Genetics of kidney stone disease

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Abstract |

Kidney stone disease (nephrolithiasis) is a common problem that can be associated with alterations in urinary solute composition including hypercalciuria. Studies suggest that the prevalence of monogenic kidney stone disorders, including renal tubular acidosis with deafness, Bartter syndrome, primary hyperoxaluria, and cystinuria, in patients attending kidney stone clinics is ~15%. However, for the majority of individuals, nephrolithiasis has a multifactorial aetiology involving genetic and environmental factors. Nonetheless, the genetic influence on stone formation in these idiopathic stone formers remains considerable and twin studies estimate a heritability of >45% for nephrolithiasis and >50% for hypercalciuria. The contribution of polygenic influences from multiple loci have been investigated by genome-wide association and candidate gene studies, which indicate that a number of genes and molecular pathways contribute to the risk of stone formation. Genetic approaches, studying both monogenic and polygenic factors in nephrolithiasis, have revealed that the following have important roles in the aetiology of kidney stones: transporters and channels; ions, protons and amino acids; the calcium-sensing receptor (a G-protein-coupled receptor) signalling pathway; and the metabolic pathways for vitamin D, oxalate, cysteine, purines and uric acid. These advances, which have increased our understanding of the pathogenesis of nephrolithiasis, will hopefully facilitate the future development of targeted therapies for precision medicine approaches in patients with nephrolithiasis.

[H1] Introduction

Kidney stone disease is a major clinical and economic health burden, affecting >15% of men and >5% of women by 70 years of age[1]. It results in >80,000 hospital episodes each year in the UK and data from the United States suggests that its prevalence has increased from 3.8% in 1976-1980 to 8.8% in 2007-2010[1–3]. Unfortunately, kidney stones are commonly recurrent with up to 50% of individuals experiencing a second episode within 10 years of their initial presentation and treatment for recurrent stone disease has been linked to a decline in renal function[4,5].

Stones that form in the kidney (FIG. 1) most commonly comprise calcium oxalate (~65%) but can also contain calcium phosphate (~10%), uric acid (~15%), magnesium ammonium phosphate (~10%), cystine (~1%), 2,8-dihydroxyadenine (<1%), xanthine (<1%), or excreted drugs such as indinavir (<1%)[6–10]. The composition of kidney stones shows worldwide geographical variation and although the proportion of calcium oxalate stones has been reported to be relatively consistent between countries, magnesium ammonium phosphate stones, which are associated with infection, are more frequent in Sub-Saharan Africa than in more developed regions[11]. Stones form in the urine when the relative concentrations of lithogenic substances, such as calcium or oxalate, are imbalanced with the concentrations of inhibitors of stone formation, such as citrate or magnesium, **[Au: Edit OK?]** resulting in crystal precipitation and aggregation[10]. Unsurprisingly, therefore, nephrolithiasis is often associated with metabolic abnormalities of urinary solute concentration or decreased urinary solubility; these abnormalities include hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, cystinuria, low urinary volume and defects in urinary acidification[8,12].

The aetiology of kidney stone disease and associated metabolic abnormalities is multifactorial, involving genetic and environmental factors. A family history of nephrolithiasis is present in 35–65% of individuals with kidney stones, whereas only 5–20% of non-stone-forming populations have a family history of this disorder[13,14]. Furthermore, twin studies have reported the heritability of kidney stone disease and urinary calcium excretion to be >45%[15–17] and individuals with a

strong family history of urolithiasis, including a parent and two siblings, have a standard incidence ratio for stone formation of >50[18]. In the majority of patients, the genetic factors and pathophysiology of kidney stones are poorly understood, although in some cases, a monogenetic disorder such as primary hyperoxaluria accounts for the observed phenotype.

In the past 5 years, studies have highlighted the clinical importance of investigating patients for genetic causes of kidney stone disease and reported that >15% of patients in specialist kidney stone clinics and ~30% of recurrent stone formers under the age of 25 years have a monogenetic molecular diagnosis[19–21]. In addition, studies of large populations, using genome-wide association studies (GWASs) and candidate gene analysis approaches, have provided insights into the common genetic variants and molecular pathways that contribute to the risk of stone formation.

This Review briefly outlines general approaches for stone prevention, describes our current understanding of the genetic influences underlying kidney stone formation and discusses the implications of a correct diagnosis on the clinical management of recurrent stone formers.

[H1] General stone prevention strategies

Guidelines from the European Association of Urology (EAU), American Urological Association (AUA), and The National Institute for Health and Care Excellence (NICE) recommend that all patients who have had an upper urinary tract calculus should be screened for hypercalcaemic disorders with measurement of serum calcium[22–24]. The AUA and EAU guidelines also suggest measurement of serum uric acid to exclude hyperuricaemia[22,23]. Individuals with recurrent stone disease, malabsorptive intestinal disorders, medical conditions predisposing to stone formation, an early age of onset of kidney stones, and those with a family history of nephrolithiasis should be considered to be at high risk of further stone formation[22,23] . For these high risk patients, the EAU and AUA guidelines advise metabolic screening with additional blood tests and a 24-hour urine collection to assess urinary excretion of calcium, oxalate, uric acid, citrate, magnesium,

inorganic phosphate, and cystine along with urinary pH and urinary volume (Box 1)[22,23]. In addition, analysis of stone composition can provide important information regarding the underlying diagnosis (Box 1)[23].

Regardless of individual risk factors, all patients are advised to increase their daily fluid intake[25], reduce animal protein consumption, and increase dietary fresh fruit and fibre[26]. Reduced oxalate intake is recommended in order to prevent a high urinary oxalate load[23]. Calcium intake should not be restricted[27], although calcium supplementation is discouraged except in patients with enteric hyperoxaluria[28]. In addition, sodium intake should be restricted as a high sodium intake can result in increased urinary calcium excretion and a reduction in urinary citrate excretion[29] (Box 1).

Other strategies aimed at preventing stone recurrence are individualized on the basis of the patient's underlying diagnosis and the results of a metabolic assessment. For those with acidic urine, with or without hypocitraturia, alkaline citrates or sodium bicarbonate will achieve alkalinization and, therefore, decrease the risk of calcium oxalate and uric acid stone formation [22]. However, caution should be employed as a high urinary pH will encourage calcium phosphate stone formation[22]. Thiazide diuretics are effective in reducing urinary calcium excretion although their precise mechanism of action remains unclear[30]. For hyperuricosuric individuals, xanthine oxidase inhibitors such as allopurinol or febuxostat can be beneficial[22].

[H1] Monogenic disorders of nephrolithiasis

The monogenetic disorders of nephrolithiasis can be classified into two categories: disorders associated with calcium-containing stones —which are radiopaque on plain abdominal X-ray — and disorders associated with stones that do not contain calcium and either demonstrate poor radiopacity or are radiolucent (Supplementary Table 1, FIG. 1).

[H2] Disorders of calcium nephrolithiasis

The disorders of calcium nephrolithiasis include autosomal dominant idiopathic hypercalciuria, autosomal dominant hypocalcaemia, Bartter syndrome, Dent disease, hereditary hypophosphataemic rickets with hypercalciuria, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, distal renal tubular acidosis, infantile hypercalcaemia, and primary hyperoxaluria (Table 1, Supplementary Table 1).

[H3] Autosomal dominant idiopathic hypercalciuria

Hypercalciuria is defined as a urinary calcium excretion of >0.1mmol/kg per 24 hours or >4mg/kg per 24 hours[31] and is the most common metabolic abnormality detected in stone formers[10]. Idiopathic hypercalciuria can be inherited as a monogenic disorder with an autosomal dominant pattern, or as part of a polygenic trait. Increased urinary calcium excretion can be caused by excess absorption (absorptive idiopathic hypercalciuria (AIH)) or by renal calcium leak. Patients with idiopathic hypercalciuria are normocalcaemic with normal parathyroid hormone (PTH) concentrations, but often have a low bone mineral density[10]. To date, two genes — adenylate cyclase 10 (*ADCY10*) and vitamin D receptor *(VDR)* — have been reported to be implicated in the aetiology of AIH[32,33]. Genetic linkage studies in three families with autosomal dominant AIH mapped the disease locus to chromosome 1q23.3-q24, which contains the *ADCY10* gene that encodes a divalent cation and bicarbonate sensor (Supplementary Table 1)[32]. DNA sequence analysis of *ADCY10* identified six sequence variations in patients with AIH, four of which were associated with a significantly increased relative risk of AIH 2.2-3.5-fold increased risk of AIH ($P<0.02$)[34]. Additional putatively deleterious alleles have since been identified in hypercalciuric stone formers[19,21].

