The genetics of kidney stone disease and nephrocalcinosis

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Abstract | Kidney stones (also known as urinary stones or nephrolithiasis) are highly prevalent, affecting approximately 10% of adults worldwide, and the incidence of stone disease is increasing. Kidney stone formation results from an imbalance of inhibitors and promoters of crystallization, and calcium-containing calculi account for over 80% of stones. In most patients, the underlying aetiology is thought to be multifactorial, with environmental, dietary, hormonal and genetic components. The advent of high-throughput sequencing techniques has enabled a monogenic cause of kidney stones to be identified in up to 30% of children and 10% of adults who form stones, with ~35 different genes implicated. In addition, genome-wide association studies have implicated a series of genes involved in renal tubular handling of lithogenic substrates and of inhibitors of crystallization in stone disease in the general population. Such findings will likely lead to the identification of additional treatment targets involving underlying enzymatic or protein defects, including but not limited to those that alter urinary biochemistry.

Kidney stones are common, with a lifetime prevalence of 5–10%; they occur more frequently in men than in women and have a high rate of recurrence[1,2]. Data from the National Health and Nutrition Examination Survey indicate that the prevalence of kidney stones in the US increased nearly threefold between 1976–1980 (3.2%) and 2007–2010 (8.8%)[3]. The prevalence of stone disease in European and Asian countries also seems to be rising, currently ranging between 5 and 10% in Europe and 1 and 19% in Asia[4–6]. Although fewer data are available, some evidence suggests that the incidence and prevalence of stone disease in children is also increasing. A US study found that the incidence of symptomatic kidney stones in children increased from 7.9 per 100,000 in 1996 to 18.5 per 100,000 in 2007, with the fastest rate of increase among adolescent girls[6]. Similar observations were made in another US study that used data from the Rochester Epidemiology Project[7]. Over the past 5 decades, the male to female incidence ratio of symptomatic kidney stone events has declined from 3.1 in 1970 to 1.3 in 2000 (REF.[8]). The reasons for these changes are not entirely clear, but increased utilization of imaging technology has led to increased stone detection in both sexes[8,9].

Kidney stones are associated with other comorbidities that impart substantial long-term disease burden, including obesity, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidaemia and metabolic syndrome rule[10–12]. Moreover, kidney stones are associated with an increased risk of chronic kidney disease (CKD) and kidney failure[13,14]. The resulting economic burden is substantial, with current annual expenditure related to stone disease exceeding $10 billion in the US when both direct and indirect costs are considered[9,15].

In this Review, we briefly discuss kidney stone pathogenesis, the known heritable features of stones and their risk factors and then provide a more detailed description of known monogenic causes. We conclude with a discussion of genome-wide association studies (GWAS) and sequence variants known to be associated with kidney stone disease in the general population.

Pathophysiology of kidney stones

Approximately 80–90% of all kidney stones contain calcium in the form of calcium oxalate (CaOx), which is often admixed with calcium phosphate (CaP) or uric acid[16,17]. Stone formation is driven at least in part by urinary supersaturation[17,18] and, in general, the urine of people who form stones is more supersaturated than that of those who do not[19]. Urinary supersaturation is determined by the complicated interaction of constituent ions, including calcium, oxalate, citrate and phosphorus. Calculated urinary supersaturation correlates with stone type, and human urine is supersaturated for CaOx most of the time[20].

Nucleation and crystal growth are essential for the initiation and development of all stone types. Nucleation, the initial formation of a crystal nidus, is the first stage in crystallization and can occur homogeneously or heterogeneously. Heterogeneous crystallization that occurs in the presence of macromolecules, such as proteins or organic polymers, generally requires a lower level of urine supersaturation than homogenous nucleation[21].

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Key points

- Kidney stone disease is a complex phenotype that results from the interactions of multiple genes with dietary and environmental factors.
- Advanced genetic testing modalities have enabled the identification of monogenic causes of kidney stones and nephrocalcinosis in select patients with severe phenotypes.
- In the past decade, genome-wide association studies have implicated common gene variants in the pathogenesis of kidney stones; many of these variants are in genes that are mutated in monogenic stone disease.
- In the future, genetic analyses could enable a personalized approach to the diagnosis and treatment of patients with rare and common varieties of kidney stones.

Two mechanisms of kidney stone initiation have been proposed: free particle and fixed particle[22,23] (FIG. 1). In the free-particle mechanism, crystals initially form within tubules and aggregate to produce large particles that can occlude collecting ducts, resulting in a plug (also known as a type II lesion)[24]. Once the tubular openings have been blocked, stones can grow on the plugs and extend into the renal pelvis. This mechanism is likely involved in the formation of CaOx stones in extreme forms of hyperoxaluria (for example, genetic or primary hyperoxaluria and enteric hyperoxaluria after bariatric surgery) as well as in the formation of uric acid and cystine stones[25–27].

In the fixed-particle mechanism, stones grow on subepithelial medullary interstitial Randall's plaques in the papillum[28]. This mechanism is currently believed to be the predominant mechanism of stone formation among people who form idiopathic calcium stones without bowel disease or systemic disorders of calcium metabolism (for example, primary hyperparathyroidism)[29,30]. Randall's plaques seem to form via CaP crystallization in the basement membrane of the thin loops of Henle, with subsequent extension into the surrounding interstitium and vasa recta[29]. Large lesions might reach the basement membrane of collecting ducts, but do not seem to adversely affect their function. It has been further hypothesized that CaP and/or CaOx deposits could migrate from the basement membrane of the loop of Henle to the surrounding interstitium to become associated with type I collagen, forming an amalgam of mineral (calcium) and organic material (collagen)[31]. CaOx and/or CaP and organic matrix layer over plaques and plugs, resulting in a stone anchored upon the renal papilla. Thus, stones are the final outcome of a complicated series of events, and the underlying pathogenic factors may vary between stone initiation and stone growth[24].

Kidney stones are associated with an increased risk of CKD[14,32]. A population-based study in Olmsted County, MN, USA, showed that people who formed incidental stones had a significantly increased risk of CKD diagnosis and of sustained estimated glomerular filtration rate <60 ml/min/1.73 m^2 compared with a matched control group[14]. In a French cohort of patients on dialysis, kidney failure was primarily attributed to stones in 3.2% of patients, with infection-associated struvite stones accounting for about half of the cases and monogenic stone disease another 13%[33]. Creatinine clearance has been shown to be lower in those who form stones than in those who do not, even after adjustment for age, sex and body weight[34]. Among stone formers, those with cystine stones had the lowest creatinine clearance. The underlying pathomechanisms of stone formation vary between patients with idiopathic CaOx stones and those who also have bowel disease, bariatric surgery and/or renal tubular acidosis, all of whom tend to have specific metabolic disturbances (for example, hyperoxaluria or persistently alkaline urine) as well as a lower creatinine clearance[14,34].

Factors such as obstructive uropathy from recurrent stone events, severe and/or repeated pyelonephritis and injury from shock wave lithotripsy could potentially increase the risk of CKD in the stone-forming population[35]. CaOx crystals might also promote kidney injury via activation of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome pathway, leading to inflammation and tubular damage[36,37]. Moreover, comorbidities that are associated with kidney stone disease, including diabetes, hypertension and obesity, are also risk factors for CKD[10]. Thus, common underlying risk factors might partially explain the association between kidney stones and CKD.

Heritable features of stone disease

Kidney stones and many associated risk factors have strongly heritable features[38] (TABLE 1) and tend to cluster in families[39,40]. Furthermore, kidney stones develop approximately three-fold more frequently in individuals with a family history of kidney stones than in those without such a history[41]. Early studies reported a family history of kidney stones in 16–37% of stone formers compared with just 4–12% of healthy individuals, yielding a heritability of stone disease of 46–63%[42,43]. In male twins the heritability of stones was estimated to be 56–57%[44], whereas in female twins the estimated heritability was somewhat lower at 46%[44,45]. More than 80% of kidney stones are composed of a majority of CaOx or CaP, and up to 70% of people with hypercalciuria who form kidney stones have a relative with stones[46,47]. Thus, the pathogenesis of calcium nephrolithiasis is currently understood to be dependent on an interplay between genetic susceptibility and environmental factors[17,46,48], and the available data suggest that the mode of inheritance is complex and polygenic[49,50].

Systemic factors

Strong evidence exists for the heritability of systemic factors related to calcium metabolism, including serum calcium[51–53] and 1,25-vitamin-D[54–56]. In addition, there is evidence of the heritability of comorbidities that are associated with kidney stone risk, including diabetes and hypertension[57]. However, the reason for the association between kidney stone risk and these conditions is not entirely clear and might relate to a common phenotypic feature that increases the risk of both diseases (for example, obesity) rather than a genetic factor.

Urinary traits

Calcium excretion. The most recognized risk factor for calcium stones[17,39,46], hypercalciuria, has been detected in up to 43% of people who form stones and their first-degree relatives[58]. Hypercalciuria is generally defined as urinary calcium excretion >200 mg per day in women and >250 mg per day in men, and may exist as an isolated

trait or in association with other metabolic disorders[47]. The causes of hypercalciuria have been described as absorptive (increased gastrointestinal absorption), resorptive (increased bone resorption) or renal (decreased renal reabsorption) losses[59]. However, phenotyping patients in this manner has not proved to be clinically useful. Moreover, key hormonal stimuli such as parathyroid hormone (PTH) and 1,25 dihydroxyvitamin D (1,25(OH)2D) have effects at all three sites.

