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The Role of Claudin in Hypercalciuric Nephrolithiasis

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Abstract

Calcium nephrolithiasis is a common condition. Family-based genetic linkage studies and genome-wide association studies (GWASs) have uncovered a run of important candidate genes involved in renal Ca^{++} disorders and kidney stone diseases. The susceptible genes include NKCC2, ROMK and ClCkb/Barttin that underlie renal salt excretion; claudin-14, -16 and -19 that underlie renal Ca^{++} excretion; and CaSR that provides a sensing mechanism for the kidney to regulate salt, water and Ca^{++} homeostasis. Biological and physiological analyses have revealed the cellular mechanism for transepithelial Ca^{++} transport in the kidney that depends on the concerted action of these gene products. Although the individual pathogenic weight of the susceptible genes in nephrolithiasis remains unclear, perturbation of their expression or function compromises the different steps within the integrated pathway for Ca^{++} reabsorption, providing a physiological basis for diagnosing and managing kidney stone diseases.

Keywords

Kidney stone; Hypercalciuria; Tight junction; Ion channel; Claudin; Genome-wide association study; Calcium; Calcium-sensing receptor; Thick ascending limb of Henle's loop; Epithelium; Inherited diseases; Knockout animals; Single-nucleotide polymorphism

Introduction

Calcium nephrolithiasis is one of the most prevalent uronephrologic disorders in western countries [1]. It is a heterogeneous disease owing to multiple genetic or environmental factors that regulates calcium salt precipitation in the urinary system. Idiopathic hypercalciuria is the most common risk factor [2]. Both nephrolithiasis and hypercalciuria can be caused by mutations in single genes underlying renal calcium excretion through mendelian heritability (Table 1). Although common nephrolithiasis is not well explained by mutations or polymorphisms in these genes, the monogenic alterations could contribute to increased individual susceptibility to calcium stones. A recent genome-wide association study (GWAS) mapped the entire human genome with over 300,000 polymorphic markers to identify loci in linkage disequilibrium with nephrolithiasis [3]. In a large cohort of patients with hypercalciuric stones from Iceland and the Netherlands, four highly correlated SNPs in the claudin-14 gene, achieved genome-wide significant association. A thorough biological analysis of each predisposing gene, no matter from rare monogenic or common polygenic disorders, will allow elucidation of the pathogenic mechanism for nephrolithiasis.

The nephrolithiatic outcome will remain to be a complex polygenic result of multiple genetic interactions within an integrated signaling cascade.

The Renal Handling of Calcium

On average, only 1 – 3 % of Ca^{++} filtered through the glomerulus is excreted. The majority of Ca^{++} reabsorption takes place paracellularly along the proximal tubule (PT: 60 – 65 % of filtered Ca^{++}) and the thick ascending limb of Henle's loop (TALH: 25 – 30 % of filtered Ca^{++}). The distal convoluted tubule (DCT) reabsorbs the remaining 8 – 10 % of filtered Ca^{++} transcellularly [4]. The transcellular process in the DCT includes three stages [5]. The first stage is Ca^{++} entry across the apical membrane through the transient receptor protein-vanilloid 5 channel (TRPV5). The following stage is intracellular diffusion of Ca^{++} bound with a chaperone protein (calbindin-D28k) from the apical to the basolateral space. The final stage is Ca^{++} exit across the basolateral membrane through the $\text{Na}^+/\text{Ca}^{++}$ exchanger (NCX1) and the Ca^{++} -ATPase (PMCA1b). Although the biological mechanism of the proximal Ca^{++} reabsorption has largely been elusive until a recent discovery of claudin-2 channel, its physiological role is well known as an advantage in the treatment of idiopathic hypercalciuria [6]. Thiazide, a diuretic frequently used to treat arterial hypertension, causes hypocalciuria as one of its side effects [7]. Micro-puncture studies in mice pointed to a prominent role for the PT in regulating the paracellular Ca^{++} reabsorption after chronic thiazide treatments [8]. Muto et al, using a knockout approach in mice, have demonstrated that the claudin-2 protein is required for the paracellular reabsorption of cations including Ca^{++} in the PT [9•]. The Ca^{++} reabsorption in the TALH is particularly interesting [10•]. Ca^{++} is passively reabsorbed from the lumen to the interstitial space through the paracellular pathway, driven by a lumen positive transepithelial voltage (V_{te}) (Fig. 1). The generation of V_{te} can be attributed to two mechanisms: (1) the active transport V_{te} owing to apical K^+ secretion through the renal outer medullary potassium channel (ROMK; KCNJ1) and basolateral Cl^- secretion through the chloride channel Kb (ClC-Kb) and Barttin (BSND), driven by NaCl reabsorption via the apical $\text{Na}^+2\text{Cl}^- \text{K}^+$ cotransporter (NKCC2); and (2) the diffusion V_{te} generated by the transepithelial NaCl concentration gradient over the cation selective paracellular channel in the TALH. In the early TALH segment, it is the first mechanism that provides a voltage around +8 mV. There is minimal contribution of diffusion potential at this early segment because the concentration gradient has not yet been built up (Fig. 1a). With continuous NaCl reabsorption along the axis of the TALH, the lumen fluid is diluted and a large NaCl gradient is generated from the peritubular space down to the lumen in the late TALH segment. Because the paracellular permeability of the TALH is cation-selective, a positive diffusion V_{te} is superimposed onto the active transport V_{te} and becomes the major source of the driving force for Ca^{++} reabsorption, which now increases substantially - up to +30 mV (Fig. 1b). The molecular mechanism of paracellular ionic transport in the TALH has been revealed by Hou et al in a series of papers [11-14]. Two claudin proteins – claudin-16 and claudin-19 interact and form a paracellular channel complex to allow selective cation permeation in the TALH [11, 12].