In other genetic linkage studies of French-Canadian families with kidney stone disease and idiopathic hypercalciuria, the locus was located to 12q12-q14, which contains the *VDR* gene (Supplementary Table 1)[33]. Heterozygous variants in *VDR* have also been identified in two hypophosphataemic stone-forming patient. Hypercalciuria was not described in these two patients, however it is unclear whether this was formally assessed[21]. A locus for autosomal

dominant hypercalciuria and nephrolithiasis has been mapped by linkage studies of a Spanish kindred to chromosome 9q33.2-q34.2 (Supplementary Table 1); this region contains approximately 170 genes, and to date, the gene causing this form of idiopathic hypercalciuria has not been identified[35].

[H3] Autosomal dominant hypocalcaemia

Autosomal dominant hypocalcaemia (ADH) is caused by heterozygous gain-of-function mutations in components of the calcium-sensing receptor (CaSR) signalling pathway, resulting in an increased sensitivity of the CaSR to alterations in extracellular calcium concentration[36,37]. *In vitro* expression analyses of ADH-associated mutants have demonstrated that the extracellular calcium concentration required to elicit a half-maximal (EC_{50}) increase in intracellular responses is lower than that required in cells expressing wild-type components[36–39]. ADH type 1 is caused by mutations in the G-protein-coupled CaSR and ADH type 2 is caused by mutations in the G-protein subunit signalling partner, Gα11 encoded by *GNA11* (Supplementary Table 1)[36,37]; in ~30% of ADH cases, the underlying molecular abnormality is unknown[40]. The majority of individuals with ADH have mild hypocalcaemia and are asymptomatic, but some experience carpopedal spasms and seizures.

In patients with ADH, hypocalcaemia is coupled with serum PTH concentrations that are inappropriately low, serum phosphate concentrations that are elevated or in the upper-normal range, and serum magnesium concentrations that are either in the low or low-normal range[36,37]. Hypercalciuria is present in ~10% of patients, putting these individuals at increased risk of developing kidney stones[41]. Treatment with active metabolites of vitamin D can precipitate hypercalciuria, nephrocalcinosis, nephrolithiasis, and renal impairment and should, therefore, be avoided in patients with ADH[36].

[H3] Bartter syndrome

Bartter syndrome is a renal tubulopathy characterized by hypokalaemic alkalosis, hypotension, hyper-reninaemic hyperaldosteronism, increased urinary prostaglandin excretion, and hypercalciuria with nephrocalcinosis, and is caused by defective sodium chloride reabsorption in the loop of Henle[42,43]. To date, mutations in six genes have been described to result in this phenotype. Bartter syndrome type I is caused by mutations in the gene encoding the bumetanide-sensitive sodium–potassium–chloride cotransporter (*NKCC2*; also known as *SLC12A1*); type II is caused by mutations in the gene encoding the renal outer-medullary potassium channel (*ROMK*; also known as *KCNJ1*); type III is caused by mutations in the gene encoding the voltage-gated chloride channel ClC-Kb (*CLCNKB*); type IV is caused by mutations in the gene encoding Barttin (*BSND*); type V is caused by mutations of gene encoding the CaSR (*CASR*); and type VI has been described in one child with a mutation in the *CLCN5* gene that encodes chloride channel protein 5 (ClC-5; also known as H^+/Cl^- exchange transporter 5) (FIG. 2)[42–44]. Types I–IV are autosomal recessive in inheritance, and type IV is associated with deafness owing to the expression of Barttin, a beta subunit required for the trafficking of CLC-Kb and CLC-Ka, in the potassium-secreting marginal cells of the scala media of the inner ear[45]. Type V Bartter syndrome displays an autosomal dominant inheritance and results from heterozygous activating mutations of the CaSR that have a much lower EC_{50} than those found in patients with ADH[42,43]; it might be that the phenotypic features of Bartter syndrome are affected by the severity of the CaSR gain-of-function mutations (Supplementary Table 1). Type VI Bartter syndrome is X-linked recessive in inheritance; mutations in *CLCN5* are more commonly associated with Dent disease. Treatment with non-steroidal anti-inflammatory drugs will decrease renal prostaglandin production and blockade of distal tubular sodium–potassium exchange with spironolactone will facilitate correction of the hypokalaemic metabolic alkalosis[46]. Electrolytes should be replaced as required[46].

[H3] Dent disease

Dent disease types 1 (DD1) and 2 (DD2) are X-linked recessive disorders of proximal renal tubular function[47,48]. DD1 is caused by loss-of-function mutations in *CLCN5* located on

chromosome Xp11.23, and DD2 is caused by mutations in a gene located on Xq26.1 that encodes inositol polyphosphate 5-phosphatase (*OCRL*), which is also implicated in the oculocerebrorenal syndrome of Lowe (Supplementary Table 1)[47,48]. Dent disease has been reported in over 250 families, with men suffering from low-molecular-weight proteinuria, hypercalciuria, nephrocalcinosis, nephrolithiasis, and a progressive decline in renal function, which causes end-stage renal disease in 30–80% by their fifth decade[49]. Female carriers of Dent disease can exhibit mild features of the disorder; hypercalciuria is reported in 50% of female carriers, but only 10 cases of female carriers suffering from nephrolithiasis have been published[50]. Dent disease can also be associated with other proximal tubular defects of reabsorption including aminoaciduria, phosphaturia, glycosuria, kaliuresis, uricosuria, and impaired urinary acidification; increased urinary pH decreases the solubility of calcium phosphate, thereby increasing the risk of nephrocalcinosis and kidney stones[51]. Rickets or osteomalacia are common and are the only extrarenal manifestations of the disease[50].

ClC-5 is primarily expressed in the proximal tubule, thick ascending limb of the loop of Henle, and the alpha intercalated cells of the collecting duct[52]. ClC-5 has a role in the receptor-mediated endocytic pathway involving megalin and cubulin whereby it facilitates solute reabsorption by the proximal tubule, endosomal acidification, and trafficking of endocytic vesicles[52]. Dent disease-associated mutations in the *CLCN5* gene that encodes ClC-5 result in diminished solute reabsorption in the proximal tubule owing to impaired chloride flow and thus likely disrupted endosomal acidification and trafficking to the apical surface (FIG. 2)[52].

OCRL has roles in vesicle trafficking, phagocytosis, cell adhesion and migration, cellular polarity, ciliogenesis, cytokinesis and intracellular signalling[53]. The OCRL variants found in DD2 are associated with a predominantly renal phenotype, although some mutations can also result in extrarenal manifestations associated with Lowe syndrome including congenital cataracts, glaucoma, mental retardation, decreased seizure threshold, muscular hypotonia, and behavioural problems[54,55]. *OCRL* mutations commonly result in a loss of 5-phosphatase activity

of phosphatidylinositol 4, 5-bisphosphate 5-phosphatase, or decreased protein levels as a result of a reduction in expression or increased degradation owing to misfolding[56]. The exact mechanisms by which *OCRL* mutations cause Dent disease and Lowe syndrome phenotypes is poorly understood; however, defective endocytic trafficking, defective cilia formation, and loss of cellular polarity have been implicated[53]. Furthermore, the severity and phenotypes of these two disorders varies widely and individuals carrying identical *OCRL* mutations can have markedly different phenotypes, suggesting that additional genetic or environmental factors might be involved[57]. **[Au: can you provide any examples of such factors?]**

No specific therapies are available to ameliorate the hypercalciuria and renal decline observed in Dent disease. A low-sodium diet can be beneficial and thiazides can be used with careful electrolyte and fluid status monitoring[58].

[H3] Distal renal tubular acidosis

Distal renal tubular acidosis (dRTA) is caused by defective hydrogen ion secretion by α-intercalated cells in the distal segments of the renal tubule[59]. The resultant increase in urinary pH increases the propensity for calcium phosphate crystals to precipitate, compounded by hypercalciuria and hyperphosphaturia secondary to bone buffering, and hypocitraturia owing to increased reabsorption in response to the metabolic acidosis[59]. Correction of the metabolic acidosis with an alkaline citrate in patients with dRTA protects bone health via reduced requirement for skeletal buffering, increases urinary citrate excretion and reduces urinary calcium excretion, thus reducing the risk of nephrolithiasis and nephrocalcinosis[60,61]. dRTA can be acquired or inherited as an autosomal dominant disorder, as a result of mutation in solute carrier family 4 member 1 (*SLC4A1*), or as an autosomal recessive disorder, owing to mutation in ATPase H+ transporting V1 subunit B1 (*ATP6V1B1*), ATPase H+ transporting V0 subunit A4 (*ATP6V0A4*), carbonic anhydrase 2 (*CA2*), forkhead box I1 (*FOXI1)* or WD repeat domain 72 (*WDR72*) and is commonly associated with hyperchloraemia and hypokalaemia (Supplementary Table 1 and FIG. 2)[59,62,63].

