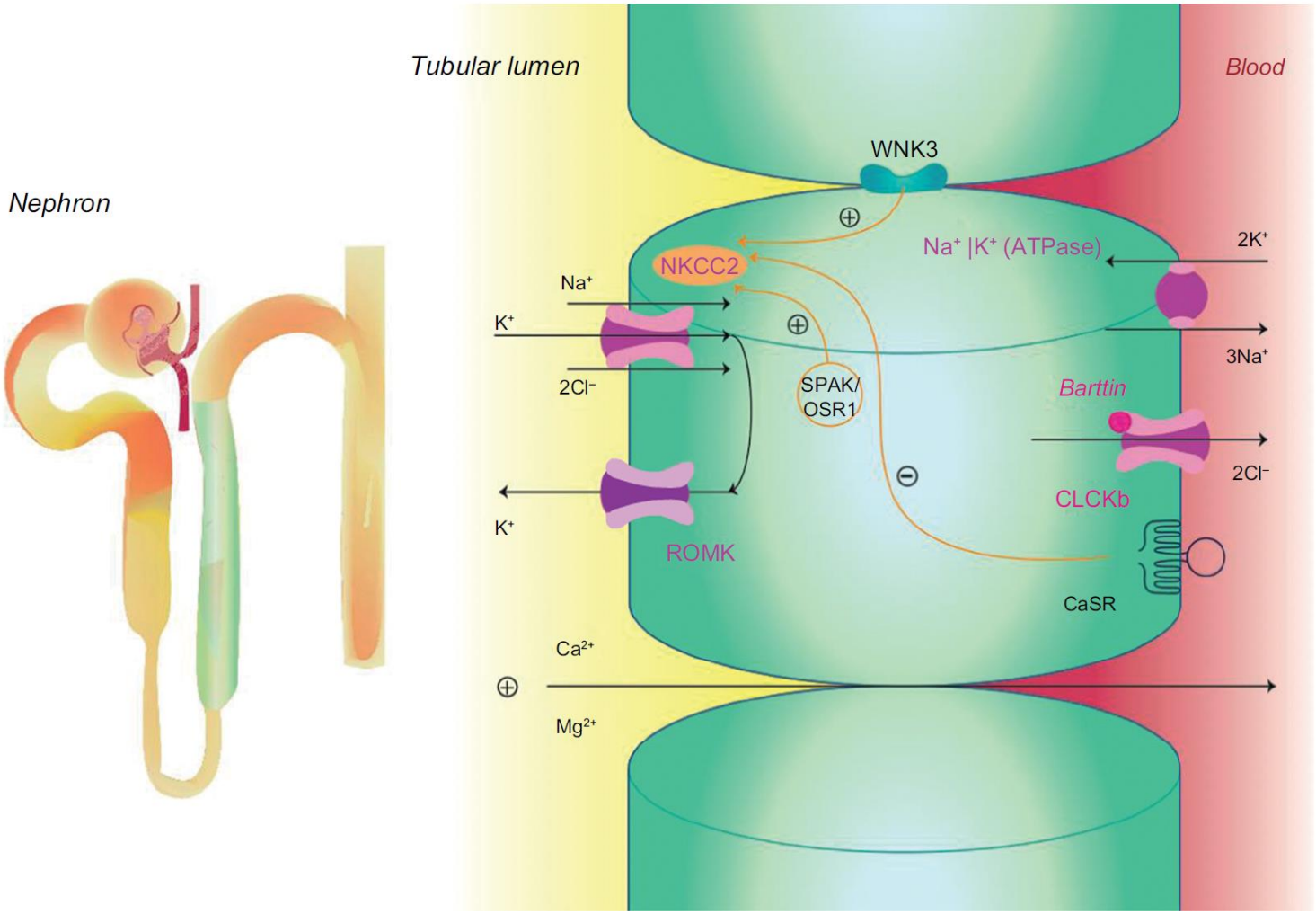
Speaker: Wen-Yuan Chang

Supervisor: Shih-Hua Lin

Introduction

- Bartter syndrome is an inherited renal tubular disorder caused by a defective salt reabsorption in the thick ascending limb of loop of Henle, resulting in salt wasting, hypokalemia, and metabolic alkalosis with relatively low levels of serum chloride
- Mutations of several genes encoding the transporters and channels involved in salt reabsorption in the thick ascending limb cause different types of Bartter syndrome.

Mechanisms of transport at thick ascending limb of the Henle's loop.



