Review

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Molecular Genetics of Bartter Syndrome

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Bartter syndrome (BS) is a heterogeneous disorder, caused by mutations in several genes which mostly encode proteins involved in ions transportation across renal cells in the thick ascending limb of the nephron. It is characterized by deficient renal reabsorption of sodium and chloride, which results in a group of certain symptoms. Different types of BS can be distinguished from different clinical manifestations, and most importantly, via analyzing possible affected gene(s) for its confirmation. A close associated syndrome which was primarily considered as a mild variant of BS, Gitelman syndrome (GS), is characterized by hypokalemic metabolic alkalosis with hypocalciuria, and hypomagnesemia. In this review, we discuss different features of BS and also GS, including clinical and genetic alterations which correspond to each type.

Keywords: Bartter Syndrome; Molecular Genetics; Child.

Running Title: Molecular Genetics of Bartter Syndrome

Bartter syndrome; a general picture

It was first in 1962 when Bartter and colleagues reported two cases with novel appearances that led to identification of a new syndrome. Bartter syndrome (BS) was characterized by hyperplasia and hypertrophy of the juxtaglomerular apparatus of the kidneys, and primary aldosteronism with hypokalemic alkalosis concomitant with normal blood pressure [1]. Thereafter, several cases have been studied, resulting in deeper understanding of the pathological and molecular characteristics of the disease [2-6]. Accordingly, type-categorization of BS has expanded to five groups, from the earlier grouping system that categorized BS to two major types, 'antenatal' and 'classic'. Thereupon, the term 'neonatal BS' has been preferred instead of 'antenatal BS', since some prenatal associated features could be observed in classical BS, as well. As a genetic disease, the new developed grouping system was largely influenced by the development of genetic causes of BS, mainly based on different responsible associated genes with the disease. Deep understanding of BS has resulted in the development of more specific and suitable treatments for this disease.

BS is a heterogeneous disorder, caused by mutations in several genes which mostly encode proteins involved in ions transportation across renal cells in the thick ascending limb of the nephron [7]. Thus, it is characterized by deficient renal reabsorption of sodium and chloride, which results in a group of certain symptoms. Different types of BS can be distinguished from different clinical manifestations, and most importantly, via analyzing possible affected gene(s) for its

confirmation. A close associated syndrome which was primarily considered as a mild variant of BS, Gitelman syndrome (GS), is characterized by hypokalemic metabolic alkalosis with hypocalciuria, and hypomagnesemia [8]. In this review, we discuss different features of BS and also GS, including clinical and genetic alterations which correspond to each type. Briefly and interestingly, the clinical and genetics classification of BS have been developed in parallel and consistently.

Pathology of Bartter syndrome

BS consists of a number of different inherited tubular disorders that each result from impairment of different parts of the transportation machinery of the thick ascending Henle's loop and/or distal convoluted tubule, leading to salt-loosing and volume depletion disorders [9]. BS was first categorized to two major types of neonatal and classical. Neonatal BS (also called Hyperprostaglandine E syndrome [10]) is the most severe form, which is mostly characterized by polyhydramnios, premature birth, growth retardation, intrauterine and postnatal polyuria concomitant with intense dehydration, and recurrent vomiting [11]. Of other symptoms, hypercalciuria, nephrocalcinosis, and sometimes end-stage renal failure and deafness can be noted [12-15]. In some cases, special appearances like a triangular-shaped face with a distinguished forehead, large eyes, strabismus, a drooping mouth, protruding ears, emaciation, and small muscles can be present [16,14]. Osteopenia, diarrhea, fever, and increases susceptibility to infection are also systematic symptoms of neonatal BS [17]. Neonatal BS is generally an autosomal recessive (AR) disorder, from which a great genetic heterogeneity has been reported. This includes types I and II of BS [7] which can be clinically distinguished from one another. In both cases, symptoms like nephrocalcinosis and hypercalcuria are markedly detectable, while massive renal NaCl excretion, metabolic alkalosis, and hypokalemia mostly exist in type I patients [18]. This speculation may not be always right, as patients bearing *SLC12A1* mutations may be diagnosed after the neonatal period [19]. Classical BS, however, manifests milder symptoms, starting from infancy to adolescence. This type has been categorized as type III BS, which has been reported to be transmitted in an AR manner [20]. Classical BS is generally associated with growth retardation (in the absence of early therapy), polyuria, polydysplasia, constipation, salt craving, vomiting, dehydration, and less frequently facial appearances [7]. Increased fractional excretion of Na, K, and Cl are the most typical findings. In addition, the presence of normal or mildly high Ca excretion is important as it may lead to distinction from GS, in which hypocalciuria is always present [21].

