

# **Nephrolithiasis Secondary to Inherited Defects in the Thick Ascending Loop of Henle and Connecting Tubules**

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## **ABSTRACT**

Twin and genealogy studies suggest a strong genetic component of nephrolithiasis. Likewise, urinary traits associated with renal stone formation were found to be highly heritable, even after adjustment for demographic, anthropometric and dietary covariates. Recent high-throughput sequencing projects of phenotypically well-defined cohorts of stone formers and large genome-wide association studies led to the discovery of many new genes associated with kidney stones. The spectrum ranges from infrequent but highly penetrant variants (mutations) causing mendelian forms of nephrolithiasis (monogenic traits) to common but phenotypically mild variants associated with nephrolithiasis (polygenic traits). About two-thirds of the genes currently known to be associated with nephrolithiasis code for membrane proteins or enzymes involved in renal tubular transport.

The thick ascending limb of Henle and connecting tubules are of paramount importance for renal water and electrolyte handling, urinary concentration and maintenance of acid-base homeostasis. In most instances, pathogenic variants in genes involved in thick ascending limb of Henle and connecting tubule function result in phenotypically severe disease, frequently accompanied by nephrocalcinosis with progressive CKD and to a variable degree by nephrolithiasis.

The aim of this article is to review the current knowledge on kidney stone disease associated with inherited defects in the thick ascending loop of Henle and the connecting tubules. We also highlight recent advances in the field of kidney stone genetics that have implications beyond rare disease, offering new insights into the most common type of kidney stone disease, i.e. idiopathic calcium stone disease.

## INTRODUCTION

Kidney stone formation depends on dietary, environmental and genetic factors. Familial aggregation of kidney stone disease was already recognized in 1874 [1]. A positive family history is present in 20-50 % of renal stone formers (SF) [2-4] and both twin [5] and genealogy [6] studies revealed a strong heritability of nephrolithiasis. The genetics of nephrolithiasis is heterogeneous and complex. Driven by technical progress in genomic sequence analysis and bioinformatics, there has been an enormous increase of knowledge in the field of kidney stone genetics in the last two decades. The spectrum ranges from infrequent but highly penetrant variants (mutations) causing mendelian forms of nephrolithiasis (monogenic traits) to common but phenotypically mild variants associated with nephrolithiasis (polygenic traits). Genome-wide association studies (GWAS) with large sample sizes up to 300'000 individuals revealed several variants that are associated with an increased or decreased risk of kidney stone disease [7-9]. The clinical relevance and contribution of these common variants to the overall burden of kidney stone disease, however, remain unclear. The situation is different at the other end of spectrum, the mendelian forms of nephrolithiasis. About 30 monogenetic forms of nephrolithiasis have been identified thus far and the list is continuously growing [10,11]. A decade ago, less than 2 % of all SF were estimated to have an underlying monogenetic cause [12]. In a recent study with a selected group of individuals suffering from recurrent nephrolithiasis or isolated nephrocalcinosis, high throughput sequencing revealed a monogenetic cause in 11.4 % of adult cases and 20.8 % of childhood-onset cases [11]. Recessive mutations were more frequent among children, dominant disease occurred more abundantly in adults. About two-thirds of the genes (~20 out of 30) currently known to be associated with monogenetic stone disease code for membrane proteins or enzymes involved in renal tubular transport.

The thick ascending limb of Henle (TALH) and connecting tubules (CNT) have a central role in renal water and electrolyte handling as well as in the maintenance of acid-base homeostasis. As such it is not surprising that mutations in genes involved in TALH and CT function can result in phenotypically severe disease. Mutations in at least 10 genes expressed in these two tubular segments are known to be associated with recurrent nephrolithiasis, including Bartter's syndrome (BS), familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) and distal renal tubular acidosis (dRTA) [13]. Apart

from rare genetic forms of stone disease, the medullary TALH is also involved in the formation of interstitial apatite deposits, known as Randall's plaques, which are thought to represent the starting point for Ca oxalate stone formation [14,15].

## **ANATOMICAL AND PHYSIOLOGICAL ASPECTS**

We will briefly review in this section several anatomical and physiological aspects that are necessary to understand the inherited defects in the TALH and CNT leading to secondary nephrolithiasis.

### **LOOP OF HENLE**

The loop of Henle comprises the descending thin limb, the ascending thin limb, and the thick ascending limb. Superficial and midcortical nephrons have a short thin descending limb or may even lack a thin descending limb, so that the TALH begins at the hairpin turn. In contrast, juxtamedullary nephrons contain a long loop extending deep into the medulla with the TALH beginning at the boundary between the inner and outer medulla. Unlike the thin descending limb, the thin ascending limb and the TALH do not express aquaporin-1 and hence are water impermeable [16]. Physiological functions of descending and ascending thin limbs have been reviewed in detail elsewhere [17]. For the sake of this review, we will place special emphasis on the TALH, which is critically involved in fluid and electrolytes homeostasis, urine concentration/dilution, acid-base homeostasis, as well as urinary protein composition [18].

