Epidemiological Science

Variants in urate transporters, ADH1B, GCKR and MEPE genes associate with transition from asymptomatic hyperuricaemia to gout: results of the first gout versus asymptomatic hyperuricaemia GWAS in Caucasians using data from the UK Biobank

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ABSTRACT

Objectives To perform a genome-wide association study (GWAS) of gout cases versus asymptomatic hyperuricaemia (AH) controls, and gout cases versus normouricaemia controls, and to generate a polygenic risk score (PRS) to determine gout-case versus AH-control status.

Methods Gout cases and AH controls (serum urate (SU) ≥6.0 mg/dL from the UK Biobank were divided into discovery (4934 cases, 56948 controls) and replication (2115 cases, 24406 controls) cohorts. GWAS was conducted and PRS generated using summary statistics in discovery cohort as the base dataset and the replication cohort as the target dataset. The predictive ability of the model was evaluated. GWAS were performed to identify variants associated with gout compared with normouricaemic controls using SU >6.0 mg/dL and <7.0 mg/dL thresholds, respectively.

Results Thirteen independent single nucleotide polymorphisms (SNPs) in ABCG2, SLC2A9, SLC22A11, GCKR, MEPE, PPM1K-DT, LOC105377323 and ADH1B reached genome-wide significance and replicated as predictors of AH to gout transition. Twelve of 13 associations were novel for this transition, and rs1229984 (ADH1B) was identified as GWAS locus for gout for the first time. The best PRS model was generated from association data of 17 SNPs; and had predictive ability of 58.5% that increased to 69.2% on including rs1229984 (ADH1B) was identified as GWAS locus for gout for the first time. The best PRS model was generated from association data of 17 SNPs; and had predictive ability of 58.5% that increased to 69.2% on including factors. Two novel SNPs rs760077 (MTX1) and rs3800307 (PRSS16) achieved GWAS significance for association with gout compared with normouricaemic controls using both SU thresholds.

Conclusion The association of urate transporters with gout supports the central role of hyperuricaemia in its pathogenesis. Larger GWAS are required to identify if variants in inflammatory pathways contribute to progression from AH to gout.

INTRODUCTION

Gout is a common form of inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals. Elevated serum urate (SU) concentration is the precursor to MSU crystal deposition, and the onset of gout. However, the majority of people with hyperuricaemia do not develop gout. For instance, in the USA, the prevalence of hyperuricaemia (defined as SU ≥7.0 mg/dL) is 20%, while that of gout is 3.9%. The reason(s) why only some people with hyperuricaemia develop gout is poorly understood. Genome-wide association studies (GWAS) have improved the understanding of the pathophysiology of hyperuricaemia and gout over the last 10–15 years. For instance, genetic variants located in urate transporters such as the ABCG2, SLC2A9 and SLC22A11 genes have been identified as risk loci for both hyperuricaemia and gout. Additional genetic variants such as GCKR and ALDH2 that play important roles in carbohydrate and alcohol metabolism respectively have been associated with both phenotypes. However, the genetic variants associated with progression from hyperuricaemia to gout remain poorly understood. To date, only a single GWAS (n=6009 Japanese adults, 2860 with gout) has examined this and revealed two novel loci: CNTN5 and MIR302F, which participate in immune and inflammatory pathways.

What is already known about this subject?

► Previous genome-wide association study (GWAS) identified loci in inflammatory genes (CNTN-5, ZNF3724 and MIR302F) as risk factors for transition from asymptomatic hyperuricaemia (AH) to gout, and was conducted in Japanese population.

What does this study add?

► This is the largest GWAS of gout cases and AH controls, and the first in Caucasian population.

► Thirteen variants in urate transporters and metabolic genes, but none in inflammatory genes associated with transition from AH to gout.

► A novel GWAS-significant gout risk locus was identified in ADH1B gene.

► Genetic and demographic factors performed moderately well in predicting gout status in AH.

How might this impact on clinical practice or future developments?

► Adults with AH should be advised lifestyle and dietary interventions that lower their serum urate levels in order to reduce their risk of gout.

