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J Urol. Author manuscript; available in PMC 2018 September 21.

Published in final edited form as:

J Urol. 2018 March ; 199(3): 623–632. doi:10.1016/j.juro.2017.09.143.

Personalized Intervention in Monogenic Stone Formers

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Abstract

Purpose—Treatment of a first-time renal stone consists of acute management followed by medical efforts to prevent stone recurrence. Although nephrolithiasis is roughly 50% heritable, the presence of a family history usually does not affect treatment since most stone disease is regarded as polygenic, ie not attributable to a single gene. Recent evidence has suggested that single mutations could be responsible for a larger proportion of renal stones than previously thought. This intriguing possibility holds the potential to change the management paradigm in stone prevention from metabolically directed therapy to more specific approaches informed by genetic screening and testing. This review synthesizes new findings concerning monogenic kidney stone disease, and provides a concise and clinically useful reference for monogenic causes. It is expected that increased awareness of these etiologies will lead to increased use of genetic testing in recurrent stone formers and further research into the prevalence of monogenic stone disease.

Materials and Methods—We assembled a complete list of genes known to cause or influence nephrolithiasis based on recent reviews and commentaries. We then comprehensively searched PubMed® and Google Scholar™ for all research on each gene having a pertinent role in nephrolithiasis. We determined which genes could be considered monogenic causes of nephrolithiasis. One gene, *ALPL*, was excluded since nephrolithiasis is a relatively minor aspect of the disorder associated with the gene (hypophosphatasia). We summarized selected studies and assembled clinically relevant details.

Results—A total of 27 genes were reviewed in terms of recent findings, mode of inheritance of stone disease, known or supposed prevalence of mutations in the general population of stone patients and specific therapies or considerations.

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[†]Supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Center for Advancing Translational Sciences.

[‡]Financial interest and/or other relationship with Allena, AstraZeneca, Cymabay, Ironwood, Revive and Ravine Group.

[§]Financial interest and/or other relationship with Ferring, Pfizer and Allergan.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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Conclusions—There is a distinct opportunity for increased use of genetic testing to improve the lives of pediatric and adult stone patients. Several genes first reported in association with rare disease may be loci for novel mutations, heterozygous disease and forme frustes as causes of stones in the broader population. Cases of idiopathic nephrolithiasis should be considered as potentially having a monogenic basis.

Keywords

kidney calculi; nephrolithiasis; precision medicine; genetics; hypercalciuria

Ten-year symptomatic stone recurrence rates in nephrolithiasis range from 12% to 56%. From a clinical perspective the key to preventing recurrent stone formation is to correctly classify the metabolic basis of the disease. While 24-hour urine collection is a mainstay of this evaluation, it often produces few actionable results.[1] Recent advances in our understanding of the genetic epidemiology of nephrolithiasis, namely that monogenic causes may be more common than previously thought,[2] have raised the likelihood that a precise genetic diagnosis is within reach for at least some idiopathic stone formers. As a result, appropriate application of genetic testing may enable progress from the current treatment model based on urinary metabolic classification to a more tailored model based on the underlying protein defect. This review outlines monogenic stone etiologies for which personalized intervention could be proposed or is available. It is hoped that heightened awareness of these genotypes will lead to a positive cycle of increased genetic diagnosis, further research and refinement of treatment approaches.

The pathogenesis of calcium nephrolithiasis is understood as an interplay between multiple causal factors whose sum determines the concentrations of lithogenic factors in the kidney and the chemical propensity of the relevant salts to precipitate. Lifestyle factors such as diet, weight, age, exercise and climate compound intrinsic and polygenic factors, including ethnicity, metabolic defects and possibly the gut microbiome.[3] Occasionally a single important factor is apparent, such as a structural defect (eg medullary sponge kidney), acquired condition (primary hyperparathyroidism, gastrointestinal malabsorption) or known monogenic cause (primary hyperoxaluria). However, most calcium stones are idiopathic.