Claudins Form the Paracellular Channel

The traditional view of ion transport is that of a tandem array of ion channels and transporters located in the cell plasma membrane conducting ionic fluxes in and out of the cell in a coordinated manner at the expense of energy. Evidence accumulated during the last decade supports the existence of a previously unrecognized, yet pivotally important class of channels, known as the *paracellular channel*. The paracellular channel is found in the tight junction (*zonula occludens*) of vertebrate epithelia responsible for the barrier to movement of ions and molecules between apical and basal compartments [15, 16]. The integral membrane proteins of the tight junction include occludin (a 65 kDa membrane protein

bearing four transmembrane domains and two uncharged extracellular loops) [17], the junctional adhesion molecules (JAMs) [18], a four-member group of glycosylated proteins and the claudins. Claudins are tetra-span proteins consisting of a family with at least 28 members [19, 20] ranging in molecular mass from 20-28 kD. Claudins have four transmembrane domains, two extracellular loops, amino- and carboxyl-terminal cytoplasmic domains, and a short cytoplasmic turn. The first extracellular loop (ECL1) of claudin consists of ~50 amino acids with a common motif (-GLWCC; PROSITE ID: PS01346) [21], and intercalating negative [14, 22] and positive [23, 24] charges that contribute to paracellular ion selectivity. The GLWCC motif is critical as a receptor for Hepatitis C virus (HCV) entry [25]. The charges in ECL1 regulate paracellular ion selectivity through electrostatic effects. The second extracellular loop (ECL2) consists of ~25 amino acids with a predicted helix-turn-helix motif that mediates intercellular claudin interactions and claudin interactions with the *Clostridium perfringens* enterotoxin (CPE) [26]. The C-terminal domain of claudin contains a PDZ (post-synaptic density 95/discs large/zonula occludens-1) binding domain (YV) that is critical for interaction with the submembrane scaffold protein ZO-1 and correct localization in the TJ [27, 28]. In renal epithelia, claudins have been shown to confer ion selectivity to the tight junction resulting in differences in the transepithelial resistance (TER) and the paracellular permeabilities. For example, claudin-4, -5, -8, -11 and -14 selectively decrease the permeability of cations through tight junctions [29-33], specifically to Na^+ , K^+ , H^+ and ammonium. Claudin-2, -15 and -16 increase cation permeability [34, 35], specifically to Na^+ , K^+ , Ca^{++} and Mg^{++} . These and other studies have led to the model of claudins forming the paracellular channel [36]. Unlike the traditional transmembrane channel, the paracellular channel is oriented perpendicular to the membrane plane and serving to join two extracellular compartments [37]. Measurement of paracellular permeability using cell membrane impermeable tracers demonstrates the 4–7 Å in diameter size selectivity of the paracellular channel [38, 39]. The paracellular channels have properties of ion selectivity, pH dependence and anomalous mole fraction effects, similar to the transmembrane channels [36, 40].

Calcium Nephrolithiasis in Monogenic Diseases

The first genetic approach to calcium nephrolithiasis is by linkage analysis. This approach is reliable to identify quantitative trait loci of monogenic disorders. The candidate genes (Table 1) are chosen for analyzing their role in renal calcium homeostasis.

