Urolithiasis

Tubular and genetic disorders associated with kidney stones

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Abstract:	This concise review summarises our current understanding and the recent developments in genetics and related renal tubular disorders that have been linked with, or have been shown to be causal in, renal stone disease. The aim is to provide a readily accessible quick and easy update for urologists, nephrologists and endocrine or metabolic physicians whose practice involves the diagnosis and management of nephrolithiasis. An important message is to always consider a seemingly rare, and usually genetic, cause of kidney stones, since some of these are emerging as more common than originally thought, especially in adult clinical practice in which a family history of stones is a common finding.
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Tubular and genetic disorders associated with kidney stones

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Introduction

Kidney stones are common in industrialized countries with a lifetime risk of up to 10% [1]. Several studies have described a significant relationship between nephrolithiasis and adverse renal outcomes, including ESRD, and the need for timely and early diagnosis, and treatment. The pathogenesis of kidney stones is mixed, including genetic and non-genetic risk factors such as diet, environment, and lifestyle. Recent studies have reported a significant percentage of adult kidney stone patients with an underlying monogenic disease [2,3]. So far more than 30 genes have been identified as causative for nephrolithiasis or nephrocalcinosis. Transmission may be autosomal dominant, autosomal recessive or X-linked. The majority of gene defects encode for proteins that are expressed in the kidney. However, several genes that are not involved directly in normal kidney function may also be a cause of kidney stones. Interestingly, the percentage of monogenic stone disease seems to be high in both children and adults, with more recessive causes found in children and more dominant cases in adults [3,2]. This review encompasses different genetic disorders that cause kidney stones and focuses on the importance of including possible underlying genetic causes of kidney stones in the differential diagnosis and metabolic work-up of recurrent kidney stone formers.

SLC7A9/SLC3A1 (Cystinuria)

Cystinuria is an autosomal recessive disease caused by mutations of 2 different genes, *SLC7A9* (solute carrier family 7 member 9) and *SLC3A1*. Together these genes encode for the 2 subunits of a dibasic amino acid (cystine, ornithine, lysine, and arginine) transport protein located in the apical membrane of the epithelial cells lining the proximal tubule and small intestine [4]. The heavy subunit rBAT (*SLC3a1*) modifies the activity of the light subunit $b_{0,b}$AT (SLC7a9), which is the transport channel. Mutations result in reduced renal reabsorption of dibasic amino acids, with high concentrations of cystine in the urine, and subsequent formation of cystine stones due to its low solubility at acid and normal (ca. 6.5) urinary pH values. To date 3 different types of cystinuria have been classified according to the type of mutation present: i) type A with mutations on both alleles of SLC3A1; ii) type B with mutations on both alleles of the SLC7A9 gene; and iii) type AB, which is very rare with 2 mutated alleles in the same gene and a mutated allele in the other gene [5]. While SLC3A1 heterozygous subjects have normal excretion of cystine, it is increased in SLC7A9 heterozygotes, although not to the levels seen in type B patients; SLC7A9 heterozygous subjects have a mildly increased risk of forming cystine stones [6].

The prevalence of cystinuria depends on the geographical region and may vary from 1:2000 in the Mediterranean to 1:100,000 in Sweden[5]. In a cohort of 272 genetically unresolved

children (n=106) and adults (n=166) from 268 families with nephrolithiasis or isolated nephrocalcinosis, mutations in *SLC7a9* were described as the most common type [4]. The first symptoms may occur during childhood, but the median age for a first stone has been reported to be 26 years [4]. Male patients seem to exhibit a more aggressive disease with a higher number of stone episodes and an earlier age of onset. Diagnosis is generally done on stone analysis or finding cystine crystals in the urinary sediment. Cystinuria and other dibasic aminoaciduria are increased. In 24-h urine, the excretion of cystine and total dibasic amino acid is higher than 1300 µmol/g creatinine and 5900 µmol/g, respectively; in B carriers levels are lower [6]. Recurrence rates are critical in cystinuria patients and the aim is to prevent recurrent stone formation by increasing the urinary solubility of cystine, and limiting its excretion. Preventive measures include significant hydration (>3L/day, especially overnight), urinary alkalinisation (an alkali ash diet or addition of oral alkali as citrate or bicarbonate), and reducing dietary salt intake. In addition, drugs that can reduce cystine to the more soluble cysteine, such as D-penicillamine, tiopronin, or captopril, can also be tried [5].

