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Classical and Modern Genetic Approach to Kidney Stone Disease

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Nephrolithiasis is one of the most widespread urinary disorders, and calcium, as calcium-oxalate or -phosphate, is by far the most frequent component of stones. Idiopathic nephrolithiasis is generally acknowledged as a disorder caused by the interaction of multiple genetic and environmental factors. Family studies showed a non-mendelian transmission of idiopathic nephrolithiasis.[1] In addition, a small group of rare monogenic disorders (distal tubular acidosis, Dent diseases, primary oxalosis) may develop calcium nephrolithiasis.[2]

The overall contribution of genetic determinants to kidney stones in a population may be estimated as heritability according to criteria of classic genetics.[3] Heritability of kidney stones may be computed by taking account of the concordance rate for nephrolithiasis in monozygotic and dizygotic twin pairs.[3] This approach was used by Goldfarb *et al*.[4] in their article published in the present issue of *Kidney International Reports*. These authors already analyzed male monozygotic and dizygotic twin pairs selected from the Vietnam Era Twin Registry in a previous work published in 2005. In these male twins, concordance rate for nephrolithiasis was found higher in monozygotic than dizygotic twins and heritability value was estimated to be 56%.[5] In the present study, these authors selected twins from the Washington State Twin Registry and for the first time calculated heritability in women and men separately. Monozygotic twins showed again a higher concordance rate for stones in comparison with dizygotic twins, and the value of heritability detected in men (57%) confirmed that previously observed in twins from the Vietnam Era Twin Registry and in other family studies,[1] whereas its value was significantly lower (46%) in women.[4,5] These findings indicate that genetic determinants may be more relevant for stone susceptibility in men than in women and this could contribute to explain the higher frequency of kidney stones in men.

Mutations at 4 genes located in the X-chromosome may cause monogenic forms of nephrolithiasis[2]: *OCRL* (Xq26.1) and *CLCN5* (Xp11.23) may cause calcium stones; *PRPS* (Xq22.3) and *HGPRT* (Xq26.2-q26.3) may cause uric acid stones. The *OCRL* gene (OMIM 3000535) encodes a phosphatidylinositol 4,5-bisphosphate-5-phosphatase located in the trans-Golgi network that regulates actin polymerization and the formation of tight and adherens junctions in the proximal tubule. Mutations at the *OCRL* gene cause oculocerebro-renal Lowe syndrome and the less severe Dent disease type 2, a proximal tubule disorder with multiple defects of reabsorption. *CLCN5* (OMIM 300009) encodes a voltage-gated chloride ion channel localized in the brush border and endocytosis vesicles in proximal tubular cells; this channel provides an electrical shunt necessary for the acidification of vesicle fluid and endocytosis pathway; its mutations cause Dent disease type 1, phenotypically indistinguishable from the type 2 disease. *PRPS* (OMIM 311850) encodes phosphoribosyl pyrophosphate synthase, which is necessary for a correct purine and pyrimidine biosynthesis; superactivity of this enzyme results in an excessive purine production, hyperuricemia, hyperuricosuria, gout, and uric acid stones. Finally, *HGPRT* (OMIM 308000) encodes hypoxanthine-guanine phosphoribosyl-transferase; its mutations lead to hypoxanthine and guanine accumulation and cause overproduction of uric acid, gout, and uric acid nephrolithiasis; complete deficiency of this enzyme causes Lesch-Nyhan syndrome. Allele variants in these 4 genes may increase susceptibility to idiopathic calcium and uric acid nephrolithiasis in men, but it is likely that variants at other genes located in the X-chromosome also may contribute to stone production.[2]

Different models of genetic determination may underlie idiopathic nephrolithiasis: variants in