The TALH is responsible for the reabsorption of 25 to 40% of filtered NaCl and thus plays a crucial role in the maintenance of extracellular volume [19]. Due to the impermeability to water, the TALH contributes to the urinary concentrating mechanism by diluting the luminal fluid, establishing a gradient of increasing osmolarity along the medulla via a countercurrent multiplication process [20]. NaCl reabsorption occurs through the co-transport of 1 Na, 1 K and 2 Cl ions mediated by NKCC2, a co-transporter expressed at the apical membrane along the entire TALH (Fig. 1) [21]. This electroneutral co-transport is driven by the Na-gradient generated by the Na/K-ATPase on the basolateral membrane and can specifically be inhibited by “loop” diuretics such as furosemide or bumetanide [22,23]. The proper functioning of NKCC2 also requires apical K channels, mainly renal outer medullary K channels (ROMK) and to a lesser extent big K (BK) channels, whose function is to “recycle” K ions back into the lumen [24,25]. Without this recycling, the low luminal K content of the TALH would indeed result in a severely impaired NKCC2-mediated NaCl transport [26]. On the basolateral side of TALH cells, the chloride channels CLC-Ka and CLC-Kb with their associated Barttin subunit mediate electrogenic

efflux of Cl ions [27], whereas the electroneutral K-Cl cotransporter KCC4 is responsible for K-dependent Cl exit (Fig. 1) [28].

The apical co-transport of 1 Na<sup>+</sup>, 1 K<sup>+</sup> and 2 Cl<sup>-</sup> ions through NKCC2 coupled to the apical recycling of K generates a lumen-positive transepithelial voltage that drives paracellular reabsorption of cations such as Na, Mg, and Ca [29]. The TALH reabsorbs 50%-70% of filtered Mg and up to 25% of filtered Ca [30,31]. Charge and size selective tight junctions composed of different types of claudins facilitate and regulate this paracellular transport [32]. In particular, claudin-16 and claudin-19 critically contribute to this task, genetic disruption of claudin-16 or -19 causes urinary Mg and Ca wasting in both mice and men [33-36]. Claudin-16 and claudin-19 form a complex with claudin-3 to build a pore for divalent cations in the TALH [37]. Claudin-14 interacts with claudin-16 and thereby attenuates Ca permeability through this tight junction pores (Fig. 1) [38]. Claudin-14 transcript and protein are upregulated by high Ca diet and downregulated by low Ca diet. A second TALH tight junction pore mainly permeable for Na is formed by claudin-10b. Conditional TALH claudin-10b KO mice exhibit increased paracellular permeabilities of Mg and Ca but greatly decreased Na permeability, resulting in hypermagnesemia, hypocalciuria, nephrocalcinosis and polyuria [39]. Together these findings indicate that there are two different paracellular permeability pathways in the TALH, a Na-permeable pathway formed by claudin-10b and a Ca- and Mg-permeable pathway formed by claudin-16 and claudin-19. If one type of claudin complex is perturbed or eliminated, the other predominates conferring only its functional permeability properties. In support of this notion, deletion of claudin-10b rescues claudin-16 deficient mice from hypomagnesemia and hypercalciuria [40]. Double mutant mice display a complete loss of paracellular cation selectivity at the level of the TALH with recruitment of downstream compensatory mechanisms. The calcium-sensing receptor (CaSR) is strongly expressed at the basolateral membrane of TALH cells, and regulates NaCl and Ca transport in this segment [41]. Activation of the CaSR by elevated extracellular Ca has been shown to reduce apical NaCl transport via the inhibition of ROMK [42]. This mitigates the lumen-positive transepithelial potential necessary for the paracellular transport of Ca, resulting in hypercalciuria. However, a recent study reported that inhibition of the CaSR causes hypocalciuria without concomitant alteration in NaCl transport, suggesting that the CaSR may primarily influence the paracellular transport pathway [43]. Indeed, results from several recent studies

demonstrate that the CaSR directly regulates the expression of claudin-14 and claudin-16 [44,38,45,46,43].

In addition to their resorptive tasks, TALH cells express and secrete uromodulin (also known as Tamm-Horsfall protein) into the urine [47]. Uromodulin is the most abundant protein physiologically present in urine and regulates blood pressure via modulation of ROMK and NKCC2 activity [48-50], prevents tubular crystallization of Ca oxalate [51,52] and also has a protective role against urinary tract infections [53].