Pathophysiology

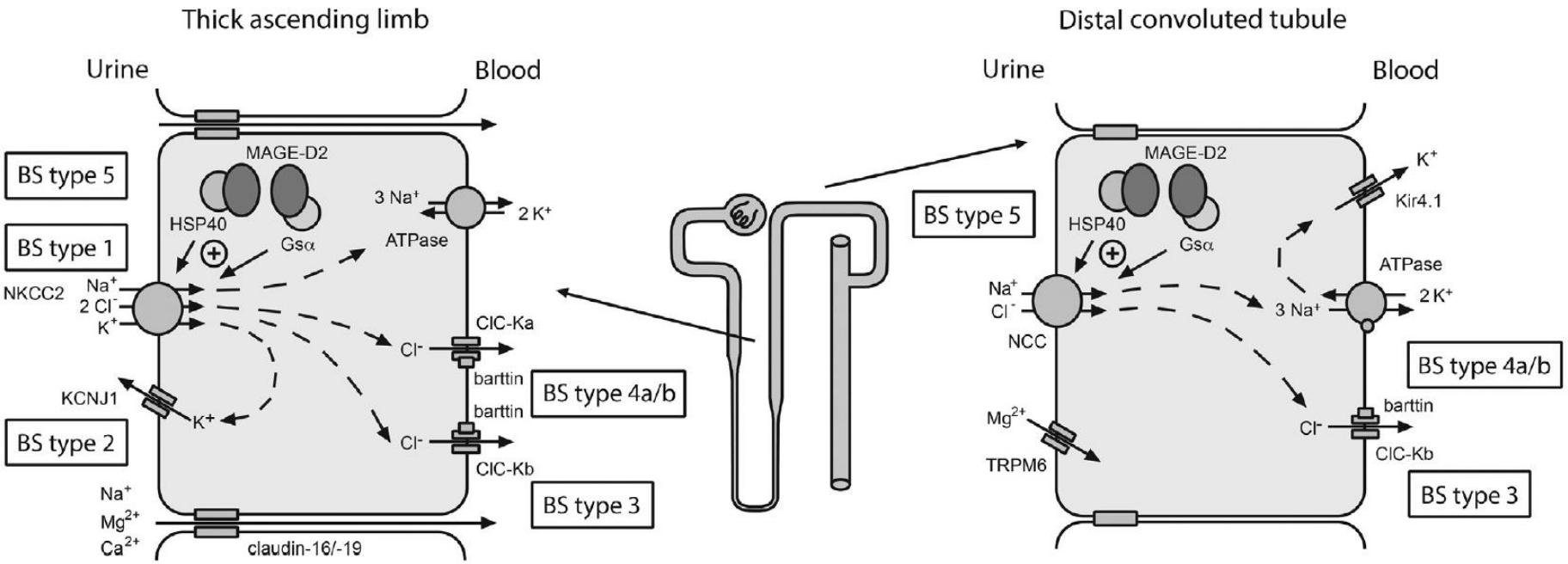
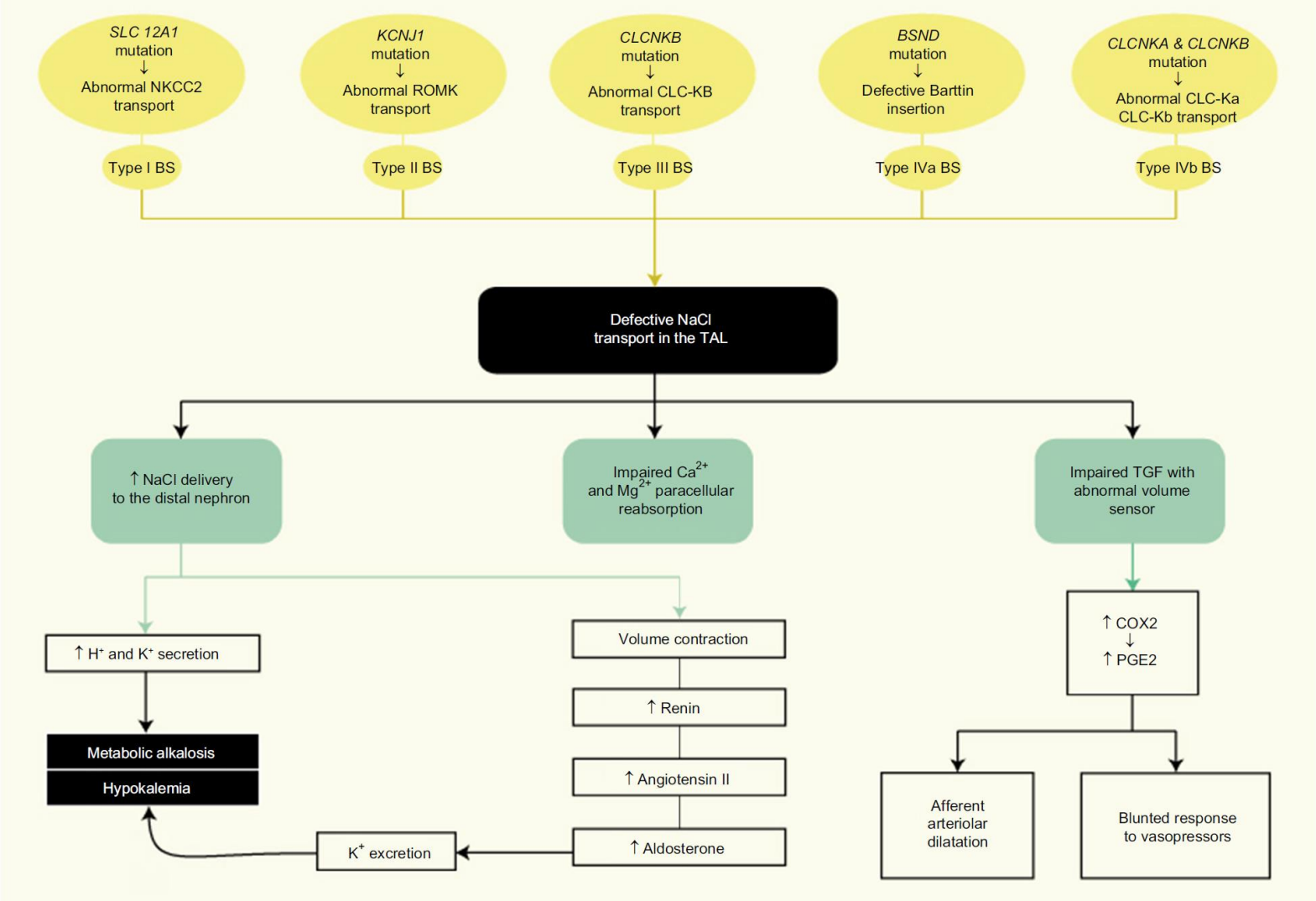