GS is mostly asymptomatic; however, transitory occurrences of weakness and tetany, concomitant with abdominal pain, fever, and vomiting have been reported in some cases. In addition, growth retardation and polyuria are mild or absent, and chondrocalcinosis is occasionally reported. The prolonged intervals without symptoms may result in the diagnosis during adult age for many cases [22-24]. Prematurity or the lack of maternal polyhydramnios are important factors to distinct GS from classical BS. Hypomagnesemia, hypokalemia, and modest metabolic alkalosis, as well as a moderate elevation in uric acid, are among detectable blood features. Notably, renal function is normal. GS can be misdiagnosed by classical BS, when hyperreninism and hyperaldosteronism are present. In those cases, normal excretion of prostaglandin E2 (PGE2) can be considered as one of the differentiations [25,7]. GS is also transmitted as an AR disorder [8].

Beside types I, II, and III, two other types (IV and V) are classified beyond neonatal or classical types, as BS with sensorineural deafness and BS associated with autosomal dominant (AD) hypocalcemia, respectively. It was centrally based on the finding of two additional genes, *BSND* and *CASR*, which are reported to cause BS with the unifying pathophysiology, loss of salt transportation by the thick ascending limb, showing the great impact of genetics on the classification of BS [26-28]. Differences in the phenotypes of BS patients are associated to the specific roles of each gene in the kidney and other organs, which may lead to specific diagnosis and treatment.

Genetics of Bartter Syndrome

BS represents a group of heterogeneous diseases consisting of several AR syndromes plus an AD type. Different genes are reported to be associated with different types of BS whose alterations, individually or sometimes in combination, lead to this heterogeneity. Genetic based classification of BS has led to emergence of five different types, plus GS as an individual territory. Notably, each type of BS can be diagnosed by considering certain clinical features, which may lead to analysis of corresponding genes for confirmation and thus

result in defined procedures for specialized treatments. The phenotype-genotype correlation in different types of BS has been indicated, leading to genetic categorization of BS [28-32].

Type I

BS type I (BS-I) (neonatal BS) is a life-threatening disease, with both renal hypokalemic alkalosis and intense systemic symptoms. The abnormalities like polyhydramnios between 24-30 weeks of gestation (resulting from fetal polyuria) and premature delivery can be observed in the neonatal period. In this period, high concentrations of chloride, versus normal sodium, potassium, calcium, and PGE2, are observed in the amniotic fluid. Neonates with BS-I have intense salt wasting and hyposthenuria, plus hyperprostaglandinuria, failure to thrive, and moderate hypokalemic metabolic alkalosis. In the affected infants, vomiting, fever, and diarrhea have been ascribed to the stimulation of the renal and systemic PGE2 activity. These conditions can be suitably treated by inhibition of PGE2 synthesis [33,34,10].

Linkage of BS to a particular gene, which led to its distinction from GS, was first reported by Simon and colleagues who showed some functions of *SLC12A1* gene [35]. *SLC12A1* is located on chromosome 15q15, has a length of about 113 kb and 26 exons, and produces 8 protein coding products as a result of alternative splicing. Sequencing the whole coding regions of this gene is the first molecular procedure in order to find possible mutation and confirm BS-I.

SLC12A1 belongs to the Na^+-dependent subgroup of solute carrier 12 (SLC12) family of transporters, and encodes renal Na-K-2Cl co-transporter (also known as *NKCC2*). SLC12A2 is highly expressed in the kidney, and is responsible for the vast majority of NaCl reabsorption in the apical membrane of epithelial cells in the thick ascending limb of Henle [35]. SLC12A1 couples with its close member SLC12A2 to actively mediate the electroneutral transportation of K^+ and Na^+, together with transportation of Cl^- across the cell membrane. Therefore, the result of SLC12A1 disruption is hypercalciuria and severe volume depletion with early presentation in BS patients. Some observed (frameshift and missense) mutations in highly conserved regions of *SLC12A1* co-segregate with the disease.

SLC12A1 is regulated by with-no-lysine kinase (WNK)-3 and angiotensin II, which may play important roles in fine-tuning of renal transepithelial NaCl transportation and kidney associated modulation of hypertension via phosphorylation by OSR1 (odd-skipped related transciption factor 1), respectively [36,37]. SLC12A1 may be blocked by bumetanide and furosemide, which are commonly used loop diuretic drugs [38,39].