### **CONNECTING and COLLECTING TUBULES**

After the TALH, the distal nephron encompasses the distal convoluted tubule (DCT), the connecting tubule (CNT) and the collecting duct (CD). With the exception of the rabbit kidney, in which the boundaries between these segments are clearly defined, the delineation is gradual in most species [54]. The CNT appears thus as a transition segment between the DCT and the CD. The CNT contains CNT-specific cells, which resemble principal cells of the CD, and intercalated cells. The CD is classically divided into three parts: the cortical collecting duct, the outer medullary collecting duct and inner medullary collecting duct. As for the CNT, the CD contains principal cells and intercalated cells, which are further subdivided in 3 subtypes including type A, type B, and non-A/non-B intercalated cells. The CD is a “salt and pepper” type epithelium, with principal cells being the main cell type with intercalated cells “sprinkled” throughout [55]. Hereditary defects in type A intercalated cells but not in other CNT and CD cells cause kidney stone disease in humans. Type A intercalated cells are found from the late DCT to the inner medullary collecting duct and are critical for urinary net acid excretion [56]. They exhibit basolateral expression of the Cl<sup>-</sup>/bicarbonate exchanger AE1 and V-ATPase activity at the apical membrane (Fig. 2) [54,57]. The V-ATPase consists of two multi-subunit complexes, the V<sub>1</sub> (head) and V<sub>0</sub> (membrane anchored) subunits [58]. The 640 kDa V<sub>1</sub> subunit is composed of subunits A, B, C, D, E, F, G and H. Mammals have two B subunits, the ubiquitous B2 isoform and the B1 isoform, which is restricted to specialized epithelia of the inner ear, epididymis and intercalated cells [59,60]. Protons furnished by the cytosolic carbonic anhydrase type II present in type A intercalated cells are translocated

against a concentration gradient by the ATP-driven V-ATPase into the urine. Contemporaneous with apical proton secretion, carbonic anhydrase liberates bicarbonate ions, which exit basolaterally via AE1.



## GENETIC DISORDERS OF THE THICK ASCENDING LOOP OF HENLE

### MONOGENETIC DISEASE

#### **Bartter syndrome**

Antenatal and classical Bartter syndromes constitute a congenital heterogeneous family of salt reabsorption disorders, which share common features such as hypokalemic metabolic alkalosis, elevated renin and aldosterone levels without hypertension, hypercalciuria, nephrolithiasis and nephrocalcinosis. The antenatal form of Bartter syndrome presents with additional severe symptoms including maternal polyhydramnios, premature birth, dehydration due to polyuria and early-onset nephrocalcinosis [61]. Five genes are currently known to cause Bartter syndrome: Mutations in the *SLCA12A1* gene coding for the Na, K, 2 Cl cotransporter NKCC2 cause Bartter syndrome type I, mutations in the *KCNJ1* gene coding for the K channel ROMK cause Bartter syndrome type II, mutations in the *CLCNKB* gene coding for the voltage-gated Cl channel ClC-Kb cause Bartter syndrome type III, mutations in the *BSND* gene coding for barttin cause Bartter syndrome type IV, and mutations in the *CASR* gene coding for the CaSR causes Bartter syndrome type V (Table 1) [62-67]. With the exception of Bartter syndrome type V, which is due to a dominant activating mutation of the *CaSR*, the other types of Bartter syndrome result from recessive loss-of-function mutations.

Mutations in the *CLCN5* gene coding for the voltage-gated chloride channel ClC-5 in the proximal tubule cause Dent disease and nephrolithiasis and may also be associated with a Bartter-like syndrome [68-70]. In addition, a severe but transient form of antenatal Bartter syndrome due to mutations in the melanoma-associated antigen D2 (encoded by the X-chromosomal *MAGED2* gene) has recently been reported [71]. *MAGED2* gene mutations are associated with polyhydramnios, prematurity and increased perinatal mortality but an association with kidney stones has not been reported.

In 2002, the first patient with Bartter syndrome and kidney stones was described [72]. The reported patient was a 28 year old male with genetically confirmed Bartter syndrome type III. He had hypercalciuria but no evidence of nephrocalcinosis, stone analysis results were not reported. In the last 20 years, several large case-series with Bartter patients were published. In an Italian long-term follow-up study of 15 patients with Bartter syndrome type I and II, an increased Ca/creatinine ratio was found

in 10 of 11 investigated children and all but one child had signs of nephrocalcinosis at diagnosis. Nephrolithiasis was not observed at baseline or during a median follow-up of 11 years [73]. In another series with 40 patients, all patients with Bartter syndrome type II had evidence of hypercalciuria and medullary nephrocalcinosis within the first weeks of life, whereas only two of 20 patients with Bartter syndrome type III displayed hypercalciuria and nephrocalcinosis [74]. The prevalence of nephrolithiasis was not reported. Similar findings were reported in another study with 52 Bartter patients: nephrocalcinosis was present in 31 of 32 cases with Bartter syndromes type I and II but only in two of 20 patients with Bartter syndrome type III [75]. The prevalence of nephrolithiasis was also not described in this study. In a nationwide Korean cohort, Bartter syndrome type III was found to be the most common form of Bartter syndrome, affecting 23 of 26 genotyped patients [76]. Hypercalciuria and nephrocalcinosis were present in ~60% and ~20% of patients, respectively, but the prevalence of nephrolithiasis was not described. In another long-time follow-up study (median follow-up 8.3 years) with 42 patients with Bartter syndrome type I to IV, all patients with Bartter syndrome type I and II had hypercalciuria and nephrocalcinosis. Out of four children with Bartter syndrome type III for which biochemical data were available, three children had hypercalciuria but only one child also displayed nephrocalcinosis. Of the four children with Bartter syndrome type IV reported, two were also found to have hypercalciuria and nephrocalcinosis [61]. Again, prevalence of nephrolithiasis was not reported. The high phenotypic variability of Bartter syndrome type III is well illustrated by a recent large retrospective study with 115 patients [77]. Clinical features of the antenatal/neonatal form were found in ~30% of patients, features of the classical form in ~45% of patients and features of a Gitelman-like form in ~25% of patients. Urinary Ca/creatinine ratio was highest in the antenatal form and lowest in the Gitelman-like form. Nephrocalcinosis followed the same distribution pattern with prevalence rates of 29.4 % in the antenatal form, 14 % in the classical form and only 3 % in the Gitelman-like form. Follow-up data (median follow-up was 8 years) were available in 77 of the 115 patients. Overall, seven patients developed nephrolithiasis (two of 26 patients with the antenatal form, five of 35 patients with the classical form but none of the 16 patients with the Gitelman-like presentation). The exact distribution between symptomatic stone events and asymptomatic stones discovered during imaging, stone composition results and urinary risk factors of stone formation other than calciuria were not reported.