Table 1 Genetics of Bartter syndrome and typical clinical findings

	Gene	OMIM	Inheritance	Protein	Clinical findings
Type I	*SLC12A1*	601678	AR	NKCC2	Prematurity, polyhydramnios, nephrocalcinosis, hypokalemic alkalosis, hyposthenuria
Type II	*KCNJ1*	241200	AR	ROMK1	Prematurity, polyhydramnios, nephrocalcinosis, hypokalemic alkalosis, hyposthenuria, transient hyperkalemia
Type III	*CLCNKB*	607364	AR	CLC-Kb	Hypokalemia, hypochloremic alkalosis
Type IVa	*BSND*	602522	AR	Barttin	Prematurity, polyhydramnios, sensorial deafness, hypokalemia, hypochloremic alkalosis
Type IVb	*CLCNKA* *CLCNKB*	613090	AR	CLC-Ka CLC-Kb	Prematurity, polyhydramnios, sensorial deafness, hypokalemia, hypochloremic alkalosis
Transient BS	*MAGE-D2*	300971	XLR	MAGE-D2	Transient salt wasting, polyhydramnios
AD hypocalcemic hypercalciuria	*CASR*	601198	AD	CaSR	Hypocalcemic hypercalciuria

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive.



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Hypertrophy of the JGA

- Another essential portion of TAL is the macula densa, a region with an interface with afferent glomerular arterioles, namely juxtaglomerular apparatus(JGA), which mediates the tubuloglomerular feedback (TGF).
- In physiological conditions, the reduction of intracellular chloride concentration at the level of macula densa cells at JGA indicates diminished filtration, resulting in activation of the TGF hence stimulating renin release and afferent arteriolar dilatation with hyperfiltration.
- In patients with BS, reduced reabsorption of chloride occurs due to the genetic defects, and an increase in chloride delivery to the macula densa .
- This impaired entry of sodium and chloride into the macula densa increases the expression of cyclooxygenase-2(COX2) stimulating the renal production of prostaglandin E2 (PGE2), also resulting in afferent arteriolar dilatation and activation of renin release by JGA

Clinical Features

- BS causes polyhydramnios, leading to premature birth
  - typically develops between the 20th and 30th weeks of gestation. Timing and severity vary according to the underlying genetic defect.
  - In BS4 and BS5, polyhydramnios is typically observed earlier than in BS1 and BS2.
- BS5 always presents antenatally, but symptoms spontaneously resolve typically around the estimated date of delivery.
- BS3 usually manifests later in life, the age of 1 year. Nevertheless, a prenatal presentation does not exclude BS3.
- Patients typically present with salt craving, failure to thrive, poor weight gain, or polyuria with polydipsia. Less frequent symptoms are related to dehydration.
- In a minority of cases, the diagnosis of BS is incidental after noticing abnormal laboratory results, discovery of nephrocalcinosis, or family screening.

uptodate

Clinical characteristics of Bartter syndrome (BS) and Gitelman syndrome (GS)[1-5]

