The Genetics of Nephrolithiasis

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Key Words

Citrate • Genetics • Hypercalciuria • Kidney stones • Mouse models • Urate

Abstract

Renal stone formation (nephrolithiasis) is a worldwide problem causing substantial morbidity and economic burden. The heritability of stone formation has long been recognized, and with the advent of the genomic era, we have the potential to define the underlying genetic defects. Renal stone formation is multifactorial, with environmental factors interacting with underlying genetic factors. Isolated genetic defects and single gene disorders which lead to stone formation have been valuable in defining renal pathophysiology, but these remain rare diseases. In this review, we examine the genetics of nephrolithiasis by considering the genetic components of defined metabolic risk factors. Hypercalciuria is the most important risk factor for calcium stone formation, although hyperoxaluria, cystinuria and other rarer defects are discussed. It is important to consider the complexity of this condition, and realize that the understanding of the genetic basis of nephrolithiasis is within our grasp.

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Introduction

Renal stone formation (or nephrolithiasis) is a common problem worldwide with an increasing incidence in Westernized societies. The prevalence of kidney stones increased in American adults from 3.8% (1976–1980) to

5.2% (1988–1994) [1]. A recent Icelandic study confirmed prevalences in 65- to 69-year-old men and women of 8.8 and 5%, respectively [2]. Self-reported kidney stones were noted in 4.7% of American adults [3]. Renal stone formation is multifactorial depending upon the interplay of environmental, anatomical and genetic factors (table 1). The recent increase in the prevalence of renal stones highlights the importance of environmental factors (such as diet) contributing to nephrolithiasis. For example, a recent report links fructose consumption, which has increased dramatically in Western societies, with stone formation [4]. Similarly, increased rates of hypertension and obesity, which are linked to nephrolithiasis, contribute to an increase in stone formation [for review, see 5]. Cross-sectional analysis of a USA adult population suggests that stone prevalence increases significantly with two or more metabolic syndrome traits [3].

There are many types of renal stone, but by far the most common are calcium-containing stones (most often calcium oxalate stones), making up 75% of all stones. This review will highlight some of the metabolic predisposing factors towards stone formation and discuss them with particular relevance to the influence of an underlying genetic predisposition. Animal models of nephrolithiasis have been useful in our understanding of stone pathophysiology and will hopefully lead to further advances in identifying the genetics of nephrolithiasis. Relevant models offering this promise are discussed. Monogenic stone-forming disorders, although rare, have led to important physiological insights and are discussed with respect to their relevance as candidate genes for ‘idiopathic’ nephrolithiasis.

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Where There Is Too Much...

Hypercalciuria

Hypercalciuria is by far the most common metabolic abnormality found in both adult and child stone formers. An increased urinary calcium concentration may be explained by various contributing mechanisms. Firstly, 'absorptive hypercalciuria', where increased gastrointestinal calcium resorption gives rise to increased serum calcium and consequently increased urinary calcium. Secondly, 'renal hypercalciuria' may occur when there are defects in the ability of the renal tubules to regulate calcium re-absorption. Thirdly, an increased bony resorption of calcium into the circulation leading to hypercalciuria may occur. Clearly, both environmental (such as diet) and genetic factors (such as solute transporters) may influence all these mechanisms. Dietary factors which tend to increase urinary calcium excretion include excessive animal protein, high sodium, alcohol and caffeine intake and low dietary fibre. Low fluid intake will increase urinary calcium concentrations.

The genetic factors underlying hypercalciuria remain elusive, but data from epidemiological studies suggest that around 20% of patients with idiopathic hypercalciuria have a family history of stones [6]. It must be noted that family history data do not always distinguish between inherited and environmental factors. Efforts to identify loci to determine heritability have been frustrated by the fact that urinary calcium excretion is quantitative. Statistical modelling was undertaken by Lored-Osti et al. [7] following analysis of stones in 221 French-Canadian families with at least two affected individuals with calcium stones. Computer programs predicted the best inheritance fit with a model of single gene co-dominant model or a mixed co-dominant/polygenic model [7]. Both models gave a heritability score of 58%, suggesting a genetic tendency underlying renal stone formation. Twin studies have also confirmed this strong heritability of hypercalciuria as was recently reviewed by Stechman et al. [8]. Two large studies have used monozygotic (genetically identical) and dizygotic twins to compare inheritance rates of kidney stones; the St. Thomas UK Adult Twin Registry examined 1,747 adult female twin pairs and showed that the heritability of hypercalciuria was 52%, with a higher correlation for calcium excretion in monozygotic twins (who share identical genotypes) compared to dizygotic twins (who share 50% of their genes). The VET Registry also showed the rate of kidney stones was greater in monozygotic twins (32.4%) than dizygotic twins (17.3%). Based on this evidence, we may conclude