It is remarkable that in the published case-series on Bartter syndrome, prevalence of nephrolithiasis is often not reported and if reported, nephrolithiasis seems to be considerably lower than the prevalence of nephrocalcinosis. Strikingly, we have not found a single published case of Bartter syndrome with the results of a stone analysis reported. In our own stone clinic, we follow one patient with Bartter syndrome and recurrent nephrolithiasis. This currently 27 year old male with a compound heterozygous *SLC12A1* mutation (c.799G>A, p.A267T and c.2752G>A, p.D918N) developed recurrent calcium nephrolithiasis at age 24. Two infrared spectroscopy-based stone analyses were performed on two consecutive stones, both yielding the same composition: 60 % octa-ca-dihydrogen phosphate and 40 % carbonate apatite. Although the patient had mild compensated metabolic alkalosis (venous plasma bicarbonate 33.4 mmol/L), he was found to be profoundly hypocitraturic (0.03 – 0.06 mmol/24 h), likely due to medullary nephrocalcinosis with mild CKD (plasma creatinine 125 - 148  $\mu$ mol/L) and a urinary acidification deficit (24 h urinary pH values between 6.6 and 6.8). Urinary Ca was significantly elevated (8.6 - 8.8 mmol/24 h), urinary volumes were between 3.1-3.4 l/24 h. In addition, the patient also had a constellation compatible with normocalcemic primary hyperparathyroidism with elevated PTH (129 pg/ml), high normal ionized plasma Ca (1.21 – 1.29 mmol/l) and low normal plasma P (0.78 – 0.94 mmol/l). The association of Bartter syndrome type I and primary hyperparathyroidism has only recently been recognized [78,79]. None of the reported six pediatric cases suffered from symptomatic kidney stones but one child had radiologic evidence of asymptomatic nephrolithiasis. Cinacalcet and potassium citrate improved biochemical abnormalities in these children. As in the reported cases, sestamibi scintigraphy and neck MRI failed to reveal a parathyroid adenoma in our patient. The patient was started on cinacalcet 30 mg twice daily and potassium citrate 30 mmol twice daily, which resulted in a significant rise of urinary citrate to 0.87 mmol/24 h and a large drop in urinary Ca excretion to 2.8 mmol/24 h. The patient had a last symptomatic stone event 20 months after treatment initiation (22 months after the first stone event) and has remained asymptomatic now since 12 months.

As outlined above, large series suggest a correlation between degree of hypercalciuria and prevalence of nephrocalcinosis / nephrolithiasis in Bartter syndrome patients. Factors favoring the development of kidney stones in Bartter syndrome remain elusive so far. Indeed, high urinary volume and high urinary citrate due to metabolic alkalosis should prevent stone formation. Similarly, reduced Ca reabsorption at

the level of the TALH should prevent Randall plaque formation and thus CaOx stone formation. These findings raise several questions. Do Bartter patients only form stones in the setting of high urinary Ca, low urinary citrate and increased urinary pH as in our case ? Are all Bartter patients forming CaP stones ? What is the site of stone formation (ductal plugging versus growth on plaques) ? Clearly, carefully conducted prospective studies with detailed clinical, genetic, biochemical and high-resolution imaging data are needed to better understand the pathophysiological mechanisms leading to kidney stone formation in Bartter patients.

### **Familial hypomagnesemia with hypercalciuria and nephrocalcinosis**

The autosomal-recessive disorder familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is caused by homozygous mutations in the claudin-16 (alias paracellin-1) and claudin-19 genes *CLDN16* and *CLDN19*, respectively (Table 1) [33,34]. Symptoms include seizures, tetany, failure to thrive, polyuria, recurrent urinary tract infections, nephrolithiasis and CKD with a substantial portion of patients eventually progressing to ESRD [80]. The phenotype of *CLDN19* mutation is similar to the *CLDN16* mutation syndrome but affected individuals additionally display ocular involvement (macular coloboma, myopia, retinitis pigmentosa, nystagmus and visual loss) [34]. Similar to Bartter syndrome, nephrocalcinosis seems to be much more prevalent than nephrolithiasis in FHHNC. While nephrocalcinosis is a universal finding in FHHNC patients, nephrolithiasis was reported in 25 % and 42 % of patients with claudin-16 and claudin-19 mutations, respectively [81,34].