	BS 1	BS 2	BS 3	BS 4a	BS 4b	Type 5*	GS
Affected gene	*SLC12A1*	*KCNJ1*	*CLCNKB*	*BSND*	*CLCNKA*; *CLCNKB*	*MAGED2*	*SLC12A3*
Typical age of presentation	Antenatal	Antenatal	0 to 5 years	Antenatal	Antenatal	Antenatal	>6 years
Polyhydramnios	Severe	Severe	Absent to mild	Severe	Severe	Very severe	Absent
Prematurity	Common	Common	Rare	Common	Common	Always	No
Neonatal hypovolemia¶	Common	Common	Rare	Common	Common	Common	Absent
Hypokalemia	Always	Transient neonatal hyperkalemia followed by hypokalemia	Always	Always	Always	Always	Always
Calcium excretion	High	High	Variable but usually normal	Variable	Variable	Variable	Low
Nephrocalcinosis	Very common	Very common	Rare and, if present, mild	Rare and, if present, mild	Rare and, if present, mild	Rare	Absent
Magnesium excretion	Normal	Normal	Normal to high	Normal to high	Normal to high	Unknown	High
Poor weight gain and growth failure	Common	Common	Common	Common	Common	No	Can be seen in prepubertal individuals. Short stature may be seen in affected adolescents and adults.
Other findings				Sensorineural hearing loss	Sensorineural hearing loss	Large for gestational age; transient disease	Chondrocalcinosis

Table 2| Main clinical and biochemical characteristics of different types of Bartter syndrome

Characteristic	Type 1	Type 2	Type 3	Type 4a	Type 4b	Type 5
Age at onset	Prenatally	Prenatally	0–5 years	Prenatally		Prenatally
Polyhydramnios	Severe	Severe	Absent or mild	Severe		Very severe
Gestational age at birth, wks, median (IQR)	32 (29–34)	33 (31–35)	37 (36–41)	31 (28–35)		29 (21–37)
Leading symptoms	Polyuria, hypochloremia, alkalosis, hypokalemia	Polyuria, hypochloremia, alkalosis, transient neonatal hyperkalemia	Hypokalemia, hypochloremia, alkalosis, failure to thrive	Polyuria, hypochloremia, alkalosis, hypokalemia		Polyuria, hypochloremia, alkalosis, hypokalemia
Calcium excretion	High	High	Variable	Variable		High
Nephrocalcinosis	Very frequent	Very frequent	Rare, mild	Rare, mild		Rare, mild
Plasma Cl/Na ratio	Normal	Normal	Decreased	Decreased		Increased
Other findings			Mild hypomagnesemia	Deafness, risk for CKD, ESRD		Large for gestational age, transient disease

Diagnosis

- The diagnosis of either BS is clinically suspected upon recognition of their characteristic features but requires genetic testing for confirmation.
- When to suspected:
  - Hypokalemic hypochloremic metabolic alkalosis
  - High urinary chloride excretion
  - Normal to low blood pressure (BP) despite elevated renin and aldosterone levels
- Genetic testing will also differentiate amongst the various types of BS.

Table 4 | Differential diagnosis of Bartter syndrome

Leading symptom	Differential diagnosis	Additional findings
Polyhydramnios of fetal origin	Aneuploidia	Abnormal karyotype
	Gastrointestinal tract malformation	Variable, empty stomach
	Congenital chloride diarrhea	Dilated intestinal loops
Salt loss	Pseudohypoaldosteronism type I	Metabolic acidosis, hyperkalemia
Salt loss with hypokalemic alkalosis	Congenital chloride diarrhea	Low urinary chloride
	Pseudo-Bartter syndrome, e.g., in CF	Low urinary chloride
	Gitelman syndrome	Hypocalciuria, hypomagnesemia
	HNF1B nephropathy	Renal malformation, cysts, MODY5, hypomagnesemia
	HELIX syndrome	Hypercalcemia, hypohidrosis, ichthyosis
	Autosomal dominant hypocalcemia	Hypocalcemia, seizures
	EAST/SeSAME syndrome	Ataxia, seizures, deafness, developmental delay
	Surreptitious vomiting	Low urinary chloride
	Surreptitious laxative use	Low urinary chloride
	Surreptitious diuretic use	Highly variable urinary chloride
Hypokalemic alkalosis without salt loss	Primary hyperaldosteronism;	Hypertension, low renin
	Apparent mineralocorticoid excess	Hypertension, low renin/ aldosterone
	Liddle syndrome	Hypertension, low renin/ aldosterone
Nephrocalcinosis	Distal renal tubular acidosis	Metabolic acidosis
	Proximal tubular defects	No metabolic alkalosis
	Familial hypomagnesemia/ hypercalciuria	No hypokalemic metabolic alkalosis, CKD
	Apparent mineralocorticoid excess	Hypertension, low renin/ aldosterone

Table 2. Acquired causes of Bartter's syndrome.
Infection: Tuberculosis
Granulomatous: Sarcoidosis
Metabolic: Diabetes
Drugs: colistin, aminoglycosides
Autoimmune disease: Sjögren's disease

