Personalized Intervention in Monogenic Stone Formers

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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.

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,

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
RTA = renal tubular acidosis
V-ATPase = vacuolar H^+ ATPase

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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.

Key Words: 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 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