The mode of inheritance of idiopathic nephrolithiasis has been discussed for decades and is usually regarded as polygenic.[2] However, heritable risk factors may involve fewer genes. For example in a French-Canadian population the heritability of hypercalciuria appeared to be attributable to a single as yet unidentified gene in 58% of patients.[4] A 2005 male twin study estimated the heritability of kidney stones to be 56%.[5] Key to the clinical relevance of this statistic is whether inherited disease in a given patient can be attributed to a monogenic cause. It has been estimated that 2% of stones in adults have a monogenic cause.[2] Exome sequencing of a panel of 30 genes in consecutive patients at a specialty stone clinic found a disease causing mutation in 11% of adults.[6] A followup study in pediatric patients found a monogenic cause in 17%.[7]

Selection bias in these series, consisting of patients referred to a specialized clinic within a tertiary care clinic, limits the usefulness of the statistics, although genetic variants residing in introns and yet to be considered genes are not represented. The actual prevalence of

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monogenic stones in the general population will be refined through continued research. However, it can be confidently stated that many patients await a genetic diagnosis.

INDICATIONS AND FUTURE PROSPECTS FOR GENETIC TESTING

Today patients are not subjected to genetic testing unless a specific disease is suspected. It must be emphasized that most rare genetic causes of stones and other renal diseases bear their own metabolic signatures, and as such should be recognized and diagnosed based on clinical findings and stepwise metabolic testing. Comprehensive listings of known monogenic causes of stones have been published.[2,8] Clinical signs suggesting an inherited disorder such as hypophosphatemia, low grade proteinuria or renal hyperechogenicity were reviewed in detail by Ferraro et al.[9] However, in the absence of any clues most cases are relegated to the “idiopathic” category (or perhaps attributed partly to poor lifestyle choices) and managed heuristically according to their metabolic characteristics. Worldwide such cases number in the millions. A certain percentage of these patients harbor a monogenic cause and thus would stand to benefit from genetic screening. While current costs are prohibitive for most patients, academic funding and clinical studies will help open the door to genetic screening, not least by clarifying its cost-effectiveness.

In an uncomplicated adult case of stones the presence of a family history does not usually affect the clinical decision-making process. Current American Urological Association guidelines on medical management of kidney stones do not include a recommendation for genetic testing. Nonetheless, as this review will show, the literature is rife with reports of stone patients whose diagnosis, and in many instances proper treatment, was elusory before genotyping. If and when targeted or whole genome sequencing becomes commonplace, it will be important to have recognized and characterized the genetic mutations causing functional compromise leading to nephrolithiasis, along with relevant specific remedies. This review attempts to provide a concise and clinically useful reference at this still early stage in our understanding of the heritability of stone disease.

MONOGENIC CAUSES OF STONE DISEASE

We reviewed genes associated with monogenic nephrolithiasis in terms of recent findings, mode of inheritance, known or supposed prevalence of mutations in the general population of stone patients and specific therapies (see Appendix). In addition to the therapies listed for each gene, genetic counseling for family members should be considered in all cases. Routine nonspecific preventive measures such as hydration, low salt diet and thiazide diuretics still apply. For this review “monogenic” disease may follow a dominant or recessive inheritance pattern with complete or incomplete penetrance.

ATP6V1B1, *ATP6V0A4*, *SLC4A1* and *CA2*: Primary Distal Renal Tubular Acidosis

Primary distal renal tubular acidosis is caused by mutations in 3 proteins: V-ATPase (with subunits encoded by *ATP6V1B1* and *ATP6V0A4*), the chloride bicarbonate exchanger AE1 (encoded by *SLC4A1*) and carbonic anhydrase II (encoded by *CA2*, which involves the proximal tubule as well). The resulting phenotype may be classified as RTA if metabolic acidosis is present. Some patients heterozygous for relevant mutations may have

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"incomplete" RTA when serum HCO3− is normal and urine pH does not decrease sufficiently in response to provocative testing. In childhood RTA may present as severe disease or go unnoticed, presenting as nephrocalcinosis, chronic kidney disease or stones in adulthood.[10] Patients homozygous for mutations in *ATP6V1B1* have dRTA with reduced serum HCO3−. Recessive mutations in *ATP6V1B1* and *ATP6V0A4* cause deafness. With defects in AE1 the disease can exhibit autosomal dominant inheritance and less severe features.[11] Mutations in V-ATPase are considered recessive and result in complete dRTA, although it has recently been reported that heterozygotes are at risk for idRTA and stones.[12]