Table 1. Major risk factors for renal stone formation

1	Urinary constituents Solute excess (calcium, oxalate, uric acid, cystine) Low urine volume Loop diuretics Decreased stone inhibitors (e.g. citrate, magnesium, pyrophosphate, Tamm-Horsfall protein, nephrocalcin, osteopontin/uroponin, bikunin, urinary trefoil factor 1, prothrombin fragment 1) Dysregulation of urinary pH Immobilisation (leading to bone resorption and hypercalciuria)
2	Water/diet/absorption Dehydration High animal protein diet High fructose diet Excess absorption of oxalate, calcium, urate
3	Anatomical considerations Medullary sponge kidney Horseshoe kidney Autosomal dominant polycystic kidney disease Space travel
4	Other medical conditions Urinary tract infections Gout Diabetes mellitus Cystic fibrosis

that a genetic predisposition is likely to account for the tendency to form stones and genes determine over 50% of the urinary calcium excretion rate.

Hypercalciuria may occur in a range of monogenic disorders and animal models. The underlying genes responsible represent candidate genes for idiopathic hypercalciuria. Whilst initial excitement was justified, and significant insights into renal tubular pathophysiology have been gained [for review, see 9], these remain rare monogenic causes of stone disease and so far have not been able to account for the majority of patients with idiopathic hypercalciuria.

Absorptive Hypercalciuria

Three families with a severe phenotype of absorptive hypercalciuria were used in a genome-wide search for linkage. A highly significant LOD score of 3.3 was shown in a single locus on chromosome 1 and sequence variants in the human soluble adenylate cyclase (sAC) gene, a divalent cation and bicarbonate sensor, were identified. The functional significance of these sequence variants has yet to be determined [10]. *TRPV5* and *TRPV6* also represent

candidate genes for absorptive hypercalciuria (see below).

Calcium-Sensing Receptor Mutations and Hypercalciuria

The *CASR* gene encodes for the calcium-sensing receptor protein, a plasma membrane G-protein-coupled receptor. The *CASR* protein is expressed in the parathyroid gland as well as specific tubular segments, bone, intestine and calcitonin-secreting C cells of the thyroid gland. Acting as an extracellular calcium sensor in these environments, the *CASR* allows control of serum calcium concentrations by stimulating PTH secretion. PTH acts on the tubules by enhancing phosphaturia, stimulating the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and promoting calcium reabsorption in the distal convoluted tubule (DCT). Mutations in *CASR* change the set-point of the sensor so that some mutations would increase the threshold of this feedback resulting in familial hypocalciuric hypercalcaemia. The converse is also seen when the *CASR* becomes oversensitive to serum calcium levels producing a familial syndrome of hypocalcaemia and hypercalciuria. Such activating mutations may lead to nephrocalcinosis and kidney stone formation. The phenotype of *CASR* mutations recently extended to a form of Bartter's syndrome (type 5) whereby activation of the basolateral *CASR* in the thick ascending limb (TAL) is thought to inhibit the ROMK potassium channel, leading to salt wasting. In the inner medullary collecting duct, activation of the apically expressed *CASR* protein occurs with elevated tubular calcium concentrations. *CASR* reduces the anti-diuretic induced water permeability of this nephron segment, and thus limits the maximal urinary concentration [11]. This mechanism acts to minimise stone formation under periods of enhanced mineral ion excretion, and abnormal responses in this pathway may contribute to nephrolithiasis.

The key question concerning *CASR* is whether polymorphisms or mild mutations contribute to idiopathic hypercalciuria. Polymorphisms in *CASR* have been described previously in patients with kidney stones and those with hyperparathyroidism. Indeed, the *CASR* polymorphism (R990G) exists in hypercalciuric (non-stone forming) females, with evidence from in vitro studies that this polymorphism had an 'activating' effect on the *CASR*, thus promoting hypercalciuria [12]. Heterozygous and homozygous carriers of the R990G allele had a significant increase in calcium excretion (7.59 vs. 5.82 mmol/24 h) in comparison with women homozygous for the 990R allele. The R990G allele occurred in 15% of hy-

percalciuric females studied (compared to only 3% of the normocalciuric control population). The precise contribution this *CASR* change is having on renal tubular calcium handling remains unclear, but certainly hypercalciuria is such a significant (and potentially modifiable) risk factor that this is an important development.