Antenatal Bartter Syndrome

Antenatal Bartter syndrome (aBS) is caused by mutations either in the NKCC2 cotransporter or in the ROMK channel, which co-operate to absorb NaCl through the apical membrane of the TALH cell [41, 42]. The ROMK channel recycles K^+ into the luminal space, essential for lowering intracellular K^+ levels and maintaining an optimal membrane potential for proper NKCC2 function. Mutations in either protein impair the net NaCl reabsorption, the apical membrane potential and the lumen-positive transepithelial potential (Fig. 1a: V_{te}). V_{te} provides the driving force for paracellular reabsorption of divalent cations including Ca^{++} and Mg^{++} therefore aBS is manifested with calciuretic phenotypes [43]. aBS patients develop massive hyposthenuric polyuria in utero that often results in premature birth. Postnatally, hypercalciuria and nephrocalcinosis occur in all affected individuals [44], in addition to salt wasting and hypokalemic metabolic alkalosis.

Classic Bartter Syndrome

Classic Bartter syndrome (cBS) is caused by mutations in the ClC-Kb channel [45]. ClC-Kb is expressed in the distal convoluted tubule (DCT) as well as in the TALH where it mediates Cl^- efflux from the cell to the interstitium. Mutations in ClC-Kb result in elevated

intracellular Cl^- levels that will inhibit the NKCC2 transporter activity, causing natriuretic phenotypes similar to aBS. The majority of patients develop hypokalemia and hypochloremia while their urinary Ca^{++} excretion levels are variable. A possible explanation for the greater variability in the calciuretic pattern of cBS compared to aBS is the additional role of CIC-Kb in the DCT where its defects cause the Gitelman phenotypes including hypocalciuria.

Bartter Syndrome with Sensorineural Deafness (BSND)

Bartter Syndrome with Sensorineural Deafness (BSND; Bartter Syndrome IV) is caused by mutations in the gene Barttin [46]. Barttin is an activating γ -subunit of the chloride channels CIC-Ka and CIC-Kb in the kidney [47]. Because Barttin is also expressed in the inner ear, its mutations will not only cause renal salt wasting defects but also sensorineural deafness, a phenotype not present in other forms of Bartter syndrome. Hypercalciuria and nephrocalcinosis are uncommon, ostensibly due to the same explanation as in cBS.

Autosomal Dominant Hypocalcemia (ADH) and Bartter Syndrome V

The Ca^{++} -sensing receptor (CaSR) is a 1,078 amino acid cell surface protein that is predominantly expressed in the parathyroid gland and the TALH of the kidney. CaSR allows regulation of the PTH secretion by the parathyroid gland and renal Ca^{++} excretion in response to alterations in extracellular Ca^{++} levels [48•]. Autosomal Dominant Hypocalcemia (ADH) is caused by gain-of-function mutations in CaSR that significantly lowered the half-maximal effective concentration (EC_{50}) for CaSR compared to that of the wild-type [49, 50]. ADH patients develop hypocalcemia and hyperphosphatemia consistent with suppressed PTH secretion. In the kidney, CaSR activation results in diminished reabsorption of Ca^{++} in the TALH, thus hypercalciuria is often observed in ADH patients. Some patients with a different kind of gain-of-function mutation in CaSR develop Bartter syndrome-like phenotypes (so named Bartter syndrome V), which include renal salt and water loss, hypokalemia and metabolic alkalosis, in addition to hypocalcemia and hypercalciuria [51, 52]. Inhibition of the ROMK channels and the NKCC2 co-transporters by CaSR via the phospholipase A2 has been postulated as the underlying biological mechanism [53].

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC)

