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INVITED REVIEW

# Heritable traits that contribute to nephrolithiasis

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**Abstract**
Urinary stones tend to cluster in families. Of the known risk factors, evidence is strongest for heritability of urinary calcium excretion. Recent studies suggest that other stone risk factors may have heritable components including urinary pH, citrate and magnesium excretion, and circulating vitamin D concentration. Several risk factors assumed purely environmental may also have heritable components, including dietary intake and thirst. Thus, future studies may reveal that genetics plays an even stronger role in urinary stone pathogenesis than previously known.

**Keywords** Calcium · Diet · Genetics · Urinary stone disease

## Introduction

Urinary stones are common with an estimated lifetime risk in the United States of 6–12% and up to 50% recurrence rate [1–4]. Recent studies suggest that the incidence of both symptomatic and asymptomatic kidney stones has continued to increase over the last three decades [5]. Due to multiple associated comorbidities, urinary stone disease represents a significant burden on the healthcare system. Passage of urinary stones is painful, and those with frequent recurrences can be afflicted with ongoing anxiety, stress and possibly depression. Furthermore, urinary stones have been associated with chronic kidney disease (CKD). This is not only true for patients with known monogenic causes (e.g., primary hyperoxaluria, Dent disease, 2-8-dihydroxyadenuria), but also other common endemic forms in the population [6–8]. Furthermore, urinary stone formers are at increased risk for other systemic diseases including myocardial infarction, independent of CKD and other risk factors [9].

An increasing body of evidence suggests that urinary stones aggregate in families [10, 11] suggesting a large genetic component. For example, urinary stones develop approximately threefold more frequently in individuals with a positive family history, and a family history of nephrolithiasis has been reported in 4–12% of healthy controls compared with 16–37% of affected individuals [12–14]. Indeed, the familial clustering index, one epidemiologic indicator of disease heritability, is greater for nephrolithiasis (2.5–4) than for diabetes mellitus (2.0) or hypertension (2.0) [4]. A study of isolated Croatian island groups provided additional evidence of a strong genetic component due to observed differences in stone prevalence between low (1.5%), moderate (2.3%), and high (5.4%) inbreeding villages [15]. Thus, it is likely that multiple genetic and environmental factors predispose to the formation of urinary stones [16], and greater understanding of the underlying heritable traits could provide important insight regarding underlying genetic factors, which in turn could help define important disease mechanisms and potential novel therapies. Here, we will discuss what is known regarding heritable risk factors for urinary stones, including the urinary composition, dietary risk factors, calcium and vitamin D homeostasis, and metabolic syndrome traits (Table 1).

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**Table 1** Heritable traits that might contribute to the overall heritability of urinary stone disease

| | Comments | Refs. |
|---|---|---|
| Urine excretions | | |
| Calcium | Strong evidence for heritability in stone formers | [13, 19–21] |
| Citrate | Significant heritability in stone formers | [13, 21] |
| Magnesium | Significant heritability in stone formers deserving further research | [13] |
| Volume | Significant heritability in stone formers | [13, 32] |
| Diet | | |
| Total protein | Significant hereditability in stone formers | [32] |
| Animal protein | Significant heritability in stone formers | [32] |
| Calcium | Significant heritability in stone formers | [32] |
| Oxalate | Significant heritability in stone formers | [32] |
| Sucrose | Significant heritability in stone formers | [32] |
| Fructose | Significant heritability in stone formers | [32] |
| Calcium metabolism | | |
| 1,25-Vitamin D | Altered vitamin D metabolism associated with kidney stones. Variable levels of heritability among different studies were reported likely due to environmental conditions. No data available about its heritability in stone formers thus far | [33–41] |
| Serum calcium | Serum calcium regulation and renal calcium transport were noted to have heritability, though research in stone formers are of need | [42–45] |
| Metabolic syndrome | Metabolic syndrome associated with kidney stones. Variable levels of heritability were reported among different studies for characteristics of metabolic syndrome, including BMI, fasting glucose, insulin, triglycerides, LDL-cholesterol, HDL-cholesterol, and systolic and diastolic blood pressure. No data available among stone formers thus far | [55–61] |