Vitamin D Receptor (VDR) Polymorphisms

There have been several genetic studies that have pointed to the *VDR* gene as being implicated in hypercalciuric nephrolithiasis. The *VDR* is within a genetic locus for hypercalciuria identified in families from northern India. *VDR* polymorphisms may define bone mineral density and calcium homeostasis, producing a 'resorptive'-type hypercalciuria, but more convincing evidence is awaited. In this regard, tissue expression of *VDR* protein may be important, as patients with idiopathic hypercalciuria had elevated *VDR* protein expression in peripheral blood monocytes [13].

Claudin-16 Mutations

Claudin-16 (*CLDN16*) is a tight junction protein and mutations in the gene encoding it, *CLDN16*, give rise to a syndrome of familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, leading to renal failure. The defect is in the TAL of the loop of Henle, where paracellular calcium and magnesium resorption occurs. Heterozygous *CLDN16* mutations may give rise to a much milder phenotype and delayed onset renal impairment. The contribution of such functional polymorphisms to idiopathic hypercalciuria has not been investigated.

Animal Models of Hypercalciuria

The genetic hypercalciuria stone (GHS)-forming rat model has been developed and refined over many years. Selected breeding of animals with hypercalciuria over 64 generations has produced Sprague-Dawley rats with a 10-fold increase in calcium excretion and with renal stone production in each animal. Detailed biochemical evaluation has suggested a systemic dysregulation of calcium metabolism as evidenced by hyperabsorption of dietary calcium, renal tubular calcium wasting and increased vitamin D-induced bone resorption of calcium. Very recently, these animals were used to identify a quantitative trait locus (hypercalciuria 1; HC1) on chromosome 1 [14]. Microarray analysis of gene expression patterns in these animals revealed many of the differentially expressed genes were involved in calcium metabolism/transport. Further studies will hopefully provide a list of candidate

genes which can be investigated in human populations of stone formers.

TRPV5 encodes the transient receptor potential vanilloid member 5 protein (TRPV5) that functions as an apical membrane epithelial Ca^{2+} channel, allowing active calcium absorption in the DCT. Hoenderop et al. [15] have generated a *Trpv5* KO mouse which displays diminished active calcium reabsorption leading to dramatic hypercalciuria. Compensatory hyperabsorption of calcium from the gut and bony calcium resorption occur, but the animals remain stone free possibly because they also display significant polyuria. The human *TRPV5* thus is a candidate gene for hypercalciuria. Polymorphisms in a related channel, TRPV6, have also been associated with absorptive hypercalciuria in humans [16]. TRPV5 may be regulated by other proteins including the WNK4 molecule. Mutations in *WNK4* give rise to autosomal dominant (AD) pseudo-hypoaldosteronism type II which includes hypercalciuria as a result of up-regulation of the sodium chloride co-transporter (NCCT) in the DCT [17]. Intriguingly, a recent analysis of families of stone formers confirmed an association of hypercalciuria and hypertension in first-degree relatives of kidney stone formers. A search for polymorphisms in genes controlling both urinary calcium and sodium handling (such as *WNK4* or *WNK1*) would be informative and genetic screens on populations of hypertensive stone formers are eagerly awaited.

Dent's disease is an X-linked disorder characterised by low molecular weight proteinuria, hypercalciuria, nephrolithiasis, nephrocalcinosis and renal failure. The disorder is caused by mutations in *CLCN5*, encoding CLC-5, a chloride/proton exchanger. Various animal models of Dent's disease have been created [9]. In the model where urinary calcium excretion is most marked, renal calcification is seen. Proximal tubular endocytosis defects may account for dysregulation of tubular PTH, vitamin D receptor protein and phosphate handling, allowing variable conditions for stone formation to occur [9]. *CLCN5* mutations however are not commonly found in patients with idiopathic hypercalciuria.

Where There Is Too Much...

Hyperoxaluria

Hyperoxaluria is also a frequently detected metabolic abnormality in adults and children, found in around 10–20% of stone formers. Genetic mechanisms underlying idiopathic hyperoxaluria have yet to be elucidated, but genes

controlling oxalate metabolism, intestinal oxalate absorption and renal oxalate excretion must be key candidates.

