
See related article, “ANCA as a Predictor of Relapse: Useful in Patients with Renal Involvement But Not in Patients with Nonrenal Disease,” on pages 537–542.

The Search for Monogenic Causes of Kidney Stones

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That kidney stones are heritable has been known at least since Archibald Garrod characterized cystinuria and noted its occurrence in siblings.1 Cystinuria has a special place in the history of genetics because by including it in a group of four disorders for which he famously termed the phrase “inborn errors of metabolism,” Garrod was called “the first human geneticist.”2 Descriptions of other genetic causes of stones followed in the 20th century and included primary hyperoxaluria (PH), adenine phosphoribosyltransferase deficiency (APRT’d, the cause of dihydroxyadenine stones), and Dent disease. Along with cystinuria, these latter three disorders have been the object of study of the Rare Kidney Stone Consortium (RKSC), part of the Rare Diseases Clinical Research Network (RDCRN) for the last 5 years.3 Although the list of causes of rare genetic kidney stones continues to grow, we chose these disorders to study as they are consequential not only

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because they cause significant and recurrent kidney stones, but also because they are all associated with CKD and end stage kidney disease.

Kidney stones are highly prevalent in the general population, affecting as many as 12% of American men and 7% of American women. These values are broadly similar to those observed elsewhere in the world. The disorders studied by the RKSC are “rare,” defined by the National Institutes of Health as affecting <200,000 individuals in the United States. PH and APRTd share an autosomal recessive inheritance, Dent disease is an X-linked recessive disorder, and cystinuria demonstrates incomplete dominant heritability, as discussed further below. These four rare diseases can account for only a minor proportion of all stones, with cystinuria being the most prevalent and amounting to about 1% of all stones and up to 7% of stones in children. The question then remains whether most kidney stones in the general population have a genetic component.

We explored this question using two twin registries. In the Vietnam Era Twin Registry, which includes only men, we demonstrated that the rate of concordance for self-reported kidney stones was 32.4% in monozygotic twins and 17.3% in dizygotic twins.4 The results suggest that heritability accounts for 56% of kidney stone prevalence. In an examination of the University of Washington Twin Registry, we recently showed that women demonstrated a similarly significant heritability, with 21% of monozygotic and 10% of dizygotic twins exhibiting concordance. This result suggests a genetic contribution of 45%.5 The sample sizes of these studies were not large enough to state that heritability of stones in women is not the same as it is in men, although kidney stones affect more men than women.

These impressive numbers demonstrating the heritability of stones remain unaccounted for to date after a plethora of studies of a variety of proposed candidate genes as well as after a small number of genome-wide association studies.6 The study by Halbritter et al. in this issue of JASN is therefore welcome in suggesting that perhaps a larger proportion of symptomatic stones are in fact the result of known, single-gene disorders.7 The study did not, by intent, attempt to reveal new genetic contributors to kidney stones.

Halbritter et al. studied 272 consecutively recruited patients (male and female children and adults) from the kidney stone clinics of three participating centers.7 The patients either had kidney stones (n = 256) or isolated nephrocalcinosis (n = 16) or both. Patients with stones thought to be caused by drugs such as vitamin D or by primary hyperparathyroidism were excluded. Halbritter et al. did not exclude some well characterized patients with established diagnoses such as cystinuria or renal hypouricemia. Because the centers are specialty clinics, such relatively unusual patients may be relatively enriched in numbers in this cohort. The authors then sought mutations in 30 genes known to cause autosomal dominant, autosomal recessive, or X-linked stones or nephrocalcinosis. They sequenced 381 coding exons, and identified a multitude of variants. They then applied a set of inclusion and exclusion criteria to the identified variants, in order to judge whether they were in fact likely to be causative of the phenotypes of interest.

When searching for rare diseases, the sample size utilized here would have to be considered small. Despite that, Halbritter et al. detected 50 mutations they judged likely to account for nephrolithiasis or nephrocalcinosis. Overall, they identified disease-causing mutations in 14 of the 30 selected genes, yielding a molecular diagnosis in 14.9% (40 of 268) of all patients, 21% of the pediatric patients, and 11% of the adult cohort. These mutations included 12 diagnoses in 8 recessive genes and 29 diagnoses in 6 dominant genes. In 16 genes of interest, no disease-causing mutations were found. Given the sample size, the contribution of these individual genes in the general population is not ruled out.