## Heritability of urinary traits

Human urine is often supersaturated with respect to stone-forming salts, which is a key factor in kidney stone pathogenesis [17]. Hypercalciuria is the best-established risk factor for calcium urolithiasis. In the male health professionals' follow-up study, men with a family history tended towards higher urinary calcium excretion [12], consistent with a previous study that demonstrated that stone formers with positive family history had a higher incidence of hypercalciuria [18]. A family study of French Canadians provided additional evidence that hypercalciuria is a heritable trait [19]. In this study, comprised of 83 sibships (212 affected sibs and 176 unaffected sibs from 71 families), urinary calcium excretion, regardless of the subtype, appeared to be the major phenotype associated with calcium urolithiasis in those families with at least two calcium stone-forming sibs [19]. In addition, urinary calcium excretion was higher in affected compared to unaffected sibs of the same sibship, suggesting that hypercalciuria is hereditary [19]. In a follow-up study by the same research team, segregation of hypercalciuria was also modeled in cohort of French–Canadian families [20]. In this report, they plotted major gene, polygenic, and mixed models to fit to 24-h urine calcium excretion from 567 individuals from 221 nuclear families of 154 pedigrees each containing at least two siblings with a history of calcium stones [20]. All of the proposed genetic models fit the data significantly better than the null model. The most parsimonious was a mixed codominant/polygenic model, but this was statistically indistinguishable from a single-gene codominant model [20]. In both of these models, the heritability attributable to the major gene was estimated to be 0.58 [20]. Data from the Genetic Determinants of Urinary Lithogenicity (GDUL) cohort study comprised of 811 individuals from 446 sibships in Rochester, Minnesota [13] supported the French–Canadian study with an estimated heritability for urinary calcium excretion of 0.25. Urinary calcium excretion was also identified as a heritable trait in a smaller identical twin study (12 sets) with an estimated heritability of 0.94 [21]. Taken together, these studies provide strong evidence for heritability of urinary calcium, and suggest it should be feasible to genetically map the quantitative trait locus.

Hypocitraturia is another known and import risk factor for calcium oxalate stone formation. Significant heritability of citrate excretion was also reported in the GDUL cohort with an estimated heritability of 0.36 [13]; in the identical twin study referenced above, the estimated heritability was 0.95 [21]. Urinary oxalate and uric acid also appeared to have heritable components in the identical twin study [21] and a pedigree analysis [22], but not in the GDUL cohort [13]. However, a heritable component for urinary magnesium

excretion (0.34) was noted in the GDUL participants [13]. A previous genome-wide association study suggested that variants in *CLDN14*, the gene encoding claudin-14, associated with urinary stone risk [11] and recent work suggested that genetic variants in *CLDN14* were associated with the ratio of urinary excretion of magnesium to calcium [23]. Thus, further study into the genetic regulation of urinary magnesium in relation to urinary stone disease appears warranted.

Low urinary volume has been consistently identified as a major risk factor for urinary stone disease and it has recurrence in many studies over the years. Interestingly, significant heritability for urinary volume was noted in the GDUL cohort, which in turn may implicate genetic regulation of thirst [13]. In addition, it is notable that a heritable component to urinary pH was also detected in the GDUL cohort that lacked any subjects with known disorders of systemic acid–base balance (e.g., renal tubular acidosis) [13].

## Heritability of dietary traits

A number of studies have implicated dietary factors, and the risk of incident and recurrent kidney stones [24–29]. Many of these dietary intakes are thought to directly or indirectly change the urinary excretion of lithogenic substances. For example, a low-sodium diet can reduce calcium excretion in hypercalciuric stone formers [27], and consuming more animal protein is associated with higher serum uric acid concentration and urinary uric acid excretion [26]. In general, an ideal stone prevention diet appears to involve overall greater intake of dietary fiber, fruits and vegetables, and this dietary pattern was associated with a reduced risk of incident kidney stones in postmenopausal women [25].