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a few specific loci could be necessary to promote stone production and, thus, exert a dominant effect; alternatively, multiple additive genes, each of them unable to cause stones by themselves, may sum their effects to increase stone risk and cause stone formation.[3] Each of these genetic models may be causal in distinct stone former groups, even though dominant and additive genes may coexist and mutually influence stone risk in patients. This complex background is further complicated by environmental factors that may influence gene expression with their epigenetic effects. In addition, many variables predisposing to kidney stones are multifactorial traits, like hypercalciuria, hypocitraturia, urinary tract obstruction, and Randall plaque extent.[6]

In the context of nephrolithiasis, findings of phenotype-genotype association studies, either testing the whole genome or candidate genes, identified a group of loci associated with kidney stones in different populations: *CASR (3q13.3-q21.1)*, *CLDN14 (21q22.13)*, *ALPL (1p36.12)*, *TRPV5 (7q34)*, *SLC34A1 (5q35.3)*, *ORAI1 (12q24.31)*, *KL (13q13.1)*, *DGKH (13q14.11)*, *AQP1 (7p14.3)*, *MGP (12p12.3)*, *SPP1 (4q22.1)*, *VDR (12q13.11)*, *PLAU (10q22.2)*, *SLC26A1 (4p16.3)*, and *SLC26A6 (3p21.3)*.[2] All these genes are autosomal and characteristics of their association with stones, in terms of variant frequency and gene product activity, suggest that they could produce additive effects in stone formation. A summary of tubular activities of their products is shown in Figure 1.[2]

Recent works observed that idiopathic patients with early onset of stone disease may carry variants in genes causing monogenic nephrolithiasis. These rare variants were detected in 29% of patients with stone disease onset before 25 years[7] and were identified at the following loci: *AGXT (2q37.3)*, *ATP6V1B1 (2p13.3)*, *CLDN16 (3q28)*, *CLDN19 (1p34.2)*, *GRHPR (9p13.2)*, *SLC3A1 (2p21)*, *SLC12A1 (15q21.1)*, *SLC9A3R1 (17q25.1)*, *SLC34A1 (5q35.3)*, *VDR (12q13.11)*, *ADCY10 (1q24.2)*, *CYP24A1 (20q13.2)*, *ATP6V0A4 (7q34)*, *SLC7A9 (19q13.11)*, *SLC2A9 (4p16.1)*, *SLC22A12 (11q13.1)*, and *SLC4A1 (17q21.31)*.[7,8] Stone formers carrying these rare variants were characterized by nephrocalcinosis, high rate of relatives with stones, and consanguineous parents, in addition to early onset of

