GENETICS

Sequence variants linked to risk of urologic disease

Two new studies published in *Nature Genetics* have shed light on the genetic causes of two common urologic diseases, identifying sequence variants associated with bladder cancer and kidney stones.

Wu and colleagues identified a variant in the prostate stem cell antigen (*PSCA*) gene, which showed consistent association with bladder cancer in populations from both the USA and Europe. Initially, the investigators conducted a genome-wide association study to analyze over 500,000 single nucleotide polymorphisms (SNPs) among 969 cases and 957 controls from an ongoing Texan case–control study. The 50 most-promising SNPs were then examined in three further US populations; one SNP—rs2294008, a missense mutation located in exon 1 of *PSCA* on chromosome 8q24—showed consistent association with bladder cancer across these populations, and in a further 9 European datasets, with an allelic odds ratio of 1.15 (95% CI 1.10–1.20).

The investigators found that rs2294008 alters the start codon of the *PSCA* gene, possibly resulting in a 9aa truncation of the primary translation product, and reduces the transcriptional activity of the PSCA promoter *in vitro*. They note that while the functional effect of the missense variant remains to be characterized, rs2294008 should be considered an independent bladder cancer susceptibility locus on 8q24.

In a separate study, researchers from Northern Europe initiated a genome-wide association study to identify sequence variants associated with risk of developing kidney stones among 1,507 cases and 34,033 controls from a population in Iceland. They identified two highly correlated nonexonic SNPs (rs219781 and rs219778) in the claudin-14 gene (*CLDN14*), which were significantly associated with risk of nephrolithiasis. Testing in further populations from Iceland and The Netherlands confirmed this association, with an allelic odds ratio of 1.23 for the two synonymous variants.

As these two SNPs are noncoding, the researchers sequenced *CLDN14*, and identified two exonic SNPs that were also associated with stone formation. They suggest that such coding variants might perturb the normal function of claudin-14, which regulates paracellular passage of ions and small solutes, to result in metabolic abnormalities that contribute to stone formation.

Nick Groves-Kirkby

Original articles Wu, X. *et al.* Genetic variation in the prostate stem cell antigen gene *PSCA* confers susceptibility to urinary bladder cancer. *Nat. Genet.* **41**, 991–995 (2009).
Thorleifsson, G. *et al.* Sequence variants in the CLDN14 gene associate with kidney stones and bone mineral density. *Nat. Genet.* **41**, 926–930 (2009).