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Studies were conducted using data from the UK Biobank resource (project ID 45987). Briefly, the UK Biobank is a prospective study of ~500 000 participants, aged 40–60 years and recruited across England, Wales and Scotland between the years 2006 and 2010. Data were collected on lifestyle and sociodemographic information, cognitive function, health status and family medical history. Participants had standard physical and functional measurements, and provided blood samples for genetic analyses. Details about recruitment and samples processing for genotyping are described elsewhere.12 13

Subjects
For this research, three phenotypes were derived from the UK Biobank cohort.

Gout cases
Gout was defined as present if any of the following criteria were met14: self-reported physician-diagnosed gout; urate-lowering therapy (ULT) prescription without a hospital diagnosis of lymphoma or leukaemia (International Classification of Diseases (ICD)-10 codes C81-C96) or a primary or secondary diagnosis of gout in hospital discharge letters using the ICD-10 codes M10, M100–M14 and M109. Participants with self-reported physician-diagnosed gout were excluded if their SU was <6.0 mg/dL and they did not report prescription of ULT at the UK Biobank visit.

AH controls
Participants with SU ≥6.0 mg/dL and not classified as gout. A threshold of ≥6.0 mg/dL was chosen as it associates with incident gout in prospective studies.11

Normouricaemia controls
Participants with SU <6.0 mg/dL and not classified as gout14 were considered as normouricaemia controls. Given the uncertainty around definition of normal SU, for example, SU <6.0 mg/dL being the treatment threshold for treat-to-target ULT while epidemiological studies use a cut-off of <7.0 mg/dL, another group of normouricaemia controls was ascertained with SU <7.0 mg/dL and not classified as gout.14

Genotyping and quality control
UK Biobank samples were genotyped by Affymetrix using two arrays: The UK BiLEVE Axiom array (n=49 950; 807 411 markers), and the UK Biobank Axiom array (n=438 427; 825 927 markers). These arrays shared 95% of content, resulting in >805 000 genotyped variants for 488 288 participants. For this study, participants with non-European ancestry were excluded to avoid population stratification. Thus, genotyping data for 409 629 European descendants were available following UK Biobank centrally performed quality control (QC) procedures. Detailed information about genotyping and QC have been described previously.13 15 Further stringent QC filters were applied using PLINK V1.9.16 Individuals with a kinship coefficient equivalent to second-degree (or greater) relatives were excluded. Individuals were also excluded if they had a heterozygosity ±3 SD from the mean, a call rate <90% or were identified as gender mismatches. Markers with a call rate <95%, or those deviating from Hardy-Weinberg equilibrium (Bonferroni-corrected p value threshold=6.82×10−8) were removed from the dataset.

Gout versus AH
A sample of 354 825 individuals with 717 091 genotyped SNPs were included in this analysis, from which the phenotypes of interest were derived. The cohort comprised 7049 cases and 64 424 controls with SU <6.0 mg/dL, and 79 531 controls with SU <7.0 mg/dL, respectively.

Statistical analyses
Baseline data were summarised using mean (SD) for continuous variables, and number (%) for categorical variables. Independent sample t-test and χ² test were used to compare continuous and categorical data, respectively.
Gout versus AH GWAS

Discovery and replication association tests were performed using PLINK V1.9. ORs and 95% CIs were computed using additive logistic regression. We adjusted for sex, age at recruitment and 10 principal components (PCs). To determine the number of independent loci from the GWAS analysis, linkage disequilibrium (LD) clumping was performed using PLINK V1.9. SNPs with a p value <5×10^-5, r^2 >0.1 and a 500 kb window from the index SNPs were assigned to the clump. Annotation of lead SNPs was conducted using the SNP2GENE tool of the Functional Mapping and Annotation of GWAS.^{17} Pairwise LD patterns from SNPs identified as independent, located in the same gene or <500 kb apart, were further analysed using the R package LDlinkR,^{18}^{19} which uses the 1000 Genomes Project data as the reference panel. HaploView was used to generate the LD plot.^{20} For the discovery analysis, genome-wide significance was set at p=5×10^-8.