APRT

The enzyme adenine phosphoribosyltransferase (APRT), coded by the *APRT* gene located on chromosome 16q24, catalyzes the conversion of adenine to adenosine monophosphate. In patients with APRT deficiency, adenosine is metabolized by xanthine oxidase to 2,8-dihydroxyadenine (DHA), which is insoluble at physiological urine pH. Affected patients develop crystalluria and recurrent kidney stones; progressive loss of renal function has also been described [7]. The inheritance of the disease is autosomal recessive and up to now 24 different mutations have been described. The diagnosis can be made with the finding of the characteristic DHA crystals in the urine (round and reddish-brown with a central Maltese cross pattern), or with infrared spectrophotometry or x-ray crystallography analysis of the stones. Treatment with dietary purine restriction and allopurinol, a xanthine oxidase inhibitor, has been reported to be effective in preventing new stone formation and progressive renal impairment [8].

Inherited renal tubular acidoses

Inherited distal renal tubular acidosis

Distal renal tubular acidosis (dRTA) is characterized by an inappropriately alkaline urinary pH in the clinical context of a non-anion gap metabolic acidosis, and is caused by defective distal urinary acidification [9]. To date, mutations in 3 different genes have been described to be causative for inherited dRTA: *ATP6V1B1*, *ATP6V0a4* and *SLC4A1*. SLC4A1 mutations usually cause autosomal dominant dRTA, while *ATP6V1B1* and *ATP6V0a4* cause recessive dRTA [9]. Clinical signs and symptoms can vary among patients, depending on the

underlying gene mutation, and vary from a mild metabolic acidosis with incidental detection of kidney stones to severe manifestations with failure to thrive and growth retardation in children, rickets/osteomalacia, severe metabolic acidosis and nephrocalcinosis [9]. Typically, kidney stones in dRTA are of the calcium phosphate type due to: i) release of calcium and phosphate from bone due to buffering acidosis, and consequent hypercalciuria; and ii) calcium phosphate precipitation in urine due to an alkaline pH. Distal RTA should be considered in children and young adults with nephrocalcinosis or with recurrent kidney stone formation, particularly if 100% apatite stones accompany metabolic acidosis or if there is a family history, especially also of deafness or impaired hearing.

ATP6V1B1 and ATP6V0a4

The vacuolar H^+-ATPase is crucial for urinary acidification and consists of two domains with at least 14 subunits in humans: i) the membrane-bound V0 domain, which is responsible for proton transfer; and ii) the cytosolic catalytic V1 domain that is necessary for hydrolysis of ATP[9]. *ATP6V1B1* and *ATP6V0A4* mutations affect 2 different subunits of the vacuolar H^+-ATPase, the B1 and a4 subunits, respectively. The B1 subunit is expressed in type A intercalated cells, as well as in the thick ascending limb of the loop of Henle [10]. In addition to type A intercalated cells, the a4 subunit is also expressed in proximal tubule cells and loop of Henle. Homozygous or compound heterozygous mutations in these subunits result in dRTA and a single-nucleotide polymorphism (SNP, c.481G>A; p.E161K) in *ATP6V1B1* has been reported to increase the risk of developing nephrolithiasis and nephrocalcinosis when compared with unaffected controls [11]. Clinically, recessive dRTA usually manifests during infancy or childhood. The majority of patients develop progressive sensorineural deafness and some patients may also show abnormal widening of the vestibular aqueduct [12]. Nephrolithiasis and nephrocalcinosis are very common and may be evident from early childhood. Recent data indicate differences in phenotype depending on the affected subunit. Experiments in a4 deficient mice have described proximal tubular dysfunction with impaired endocytosis, low molecular weight (tubular) proteinuria (LMWP), phosphaturia and accumulation of lysosomal material in proximal tubule cells [13]. These novel findings may indicate an important contributory role of the proximal tubule in the pathogenesis of dRTA. Treatment consists mainly of alkali supplementation; however, no beneficial effect of alkali has been demonstrated for nephrocalcinosis or deafness [14].

SLC4A1

SLC4A1 encodes the chloride bicarbonate exchanger AE1 (Anion exchanger 1, Band 3) located on the basolateral membrane of type A intercalated cells. AE1 exchanges intracellular bicarbonate for chloride, transferring newly generated bicarbonate into blood [15]. In Caucasians AE1 mutations causing dRTA are mainly autosomal dominant. Interestingly, AE1 is also expressed in erythrocytes, and autosomal recessive mutations in

AE1 have been shown to cause Southeast Asian Ovalocytosis, Hereditary Spherocytosis, and dRTA [15]. However, the disease manifestation is usually renal or haematological, and in only rare cases patients can present with a combined renal and haematological phenotype. Interestingly, the haematological phenotype is improved by alkali therapy [16].