Recurrent stone formers commonly exhibit impaired ability to acidify their urine, a finding that has been poorly investigated.[12] Dhayat et al studied 555 recurrent stone formers and found 32 heterozygotes with a V-ATPase mutation at the single nucleotide polymorphism p.E161K.[13] This subgroup demonstrated a high prevalence of idRTA after an acid loading test (53% vs 15% in those without the mutation, $p = 0.001$) and an increased proportion of stones containing calcium phosphate (70% vs 39%, $p < 0.01$). The exon sequencing study by Halbritter et al found homozygosity at p.E161K in 1 patient with recurrent stones, leading to a new diagnosis of dRTA and deafness.[6]

It is already recommended that idRTA be considered in patients with recurrent calcium phosphate stones or fasting urine pH greater than 5.8.[14] However, recent studies and case reports reveal that genetic testing can uncover complete or incomplete primary dRTA when it remains clinically imperceptible or difficult to diagnose.[6,10] Therapeutic implications for stone patients with dRTA include alkali administration, referral for audiometry testing and monitoring for CKD.[6] Whether diagnosis of idRTA has specific implications has not been established.

CYP24A1: Infantile Idiopathic Hypercalcemia

Infantile idiopathic hypercalcemia was recently linked to homozygous inactivating mutations in the 1,25(OH)2D 24-hydroxylase,[15] a cytochrome P450 encoded by *CYP24A1* that serves to inactivate calcidiol and calcitriol. The resultant unchecked accumulation of calcitriol, especially after supplementation with vitamin D, results in an absorptive hypercalcemia, which can be fatal in infants. IIH may also be caused by *SLC34A1*, as discussed elsewhere in this review. Biallelic mutations of *CYP24A1* have been implicated in less severe phenotypes, including adult onset nephrolithiasis, nephrocalcinosis and hypercalcemia. [15–18] These patients possess a metabolic phenotype of hypercalcemia, increased 1,25(OH)2D, decreased 24,25(OH)2D and suppressed PTH.

Preliminary evidence suggests that heterozygous carriers—a not insignificant portion of the general population—may be predisposed to lithiasis.[15,16,19] Possibly congruent with this hypothesis is the finding that, compared to matched controls, first-time stone formers have significantly increased serum calcium and 1,25(OH)2D, and 24,25(OH)2D-to-25(OH)D ratio.[20] Since vitamin D supplementation is thought to precipitate illness in IIH, those with adult onset forms could be sensitive to supplementation. However, vitamin D supplementation is not a significant cause of kidney stones in the general population. A knockout mouse model demonstrated that nephrocalcinosis developed in response to vitamin D administration in homozygotes but not heterozygotes.[21]

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Initial testing should include 1,25(OH)2D and 25(OH)D levels. A reduced 24,25(OH)2D-to-25(OH) D ratio is helpful as an indicator of enzyme function. Pending further study to establish the most effective long-term therapy, vitamin D intake, sun exposure and tanning bed use should be restricted. Fluconazole, an inhibitor of steroid hormone synthesis, has been used successfully to decrease serum calcium and 1,25(OH)2D,[17] although the tolerability and safety of such long-term therapy have not been established.

SLC7A9 and *SLC3A1*: Cystinuria

Cystinuria, the most common monogenic cause of kidney stones, is triggered by mutations of *SLC7A9* or *SLC3A1*, the protein products that together constitute the proximal tubule transporter mediating reabsorption of filtered cystine. This disorder is classically autosomal recessive, although some *SLC7A9* mutations exhibit autosomal dominant inheritance with incomplete penetrance regarding stone formation.[22] Halbritter et al performed gene sequencing in 272 stone patients and surprisingly found 6 patients with heterozygous *SLC7A9* mutations in whom a diagnosis of cystinuria had not been considered.[6] Three of the 6 patients had calcium stones, serving as a reminder that cystine stones are not the rule in cystinuria. Heterozygous cystinuria may be a risk factor for calcium stone disease.[23]

The variable presentation of cystinuria and consequent likelihood of missed diagnosis have led to the recommendation that all idiopathic stone formers be screened for cystinuria.[24] It is noteworthy that it is simpler and more cost effective to conduct metabolic rather than genetic screening. For patients in whom stone composition or genetic screening uncovers cystinuria the urine cystine should be quantitated and standard preventive measures should be recommended, including hydration, protein and salt reduction, and administration of alkali if warranted. Cystine binding thiol drugs serve as second-line preventive therapy.