Type II

BS Type II (BS-II) (neonatal BS) is an AR hypokalemic renal salt-wasting disease caused by alterations in the *KCNJ1* (also known as *ROMK*), which encodes KCNJ1 channel. KCNJ1 protein plays crucial roles in potassium recycling located in the thick ascending limb of Henle's loop, and potassium secretion in the distal tubule and cortical collecting duct. Infants with BS-II are transiently hyperkalemic, which results from KCNJ1 channel dysfunction in potassium secretion in the distal convoluted tubule and cortical collecting duct. BS-II is described by symptoms like elevated Ca^{2+} excretion leading to nephrocalcinosis, hypokalemic metabolic alkalosis, natriuresis, diuresis, and elevated prostaglandin E2 and renin [40-42,30].

KCNJ1 channel is responsible for a remarkable portion of reabsorption of sodium and potassium that are unfiltered at glomerulus, and confects the pathway for potassium recycling that is essential for SLC12A1 co-transporter [43,44]. It was first speculated that in kindreds of BS who did not show mutations in *SLC12A1*, dysfunctional regulators of the co-transporter might also lead to BS, as well. Interestingly and notably, as the first evidence of the heterogeneity of BS [41], KCNJ1 mutation showed the latter. In order to regulate renal potassium handling, KCNJ1 interacts with WNK kinases [45,46], Src family protein tyrosine kinase [47], POSH (plenty of SH3) [48], and protein kinase C (PKC) [49].

KCNJ1 is located on chromosome 11q24, has a length of about 34 kb, and consists of just two exons. It produces seven different isoforms, among which there are six protein codings. Sequencing the entire coding region of *KCNJ1* is the first molecular procedure for mutation detection, and therefore for proving BS-II. Mutations in KCNJ1 drastically alter the conformation of the channel, resulting in loss of potassium channel activity through the phosphorylation sites alteration, or frameshift the gene open reading frame (ORF) [41].

Prenatal diagnosis is available through biochemical examinations of amniotic fluid and maternal urine, in which electrolytes in the amniotic fluid is shown to be high, except for

potassium. On the other hand, urinary chloride, calcium, and sodium are low, suggesting predicting parameters in prenatal diagnosis of BS-II [50].

Type III

BS Type III (BS-III) or classical BS is an AR disorder, which is centrally characterized by hypokalaemic alkalosis with salt-wasting, low blood pressure, normal magnesium, hyper/normocalciuria, and absence of nephrocalcinosis. Patients harbor mutations in the renal chloride channel gene, *CLCNKB*, which cause loss of function and consequently impairment in the reabsorption of chloride in the thick ascending limb of the Henle's loop [20].

CLCNKB, which encodes a member of the family of voltage-gated chloride channels, is located on chromosome 1p36, has a length of about 14 kb, and consists of 20 exons. Resulting from alternative splicing, three different isoforms are produced from this gene. A close member of this family, *CLCNKA*, is also located in close proximity and has shown to play roles in the pathogenesis of the disease. Different kinds of alterations including missense or nonsenses mutations, and large deletions have been reported as loss of function mutations. In some cases, large deletions have been driven from unequal crossing over between *CLCNKB* and *CLCNKA* [20]. Notably, it has been recently shown that in mild phenotypes, certain mutations can lead to specific behaviors in the channel. Mutations around the selectivity filter can result in hyperactivity of heterologous expression systems, and decreased surface expression [51,52].

Certain polymorphisms/mutations in *CLCNKB* gene has shown to be associated to essential hypertension [53].

Type IV

BS type IV (BS-IV), which is the most severe life-threatening among different types of BS, is an AR disorder generally characterized by neonatal volume depletion, premature birth imputable to polyhydramnios, sensorineural deafness, severe renal salt-wasting, and polyuria [14,27]. Mutation in *BSND*, which encodes **barttin** (BSND), is shown to be responsible for this condition. BSND is a crucial accessory subunit of chloride channels, and is expressed in the kidney and inner ear. A variety of *BSND* mutations cause phenotypes of different severity that lead to its dysfunctional interactions with ClC-K channel, causing impairment of chloride reabsorption in the nephron as well as potassium secretion in the stria vascularis and the vestiblar labyrinth [31,54,55].

BSND is located on chromosome 1p32, with only one transcript, 4 exons and a length of about about 13kb. Sequence analysis of its entire coding region and deletion/duplication analysis is available for the genetic confirmation of BS-IV. Laboratory manifestations also include hypokalemic metabolic alkalosis, normotensive hyperreninemic hyperaldosteronism, and increased urinary sodium, potassium, and chloride [56].