Inherited combined proximal and distal renal tubular acidosis

Carbonic anhydrase II

Carbonic anhydrases (CA) are zinc metalloenzymes that catalyze the bi-directional interconversion of carbon dioxide and water to HCO_3^- and H^+. Several isoforms of CA are expressed in the human kidney: CA II is the most abundant kidney isoform and the only isoform present in osteoclasts [17]. CA II is expressed in all nephron segments and autosomal recessive mutations result in a combined proximal and distal form of RTA. The prevalence of CA II deficiency is very high in Arabic patients due to a splice junction mutation [18]. As well as RTA, the clinical phenotype can include osteopetrosis, cerebral calcification, facial dysmorphism with low set ears, hypertelorism, and a depressed nasal bridge plus mild conductive hearing loss [17]. RTA is characterized by defective urinary acidification and additional urinary bicarbonate loss, resulting in kidney stone formation or nephrocalcinosis [19]. In contrast, mutations in *SLC4A4* encoding for NBCe1 (the proximal tubule basolateral electrogenic sodium bicarbonate co-transporter) cause isolated proximal RTA and ocular abnormalities without nephrolithiasis or nephrocalcinosis [20].

Mutations of renal sodium phosphate co-transporters

SLC34A3 (Hereditary Hypophosphatemic Rickets with Hypercalciuria, HHRH)

SLC34A3 (solute carrier family 34, member 3) encodes the sodium-dependent phosphate co-transporter 2c (NPT2c), which is located in the proximal tubule and mediates phosphate reabsorption across the apical brush border membrane [21]. Homozygous or compound heterozygous mutations of *SLC34A3* cause hereditary hypophosphatemic rickets with hypercalciuria (HHRH), which is characterized by hypophosphatemia from increased renal phosphate losses, hypercalciuria, elevated $1,25(OH)_2$-vitamin D levels, and rickets [22,23]. A genetic diagnosis of this form of rickets, which is vitamin D-resistant, is important so as to avoid unnecessary treatment with vitamin D, which risks causing hypercalcaemia, hypercalciuria, nephrocalcinosis, renal stones and renal failure.

A recent study of 133 individuals from 27 kindreds, with known and novel mutations of *SLC34A3* has found a significantly increased risk for nephrolithiasis or nephrocalcinosis in homozygous mutants when compared with their healthy relatives carrying the wild type allele or the general population (46% vs. 6% vs. 5.64%) [24]. Also, a small genome-wide

association study (GWAS) identified SLC34a3 as a locus for hypercalciuric kidney stone disease [25]. Heterozygous *SLC34A3* mutation carriers can present with isolated hypercalciuria similar to patients with so-called idiopathic hypercalciuria (IH). However, the biological and clinical significance of heterozygous mutations, which are quite frequent, is still unknown. Thus, future studies will be necessary to understand the contribution, if any, of heterozygous mutations to the risk of kidney stone disease. Treatment of HHRH with oral phosphate can reverse hypophosphatemia, hypercalciuria, and cure bone disease, but can overshoot and stimulate PTH secretion, which needs to be monitored.

SLC34A1

SLC34A1 (solute carrier family 34, member 1) encodes for the sodium-dependent phosphate co-transporter 2a (NPT2a), which is expressed mainly in the kidney proximal tubule, and like SLC34A3 is responsible for renal phosphate reabsorption [21]. Only a few patients have been reported with mutations in the *SLC34A1* gene presenting with nephrolithiasis and hypophosphatemia caused by a renal phosphate leak (Hypophosphatemic nephrolithiasis/osteopetrosis-1 and Fanconi renotubular syndrome-2) [26-28]. However, experiments using the reported NPT2a mutations (Single nucleotide changes resulting in missense mutations -A48F and V147M- with a dominant effect) expressed in Xenopus oocytes and renal OK cells could not confirm any changes in transporter expression or substrate affinity, and only showed lower transport activity [29]. Furthermore, polymorphisms in the *SLC34A1* gene seem to be quite frequent without affecting renal phosphate excretion in many individuals [30]. Conversely, expression of an in-frame duplication of 21 bp in Xenopus oocytes and renal OK cells resulted in elimination of phosphate transport capacity. This mutation was previously reported in siblings from a consanguineous family suffering from hypophosphatemia and hypercalciuria due to a secondary increase in 1,25-$(OH)_2$-Vit. D levels [28]. Furthermore, a very recent study investigated relatives of a 16.5 year-old boy with nephrocalcinosis and chronic kidney disease (CKD), but with no bone disease. Genetic testing revealed a homozygous missense mutation in SLC34A1[31]. However, out of 6 heterozygous carriers of this mutation, only 2 presented with kidney stones, and one individual with kidney stones carried two wild-type SLC34A1 alleles. Thus, the biological and clinical significance of SLC34A1 mutations (heterozygous or homozygous) in the context of kidney stone disease remains uncertain.