SLC34A3 and *SLC34A1*: Hereditary Hypophosphatemic Rickets with Hypercalciuria

Sodium-dependent phosphate co-transporters 2c and 2a (NPT2c, NPT2a), encoded by *SLC34A3* and *SLC34A1*, respectively, enable reabsorption of phosphate in the proximal tubule. Biallelic mutation of *SLC34A3* causes HHRH, a form of rickets in which phosphate wasting causes an increase in 1,25(OH)2D, leading to absorptive hypercalciuria and stones. Patients with HHRH may also present with normophosphatemia, short stature, hypercalciuria and nephrolithiasis.[25]

Kindred evidence suggests that heterozygotes can experience a forme fruste of HHRH with hypercalciuria and osteopenia.[25] A meta-analysis of kindred data showed that stones or nephrocalcinosis occurred in 46% of biallelic *SLC34A3* mutations and in 16% of heterozygotes.[26] Relative to homozygotes, heterozygotes had an intermediate degree of serum phosphate depression and 1,25(OH) 2D increase. Despite the “rickets” designation, late adult onset of HHRH with osteomalacia and recurrent stones was recently reported.[27] A likely heterozygous individual was successfully treated with phosphate, and the authors surmised that heterozygous HHRH may be an overlooked cause of idiopathic low bone density and hypercalciuria.

Homozygous mutation of *SLC34A1* also causes phosphate wasting and a consequent excess of calcitriol. However, it does not cause rickets. The resultant syndrome is IIH, which can

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also be caused by *CYP24A1* deficiency for the same reason—excess calcitriol—but by a different mechanism, as noted previously. Stone disease was noted in 3 of 26 kindred heterozygotes (12%).[28] In addition, 5 heterozygotes were identified in a cohort of 143 children with stones.[7] The suggestion that *SLC34A1* could be a risk allele is supported by a genome-wide association study of Icelanders in which the gene conferred a 2.4 odds ratio of recurrent stones.[29] It would be intriguing if future studies focused on whether phosphate supplementation has a measurable effect on stone recurrence in heterozygous patients.

A related gene meriting mention is *SLC9A3R1*, encoding the sodium-hydrogen exchanger regulatory factor 1 (NHERF1), a necessary chaperone for NPT2a.[30] Heterozygous mutations of this gene may cause phosphate wasting, stones and osteomalacia. [6,7] Thus, this gene should be included with *SLC34A3* and SLC34*A1* as part of sequencing panels.

Reports indicate that treatment of HHRH by oral phosphate supplementation without vitamin D or bisphosphonates is effective, and that therapy can be monitored via 1,25(OH)2D level.[27,28] Phosphate supplementation is also effective in treating IIH due to *SLC34A1*. While further study is needed to determine if forme frustes of HHRH and IIH are prevalent in the general population of stone formers, a trial of phosphate therapy might be considered for those observed to have a mutation and increased 1,25(OH)2D. Preliminary evaluation of carriers might include serum and urine phosphate, 1,25(OH)2D level and bone densitometry.

AGXT, *GRHPR* and *HOGA1*: Primary Hyperoxaluria

Primary hyperoxaluria arises from errors of hepatic amino acid metabolism at *AGXT*, *GRHPR* and *HOGA1*, causing PH types 1, 2 and 3, respectively. This condition may present as infantile ESKD, childhood or adult nephrocalcinosis and recurrent nephrolithiasis or occasional stone formation, or it can remain clinically silent. Affected patients are predisposed to forming calcium oxalate monohydrate stones. PH types 2 and 3 lead to lesser urinary oxalate excretion, correlating with a significantly better prognosis. PH should be considered if urine oxalate excretion exceeds 70 to 80 mg per day. Genotyping is critical to treatment as PH type 1 caused by *AGXT* Gly170Arg and Phe152Ile mutations is responsive to pyridoxine therapy.[31] For other mutations a trial of pyridoxine may be worthwhile.

Other significant benefits of early genetic diagnosis include 1) prediction of a benign or serious disease course, 2) the opportunity to avoid liver biopsy and its attendant risks, 3) prevention of systemic oxalosis, and referral for cardiac and ophthalmological screening, 4) time to consider and plan for curative liver transplantation and 5) participation in clinical trials.[6,31] For PH type 1 renal transplantation with concomitant liver transplantation is preferred since the disease will otherwise recur in the transplanted kidney. In patients with ESKD urine oxalate is unreliable, and, therefore, genetic testing may be the only way to exclude a diagnosis of PH.