The heritability of urinary calcium excretion has been estimated to be ~40%[39,60]. In a study of French-Canadian families, hypercalciuria was the only metabolic phenotype that was associated with kidney stone formation[61]. Daily urine calcium excretion was higher in sibships with kidney stones than in unaffected sibships (0.64 ± 0.33 versus 0.50 ± 0.22 mmol Ca^{2+}/mmol creatinine, $P < 10^5$) and hypercalciuria was associated with early-onset and recurrent stone disease. Thus, this study suggested, but did not prove, that hypercalciuria is hereditary[61]. In a follow-up study of the same population, a mixed model with codominant and polygenic components adjusted for confounders provided the best fit for 24-h urine calcium excretion[62]. The heritability attributable to a major gene was estimated to be 0.58 in both the mixed codominant and polygenic model and a single-gene codominant model. Overall, the available studies provide strong evidence of the heritability of urinary calcium and suggest the possibility of genetically mapping the quantitative trait loci.

Citrate excretion. Hypocitraturia (low urinary citrate excretion) is a risk factor for stone formation that is present in up to 60% of people who form CaOx stones[63]. In the urine, citrate can chelate calcium and serve as a crystallization inhibitor. The amount of citrate present in the final urine is determined by the amount of filtered citrate that is reabsorbed in the proximal tubule, which is in turn dependent on systemic acid–base balance. Acidosis leads to reduced renal citrate excretion and increased metabolism of reabsorbed citrate via the citric acid cycle to produce bicarbonate ions, whereas alkalosis has the opposite effect. Diets that are low in fruits and vegetables and high in animal protein favour hypocitraturia. Other important causes of hypocitraturia include chronic diarrhoea or renal tubular acidosis[64]. In a US community cohort, the heritability of urinary citrate excretion was reported to be 0.36 (REF.[60]), whereas the estimated heritability in an identical twin study was 0.95 (REF.[65]).

Other factors. Among other important urinary lithogenic molecules, heritable components for urinary oxalate and uric acid excretion were noted in an identical twin study[65]. Heritable components for urinary

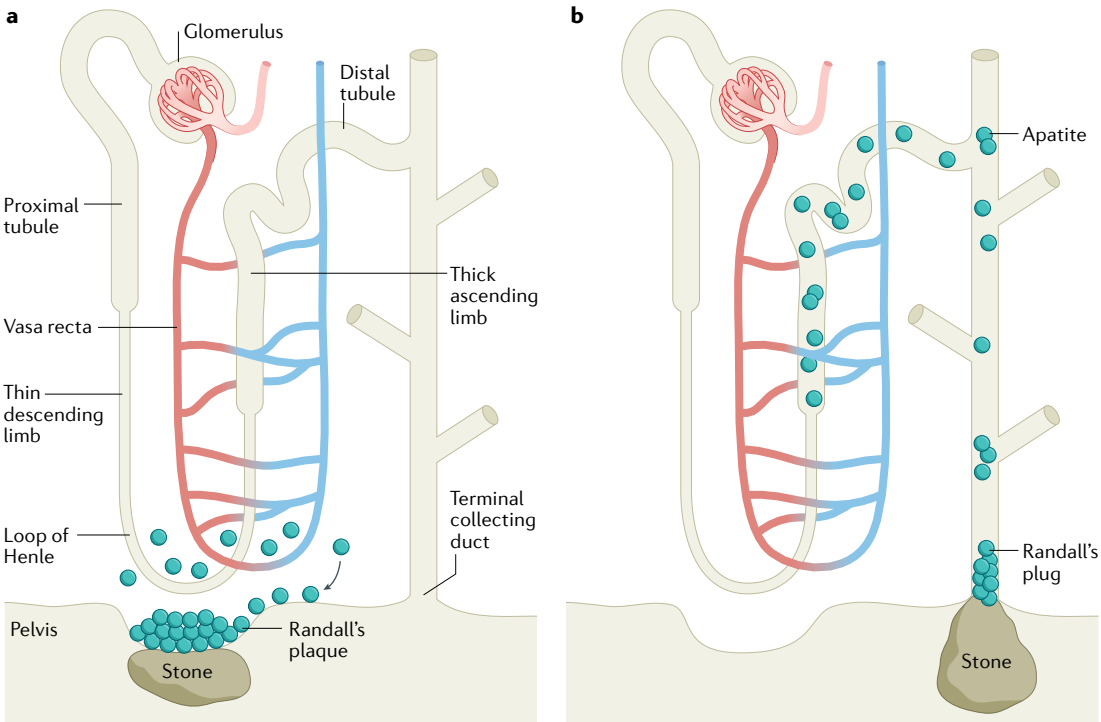

Fig. 1 | **Potential mechanisms of kidney stone initiation.** Two major pathways that create an anchoring site for kidney stone formation have been proposed. **a** | In the fixed particle mechanism, stones grow on Randall's plaques formed of interstitial apatite crystals within the renal medulla. These plaques might originate via transcytosis from the tubular lumen or directly nucleate in the lumen. Randall's plaques seem to be more numerous in people who form stones than in those who do not. They grow over time and erode through the urothelium via unclear mechanisms. Plaques that become exposed to the pelvic urine anchor the growth of calcium phosphate or calcium oxalate stones. **b** | In the free-particle mechanism, crystals form owing to supersaturations within the tubular fluid. Adhesion of crystals to collecting duct cells or crystal aggregation might lead to the formation of Randall's plugs that develop in the terminal collecting ducts and provide an anchoring site for stone growth. Reproduced with permission from Khan et al.[30], Springer Nature Limited.

Table 1 | **Factors that might contribute to the overall heritability of kidney stone disease**

Factor	Comment	Estimates of heritability (h^2)*	Refs
Systemic factors			
1,25-Dihydroxyvitamin D	Variable levels of heritability (no data available for people who form stones)	0.16–0.48	54–56
Serum calcium	Serum calcium regulation and renal calcium transport (further research needed in people who form stones)	0.21–0.45	51–53
Metabolic syndrome	Variable heritability (no data available for people who form stones)	Wide range of variance	57
Urinary excretion factors			
Calcium	Strong evidence for heritability	0.25, 0.94	60,65
Citrate	Significant heritability	0.36	60,65
Magnesium	Significant heritability	0.34	60
Volume	Significant heritability	0.24	60
Dietary factors			
Total protein	Significant heritability	0.37	69
Animal protein	Significant heritability	0.24	69
Calcium	Significant heritability	0.50	69
Oxalate	Significant heritability	0.22	69
Sucrose	Significant heritability	0.38	69
Fructose	Significant heritability	0.23	69

*h^2 is a measure of total variance in phenotype from differences in genotype.

magnesium excretion, urine volume and pH were also found in a US community cohort[60]. The observed heritability of urinary volume could potentially result from underlying genetic factors that influence thirst, vasopressin release or vasopressin receptors in the collecting duct.

Dietary traits

A wide variety of dietary factors, including intake of sodium, calcium, protein and water have been associated with increased kidney stone risk[66–68]. Although preferences for dietary factors have often been assumed to be environmental in nature, the available data now support a hereditary component[69,70]. Dietary preferences that are associated with kidney stone risk and have a strong heritable component include intake of animal protein, calcium, oxalate, sucrose and fructose; these dietary factors remained significantly associated with stone risk after adjustment for age, sex, height and weight[71,72]. The distinction between genetic and environmental risk factors might, therefore, be blurred, with certain individuals predisposed to dietary preferences that increase stone risk.

Patient management

Dietary modification can safely and effectively alter the urine composition of lithogenic factors, such as oxalate, calcium and citrate. However, robust evidence that these changes can impact long-term risk of stone events is lacking[5]. The American Urological Association guidelines recommend that all patients who form kidney stones strive for a fluid intake that produces a urine volume of at least 2.5 l daily[73]. For higher risk groups, such as patients with cystinuria, water intake to achieve a daily urine output of at least 3 l has been recommended. As dietary sodium has been linked to urinary calcium excretion, patients are advised to limit total daily sodium intake to 1,000–1,200 mg (<100 mEq)[73,74]. Dietary sodium and animal protein restriction can also reduce urinary cystine excretion[75]. Pharmacological interventions include thiazide diuretics (e.g. chlorthalidone 25–50 mg daily) for hypercalciuria[74,76], potassium citrate (<300 mg per 24 h) to increase urinary excretion of the crystallization inhibitor citrate or to raise the urinary pH (target >6.5 for uric acid stones, >7 for cystine stones; 20–30 mEq twice daily) or a xanthine oxidase inhibitor (e.g. allopurinol 100–300 mg per day) for the subgroup of CaOx stone formers with hyperuricosuria[74]. Improved knowledge of the monogenic causes of kidney stones as well as of gene variants that influence kidney stone risk in the general population may lead to the identification of novel therapeutic targets and facilitate a more personalized approach to therapy.

Monogenic forms of stone disease

Monogenic forms of kidney stone disease were previously thought to account for less than 2% of all cases, but accumulating data suggest that they might be more common[46,77,78]. In a prospective study that recruited participants from kidney stone clinics at three major teaching hospitals in the USA, UK and North Macedonia over a period of 2 years, a high-throughput mutation analysis identified a single-gene cause of nephrolithiasis in 11% of adult and 17–29% of paediatric patients who formed stones[77]. In an international cohort of 79 families with paediatric CKD onset and suspected nephrolithiasis, monogenic mutations were identified in 50 families by whole-exome sequencing with homozygosity mapping[79]. Another study that included 65 patients from 51 families with a history of kidney stones or ultrasonographic findings of nephrocalcinosis before the age of 25 years, identified 19 different mutations using whole-exome sequencing, 7 of which had not previously been reported[80].