BS-IV is also shown to have a digenic inheritance resulting from double homozygous mutations in *CLCNKA* and *CLCNKB*, resulting in indistinguishable phenotypes from *BSND* mutations. This is probably due to the proximity of these two genes, which in some cases can be the target of large deletions involving both. Dysfunctional BSND results in 'double knockout' of *CLCNKA* and *CLCNKB*, and rationalizes the outcome of both *CLCNKA* and *CLCNKB* dysfunctions to cause the same disease [57,58]. Notably, it has been reported that a certain kind of mutation can interfere with the wild functional BSND in the inner ear but not in the kidney, resulting in non-syndromic deafness [59].

Type V

In BS type V (BS-V), gain-of-function mutations in the extracellular Ca^{2+}-sensing receptor gene (*CASR*) lead to AD hypocalcemia, characterized by decreased chloride reabsorption, negative balance of sodium chloride, secondary hyperaldosteronism, and hypokalemia [28,60]. Different clinical presentations in BS-V patients can be determined from different activating mutations in *CASR* [61]. In these patients, calcium metabolism is abnormal, the level of parathyroid hormone is low, and renal calcium excretion is high. They are secondary to CaSR hyperactivation at low serum calcium concentrations that leads to abnormal inhibition of parathyroid hormone [62,63].

The CaSR is a member of the G protein–coupled receptor (GPCR) family and stimulates MAPK (mitogen-activated protein kinase)-ERK (extracellular signal-regulated kinases) signaling cascades. Hyper-activated CaSR leads to excessive signal transduction pathways, and therefore an increased cytosol calcium gradient excreted from the endoplasmic reticulum, which explains the higher sensitivity of mutant CaSR to external calcium [64]. *CASR* is located on chromosome 3q13 with a length of 104kb, contains seven

exons, and produces four different transcripts. Sequence analysis of the entire coding region of *CASR* is the test of choice for genetic confirmation of BS-V.

Gitelman syndrome

Gitelman syndrome (GS) represents an AR salt-losing tubulopathy with hypokalemic hypomagnesemic hypocalciuria, metabolic alkalosis, and hyperreninemic hyperaldosteronism, associated with normal blood pressure. GS is shown to be caused by mutations in *SLC12A3*, which is a renal thiazide-sensitive co-transporter, mediating the reabsorption of sodium and chloride in the distal convoluted tubule. A variety of different non-conservative loss-of-function mutations have been shown to cause GS [8].

SLC12A3 is located on chromosome 16q13, with a length of 51kb and 26 exons. It produces six different transcripts including four protein coding isoforms.

Modifier genes and/or environmental factors have also been identified to play important roles in the outcome function of affected genes. Mutations in *CLCNKB*, for example, have been shown to result in two different phenotypes among two sisters, one with severe symptoms of classic BS in the neonatal period accompanied by deafness, and the other with no symptoms [65]. A distinct mutation in *BSND* among three brothers has also been shown to cause different phenotypes, again indicating the possible role for other genes and/or environmental factors [56].