SLC4A1 is located on chromosome 17q21.31 and encodes a chloride–bicarbonate exchanger, AE1 (also known as band 3 anion transport protein), which is expressed on the basolateral membrane of α-intercalated cells (FIG. 2). AE1 also mediates chloride and bicarbonate exchange on erythrocyte membranes and polycythaemia is sometimes observed in these patients[64]. Homozygous or compound heterozygous mutations have also been described in Asian populations in association with dRTA, ovalocytosis and spherocytosis[65–67].

ATP6V1B1 and *ATP6V0A4* encode subunits B1 and A4, respectively, of the H^+-ATPase (proton) pump in α-intercalated cells (FIG. 2)[68,69]. Mutations in the gene encoding the B1 subunit of the proton pump in α-intercalated cells can also be associated with sensorineural hearing loss, as the protein encoded by *ATP6V1B1* has a role in ear endolymph pH homeostasis, and the resulting alkaline environment has been proposed to impair hair cell function[68]. Mouse studies have shown that the protein encoded by *FOXI1* regulates the expression of AE1 and also expression of subunits B1 and A4 of the H^+-ATPase[63]. Genotype–phenotype analyses of the *ATP6VB1* polymorphism, rs114234874 (where the allele frequency of the major allele (G), encoding Glu161, was 94% and allele frequency of the minor allele (A), encoding Lys161, was 6%) in a stone-forming population revealed that those carrying the minor Lys161 variant had an increased prevalence of incomplete dRTA and an increased prevalence of calcium-phosphate stones[70]. Thus, the Lys161 variant of the B1 subunit of the α-intercalated cell proton pump, which has a minor allele frequency of 3% in the ExAC database (see Related links) might confer an increased risk of calcium-phosphate stone formation in the biochemically normal population[71]. Another genotype–phenotype analysis has reported that single nucleotide polymorphisms (SNPs) in *ATP6V0A4* are likely to be associated with urinary pH[72], and although *ATP6V0A4* mutations are not typically associated with hearing loss, some patients with mutations in this gene have been reported to develop hearing loss in childhood or by the second decade of life[73,74]. In a cohort of 89 patients with dRTA, mutations in *SLC4A1*, *ATP6V0A4*, and *ATP6V1B1* were present in 80% of the cohort, indicating that other genes are likely to be involved in the aetiology of this disease;

however, sequencing of *CA2*, *WDR72*, and *FOXI1* – mutations in which are also associated with dRTA - was not performed[75].

[H3] Hereditary hypophosphataemic rickets with hypercalciuria

Hereditary hypophosphataemic rickets with hypercalciuria (HHRH) is a rare autosomal recessive disorder characterized by rickets, short stature, increased renal phosphate clearance, hypercalciuria with normocalcaemia, increased gastrointestinal absorption of calcium and phosphate owing to an elevated serum concentration of 1,25-dihydroxyvitamin D, and suppressed parathyroid function[76–80]. HHRH was first described in a large consanguineous Bedouin kindred and homozygosity mapping studies identified that all affected individuals had a deletion in *SLC34A3*[76], which encodes the sodium-dependent phosphate transport protein 2c (NPT2c, FIG. 2). Further studies have identified homozygous or compound heterozygous mutations in *SLC34A3* in patients with HHRH[77–80]. Heterozygous carriers of *SLC34A3* mutations are reported to be at increased risk of renal calcification and stones, and might have increased urinary calcium excretion with or without a reduction in bone mineral density[19,78] (Supplementary Table 1).

The combination of hypophosphataemia, osteoporosis and nephrolithiasis has also been reported in patients with heterozygous variants in the *SLC34A1* gene encoding the sodium-dependent phosphate transport protein 2a (NPT2a)[81] and such mutations have been associated with hypophosphataemic hypercalciuric stone formation, without an overt skeletal phenotype, in population studies (Supplementary Table 1 and FIG. 2)[19–21]. *In vitro* expression of these identified *SLC34A1* variants in *Xenopus laevis* oocytes and opossum kidney cells to study the effects on NPT2a function yielded conflicting results, thereby questioning the role of *SLC34A1* in hypophosphataemic hypercalciuric stone disease [73–75]. However, other human and rodent *in vivo* studies have supported a role for *SLC34A1* in hypophosphataemic hypercalciuric stone disease by revealing the following: the *SLC34A1* region was significantly associated with kidney stone disease in GWASs; homozygous ablation of *Slc34a1* (also known as *Npt2a*) in mice (*Slc34a1*$^{-/-}$) resulted in increased urinary phosphate excretion, hypophosphataemia, elevation in

serum levels of 1,25-dihydroxyvitamin D, hypercalcaemia, decreased serum parathyroid hormone levels, increased serum alkaline phosphatase activity and hypercalciuria[82]; and that homozygous *SLC34A1* mutations lead to infantile hypercalcaemia[83–85]. Interestingly, NPT2a is reported to interact with the sodium/hydrogen exchange regulatory cofactor NHE-RF1 (NHERF1), encoded by *SLC9A3R1* and heterozygous missense *SLC9A3R1* variants, some of which have been shown to result in a loss-of-function *in vitro*, have been detected in hypophosphataemic patients with nephrolithiasis[19–21,86]. Moreover, mice with a targeted NHERF1 knockdown have phosphate wasting associated with an aberrant localization of Npt2a (Supplementary Table 1)[87,88]. Patients with *SLC34A1* and *SLC9A3R1* variants have a less severe bone phenotype than do those with *SLC34A3* mutations, and this might result from the ability of NPT2c to compensate, in part, for NPT2a deficiency[89].

Renal phosphate wasting and hypophosphataemia can result in suppression of fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate homeostasis and activates 24-hydroxylase (encoded by cytochrome P450 family 24 subfamily A member 1, *CYP24A1*), which is an enzyme that promotes catabolism of the active form of vitamin D 1,25-$(OH)_2D_3$ via 24-hydroxylation (FIG. 3)[83]. Low FGF23 levels and hypophosphataemia reduce *CYP24A1* expression and therefore increase sensitivity to vitamin D[83]. Thus, vitamin D supplementation in these patients can result in hypercalcaemia and an increased risk of kidney stone formation and should be used with caution[83].

[H3] Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis

Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive disorder affecting the loop of Henle and the medullary thick ascending limb[90]. This condition is characterized by increased urinary magnesium and calcium excretion that typically presents in childhood, occasionally affected individuals will experience seizures or tetany owing to hypomagnesaemia or hypocalcaemia[90]. Patients might also have polydipsia and polyuria, incomplete distal renal tubular acidosis, hyperuricaemia, hypocitraturia, defects of tooth

enamel, and ~33% will have chronic renal failure by adolescence[91–93]. Genetic studies in 12 FHHNC kindreds identified homozygous and heterozygous missense mutations in claudin-16 (*CLDN16*), also referred to as paracellin-1 (*PCLN-1*) (Supplementary Table 1)[90]. To date, over 50 *CLDN16* mutations have been reported in patients with FHHNC[92] and in some rare cases these are related to self-limiting childhood hypercalciuria without notable disturbance of magnesium homeostasis or renal function impairment[94]. An identical renal phenotype with associated severe ocular involvement including macular colobomata, myopia and horizontal nystagmus has also been reported in association with *CLDN19* mutations (Supplementary Table 1)[93,95].

Claudins are transmembrane proteins that, alongside occludin and junctional adhesion molecules, form intercellular tight junctions that mediate paracellular ion reabsorption in epithelia[96,97]. In the kidney, claudin-16 and claudin-19 are expressed in the thick ascending limb of the loop of Henle and confer tight junction cation selectivity, enabling reabsorption of calcium and magnesium driven by an electrochemical gradient (FIG. 2)[96,97]. Thus, loss-of-function mutations in these proteins result in renal calcium and magnesium wasting. Claudin-16 is exclusively expressed in the kidney but claudin-19 is also expressed in human retinal pigment epithelium which accounts for the extrarenal phenotype seen with *CLDN19* mutations[98].

Individuals with FHHNC require magnesium supplementation to replace urinary losses, vitamin D replacement should be used with caution as this may exacerbate hypercalciuria[92].