For replication analysis, the 13 variants that reached genome-wide significance in the discovery analysis were tested for association with gout in the replication cohort. Logistic regression was adjusted for sex, age and 10 PCs. A Bonferroni-corrected p value of <0.004 (0.05/13) was used to determine significant associations in the replication analysis. The results from the discovery GWAS and the replication analysis were combined by meta-analysis using PLINK. The fixed-effects model was used to estimate pooled ORs and 95% CI, and Cochran’s Q test p values and I^2 values were used to assess heterogeneity.

Linear regression was used to examine the effect of GWAS hits on SU levels. This was performed using the full cohort, and adjusted for sex and age at recruitment. Beta-coefficients and SEs, and adjusted beta-coefficients and SEs were calculated. As previous GWAS^{10}^{21} have used a cut-off of 7.0 mg/dL to define hyperuricaemia, a sensitivity analysis was conducted to evaluate if the association of GWAS hits and gout remained significant if controls had a SU ≥7.0 mg/dL.

Polygenic risk score

PRS was calculated using PRSice-2.^{22} The discovery GWAS summary statistics were used as the base dataset, while the replication cohort genotype-phenotype data were used as the target dataset. Clumping parameters in PRSice were set to an r^2 >0.1 and a 500 kb window from the index SNPs, which generated a final number of 266 754 SNPs available for PRS calculation. ORs and p values from the GWAS summary statistics were used to calculate the best PRS model, which was generated from testing different p value thresholds. The best-fit model was defined by the largest Nagelkerke’s R^2 value. Logistic regression was used to estimate the effect of the demographic variables for inclusion into the predictive models using SPSS Statistics 24. The area under the receiving operative characteristic curve (AUROC) was used to evaluate the predictive ability of the PRS, demographic characteristics (age, sex and body mass index (BMI)) and combined models.

Gout versus normouricaemia GWAS

Two GWAS were conducted. Prior to conducting these analyses, both datasets underwent the same genotyping QC filters as described earlier. The association tests were performed with PLINK V1.9, using age, sex and the first 10 PCs as covariates.

RESULTS

Demographic characteristics

Following genotype QC filters, data for 7049 gout cases and 81 354 AH controls were included. The entire cohort comprised 80.77% men, and their mean (SD) age, BMI and SU were 57.87 (7.77) years, 29.63 (4.81) kg/m^2 and 6.92 (0.88) mg/dL, respectively. This cohort was divided into the discovery and replication datasets (table 1, figure 1). The two datasets had comparable disease and demographic characteristics.

Gout versus AH GWAS

An additive logistic regression was performed to test the association between gout and 710 030 variants. Thirty-four SNPs reached genome-wide significance and after filtering for tight LD (r^2 <0.2), 13 SNPs were identified as independent associations (figure 2). These lead SNPs were selected for the replication study, where they were tested for association with gout in the remaining 30% of the dataset. Successful replication was defined if the p value was <0.004. Summary results for both the discovery and the replication analyses are shown in table 2. The SNP with the greatest effect was rs2231142 in ABCG2 gene with OR=1.66 (2.05×10^-78) in the discovery stage, and OR=1.64 (1.17×10^-13) in the replication stage. This was followed by a novel locus: rs12299894 in ADH1B gene (OR=1.51, p=5.0×10^-12; OR=1.44, p=4.77×10^-5). The remaining SNPs were located in or near GCKR, PPM1K-DT, SLC2A9, MEPE, LOC105377323 and SLC22A11. Pairwise LD parameters were evaluated for SNPs located within the same gene or in genes <500 kb apart (online supplemental figure S1).

Genetic variants and SU

All lead SNPs associated with SU, with rs2231142 (ABCG2) and rs16890979 (SLC2A9) showing the greatest effects: adjusted β=0.107 and p=1.21×10^-30, and adjusted β=-0.055 and p=1.67×10^-42, respectively (online supplemental table S1). On sensitivity analysis examining the association between 13 lead SNPs and gout, excluding AH controls with SU <7.0 mg/dL, the ORs diminished in magnitude but remained significant (online supplemental table S2).