Conflict of Interest

None declared

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None declared

References

1. Bartter FC, Pronove P, Gill JR, Jr., Maccardle RC. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. A new syndrome. The American journal of medicine 1962;33:811-828.
2. Goodman AD, Vagnucci AH, Hartroft PM. Pathogenesis of Bartter's syndrome. The New England journal of medicine 1969;281(26):1435-1439. doi:10.1056/NEJM196912252812601
3. Miyoshi A, Makino H, Hiramatsu M, et al. Bartter's syndrome--case report. Acta medica Okayama 1979; 33(4):305-314.
4. Daniluk U, Kaczmarski M, Wasilewska J, Matuszewska E, Semeniuk J, Sidor K, Krasnow A. [Bartter syndrome--case report]. Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego 2004;16 (94):375-377.
5. Dillon MJ, Shah V, Mitchell MD. Bartter's syndrome: 10 cases in childhood. Results of long-term indomethacin therapy. The Quarterly journal of medicine 1979;48(191):429-446.
6. Tsukamoto T, Kobayashi T, Kawamoto K, Fukase M, Chihara K. Possible discrimination of Gitelman's syndrome from Bartter's syndrome by renal clearance study: report of two cases. American journal of kidney diseases : the official journal of the National Kidney Foundation 1995;25(4):637-641.
7. Rodriguez-Soriano J. Bartter and related syndromes: the puzzle is almost solved. Pediatr Nephrol 12 1998;(4):315-327.
8. Simon DB, Nelson-Williams C, Bia MJ, et al. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nature genetics 1996;12(1):24-30.
9. Seyberth HW, Schlingmann KP. Bartter- and Gitelman-like syndromes: salt-losing tubulopathies with loop or DCT defects. Pediatr Nephrol 2011;26 (10):1789-1802. doi:10.1007/s00467-011-1871-4
10. Seyberth HW, Koniger SJ, Rascher W, Kuhl PG, Schweer H. Role of prostaglandins in hyperprostaglandin E syndrome and in selected renal tubular disorders. Pediatr Nephrol 1987;1 (3):491-497.
11. Proesmans W. Bartter syndrome and its neonatal variant. European journal of pediatrics 1997;156 (9):669-679.
12. Pierratos A, Couture RA, Hierlihy PJ, Bell RC, Levine DZ. Bartter's syndrome, nephrocalcinosis and renal insufficiency. CMAJ: Canadian Medical Association journal = journal de l'Association medicalecanadienne 1989;141(10):1055-1057.
13. Jeck N, Reinalter SC, Henne T, et al. Hypokalemic salt-losing tubulopathy with chronic renal failure and sensorineural deafness. Pediatrics 2001;108 (1):E5.
14. Landau D, Shalev H, Ohaly M, Carmi R.

Infantile variant of Bartter syndrome and sensorineural deafness: a new autosomal recessive disorder. American journal of medical genetics 1995;59 (4):454-459.
15. Maruyama H, Shinno Y, Fujiwara K, et al. Nephrocalcinosis and placental findings in neonatal bartter syndrome. AJP reports 2013;3(1):21-24.
16. James T, Holland NH, Preston D. Bartter syndrome. Typical facies and normal plasma volume. Am J Dis Child 1975;129(10):1205-1207.
17. Leonhardt A, Timmermanns G, Roth B, Seyberth HW. Calcium homeostasis and hypercalciuria in hyperprostaglandin E syndrome. The Journal of pediatrics 1992;120(4 Pt 1):546-554.
18. Williams MP, Jones CL, Johnstone LM, Walker RG, McCredie DA, Powell HR. An extreme example of the neonatal form of Bartter's syndrome. Pediatr Nephrol 1996; 10(4):496-497.
19. Betinnelli A, Casari G, Mastroianni N. Atypical cases of the hypercalciuric variant of Bartter syndrome: importance of molecular diagnosis. Pediatr Nephrol 1997;11:C49.
20. Simon DB, Bindra RS, Mansfield TA, et al. Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. Nature genetics 1997;17(2):171-178. doi:10.1038/ng1097-171.
21. Clive DM. Bartter's syndrome: the unsolved puzzle. American journal of kidney diseases : the official journal of the National Kidney Foundation 1995;25 (6):813-823.
22. Marco-Franco JE, Morey A, Ventura C, Gasco JM, Alarcon A. Long-term evolution and growth patterns in a family with Bartter's syndrome. Clinical nephrology 1994;42(1):33-37.
23. Bettinelli A, Metta MG, Perini A, Basilico E, Santeramo C. Long-term follow-up of a patient with Gitelman's syndrome. Pediatric Nephrology 1993;7 (1):67-68.
24. Smilde TJ, Haverman JF, Schipper P, et al. Familial hypokalemia/hypomagnesemia and chondrocalcinosis. The Journal of rheumatology 1994;21 (8):1515-1519.
25. Luthy C, Bettinelli A, Iselin S, et al. Normal prostaglandinuria E2 in Gitelman's syndrome, the hypocalciuric variant of Bartter's syndrome. American journal of kidney diseases : the official journal of the National Kidney Foundation 1995;25 (6):824-828.
26. Hebert SC. Bartter syndrome. Current opinion in nephrology and hypertension 2003;12 (5):527-532.
27. Birkenhager R, Otto E, Schurmann MJ, et al. Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. Nature genetics 2001;29 (3):310-314.
28. Vargas-Poussou R, Huang C, Hulin P, et al. Functional characterization of a calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with a Bartter-like syndrome. Journal of the American Society of Nephrology : JASN 2002;13(9):2259-2266.
29. Károlyi L, Konrad M, Köckerling A, et al. Mutations in the gene encoding the inwardly-rectifying renal potassium channel, ROMK, cause the antenatal variant of Bartter syndrome: evidence for genetic heterogeneity. Human Molecular Genetics 1997;6(1):17-26.
30. Brochard K, Boyer O, Blanchard A, et al. Phenotype-genotype correlation in antenatal and neonatal variants of Bartter syndrome. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2009;24(5):1455-1464.
31. Janssen AG, Scholl U, Domeyer C, Nothmann D, Leinenweber A, Fahlke C. Disease-causing dysfunctions of barttin in Bartter syndrome type IV. Journal of the American Society of Nephrology. JASN 2009;20(1):145-153.
32. Konrad M, Vollmer M, Lemmink HH, et al. Mutations in the chloride channel gene CLCNKB as a cause of classic Bartter syndrome. Journal of the American Society of Nephrology. JASN 2000;11(8):1449-1459.
33. Ohlsson A, Sieck U, Cumming W, Akhtar M, Serenius F. A variant of Bartter's syndrome. Bartter's syndrome associated with hydramnios, prematurity, hypercalciuria and nephrocalcinosis. Acta paediatrica Scandinavica 1984;73(6):868-874.
34. Proesmans W, Devlieger H, Van Assche A, et al. Bartter syndrome in two siblings--antenatal and neonatal observations. The International journal of pediatric

