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Letter to the Editor

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Letter to the Editor (Other)

SNP-based heritability estimates of gout and its subtypes determined by genome-wide association studies of clinically defined gout

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Rheumatology key message

- Heritability estimates of clinically defined gout and its subtypes were first determined by genome-wide meta-analyses.

Dear Editor, Gout is the most common form of inflammatory arthritis associated with elevated serum urate (hyperuricaemia). It has three major subtypes: renal underexcretion (RUE) type, renal overload (ROL) type and the combined (RUE + ROL) type (Fig. 1A). Historically associated with overindulgence in meats, seafood and alcohol, gout has been called the 'disease of kings'. However, literature reveals gout to have been understood as a hereditary trait as early as the second century [1]. Nevertheless, unlike with serum urate [2], the heritability of gout, i.e. the percentage variance of phenotype that is explained by inherited genetic variants, remains inconclusive.

A classic twin study conducted in the USA reported that despite confirmation of the strong heritability of hyperuricaemia, individual variability in gout was substantially influenced by environmental factors shared between co-twins, not by genetic factors [3]. In contrast, a cross-sectional study of a Taiwanese population suggested a genetic predisposition to gout [4]. Another study using the UK Biobank Resource, which calculated heritability estimates of gout (proportion of variance in gout explained by common inherited genetic variants based on an additive model of inheritance), suggested that in European individuals, the common genetic variant-mediated heritabilities of high serum urate and gout were similar [5]. However, these previous studies analysed gout patients that included self-reported cases. No information is available on the heritability of gout subtypes, as it has hitherto been unclear as to whether a genetic association of this type may apply to other populations. To address these issues, we herein investigated heritability estimates of gout, including its subtypes, in Japanese populations.

Via genome-wide association study (GWAS) meta-analyses of clinically defined gout with its subtypes in Japanese gout cases and normouricaemic controls (serum urate $\leq$7 mg/dl; without a past history of gout) of Japanese males, we previously identified genomic loci that influence gout susceptibility [6]. To extend the range covered for serum urate concentrations in controls and create a more generalized population, we herein employed 'non-gout controls' by adding asymptomatic hyperuricaemic controls comprising Japanese males (serum urate >7 mg/dl; without gout), an excluded population in our previous studies [6], to the normouricaemic controls. This allowed us to estimate the heritability of clinically defined gout by reconducting GWAS meta-analyses (3053 gout cases *vs* 5637 non-gout controls; Fig. 1B–E). Details of the results and related methods are described in the supplementary material, available at *Rheumatology* online. From the results [i.e. summary statistics of 1,029,593 single nucleotide polymorphisms (SNPs), which have a minor allele frequency (MAF) $\geq$1% and were not palindromic SNPs], we estimated the SNP-based heritability of gout (Fig. 1F, Supplementary

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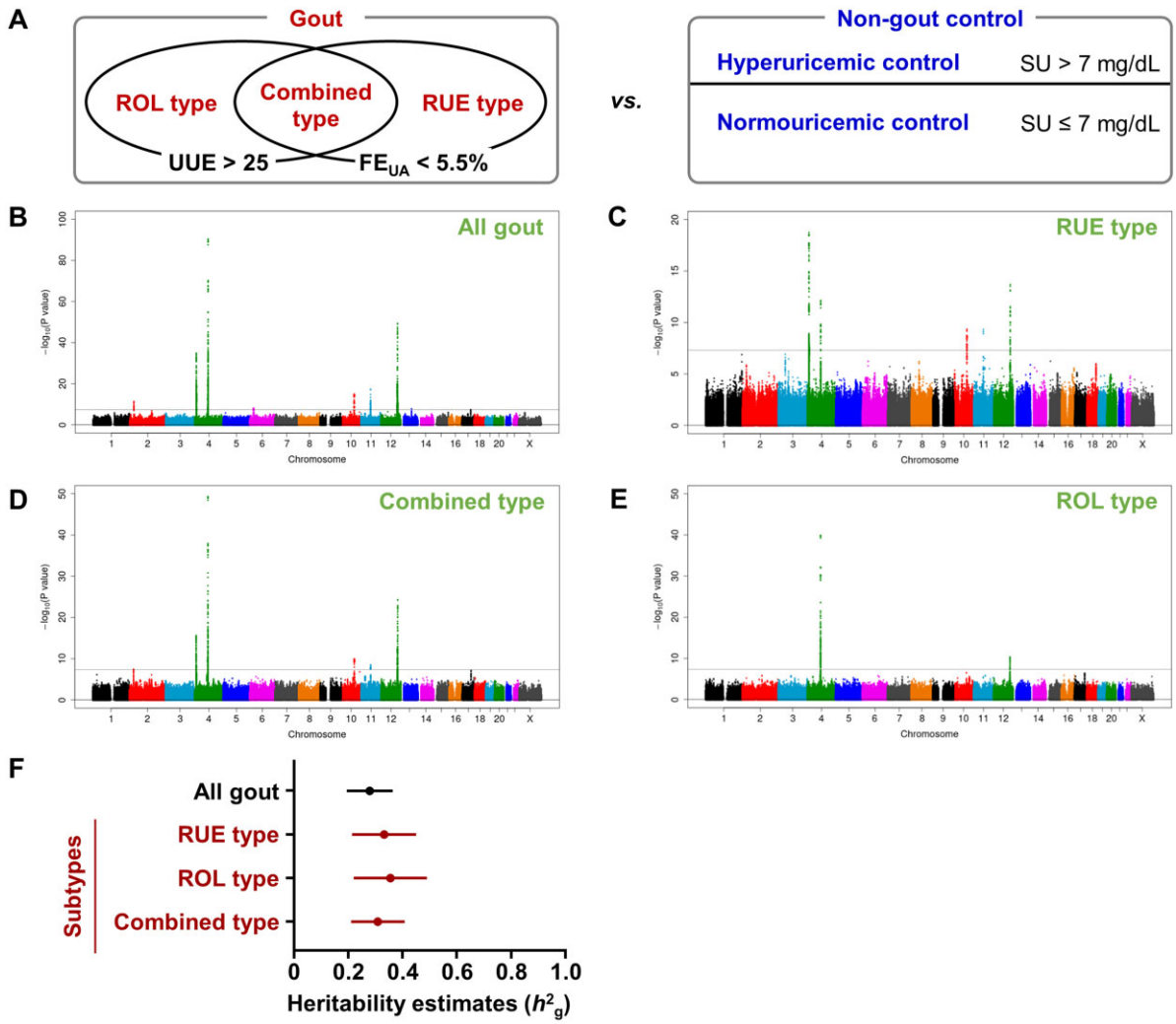