CYP24A1 (Idiopathic Infantile Hypercalcaemia)

1,25-$(OH)_2$-24-Hydroxylase (CYP24A1) is a mitochondrial cytochrome P-450 enzyme mainly present in kidney and intestine. CYP24A1 protects against Vitamin D toxicity by inactivating both, 25-OH- (calcidiol) and 1,25-$(OH)_2$-Vit. D (calcitriol). Homozygous inactivating mutations

of CYP24A1 gene lead to increased 1,25-$(OH)_2$-Vit. D and cause idiopathic infantile hypercalcemia (Lightwood syndrome), a rare autosomal recessive disease manifesting since the first months of life and characterized by severe hypercalcemia, low PTH, nephrocalcinosis, nephrolithiasis and renal failure [32].

Recently described cases have expanded the phenotypic spectrum of disorders due to loss of function mutations of *CYP24A1* to cases with recurrent nephrolithiasis starting in early adulthood, with hypercalciuria, and serum calcium mildly or intermittently increased. Carriers of the mutated *CYP24A1* gene may have high or borderline elevated 1,25-$(OH)_2$-Vit. D levels, hypercalciuria, and kidney stones [32-35]. In addition, the frequency of homozygosity for mutated *CYP24A1* in the general population was predicted to be 4-20% according to dbSNP (NCBI-Single Nucleotide Polymorphism Database) suggesting a causative role for *CYP24A1* in the formation of calcium-containing renal stones in a significant proportion of the population [36]. Interestingly some data even suggest that patients with mutations in *CYP24A1* can develop CKD [32,33]. Mutations in *CYP24A1* should be considered in patients with kidney stones and idiopathic hypercalciuria, especially if hypercalcemia with suppressed PTH is noted. The disease is treated by reducing calcium load (low calcium diet, low vitamin D intake and oral sodium cellulose phosphate), and -in severe cases- with ketoconazole to inhibit 25-OH-Vitamin D-1α-hydroxylase.

Disorders of the Calcium Sensing Receptor

Familial hypocalciuric hypercalcemia (FHH, familial benign hypercalcemia) is an autosomal-dominant disease caused by mutations in 3 different genes: i) inactivating mutations of the calcium sensing receptor (*CASR*) gene (FHH type 1, most common type); ii) loss-of-function mutations of AP2S1 that encodes the adaptor-related protein complex 2, σ-2 subunit (FHH type 2); and iii) GNA11 that encodes the $G_{\alpha 11}$ protein (FHH type 3) [37]. FHH is characterized by mild hypercalcemia, low or normal PTH levels, a urinary calcium to creatinine ratio (CCCR) <0.01, and a benign clinical course. Recent studies have highlighted the importance of FHH as a differential diagnosis for primary hyperparathyroidism (pHPT) with significant overlap in the phenotype [38,37]. Interestingly, a recent study from Italy has described the prevalence of kidney stones in up to 3 out of 13 (23%) patients with *CASR* mutations or polymorphisms previously selected for genetic testing based on clinical and biochemical feature compatible with FHH [38]. It is difficult to explain the lithogenic role of loss of function mutations of the CASR gene especially in view of the associated hypocalciuria. Confirmation of the association with nephrolithiasis in larger cohorts is needed.

Activating mutations of the gene for the CASR extracellular domain lead to autosomal dominant hypocalcemia with hypercalciuria [39]. Clinical manifestations mirror

hypoparathyroidism, with mild, asymptomatic hypocalcemia and marginally high phosphatemia but with low-normal serum PTH. Hypercalciuria results from inhibition by CASR of both active and passive calcium reabsorption in the thick ascending limb of Henle's loop. However, this is a very rare condition and to our knowledge the association with renal stones has not been reported.