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC) is caused by mutations in two genes: claudin-16 (also known as paracellin-1) and claudin-19, members of the claudin gene family of the tight junction [54, 55]. While claudin-16 is expressed exclusively in the TALH of the kidney, claudin-19 has a broader expression profile, found in the TALH of the kidney and the pigment epithelium of the retina. Claudin-16 mediates paracellular cation permeation in the TALH [14]. Claudin-19 increases the cation selectivity of the claudin-16 channel by blocking anion permeation [12]. The paracellular cation selectivity is required for generating the lumen-positive diffusional V_{te} (Fig. 1b), which drives Ca^{++} and Mg^{++} reabsorption in the TALH [10•]. FHHNC patients develop the characteristic triad of hypomagnesemia, hypercalciuria and nephrocalcinosis, compatible with the biological function of claudin-16 and claudin-19. In early childhood, FHHNC patients may also have recurrent urinary tract infections, polyuria/polydipsia, nephrolithiasis and failure to thrive. Additional abnormalities include elevated serum PTH levels, incomplete distal tubular acidosis, hypocitraturia, hyperuricemia and progressive chronic renal failure [56, 57]. The renal tubular phenotypes are indistinguishable from patients with mutations in claudin-16 from those with claudin-19. The phenotypic similarity of two genotypes can be explained by direct interaction between two claudin proteins that was demonstrated by Hou et al using several criteria [11, 12]. Claudin-19 mutations are

invariably associated with severe ocular abnormalities (including severe myopia, nystagmus, or macular coloboma), later renamed FHHNC with severe ocular involvement.

GWAS Identifies Regulatory Gene for Renal Calcium Excretion

The genome-wide association study (GWAS) maps the entire human genome with polymorphic markers to identify loci in linkage disequilibrium with common disease phenotypes [58]. The associated polymorphic markers are considered to mark a region of the human genome that contains genes influencing the risk of disease (the *odds ratio*). While GWAS is able to identify genetic variants associated with a disease, these variants themselves cannot specify which genes are causal or the underlying biological mechanism. A GWAS study was recently conducted in 3,773 hypercalciuric kidney stone patients and 42,510 controls from Iceland and the Netherlands [3]. These individuals were genotyped for 303,120 polymorphic markers selected from International HapMap project. Four common, synonymous variants in the claudin-14 gene locus were significantly associated with kidney stones. Two of them, rs219778[T] and rs219781[C], are non-exonic SNPs. They are located 2,020 bp apart on either side of the claudin-14 coding exon. Their odds ratio (OR) is 1.30 ($p=3.2 \times 10^{-8}$). The other two SNPs are exonic, causing silent mutations in the claudin-14 protein: rs219779[C] (R81R) and rs219780[C] (T229T). The OR for rs219779[C] is 1.23 ($p = 1.7 \times 10^{-12}$); for rs219780[C] is 1.25 ($p=4.0 \times 10^{-12}$). Both exonic SNPs show significant association with decreased bone mineral density (BMD). The urinary Ca^{++} excretion is significantly higher in homozygous carriers of rs219780[C] compared to non-carriers.

The biological analyses of claudin-14 function were initially focused upon its role in the inner ear. Two rare mutations in the claudin-14 gene (398delT and 254T4A) were found to cause the nonsyndromic recessive deafness – DFNB29 in humans [59]. Claudin-14 knockout mice are deaf, owing to rapid degeneration of the cochlear outer hair cells (OHC) [60]. Electrophysiological experiments have revealed that claudin-14, when overexpressed in epithelial cells, selectively blocks the paracellular permeation of cations, including K^+ [60]. The paracellular barrier provided by claudin-14 is important for maintaining the K^+ gradient between perilymph and endolymph of the hair cell. However, neither hypercalciuria nor nephrolithiasis has been found in DFNB29 patients or claudin-14 knockout animals [59, 60]. The renal localization of claudin-14 has been controversial. Immunofluorescence analysis demonstrated claudin-14 gene expression in the TALH and the proximal tubules of mouse kidneys [61], while another study reported no claudin-14 expression in the kidney [62]. Using a claudin-14 *lacZ* reporter mouse, Gong et al have found the promoter activity of claudin-14 exclusively localized in the TALH of the kidney [63•]. The mRNA and protein level of claudin-14, however, were extremely low in kidneys of mice fed a normal diet. Feeding mice a high Ca^{++} diet profoundly upregulated the mRNA and protein levels of claudin-14 in the TALH segment. Consistent with previous recordings, claudin-14 functions as a barrier for paracellular cation permeation. When co-expressed with claudin-16, claudin-14 inhibits the permeability of claudin-16, a known paracellular cation channel in the TALH. While the claudin-14 knockout mice show normal renal function under basal dietary condition, their kidney excreted significantly less Ca^{++} and Mg^{++} than wild-type animals when fed a high Ca^{++} diet [63•]. Claudin-14 plays a regulatory role in renal Ca^{++} homeostasis. The observed association between claudin-14 and hypercalciuric nephrolithiasis can be explained by claudin-14 deregulation that blocks the claudin-16 channel and phenocopies FHHNC to variable degrees. The exact mechanism for claudin-14 deregulation in kidney stone patients remains elusive. The common SNPs discovered by the GWAS study are less likely to be causal owing to their low odds ratios. Nevertheless, the claudin-14 gene locus may contain susceptible genetic variations with medium to high penetrance. These variants, though predicted to be rare, will not only provide useful

diagnostic biomarkers but also elucidate causal mechanisms underlying kidney stone pathogenesis.