Saudi J Kidney Dis Transpl 2020;31(5):1144-1147

Kidney International (2021) 99, 324–335

Treatment

Table 2 Treatment options and clinical controversies in Bartter syndrome

Drugs	Rationale for using	Limitations and clinical controversies
KCl supplements	• Correction of hypokalemia	• Hypokalemia usually persists but less pronounced
Spironolactone/eplerenone (aldosterone receptor blockers)	• K^+-sparing diuretics (help correction of hypokalemia)	• Aldosterone levels could be lower because of hypokalemia • Gynecomastia can limit spironolactone use
Amiloride (ENaC blocker)	• K^+-sparing diuretics (help correction of hypokalemia)	• Could work better than spironolactone and eplerenone to raise serum K^+ levels and reverse metabolic alkalosis
ACEi and ARB not routine	• Help to correct hypokalemia • Reduce proteinuria if present	• Caution is necessary due to the risk of hypotension and AKI
NSAIDs symptomatic patients + gastric acid inhibitors	• Reduce urinary volume helping to further correct hypokalemia	• Gastrointestinal side effects • Potential nephrotoxicity • Not established which NSAID provides best efficacy/less side effects • Gradual discontinuation during school age or lifelong maintenance? • Potential risks vs benefits of antenatal treatment

premature closure of the ductus arteriosus or necrotizing enterocolitis

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- In the general population, guidelines suggest aiming for potassium levels >3.0 mmol/l
- Renin and aldosterone levels may be helpful in assessing the adequacy of NSAID treatment
- Commonly used NSAIDs are indomethacin (1–4 mg/kg/d divided in 3–4 doses), ibuprofen (15–30 mg/ kg daily in 3 doses), and celecoxib (2–10 mg/kg/d in 2 doses), taper down if stable
- Data on long-term outcomes in BS are sparse.
- Whereas nephrocalcinosis and hypercalciuria are present in the majority of patients (except BS3), the prevalence of symptomatic urolithiasis in BS appears to be relatively low.
- Chronic kidney disease is common in BS, and patients with BS1 and BS4 may have more severe chronic kidney disease progression than those with BS2 and BS3

Late-onset Bartter Syndrome Type II

Clinical Case Report

Medicine

OPEN

A novel compound heterozygous *KCNJ1* gene mutation presenting as late-onset Bartter syndrome

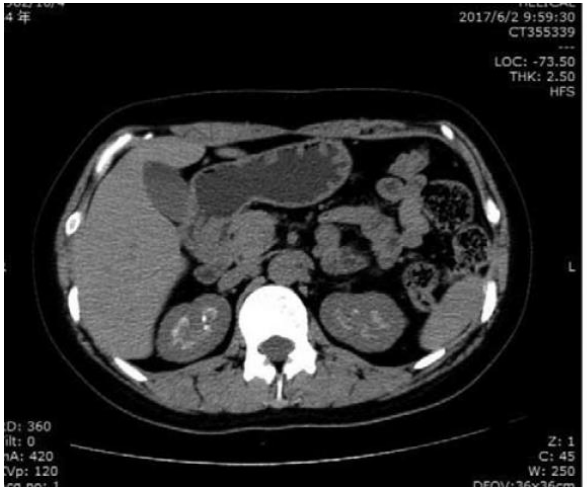
Case report

Jingyi Li, MD[a,*], Shoulong Hu, MD[b], Yi Nie, MSc[a], Rongfeng Wang, MBBS[c], Ming Tan, PhD[a], Hongmei Li, MBBS[a], Shuanli Zhu, MSc[a]

- 34 years old woman
- height :173cm, weight :68.5 kg
- pulse 96/min, respiratory rate 20/min,

and blood pressure 110/80 mm Hg.

- History of polyhydramnios, polyuria and Polydipsia in neonate
- Bilateral medullary nephrocalcinosis
- S/S: weakness
- Family history: denied