Nevertheless, other interesting studies suggest a role of the *CASR* gene in nephrolithiasis. A GWAS of 106,856 Icelanders, including 2,636 individuals with a history of kidney stones, identified sequence variants in *CASR* and a suggestive association with kidney stones [40]. These variations in intron 1 may decrease the transcriptional activity of the *CASR* gene promoter 1 and the expression of the CaSR protein in the kidney, as previously described for two single nucleotide polymorphisms in normocitraturic stone formers by Vezzoli et al. [41], and thereby change the response of the CaSR to extracellular calcium. Consequently, impaired distal urinary acidification and reduced dilution capacity may result in stone formation [41,38,42].

SLC22A12/SLC2A9 (Hereditary renal hypouricemia, RHUC)

Hereditary renal hypouricemia is caused by recessive mutations in two different genes, *SLC22A1* and *SLC2A9*, encoding the proximal renal tubular urate transporter 1, URAT1, and what was originally thought to be a glucose transporter, GLUT9, respectively [43]. However, GLUT9 belongs to the family of GLUT proteins that mediate transepithelial transport of monosaccharides and represents the only member that also and preferentially transports urate. Transcellular urate transport is via the apical reabsorption of urate by URAT1, followed by basolateral urate exit via GLUT9. Loss-of-function mutations in *SLC22A1* affect the majority of patients with RHUC. The phenotype is variable and includes asymptomatic patients and patients with uric acid nephrolithiasis or exercise-induced acute kidney injury (AKI). Patients with homozygous GLUT9 mutations present with more pronounced hypouricemia and are more prone to nephrolithiasis, and AKI after exercise. However, the underlying mechanism for AKI is still unknown; mechanisms such as urate nephropathy or increased oxidative stress during exercise with renovascular spasm and vasoconstriction leading to renal tissue damage have been proposed [44,43]. Typical histological and imaging findings of repeated vasoconstriction in kidney biopsies from patients with *GLUT9* mutations are supportive of the oxidative stress/vasoconstriction hypothesis [45,43]. Therapy consists of adequate fluid intake during exercise and, interestingly, allopurinol, which has been reported to be beneficial by reducing the load of filtered urate [46], but may also have something to do with its intrinsic antioxidant properties. Better-targeted therapies for these patients are needed, since they are at increased risk of developing ESRD as a result of recurrent episodes of AKI.

CLCN5/OCRL1 (Dent Disease and Lowe Syndrome)

X-linked mutations in *CLCN5* cause Dent disease (or Dent disease type 1) that is characterized by low molecular weight proteinuria, hypercalciuria, nephrolithiasis and nephrocalcinosis with renal impairment progressing to ESRD in many patients [47]. Some patients may also present with hypophosphatemic rickets or osteomalacia, and even a more generalized proximal tubular dysfunction (e.g., Fanconi syndrome). *CLCN5* encodes for the renal chloride/proton exchanger ClC-5 and plays an important role in receptor-mediated endocytosis [48]. The cause of ESRD in Dent disease is not fully understood, and is not inevitable and, surprisingly, does not correlate with the degree of nephrocalcinosis present. Interestingly, kidney biopsies of asymptomatic patients show a focal segmental glomeruloscerosis (FSGS) pattern in a substantial number [49]. Female carriers can rarely present with the same phenotypic characteristics as males, but only one female case has been reported to develop ESRD [50].

Mutations in *OCRL1* cause Lowe syndrome (or Dent disease type 2), a disease with a similar renal phenotype to Dent disease 1, but with additional multi-system clinical manifestations, including mental retardation, cataracts, and epilepsy. OCRL1 encodes for the inositol polyphosphate 5-phosphatase OCRL-1 and is involved in several cellular processes including control of endocytic recycling, endosome-to-Golgi transport, and early endocytosis. Recently, OCRL1 has also been described to be crucial for the response of lysosomes to the autophagic cargo [51]. Thus, defective OCRL1 leading to impaired autophagic flux may underlie progressive kidney dysfunction in Lowe syndrome. Diagnosis is based on the presence of low-molecular weight proteinuria, hypercalciuria and at least one of the following: nephrocalcinosis, kidney stones, hypophosphatmia, microhematuria, and renal failure. The diagnosis is supported by a history of X-linked inheritance of nephrolithiasis and renal failure and is confirmed by the identification of mutations in either the *CLCN5* gene (Dent disease 1) or the *ORCL1* gene (Dent disease 2). Thiazide diuretics may be effective in treating hypercalciuria[52]. In ClC-5-deficient mouse model a high citrate diet seems to delay progression of renal disease [53].