nephrology 1985;6(1):63-70.
35. Simon DB, Karet FE, Hamdan JM, DiPietro A, Sanjad SA, Lifton RP. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. Nature genetics 1996;13(2):183-188.
36. Gonzalez-Villalobos RA, Janjoulia T, Fletcher NK, Giani JF, Nguyen MT, Riquier-Brison AD, et al. The absence of intrarenal ACE protects against hypertension. The Journal of clinical investigation 2013;123(5):2011-2023.
37. Richardson C, Sakamoto K, de los Heros P, et al. Regulation of the NKCC2 ion cotransporter by SPAK-OSR1-dependent and -independent pathways. Journal of cell science 2001;124(Pt 5):789-800.
38. Markadieu N, Delpire E. Physiology and pathophysiology of SLC12A1/2 transporters. Pflugers Archiv : European journal of physiology 2014;466(1):91-105.doi:10.1007/s00424-0131370- 5
39. Mederle K, Mutig K, Paliege A, et al. Loss of WNK3 is compensated for by the WNK1/SPAK axis in the kidney of the mouse. American Journal of Physiology-Renal Physiology 2013;304(9):F1198-F1209.
40. Bailey MA, Cantone A, Yan Q, et al. Maxi-K channels contribute to urinary potassium excretion in the ROMK-deficient mouse model of Type II Bartter's syndrome and in adaptation to a high-K diet. Kidney international 2006;70(1):51-59.
41. Simon DB, Karet FE, Rodriguez-Soriano J, et al. Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K+ channel, ROMK. Nature genetics 1996;14(2):152-156.
42. Derst C, Konrad M, Kockerling A, et al. Mutations in the ROMK gene in antenatal Bartter syndrome are associated with impaired K+ channel function. Biochemical and biophysical research communications1997;230(3):641-645. doi:10.1006/bbrc.1996.6024
43. Malnic G, Klose RM, Giebisch G. Microperfusion study of distal tubular potassium and sodium transfer in rat kidney. The American journal of physiology 1996;211(3):548-559.
44. Hebert SC, Mount DB, Gamba G. Molecular physiology of cation-coupled Cl-cotransport: the SLC12 family. Pflugers Archiv : European journal of physiology2004;447(5):580-593. doi:10.1007/s00424-003-1066-3
45. Liu Z, Wang HR, Huang CL. Regulation of ROMK channel and K+ homeostasis by kidney-specific WNK1 kinase. The Journal of biological chemistry 2009;284(18):12198-12206. doi:10.1074/jbc.M806551200
46. Murthy M, Cope G, O'Shaughnessy KM. The acidic motif of WNK4 is crucial for its interaction with the K channel ROMK. Biochemical and biophysical research communications 2008;375(4):651-654.
47. Yue P, Lin DH, Pan CY, et al. Src family protein tyrosine kinase (PTK) modulates the effect of SGK1 and WNK4 on ROMK channels. Proceedings of the National Academy of Sciences of the United States of America2009;106(35):15061-15066. doi:10.1073/pnas.0907855106
48. Lin DH, Yue P, Pan CY, et al. POSH stimulates the ubiquitination and the clathrin-independent endocytosis of ROMK1 channels. The Journal of biological chemistry 2009;284(43):29614-29624. doi:10.1074/jbc.M109.041582
49. Lin D, Sterling H, Lerea KM, Giebisch G, Wang WH. Protein kinase C (PKC)-induced phosphorylation of ROMK1 is essential for the surface expression of ROMK1 channels. The Journal of biological chemistry 2002;277(46):44278-44284.
50. Matsushita Y, Suzuki Y, Oya N, et al. Biochemical examination of mother's urine is useful for prenatal diagnosis of Bartter syndrome. Prenatal diagnosis 1999;19(7):671-673
51. Andrini O, Keck M, L'Hoste S, et al. CLCNKB mutations causing mild Bartter syndrome profoundly alter the pH and Ca dependence of ClC-Kb channels. Pflugers Archiv : European journal of physiology November 2013. 10.1007/s00424-013-1401-2
52. Keck M, Andrini O, Lahuna O, et al. Novel CLCNKB mutations causing Bartter syndrome affect channel surface expression. Human mutation 2013;34(9):1269-1278. doi:10.1002/humu.22361.
53. Su X, Chang P, Liu Z, Yan M, Liu G, Cui H. Association of CLCNKB haplotypes and