PRS model

A PRS for all cases and controls was constructed with PRSice using the replication cohort as the test dataset. The best-fit p value threshold that gave the highest Nagelkerke’s R^2 (0.016) was 4.0×10^-6, and included 17 SNPs (online supplemental table S3). The mean (±SD) PRS for cases was 0.018 (±0.017), and the PRS model was evaluated using the AUROC curve, and compared with the demographics model (age, sex and BMI) and combined model (age, sex, BMI and PRS). The AUC for each model was 58.5%, 66.7% and 69.2%, respectively (figure 3).

Gout versus normouricaemia

We conducted two GWAS of gout versus normouricaemia using SU cut-off values <6.0 mg/dL and <7.0 mg/dL, respectively. The first GWAS identified 32 lead SNPs, while the second identified 46 lead SNPs (online supplemental table S4). Three novel SNPs (rs760077, rs3800307 and rs112277299 in MX1, PRSS16 and AP5B1 genes, respectively) associated with gout compared with SU <6 mg/dL with GWAS significance. Two (rs760077 and rs3800307) remained GWAS significant when a higher SU threshold of <7 mg/dL was used to define normouricaemia.
We then plotted the OR of each lead SNP in the gout versus AH-control GWAS and the gout versus SU <6 mg/dL GWAS (figure 4A). To be consistent with our sensitivity analysis, we plotted the OR of the 13 lead SNPs on excluding AH controls with SU 6–7 mg/dL, with the gout versus SU <7 mg/dL GWAS (figure 4B). The same loci were responsible for transition from AH to gout in a GWAS.5 21 25 26 This is the first such report.

**DISCUSSION**

This is the largest GWAS to date and the first in Caucasians to examine the SNPs associated with transition from AH to gout. Using UK Biobank data, it identified 13 independent SNPs from 8 loci that reached genome wide significance for association with gout versus AH, and replicated. These loci include urate transporters, metabolic pathway genes (eg, GCKR, ADH1B) and MEPE gene that regulates renal phosphate handling and skeletal mineralisation.23 The latter may promote progression to gout via pro-mineralising osteopontin-like function or via low phosphate levels that associates with incident hyperuricaemia.24 The identified loci in PPM1K-DT and LOC105377323 were in non-coding regions and their molecular mechanism is unclear.

Of the eight loci, ABCG2, SLC2A9, SLAC22A11, PPM1K-DT, GCKR and MEPE have previously been associated with gout or SU levels in different populations but never in the transition from AH to gout in a GWAS.12 21 25 26 This is the first such report. In a previous study, Tin et al generated a genetic risk score using variants associated with SU and examined their ability to predict gout cases in 334 800 UK Biobank participants not specifically selected for high SU levels. Ours is the first study to attempt to generate a PRS for predicting gout status in an AH population that is, those with SU ≥6.0 mg/dL, and reports an AUC of...
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58.5% for genetic factors alone, which increased to just under 70% when demographic factors were added. This is lower than the AUC of 67.2% from genetic factors alone in the study by Tin et al and is likely to be due to lower genetic variance due to selection of a high SU control group. 25 A smaller study using