CLDN14

CLDN14 encodes for Claudin-14, a member of the claudin family that is expressed at epithelial tight junctions in the thick ascending limb of the loop of Henle [54]. Claudin-14 is involved in the paracellular transport of ions and small solutes, and variants in CLDN14 have been associated with kidney stones and reduced bone mineral density (BMD)[55]. Furthermore, the *CLDN14* SNP rs113831133 has been reported to be associated with lower

urinary calcium excretion, suggesting that Claudin-14 is involved in controlling renal calcium excretion [56]. Interestingly, a second variant, rs219780, which is very common in the general population, has been identified as a risk variant with 1.64x greater risk for kidney stone formation [55]. However, genetic validation studies in larger sample sets will be necessary to confirm the role of Claudin-14.

CLDN16/CLDN19 (Familial hypomagnesemia with hypercalciuria and nephrocalcinosis, FHHNC)

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive disease caused by mutations in *CLDN16* or *CLDN19*. Claudin-16 and -19 are expressed in the thick ascending limb of the loop of Henle and mediate the paracellular reabsorption of calcium and magnesium [57,58]. FHHNC patients develop CKD in early childhood and adolescence due, in part, to hypercalciuria, kidney stones and nephrocalcinosis [57]. Other disease manifestations include seizures, muscular tetany, failure to thrive, ocular abnormalities, increased PTH levels, recurrent urinary tract infections (UTI) (a likely actor in CKD progression), incomplete dRTA, and hypocitraturia [57,59]. In contrast to patients with Dent disease, progression to ESRD correlates with the severity of nephrocalcinosis and appears to be predicted by the genotype. Of note, healthy family members may also be significantly affected by hypercalciuria, UTI and kidney stones [59]. There is no effective therapy for FHHNC. Magnesium supplements are necessary to correct hypomagnesemia, but have not been shown to be beneficial and have no long-term effect on calcium excretion [59]. Treatment with thiazide diuretics can reduce calciuria in the short-term in patients with *CLDN16* mutations [60]. No treatment has been shown to delay CKD progression. When ESRD is reached, kidney transplantation is the treatment of choice, and normalises renal magnesium and calcium handling.

Primary hyperoxalurias

Primary hyperoxaluria (PH) is caused by recessive mutations in different hepatic enzymes resulting in endogenous accumulation of oxalate with subsequent hyperoxaluria. So far, three different genes have been identified to cause PH, namely *AGT*, *GRHPR*, and *HOGA1* [61], although other genes encoding proteins involved in glyoxylate metabolism have been postulated [62].

AGXT (Primary hyperoxaluria type 1, PH1)

PH1 is the most common type of primary hyperoxalurias and is caused by recessive mutations in the *AGXT* gene encoding for the liver-specific peroxisomal enzyme alanine glyoxylate aminotransferase (AGT). AGT catalyzes the transamination of glyoxylate to

glycine and lack of AGT or loss of activity result in over-production of oxalate and glycolate. More than 170 mutations have been identified to cause PH1 [61]. Interestingly, some mutations (Gly170Arg and Phe15Ile) have been demonstrated to be pyridoxine-sensitive, while other genotype-phenotype relationships have not been described as yet [63]. Moreover, siblings with the same genotype may present with a different clinical course[63]. Renal manifestations usually include recurrent kidney stones or nephrocalcinosis progressing to ESRD between 20 and 30 years of age in the majority of patients [61]. In addition, other organs may be involved by systemic deposition of oxalate crystals in bone, heart, and skin. Increased urinary excretion of oxalate (> 1 mmol/24h) with calcium oxalate monohydrate kidney stones and impaired renal function are highly suggestive of PH1, and diagnosis can be confirmed by genetic testing. Detection of oxalate crystals in kidney biopsy tissue or elevated urinary glycolate levels are also indicative of PH1 [61]. Supportive treatment includes high oral fluid intake, alkali citrate, and pyridoxine in a subset of patients with pyridoxine-sensitive mutations. As to renal replacement therapy, in adults hemodialysis should be initiated in ESRD or in CKD if there are signs of systemic oxalosis [61]. Since there is an increased risk of systemic oxalosis at the start of renal replacement therapy, daily dialysis sessions are recommended to increase dialysis efficiency and maximise oxalate removal. Also, a combination of peritoneal dialysis with hemodialysis may be considered in cases with inadequate oxalate removal (plasma oxalate levels > 30 µmol/L at the end of each dialysis session) or with a high risk of systemic oxalosis [61]. Currently, the only curative therapy for PH1 is pre-emptive liver transplantation or sequential or combined liver and kidney transplantation, the latter being the preferred method in the majority of the patients. Fortunately, there is some light at the end of the tunnel with several new therapeutic developments in the pipeline, including gene therapy, hepatocyte transplantation, substrate reduction therapy via RNAi, and AGT chaperone treatment [64,61].