Although the genes studied were selected because they were already known to cause kidney stones when mutated, there were several interesting findings. The most frequently identified gene containing important mutations was SLC7A9, which codes for b0,+ AT, the light component of the proximal tubule’s cystine transporter, and which is one of the two genes responsible for cystinuria. The other gene is SLC3A1, which codes for rBAT, the protein that traffics b0,+ AT, the actual amino acid transporter, to the proximal tubular cells’ apical membrane. Here, three patients with homozygous SLC3A1 mutations, previously diagnosed by stone composition, were identified. Long thought to be an autosomal recessive disorder, the International Cystinuria Consortium recognized that mutations in SLC7A9 led to a dominant disorder of variable penetrance, often termed “incomplete” or “partially” dominant.8 Some heterozygotic patients have enough cystine excretion to form stones, depending in part on genotype and likely on diet and fluid intake as well. Here the authors found 17 individuals with stones or nephrocalcinosis with heterozygous SLC7A9 mutations, some of whom had been undiagnosed, with no stones to analyze. Several had also formed calcium oxalate or calcium phosphate stones. That cystine may affect in vitro solubility of calcium was previously demonstrated.9 Whether the finding that heterozygous SLC7A9 mutations are found in some calcium stone formers represents a random coincidence of no pathophysiologic significance or a causative factor, and whether there are implications for treatment, are not known.

Three mutations in ADCY10, the gene encoding a bicarbonate-responsive soluble adenyl cyclase, were also demonstrated. This finding is of interest because the relationship between kidney stones and this protein has been uncertain. The protein has diverse effects to modulate epithelial acid-base and calcium transport. Although some kindreds with hypercalciumia and low bone mineral density were linked to this gene, evidence demonstrating that the known mutations are responsible for the kidney stone phenotype is lacking.10 Further characterization of the physiologic significance
of this genotype and its ability to produce the associated phenotype appears warranted.

Always of interest is the question of whether measuring serum phosphate concentrations is an important screening procedure in calcium stone formers. Patients with mutations in phosphate cotransporters may present with hypophosphatemia, may have associated bone mineral loss, and may benefit from phosphate supplementation. In the study by Halbritter et al., two patients with mutations in SLC9A3R1, which encodes a sodium/hydrogen exchanger regulatory cofactor (mutations of which are responsible for hypophosphatemic nephrolithiasis/osteoporosis), were identified. Two patients, one with a mutation in SLC34A1 and one in SLC34A3, both encoding type II sodium/phosphate cotransporters, were also found. These diagnoses have implications for kidney stone prevention and monitoring of bone mineral density.

CLDN14 is one gene that would have been of interest to include (not studied here). The gene codes for claudin 14, a determinant of paracellular calcium and magnesium transport in the thick ascending limb. Variants in the gene appeared to account for as much as 25% of hypercalciuria in Iceland and The Netherlands. The affected cohort was also shown to have reduced bone mineral density, supporting the plausibility of a defect in renal calcium absorption. In one study of the genetics of urine calcium excretion, however, CLDN14 variants were not associated with hypercalciuria; in fact, one single nucleotide polymorphism (SNP) was associated with lower urine calcium excretion. Whether the small sample studied here would have revealed additional data is unknown. Two cases of mutations in CLDN16 (and none in CLDN19), leading to familial hypomagnesemia with hypercalciuria and nephrocalcinosis, previously diagnosed clinically, were confirmed by genetic sequencing.

Although the clinical data presented here are sparse, it would seem likely that a number of these patients would have been empirically, and incorrectly, diagnosed with medullary sponge kidney. This diagnosis is often made by radiologists in patients with nephrocalcinosis, seen either by ultrasonography or by plain radiography. Without administration of intravenous contrast, however, the diagnosis cannot be made confidently. Application of broad genetic screening, such as performed in the study by Halbritter et al., might correctly reclassify many such stone formers. A negative finding was that no cases of mutations in the calcium-sensing receptor gene (CASR) were found. Previous studies have suggested that the activity of the CaSR is a determinant of urinary calcium excretion, and that SNPs in the encoding gene have hereditary influences. Other studies have not confirmed these observations. However, the absence of mutations here does not rule out an effect of SNPs on the kidney stone phenotype.