Features that increase the likelihood of a monogenic cause of stones include the onset of kidney stone disease during childhood, multiple recurrent stone events, nephrocalcinosis, pathological urinary crystals or the concurrent presence of ocular or hearing defects (TABLE 2). However, genetic testing is required to obtain a firm diagnosis (BOX 1).

Forms associated with hypercalciuria

Most of the known monogenic causes of kidney stone disease are associated with hypercalciuria (TABLE 3).

Dent disease and Lowe syndrome. Dent disease is an X-linked recessive form of nephrocalcinosis or nephrolithiasis that affects males[81–83]. Dent disease 1 (OMIM 300009) is caused by mutations in *CLCN5* (Xp11.22; ~60% of cases[84]), whereas Dent disease 2 (OMIM 300555) is caused by mutations in *OCRL*

(Xq25; ~15–20% of cases)[85]. However, 25% of patients with an apparent Dent phenotype lack a known genetic cause[84,86,87]. Mutations in *OCRL* are also associated with Lowe syndrome (OMIM 309000), a more severe phenotype that includes cataracts and developmental delay in addition to the renal abnormalities[85,87]. Although hypercalciuria and nephrocalcinosis are common in patients with Lowe syndrome, kidney stones are reported in only 10–20% of these patients[88,89]. Why certain *OCRL* mutations cause Lowe syndrome whereas others cause Dent disease 2 is not entirely clear, but the location of the mutation within the gene might be important[89].

A clinical diagnosis of Dent disease is based on the presence of elevated urinary low molecular weight protein (LMWP), hypercalciuria and at least one of the following: nephrocalcinosis, kidney stones, haematuria, hypophosphataemia or CKD[90]. Patients might present with signs and symptoms related to hypercalciuria or urinary stones, such as microscopic or gross haematuria, dysuria and flank or abdominal pain[86]. Elevated urinary LMWP seems to be nearly universal[85] and can be detected by measuring β2-microglobulin, α1-microglobulin or retinol-binding protein. Nephrocalcinosis is seen in ~75% of patients with Dent disease 1[91] but only 30–50% develop kidney stones, which are typically composed of CaOx and/or CaP[49,78,90]. Interestingly, the presence and severity of nephrocalcinosis do not seem to correlate with CKD progression[85]. Although stone formation and nephrocalcinosis are thought to be mediated by hypercalciuria in Dent disease, the mechanism by which hypercalciuria occurs is not well understood and is not explained by the underlying defect in endocytosis[92].

Female carriers of Dent disease are generally asymptomatic but can show wide phenotypic variation, including modestly increased urinary LMWP, hypercalciuria and nephrocalcinosis[93,94]. Although female carriers rarely, if ever, develop kidney failure[94], CKD has been described in three patients[95].

CLCN5 encodes the electrogenic Cl^-/H^+ exchange transporter 5 (ClC5), which is mainly expressed in the proximal tubule and α-intercalated cells of the collecting duct[96]. More than 130 unique *CLCN5* mutations have been identified, most of which are missense or nonsense[96]. Filtered low-molecular weight proteins are reabsorbed in the proximal tubule via endocytic pathways that involve cell surface megalin and cubilin. As ClC5 seems to have an essential role in acidification of vesicles in the proximal tubule, mutations in *CLCN5* might result in impairment of lysosomal function and abnormal reabsorption and processing of low molecular weight proteins[97]. Studies in mice have confirmed that *ClCN5* knockout results in abnormal endosomal function[98].

OCRL mutations were initially identified in 12 families that had a phenotype resembling Dent disease in the absence of *CLCN5* mutations[91]. *OCRL* mutations might manifest as Dent disease 2 when only the kidney is affected or as Lowe syndrome when other more severe extrarenal phenotypes are present, such as developmental delay, cataracts and short stature. Although a wide overlap of renal manifestations has been reported, nephrocalcinosis is more prevalent in Dent disease 2 (40%) and kidney failure more common in Lowe syndrome. However, an apparent phenotypic continuum exists and Dent disease 2 can be viewed as a mild variant of Lowe syndrome[99].

OCRL encodes inositol polyphosphate 5-phosphatase OCRL, which hydrolyses phosphatidylinositol 4,5-bisphosphate (PIP2)[86] and is expressed ubiquitously in human tissues[99]. *Ocrl*-knockout mice have no renal or extra-renal abnormalities; however, simultaneous deficiency of *Ocrl* and *Inpp5b* (which encodes another PIP2 5-phosphatase) results in a lethal phenotype, suggesting that INPP5B can compensate for the absence of *OCRL*, at least in mice[99]. Thus, the phenotypic variability in patients with *OCRL* mutations has been speculated to

Table 2 | **Features that suggest a monogenic cause of kidney stones**

Monogenic cause	History and physical examination	Medical imaging findings	Kidney function	Urine findings	Stone type	Biochemical risk factors
Primary hyperoxaluria	Ocular crystals in patients with kidney failure	Nephrocalcinosis High stone burden	Elevated serum creatinine and/or reduced GFR Acute kidney injury	Calcium oxalate monohydrate crystals	Calcium oxalate monohydrate	Markedly increased urinary oxalate excretion (2× normal without enteric cause)
Dent disease	Young male		Elevated serum creatinine and/or reduced GFR	Low molecular weight proteinuria	Calcium oxalate or calcium phosphate	Hypercalciuria
Renal tubular acidosis	Reduced hearing			Calcium phosphate crystals	Calcium phosphate	Alkaline urine, hypocitraturia, hypercalciuria
Cystinuria	NA	High stone burden		Cystine crystals	Cystine	Positive urinary sodium nitroprusside test (confirm with quantitative urine cysteine)
APRT deficiency	Reddish-brown diaper stain	Radiolucent kidney stones that are not consistent with uric acid		Dihydroxyadenine crystals	Dihydroxyadenine	Increased urinary dihydroxyadenine

APRT, adenine phosphoribosyltransferase deficiency; GFR, glomerular filtration rate; NA, not applicable.

Box 1 | **Genetic testing**

As considerable overlap exists in the phenotype of many urinary stone diseases, genetic testing is often helpful in obtaining a firm diagnosis. However, careful analysis of detected variants is often necessary for correct interpretation of the results. Technological advances are rapidly expanding the availability of genetic testing in routine clinical care. Although Sanger sequencing was previously the 'gold standard' in diagnostics owing to its high sensitivity and specificity, screening multiple genes simultaneously using next-generation sequencing (NGS) approaches is now preferred. NGS can provide selective sequencing of a group of candidate genes, screen the entire coding portion of the genome (whole-exome sequencing), or enable whole genome sequencing. NGS gene panels that analyse a portion of the exome are often favoured for diagnostics because they are cost-effective and only screen known disease-associated genes, so the results are easy to interpret. For research screening, the whole-exome sequencing or whole-genome sequencing technique provides a more comprehensive assessment of the genome and enables new gene discovery. However, when employing these methods for diagnostics, there is a high possibility of detecting incidental findings unrelated to the known patient phenotype. Moreover, interpreting findings in non-coding segments of the genome is challenging.

result from variable expression of INPP5B or other compensating enzymes[99]. Reduced OCRL activity resulting in accumulation of PIP2 is thought to alter cell signalling involved in endocytosis, thereby providing a potential explanation for the similar phenotypes in Dent disease 1 and Dent disease 2 (REF.[100]).

The care of patients with Dent disease is supportive, focusing on strategies to reduce hypercalciuria and hopefully reduce the risk of nephrolithiasis and nephrocalcinosis (Supplementary Table 1). In a small uncontrolled trial in 7 boys with mild Dent disease 1, treatment with high-dose thiazide diuretics (>0.4 mg/kg/day) decreased urine calcium excretion measured following a 12-h period with no dietary calcium intake, but was associated with adverse effects such as dehydration and hypokalaemia[101]. Most patients with Dent disease 1 progress to kidney failure by the age of 40 years[92]. Kidney transplantation is often successful as the disease does not recur in the allograft[87].

Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal-recessive disorder caused by mutations in *CLDN16* or *CLDN19*, which encode the integral membrane tight junction proteins claudin-16 (also known as paracellin-1) and claudin-19, respectively[102]. Biallelic *CLDN16* (3q27) mutations result in FHHNC alone (OMIM 248250), whereas mutations in *CLDN19* (1p34.2) result in FHHNC with severe ocular abnormalities (OMIM 610036)[102,103]. *CLDN16* is the major locus with more than 40 predominantly missense mutations affecting the first extracellular loop of the protein. The most common mutation, p.Leu151Phe, has been detected in patients of European ancestry from Germany and Eastern Europe[104]. Fewer than 10 mutations have been described in *CLDN19*, the most common being a missense mutation p.Gly20Asp observed in patients of Spanish or French ancestry[105]. Substantial interfamilial variability and intrafamilial concordance exist, suggesting genotype–phenotype correlations, with progression to CKD more common in patients with *CLDN19* mutations (61% develop kidney failure) than those with *CLDN16* mutations (33% develop kidney failure)[106]. However, children with complete loss of function of claudin-16 have a more severe presentation with early onset CKD and progression to kidney failure, compared with patients with reduced claudin-16 function[102,107]. Kidney stones are not common but have been reported in affected kindreds[108].