Supportive treatments are hydration and administration of alkali. Potassium citrate or potassium/sodium neutral phosphate may help inhibit calcium oxalate crystallization. Advanced biotechnological therapies, such as administering small interfering RNA, are

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being studied.[31] In *HOGA1* mutations (PH type 3) a vegetarian diet to reduce hydroxyproline intake has been hypothesized to be useful.

APRT: Dihydroxyadeninuria

Adenine phosphoribosyltransferase deficiency is among the most easily recognizable rare causes of nephrolithiasis, provided timely stone analysis is performed, since it manifests as unique radiolucent stones composed of 2,8-dihydroxyadenine. Adenine phosphoribosyltransferase activity in red blood cells should be absent and 2,8-dihydroxyadenine should be present in urine. Unfortunately the disease is often undiagnosed in homozygotes, who are at high risk for CKD due to crystal nephropathy.[22] If a transplant is provided before the diagnosis is made, the disease will recur in the transplanted kidney. Treatment is possible with allopurinol or febuxostat, along with purine restriction and hydration. A trial comparing allopurinol and febuxostat is pending review.

SLC22A12 and *SLC2A9*: Renal Hypouricemia

Proximal tubular reabsorption of urate occurs across the apical membrane via URAT1 and across the basolateral membrane via GLUT9, respectively encoded by *SLC22A12* and *SLC2A9*. Dominant or recessive mutations in either gene may cause renal hypouricemia, variably presenting with hypercalciuria, stones, hematuria or exercise induced acute kidney injury.[32] Stones may be uric acid or calcium based. Previously unrecognized renal hypouricemia was identified in 3 of 272 stone patients.[6] Discovery of pertinent mutations should prompt reassessment of serum uric acid, as well as a careful assessment of whether the patient is prone to exercise induced AKI since repeated injury may cause CKD. Allopurinol has been used to prevent recurrence of exercise induced AKI.[33]

XDH: Xanthinuria

Another disorder characterized by hypouricemia and radiolucent stones is hereditary xanthinuria, caused by recessive mutations in *XDH*, which encodes xanthine dehydrogenase, also known as xanthine oxidase. Urine alkalinization therapy is controversial but possibly beneficial based on the pKa of xanthine.[34] The primary therapy is dietary purine restriction and hydration.[35,36] Drugs metabolized by xanthine dehydrogenase should be avoided, especially when concomitant mutation in aldehyde oxidase is present (xanthinuria type 2).

CLDN16 and *CLDN19*: Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

CLDN16 and *CLDN19* encode claudin proteins, responsible for the permeability of the tight junctions, affecting the paracellular reabsorption of calcium and magnesium in the thick ascending limb of the loop of Henle.[22] Homozygous loss of function may result in cation wasting and nephrocalcinosis, a rare disease known as familial hypomagnesemia with hypercalciuria and nephrocalcinosis. Symptoms include seizures, tetany, failure to thrive, blindness (specific to *CLDN19*), stones and ESKD. A kindred analysis in 1995 (before discovery of the gene) documented a prevalence of hypercalciuria of 42% in family members of the proband, while 15% had recurrent stones.[36] A more comprehensive study found that 13 of 23 families contained relatives affected by hypercalciuria and/or stones.[37]

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Homozygous *CLDN16/19* mutations should prompt monitoring for seizures. *CLDN19* mutations should prompt eye examination.

Discovery of *CLDN16/19* mutations in idiopathic calcium stone formers might suggest a strong clinical focus on evaluating and treating for hypercalciuria. No targeted therapy has emerged for those affected by *CLDN* mutations. However, basic research into the claudins continues.[38] In a study of Icelandic and Dutch patients mutations in *CLDN14* were associated with kidney stones, hypercalciuria and decreased bone mineral density.[39] However, this finding has not been reproduced in American populations thus far. Large sequencing studies are needed to investigate the link between claudin mutations and hypercalciuria.