[H3] Infantile hypercalcaemia

Biallelic loss-of-function mutations in *CYP24A1* have been reported in families with infantile hypercalcaemia and nephrocalcinosis or severe hypercalcaemia following vitamin D supplementation (Supplementary Table 1, FIG. 3)[99]. Furthermore, such *CYP24A1* mutations have been reported in adults with hypercalcaemia and hypercalciuria, and treatment with fluconazole or ketoconazole, which are inhibitors of vitamin D synthesis, has been shown to be effective in treating hypercalcaemia and nephrolithiasis[100–102].

Biallelic mutations in *SLC34A1* have also been identified as being a cause of infantile hypercalcaemia associated with nephrocalcinosis and hypercalciuria; in this case, the renal phosphate wasting results in increased production of 1,25-$(OH)_2D_3$. These patients can be effectively treated with phosphate supplementation to normalize serum phosphate levels and prevent the FGF23 suppression that leads to perturbations in vitamin D and calcium metabolism[83,103].

[H3] Primary hyperoxaluria

Primary hyperoxaluria is a rare autosomal recessive disorder that is associated with excess oxalate production and urinary oxalate excretion, increasing the risk of calcium oxalate stone formation and nephrocalcinosis[104]. The nephrocalcinosis can lead to renal failure resulting in inadequate oxalate excretion that leads to systemic oxalate deposition in organs such as the heart, eyes, and bones[105]. Three forms of primary hyperoxaluria exist: primary hyperoxaluria type 1 (PH1), caused by mutations in the liver specific alanine–glyoxylate and serine–pyruvate aminotransferase (*AGXT)*, is the most severe form; PH2, caused by glyoxylate and hydroxypyruvate reductase (*GRHPR*) mutations, has a slower progression to end-stage renal disease (ESRD); and PH3, caused by mutations in 4-hydroxy-2-oxoglutarate aldolase 1 (*HOGA1*), is least likely to progress to ESRD (Supplementary Table 1)[104].

In PH1, the reduction in functional alanine–glyoxylate aminotransferase (AGT) results in impaired metabolism of glyoxylate to glycine leading to glyoxylate either being oxidized to oxalate or reduced to glycolate[104,106]. The most common *AGXT* mutation is pGly170Arg (~30% of mutant alleles) and results in mis-targeting of AGT to the mitochondria, which can be ameliorated with pyridoxine treatment[104,106]. PH1 accounts for ~80% of cases of primary hyperoxaluria and has a median age of presentation of 5.2 years, with ESRD being present in 57% of patients by 40 years of age[104]. In patients with PH1 who have ESRD , combined liver and renal transplantation is preferable to renal transplantation alone as it will completely correct

the metabolic abnormality[107]; a diagnosis of PH1 should therefore be considered before kidney transplantation in patients with renal failure caused by stone disease.

PH2 is caused by mutations of *GRHPR*, which encodes the ubiquitously expressed glyoxylate reductase/hydroxypyruvate reductase (GR/HPR) that catalyses the reduction of glyoxylate to glycolate and hydroxypyruvate to D-glycerate. In the absence of GR/HPR glyoxylate is metabolized to oxalate and hydroxypyruvate is metabolized to L-glycerate; patients with PH2 therefore show increased excretion of oxalate and L-glycerate[108,109]. PH2 accounts for ~10% of cases of primary hyperoxaluria, has a median age of presentation of 7.4 years and ESRD is present in 18% of patients at 40 years of age[104].

Patients with PH3 have dysfunctional 4-hydroxy-2-oxoglutarate aldolase (HOGA), an enzyme that catalyses cleavage of 4-hydroxy-2-oxoglutarate (HOG) to pyruvate and glyoxylate; the resulting accumulation of HOG is thought to inhibit GR/HPR function[110]. PH3 accounts for ~10% of cases of PH and has a median age of presentation of 2.6 years; however, despite the early age of presentation, only 4% of patients have ESRD at 40 years of age[104]. Some *HOGA1* mutation carriers have been reported to be idiopathic stone formers, thereby suggesting that heterozygous *HOGA* mutations might represent a risk factor for stone formation[111].

In addition to these classical descriptions of primary hyperoxaluria, homozygous loss-of-function mutations of solute carrier family 26 member 1 (*SLC26A1)*, which encodes the protein sulfate anion transporter 1, have been reported in two patients with nephrolithiasis, one of whom also had hyperoxaluria[112]. These findings are consistent with reports of hyperoxaluria and nephrolithiasis in Slc26a1$^{-/-}$ mice[113]. Sulfate anion transporter 1 is a basolateral sulfate–oxalate exchanger that is expressed in the kidney, liver and intestines and the mutations reported in humans result in impaired anion exchange in HEK293T cells[112].

In cases of primary hyperoxaluria restriction of oral oxalate is of limited value, inhibitors of urinary calcium oxalate crystallization might be beneficial and aggressive urinary dilution should be encouraged[114].

[H2] Non-calcium nephrolithiasis disorders

The disorders of non-calcium nephrolithiasis include cystinuria, hereditary hyperuricosuria, hereditary xanthinuria, and adenine phosphoribosyltransferase deficiency (Supplementary Table 1).

[H3] Cystinuria

Cystinuria arises as a result of defective amino acid transport in the proximal tubule and accounts for ~5% of stone cases in the paediatric population, but only 1% of adult stone cases[115]. Amino acids are freely filtered at the glomerulus and, in health, 99% of filtered cysteine is reabsorbed[115]. Mutations in solute carrier family 3 member 1 (*SLC3A1*) or solute carrier family 7 member 9 (*SLC7A9*) which encode neutral and basic amino acid transport protein (rBAT) and $b^{o,+}$-type amino acid transporter 1 ($b^{o,+}AT$), respectively, result in impaired reabsorption of cysteine and of the dibasic amino acids ornithine, lysine and arginine leading to hyperexcretion. rBAT and $b^{o,+}AT$ proteins form heterodimers via a disulfide bridge to make up the $b^{o,+}$ amino acid transport system (Supplementary Table 1 and FIG. 2)[115]. At a normal pH, ornithine, lysine and arginine are soluble, but cysteine forms a dimer, cystine, which is relatively insoluble, resulting in crystal precipitation and stone formation[115].

Historically, cystinuria was classified into three types defined by the urinary cystine excretion patterns of the heterozygous parents of affected individuals. Type I heterozygotes had a normal urinary cystine excretion (<100μmol/g creatinine), type II heterozygotes demonstrated a marked increase in urinary cystine excretion (>900 μmol/g creatinine), and type III heterozygotes showed a moderate increase urinary cystine excretion (100–900μmol/g creatinine)[116]. With increased understanding of the molecular basis of the disease, a new classification system with two types was adopted[116]. Type A is caused by defects in *SLC3A1* and is inherited in a true autosomal recessive manner, with heterozygotes having a normal urinary cystine excretion. Type B is caused by *SLC7A9* variants and is autosomal dominant with incomplete penetrance, with

heterozygotes having a variable degree of cystine hyperexcretion, some being within the normal range (Supplementary Table 1)[117]. A digenic inheritance has also been proposed and heterozygous type AB individuals have been identified[117]. However, a study of patients with cystinuria has revealed that for a cystinuric phenotype, two mutated alleles in the same gene are required in addition to the mutated allele in the second gene; moreover, type AB double heterozygotes were not reported to form kidney stones[117].

Medical management of patients with cystinuria aims to prevent stone formation. Four main approaches are being used: urinary dilution; dietary modification to reduce intake of the cysteine precursor methionine; urinary alkalinization to increase cystine solubility; and thiol-binding drugs, such as D-penicillamine and α-mercaptopropionylglycine, which reduce insoluble cystine to soluble cysteine[9]. Thiol-binding drugs are introduced if stone formation persists despite urinary alkalinization[9].

[H3] Hereditary hyperuricosuria

Hereditary hyperuricosuria can result from a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) encoded by *HPRT1*, hyperactivity of phosphoribosyl pyrophosphate synthase (PRPPS; also known as ribose-phosphate pyrophosphokinase 1) encoded by phosphoribosyl pyrophosphate synthetase 1 (*PRPS1*) or defective tubular urate reabsorption owing to mutations of solute carrier family 22 member 12 (*SLC22A12*) or solute carrier family 2 member 9 (*SLC2A9*) (Supplementary Table 1)[118–120].

HGPRT has a central role in purine metabolism (FIG. 4) and is encoded by *HPRT1* located on chromosome Xq26. *HPRT1* mutations result in a partial or complete loss of enzyme function with complete deficiency being associated with Lesch–Nyhan syndrome[118]. Lesch–Nyhan syndrome is an X-linked recessive disorder characterized by the following: hyperuricaemia; hyperuricosuria; uric acid urolithiasis; neurological manifestations including psychomotor delay, intellectual disability and self-mutilation; and renal failure in childhood[118]. Partial loss-of-function mutations in the gene that encodes hypoxanthine-guanine phosphoribosyltransferase

(*HPRT1*) have a less severe phenotype and the mildest form, Kelley–Seegmiller syndrome, typically presents with uric acid stones and the metabolic manifestations of excessive purine production rather than with neurological manifestations (Supplementary Table 1)[118,121].