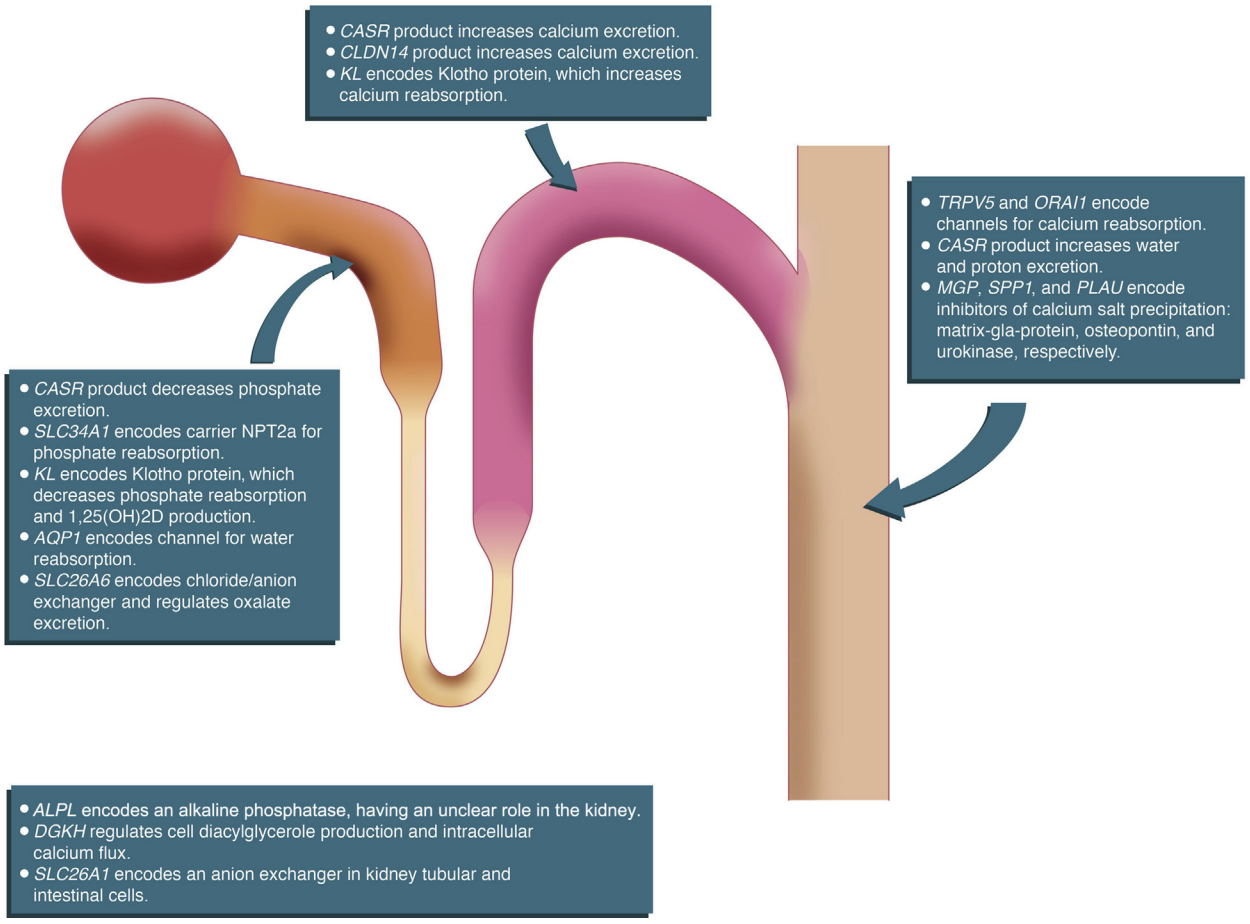

Figure 1. Genes implicated in idiopathic kidney stones retrieved by replicated association studies.[2] The figure reports the activity of these gene products and their relative tubular region of activity.

the disease.[8] These characteristics suggest that these genes may significantly influence clinical history of patients and stone risk, thus producing a dominant effect in stone disease.

Heritability estimates the averaged effect of genetic determinants on stone production variance in a specific population.[3] The study of Goldfarb *et al.*[4] suggests that approximately one-half of susceptibility to kidney stones may be sustained by genes; however, the weight of genes may be different and differently combined with environmental factors in each stone former. Predicting stone risk in single individuals needs to consider variants at all causal loci, environment characteristics, and epigenetic effects of environmental factors on gene expression. Current technological advances exploring genetic variants in the whole genome allow prediction of individual stone risk and, together with improvements in statistical analysis methods, also estimation of heritability of complex traits, like stone disease in unrelated individuals.[9] However, heritability estimated by such genomic tools cannot include epigenetic influences and rare genetic variants, thus resulting in heritability estimates lower than those provided by studies in twins. Only recovering such missing heritability in large cohorts will provide a heritability estimation similar to that detected by twin studies.[9]

In conclusion, heritability estimation by twin study remains a relevant reference for modern genetic studies. The overall analysis of loci associated with nephrolithiasis combined with findings of lifestyle analysis and epigenomic investigation may provide stone-risk parameters useful for the clinical evaluation of patients by also taking into account gender variability, as indicated by the present work of Goldfarb *et al.*[4]

DISCLOSURE

All the authors declared no competing interests.

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