CASR: Autosomal Dominant Hypocalcemia

As alluded to previously, CaSR is expressed in the tubules and participates in the regulation of calcium reabsorption. CaSR is also used by the parathyroid glands to regulate PTH secretion. Activating mutations of *CASR* cause autosomal dominant hypocalcemia, which is sometimes accompanied by hypercalciuria with nephrocalcinosis and stones, especially when calcium and vitamin D are supplemented.[40] The calcium set point is effectively lowered while the regulatory apparatus remains intact. In patients with such mutations it is important to avoid supplementation unless they are symptomatic from hypocalcemia.[40] CaSR antagonists (calcilytics) in development are a promising solution for *CASR* activating mutations.[41]

Heterozygous inactivating mutations in *CASR* result in familial hypocalciuric hypercalcemia, also called familial benign hypercalcemia to emphasize that it is often asymptomatic. This hypocalciuric condition is associated with nephrolithiasis, which can be explained by impairment of other effects mediated through CaSR, such as increased phosphate reabsorption, decreased concentrating ability and urine acidification.[42] CaSR agonists (calcimimetics) are not indicated unless patients are symptomatic from hypercalcemia. Genetic testing can help prevent confusion with primary hyperparathyroidism and avoid unnecessary surgery.

CLCN5 and *OCRL*: Dent Disease and Lowe Syndrome

Dent disease types 1 and 2 are tubulopathies characterized by low molecular weight proteinuria, hypercalciuric nephrolithiasis and nephrocalcinosis, and frequent progression to ESKD.[22,43] Type 1 is caused by X-linked recessive mutations in *CLCN5*, encoding an H +/Cl− exchanger. Since the disease is rare and has a variable presentation, it may escape clinical diagnosis. Therefore, recognition by genetic screening (as reported in 1 instance[6]) will enable avoidance of unnecessary biopsy or allow empirical immunosuppressive therapy, as well as the opportunity to plan for curative transplant.[43] However, it is noteworthy that low molecular weight proteinuria, comprising retinol binding protein and β2-microglobulin, is a hallmark of the disease and a better route to diagnosis.

Dent disease type 2, also called oculocerebrorenal syndrome of Lowe, is caused by mutation in *OCRL*, encoding a lipid phosphatase. In addition to tubulopathy, there are ocular, cognitive and neural manifestations. In a cohort of 143 pediatric stone patients a genetic

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diagnosis was made in a 7-year-old child with idiopathic hypercalciuria, leading to ophthalmological consultation and monitoring for seizures.[7]

CLCNKB: Bartter Syndrome

Bartter syndrome is a group of 5 recessive disorders resulting from defective sodium chloride reabsorption in the thick ascending limb of the loop of Henle. The 5 types have a common presentation of hyperreninemia, hypokalemia and metabolic alkalosis. Types 1 and 2 are associated with stones and present in the neonatal period. Type 3, classic Bartter syndrome, is caused by defects in a basolateral chloride channel encoded by *CLCNKB*. This entity may present later, and has been reported to be diagnosed as late as age 28 years with a presentation of stones.[44] This presentation is highly unusual but is included here for completeness as the disease may be treated with mineral supplementation and indomethacin.[45] Patients with type 4 disorder typically suffer from salt-wasting hyperuria and electrolyte imbalances. Type 5 is essentially a severe form of autosomal dominant hypocalcemia (discussed previously) in which overactivity of CaSR impairs sodium chloride reabsorption.

PRPS1: Phosphoribosyl Pyrophosphate Synthetase Superactivity

The X-linked gene *PRPS1* encodes phosphoribosyl pyrophosphate synthetase, the enzyme that converts ribose 5-phosphate into 5-phosphoribosyl 1-pyrophosphate, which is needed for purine synthesis. Activating mutations cause pyrophosphate synthetase superactivity, which results in an excess of purines and consequent hyperuricemia. Milder phenotypes may present with uric acid stones. Unfortunately activating mutations are not fully characterized, so diagnosis must be made via enzyme activity assay or mRNA quantitation.[46] Treatment is with allopurinol and a purine restricted diet.

NEW PROSPECTS

SLC26A1 and *ADCY10* are not as well studied in association with nephrolithiasis. However, they are included here to emphasize that research continues to demonstrate potential new monogenic causes of stone disease.

SLC26A1: Hyperoxaluria and Hepatotoxicity

SLC26A1 encodes the sulfate anion transporter 1, which carries sulfate, oxalate and bicarbonate in the proximal tubule and collecting duct. A 2016 sequencing study of candidate genes revealed 2 patients with homozygous mutations in SLC26A1 causing impaired protein function and early onset calcium oxalate nephrolithiasis.[47] Sat1−/− mice exhibit hyperoxaluria, hypersulfaturia, nephrocalcinosis, stones and increased susceptibility to acetaminophen induced liver damage.[48] At this preliminary stage the only therapeutic recommendation that can be made for patients with *SLC26A1* mutation is to use acetaminophen cautiously.