hypertension in Mongolian and Han populations. Clin Exp Hypertens 2012;34(7):482-487. doi:10.3109/10641963.2012.666602
54. Estevez R, Boettger T, Stein V, et al. Barttin is a Cl- channel beta-subunit crucial for renal Cl- reabsorption and inner ear K+ secretion. Nature 2001;414(6863):558-561.
55. Uchida S, Sasaki S. Function of chloride channels in the kidney. Annual review of physiology 2005;67:759-778.
56. Park CW, Lim JH, Youn DY, et al. Renal dysfunction and barttin expression in Bartter syndrome Type IV associated with a G47R mutation in BSND in a family. Clinical nephrology 2011;75 Suppl 1:69-74.
57. Kramer BK, Bergler T, Stoelcker B, Waldegger S. Mechanisms of Disease: the kidney-specific chloride channels ClCKA and ClCKB, the Barttin subunit, and their clinical relevance. Nature clinical practice Nephrology 2008;4(1):38-46.
58. Nozu K, Inagaki T, Fu XJ, et al. Molecular analysis of digenic inheritance in Bartter syndrome with sensorineural deafness. Journal of medical genetics 2008;45(3):182-186. doi:10.1136/jmg.2007.052944
59. Riazuddin S, Anwar S, Fischer M, et al. Molecular basis of DFNB73: mutations of BSND can cause nonsyndromic deafness or Bartter syndrome. American journal of human genetics 2009;85 (2):273-280.
60. Watanabe S, Fukumoto S, Chang H, et al. Association between activating mutations of calcium-sensing receptor and Bartter's syndrome. Lancet 2002;360 (9334):692-694.
61. Kinoshita Y, Hori M, Taguchi M, Watanabe S, Fukumoto S. Functional Activities of Mutant Calcium-Sensing Receptors Determine Clinical Presentations in Patients With Autosomal Dominant Hypocalcemia. The Journal of clinical endocrinology and metabolism2013;jc20133430. doi:10.1210/jc.2013-3430
62. Chattopadhyay N, Brown EM. Role of calcium-sensing receptor in mineral ion metabolism and inherited disorders of calcium-sensing. Molecular genetics and metabolism 2006;89(3):189-202.
63. Egbuna OI, Brown EM. Hypercalcaemic and hypocalcaemic conditions due to calcium-sensing receptor mutations. Best practice & research Clinical rheumatology2008;22(1):129-148. doi:10.1016/j.berh.2007.11.006
64. Ranieri M, Tamma G, Di Mise A, et al. Excessive Signal Transduction of Gain-of-Function Variants of the Calcium-Sensing Receptor (CaSR) Are Associated with Increased ER to Cytosol Calcium Gradient. 2013;PloS one 8 (11):e79113. doi:10.1371/journal.pone.0079113
65. Robitaille P, Merouani A, He N, Pei Y. Bartter syndrome in two sisters with a novel mutation of the CLCNKB gene, one with deafness. European journal of pediatrics 2011;170(9):1209-1211.
66. Verberckmoes R, van Damme BB, Clement J, Amery A, Michielsen P. Bartter's syndrome with hyperplasia of renomedullary cells: successful treatment with indomethacin. Kidney international 1976;9(3):302-307.
67. Zhu JX, Xue H, Ji T, Xing Y. Cellular localization of NKCC2 and its possible role in the Cl- absorption in the rat and human distal colonic epithelia. Translational research : the journal of laboratory and clinical medicine 2011;158(3):146-154.
68. Ji T, Liu S, Zheng LF, et al. Cellular distribution of NKCC2 in the gastric mucosa and its response to short-term osmotic shock. Cell and tissue research 2012;348(1):155-165.
69. Lopes CM, Zhang H, Rohacs T, Jin T, Yang J, Logothetis DE. Alterations in conserved Kir channel-PIP2 interactions underlie channelopathies. Neuron 2002; 34(6):933-944.