Claudin-16 is exclusively expressed in the thick ascending limb (TAL) of the loop of Henle, whereas claudin-19 is expressed in the TAL and the tight junctions of the retina, explaining the ocular disease in patients with *CLDN19* mutations[102]. Claudins are essential to permit paracellular reabsorption of calcium and magnesium in the TAL and distal convoluted tubule[109]. This selective paracellular transport is driven by a lumen-positive transepithelial voltage generated by the activity of both the Na-K-2Cl$^-$ cotransporter (NKCC2) and the renal outer medullary potassium (ROMK) channel at the apical membrane (FIG. 2). Another tight junction protein in the TAL, claudin-14, inhibits the divalent cation permeability of the claudin-16–claudin-19 oligomer[110]. Stimulation of the calcium sensing receptor (CaSR) by extracellular calcium enhances claudin-14 expression via decreased production of two microRNAs, miR-9 and miR-374 (REF.[110]). The net result is increased claudin-14-mediated suppression of claudin-16–claudin-19 permeability, which reduces calcium reabsorption and promotes renal calcium excretion[111].

FHHNC is characterized by magnesium and calcium wasting, resulting in persistent hypomagnesaemia, marked hypercalciuria, early nephrocalcinosis and progressive CKD[109]. The majority of patients present during childhood with recurrent urinary tract infections, polyuria or polydipsia, nephrocalcinosis and/or failure to thrive[104,106]. In addition to hypomagnesemia, hypercalciuria and nephrocalcinosis, which are always observed, some patients might have elevated serum PTH levels, a urine acidification defect and hypocitraturia[104]. CKD is common in childhood with one-third of patients reaching kidney failure during adolescence[102,106]. The ocular abnormalities that are associated with *CLDN19* mutation include severe myopia, macular coloboma and nystagmus[109].

FHHNC is a diagnostic consideration among children who present with a history of recurrent kidney stones, nephrocalcinosis and renal impairment[78]. Diagnosis of FHHNC is further supported by the presence of hypomagnesaemia, hypercalciuria, hypocalcaemia, incomplete distal renal tubular acidosis (dRTA) and hypocitraturia[47]. Kidney biopsy findings are generally not diagnostic and, in most cases, the nonspecific finding of chronic tubulointerstitial nephropathy is observed. Patients with FRHHNC do not have hypokalemic metabolic alkalosis, which differentiates this disorder from Bartter and Gitelman syndromes. In addition, hypocalciuria is an important feature that differentiates Gitelman syndrome from FHHNC[78]. A diagnosis of FHNNC is confirmed by the presence of biallelic *CLDN16* or *CLDN19* mutations.

No universally effective therapeutic intervention exists for FHHNC. Medical management includes high-dose magnesium supplements and thiazide

diuretics to reduce urinary calcium excretion and progressive nephrocalcinosis (Supplementary Table 1). However, thiazide diuretics do not meaningfully reduce urinary calcium excretion or delay CKD progression, and the associated risk of magnesium wasting often prohibits their use[47,104]. As intrarenal prostaglandin E2 inhibits TAL solute reabsorption, patients with FHHNC have also been treated with indomethacin, which inhibits prostaglandin production. However, the experience is limited and this approach does not seem to substantially reduce urinary magnesium or urinary calcium excretion[106]. If kidney failure occurs, kidney transplantation can correct the renal defect[104,106].

Hereditary distal renal tubular acidosis. Primary dRTA is most common in children and is caused by impaired urinary acidification in the cortical collecting tubule resulting from a genetic disorder involving transporters[112,113]. Primary dRTA is caused by biallelic mutations in *ATP6V0A4*, *ATP6V1B1*, *SLC4A1* or more rarely, *FOXI1*, *WDR72* or *ATP6V1C2*, and monoallelic *SLC4A1* mutations[114,115]. Hereditary dRTA typically

Table 3 | **Monogenic causes of nephrolithiasis or nephrocalcinosis associated with hypercalciuria**

Disease (OMIM)	Gene	Inheritance	Phenotype
Dent disease 1 (300009)	*CLCN5*	XR	LMW proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis, kidney failure by the 4th to 5th decade
Dent disease 2 (300555)	*OCRL*	XR	LMW proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis (less frequent than in Dent disease 1)
Lowe syndrome (309000)			Cataracts, mild intellectual disability, seizures, amino aciduria, vitamin D-resistant rickets, nephrocalcinosis
Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (248250)	*CLDN16*	AR	Renal hypomagnesaemia, hypercalciuria, failure to thrive, nephrocalcinosis, progression to kidney failure in adolescence
Familial hypomagnesaemia with hypercalciuria, nephrocalcinosis and severe ocular involvement (610036)	*CLDN19*	AR	Renal hypomagnesaemia, hypercalciuria, failure to thrive, nephrocalcinosis, progression to kidney failure in adolescence, severe ocular abnormalities
Distal renal tubular acidosis	*FOXI1*	AR	Nephrocalcinosis, distal renal tubular acidosis, medullary cysts, early onset sensorineural deafness
	WDR72	AR	Amelogenesis imperfecta, distal renal tubular acidosis
	ATP6V1C2	AR	Hypokalaemia, distal renal tubular acidosis, nephrolithiasis, nephrocalcinosis, early kidney failure
Renal tubular acidosis with osteopetrosis (259730)	*CA2*	AR	Nephrocalcinosis, nephrolithiasis, osteopetrosis, brain calcification
Hereditary hypophosphataemic rickets with hypercalciuria (241530)	*SLC34A3*	AR	Early onset, rickets, short stature, renal wasting of phosphate and calcium, nephrolithiasis, reduced serum PTH
Idiopathic hypercalciuria and low bone density (193100)	*SLC34A3*	AD	Rickets, hypophosphataemia, nephrocalcinosis
Infantile hypercalcaemia (143880)	*CYP24A1*	AR	Hypercalcaemia, elevated 1,25(OH)2D, decreased 24,25(OH)2D, suppressed serum PTH with or without calcium stones
Idiopathic infantile hypercalcaemia (616963)	*SLC34A1*	AR	Hypophosphataemia, elevated 1,25(OH)2D, hypercalciuria
Bartter syndrome type I, antenatal (601678)	*SLC12A1*	AR	Antenatal or neonatal presentation with polyhydramnios, low-birthweight, hypokalaemia, metabolic alkalosis, secondary hyperaldosteronism
Bartter syndrome type II, antenatal (241200)	*KCNJ1*	AR	Antenatal or neonatal presentation with polyhydramnios, low-birthweight, hypokalaemia, metabolic alkalosis, secondary hyperaldosteronism; few reports of adult onset presentation with nephrocalcinosis and CKD
Bartter syndrome type III (607364)	*CLCNKB*	AR	Severe hypokalaemia metabolic alkalosis, secondary hyperaldosteronism, later symptom-onset
Bartter syndrome type IVa (602522)	*BSND*	AR	Hypercalciuria, congenital deafness, kidney failure
Bartter syndrome type IVb (613090)	*CLCNKB* or *CLCNKA*	DR	Renal salt wasting, sensorineural deafness
Bartter syndrome type V (300971)	*MAGED2*	XR	Salt wasting, polyuria, hypokalaemia, hypercalciuria, nephrocalcinosis, in utero onset
Autosomal dominant hypocalcaemia (601198)	*CASR*	AD	Hypocalcaemia, hypercalciuria, normal serum PTH owing to activating mutations
Familial hypocalciuric hypercalcaemia (145980)	*CASR*	AD	Hypercalcaemia, hypocalciuria, normal to elevated serum PTH owing to inactivating mutations.
Autosomal-dominant hypocalcaemia (145981)	*GNA11*	AD	Hypocalciuric hypercalcaemia

1,25(OH)2D, 1,25 dihydroxyvitamin D; 24,25(OH)2D, 24,25-dihydroxyvitamin D; AD, autosomal dominant; AR, autosomal recessive; CKD, chronic kidney disease; DR, digenic recessive; LMW, low molecular weight; OMIM, Online Mendelian Inheritance in Man; PTH, parathyroid hormone; XR, X-linked recessive.