| SNP       | Chr | bp   | Gene      | A1 | Freq | Discovery GWAS | P value | Replication stage | P value | Meta-analysis* | P value | Cochrane’s Q p value | I² |
|-----------|-----|------|-----------|----|------|----------------|---------|-------------------|---------|---------------|---------|---------------------|----|
| rs1260326 | 2   | 27730940 | GCKR      | T  | 0.41 | 1.13 (1.08 to 1.17) | 3.54×10⁻⁸ | 1.15 (1.08 to 1.23) | 2.54×10⁻⁵ | 1.14 (1.10 to 1.18) | 5.10×10⁻¹² | 0.61 | 0 |
| rs2231142 | 4   | 89052323 | ABCG2     | T  | 0.14 | 1.66 (1.58 to 1.76) | 2.05×10⁻⁷ | 1.64 (1.51 to 1.78) | 1.87×10⁻³ | 1.65 (1.58 to 1.73) | 3.33×10⁻⁹ | 0.75 | 0 |
| rs13120300 | 4  | 89033527 | ABCG2     | C  | 0.28 | 0.82 (0.78 to 0.86) | 1.56×10⁻⁶ | 0.84 (0.78 to 0.91) | 3.43×10⁻⁶ | 0.83 (0.79 to 0.86) | 3.66×10⁻⁶ | 0.50 | 0 |
| rs7671290 | 5   | 89126647 | ABCG2     | T  | 0.48 | 1.16 (1.11 to 1.21) | 3.21×10⁻¹² | 1.15 (1.08 to 1.23) | 1.13×10⁻³ | 1.16 (1.12 to 1.20) | 1.58×10⁻¹⁶ | 0.88 | 0 |
| rs4639211 | 4   | 89249061 | PPM1K-DT  | C  | 0.07 | 1.41 (1.31 to 1.52) | 6.97×10⁻²⁰ | 1.26 (1.12 to 1.42) | 1.21×10⁻⁴ | 1.37 (1.28 to 1.45) | 1.55×10⁻²² | 0.11 | 61.62 |
| rs2379336 | 4   | 89126768 | PPM1K-DT  | C  | 0.08 | 1.35 (1.26 to 1.45) | 8.19×10⁻¹⁷ | 1.26 (1.12 to 1.40) | 6.29×10⁻⁵ | 1.32 (1.25 to 1.40) | 4.79×10⁻¹⁰ | 0.27 | 19.60 |
| rs1565207 | 4   | 89239492 | PPM1K-DT  | A  | 0.28 | 1.14 (1.09 to 1.20) | 6.82×10⁻⁹ | 1.12 (1.05 to 1.20) | 1.07×10⁻³ | 1.14 (1.10 to 1.24) | 3.38×10⁻¹⁳ | 0.76 | 0 |
| rs16890979 | 4  | 9222167 | SLC2A9    | T  | 0.17 | 0.79 (0.74 to 0.83) | 3.19×10⁻¹⁶ | 0.73 (0.67 to 0.80) | 1.05×10⁻¹¹ | 0.77 (0.74 to 0.81) | 5.45×10⁻⁶⁶ | 0.19 | 42.09 |
| rs16891234 | 4  | 9946163 | SLC2A9    | C  | 0.24 | 1.16 (1.11 to 1.22) | 6.06×10⁻¹⁰ | 1.13 (1.05 to 1.22) | 8.86×10⁻⁰⁴ | 1.15 (1.11 to 1.20) | 2.72×10⁻¹² | 0.57 | 0 |
| rs1229984 | 11  | 100239319 | ADH1B     | T  | 0.03 | 1.51 (1.34 to 1.69) | 5.00×10⁻¹² | 1.44 (1.21 to 1.72) | 4.77×10⁻⁷ | 1.49 (1.35 to 1.64) | 1.15×10⁻¹⁵ | 0.68 | 0 |
| rs113791499 | 4 | 88591554 | LOC105377323 | A | 0.02 | 1.42 (1.26 to 1.60) | 7.99×10⁻⁹ | 1.47 (1.22 to 1.77) | 5.47×10⁻⁰⁵ | 1.43 (1.30 to 1.59) | 2.10×10⁻² | 0.76 | 0 |
| rs114580333 | 4  | 88790118 | MEPE      | A  | 0.02 | 1.44 (1.26 to 1.63) | 3.01×10⁻⁰⁸ | 1.39 (1.15 to 1.69) | 9.18×10⁻⁰⁴ | 1.42 (1.28 to 1.59) | 1.10×10⁻⁰⁵ | 0.79 | 0 |
| rs2078267 | 11  | 64334114 | SLC22A11  | C  | 0.47 | 1.16 (1.11 to 1.21) | 1.72×10⁻¹² | 1.14 (1.07 to 1.22) | 6.27×10⁻⁰⁵ | 1.15 (1.11 to 1.20) | 6.65×10⁻¹⁶ | 0.62 | 0 |

*Fixed-effects meta-analysis of the discovery GWAS and the replication analysis.
†Adjusted for age, sex and 10 first PCs.
A1, allele 1/effect allele; aOR, adjusted OR; bp, base pair position; Chr, chromosome; Freq, frequency; GWAS, genome-wide association study; PC, principal component; SNP, single nucleotide polymorphism; SU, serum urate.
candidate gene hypothesis reported nominal association for ABCG2 polymorphism and gout versus hyperuricaemia. The only previous gout versus hyperuricaemia GWAS was conducted in a Japanese population and reported rs7927466 in CNTN5, rs9952962 in MIR302F and a suggestive locus rs12980365 in ZNF724 that do not affect SU. Although rs7927466 is not included in the UK Biobank genotype platform, it is covered by its proxy SNP rs7942264 (r²=1) that did not show an association with gout; neither did rs12980365. MIR302F was not included in UK Biobank and further research on this gene is needed.