ADCY10: Absorptive Hypercalciuria

The soluble adenylyl cyclase encoded by *ADCY10* is a widely expressed pH sensor. The gene was identified as a locus for single nucleotide polymorphisms associated with autosomal dominant absorptive hypercalciuria[49] but received little attention subsequently

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and was not proved to be a monogenic stone factor. Intriguingly novel point mutations in the gene were seen in 3 stone patients with idiopathic hypercalciuria,[6] while a related pediatric study found 2.[7] These observations suggest a need for definitive study of the validity of soluble adenylyl cyclase as a causal factor in hypercalciuric nephrolithiasis and an explanation of the underlying pathogenesis. Hypothetically a finding of mutation in *ADCY10* could prompt investigation for hypercalciuria and a bone density examination.

CONCLUSIONS

For many clinicians genomic medicine has been perpetually on the verge of becoming useful, inexpensive and more widely applicable. While developments in the urology armamentarium have made stone management simpler than before, the potential for major improvements in prevention of recurrent stones is not negligible. Enhanced diagnosis through genotyping will enrich patient populations with recognized entities, enabling further study and treatment development. There is already a wide opening for increased use of genetic testing, at first in the form of targeted confirmatory testing and later in panel based screening, to improve the lives of stone patients. It is also clear that several genes first reported in association with rare diseases may be loci for novel mutations, heterozygous disease and forme frustes causing stones in the broader population. Taken together, it is conceivable that the sum of all monogenic and perhaps oligogenic stone diseases represents a clinically significant proportion of patients previously classified as having idiopathic nephrolithiasis.

Acknowledgments

Supported by Grant U54KD083908 from the Rare Kidney Stone Consortium (NIH Rare Diseases Clinical Research Network, coordinated by NIH Office of Rare Diseases Research and National Institute of Diabetes and Digestive and Kidney Diseases).

Abbreviations and Acronyms

AKI	acute kidney injury
CaSR	calcium-sensing receptor
CKD	chronic kidney disease
dRTA	distal renal tubular acidosis
ESKD	end-stage kidney disease
HHRH	hereditary hypophosphatemic rickets with hypercalciuria
idRTA	incomplete distal renal tubular acidosis
IIH	infantile idiopathic hypercalcemia
PH	primary hyperoxaluria
PTH	parathyroid hormone

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RTA	renal tubular acidosis
V-ATPase	vacuolar H+ ATPase

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APPENDIX

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Monogenic causes of kidney stones and available treatments

Gene	Protein	Role in stone disease	Mode of inheritance	Metabolic phenotype	Treatment available
ATP6V1B1, ATP6V0A4	Vacuolar ATPase (V-ATPase)	Primary distal renal tubular acidosis	Autosomal recessive, but "incomplete" acidosis in some heterozygotes	± Metabolic acidosis Impaired urine acidification Calcium phosphate stones, frequently	Alkali therapy Referral for audiometry Monitor for CKD
SLC4A1	Chloride bicarbonate exchanger (AE1)	Primary distal renal tubular acidosis	Autosomal dominant		Alkali therapy Monitor for CKD
CA2	Carbonic anhydrase II (CA2)	Primary proximal and distal renal tubular acidosis	Autosomal recessive		
CYP24A1	Cytochrome P450 1,25$(OH)_2$D 24-hydroxylase	Infantile idiopathic hypercalcemia	Autosomal recessive; evidence suggesting incomplete dominance	Hypercalcemia Elevated 1,25$(OH)_2$D Decreased 24,25$(OH)_2$D Suppressed PTH	Restrict excess vitamin D, sun exposure Fluconazole
SLC7A9	Basic amino acid transporter system $b^{0,+}$	Cystinuria	Autosomal dominant with incomplete penetrance	Elevated urine cystine Cystine stones	Standard preventative measures (hydration, protein and sodium restriction, alkalinization therapy)
SLC3A1	Basic amino acid transporter system $b^{0,+}$	Cystinuria	Autosomal recessive	± Calcium stones	Binding and reducing agents May be resistant to shock wave lithotripsy
SLC34A3	Sodium-dependent phosphate co-transporter 2c (NPT2c)	Hereditary hypophosphatemic rickets with hypercalciuria	Autosomal recessive; evidence suggesting incomplete	Hypophosphatemia Elevated 1,25$(OH)_2$D	Phosphate supplementation Restrict excess vitamin D
SLC34A1	Sodium-dependent phosphate co-transporter 2a (NPT2a)	Idiopathic infantile hypercalcemia	dominance	Hypercalciuria Phosphaturia	Bone densitometry
SLC9A3R1	Sodium–hydrogen exchanger regulatory factor 1 (NHERF1)	Hypophosphatemic nephrolithiasis/osteoporosis	Autosomal dominant	Calcium stones Low bone density	
AGXT	alanine-glyoxylate aminotransferase	Primary hyperoxaluria type 1	Autosomal recessive	Urine oxalate >70–80 mg/day Calcium oxalate monohydrate stones	Pyridoxine therapy (PH1: Gly170Arg, Phe152Ile, other mutations)
GRHPR	Glyoxylate and hydroxypyruvate reductase	Primary hyperoxaluria type 2	Autosomal recessive		Liver transplantation to prevent disease recurrence in transplanted kidney (PH1)
HOGA1	4-hydroxy-2-oxoglutarate aldolase 1	Primary hyperoxaluria type 3	Autosomal recessive		Cardiac and ophthalmologic screening (if CKD) Hydration and alkali therapy Limit hydroxyproline intake (PH3)
APRT	Adenine phosphoribosyltransferase	Dihydroxyadeninuria	Autosomal recessive	2,8-dihydroxyadenine stones	Xanthine oxidoreductase inhibitors Purine restriction Monitor for CKD Radiolucent stones