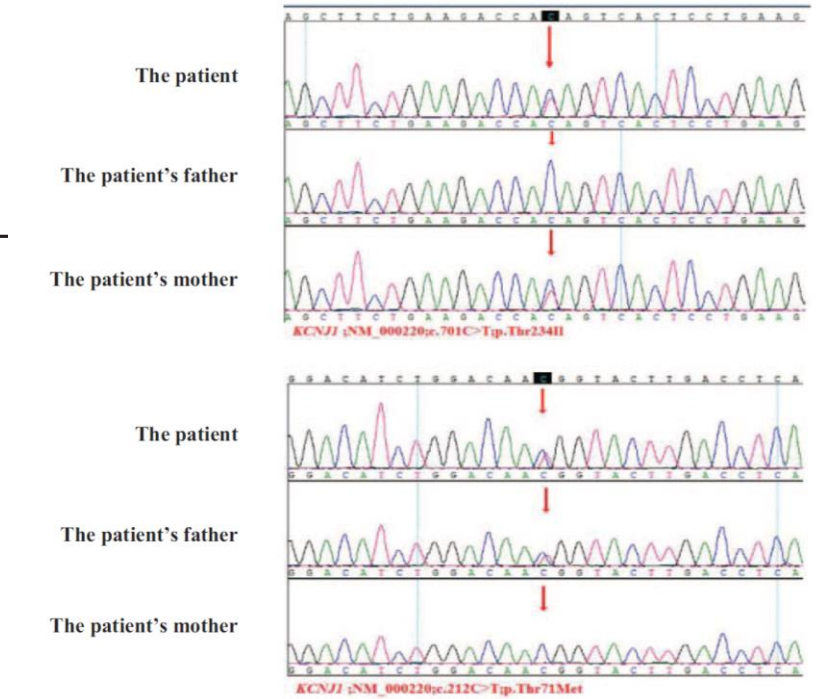


Laboratory studies revealed hypokalemia, metabolic alkalosis, hypercalciuria, hyperparathyroidemia, and hyperreninemia.

Table 1

The patient was admitted to the hospital on 30th May and discharged on 9th June; after hospitalization the patient came back to have the examination on 25th June.

	Reference ranges	05–31	06–01	06–04	06–05	06–07	06–08	06–25
Plasma sodium, mmol/L	135–147	140.0	141.0	143.0	143.9	138.0	144.6	143.1
Plasma chlorine, mmol/L	99–110	95.6	98.9	97.3	97	93.4	99.2	99.1
Plasma potassium, mmol/L	3.5–5.3	2.4	3.29	3.21	3.02	3.0	3.99	3.38
Plasma bicarbonate, mmol/L	22–29	27.5	27.5	30.9	31.3	29.4	31.4	27.9
Plasma calcium, mmol/L	2.1–2.55	2.39	2.10	2.27	2.32	2.44	2.32	2.33
Plasma phosphate, mmol/L	0.87–1.45		1.05	1.04			0.78	
Plasma magnesium, mmol/L	0.6–1.05		0.67		0.86			
Plasma creatinine, μmol/L	45–106	105	99	98	104	95	103	102
Plasma parathyroid hormone, pmol/L	1.6–6.9		12.77				18.97	
Urinary sodium, mmol/day	30–260		60					
Urinary potassium, mmol/day	51–102		93.7					
Urinary chlorine, mmol/day	110–250		218.5					
Urinary pH	4.8–7.4		8.5					
Urinary SG	1.015–1.025		1.004					
Urinary calcium, mmol/day	2.5–6.3		6.9					
Urinary phosphate, mmol/day	13–42		16.4					



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Exceptional Case

EXCEPTIONAL CASE

Late-onset Bartter syndrome type II

Benjamin Gollasch[1], Yoland-Marie Anistan[2], Sima Canaan-Kühl[3] and Maik Gollasch[2,3]

- A 43-year-old German woman
- strong thirst and polyuria in childhood
- Family history: denied
- bilateral nephrocalcinosis by ultrasound during her second pregnancy
- The blood pressure was normotensive (136/80mmHg)