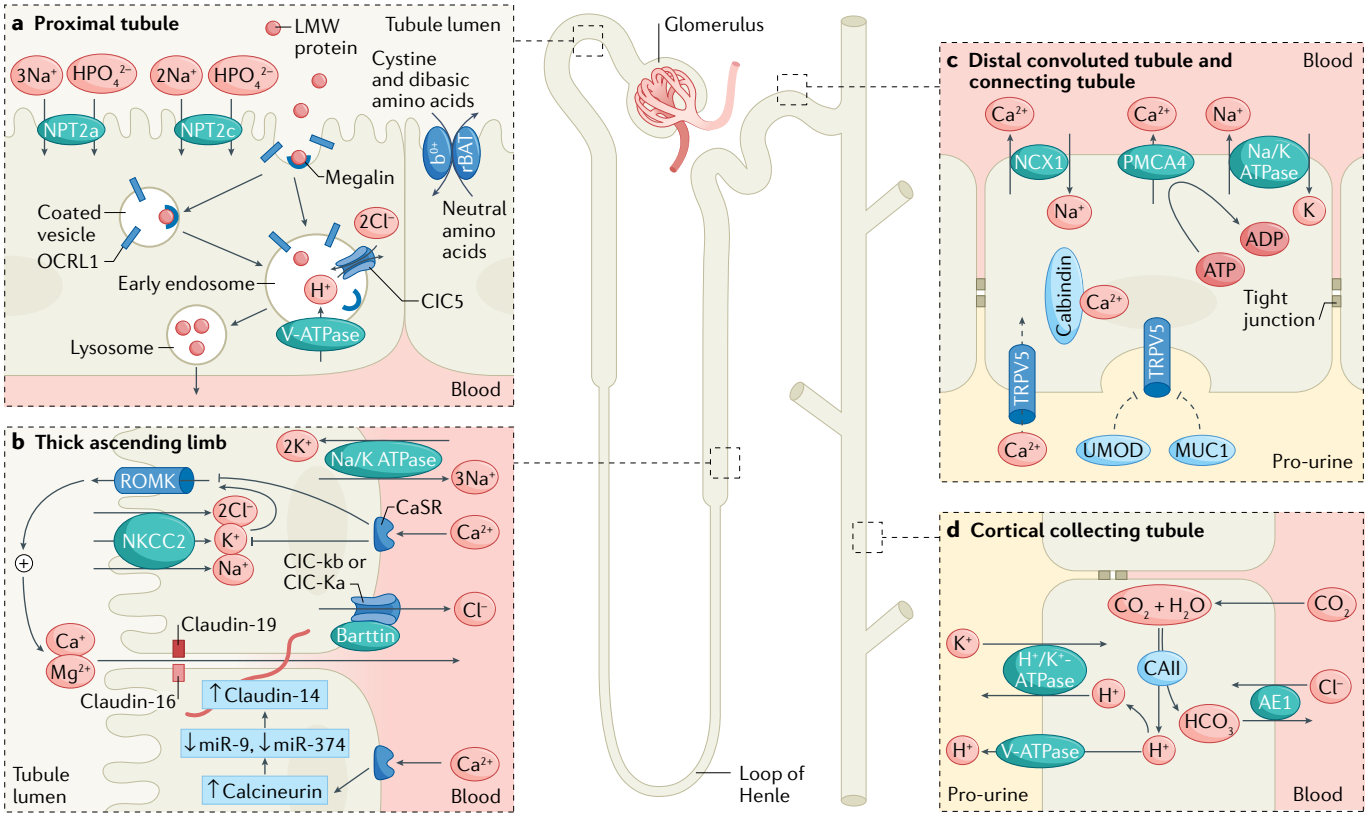

Fig. 2 | **Kidney mechanisms of nephrocalcinosis and kidney stone disease. a** | In the proximal tubule, phosphate reabsorption occurs via sodium-dependent phosphate transport protein 2a (NPT2a) and sodium-dependent phosphate transport protein 2a (NPT2c). Loss of NPT2a or NPT2c activity results in renal phosphorus wasting, indirectly resulting in increased formation of 1,25 dihydroxyvitamin D, hypercalciuria and nephrocalcinosis. Biallelic mutations in *SLC34A1* or *SLC34A3*, which encode NPT2a and NPT2c, respectively, cause hypophosphataemic rickets with hypercalciuria. Cystine and dibasic amino acids are taken up from the tubular lumen via a heterodimeric apical transport system. Mutations in *SLC3A1* or *SLC7A9*, which encode the rBAT and b^{0+}-type amino acid transporter 1 subunits of this transport system, respectively, result in cystinuria. Mutations in *CLCN5*, which encodes Cl^-/H^+ exchange transporter 5 (ClC5), and *OCRL*, which encodes inositol polyphosphate 5-phosphatase OCRL, cause Dent disease 1 and Dent disease 2, respectively. These mutations alter endocytosis and lysosomal function in the proximal tubule and thus impair receptor-mediated reabsorption of proteins from tubular fluid. The net result is marked low molecular weight (LMW) proteinuria. Hypercalciuria is also observed in Dent disease, perhaps due to distal tubular effects of disordered reabsorption of parathyroid hormone. **b** | Sodium, chloride and potassium are reabsorbed via apical NKCC2 in the thick ascending limb of the loop of Henle. Back leak of potassium into the lumen via ROMK creates a transepithelial voltage gradient that drives paracellular reabsorption of calcium, magnesium and sodium. Mutations in *SLC12A1*, which encodes NKCC2, cause Bartter syndrome type I, whereas mutations in *KCNJ1*, which encodes ROMK, cause Bartter syndrome type II. In these syndromes, loss of paracellular calcium reabsorption leads to the development of hypercalciuria, nephrolithiasis and nephrocalcinosis. Biallelic mutations in *CLCNKB*, which encodes the chloride channel protein ClC-Kb, cause Bartter syndromes type III or IV. Biallelic mutations in *CLCNKA*, which encodes ClC-ka, and in *BSND*, which encodes the chaperone protein Barttin, have been associated with Bartter syndrome type IV. A transient antenatal Bartter syndrome caused by hemizygous mutations in *MAGED2*, which encodes a protein with a role in cell-cycle regulation (not shown), is sometimes termed Bartter syndrome type V. Loss of function mutations in *CASR*, which encodes the calcium sensing receptor (CaSR), increase the threshold for calcium sensing in the parathyroid glands and kidney and therefore result in increased tubular reabsorption of calcium and the benign condition familial hypercalcaemia and hypocalciuria, whereas gain of function mutations in *CASR* result in a phenotype that is also sometimes termed Bartter syndrome type V. Biallelic mutations in *CLDN16* or *CLDN19* cause familial hypomagnesaemia with hypercalciuria and nephrocalcinosis. These genes encode the tight junction proteins, claudin-16 and claudin-19, respectively, which are essential for paracellular reabsorption of calcium and magnesium in the thick ascending limb and distal convoluted tubule. Mutations that reduce the functional activity of the claudin-16–claudin-19 complex result in reduced reabsorption of calcium and magnesium, increased urinary calcium excretion and increased risk of nephrocalcinosis and nephrolithiasis. Claudin-14 is upregulated in response to increased serum calcium sensed by the basolateral CaSR and acts to decrease thick ascending limb paracellular permeability to divalent cations. Variants in *CLDN14*, which encodes claudin-14, have been associated with kidney stone disease in genome-wide association studies. **c** | Calcium transport in the distal convoluted tubule and connecting tubule involves uptake through transient receptor potential vanilloid 5 (TRPV5) at the apical membrane, shuttling by calbindin and extrusion via plasma membrane calcium-transporting ATPase 4 (PMCA4) and sodium-calcium exchanger 1 (NCX1). TRPV5 endocytosis is regulated by urinary uromodulin (UMOD) and Mucin-1 (MUC1). Hypercalciuria is an important kidney stone risk factor, and modulation of TRPV5 activity by these proteins seems likely to modulate this risk. Variants in *UMOD* and *TRPV5* have been associated with risk of kidney stones in genome-wide association studies. **d** | In the cortical collecting tubule, the apical V-ATPase and H^+/K^+-ATPase, intracellular carbonic anhydrase II (CAII), and the basolateral chloride bicarbonate counter transporter anion exchange protein 1 (AE1) have key roles in distal tubular acidification. Mutations in the genes encoding these proteins can result in distal renal tubular acidosis.

presents in infancy with failure to thrive; later manifestations are usually associated with monoallelic *SLC4A1* mutations, which can also cause red blood cell abnormalities[116]. *ATP6V0A4* mutations are associated with the most severe metabolic acidosis. *ATP6V1B1* and *FOXI1* mutations are associated with early onset deafness, whereas *ATP6V0A4* mutations cause later onset of deafness[113,117,118] (FIG. 2).

ATP6V0A4, ATP6V1B1 and *ATP6V1C2* encode the A4, B1 and C2 subunits of the vacuolar (V)-type H^+-ATPase, whereas *SLC4A1* encodes the chloride bicarbonate counter transporter anion exchange protein 1 (AE1). *WDR72* encodes WD repeat-containing protein 72, which has been implicated in the trafficking of V-type-ATPases. *FOXI1* encodes a transcription factor, forkhead box protein I1, that regulates the function of AE1, anion exchange protein 4 (AE4) and the V-type ATPase subunits[119]. All of these proteins are expressed in type A intercalated cells. Mutations in either V-type H^+-ATPase, which excretes H^+ protons into the urine, or AE1, which reabsorbs $HCO3^-$ into the circulation, account for 85% of diagnosed causes of primary dRTA[113]. An incomplete dRTA phenotype has been reported in patients with monoallelic variants in *ATP6V1B1* or *ATP6V0A4*[120,121].

dRTA is suspected when hyperchloremic metabolic acidosis is present in the setting of normal kidney function. Initial clinical manifestations include polyuria, polydipsia, emesis, constipation, diarrhoea, decreased appetite and episodes of dehydration[117]. Nephrolithiasis and nephrocalcinosis are also common features[122]. As CaP precipitates at high pH, a persistently alkaline urine predisposes to nephrocalcinosis and nephrolithiasis[116]. Chronic metabolic acidosis also promotes loss of bone calcium, resulting in hypercalciuria and promoting nephrocalcinosis[113].

Treatments for dRTA focus primarily on correcting the underlying metabolic acidosis[113] (Supplementary Table 1). Patients are typically provided with alkali in the form of twice daily oral potassium citrate. Although this treatment corrects chronic metabolic acidosis, the persistently alkaline urine is not changed; thus patients are at continued risk for CaP stones and nephrocalcinosis[116].

Renal tubular acidosis with osteopetrosis. Biallelic mutations in *CA2* are associated with RTA with osteopetrosis (OMIM 259730) and cerebral calcification[123,124]. *CA2* encodes carbonic anhydrase II (CAII), which is essential for net movement of H^+ and $HCO3^-$ in the proximal and distal segments of the renal tubule. Patients have markedly increased bone density, leading to progressive bone marrow replacement and pancytopenia. Typical phenotypic features include intellectual disability, short stature and basal ganglial calcifications[125] High-dose alkali (10–15 mg/kg per day) combined with hydrochlorothiazide (12–25 mg) has been used to treat RTA with osteopetrosis, but treatments are largely supportive and patients have high morbidity and mortality.