Mutations in *PRPS1*, located on chromosome Xq22.3, result in increased PRPPS activity that is associated with hyperuricaemia, hyperuricosuria and gout[122,123]. In addition, hearing loss, uric acid stones and intellectual disability have been described in men with such mutations and some heterozygous women also have uric acid lithiasis, gout and hearing loss (Supplementary Table 1)[119,120,124].

HGPRT deficiency syndrome and PRPPS superactivity can be successfully treated with xanthine oxidase inhibitors (allopurinol or febuxostat) to reduce hyperuricaemia and hyperuricosuria. However, careful titration is required in complete HGPRT deficiency and PRPPS superactivity as hyperxanthinuria and hyperhypoxanthinuria can occur[118]. .

Loss-of-function mutations in *SLC22A12* or *SLC2A9*, which encode the proximal tubular uric acid reabsorption transporters urate anion exchanger 1 (URAT1; also known as solute carrier family 22 member 12) and glucose transporter type 9 (GLUT9; also known as solute carrier family 2, facilitated glucose transporter member 9, respectively, are associated with renal uric acid wasting (FIG. 2)[125]. The resulting hyperuricosuria can either be asymptomatic or associated with nephrolithiasis and in a minority of patients, exercise-induced acute renal failure can occur[126]. The mechanism behind this renal insult is unclear but might relate to urate nephropathy owing to increased uric acid production during exercise or owing to renal reperfusion injury as a result of exercise-induced vasoconstriction in the absence of the free-radical scavenger, uric acid[126]. The disorder can occur as an autosomal recessive or an autosomal dominant disease in which patients have biallelic and heterozygous mutations, respectively[19,125–128].

In all forms of hereditary hyperuricosuria urinary alkalinization will improve uric acid solubility, and should be used in combination with a high fluid intake[129]. Xanthine oxidase inhibitors can be beneficial in decreasing uric acid production and therefore the filtered renal load[129,130].

[H3] Hereditary xanthinuria

Hereditary xanthinuria is an autosomal recessive disorder also caused by defective purine metabolism. Two types of hereditary xanthinuria have been defined. Type 1 is the consequence of mutations in xanthine dehydrogenase (*XDH*), and type 2 is caused by mutations in molybdenum cofactor sulfurase (*MOCOS*), which is an essential cofactor in the activation of XDH and aldehyde oxidase (Supplementary Table 1, FIG. 4)[131,132]. These enzymatic deficiencies result in reduced levels of uric acid in serum and urine and increased levels of xanthine; hypoxanthine is recycled by hypoxanthine-guanine phosphoribosyltransferase. Metabolic disturbances can be silent or can cause radiolucent xanthine urolithiasis or myopathy owing to xanthine deposits[131,133]. A low purine diet and high fluid intake might help to reduce the frequency of xanthine stone formation[134].

Molybdenum cofactor deficiency also results in hyperxanthinuria and is caused by autosomal recessive mutations in genes encoding components of the molybdenum cofactor synthesis pathway, such as molybdenum cofactor biosynthesis protein 1 (encoded by *MOCS1*), molybdopterin synthase sulphur carrier subunit (encoded by *MOCS2*) and gephyrin (encoded by *GPHN*) (Supplementary Table 1)[135]. In addition to the biochemical phenotype of isolated xanthinuria, this disorder results in increased sulphite levels which causes psychomotor retardation, failure to thrive, seizures and hypotonia[135,136].

[H3] Adenine phosphoribosyltransferase deficiency

Deficiency of adenine phosphoribosyltransferase (APRT) is caused by homozygous or compound heterozygous *APRT* mutations (Supplementary Table 1). Reduced APRT function causes accumulation of adenine, which is subsequently oxidized by XDH to form 2,8-dihydroxyadenine (FIG. 4); 2,8-dihydroxyadenine is highly insoluble in urine and results in crystalluria and radiolucent 2,8-dihydroxyadenine stone disease. Nephrolithiasis is the most common clinical manifestation in patients with APRT deficiency. In addition, up to 20% of patients have end-stage renal failure at presentation owing to tubulointerstitial injury from crystal

deposition or obstruction, which commonly leads to the requirement for renal dialysis or transplantation[137,138]. A diagnosis can be made by stone analysis, identification of 2,8-dihydroxyadenine crystals in urine, renal biopsy, or identification of reduced APRT activity in erythrocytes[138]. Two types of APRT have been described based on either total (type I) or partial (type II) APRT deficiency *in vitro;* however, the *in vitro* characterization of the mutant protein does not seem to alter the *in vivo* phenotype[138]. Type II APRT has only been described in Japanese populations[139].

Allopurinol and febuxostat are effective at reducing 2,8-dihydroxyadenine production and can be used to prevent recurrent stone formation and progression of renal failure in patients with APRT[137,140]. To date, <300 cases have been reported, but this disorder is predicted to be underdiagnosed as homozygosity at the APRT locus is estimated to be between 1 in 50,000 and 1 in 100, 000[49,138,141].

[H1] Polygenetic nephrolithiasis risk factors

Large-scale population-based studies have also been employed to identify genes conferring risk of kidney stone formation through candidate gene approaches and GWASs.

[H2] Genome-wide association studies

GWASs have reported associations of renal stone disease with 25 loci (Box 2)[84,85,142–146]. Three of these loci - *CASR*, *CYP24A1*, and *SLC34A1* - are linked to genes implicated in monogenic disorders of nephrolithiasis[19–21,36,37,83,99,103].

The first GWAS in kidney stone disease was performed in Dutch and Icelandic populations in 2009 and identified two synonymous variants in claudin-14 (*CLDN14*, rs219779 and rs219780) that were associated with nephrolithiasis and bone mineral density[142]. These SNPs were also found to be associated with **[Au: "increased"?]** serum alkaline phosphatase (ALP), serum magnesium, serum parathyroid hormone and urinary calcium excretion[142]. Additional

observational studies have confirmed correlations with SNPs in *CLDN14* and urinary calcium excretion[147,148]. *CLDN14* encodes claudin-14, a member of the claudin transmembrane tight junction family of proteins that, like claudin-16 and claudin-19, is expressed in the thick ascending limb of the loop of Henle (FIG. 2)[148,149]. CaSR activation is thought to increase expression levels of claudin-14 in the thick ascending limb of the loop of Henle and thereby decrease paracellular calcium reabsorption[149]. *In vitro* studies have indicated that an intronic SNP that is associated with an increased risk of kidney stones and hypercalciuria might result in increased claudin-14 expression which might be involved in the pathophysiology of hypercalciuria[148].

Results from four further kidney stone GWASs have been reported, including one trans-ethnic meta-analysis of UK and Japanese cohorts, identifying 25 loci of interest (Box 2), 11 of which have been replicated in these GWASs[84,85,143,144]. One replicated locus is ~38kb upstream of *CYP24A1*, mutations in which result in infantile hypercalcaemia (FIG. 3). Individuals homozygous for the increased risk allele rs17216707 are reported to have increased mean serum calcium concentrations and more stone episodes when compared with heterozygotes[143]. It has been proposed that individuals carrying the *CYP24A1* increased-risk allele might have reduced activity of the 24-hydroxylase enzyme and therefore an increased sensitivity to vitamin D[143]. Moreover, it has been **[Au: ok to change "it has been " to "we performed a meta-analysis that"]** suggested that studies are required to investigate the effects of withholding vitamin D supplementation and the use of inhibitors of vitamin D synthesis in patients who are recurrent stone formers and homozygous for the high-risk allele[143].

A suggestive association between kidney stone disease and the *CASR* locus has been identified ($p=2x10^{-8}$, significance threshold in this data set defined as $p<1.8x10^{-9}$) and subsequently replicated ($p=3.5x10^{-5}$)[84,143]. Furthermore, five additional kidney stone disease loci—diacylglycerol kinase delta (*DGKD*), diacylglycerol kinase eta (*DGKH*), WD repeat domain 72 (*WDR72*), GIPC1 PDZ domain containing family member 1 (*GIPC1*), and breakpoint cluster region (*BCR*)[143] — are proposed to be linked with genes that influence CaSR signalling. The

CaSR has a central role in calcium homeostasis with gain-of-function CaSR mutations resulting in ADH and Bartter syndrome type V (FIG. 2)[36,42,43]. Furthermore, the CaSR polymorphism Arg990Gly that is found more commonly in hypercalciuric individuals than in the normocalciuric population has been reported to cause a gain-of-function *in vitro*[150–152]. However, rare variants in the CaSR were not found to be associated with urinary calcium excretion in a study of 960 individuals[147], and the CaSR variants were not linked with idiopathic hypercalciuria in a nonparametric linkage analysis of 64 French Canadian sibships[153]. The roles of the variants in the CaSR and components of its signalling pathway in renal stone disease remain to be fully defined; however inhibitors of the CaSR (which are termed calcilytics) have been proposed as a potential therapeutic option for those carrying high-risk CaSR-associated alleles[143].