An Integrated Signaling Pathway Underlying Calcium Transport in the TALH

The thick ascending limb of Henle's loop (TALH) is a predominant renal tubular segment responsible for Ca^{++} reabsorption. The epithelial cells in the TALH form a water-impermeable barrier, actively transport Na^+ and Cl^- via the transcellular route, and provide a paracellular pathway for selective reabsorption of Ca^{++} [10•]. The paracellular reabsorption of Ca^{++} is driven by a lumen positive transepithelial voltage (V_{te} ; Fig. 1). It is clear that two basic prerequisites are required for the generation of V_{te} : (1) a large transepithelial NaCl gradient dependent on the concerted actions of NKCC2-ROMK-CICKb-Barttin; (2) a cation selective paracellular channel dependent on the interaction of claudin-16 and claudin-19. Monogenic diseases such as the Bartter syndrome and the FHHNC syndrome are caused by mutations in the genes underlying both prerequisites (Table 1). The process of Ca^{++} reabsorption in the TALH is tightly regulated by CaSR that monitors circulating Ca^{++} levels and adjusts renal excretion rates accordingly [48•]. How CaSR regulates Ca^{++} transport is particularly interesting. It was previously suggested that CaSR activation dampened the transepithelial NaCl transport in the TALH [52, 53], thus affecting the prerequisite "1" for Ca^{++} reabsorption. A recent study by Loupy et al has elegantly shown that CaSR regulates Ca^{++} reabsorption in the TALH tubules through changes in paracellular but not transcellular permeabilities [64•], which provides a strong proof that the CaSR effect is mediated through the prerequisite "2". Gong et al have identified two microRNA molecules, miR-9 and miR-374, from the TALH cells, both of which are directly regulated by CaSR [63•]. MiR-9 and miR-374 recognize partially complementary binding sites located in 3'-UTRs of the claudin-14 mRNA, suppress its translation and induce its mRNA decay in a synergistic manner. Under normal dietary conditions, miR-9 and miR-374 repress the gene expression level of claudin-14 and protect the claudin-16 channel function. High Ca^{++} intake or CaSR activation significantly downregulates the expression levels of miR-9 and miR-374, which causes a reciprocal increase in claudin-14 expression levels. The aggregation of claudin-14 proteins in the tight junction inhibits the cation selectivity of claudin-16 channel discussed elsewhere in this review, and reduces Ca^{++} reabsorption in the TALH tubules.

The Paradox of Hypercalciuria in Kidney Stone Diseases

There are two primary pathogenic mechanisms for calcium nephrolithiasis [1]. (1) Calcium phosphate (CaP) stones form as a result of calcium phosphate precipitation in the lumen of the inner medullary collecting duct (also known as the Bellini duct). (2) Calcium oxalate (CaOx) stones form as a result of calcium oxalate precipitation on the Randall's plaque in the interstitium surrounding the thin descending limb of Henle's loop (tDLH). The driving force for both types of calcium precipitation is their supersaturation (SS) in the urine [65], ostensibly related to the urinary Ca^{++} level. Hypercalciuria is known to increase the SS value for both CaP and CaOx stones. Unlike the CaP stone found in the luminal space of the Bellini duct, the CaOx stone is formed in the basement membrane of the tDLH [66], a compartment separated from the tubular lumen by the tight junction. Increases in luminal Ca^{++} levels as a consequence of hypercalciuria will not correlate directly with interstitial Ca^{++} level changes. It has been hypothesized that water reabsorption in the collecting duct facilitates Ca^{++} reabsorption under hypercalciuric states [67]. However, there is not yet a determined transport mechanism for Ca^{++} in the collecting duct. An alternative mechanism has recently been postulated by Breiderhoff and colleagues [68•]. Through analyzing a TALH conditional knockout mouse model for claudin-10, the authors discovered that the knockout animals developed hypermagnesemia, hypomagnesiuria and hypocalciuria, exactly