Hereditary hypophosphataemic rickets with hypercalciuria. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH; OMIM 2414530) is caused by biallelic mutations in *SLC34A3*, which encodes sodium-dependent phosphate transport protein 2 C (NPT2c). More than 40 different mutations in have been reported in biallelic cases[126,127]. Monoallelic *SLC34A3* variants can also result in idiopathic hypercalciuria and low bone density[128].

HHRH is characterized by rickets, reduced renal phosphate reabsorption, hypophosphatemia, hypercalciuria, nephrolithiasis and increased 1,25(OH)2D production in the kidney[126,127,129]. Increased 1,25(OH)2D results in hypercalciuria through enhanced intestinal calcium and phosphorus absorption, increased mobilization from bone, and increased calcium and decreased phosphorus reabsorption in the distal kidney due to suppression of PTH secretion (FIG. 2).

Treatment of HHRH consists of oral neutral phosphorus supplements and avoidance of active vitamin D analogues (Supplementary Table 1). However, long-term data regarding the effectiveness of oral phosphorus for decreasing renal calcification and bone loss is lacking[126].

Infantile hypercalcemia type 1. Infantile hypercalcaemia type 1 (HCINF-1; OMIM 143880) is caused by biallelic mutations in *CYP24A1*, with more than 40 described to date[130,131].These mutations normally follow an autosomal recessive pattern of transmission but autosomal-dominant transmission with partial penetrance has also been described[132]. As *CYP24A1* encodes 1,25-dihydroxyvitamin D(3) 24-hydroxylase[130], loss of *CYP24A1* results in inappropriate accumulation of active 1,25(OH)2D. Two distinct biallelic phenotypes have been described, both of which frequently include nephrolithiasis[133]. Patients with the more severe phenotype present in infancy with symptomatic hypercalcaemia, severe dehydration, vomiting and failure to thrive, whereas those with the less severe phenotype present later in childhood or adulthood with hypercalcaemia that can be asymptomatic or associated with nephrocalcinosis, kidney stones or CKD. Patients with monoallelic *CYP24A1* mutations might be asymptomatic or have mild CaOx crystal disease and occasionally present with hypercalcaemia[132,134]. Treatment of HCINF-1 is based on eliminating exogenous vitamin D precursors, limiting calcium intake and generous fluid administration (Supplementary Table 1).

Although most patients with biallelic *CYP24A1* mutations present with infantile hypercalcaemia, identical biallelic *CYP24A1* mutations among adolescents and adults who present with recurrent kidney stones are increasingly being identified[135,136]. Among patients who present in adulthood, hypercalcemia is less pronounced and intact PTH is suppressed (unlike in patients who present as infants). There is an impression that hypercalcaemia and hence disease severity might diminish with age.

Once a diagnosis of CYP24A1 deficiency is established, dietary intake of vitamin D and calcium should be reduced or avoided[46,134]. As patients have inappropriately high 1,25(OH)2D concentrations, these measures do not typically cause inappropriately low net calcium absorption. However, it is prudent to closely monitor bone health and the levels of related hormones (for example, PTH)

when instituting such restrictions. Low-dose fluconazole and rifampin can reduce the concentration of 1,25(OH)2D by altering the activity of cytochrome P450 enzymes involved in 1,25(OH)2D synthesis and degradation, and thus lower serum calcium concentration and urinary calcium excretion[46,137,138]. However, concerns exist about the long-term hepatic safety of these agents.

Infantile hypercalcaemia type 2. Patients with infantile hypercalcaemia type 2 (HCINF-2; OMIM 616963) harbour biallelic *SLC34A1* mutations[139]. Nearly 30 different mutations have been described, although the importance of the in frame deletion p.Val91_Ala97del has been questioned as it is found on ~1.7% of alleles in normal populations[131,139]. Whether single pathogenic alleles are associated with an increased risk of kidney stones is unclear[140]. In a large Pakistani cohort of individuals with nephrolithiasis (235 families), high-throughput exon sequencing detected a monogenic cause in 7% of patients (17 families) with *SLC34A1* monoallelic mutations detected in 16 of 17 patients[141].

SLC34A1 encodes sodium-dependent phosphate transport protein 2 A (NPT2a). Loss of NPT2a in patients with HCINF-2 results in proximal tubular renal phosphate wasting, hypophosphataemia, and compensatory increases in 1,25(OH)2D that in turn favour hypercalcaemia and hypercalciuria[131]. Nephrocalcinosis is also commonly observed in these patients[142].

Phosphate supplementation is likely beneficial for patients with HCINF-2[139]. As for patients with *CYP24A1* mutations, an azole antifungal agent may be used to lower circulating 1,25(OH)2D levels by inhibiting 1α-hydroxylase, however concerns exist about the long-term safety of this treatment. Thus, phosphate supplementation with a low calcium diet and avoidance of vitamin-D supplements is often employed as the first line strategy, together with close monitoring to minimize the risk of nephrocalcinosis or osteopenia (Supplementary Table 1).

Bartter syndrome. Bartter syndrome is a group of channelopathies that affect TAL transporter proteins that are involved in sodium chloride reabsorption[84]. These disorders manifest with autosomal recessive inheritance and result in excessive urinary sodium losses associated with hypokalaemia, metabolic alkalosis and hyperaldosteronism and/or hyperreninaemia[143] (FIG. 2). Hypercalciuria is a universal feature, whereas nephrocalcinosis is most frequently observed with Bartter syndromes I, II and V[144].

Bartter syndromes I (OMIM 601678) and II (OMIM 241200) usually present with nephrocalcinosis during the antenatal or postnatal period[144]. Biallelic mutations in *SLC12A1*, which encodes the kidney-specific Na-K-Cl symporter (NKCC2), or in *KCNJ1*, which encodes the ATP-sensitive inward rectifier potassium channel 1 (ROMK), cause Bartter syndromes I and II, respectively[145,146]. Bartter syndrome II may initially present with hyperkalaemia in infancy, but evolve to hypokalaemia in the postnatal period[147]. More than 70 *SLC12A1* mutations and 40 *KCNJ1* mutations have been described to date. A patient who presented in adulthood with incidental nephrocalcinosis associated with biallelic *KCNJ1* missense mutations has also been described[147]. The COX inhibitors indomethacin seems to be effective in antenatal Bartter syndromes, whereas potassium-sparing diuretics or angiotensin-converting enzyme inhibitors are often used to correct the metabolic disturbances in adult Bartter syndrome II[147,148] (Supplementary Table 1)

Bartter syndrome III (OMIM 607364) is caused by biallelic mutations in *CLCNKB*, which encodes the chloride channel protein ClC-Kb. This syndrome usually presents in the teenage years or later with a phenotype of severe hypokalaemic alkalosis and, less commonly, hypercalciuria and nephrocalcinosis[149,150]. Treatments centre around potassium and magnesium repletion.

Bartter syndrome IVA (OMIM 602522) is associated with sensorineural deafness and early onset CKD that is not responsive to indomethacin[151]. Biallelic mutations in *BSND*, which encodes Barttin, a chaperone protein for the chloride channel proteins ClC-Ka and ClC-Kb, result in Bartter syndrome IVA (OMIM 613090). Rare biallelic mutations in *CLCNKB* and the adjacent *CLCNKA*, which encodes ClC-Ka, have been associated with a similar phenotype termed Bartter syndrome IVB (OMIM 613090), which has digenic recessive inheritance[152]. A transient antenatal Bartter syndrome with X-linked recessive inheritance, sometimes termed Bartter syndrome V (OMIM 300971), is caused by hemizygous mutations in *MAGED2*, which encodes melanoma-associated antigen D2, a protein with a role in cell cycle regulation[153]. Treatments for Bartter syndrome IVA, IVB and V are supportive, including repletion of potassium and other electrolytes.

Autosomal-dominant hypocalcaemia with hypercalciuria. Monoallelic gain of function mutations in *CASR*, which encodes the CaSR, are associated with autosomal dominant hypocalcaemia with hypercalciuria (ADHH; OMIM 601198)[154]. More than 70 ADH-causing *CASR* mutations have been identified, all of which increase the sensitivity of the CaSR to extracellular Ca^{2+} and are clustered in the CaSR dimer interface, which is the region of G protein binding[155,156]. Gain-of-function mutations in *CASR* expressed on the basolateral surface of TAL cells in the loop of Henle lead to inhibition of the activity of NKCC2 and ROMK proteins via intracellular feedback signalling, resulting in a Bartter-like phenotype[157], which is sometimes termed Bartter syndrome V[158] (FIG. 2). More rarely, monoallelic gain of function mutations in *GNA11*, which encodes a G protein involved in extracellular $Ca2^{+}$ sensing, have been associated with ADHH[159].

The human CaSR is predominantly expressed in the parathyroid gland and kidney[47]. Stimulation of parathyroid CaSR inhibits the release of PTH, resulting in systemic effects on bone, intestine and kidney that lead to reductions in serum calcium and phosphorus levels. Patients with ADHH therefore have a phenotype similar to that of hypoparathyroidism. Administration of vitamin D and calcium can markedly worsen hypercalciuria, nephrocalcinosis and CKD risk in these patients[154]. Thus, the minimum doses of calcium and vitamin D should be employed to alleviate symptoms.