ALPL encodes the alkaline phosphatase tissue-nonspecific isozyme (ALPL), which is expressed in renal proximal tubular cells, and protective alleles and risk alleles for kidney stones associated with increased and reduced ALP levels, respectively, have been defined[84]. These findings led to the proposal that alterations in the hydrolysis of pyrophosphate to free phosphate confers an increased risk of stone formation[84]. The *ALPL* SNP rs1256328 has since been found to be associated with kidney stone disease in a Chinese cohort[154]. Furthermore, loss-of-function mutations in *ALPL* result in hereditary hypophosphatasia, which is characterized by dentition abnormalities, osteomalacia, elevated serum levels of inorganic phosphate and occasionally hypercalcaemia and/or hypercalciuria[155]. Other loci confirmed in other GWASs to be associated with renal stone disease include *GCKR*, *SLC34A1*, *AQP1*, *POU2AF1*, *WDR72* and *UMOD*[84,85,142–146].

A rare missense variant in the gene encoding transient receptor potential cation channel subfamily V member 5 (*TRPV5*), Leu530Arg, was found to be associated with kidney stones in an Icelandic population[84]. However, this locus was not reported in subsequent studies[143,144]. TPRV5 is a calcium-selective cation channel that is known to be involved in intestinal and renal calcium reabsorption. *TRPV5*-knockout mice have been found to be hypercalciuric with enhanced intestinal calcium absorption and to have reduced cortical and trabecular bone thickness[156].

570 Furthermore, mice with the *TRPV5* missense mutation Ser682Pro have autosomal dominant
571 hypercalciuria[157], and the missense variant Leu530Arg was found to abolish calcium uptake in
572 *Xenopus laevis* oocytes *in vitro*[158]. Investigations of 20 hypercalciuric patients screened for
573 *TRPV5* polymorphisms identified eight coding sequence SNPs in *TRPV5*, including three
574 nonsynonymous variants, but none of the nonsynonymous variants were shown to alter the
575 function of TRPV5 *in vitro*[159]. However, one of these variants (rs4236480) was reported to be
576 associated with increased stone number in a Taiwanese population[160].

577 ***[H2] Case–control studies***

578 Case–control studies have investigated the role of biologically plausible candidate genes in the
579 development of nephrolithiasis, and have identified associations with genes including solute
580 carrier family 26 member 6 (*SLC26A6*); *TRPV5*; transient receptor potential cation channel
581 subfamily V member 6 (*TRPV6*); *VDR*; homeodomain-interacting protein kinase 2 (*HIPK2*);
582 osteopontin (*OPN*; also known as secreted phosphoprotein 1 (*SPP1*)); matrix Gla protein (*MGP*);
583 and plasminogen activator, urokinase (*PLAU*)[159–162].

584 As *Slc26A6*-null mice have been reported to be hyperoxaluric and to develop calcium oxalate
585 kidney stones, *SLC26A6*, which encodes an oxalate transporter, was investigated in a case–
586 control study[161,163]. The case-control study identified a *SLC26A6* variant to be associated with
587 kidney stone disease[161], and this variant paradoxically was associated with increased SLC26A6
588 expression in the kidneys of stone-forming patients[164]. Case control studies have also identified
589 that a *TRPV6* haplotype might**]** increase the risk of absorptive hypercalciuria via increased
590 permeability of the TRPV6 calcium channel[162]. Associations between common variants in *VDR*
591 and kidney stone formation have been examined in multiple case–control studies with conflicting
592 results[165–171]. However, two meta-analyses of these studies suggested that two **[Au: is "two"**
593 **correct here?]** polymorphisms in the 3' untranslated region of *VDR* are associated with **[Au:**
594 **"increased"?]** risk of kidney stone disease[172,173].

Case–control studies have also identified genetic polymorphisms associated with kidney stone disease in the following genes: *HIPK2* (the protein product of which is thought to have a role in renal tubule epithelial cell apoptosis and renal fibrosis[174]; *SPP1* which encodes an inhibitor of stone formation[175–177]; *MGP*, the protein product of which inhibits hydroxyapatite nucleation and formation of calcium oxalate monohydrate[178,179]; and a variant in the 3' UTR of the urokinase gene, which encodes a protein that degrades the organic matrix of kidney stones[180]. Further studies are required to elucidate the role of these genetic polymorphisms in kidney stone pathogenesis.

[H1] Clinical implications

Studies have indicated that monogenetic causes of kidney stone disease are likely under-diagnosed in the stone-forming population, particularly in individuals under 25 years of age[19–21]. However, these studies have also revealed that stone-forming patients with mutations in genes such as *AGXT* or *SLC34A1* do not always have the classical biochemical phenotypes that are associated with these genetic variants meaning that diagnosis in practice can be difficult[20,181]. Failure to diagnose a monogenetic defect can result in suboptimal management and missed opportunities to screen for associated disease manifestations (FIG 5). Genetic counselling is appropriate in patients diagnosed with monogenetic disorders so that they understand the hereditary nature of their condition.

Recurrent stone formers who are children or young adults, or have a strong family history of kidney stone disease or parental consanguinity, should be considered to be at high risk of an inherited disorder[20]. Consideration of these patients in a multidisciplinary team that includes urologists, nephrologists, endocrinologists, clinical biochemists, and clinical geneticists should be considered to streamline relevant biochemical and genetic testing and to facilitate selection of optimal treatment strategies. For individuals with a specific biochemical phenotype, targeted screening for genetic mutations might be possible (Table 1). For others without a specific biochemical phenotype, and particularly in the paediatric population where the prevalence of

monogenic diagnoses might be as high as 30%[20], a whole-exome sequencing approach might be required to diagnose or exclude a monogenetic diagnosis[181]. Establishing the genetic aetiology of the disorder in individuals with recurrent idiopathic stone formation remains a challenge, but it seems plausible that a genome-guided precision medicine approach that facilitates targeting of the relevant biological pathways might become available in the future; such approaches have not yet been attempted and would require careful evaluation in clinical trials[143].

[H1] Conclusions

Kidney stone disease is a common problem with a complex aetiology that can occur as a result of a monogenetic disorder or as part of a polygenic trait. Studies of monogenic disorders of nephrolithiasis have increased our understanding of the transporters, channels, and receptors that are involved in regulation of the composition of the renal tubular fluid, and provided valuable insights into the pathways that contribute to risk of stone formation. The prevalence of monogenic stone disease has likely been underestimated and correct diagnosis will guide management, enable screening for other disease phenotypes and also facilitate genetic counselling. Furthermore, with the rapid advances that are being made in genomic medicine it is plausible that in the future, individualized drug therapies might become available based on polygenic genotype **[Au: phenotype?]** in individuals who are currently considered recurrent idiopathic stone formers. These precision medicine approaches might become a reality as genetic studies continue to increase our understanding of the pathways that underlie kidney stone formation.

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Key points

- Studies suggest that the prevalence of monogenic kidney stone disease in patients attending kidney stone clinics is ~15%.
- For patients without a monogenic cause of nephrolithiasis, the heritability of kidney stone disease and hypercalciuria is >45% and >50%, respectively.
- Increased understanding of the genetic factors contributing to kidney stone disease helps to improve our understanding of the pathogenesis of this condition.
- Identification of a monogenic cause of kidney stone disease facilitates optimal stone prevention management and identification of associated phenotypes.
- Advances in our understanding of the polygenic factors contributing to risk of kidney stone disease might enable a precision medicine approach.

Table 1 | Monogenetic causes of kidney stones classified by urinary phenotype.