CKD progression was found to be unaffected by magnesium salts or thiazide diuretics but early treatment with vitamin D and Ca was essential to maintain growth in children [82]. In a more recent small cross-over study with four male and four female patients with FHHNC due to homozygous *CLDN16* mutations, short-time administration of hydrochlorothiazide effectively reduced urinary Ca to a variable degree without significant alteration of urinary Mg excretion, but long-term treatment data are lacking [83]. Interestingly, in larger pedigree analyses, hypercalciuria and nephrolithiasis but not nephrocalcinosis or hypomagnesemia were observed in otherwise healthy family members, suggesting that pathogenic *CLDN16* variants may be associated with “idiopathic” Ca stones [80,84,81].

## VARIANTS

### **Claudin-14**

A GWAS in 3773 SF and 42,510 healthy controls from Iceland and the Netherlands found common synonymous variants in the *CLDN14* gene encoding claudin-14 to be associated with an increased risk for kidney stones and reduced bone mineral density (Table 1) [8]. The synonymous variant rs219780(C) was present in a homozygous state in 62 % of the population and conferred an estimated 1.64 -fold increased risk for the development of kidney stones compared to noncarriers. The rs219780(C) variant was also significantly associated with increased urinary Ca and serum parathyroid hormone and reduced serum total CO<sub>2</sub>, but was not associated with serum Ca, P or vitamin D.

Another study investigated the association of rare variants (allele frequencies <2%) in 40 candidate genes in 960 individuals with low and high 24-hour urinary Ca excretion from the Nurses' Health Studies I & II and the Health Professionals Follow-up Study [85]. None of the rare gene variants assessed were found with increased frequency in the low vs. high urinary Ca groups. The analysis of variants with allele frequencies  $\geq 2\%$  suggested an association of the non-synonymous *CLDN14* variant rs11383113 (c.11C>T, p.Thr4Met) with lower urinary Ca excretion. The *CLDN14* gene variant rs219780, which had been reported to increase the risk for kidney stones in the Icelandic and Dutch population, did not segregate between the groups with low and high 24-hour urinary Ca excretion [8,85]. In another study with 200 kidney SF and 200 healthy controls from the eastern part of India, the two variants rs219777 and rs219778 in the *CLDN14* gene were found to be strongly associated with kidney stone disease, but no significant association was found with urinary or serum Ca [86]. A more recent study described the association of the *CLDN14* gene variant rs78250838:C>T in an intronic cis-regulatory element with early-onset hypercalciuria and kidney stones in children [87]. *In vitro* studies revealed that this variant enhances claudin-14 expression, thereby increasing urinary Ca excretion and promoting calcium stone formation.

### **Calcium-sensing receptor**

Vezzoli et al. were the first to report a positive association of the non-synonymous *CaSR* gene variant rs1042636 (p.R990G) in exon 7 with urinary Ca excretion in a cohort of kidney SF [88]. The association of this *CASR* variant with urinary Ca excretion and calcium nephrolithiasis has been reproduced in other ethnic cohorts [86,89]. Several other non-synonymous (rs1801725 and rs1801726), intronic (rs17251221 and rs1501899) and 5' UTR (rs7652589) *CASR* gene variants have also been associated with kidney stone disease in recent years (Table 1) [86,89-94].

In a large follow-up GWAS with 5419 kidney stone cases and 279'870 controls in Iceland, additional genomic sequence variants associated with kidney stone disease were identified [7]. Relevant for this review is the observed association of a novel variant in a regulatory region in the first intron of the *CASR* gene rs7627468(A) that was found to be positively associated with kidney stone disease (odds ratio 1.16), increased serum total and ionized Ca and decreased 25-hydroxy vitamin D (Table 1).

### **Uromodulin**

Rare mutations in the *UMOD* gene cause autosomal-dominant tubulointerstitial kidney disease (ADTIK), which is associated with progressive worsening of kidney function, hyperuricemia, gout and arterial hypertension but not kidney stones [47]. In a GWAS for CKD in an Icelandic population, a common variant rs4293393(T) at the *UMOD* gene locus was found to be associated with an increased risk for the development of CKD and gout but to confer protection against kidney stones (Table 1) [95].

## GENETIC DISORDERS OF THE CONNECTING TUBULES

### MONOGENETIC DISEASE

#### Distal renal tubular acidosis

Lightwood provided the first description of congenital distal renal tubular acidosis (dRTA) in an autopsy series of six children in 1935 [96]. Five monogenetic forms of dRTA are currently known: autosomal-recessive and autosomal-dominant mutations in the anion exchanger 1 (AE1, encoded by *SLC4A1* gene), autosomal-recessive mutations in the B1 and a4 subunits of the V-ATPase (encoded by *ATP6V1B1* and *ATP6V0A4* genes, respectively), autosomal-recessive mutations in the transcription factor Foxi1 (encoded by the *FOXI1* gene) and autosomal-recessive mutations in carbonic anhydrase type II (encoded by the *CA2* gene) (Table 2) [97-103]. *Sensu stricto*, *CA2* mutations cause a combined proximal-distal RTA, also known as type III RTA, but the renal phenotype is very similar to isolated cases of inherited dRTA.