Previously, dietary habits were thought to be largely due to shared environment and culture. However, a paired twin study revealed that 44% of the variance in meal frequency and 65% of the variance in meal size could be attributed to heredity [30]. Data from the Erasmus Rucphen Family (ERF) study that investigated a young genetically isolated population also demonstrated that dietary intake patterns are heritable and can also predict obesity risk [31]. These findings indicate that prospective intervention regarding diet habits could potentially decrease the subsequent risk of certain diseases including urinary stones.

Heritability of dietary risk factors for urinary stones was also recently investigated in the GDUL cohort [32]. Many key dietary features previously associated with urinary stone risk appeared to have a strong heritable component including intakes of dietary protein, animal protein, calcium, oxalate, sucrose and fructose, and remained statistically significant even after adjustment for age, sex, height and weight [32]. In this study, three dietary components (total protein, calcium, and sucrose) had strongly positive heritable components, with additional environmental contributions [32]. These findings suggest that the line between genetic and environmental risk factors may be more blurred than previously appreciated, and that certain individuals may be predisposed to dietary preferences that increase stone risk [32]. It is possible that the strong genetic correlations between the various dietary intakes with heritable components identified in the GDUL cohort could be the result of underlying taste preferences which are known to have genetic components and also influence eating behaviors; alternatively, genetic factors might influence consumption of foods rich in calcium, protein and sucrose via other pathways yet to be defined [32].

## Altered calcium and vitamin D homeostasis

The formation and growth of calcium stones requires delivery of calcium to the urinary space. Calcium homeostasis is normally tightly regulated through an integrated hormonal system that controls calcium transport in the bone, gut and kidney [33], all of which can be impacted by vitamin D metabolism [34]. Vitamin D can be acquired via dietary intake or de novo synthesis in the skin. It is hydroxylated in the liver to 25-hydroxyvitamin D (25[OH]D) and released into the serum. 25(OH)D is further hydroxylated in the kidney to form the active metabolite 1,25-dihydroxyvitamin D (1,25 (OH) 2D). Studies in male patients with active kidney calcium stones demonstrated that higher serum 1,25 (OH) 2D was associated with higher urinary excretion of calcium [35]. Furthermore, a prospective case–control study of men in the Health Professionals Follow-Up Study found that higher plasma 1,25(OH)2D, even in ranges considered normal, is independently associated with higher risk of symptomatic kidney stones [36]. Data from Olmsted County, MN, also revealed the serum Ca and 1,25(OH)VD were increased in a cohort of first-time male and female calcium stone formers compared to controls [1]. Interestingly, the Olmsted County study also revealed that the ratio of serum 24,25(OH)2D/25(OH)D was increased in the first-time stone formers, and that PTH concentrations were slightly higher [1, 34]. These findings suggest that first-time calcium stone kidney formers may have a subtle abnormality in calcium metabolism that includes decreased 24-hydroxylase activity, the enzyme that converts 25(OH)D to a less active form of vitamin D [1, 34]. Patients with mutations in *CYP24A1*, the gene that encodes 24-hydroxylase, can present with profound hypercalciuria [1, 34]. Conversely, circulating concentrations of 25(OH)D do not appear to associate with kidney stone risk [36]. Vitamin D intake in recommended amounts has not been independently associated with kidney stone risk [37, 38].

Data from the German Asthma Family Study Group in sib children pairs revealed that, after adjusting for sex

and age, 25-OH-D3 levels had a heritability of 0.8 while for 1,25-(OH)2-D3 heritability was only 0.3 [39]. In the cross-sectional Insulin Resistance Atherosclerosis Family Study, the heritability of 25(OH)D ranged from 0.227 to 0.413 after adjustment for sex, age, solar radiation, BMI, and physical activity, and heritability for 1,25(OH)2D ranged from 0.162 to 0.484 after adjustment for sex, age, BMI, and 25(OH)D [40]. These results indicate a moderate genetic contribution to both 25(OH)D and 1,25(OH)2D circulating concentrations. Furthermore, twin studies suggested that serum 25(OH)D concentrations are highly heritable during the winter compared to the summer [41]. Thus, environmental conditions (e.g., sun exposure) may potentially cloud the potential influence of heritability of serum 25 (OH) D concentrations. There are no data on the heritability of either 25(OH)D or 1,25(OH)2D in a cohort of stone formers.