Disorder	Genes	Inheritance	Phenotype	Management
Hypercalciuria				
Familial hypercalciuria	*ADCY10, VDR*	AD	Normocalcaemia	Thiazide
Autosomal dominant hypocalcaemia	*CASR, GNA11*	AD	Hypocalcaemia, hyperphosphataemia, inappropriately low PTH.	Use caution with vitamin D and hypocalcaemia correction as they might cause hypercalciuria
Bartter syndrome	*NKCC2* (*SLC12A1*), *ROMK (KCNJ1), CLCNKB, BSND, CASR, CLCN5*	AD, AR or XLR	Hypokalaemia, alkalosis	Indometacin, aldosterone antagonist, electrolytes as required

Dent's disease	*CLCN5, OCRL*	XLR	LMW proteinuria and renal impairment in men; solitary hypercalciuria in female carriers.	Screen for osteomalacia and opthalmology phenotypes if *OCRL* mutation; use thiazides with caution
Hypophosphataemic rickets	*SLC34A1, SLC34A3, SLC9A3R1*	AR	Low serum phosphate, increased phosphate excretion, elevated 1,25 vitamin D	Screen for osteomalacia; phosphate replacement without vitamin D
Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis	*CLDN16, CLDN19*	AR	Low serum calcium and magnesium, raised urinary magnesium; *CLDN19* mutations associated with macular colobomata, myopia and nystagmus	Magnesium replacement; use caution with vitamin D replacement; assess for opthalmological phenotypes with *CLDN19* mutations
Infantile hypercalcaemia	*CYP24A1, SLC34A1*	AR	Hypercalcaemia	*CYP24A1*: inhibitor of vitamin D synthesis (e.g. fluconazole) *SLC34A1*: phosphate replacement
Cystinuria				
–	*SLC3A1, SLC7A9*	**AR or AD with incomplete penetrance**	Solitary cystinuria	Urinary alkalinization; thiol-binding drugs such as D-penacillamine, alpha-mercaptopropionylglycine and captopril; aggressive urinary dilution
Hyperuricosuria				
Defective purine metabolism	*HRPT1, PRPS1*	XLR	Hyperuricaemia, learning,disability, renal failure, hearing loss (*PRPS1*)	Urinary alkalinization; allopurinol or febuxostat; hearing screening; monitor renal function;
Renal uric acid wasting	*SLC22A12, SLC2A9*	AD or AR	Hypouricosuria	Urinary alkalinization; allopurinol or febuxostat
Xanthinuria				
–	*XDH, MOCOS, MOCS1, MOCS2, GPHN*	AR	Hypouricosuria. *MOCS1, MOCS2, GPHN* mutations result in increased serum sulphite levels that can cause seizures, hypotonia.	Low purine diet; neurological screening for *MOCS1, MOCS2* and *GPHN* mutations
Failed urinary acidification				
–	*SLC4A1, ATP6VB1, ATP6VA4, CA2*	AD or AR	Hypokalaemia, hyperchloraemia, hypercalciuria, hyperphosphaturia, hypocitraturia. hearing loss with *ATP6VB1* and *ATP6VA4* mutations	Alkalinization with sodium bicarbonate or alkaline citrate; hearing screening; assessment for osteomalacia
Hyperoxaluria				
–	*AGXT, GRHPR, HOGA1, SLC26A1*	AR	Renal impairment, hyperoxalaemia and systemic oxalate deposition; orthopaedic, cardiac and opththalmological phenotypes	Pyridoxine for *AGXT* mutations; assess for systemic oxalate deposition; no requirement for strict oral oxalate. In contrast, oral oxalate restriction is beneficial in enteric hyperoxaluria; increase urinary inhibitors of calcium oxalate crystallization with potassium citrate, magnesium oxide and orthophosphate; aggressive urine dilution
Dihydroxyadenine crystals				
–	*APRT*	AR	Radiolucent stones and renal impairment	Allopurinol or febuxostat

AD; autosomal dominant; AR, autosomal recessive; LMW, low molecular weight; XLR, X-linked recessive.

Figure 1 | Radiographic appearance of kidney stone disease in three patients. Upper panel images are plain abdominal radiographs and lower panel images are non-contrast CT sagittal sections. Stones are marked with squares and/or circles in the upper panels and with arrows in the lower panels. R, right; L, left. **a |** Calcium oxalate stone in the left kidney appearing radiopaque on plain abdominal radiograph. **b |** Cystine stone in the left kidney that demonstrates reduced radiopacity and is faintly visible on plain abdominal radiograph. **c |** Uric acid stone in right ureter is radiolucent and not visible on plain abdominal radiograph.

Figure 2: Monogenetic disorders of nephrolithiasis resulting in renal tubular dysfunction. a | In the proximal convoluted tubule, low molecular weight (LMW) proteins (black circles) are endocytosed by megalin and cubulin (red apical receptor). Endosomal acidification occurs via hydrogen ion transport via chloride channel protein 5 (ClC-5) (also known as H^+/Cl^- exchange transporter 5 and encoded by *CLCN5*) and V-ATPase and enables ligand-receptor dissociation and receptor recycling. *CLCN5* mutations are found in Dent disease. Phosphate uptake in the proximal tubule takes place via NPT2a and NPT2c transporters; mutations in genes encoding these proteins are found in hereditary hypophosphatemic rickets with hypercalciuria. Dibasic amino acids are reabsorbed from the tubular lumen via the $b^{o,+}$ amino acid transport system, a heterodimer comprised of rBAT and $b^{O,+}$AT subunits. Mutations in rBAT and $b^{O,+}$AT are found in patients with cystinuria. Uric acid enters the proximal tubular cells via solute carrier family 22 member 12 (also known as urate anion exchanger 1 (URAT1)) and exits the basolateral membrane via solute carrier family 2, facilitated glucose transporter member 9 (GLUT9). Mutations in genes encoding URAT1 and GLUT9 are found in hereditary hyperuricosuria. **b |** In the thick ascending limb of the loop of Henle, sodium–potassium–chloride cotransporter 2 (NKCC2, also known as SLC12A1) and renal outer-medullary potassium channel (ROMK; also known as KCNJ1) establish a lumen-positive trans-tubular potential difference that drives calcium (Ca^{2+}) reabsorption. The calcium-sensing receptor (CaSR) acts to inhibit NKCC2. Sodium ions (Na^+) are transported across the basolateral membrane via Na^+-K^+ ATPase and Cl^- via the voltage-gated chloride channel CLC-Kb, which acts with Barttin. Mutations in genes encoding NKCC2,

ROMK, CLC-Kb, Barttin and the CaSR result in Bartter syndrome. Claudins maintain tight junctions in the thick ascending limb of the loop of Henle and regulate the degree to which the junctions are permeable to cations. Mutations in *CLDN16* and *CLDN19* result in familial hypercalciuric hypomagnesaemia with nephrocalcinosis. **c |** In the collecting duct, carbonic anhydrase 2 (CA2) catalyses the conversion of water and carbon dioxide into hydrogen ions and bicarbonate within α-intercalated cells. Hydrogen ions are secreted into the lumen via the H^+-ATPase and H^+/K^+-ATPase pumps and bicarbonate exits the basolateral membrane via chloride–bicarbonate exchanger, AE1 (also known as band 3 anion transport protein). Mutations in genes encoding H^+-ATPase, AE1 and CA2 result in impaired urinary acidification and distal renal tubular acidosis.

Figure 3 | Vitamin D metabolism. 7-dehydrocholesterol is converted to cholecalciferol (vitamin D) in the skin under the influence of ultraviolet light and heat. Cholecalciferol is also available through dietary intake. Cholecalciferol undergoes 25-hydroxylation in the liver by vitamin D 25-hydroxylase (encoded by *CYP2R1*), converting it to 25-hydroxyvitamin D (25-(OH)D_3). The final step in the activation of vitamin D takes place in the kidney where 25-hydroxyvitamin D 1α-hydroxylase (encoded by *CYP27B1*) hydroxylates 25-(OH)D_3 at the 1α position to form 1,25-dihydroxyvitamin D (1,25-$(OH)_2D_3$), also called calcitriol. Active vitamin D (1,25-$(OH)_2D_3$) is inactivated by 1,25-dihydroxyvitamin D_3 24-hydroxylase (encoded by *CYP24A1*) which generates a 24-hydroxylated form 1,24,25-trihydroxyvitamin D (1,24,25-$(OH)_2D_3$). CYP24A1 also hydroxylates 25-(OH)D to form 24,25-dihydroxyvitamin D (24,25-(OH2)D_3).

Figure 4 | Schematic representation of purine metabolism. Purine nucleotides are synthesized via the phosphorylation of ribose-5-phosphate by phosphoribosyl pyrophosphate synthase (PRPPS; also known as ribose-phosphate pyrophosphokinase 1) to form phosphoribosyl pyrophosphate (PRPP). Hypoxanthine guanine phosphoribosyltransferase (HGPRT, encoded by *HPRT1*) and adenine phosphoribosyltransferase (APRT) form part of the salvage pathway, converting free bases (adenine, hypoxanthine and guanine) back to nucleoside-5'-monophosphates adenosine monophosphate (AMP), inosine monophosphate (IMP) and guanosine monophosphate (GMP). Xanthine dehydrogenase (XDH) catalyses the formation of uric acid from hypoxanthine and 2,8-dihydroxyadenine from adenine. Molecular defects in the enzymes PRPPS, HGPRT, XDH and APRT (shown in red) can result in hyperuricosuria or increased 2,8-dihydroxyadenine excretion.