ADH1B was identified as a risk variant for gout versus AH. It has never previously been associated with gout in a GWAS—even when compared with general population. ADH1B mediates the oxidation of ethanol into acetaldehyde. The SNP rs1229984 in ADH1B causes a change of an arginine to histidine, increases ethanol clearance in liver, facilitates its conversion to highly reactive acetaldehyde, increases the NADH/NAD ratio that results in high lactic acid levels and increased urate reabsorption via URAT1. The risk allele of rs1229984 also promotes a ‘flush response’ to alcohol and reduces the amount of alcohol consumed. Thus, the association between this polymorphism and gout may be due to increased production and reabsorption of urate from per unit alcohol consumed. This is consistent with the observation by Yokoyama et al in which rs1229984 associated with SU≥7 mg/dL (OR (95% CI) 2.04 (1.58 to 2.65)), while the daily alcohol intake was comparable across variants. In agreement with our study, Sakiyama et al evaluated the effect of rs1229984 in ADH1B gene on gout. They reported an increased risk for gout with OR of 1.69 and 1.80 for His/Arg and His/His genotypes, respectively, which remained significant after correcting for alcohol consumption. However, in their study patients with gout and rare variants of the SNP had greater alcohol consumption, suggesting an additional role for the latter.

Urate transporters ABCG2, SLC2A9 and SLC22A11 play essential roles in pathogenesis of hyperuricaemia. SLC2A9 has the strongest effect on SU, accounting for 2%-3% of variance, followed by ABCG2 that explains 1% of SU variation. Although both loci have also been associated with gout, GWAS of gout cases versus controls have shown a greater effect of ABCG2 than SLC22A9. In this study, rs2231142 in ABCG2 had a larger effect size on gout status compared with AH-control than the GWAS hit rs12498742) and also twice as much effect on SU than the latter. This supports the hypothesis that ABCG2 plays a causal role in transition from hyperuricaemia to gout via its effect on SU. However, additional mechanisms such as defects in ABCG2 causing deficient autophagy may also operate.

Our GWAS comparing gout cases with normouricaemic controls did not identify any inflammatory genes. A large number of lead SNPs were identified at genome-wise significant level. Most have been associated with gout or SU previously. However, we identified three novel SNPs associated with gout compared with SU < 6.0 mg/dL. Of these, rs11227299 (AP5B1) is associated with reduced estimated glomerular filtration rate and may cause gout by resulting hyperuricaemia. The variants in MTX1 and PRSS16 genes associated with gout compared with SU < 6.0 mg/dL, also associate with Parkinson’s disease and schizophrenia. This is consistent with the negative associations between Parkinson’s disease and gout, and schizophrenia and elevated SU.

This is the first GWAS to examine transition from AH to gout in Caucasians. Other strengths include a large sample size, and assessment of transition from AH to normouricaemia to gout in the same source population. However, there are several caveats to this study. First, gout definition was not based on American College of Rheumatology/European League Against Rheumatism classification criteria, but was ascertained via self-report of physician diagnosis, hospital diagnoses and ULT prescriptions. However, the UK Biobank data collection predates the classification criteria. In addition, the classification of AH controls was based on a single SU measurement, which could have been affected by diet during the previous days. Additionally, the use of non-imputed data limited the discovery power of the GWAS and PIRS.

In conclusion, this study identified 13 GWAS significant risk loci, 12 of which have never previously been associated with the transition from AH to gout at GWAS level. The preponderance of urate transporters and metabolic genes that affect SU levels support the central role of hyperuricaemia in the pathogenesis of gout. Larger GWAS are required to identify if variants in inflammatory pathways also contribute to this transition.

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