Forms not associated with hypercalciuria

A small number of genes that are associated with the development of kidney stones that are composed of components other than calcium have been described (TABLE 4).

Primary hyperoxaluria. The primary hyperoxalurias are rare inborn errors of glyoxylate metabolism that result in marked hepatic overproduction and urinary excretion of oxalate, typically >1 mmol/1.73 m^2 per 24 h (normal excretion is <0.46 mmol/1.73 m^2 per 24 h)[160,161]. The excess oxalate cannot be degraded by humans; thus, it is excreted by the kidneys, resulting in high urinary concentrations that favour the formation of CaOx crystals, nephrocalcinosis and kidney stones[162]. To date, three distinct types of primary hyperoxaluria have been described, which involve different enzymes in the oxalate metabolic pathway[161].

Primary hyperoxaluria 1 (PH1; OMIM 259900) is caused by biallelic mutations in *AGXT*, which encodes the liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT), and accounts for ~80% of cases[163]. Reduced activity of AGT results in glyoxylate accumulation, which in turn leads to overproduction of oxalate and glycolate[164]. To date, more than 200 *AGXT* mutations have been described[165]. Some of these mutations result in incomplete AGT folding in the endoplasmic reticulum, which leads to mistargeting of AGT to mitochondria instead of peroxisomes[166,167]. The p.Gly170Arg mutation, which is in strong linkage disequilibrium with the common variant p.Pro11Leu (15% of all alleles), resulting in co-segregation, is the most common mistargeting mutation, accounting for approximately 20% of PH1 alleles. Patients who are heterozygous for the p.Gly170Arg mutation have more severe disease and partially respond to treatment with pharmacological doses of pyridoxine (vitamin B6), whereas those who are homozygous for this mutation have milder disease and respond completely to pyridoxine[165,168–170]. Patients with other likely mistargeting mutations in *AGXT*, such as p.Gly41Arg, might also respond to pyridoxine[171] (Supplementary Table 1).

Primary hyperoxaluria 2 (PH2; OMIM 260000) is caused by biallelic mutations in *GRHPR*, which encodes glyoxylate reductase/hydroxypyruvate reductase (GRHPR), and accounts for approximately 10% of cases of primary hyperoxaluria. The frameshifting c.103delG mutation is the most common[165,172]. Loss of GRHPR function is associated with hyperoxaluria and L-glyceric aciduria[78,173]. Patients with PH2 might have slightly lower urinary oxalate excretion than those with PH1, and generally have a milder phenotype. However, most patients with PH2 experience recurrent kidney stones and progressive CKD and kidney failure are common[161,173,174].

Primary hyperoxaluria 3 (PH3; OMIM 613616) is the most recent subtype to be identified and results from mutations in *HOGA1*, which encodes the liver-specific mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA1)[161,175,176]. PH3 accounts for ~12% of cases of primary hyperoxaluria with c.700 + 5 G > T and p.Glu315del the most common mutations. As HOGA1 catalyses the final step of hydroxyproline metabolism (4-hydroxy-2-oxoglutarate to glyoxylate and pyruvate)[176,177], PH3 is characterized by elevated urinary oxalate and hydroxy-oxo-glutarate excretion[178,179]. Patients with PH3 often have an earlier onset of symptomatic stone disease but a lower risk of kidney failure than those with PH1 or PH2 (REFS[161,175]). Nonetheless, they can develop CKD and frequent stone events and surgeries are common[180].

High fluid intake and inhibitors of CaOx crystallization (such as citrate or neutral phosphate) are used to decrease the risk of stone formation and renal injury in patients with primary hyperoxaluria[160]. Orthotopic liver transplantation is a definitive treatment to correct the metabolic defect in PH1. In patients with PH1 and kidney failure, combined liver and kidney transplantation or kidney after liver transplantation have been employed as the risk of recurrent oxalate nephropathy is high after kidney transplantation alone[181]. Pharmacological pyridoxine (5–10 mg/kg/day) is an essential part of the treatment regimen in responsive patients, who most often have mistargeting mutations[182]. Newer treatment options include oral oxalate-degrading enzymes delivered alone or within bacteria. Liver-targeted RNA interference agents that block endogenous hepatic oxalate production are currently undergoing clinical trials[167,183] (Supplementary Table 1).

Cystinuria. Cystinuria (OMIM 220100) is one the most common genetic stone diseases and is estimated to cause up to 10% of all paediatric urinary stones[143,184].The worldwide prevalence is estimated to be 1 in 7,000, ranging from 1 in 2,500 among Libyan Jews to 1 in 100,000

Table 4 | **Monogenic cause of nephrolithiasis not associated with hypercalciuria**

Disease name (OMIM)	Gene	Inheritance	Phenotype
Primary hyperoxaluria type I (259900)	*AGXT*	AR	Early onset recurrent calcium oxalate nephrolithiasis, nephrocalcinosis, systemic oxalosis, frequent progression to kidney failure
Primary hyperoxaluria type II (260000)	*GRHPR*	AR	Recurrent calcium oxalate nephrolithiasis, nephrocalcinosis
Primary hyperoxaluria type III (613616)	*HOGA1*	AR	Early onset and recurrent calcium oxalate nephrolithiasis
Cystinuria (220100)	*SLC3A1 or SLC7A9*	AR	Early onset recurrent cystine nephrolithiasis, progression to CKD
	SLC7A9 or SLC3A1	AD	Cystine nephrolithiasis, potentially milder phenotype
	SLC3A1 and *SLC7A9*	DD, TA	Cystine nephrolithiasis, potentially milder phenotype
Adenine phosphoribosyltransferase deficiency (614723)	*APRT*	AR	2,8-dihydroxyadenine stones, crystalluria, progressive CKD

AD, autosomal-dominant; AR, autosomal-recessive; CKD, chronic kidney disease; DD, digenic dominant; OMIM, Online Mendelian Inheritance in Man; TA, triallelic.

in a Swedish population[78]. The disease usually results from biallelic mutations in *SLC3A1* or *SLC7A9*, which encode rBAT and b^{0+}-type amino acid transporter 1, the subunits of a proximal tubular transporter that reabsorbs cystine, ornithine, lysine and arginine[185,186] (FIG. 2). However, monoallelic cases of cystinuria (usually with *SLC7A9* mutations) that may or may not have a milder phenotype have also been described, as have monoallelic digenic and even triallelic cases[77,187]. To date, more than 200 pathogenic nucleotide variants and large gene rearrangements have been described, without any clear genotype–phenotype associations[78].

As cysteine is poorly soluble in urine, cystinuria is characterized by frequently recurrent cystine stones[184]. Patients with cystinuria can develop CKD owing to recurrent stones, obstructive uropathy and repeated urological interventions. The presence of characteristic hexagonal cystine crystals in the urine or identification of cystine in a passed or removed stone is pathognomonic and diagnostic. Hyperhydration to dilute the urine is the mainstay of therapy. Low sodium and protein intake can also reduce urinary cystine excretion, whereas urinary alkalization can improve cysteine solubility. Thiol drugs such as D-penicillamine and tiopronin that form cysteine-drug dimers and thereby reduce cystine concentrations are also effective treatment options if hyperhydration, dietary measures and urinary alkalinization do not suffice[188] (Supplementary Table 1).

Adenine phosphoribosyltransferase deficiency. Adenine phosphoribosyltransferase deficiency (APRTd; OMIM 614723) is a rare inborn error of purine (adenine) metabolism characterized by the generation of a large amount of the highly insoluble compound 2,8 dihydroxyadenine (DHA), which is excreted by the kidney, favouring the formation of DHA stones and progressive CKD secondary to crystalline nephropathy[78,189,190]. APRTd is caused by biallelic *APRT* mutations. More than 50 of these mutations have been reported to date, most of which are single base-pair changes or small deletions[191]. Up to 70% of affected Japanese patients have the same missense mutation (p.Thr136Met), whereas the most common mutation in European families is a splice site mutation (c.400 + 2dupT)[189,191,192].

Patients with APRTd can be diagnosed based on absent red blood cell APRT activity, elevated DHA excretion, detection of DHA in a stone analysis or *APRT* genetic testing[143]. Urinary DHA crystals have a characteristic appearance under light and polarized light microscopy, with a central Maltese cross pattern often observed[78,193]. They are radiolucent and, hence, can be confused with uric acid stones. As both CaOx and DHA crystals are birefringent under polarizing light, cases of APRTd have been confused with primary hyperoxaluria. Patients often present with kidney stones, but advanced CKD without a prior history of stones is also common[193]. At least 15% of patients are diagnosed after the onset of kidney failure[78].

The xanthine oxidase inhibitors allopurinol and febuxostat decrease DHA synthesis and prevent new kidney stone formation, renal DHA deposition and progressive crystal nephropathy[189,190]. A small study published in 2018 suggested that febuxostat might be more effective than allopurinol for reducing DHA excretion[194] (Supplementary Table 1). Importantly, APRTd can recur in a transplanted kidney unless xanthine oxidase inhibitor therapy is maintained[143].

