Nephrolithiasis is a major health burden with a poorly understood pathogenesis. We conducted a genome-wide association study in British and Japanese populations identifying twenty nephrolithiasis-associated loci. Mutations in the calcium-sensing receptor (CaSR) cause disorders of calcium homeostasis and five identified loci (DGKD, DGKH, WDR72, GPIC1 and BCR) were predicted to influence CaSR-signalling.

In a validation population, we demonstrated that genotype at the DGKD-associated locus correlated with urinary calcium excretion but not serum calcium concentration. In vitro studies demonstrated that knockdown and overexpression of DGKD resulted in biased CaSR-signalling. Thus, treatment of CaSR-expressing HEK cells with DGKD-targeted siRNA (DGKD-KD), resulted in decreased MAPK responses to alterations in extracellular calcium concentration ([Ca2+]e), as assessed by SRE-reporter and ERK-phosphorylation (pERK) assays, when compared to cells treated with scrambled siRNA (WT) but without alteration in intracellular calcium responses ([Ca2+]i as assessed by NFAT-reporter and Fluo-4 calcium assays (SRE maximal response DGKD-KD =5.28 fold change vs. WT=7.20 p=0.0065, pERK maximal response DGKD-KD=24.77, vs. WT=39.46 fold change, p=0.0056). Conversely, DGKD overexpression (DGKD-OE) increased MAPK responses but suppressed [Ca2+]i responses to alterations in [Ca2+]e (SRE maximal response DGKD-OE =14.13 fold change vs. WT=9.06 fold change, p=0.01; NFAT maximal response DGKD-OE=15.67 fold change vs WT=59.16 fold change, p=0.0001).

Our results demonstrate that alterations in DGKD expression cause biased CaSR-signalling. This biased signalling may provide an explanation for the correlation of genotype at the DGKD-associated locus with urinary calcium excretion but not serum calcium concentration. Our findings suggest that biased CaSR-signalling may be a common cause of nephrolithiasis.