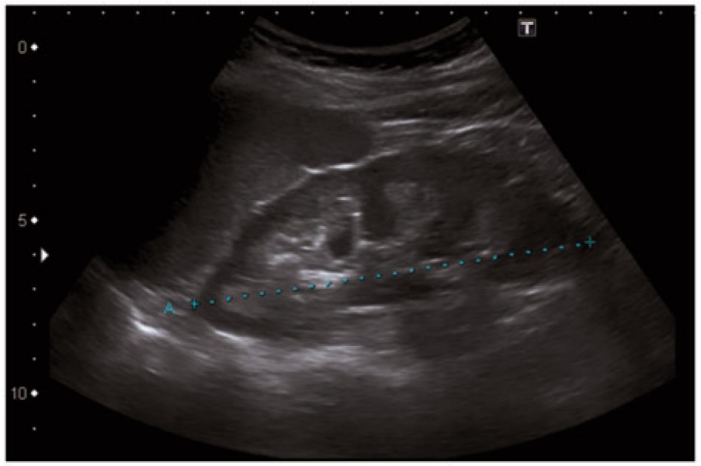
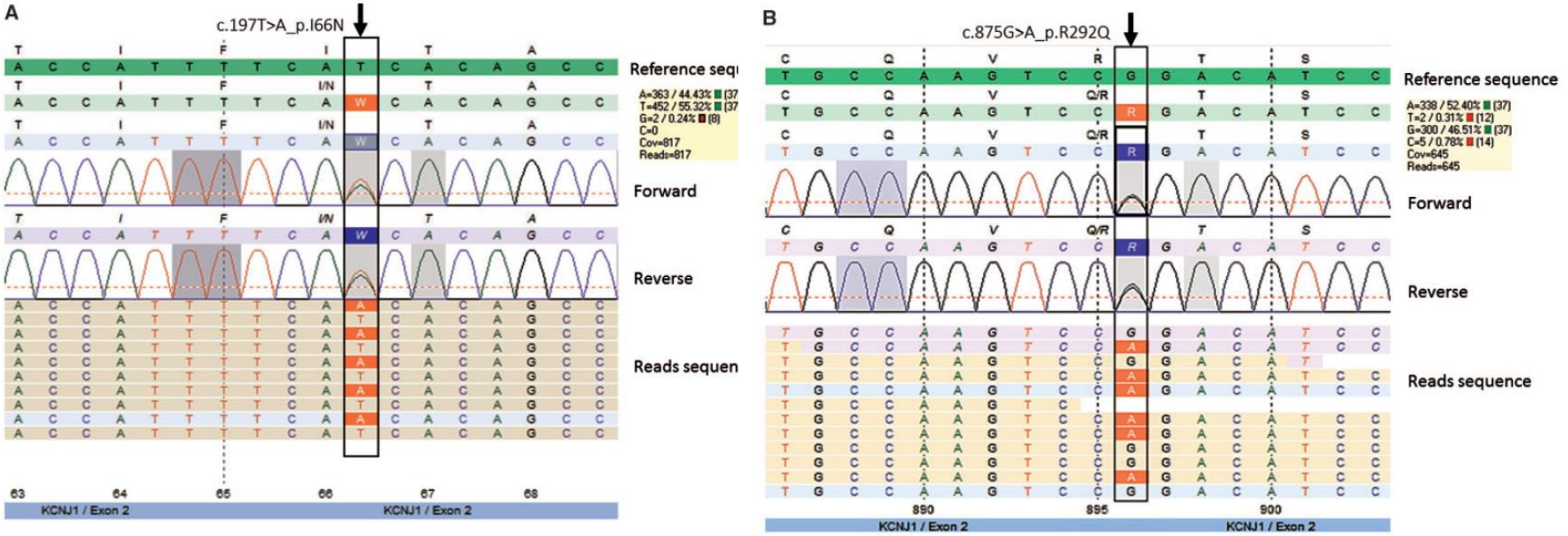


Fig. 1. Ultrasound image demonstrating renal medullary nephrocalcinosis in the patient's left kidney. This ultrasound image shows increased echogenicity of the renal medulla. Kidney size, 11.5 cm (blue dotted line).

- K:3.0 mmol/L, Ca: 2.31 mmol/L,
- Na:139mmol/L, Cl:104mmol/L, Mg:0.87mmol/L, P:0.9mmol/L
- Hyperaldosteronism (515ng/L, 847 ng/L) (normal range 30–340)
- Hyperreninaemia (43.1ng/L, 25.6ng/L) (normal range 2.0–24.6)
- Venous blood: pH 7.37, HCO3 28.2mmol/L, pCO2 56.9mmHg, PO2 29.4mmHg
- Increased calcium excretion in the urine :7.5mmol/day (normal range <6.2mmol/day)
- FENa (2.3%),FEK (22%), FECl (2.52%):increased
- Serum creatinine was 1.10mg/dL