Hereditary xanthinuria. Hereditary xanthinuria is an autosomal-recessive disorder associated with defective purine metabolism. Type 1 xanthinuria (OMIM 278300) results from mutations in *XDH*, which encodes xanthine dehydrogenase/oxidase (XDH), whereas type 2 xanthinuria (OMIM 603592) is caused by mutations in *MOCOS*, which encodes molybdenum cofactor sulfurase (MOCOS), an essential cofactor in the activation of XDH and aldehyde oxidase[195,196]. Deficiencies in XDH or MOCOS result in low serum uric acid concentrations and increased concentrations of the oxypurine precursors xanthine and hypoxanthine. Type 2 xanthinuria also results in an increased serum sulphite concentration, which distinguishes this disorder from type 1 xanthinuria[197].

Type 1 xanthinuria might be asymptomatic[198] or present with myopathy, whereas type 2 xanthinuria can present with psychomotor retardation, failure to thrive, seizures and hypotonia resulting from increased sulphite levels[197,199]. Xanthine kidney stones occur in about 30% of patients. Diets low in purine and high in fluid may offer some protection against xanthine lithogenesis[200].

Common variants associated with kidney stones

Knowledge about the genetic basis of kidney stone disease in the general population is still in the early stages. However, genetic factors that are associated with nephrolithiasis have been identified by GWAS of large populations. Many of the genes that have been implicated in kidney stone risk by GWAS, including *CASR*, *SLC34A1* and *CYP24A1*, are also monogenic causes of urinary stone disease or nephrocalcinosis (Supplementary Table 2).

A GWAS that included 3,773 patients with kidney stones and 42,510 control individuals from Iceland and the Netherlands, identified four single nucleotide polymorphisms (SNPs) in or close to the *CLDN14* gene on chromosome 21 that were associated with kidney stone disease (OR = 1.25)[201]. The study found that 62% of the Icelandic general population were homozygous for one of these SNPs, rs219780[C], which was associated with a 1.64 times greater risk of developing kidney stones than that of non-carriers. The strongest association with kidney stone risk was seen for the *CLDN14* sequence variant rs199565725[AAC], which is in strong linkage disequilibrium with rs219780[C].

In a cohort of 8,450 Icelanders and 3,601 Danish women, rs219780[C] and another *CLDN14* variant, rs219779[C], were associated with decreased bone mineral density at the hip and spine[201–203]. These variants were associated with kidney stones in the Icelandic cohort but this association was not verified in the Danish cohort. The researchers reported a trend towards an association between rs219780[C] and serum total CO_2, serum PTH and urine calcium; however, no association was observed between the kidney stone risk variants and serum calcium, phosphate, 1,25(OH)2D or serum PTH[201,203]. Overall, however, the available data

suggest that common *CLDN14* variants alter calcium metabolism and kidney stone risk.

A GWAS that included data from 11,130 patients with kidney stones and 187,639 controls, identified 9 SNPs in *CLDN2* that were associated with an increased risk of kidney stone disease[204]. *CLDN2* encodes claudin-2, which has a role in the regulation of paracellular calcium reabsorption in the proximal nephron. In mice, loss of claudin-2 function led to hypercalciuria[204]. Compared with wild type mice, claudin-2-knockout mice had a more positive calcium balance and an exaggerated reduction in urinary calcium excretion with dietary calcium restriction. The researchers hypothesized that claudin-2 deletion might result in increased gut calcium absorption owing to reduced colonic paracellular calcium permeability. Deletion of claudin-2 in a mouse model was also associated with reduced proximal tubular cation reabsorption[205]. These findings provide a conceptual framework for the coexistence of reduced renal calcium reabsorption and increased gastrointestinal calcium absorption in patients with idiopathic CaOx stone formation[204,206].

Uromodulin (also known as Tamm Horsfall protein) is the most abundant protein in mammalian urine and has been implicated in urinary crystallization and kidney stone disease[207]. A variant in *UMOD*, which encodes uromodulin, conferred protection against kidney stones in a large Icelandic study that included 5,419 patients with kidney stones and 279,870 controls (OR 0.88, $P = 5.7 \times 10^{-5}$)[203]. *UMOD* variants that increase urinary UMOD excretion have been associated with CKD risk in Icelandic and Dutch populations[207,208]. Specific monoallelic mutations in *UMOD* are also associated with autosomal-dominant tubulointerstitial kidney disease[209]. Missense variants in *SLC34A1* (pTyr489Cys) and *TRPV5* (p.Leu530Arg) were associated with recurrent kidney stone formation in this Icelandic cohort[202]. Renal calcium wasting, decreased bone mass and increased gut absorption have been demonstrated in *TRPV5*-knockout mice[210]. This finding is unsurprising because *TRPV5* encodes a calcium channel transporter protein that is located on the apical side of the distal convoluted tubule and is stimulated by PTH and 1,25(OH)2D[211,212] (FIG. 2).

A Japanese GWAS study that included 5,892 patients with kidney stones and 17,809 controls, identified associations between common variants of *SLC34A1* (OR 1.19, $P = 8.5 \times 10^{-12}$), *AQP1* (which encodes aquaporin 1; OR 1.22, $P = 2.2 \times 10–14$) and *DGKH* (which encodes diacylglycerol kinase; OR 1.14, $P = 4.6 \times 10^{-9}$) and calcium kidney stones[213]. In a subsequent Japanese analysis, the *SLC34A1* variant was also associated with reduced estimated glomerular filtration rate ($P = 6.54 \times 10^{-8}$).

A GWAS of 28.3 million sequence variants in a large Icelandic population comprising 5,419 people who formed kidney stones (including 2,172 with recurrent stones) and 279,870 controls, identified associations between common sequence variants in *CLDN14*, *SLC34A1* and *ALPL* (which encodes alkaline phosphatase) and risk of kidney stones, as well as a suggestive association for a *CASR* variant ($P = 2 \times 10^{-8}$)[202]. A total of 31 *CLDN14* variants were significantly associated with any stone event, including six variants that were associated with recurrent kidney stones.

Two *ALPL* variants, rs1256328 and a missense variant rs34605986, were associated with kidney stone risk (OR = 1.19, $P = 8.9 \times 10^{-8}$). The rs1256328 variant was also associated with kidney stone disease in a large Han Chinese population (331 patients with kidney stones and 553 healthy individuals)[214]. Mutations in *ALPL* are associated with defective mineralization of hard tissues, including bone and tooth, and increased serum calcium levels[214].

The largest GWAS study to date that investigated kidney stones as a phenotype identified 20 loci in 12,123 people who formed stones and 417,378 control individuals from a British and Japanese cohort[215]. Seven of these loci had not previously been associated with kidney stone disease. A *CYP24A1*-associated locus (rs17216707) was associated with serum calcium concentration and episodes of stone recurrence and this finding was validated in a cohort of 440 patients with kidney stones. Variants in *CYP24A1* have previously been suggested to be common risk factors for kidney stone formation based on data from very small case series[135]. Five of the other identified loci (*DGKD* (diacylglycerol kinase delta), *DGKH* (diacylglycerol kinase eta), *WDR72* (WD repeat-containing protein 72), *GPC1* (glypican 1) and *BCR* (breakpoint cluster region protein)) have roles in the *CaSR* signalling pathway. In the validation cohort, the *DGKD*-associated locus correlated with urinary calcium excretion in male but not female patients who form stones[215]. These data implicate the CaSR signal transduction pathway in calcium metabolism and kidney stone disease and suggest that the genetics of stone disease might differ between men and women.

A meta-analysis of a large cohort from Europe ($n = 3{,}969$) and the USA ($n = 2{,}493$) was aimed at identifying genetic regions associated with urinary traits that are important for kidney stone risk (urine volume and urinary calcium, magnesium and uric acid excretion)[38]. The study identified a region near the magnesium transport gene *TRPM6* that was significantly associated with 24-h urine magnesium excretion and a region upstream of *CYP24A1* that was associated with urinary calcium excretion. In contrast to *CYP24A1*, which has been implicated in hypercalcaemia, hypercalciuria, nephrocalcinosis and kidney stone disease, *TRPM6* has not previously been associated with kidney stone risk. However, genetic changes in *TRPM6* can influence magnesium absorption and magnesium has multiple secondary effects that could alter kidney stone risk, for example, by altering potassium homeostasis or urinary crystallization.

Although GWAS data from large populations have shed light on the complex genetic and molecular pathways that can potentially result in an increased risk of kidney stones, there are limitations in interpreting the pathophysiological relevance of the identified variants and susceptibility loci. For most variants, the relative risks of stone formation are relatively modest, ranging from 1.1 to 1.25. A polygenic risk score (PRS) that combines the individual effects of multiple SNPs has been proposed. This PRS was found to be a better tool for urinary stone risk prediction (OR 1.2, 95% CI 1.13–1.26) than any individual GWAS significant SNP

used alone[216]. This finding was validated in an external cohort. Importantly, the PRS was associated with urinary stone risk regardless of the presence or absence of clinical risk factors such as hypertension, obesity, diabetes and gout. These findings highlight the complex and polygenic nature of urinary stone disease. The potential role of epigenetic changes in urinary stone risk also need to be investigated given the known role of environmental factors in stone disease risk and in gene transcription and expression[217].

Conclusions

In the past decade, much has been learned about the genetic and molecular basis of kidney stone disease. The application of high-throughput sequencing techniques to patients with clear risks of a monogenic cause of stone disease has led to the identification of a small number of causative genes that seem to account for many cases. Although kidney stones are common in the general population and seem to have a strong heritable component, the underlying genetics are still emerging. Nevertheless, several genes have been implicated in relatively large GWAS studies; many of these genes are also involved in monogenic stone disease. Further studies are required to facilitate a precision medicine-based approach to the treatment of recurrent kidney stone disease, possibly by targeting individual gene products and/or the physiological pathways in which they have a role.

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