Box 1 | Investigations and dietary stone prevention strategies for kidney stone formers

Investigations

Blood tests: calcium, chloride, creatinine, bicarbonate, potassium, phosphate, uric acid, PTH in cases where serum calcium is high normal or high.
24 hour urine collection: calcium excretion, oxalate excretion, uric acid excretion, citrate excretion, sodium excretion, magnesium excretion, phosphate excretion, cystine excretion, urinary volume, urinary pH
Stone analysis

Dietary stone prevention strategies

Increase: fluid intake, dietary fresh fruit, dietary fibre

Reduce: dietary animal protein, dietary sodium, dietary oxalate

Box 2: Candidate genes from kidney stone genome-wide association studies

ABCG2: ATP binding cassette subfamily G member 2

ALPL: Alkaline phosphatase, biomineralization associated

AQP1: Aquaporin 1

BCAS3: BCAS3 microtubule associated cell migration factor

BCR: BCR activator of RhoGEF and GTPase

CASR: calcium-sensing receptor

CLDN14: claudin 14

CYP24A1: cytochrome P450 family 24 subfamily A member 1

DGKD: diacylglycerol kinase delta

DGKH: diacylglycerol kinase eta

EPB41L2: erythrocyte membrane protein band 4.1 like 2

FTO: FTO alpha-ketoglutarate dependent dioxygenase

GIPC1: GIPC PDZ domain containing family member 1

GCKR: glucokinase regulator

HIBADH: 3-hydroxyisobutyrate dehydrogenase

KCNK5: Potassium two pore domain channel subfamily 5 member 5

POU2AF1: POU class 2 homeobox associating factor 1

SLC22A2: solute carrier family 22 member 2

SLC34A1: solute carrier family 34 member 1

SCNN1B: sodium channel epithelial 1 beta subunit

SOX9: SRY-box transcription factor 9

TFAP2B: transcription factor AP-2 beta

TRPV5: transient receptor potential cation channel subfamily V member 5

WDR72: WD repeat domain 72

UMOD: uromodulin

Supplementary **Table 1 | Monogenetic causes of kidney stone disease**

Disease	Inheritance	Gene	Chromosomal location	Gene product	OMIM number	Stone X-ray appearance
Idiopathic hypercalciuria	AD	*ADCY10*	1q24.2	Adenylyl cyclase	143870	Radiopaque
	AD	*VDR*	12q13.11	Nuclear hormone receptor for vitamin D3	-	
	AD	?	9p33.2-q34.2	**?**	-	
Autosomal dominant hypocalcaemia						Radiopaque
Type 1	AD	*CASR*	3p21.1	Calcium-sensing receptor	601199	
Type 2	AD	*GNA11*	19q13.3	G-protein subunit α11	615361	
Bartter syndrome						Radiopaque
Type I	AR	*NKCC2* (*SLC12A1*)	15q21.1	Sodium–potassium–chloride cotransporter	601678	
Type II	AR	*ROMK* (*KCNJ1*)	11q24.3	ATP-sensitive potassium channel	241200	
Type III	AR	*CLCNKB*	1p36.13	Voltage-gated chloride channel CLCNKB	607364	
Type IV	AR	*BSND*	1p32.3	Barttin encoded by *BSND* is an essential subunit for the CLCNKB chloride channel	602522	
Type V	AD	*CASR*	3p21.1	Calcium-sensing receptor	601198	
Type VI	XLR	*CLCN5*	Xp11.23	Voltage-gated chloride channel	-	
Dent disease						Radiopaque
Type 1	XLR	*CLCN5*	Xp11.23	Voltage-gated chloride channel	300009	
Type 2	XLR	*OCRL*	Xp26.1	Inositol polyphosphate 5-phosphatase	300555	
Hereditary hypophosphataemic rickets with hypercalciuria	AR	*SLC34A3*	9q34.3	Sodium-dependent phosphate transporter 2c	241530	Radiopaque
Hypophosphataemia and nephrolithiasis						Radiopaque
Type 1	AD	*SLC34A1*	5q35.3	Sodium-dependent phosphate transporter 2a	612286	
Type 2	AD	*SLC9A3R1*	17q25.1	Sodium/hydrogen exchange regulatory Factor 1	612287	

Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis	AR	*CLDN16*	3q28	Claudin-16	248250	Radiopaque
Familial hypomagnesaemia with hypercaclciuria and nephrocalcinosis with severe ocular involvement	AR	*CLDN19*	1q34.2	Claudin-19	248190	Radiopaque
Autosomal dominant distal renal tubular acidosis	AD	*SLC4A1*	17q21.31	Chloride/bicarbonate exchanger, AE1	1479800	Radiopaque
Autosomal recessive distal renal tubular acidosis with progressive nerve deafness	AR	*ATP6V1B1*	2p13.3	B1 subunit of α-intercalated cell H^+-ATPase	267300	Radiopaque
Autosomal recessive distal renal tubular acidosis	AR	*ATP6V0A4*	7q34	A4 subunit of α-intercalated cell H^+-ATPase	602722	Radiopaque
Autosomal recessive distal renal tubular acidosis	AR	*CA2*		Carbonic anhydrase 2		Radiopaque
Autosomal recessive distal renal tubular acidosis	AR	*WDR72*		WD repeat-containing protein 72		Radiopaque
Autosomal recessive distal renal tubular acidosis	AR	*FOXI1*		Forkhead box protein I1		Radiopaque
Infantile hypercalcaemia						Radiopaque
Type 1	AR	*CYP24A1*	20q13.2	24-hydroxylase enzyme	143880	
Type 2	AR	*SLC34A1*	5q35.3	Sodium-dependent phosphate transporter 2a	616963	
Primary hyperoxaluria						Radiopaque
Type 1	AR	*AGXT*	2q37.3	Peroxisomal alanine-glyoxylate amino-transferase	259900	

Type 2	AR	*GRHPR*	9q13.2	Glyoxylate reductase/hydroxypyruvate reductase	260000	
Type 3	AR	*HOGA1*	10q24.2	4-hydroxy-2-oxoglutarate aldolase	613616	
Calcium oxalate nephrolithiasis	AR	*SLC26A1*	4p16.3	Basolateral sulfate/oxalate exchanger	167030	
Cystinuria						Poor radiopacity
Type A	AR	*SLC3A1*	2p21	rBAT (part of $b^{o,+}$ amino acid transport system)	220100	
Type B	AD	*SLC7A9*	19q31.11	$b^{o,+}$AT (part of $b^{o,+}$ amino acid transport system)	220100	
Lesch–Nyhan or Kelley–Seegmiller syndrome	XLR	*HPRT1*	Xq26.2-q26.3	Hypoxanthine guanine phosphoribosyltransferase	300322	Radiolucent
PRPPS superactivity	XLR	*PRPS1*	Xq22.3	Phosphoribosyl pyrophosphate synthase	311850	Radiolucent
Renal hypouricaemia						Radiolucent
Type 1	AR	*SLC22A12*	11q13.1	URAT1 (proximal renal tubular uric acid transporter)	607096	
Type 2	AD/AR	*SLC2A9*	4p16.1	GLUT9 (proximal renal tubular uric acid transporter)	606142	
Hereditary xanthinuria						Radiolucent
Type 1	AR	*XDH*	2p23.1	Xanthine dehydrogenase	607633	
Type 2	AR	*MOCOS*	18q12.2	Molybdenum cofactor sulfurase	603592	
Molybdenem cofactor deficiency						Radiolucent
Type A	AR	*MOCS1*	6p21.2	Molybdenum cofactor biosynthesis protein 1	603707	
Type B	AR	*MOCS2*	5q11.2	Molybdenum synthase sulfur carrier subunit	603708	
Type C	AR	*GPHN*	14q23.3-q24.1	Gephyrin (catalyst for molybdenum cofactor biosynthesis)	603930	

Adenine phosphoribosyltransferase deficiency	AR	*APRT*	16q24.3	Adenine phosphoribosyltransferase	614723	Radiolucent

AD, Autosomal dominant; AR, Autosomal recessive; XLR, X-linked recessive. Disorders of calcium nephrolithiasis. Disorders of non-calcium nephrolithiasis.