Proximal renal tubules possess chloride-oxalate exchangers (such as SLC26A6) which help regulate serum oxalate concentrations. *SLC26A6* knockout mice demonstrate hyperoxaluria and calcium oxalate stone formation. The mechanism of hyperoxaluria is via a net hyperabsorption of oxalate, secondary to failure of oxalate secretion into the gut, leading to raised serum oxalate which leads to hyperoxaluria [18]. Hyperabsorption of oxalate seems to be a key mechanism in patients with idiopathic hyperoxaluria and stone formation, perhaps implicating this gene in human disease. Monogenic forms of hyperoxaluria, where there is overproduction of oxalate, have been reviewed by Cochat et al. [19].

A further 'genetic' consideration, outside the human genome, is relevant to oxalate stone formation. We have evolved and play host to a huge consortium of microbes within our digestive tract. This 'microbiome' may influence renal stone formation. Thus the identity and genetic make up of our gut organisms may influence our own bodies' metabolism. Individual species of organisms may play specific roles within our gut to enhance our metabolism. The gut organism *Oxalobacter formigenes* is an anaerobic commensal organism and is able to degrade oxalate from the diet using its enzyme oxalyl-CoA decarboxylase. Low rates of colonization with *O. formigenes* correlated with hyperoxaluria in calcium oxalate stone formers [20]. Re-introduction to the gut of bacteria that are able to degrade oxalate in this way may prove to be a useful therapeutic manipulation for stone formers. Certainly, with the advances of screening patients' urine (and faeces) to produce a metabolomic profile may identify patients at risk of calcium oxalate stone formation. This would depend on not their own genetic makeup, rather by the genes within the organisms the patients are hosting.

Where There Is Too Much...

Hyperuricosuria

This urinary abnormality is detected in 2–8% of children with nephrolithiasis. Medical causes underlying hyperuricosuria include myeloproliferative disorders, chronic diarrhoeal states, insulin resistance and monogenic metabolic disorders, such as Lesch-Nyhan syndrome. Defects in renal excretion of uric acid may cause urate stones, with these stones forming preferentially in acidic urine. Molecular identities of urate transporters

now include the human urate transporter 1 (hURAT1) and loss of function mutations have been found in subjects with idiopathic renal hypouricaemia and nephrolithiasis [21].

Where There Is Too Much...

Cystinuria

Cystine stones are rare and only account for 5% of paediatric stones and 1–2% of adult stones. Stones may occur in young children or not until adulthood, with a median age at onset of around 12 years. This is an example of an autosomal recessive disorder, with defects in a cystine/dibasic amino acid transporter (and its subunit) giving rise to excessively high urinary cystine levels, which precipitate to form stones. Two genes are known, *SLC3A1* and *SLC7A9*, but it is noteworthy that in around 25% of cystinuria patients, mutations may not be found in these genes, implicating other unknown gene defects [22]. Cystinuria as an inherited cause of renal stones may be used as a paradigm for other forms of stone formation. Thus, despite known gene defects, the urinary cystine concentrations vary from patient to patient, and the tendency to form stones may be precipitated by environmental as well as genetic factors. For example, not all patients with proven *SLC3A1* and *SLC7A9* mutations form stones, and patients with apparently lower urinary concentrations of cystine may be averse to stone formation compared to those with higher urinary cystine concentrations. As well as intratubular cystine crystals, calcium phosphate crystals are also often seen (possibly as a result of treatment by urinary alkalinisation) which may provide a nidus for progressive calculi formation.

Where There Is Too Little...

Hypocitraturia

As a natural inhibitor of stone formation in the urine, citrate is an important solute. In paediatric patients hypocitraturia has been reported in up to 10% of stone formers. Any cause of chronic metabolic acidosis will tend to increase proximal tubular citrate absorption in order to compensate, thus promoting stone formation. Renal citrate transporters include the Na⁺-coupled citrate transporter (NaCT, *SLC13A5*). Mutations in such transporters leading to calculi have not yet been described, but these transporters must be considered both as a candidate gene

for nephrolithiasis, and as a target for therapeutic intervention. It is important to remember that monogenic forms of renal tubular acidosis [for review, see 23] may give rise to both hypocitraturia and hypercalciuria, leading to significant nephrocalcinosis and nephrolithiasis.