Figure 1. Overview of the results of meta-analyses and SNP-based heritability estimates of gout. **(A)** Design of GWASs (gout cases *vs* non-gout controls) conducted in this study. (Left) Subtype classification of gout. UUE, urinary urate excretion (mg/h/1.73 m^2); FE_{UA}, fractional excretion of uric acid (%). FE_{UA} was calculated using the following equation: ([urine urate]/[serum urate]) × ([serum creatinine]/[urine creatinine]) × 100. (Right) Classification of non-gout controls. In addition to normouricaemic subjects without gout characterized by serum urate (SU) ≤7 mg/dL (normouricaemic control), hyperuricaemic subjects without gout characterized by SU >7 mg/dL (hyperuricaemic control) were employed. **(B–E)** Manhattan plots of genome-wide meta-analyses for genetic loci that influence the risk of gout: **(B)** all gout, **(C)** RUE type, **(D)** combined (RUE + ROL) type and **(E)** ROL type. SNPs with a minor allele frequency ≥1% were analysed. The horizontal axis represents chromosomal positions; the vertical axis indicates the $-\log_{10}$(*P*-value) for assessment of the association. Horizontal lines represent the genome-wide significance threshold ($\alpha = 5 \times 10^{-8}$). Information on significant loci identified in the present genome-wide meta-analysis is summarized in Supplementary Table S5, available at *Rheumatology* online. **(F)** Estimation of the SNP-based heritability of gout and its subtypes using clinically defined gout patients in Japanese populations (*vs* non-gout controls). Horizontal bars indicate the standard error of heritability. Further information, including the prevalence of gout and each subtype, and a comparison with the SNP-based heritability estimates of gout (*vs* normouricaemic controls) are shown in Supplementary Table S1, available at *Rheumatology* online

Table S1, available at *Rheumatology* online) by the use of linkage disequilibrium score regression, as described previously [7], with minor modifications. After adjusting for the effects of covariates, the heritability for all gout was estimated at 27.9% when subjects without gout were selected as controls. These results indicate that genetic factors are significant contributors to individual variability in gout.

We next investigated the SNP-based heritability of three major subtypes of gout: the RUE type (654 cases), the ROL type (486 cases) and the combined type (905 cases) (Fig. 1F). The heritability estimates were 33.2% for the RUE type, 35.5% for the ROL type and 30.9% for the combined type, confirming genetic influence. Strong genetic correlations were also detected among the major subtypes (Supplementary Table S2, available at *Rheumatology* online). Although heritability estimates for the normal type (the minor subtype of gout) could not be obtained owing to the small sample size (92 cases), our findings will improve the understanding of the genetic basis of the risk of gout.

To estimate polygenic contributions to the heritability of gout, single nucleotide variations (SNVs) were then categorized into 53 overlapping functional categories based on annotation data according to the full baseline model, as previously described [8]. When focused on only the SNPs, no significant enrichments were observed; however, expanding the analysis targets to SNVs with MAF ≥0.1% enabled us to detect statistically significant enrichments in four functional categories (Supplementary Table S3, available at *Rheumatology* online). These results suggest the important contributions to heritability of somewhat rare genetic

variations in non-coding regions. Further results of meta-analyses using SNVs and the SNV-based heritability of gout, including major subtypes, are summarized in Supplementary Fig. S1 and Table S4, available at *Rheumatology* online.

We acknowledge a limitation to this study. There seems to be a divergence between SNP-based heritability estimates for gout uncovered in this study (Fig. 1F) and those for serum urate (~14%) previously reported in similar Japanese populations [7]; however, the reasons for this remain unclear. One possibility is the previously noted theoretical underestimation of heritabilities in this type of SNP-based survey, especially for serum urate [2].

In summary, we uncovered the relative contributions of heritability to phenotypic variation of gout and several of its subtypes. This study is the first to provide heritability estimates for clinically defined gout and to quantitatively show the existence of genetic predisposition to its three major subtypes.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

Data are available upon reasonable request to the corresponding author.

Authors' contributions

H.M. conceived and designed the study with the assistance of Y.T., M.N., A.N. and Y.K. Y.T., M.N., A.N., Y.K., H.N. and H.M. analysed the data. M.N. performed the statistical analysis. K.W., K.M. and H.M. were involved in sample collection. H.M. organized this collaborative study. A.N. and Y.K. provided intellectual input and assisted with the preparation of the manuscript. Y.T., M.N., and H.M. wrote the manuscript. Y.T., M.N., and A.N. contributed equally to this work.

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Conflicts of interest: The authors have declared no conflicts of interest.

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