opposite phenotypes to those found in the claudin-16 knockout. Surprisingly, the claudin-10 knockout mice also developed interstitial nephrocalcinosis in the outer medulla. Perfusion studies of the isolated TALH tubules from claudin-10 knockout mice demonstrated paracellular hyper-absorption of both Ca^{++} and Mg^{++} . The hyperabsorption of Ca^{++} will increase the interstitial Ca^{++} concentration and stimulate local Ca^{++} precipitation. It is not known whether the increased Ca^{++} reabsorption in the TALH represents a mechanism for kidney stone formation on the Randall's plaque, because the Ca^{++} precipitates in claudin-10 knockout mouse kidneys appeared confined to the TALH but not the tDLH. It is noteworthy that idiopathic nephrolithiasis has been associated with not only gain-of-function but also loss-of-function (expression) polymorphisms in the CaSR gene. While the non-synonymous SNP – R990G produced a gain of CaSR function and inflicted a higher risk of hypercalciuric nephrolithiasis [69, 70], two synonymous SNPs (rs6776158 and rs1501899) causing a significant decrease in renal CaSR mRNA levels, were highly associated with normocitraturic nephrolithiasis [71, 72]. Decreased CaSR expression in the kidney could increase paracellular Ca^{++} reabsorption in the TALH, resulting in interstitial Ca^{++} precipitation and hypocalciuria. Although hypocalciuria itself is not a risk factor for kidney stone, reduced Ca^{++} delivery to the collecting duct could impair the cellular mechanism for urinary acidification and concentration, two well-known factors for CaOx stones.

Conclusion

Recent genetic advances have revealed a number of susceptible genes for calcium nephrolithiasis in the kidney: CaSR, NKCC2, ROMK, ClCkb/Barttin, claudin-14, -16 and -19. These gene products form an integrated signaling pathway in the kidney to regulate Ca^{++} excretion. Mutations and polymorphisms affecting the gene function or expression invariably result in deregulation of urinary Ca^{++} levels and kidney stone phenotypes. Claudins, as part of the paracellular channel, are being recognized as the critical molecules underpinning renal handling of Ca^{++} and various Ca^{++} related kidney diseases. Novel mechanisms such as micro-RNA mediated gene silencing offer new therapeutic tools to clinically manipulate claudin molecules in vivo in the kidney. What remain largely unknown are the precise pathogenic role that claudins play in kidney stone diseases and the additional transport mechanisms for Ca^{++} in the kidney that have not been fully revealed.

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Fig. 1.

Trans epithelial ionic transport in the thick ascending limb of Henle's loop (TALH). **a** When similar salt concentrations are present at the luminal and basolateral sides, the luminal spontaneous potential V_{te} of +8 mV is generated by the concerted action of luminal K^+ channels, basolateral Cl^- channels, the $Na^+2Cl^-K^+$ cotransporter, and the Na^+ , K^+ -ATPase. V_{te} drives Na^+ absorption through the paracellular pathway. **b** When a dilute luminal fluid is present after $NaCl$ absorption along the water-impermeable TAL, the luminal potential V_{te} of +30 mV is now generated as a diffusion voltage by the 'backleak' of Na^+ . The diffusion voltage depends on the cation permselectivity of the tight junction. The membrane voltage (V_m) trace depicts the virtual measurement by an electrode that is pushed from the basolateral side through the cell to the luminal side. Modified from Figure 1 in ref 10

Table 1

Monogenic hereditary diseases causing nephrolithiasis and/or nephrocalcinosis

Disorder	OMIM	Inheritance	Gene	Protein
Antenatal Bartter syndrome (aBS)	601678	AR	SLC12A1	NKCC2, Na ⁺ K ⁺ 2Cl ⁻ co-transporter
	241200	AR	KCNJ1	ROMK, renal outer medullary potassium channel
Bartter syndrome with sensorineural deafness (BSND)	602522	AR	BSND	Renal chloride channel -subunit, Barttin
Classic Bartter syndrome (cBS)	602023	AR	CLCNKB	CLC-Kb, distal tubule chloride channel
Autosomal dominant hypoparathyroidism / Bartter syndrome V (ADH/BS-V)	601198	AD	CASR	CaSR, Ca ²⁺ sensing receptor
Familial hypomagnesemia with hypercalciuria/nephrocalcinosis (FHHNC)	248250	AR	CLDN16	Claudin-16 tight junction protein
	248250	AR	CLDN19	Claudin-19 tight junction protein

AD autosomal dominant; *AR* autosomal recessive