Clinically, diagnosis of dRTA (also known as RTA type I) is straightforward and provocative tests are usually not needed. Typical laboratory features include hypokalemia, systemic normal anion gap acidosis (in the absence of extrarenal alkali losses), hypocitraturia, hypercalciuria and urinary pH >6.5. DRTA can be acquired or inherited, and separation between the two is critical as it will have diagnostic and therapeutic consequences (e.g. immunosuppression for Sjögren's syndrome). Apart from obtaining a detailed family history, extrarenal manifestations can be helpful in identifying and differentiating inherited cases. In general, phenotype is milder and age of diagnosis significantly later with dominant *SLC4A1* mutations compared to recessive forms of dRTA [104,105]. Systemic metabolic acidosis may even be absent in dominant *SLC4A1* mutations, a constellation known as incomplete dRTA [106-108]. B1 and a4 subunits of the V-ATPase are expressed in the stria vascularis of the inner ear and almost all patients with recessive *ATP6V1B1* mutations and about half of patients with recessive *ATP6V0A4* mutations develop progressive, bilateral sensorineural hearing loss [104]. For unknown reasons, onset of hearing loss occurs at a younger age and the phenotype is more severe in patients with *ATP6V1B1* mutations [105,109,104]. Sensorineural hearing loss can be accompanied by enlargement of the vestibular aqueduct and endolymphatic sac and may contribute to the onset or the progression of hearing

impairment [110-112]. *SLC4A1* mutations can cause isolated dRTA, isolated hemolytic anemia or both [113,114]. DRTA due to dominant *SLC4A1* mutations is not associated with hemolytic anemia, unless dominant mutations are present in a homozygous or compound heterozygous state [114,113]. Recessive *SLC4A1* mutations with combined dRTA and hemolytic anemia have been reported in Southeast Asian patients, but recessive *SLC4A1* mutations can also cause isolated dRTA [115,114]. Patients with recessive *CA2* mutations can be separated from other forms of inherited dRTA by a wealth of characteristic extrarenal features including intracerebral calcifications, psychomotor retardation, abnormal teeth with enamel hypoplasia and osteopetrosis, which can be severe, leading to optic nerve entrapment and blindness [102,116].

The sequelae of dRTA are recurrent nephrolithiasis, nephrocalcinosis and low bone mass. While nephrocalcinosis is almost a universal finding in inherited dRTA, the prevalence of nephrolithiasis is unknown and has not been reported in large cohort studies [105,104]. Hypercalciuria (due to increased release of Ca from bone and decreased renal Ca reabsorption), hypocitraturia (due to augmented proximal tubular citrate reabsorption) and alkaline urinary pH are the three principal lithogenic factors in dRTA and favor CaP precipitation [117-120]. The typical renal calculus in dRTA consists of carbonate apatite and has a characteristic morphology with a smooth aspect and a glazed brown-yellow appearance with tiny cracks [121,122]. Nephrocalcinosis is almost a universal finding in inherited dRTA and frequently associated with reduced GFR [104]. The pathogenesis of nephrocalcinosis in dRTA is unknown but possibly involves the same lithogenic factors that also foster the development of stones. Patients with dRTA typically present with low bone mass (exception are patients with *CA2* mutations), primarily due to reduced bone formation and turnover rates, and to some extent defective mineralization and reduced non-collagenous proteins [123-125]. Alkali therapy is the cornerstone of dRTA treatment. In children, alkali improves bone turnover and somatic growth [126,127]. In adults with dRTA, alkali therapy decreases calciuria, increases citraturia, reduces stone formation, normalizes bone formation and increases bone density [128,118,129,125]. K-citrate is preferable over Na-citrate because K-citrate tends to reduce calciuria in addition to increasing citraturia, whereas Na-citrate at equimolar doses can increase calciuria [128].



## VARIANTS

### V-ATPase B1 subunit

Impaired urinary acidification capacity in the absence of systemic acidosis is a frequent finding in recurrent SF and has been designated “incomplete dRTA” [108,130-133]. There is a positive association of kidney stone CaP content and the prevalence of a urinary acidification deficit in SF [134,135]. In most SF, the cause of the urinary acidification deficit remains obscure and maybe due to acquired or inherited conditions. Recent studies revealed that heterozygous carriers of a recessive *ATP6V1B1* truncation mutation c.1401\_1402dupGT; p.F468fsX487 or SF heterozygous for the non-synonymous *ATP6V1B1* polymorphism c.481G>A; p.E161K exhibit a urinary acidification deficit in the absence of systemic acidosis, reduced urinary citrate and an increased prevalence of CaP containing kidney stones (Table 2) [136,137]. In an unselected cohort of SF referred for metabolic work-up to a tertiary care stone clinic, the prevalence of the *ATP6V1B1* c.481G>A;p.E161K polymorphism was 5.8 % [137]. Compound heterozygosity or homozygosity for the *ATP6V1B1* c.481G>A; p.E161K polymorphism was reported to be associated with overt dRTA [138,11]. *In vitro* studies demonstrated intact integration of p.E161K B1 subunits into the V-ATPase complex but greatly reduced pump function [139,136]. No evidence for a dominant-negative effect of p.E161K B1 subunits was observed in these studies, suggesting haploinsufficiency in heterozygous carriers as underlying mechanism. If other known V-ATPase B1 or a4 subunit mutations also cause a detectable deficit in urinary acidification in a heterozygous state is currently unknown. Thus, it is conceivable but yet unproven that additional allelic variants in *ATP6V1B1* or in other genes associated with urinary net acid excretion are associated with a urinary acidification deficit, reduced urinary citrate excretion and an increased risk of CaP stone formation. In mice genetic deletion of the type A intercalated cell apical ammonia transporter *Rhcg*, the basolateral K-Cl-cotransporter *KCC4* or the basolateral chloride/bicarbonate exchanger *SLC26A7* cause dRTA [63-65]. To date, however, pathogenic variants in these transporters have not been reported in patients with dRTA and nephrolithiasis.

