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ALPK1 affects the flares of gout by regulating SLC22A12/URAT1

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Abstract

Background:

ALPK1 encoding an unclearly functional kinase is recently identified as a susceptible gene of gout. *URAT1* (encoded *by SLC22A12*) mediates urate reabsorption and is therefore associated with the gout development. Here, we investigated the interactions between *ALPK1* and *URAT1*.

Methods:

The effects of overexpressed *ALPK1* on *URAT1* protein expression were evaluated *in vivo* in hALPK1 transgenic mice. For cellular interaction, the mRNA expression levels of *ALPK1* and *URAT1* co-transfected into human embryonic kidney 293 cells (HEK-293) were examined. The clinical dataset consisted of 1122 case-control samples (373 gout, 444 hyperuricaemia and 305 controls). **Four** *ALPK1* and *SLC22A12* loci were genotyped.

Results:

Both transgenic and endogenous ALPK1 were detected in mouse renal proximal tubule cells. The hALPK1 transgenic mice displayed with lower expression of URAT1 (P=0.0045). In HEK-293 cells, *ALPK1* significantly decreased *URAT1* mRNA expression (P<0.05). Nonetheless, the *ALPK1* major loci and *SLC22A12* rs3825016 [C/C] were independently (odds ratio [OR] ≥1.67, $P \leq 5.00\times10^{-3}$) and jointly (OR ≥2.97, $P \leq 1.38\times10^{-5}$) associated with gout risk. However, comparisons of the rs3825016 [C/T] + [C/T] and [C/C] for the *ALPK1* major loci revealed a decreased risk of gout between the groups (ratio of OR, 0.51 to 0.69 times).

Conclusions:

ALPK1 inhibited URAT1 expression. Based on the results, ALPK1 might decrease urate reabsorption via URAT1, appeared to be negatively associated with gout. These findings suggest that ALPK1 affects gout flares by regulating SLC22A12 urate uptake in an innate bidirectional manner and implicated to urate-lowering therapies.