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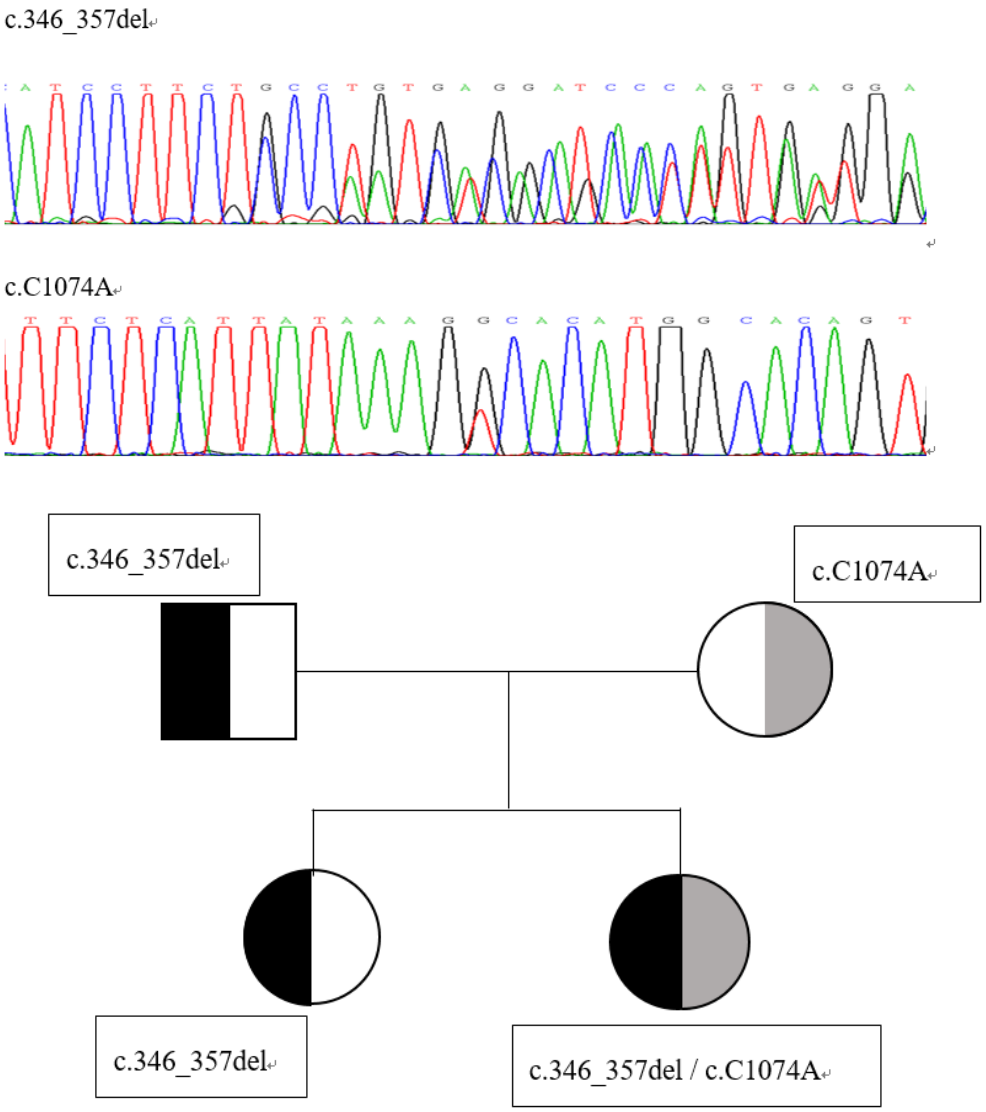
Late-Onset Bartter Syndrome Type II Due to a Homozygous Mutation in *KCNJ1* Gene: A Case Report and Literature Review

Table 2. Summary of previously reported similar cases.

Author	Age of presentation	Sex	Clinical presentation	Relevant investigations	Type of mutation in *KCNJ1* gene	DNA sequence change	Amino acid change	Treatment
Huang et al., 2014 [3]	35	Male	Incidental finding of nephrocalcinosis in lumbar spine X-ray done for low back pain	– Potassium: 2.8 mmol/l – Creatinine: 122 umol/l – 24-hour calcium excretion: 4.34 mmol/day	A homozygous missense mutation	c.658C>T	p.Leu220Phe	Potassium supplementation and spironolactone
Gollasch et al., 2017 [4]	43	Female	Incidental finding of nephrocalcinosis in ultrasound done during pregnancy	– Potassium: 2.8 mmol/l – Creatinine: 97 umol/l – 24-hour calcium excretion: 7.5 mmol/day	A compound heterozygous missense mutation	c.197T>A (novel mutation) c.875G>A	p.Ile66Asn p.Arg292Gln	Potassium supplement and angiotensin-converting-enzyme inhibitors (ramipril)
Li et al., 2019 [5]	34	Female	Weakness. persistent polyuria and polydipsia; weight and height were normal	– Potassium: 2.4 mmol/l – Creatinine: 97 umol/l – 24-hour calcium excretion: 6.9 mmol/day	A compound heterozygous missense mutation	c.701C>T (novel mutation) c.212C>T	p.The234Ile p.Thr71Met	Potassium supplementation
Sharma et. al., 2011 [6]	8.5	Female	Persistent polyuria and polydipsia; fifth percentile for weight and height	– Potassium: 2.5 mmol/l v Creatinine: 44 umol/l – Ca/creatinine 0.91 mg/mg (normal \0.2)	A novel compound heterozygous mutation	c.268G>T c.632T>G	p.Gly90Trp p.Ile211Ser	Potassium supplementation and nonsteroidal anti-inflammatory drugs (NSAIDs)
Present case	26	Male	Weakness. persistent polyuria and polydipsia; weight and height were normal	– Potassium: 1.7 mmol/l – Creatinine: 96 umol/l – 24-hour calcium excretion: 3.5 mmol/day	A homozygous missense mutation	c.658C>T	p.Leu220Phe	Potassium supplement and Aldosterone antagonists

Back to Our case

- Novel *KCNJ1* mutation:
  - c.346_357del(p.116_119del)
  - c.1074C>A(p.C358X)
- Over 40 *KCNJ1* mutations had been reported.
- More investigations are needed to study the correlations between gene mutations and phenotype variability.



Thanks for your attention.