GRHPR (Primary hyperoxaluria type 2, PH2)

PH2 is caused by recessive mutations in the *GRHPR* gene encoding for the ubiquitously expressed glyoxylate reductase/hydroxypyruvate reductase (GRHPR) enzyme [61]. GRHPR is primarily expressed in the liver and mutations result in over-production of both oxalate and L-glyceric acid. PH2 patients present with recurrent urolithiasis, but in contrast to PH1, their clinical course is less severe with only a minority of patients developing CKD and ESRD. In addition to increased urinary oxalate levels, L-glycerate excretion may also be increased in PH2 patients [61]. As for PH1 and especially after exclusion of PH1, genetic testing for PH2 should be performed to confirm diagnosis. Conservative treatment is similar to PH2, except for pyridoxine administration (unresponsive). The current treatment of choice is isolated kidney transplantation; however, the less severe course of PH2 means that only a few

patients have required transplantation, although immediate recurrence with subsequent rapid graft loss has been reported in one patient [65,64,61,66].

HOGA1 (Primary hyperoxaluria type 3, PH3)

Mutations in the liver-specific mitochondrial 4-hydroxy-2-oxoglutarate aldolase (*HOGA*) enzyme have been described recently to cause PH3 [61]. HOGA plays an important role in hydroxyproline metabolism and is thought to generate excess oxalate; however, the exact mechanism of increased oxalate production in PH3 has not been completely elucidated. Of the PH subtypes, PH3 has the mildest phenotype and patients typically present with recurrent kidney stones early in life. Interestingly, in addition to hyperoxaluria, significant hypercalciuria and increased uric acid excretion have been observed in PH3 patients [67,68]. Interestingly, the clinical course can improve over time and no cases of PH3 patients with ESRD have been reported [69]. The presence of HOG precursors, in addition to hyperoxaluria and hypercalciuria, is suggestive of PH3, which can be confirmed by genetic testing. To date there are no specific treatment recommendations -though a low animal protein diet has been suggested- and no guidelines for renal replacement therapy or transplantation in PH3.

The 'newest kid on the block': SLC26a1

SLC26A1 (SAT1, solute carrier family 26 member 1) was initially cloned as a sulphate transporter in the liver and functions as an electroneutral anion exchanger that exchanges sulphate for bicarbonate or oxalate, as well as oxalate for bicarbonate [2]. In the kidney SlC26a1 is located in the proximal tubule and *Slc26a1* deficient mice are hyposulphatemic, with increased urinary sulphate excretion, and calcium oxalate kidney stones if hyperoxaluria is also present. A recent study has identified recessive mutations in *SLC26A1* in 2 unrelated individuals with calcium oxalate kidney stones [2]. Experimental data have shown that mutations in *SLC26A1* result in decreased transporter activity and nephrolithiasis. Notably, another member of the SLC26 family, namely *SLC26A6* has also recently been described to be potentially associated with calcium oxalate kidney stones [70]. These data are supported by previous animal studies that demonstrated that mice deficient for *SLC26A6* suffer from hyperoxaluria with a high incidence of calcium oxalate urolithiasis [71].

Conclusion

There is no short cut to diagnosing genetic forms of nephrolithiasis. It is still crucial to take a family history and thoroughly investigate patients for the clinical manifestations of inherited disorders. Pointers to inherited disease in renal stone patients are many, for example, early age of onset, family cases, consanguineous parents, highly-active and

recurrent stone disease, associated nephrocalcinosis, renal hyperechogenicity, associated tubular dysfunction and related manifestations (short stature, growth retardation, polyuria, bone disorders), renal failure and extra-renal manifestations such as sensorineural hearing defects, ocular abnormalities, and neurological disorders [72].

Disclosures

All authors have nothing to disclose.