The genetic contributors to the hereditary nature of stones in general and calcium stones in particular remain entirely unclear. As is the case for diseases such as diabetes and hypertension, calcium nephrolithiasis is likely to be a complex, multigenic disorder. Studying rare diseases, as demonstrated by the RDCRN and by Halbritter et al., should continue to yield insights into less rare ones. The oft-quoted estimate is that 1 in 10 people are affected by a rare disease. Considered together, in other words, rare diseases are not rare. As genetic discovery progresses, the number of “common” cases of kidney stones may be eroded and revealed to be an abundance of rare diseases.

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REFERENCES


See related article, “Fourteen Monogenic Genes Account for 15% of Nephrolithiasis/Nephrocalcinosis,” on pages 543–551.

**Electroacupuncture Therapy for Muscle Atrophy in CKD: Is There a Needle in the Haystack?**

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Muscle wasting is highly prevalent among patients with CKD. The cellular mechanisms of muscle atrophy have been identified, yet definitive treatment to prevent or reverse this complication is not fully in sight. Despite proven efficacy in persons without kidney disease, resistance exercise training has not consistently and convincingly been shown to improve lean body mass in patients with CKD.1 Several novel interventions, such as blocking the Stat3 signaling pathway by C188–9 and inhibiting myostatin using anti-myostatin peptibody and miRNA-27, are being explored, offering a glimmer of hope.

In this issue of *JASN*, Hu et al.2 report their results of studying the effects of low-frequency electrical stimulation (LFES) in mice with CKD-induced muscle atrophy. Specifically, the investigators treated 5/6-nephrectomized mice and control mice with LFES for 15 days. In CKD mice, LFES prevented soleus and extensor digitorum longus muscle weight loss and loss of hind-limb muscle grip. LFES countered the CKD-associated decline in the IGF-1 signaling pathway and led to increases in markers of protein synthesis and myogenesis. LFES acutely increased the expression of inflammatory cytokines (IFN-γ and IL-6), which was accompanied by infiltration of muscle with M1 macrophages in the early phase followed by M2 macrophages 2 days later. The IGF-1 expression in the muscle was temporarily related to accumulation of M2 macrophages. The authors also noted that expression of miRNA-1 and -206, which inhibit IGF-1 translation, decreased in the acute response phase after LFES and increased at a later phase. Hu et al. concluded that LFES ameliorates CKD-induced skeletal muscle atrophy by upregulation of the IGF-1 signaling pathway.

While these findings are interesting and novel, many unanswered questions still remain regarding the mechanism of action and utility of LFES in the clinical setting. For example, which component of LFES is key to this effect, the acupuncture or the electrical stimulation? In the metaphysical concept, acupuncture is based on the belief that energy or *chi* travels through hypothetical channels called “meridians.” Disturbance of *chi* causes disease, which could be restored by inserting needles in specific points of the body. There is no supporting scientific evidence for the existence of *chi* life force or meridians. However, a National Institutes of Health consensus conference concluded that there was positive evidence for its effectiveness for certain conditions.3 Electroacupuncture treatment is an acupuncture method that uses stimulation of acupuncture needles with a low-frequency microcurrent. Electroacupuncture increases blood flow and oxygenation of skeletal muscles4 and has been applied for recovery from skeletal muscle fatigue and musculoskeletal disorders. Onda et al.5 showed that acupuncture with and without electrical stimulation ameliorated skeletal muscle atrophy in mice that were subjected to hind-limb suspension. Acupuncture down-regulated the genes involved in muscle breakdown (atrogin-1 and muscle RING-finger protein-1) and upregulated Akt1 and Transient receptor potential cation channel subfamily V member 4, which are positive regulators of protein synthesis. In another study, Takaoka et al.6 demonstrated that electroacupuncture treatment induced satellite cell proliferation in nonatrophic skeletal muscle through the suppression of myostatin expression.

Does LFES mediate its effect through modulation of microRNA (miRNA) expression? miRNAs are small noncoding