Pyrophosphate Defects

Inorganic pyrophosphate (PP_i) was identified as a normal component of urine and a potent inhibitor of calcification over 46 years ago. PP_i is able to bind to the surface of basic calcium phosphate crystals and blocks crystal growth. More recently, the molecular identity of a PP_i transporter, named ANKH, which is able to transport PP_i to the extracellular space, has been discovered. Human mutations in *ANKH* give severe phenotypes, including hypermineralisation disorder known as cranio-metaphyseal dysplasia and calcium pyrophosphate dihydrate deposition disease (CCAL2). Hypopyrophosphaturia is associated with renal stone formation. We have recently demonstrated expression of ANKH in the collecting tubules of both the mouse [24] and human kidney, and we hypothesize that at this location of maximal urinary concentration mis-regulation of the channel or polymorphisms affecting channel properties may predispose to renal stone formation.

Tamm-Horsfall Protein Defects

Tamm-Horsfall protein (THP, alias uromodulin), the most abundant urinary protein in man, is synthesised within the tubular cells of the TAL of the loop of Henle. The protein is anchored to the plasma membrane by a glycosylphosphatidylinositol anchor and released into the urine by proteolytic cleavage. Patients with mutations in *UMOD*, the gene encoding THP, exhibit unexplained hyperuricaemia and gout, medullary cystic kidney disease or familial juvenile hyperuricaemic nephropathy. *UMOD* mutations have not been associated with renal calculi in humans. In contrast, *UMOD* knockout mice are susceptible to urinary tract infections (from fimbriated *Escherichia coli*) and calcium oxalate crystals, hinting that THP has multiple roles within the urinary tract. Unlike humans, mice possess a uricase enzyme, which allows further metabolism of uric acid to the more soluble allantoin, which may account for some of these phenotypic differences.

Recurrent calcium stone-forming patients have been shown to excrete increased quantities of abnormal THP, with a change in its chemical composition to include more sialic acid residues [25]. Whether there is a genetic basis for this structural change has not been explored. Maturation of THP may be regulated by other genetic factors (such as *DPM2* and *DOLPP1*) and these again represent candidate genes for nephrolithiasis [9].

Other Genetic Considerations

Congenital defects such as medullary sponge kidney may sometimes be inherited in an AD fashion. The underlying gene defect responsible for these congenital collecting duct abnormalities has yet to be discovered. It is worth noting that although the anatomical defects in the collecting ducts themselves predispose to calcium salt precipitation, underlying hypercalciuria, metabolic acidosis and hypocitraturia may also be present in patients with medullary sponge kidney.

Painstaking work using DNA from a Spanish kindred (from La Gomera) has recently produced the first locus (*NPL1*) for AD nephrolithiasis on chromosome 9q33.2–q34.2. The locus is large (14 MB) and contains many putative candidate genes (e.g. *DPM2* and *DOLPP1*), but specific gene mutations have yet to be defined [26].

Polymorphisms of matrix Gla protein (MGP), which (like ANKH) plays a role in determining calcification of extracellular matrix and is expressed in the kidney, have been associated with renal stones in humans. The *MGP* knockout mice die at 8 weeks of age from arterial calcification, whereas humans with certain polymorphisms were at increased risk of renal stone formation compared to controls [27].

Nephrolithiasis in the ‘-omics’ Era

As described above, modern technologies now allow individuals with stone formation to be investigated in terms of their metabolomic profile, defined from the complex interaction of genes, gut microbes and environmental factors. Urine composition in stone-forming patients may also be investigated using proteomic studies. This may allow the determination of a set of urinary biomarkers for renal stone disease which will be applicable to clinical practice. In parallel, modern day genomics now allows genome-wide association studies (often using SNP analysis of densities >500 K) to be performed in populations of stone formers, which will help identify the heritable components of complex traits such as hypercalciuria. This approach, which must use large numbers of case-control DNA samples, has successfully been employed in determining genomic regions associated with susceptibility to Crohn’s disease. These studies avoid the bias towards ‘candidate genes’ but may be fraught with difficulties such as false-positive associations. DNA capture technology (such as NimbleGen) followed by high throughput sequencing can now be deployed to solve known or putative ‘loci’. Indeed, this technology allows capture of 30 MB of DNA allowing sequencing of large loci (e.g. *NPL1* [26]) in a very short time scale. Results from these endeavours are eagerly awaited.

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