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Table

Table 1: Summary of genes associated with kidney stones and disease characteristics

Gene	*Disease*	*Typical laboratory findings*	*Typical clinical features*	*Treatment*
SLC7a9 *SLC3a1*	Cystinuria	Increased urinary cystine excretion or excretion of dibasic amino acids	Cystine stones, nephrocalcinosis	Hydration, urinary alkalinization, salt restriction, drugs that reduce cystine to cysteine, such as D-penicillamine, tiopronin, or captopril
APRT		DHA crystals in the urine (round and reddish-brown with a central Maltese cross pattern)	crystalluria and recurrent kidney stones; progressive loss of renal function	Dietary purine restriction, allopurinol
ATP6V0a4 *ATP6V1B1*	Autosomal recessive dRTA	Non-anion gap metabolic acidosis, alkaline urine pH, hypokalemia, hypercalciuria	Calcium phosphate stones, nephrocalcinosis, sensorineural hearing loss, failure to thrive, rickets, additional proximal tubular dysfunction in patients with ATP6V0a4 mutations	Alkali therapy with potassium citrate and/or sodium bicarbonate
SLC4a1	Autosomal dominant dRTA	Non-anion gap metabolic acidosis, alkaline urine pH, hypokalemia, hypercalciuria	Nephrocalcinosis, autosomal recessive mutations cause Southeast Asian Ovalocytosis, Hereditary Spherocytosis, and dRTA	Alkali therapy with potassium citrate and/or sodium bicarbonate
CAII	Proximal and distal renal tubular acidosis	Non-anion gap metabolic acidosis, bicarbonaturia	Nephrocalcinosis, kidney stones, osteopetrosis, cerebral calcification, mental retardation, facial dysmorphism and mild conductive hearing loss	Alkali therapy with potassium citrate and/or sodium bicarbonate
SLC34a1	Hypophosphatemic nephrolithiasis/osteopetrosis-1 and Fanconi renotubular syndrome-2	Hypophosphatemia, hyperphosphaturia, hypercalciuria, elevated $1,25(OH)_2$-vitamin D levels	Nephrolithiasis, osteopetrosis, nephrocalcinosis, potentially CKD	Phosphate supplementation

SLC34a3	HHRH	Hypophosphatemia, hyperphosphaturia, hypercalciuria, elevated 1,25$(OH)_2$-vitamin D levels	Nephrolithiasis, nephrocalcinosis, rickets	Phosphate supplementation
CYP24a1	Idiopathic infantile hypercalcemia	Hypercalcemia, elevated 1,25-$(OH)_2$-Vit. D levels, hypercalciuria	Nephrolithiasis, nephrocalcinosis, failure to thrive, disease can be unmasked after vitamin D (calcidiol) administration, patients may develop CKD	Diuretics, corticosteroids, bisphosphonates, vitamin D withdrawal
CasR *AP2S1* *GNA11*	FHH	Mild hypercalcemia, normal to slightly elevated PTH levels, CCCR < 0.01	May mimick primary hyperparathyroidism	Adequate fluid intake
SLC22a12 *SLC2a9*	RHUC	Hypouricemia, hyperuricosuria	Nephrolithiasis, exercise-induced AKI, patients may develop ESRD after recurrent AKIs	Adequate fluid intake during exercise, allopurinol
CLCN5	Dent disease	LMWP, Fanconi syndrome	Nephrolithiasis, nephrocalcinosis, CKD with progression to ESRD	Isolated kidney transplantation
OCRL1	Lowe syndrome	LMWP, Fanconi syndrome	Nephrolithiasis, nephrocalcinosis, CKD with progression to ESRD, mental retardation, cataract, and epilepsy	Isolated kidney transplantation
CLDN16 *CLDN19*	FHHNC	Hypomagnesemia, hypercalciuria, increased PTH levels, incomplete distal renal tubular acidosis, hypocitraturia	Nephrocalcinosis progressing to CKD/ESRD, seizures, muscular tetany, failure to thrive, ocular abnormalities, recurrent UTI	Isolated kidney transplantation
CLDN14		Hypercalciuria	Nephrolithiasis, reduced BMD	No specific recommendations available yet
AGXT	PH1	Hyperoxaluria, increased urinary excretion of glycolate	Calcium oxalate monohydrate stones, development of CKD with progression to ESRD in the second	Hydration, urinary alkalinization, pyridoxine in selected patients, combined liver and kidney

			or third decade of life, risk of systemic oxalosis involving bone, skin, heart etc.	transplantation
GRHPR	PH2	Hyperoxaluria, increased urinary excretion of L-glyceric acid	Calcium oxalate monohydrate stones, few cases reported with CKD/ESRD	Hydration, urinary alkalinization, isolated kidney transplantation
HOGA1	PH3	Hyperoxaluria, hypercalciuria, hyperuricosuria	Calcium oxalate monohydrate stones mild clinical course	
SLC26a1		Hyperoxaluria	Calcium oxalate stones, nephrocalcinosis	No specific recommendations available yet