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Gene	Protein	Role in stone disease	Mode of inheritance	Metabolic phenotype	Treatment available
SLC22A12, SLC2A9	URAT1, GLUT9	Renal hypouricemia	Autosomal dominant or recessive	Hypouricemia Hypercalciuria Uric acid or calcium stones	Xanthine oxidoreductase inhibitors Monitor for CKD and exercise-induced AKI Radiolucent stones
XDH	Xanthine oxidoreductase	Xanthinuria	Autosomal recessive	Xanthine stones Hypouricemia	Purine restriction, hydration Radiolucent stones
CLDN16	Claudin-16	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	Autosomal recessive; evidence for incomplete dominance	Calcium and magnesium wasting	Focus on treating hypercalciuria Monitor for seizures
CLDN19	Claudin-19	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	Autosomal recessive; evidence for incomplete dominance	Heterozygotes can have hypercalciuria and calcium stones; low bone density (*CLDN14*)	Focus on treating hypercalciuria Ophthalmologic screening
CASR	Calcium-sensing receptor *(activating mutations)*	Autosomal dominant hypocalcemia	Autosomal dominant	Hypocalcemia Hypercalciuria Normal PTH Calcium stones	Avoid calcium and vitamin D supplementation CaSR antagonists (calcilytics) are under development
CASR	Calcium-sensing receptor *(inactivating mutations)*	Familial hypocalciuric hypercalcemia	Autosomal dominant	Hypercalcemia Hypocalciuria Normal to high PTH Calcium stones (in some)	CaSR agonists (calcimimetics)
CLCN5	H^+/Cl^- exchange transporter 5	Dent disease type 1	X-linked recessive	Low molecular weight proteinuria	Renal transplantation
OCRL	Inositol polyphosphate 5-phosphatase	Dent disease type 2 (Lowe syndrome)	X-linked recessive	Hypercalciuria	Ophthalmologic screening Monitor for seizures Renal transplant
CLCNKB	Chloride channel Kb	Bartter syndrome type 3	Autosomal recessive	Hypokalemia Metabolic alkalosis Hypercalciuria	Mineral supplementation Indomethacin
PRPS1	Phosphoribosyl pyrophosphate synthetase	Phosphoribosyl pyrophosphate synthetase superactivity	X-linked recessive	Hyperuricemia Uric acid stones	Xanthine oxidoreductase inhibitors Purine restriction
SLC26A1	Sulfate anion transporter 1	Calcium oxalate nephrolithiasis	To be determined	In mice: hyperoxaluria, hypersulfaturia	Use acetaminophen with caution
ADCY10	Soluble adenylyl cyclase	Autosomal dominant absorptive hypercalciuria	Autosomal dominant	Hypercalciuria	None yet demonstrated Suggest bone densitometry and focus on hypercalciuria

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