Table 1. Different types of Bartter and Gitelman syndrome. Key symptoms, linked gene(s), and corresponding information for each gene, regarding description, other names, locus, neighboring genes, and functions, for different types of Bartter syndrome and Gitelman syndrome have been included.

Types (mode of inheritance)	Symptoms	Linked gene(s)	Gene description	Also known as	Locus	Neighboring genes	Gene(s) function(s)
BS Type I (AR)	Severe volume depletion, hypokalaemia, metabolic alkalosis with high prenatal mortality, nephrocalcinosis	SLC12A1	Solute carrier family 12 (sodium/potassium /chloride transporter), member 1	NKCC2, BSC1	15q15-q21.1	MYEF2, CTXN2, DUT, SLC24A5, FBN1	Reabsorption of NaCl in kidney [35], colonic Cl^- absorption coupled with HCO^{3-} secretion [67], maintaining cell volume homeostasis under hypertonic conditions [68],
BS Type II (AR)	Elevated Ca^{2+} excretion leading to nephro-calcinosis, hypokalemic metabolic alkalosis, natriuresis, diuresis, and elevated prostaglandin E2 and renin	KCNJ1	Potassium inwardly-rectifying channel, subfamily J, member 1	ROMK, ROMK, KIR1.1	11q24	KCNJ5, FLI1, C11orf45, TP53AIP1, SENCR	Resting membrane potential and cell excitability [69], potassium recycling in thick ascending limb of Henle's loop, and potassium secretion in the distal tubule and cortical collecting duct [40]
BS Type III (AR)	Hypokalaemic alkalosis with salt-wasting, low blood pressure, normal magnesium, hyper/normo-calciuria, and absence of nephrocalcinosis	CLCNKB	Chloride channel, voltage-sensitive Kb	CLCKB, ClC-K2, ClC-Kb	1p36	CLCNKA, FAM131C, EPHA2, LOC440568	Regulation of cell volume, membrane potential stabilization, signal transduction and transepithelial transport, renal salt reabsorption
BS Type IV (AR)	Neonatal volume depletion, premature birth imputable to polyhidramnios, sensorineural deafness, sever renal salt-wasting, and polyuria	BSND	Bartter syndrome, infantile, with sensorineural deafness (Barttin)	BART, DFNB73	1p32.1	TMEM61, PCSK9, TRNAK-CUU, USP24	Cl^- channel beta-subunit responsible for renal Cl^- reabsorption and secretion of K^+ inner ear [54]
		CLCNKA + CLCNKB	Chloride channel, voltage-sensitive Ka,	CLCK1, ClC-K1, hClC-Ka	1p36	LOC440568, HSPB7, CLCNKB, C1orf64	
			Chloride channel, voltage-sensitive Kb	CLCKB, ClC-K2, ClC-Kb	1p36	CLCNKA, FAM131C, EPHA2, LOC440568	Regulation of cell volume, membrane potential stabilization, signal transduction and transepithelial transport, renal salt reabsorption
BS Type V (AD)	Decreased chloride reabsorption, negative balance of sodium chloride, secondary hyperaldosteronism, and hypokalemia	CASR	Calcium-sensing receptor	CAR, HH, FIH, HHC, EIG8, HHC1, NSHPT, PCAR1, GPRC2, HYPOC1	3q13	HNRNPAP23, CSTA, CD86, ILDR1	G protein-coupled receptor signaling, maintenance of mineral ion homeostasis
Gitelman syndrome (AR)	Hypokalemic hypomagnesemic hypocalciuria, etabolic alkalosis, and hyperreninemic hyperaldostronism, associated with normal blood pressure	SLC12A3	solute carrier family 12 (sodium/chloride transporter), member 3	NCC, TSC, NCCT	16q13	RPS24P17, MIR138-2, HERPUD1, NUP93, CETP	
		CLCNKB	Chloride channel, voltage-sensitive Kb	CLCKB, ClC-K2, ClC-Kb	1p36	CLCNKA, FAM131C, EPHA2, LOC440568	Regulation of cell volume, membrane potential stabilization, signal transduction and transepithelial transport, renal salt reabsorption