## CONCLUSIONS

Recognition of monogenetic forms of nephrolithiasis in the TALH and CNT is of prime clinical importance. The phenotype is well defined and traits are highly penetrant, making genetic testing a powerful diagnostic tool with prognostic and therapeutic relevance. In contrast, the impact of common, phenotypically mild variants in TALH or CNT genes on stone recurrence, disease progression and treatment response remains unclear. Thus, genetic testing for these common variants therefore has currently no role in the clinical care of patients suffering from kidney stones.

The identification of patients with inherited forms of nephrolithiasis remains a challenge, the main obstacle being differentiation from idiopathic stone disease. A detailed history and thorough clinical examination of the patient as well as the alertness of the treating physician are key. Red flags pointing to inherited kidney stone disease are early onset of disease, positive family history, consanguinity of parents, progressive renal failure, nephrocalcinosis, tubular dysfunction or extrarenal manifestations. Diagnosis is greatly facilitated if an expert environment with established collaborations between nephrologists, urologists and geneticists is available. With novel and specific treatment options at the horizon and a continued high rate of discoveries in the field, the relevance of recognition and diagnosis of inherited forms of nephrolithiasis will increase considerably in the next years.

About half of all inherited disorders of the kidney currently known to be associated with nephrolithiasis or nephrocalcinosis localize to the TALH or the CT. Molecular and phenotypic investigations of these rare disorders have greatly expanded our knowledge in renal physiology. Nevertheless, our understanding of the basic mechanisms leading to stone formation and/or interstitial calcifications in these patients remains poor. A large knowledge gap also exists on how to best treat these patients to prevent stone recurrence and progression of nephrocalcinosis, and the associated CKD. Clearly, there is a dire need for more basic and clinical research efforts in this neglected area. Studying these rare monogenetic forms of stone disease offers a unique opportunity to unravel general mechanisms of calcium stone formation and may lead to the development of novel diagnostic and therapeutic strategies for SF.

## **DISCLOSURES**

The authors declare no conflicts of interest. DF has served as a consultant for Otsuka Pharmaceuticals.

DF has received unrestricted research funding from Novartis, Abbvie and Otsuka Pharmaceuticals.

## **ACKNOWLEDGEMENTS**

DF was supported by the Swiss National Centre of Competence in Research NCCR TransCure and the Swiss National Science Foundation (grants # 31003A\_135503, 31003A\_152829 and 33IC30\_166785/1).

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## TABLES

**Table 1. Genetic disorders of the TALH associated with kidney stones.**

Gene	Mode of inheritance	Clinical features
<b>Monogenetic Disease</b>		
<i>SLC12A1</i>	Autosomal-recessive	Bartter syndrome type I [64].
<i>KCNJI</i>	Autosomal-recessive	Bartter syndrome type II [63].
<i>CLCNKB</i>	Autosomal recessive	Bartter syndrome type III [65].
<i>BSND</i>	Autosomal-recessive	Bartter syndrome type IV [67].
<i>CASR</i>	Autosomal-recessive	Bartter syndrome type V [66].
<i>CLDN16</i>	Autosomal-recessive	FHHNC [33]. Heterozygous <i>CLDN16</i> mutations have been associated with hypercalciuria and nephrolithiasis in pedigree analyses [80,84,81].
<i>CLDN19</i>	Autosomal-recessive	FHHNC with ocular involvement [34].
<b>Variants</b>		
<i>CLDN14</i> rs219780 rs219781 rs219778	-	Synonymous variants identified by GWAS associated with increased risk for kidney stones, low bone mass, increased urinary Ca and serum parathyroid hormone and reduced serum total CO <sub>2</sub> in Icelandic and Dutch population [8]. Variants are also associated with increased risk for kidney stones but not with urinary Ca in Indian population [86]. No association found with urinary Ca in North American population [85].
<i>CLDN14</i> rs113831133	-	Non-synonymous variant (c.11C>T, p.Thr4Met) associated with reduced urinary Ca excretion in North American population [85].

