

Response to: 'Correspondence on 'Variants in urate transporters, ADH1B, GCKR and MEPE genes associated with transition from asymptomatic hyperuricaemia to gout: results of the first gout versus asymptomatic hyperuricaemia GWAS in Caucasians using data from the UK Biobank' by Takei *et al*

Takei *et al* conducted a genome-wide association study (GWAS) in European individuals with gout versus asymptomatic hyperuricaemia controls. They reported nine independent genetic variants in or near *ABCG2*, *SLC2A9*, *GCKR*, *ADH1B*, *SLC22A11*, *PDX1*, *MLXIPL* and *CNBD1* associated with gout using 'a more stringent' threshold of $r^2 < 0.01$ for linkage disequilibrium (LD) clumping. Compared with our study, they found three additional loci in *PDX1* (rs182200427), *MLXPIL* (rs7805504) and *CNBD1* (rs181604403) that were not included in the non-imputed UK Biobank dataset used in our study. And more importantly, they reported a single SNP in *ABCG2* (ie, rs2231142) locus associated with gout after conditioning on rs2231142.¹

In our analysis, we reported 13 independent genetic variants mapped to *ABCG2*, *SLC2A9*, *SLC22A11*, *GCKR*, *ADH1B*, *MEPE*, *PPM1K-DT* and *LOC105377323*. Eight of which are located in chromosome 4, near the *ABCG2* locus. To determine independent associations, we selected a $r^2 < 0.1$ for LD clumping, which is lower than the standard threshold ($r^2 < 0.2$) used in many GWAS, and a p value $< 5.0 \times 10^{-8}$. We performed further analyses looking at pairwise LD comparisons among these loci, using LDlinkR² with the 1000 Genomes dataset as the reference panel. Additionally, LD clumping was also performed using PRSice-2³ for the polygenic risk score generation, using the same UK Biobank dataset as the reference panel for LD estimations. Both analyses retained the 13 single nucleotide polymorphisms (SNPs) as independent associations, and the LD pattern in our supplementary figure 2 did not prompt us to conduct conditional analyses.

We acknowledge that using a more stringent r^2 cut-off reduces the number of independent variants. However, *ABCG2* gene has shown evidence of complex LD structure. Additional SNPs within the same locus have been associated to gout. For instance, rs3114018 ($r^2 > 0.2$ with rs7672194, reported in our study) located in a different haplotype block from rs2231142 has been related to gout risk.⁴

Moreover, a study by Zelenchuk *et al* reported that changes to the N-terminal region of MEPE contribute to hyperuricaemia and a reduction in fractional excretion of uric acid in a mouse model.⁵ Therefore, the role of MEPE in purine metabolism merits additional research to identify if genetic variants within this locus contribute to serum urate variation either by regulating nearby urate transporter genes, or via other effects such as those on renal phosphate handling.

Deep sequencing of the *ABCG2* gene and upstream and downstream regions to capture *MEPE*, *PPM1K-DT* and *LOC105377323* is required to determine underlying functional rare variants that could influence gout risk.

The final comment of Takei and colleagues is correct. We highlighted the closest gene to the significant variant at each locus, as is tradition, but we acknowledge that it may be any within the locus which we should have stated clearly.

We would like to take this opportunity to thank Takei and colleagues for undertaking this additional work.

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