Heritability estimates for serum calcium range from 0.21 to 0.45 in published twin studies [42–45] and from a study of nuclear families randomly selected from the general population [45]. Interestingly, studies in the general population also suggest a genetic influence on renal calcium handling with heritability estimates for 24-h urine calcium clearance, excretion, and fractional excretion of 45%, 44%, and 51%, respectively [45]. Thus, further investigation regarding the genetics of serum calcium regulation and renal calcium transport in cohorts of calcium stone formers are likely to be informative.

## Metabolic syndrome traits

Elements of the metabolic syndrome include central obesity, hypertension, dyslipidemia, and hyperglycemia [46], which are at least partly dependent on reduced insulin sensitivity and hyperinsulinemia [47]. Systematic review and meta-analysis of studies have demonstrated that the metabolic syndrome is associated with a urinary stone risk [47, 48].

Obesity, especially central obesity, is associated with the occurrence and recurrence of kidney stones [48]. Kidney stones in obese individuals are mainly composed of calcium oxalate and uric acid [49], and obese stone formers had higher urinary excretions of sodium, calcium, uric acid and citrate, plus a lower urinary pH [50]. Furthermore, a recent study suggested that calcium stone formers with low amounts of Randall's Plaque tended to be obese [51]. Thus, patients with obesity and metabolic syndrome may have distinct pathogenic risks for stone formation and growth that differ from the non-obese population. Many studies have also demonstrated an independent association between urinary stones and hypertension [52]. The risk of urinary stones may be even higher in hypertensive individuals who are also obese [53]. Although the precise pathophysiology of the epidemiological association between hypertension and nephrolithiasis is not entirely clear, it has been proposed that the metabolic syndrome, insulin resistance, and atherosclerosis may be important underlying features [54].

Many of the metabolic syndrome traits appear to have underlying genetic risks with heritability estimates ranging from 24 to 90% for BMI [55–57], 10–75% for fasting glucose [55, 58, 59], 20–55% for fasting insulin [55], 0.03–72% for triglycerides [55], 25–98% for LDL-cholesterol [55], 30–80% for HDL-cholesterol [55], 30–74% for total cholesterol [55], 20–71% for SBP [55], and 10–50% for DBP [55]. These differences may be due in part to individual study designs, or may represent meaningful variations since heritability can depend on context, sex, or age [55, 60, 61]. A recent study in an unselected sample of adults ranging in age between 18 and 98 years suggested that the genetic contribution to metabolic syndrome traits is moderate to large in both sexes and across all ages [55]. Thus, the increasing prevalence of the metabolic syndrome over recent decades may be largely due to lifestyle changes. To date, there are no published data regarding the heritability of metabolic traits among kidney stone formers.

## Conclusions

For many decades, it has been appreciated that urinary stones tend to cluster in families, thus implicating genetic factors. Of the known risk factors, evidence is strongest for heritability of urinary calcium excretion. Studies that are more recent suggest that numerous other urinary stone risk factors may have heritable components, ranging from urinary pH, citrate and magnesium excretion, to circulating vitamin D concentrations. Interestingly, several risk factors assumed purely environmental now also have evidence for a heritable component including specific dietary intakes and total urine volume (thus potentially implicating the genetics of thirst). Thus, future studies may reveal that genetics plays a much stronger role in urinary stone pathogenesis than previously known.

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## Compliance with ethical standards

**Conflict of interest** John C Lieske declares that he has no conflict of interest. Xiangling Wang declares that she has no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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