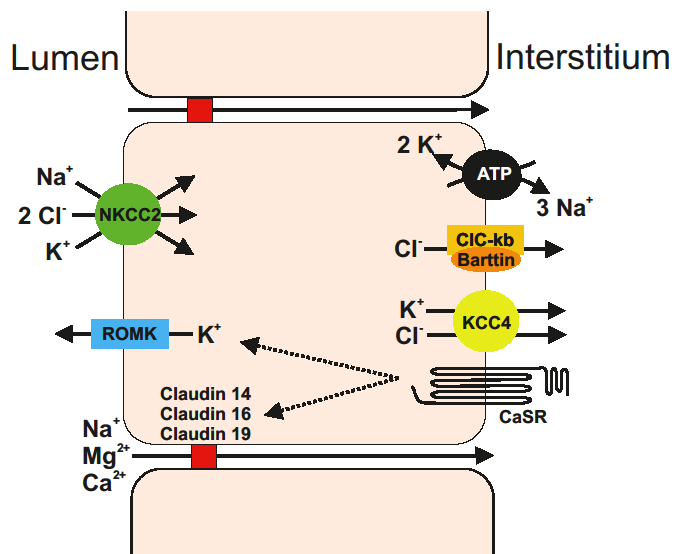
<p><i>CASR</i>  <i>rs1801725</i>  <i>rs1042636</i>  <i>rs1801726</i></p>	-	Non-synonymous variants (p.A986S, p.R990G and p.Q1011E) in Exon 7 associated with increased risk for kidney stones and increased urinary Ca excretion [88,86,89].
<p><i>CASR</i>  <i>rs17251221</i>  <i>rs1501899</i>  <i>rs7652589</i></p>	-	Intronic or 5'UTR variants associated with increased risk for kidney stones [86,89-94].
<p><i>CASR</i>  <i>rs7627468</i></p>	-	Variant in a regulatory region of the first intron identified by GWAS associated with increased risk for kidney stones, increased serum total and ionized Ca and decreased 25-hydroxy vitamin D [7].
<p><i>UMOD</i>  <i>rs4293393</i></p>	-	Variant identified by GWAS associated with increased risk for CKD and gout but reduced risk for kidney stones in Icelandic and Dutch population [95].

**Table 2. Genetic disorders of the CNT associated with kidney stones.**

Gene	Mode of inheritance	Clinical features
<b>Monogenetic Disease</b>		
<i>ATP6V1B1</i>	Autosomal-recessive	DRTA, early onset sensorineural hearing loss [97].
<i>ATP6V0A4</i>	Autosomal-recessive	DRTA, late onset sensorineural hearing loss [98].
<i>SLC4A1</i>	Autosomal recessive or autosomal-dominant	DRTA, hemolytic anemia (rare). Maybe incomplete dRTA in case of autosomal-dominant mutation [107].
<i>FOXII</i>	Autosomal-recessive	Early onset sensorineural hearing loss [99].
<i>CAII</i>	Autosomal-recessive	Mixed pRTA and dRTA. Intracerebral calcifications, psychomotor retardation, abnormal teeth with enamel hypoplasia, osteopetrosis in severe cases causing optic nerve entrapment and blindness [101].
<b>Variants</b>		
<i>ATP6V1B1</i> c.481G>A;p.E161K	-	Urinary acidification deficit, elevated urinary pH, increased prevalence of CaP containing kidney stones in heterozygous SF [137]. Overt dRTA in homozygous carriers of the variant (1 patient reported) or if compound heterozygous with other pathogenic <i>ATP6V1B1</i> variant [11,138].
<i>ATP6V1B1</i> c.1401_1402dupGT; p.F468fsX487	-	Urinary acidification deficit, elevated urinary pH, CaP containing kidney stones in heterozygous carriers [136]. Overt dRTA in homozygous carriers of the variant [139].

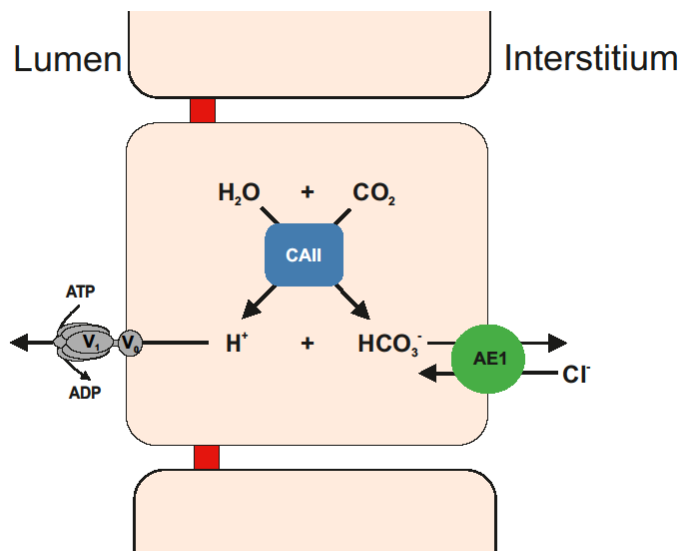


## FIGURES



**Figure 1. Schematic representation of a TALH cell.**

Abbreviations: NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary K channel; CIC-Kb, voltage-gated Cl channel Kb isoform ; KCC4, K-Cl cotransporter; CaSR, calcium-sensing receptor.



**Figure 2. Schematic representation of a Type A intercalated cell.**

Abbreviations: AE1, anion exchanger 1; CAII, carbonic anhydrase type II; V, membrane-anchored subunit of the V-ATPase; V, head subunit of the V-ATPase.