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Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study

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Abstract

Background—Hyperuricemia, a highly heritable trait, is a key risk factor for gout. We aimed to identify novel genes related to serum uric acid (UA) and gout.

Methods—Genome-wide association studies (GWAS) were conducted for serum UA in the Framingham Heart Study (FHS; n=7699) and the Rotterdam Study (RS; n=4148). Genome-wide

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Author Contributions

CF, JW, and JC drafted and critically revised the manuscript, contributed to the study design, analysis, and interpretation of the data. EB performed the follow-up genotyping and critically revised the manuscript. CV coordinated the blood collection and storage, the statistical analyses and bioinformatics, critically revised the manuscript, and contributed to the interpretation of the data. FR coordinated the genome-wide association genotyping, bioinformatics, critically revised the manuscript, contributed to the study design, analysis, and interpretation of the data. AK performed the statistical analyses, drafted the manuscript, critically revised the manuscript, and contributed to the study design and interpretation of the data. DL collected the clinical data, contributed to the interpretation of the data, and critically revised the manuscript. SH performed the statistical analyses, coordinated the genome-wide association genotyping, bioinformatics, and contributed to the interpretation of the data. WK contributed to the study design, interpretation of the data, and critically revised the manuscript. EJB contributed to the study design and critically revised the manuscript. AH collected the clinical data, critically revised the manuscript, contributed to the study design, and supervised the research. QY performed the statistical analyses, drafted parts of the manuscript, critically revised the manuscript, contributed to the study design, and interpretation of the data. BA contributed to the interpretation of the data and critically revised the manuscript. AD performed the statistical analyses, drafted the manuscript, and contributed to the study design and interpretation of the data.

significant SNPs were replicated among white (n=11024) and black (n=3843) Atherosclerosis Risk in Communities (ARIC) Study participants. The association of these SNPs was evaluated with gout; results in whites were combined using meta-analysis.

Results—Three loci in FHS and two in the RS showed genome-wide significance with UA. Top SNPs in each locus were: missense SNP rs16890979 in *SLC2A9* ($p=7.0\times10^{-168}$ [whites]; 2.9×10^{-18} [blacks]), missense SNP rs2231142 in *ABCG2* ($p=2.5\times10^{-60}$ [whites]; 9.8×10^{-4} [blacks]), and rs1165205 in *SLC17A3* ($p=3.3\times10^{-26}$ [whites]; 0.33 [blacks]). All SNPs showed direction-consistent association with gout in whites: rs16890979 (OR 0.58 per T allele, 95% CI 0.53–0.63, $p=1.2\times10^{-31}$), rs2231142 (OR=1.74 per T allele, 1.51–1.99, $p=3.3\times10^{-15}$), and rs1165205 (OR=0.85 per T allele, 0.77–0.94, p=0.002). In ARIC blacks, rs2231142 showed a direction-consistent association with gout (OR=1.71, 1.06–2.77, p=0.028). An additive genetic risk score (0–6) comprised of high risk alleles at the three loci showed graded associations in each study across scores with UA (from 272–351 μmol/l [FHS], 269–386 μmol/l [RS], and 303–426 μmol/l [ARIC whites]) and gout (prevalence 2–13% [FHS], 2–8% [RS], 1–18% [ARIC whites]).

Conclusions—We identified three genetic loci (two novel including a candidate functional variant Q141K in *ABCG2*) related to UA and gout. A score based on genes with a putative role in renal urate handling showed a substantial risk gradient for gout.

Keywords

genome-wide association; uric acid; gout; epidemiology

Introduction

Gout is one of the most common forms of arthritis (1,2). Gout currently affects over 700,000 adults in the United Kingdom (2) and nearly 3 million adults in the United States (3), accounting for almost 4 million annual outpatient visits (4), with a substantial economic burden (5). Epidemiological studies from a range of countries suggest that the prevalence and incidence of gout are increasing (6). Gout is characterized by joint pain, inflammation, and painful tophi, and can result in joint destruction and disability if untreated (7).

Uric acid is the end product of purine metabolism in humans, and levels are primarily determined by endogenous metabolism (synthesis and cell turnover), and the rate of excretion and reabsorption in the kidney (1). Humans lack uricase, the enzyme responsible for converting uric acid into its more soluble and excretable form. Renal excretion of urate is responsible for the majority of hyperuricemia and gout (8). Thus, understanding the molecular mechanisms of urate transport in the kidney has potential research and clinical implications.

Known risk factors for gout include hyperuricemia, obesity, hypertension, diuretic use, and alcohol consumption (9). Despite extensive research in the area of renal urate transport, the mechanisms influencing serum uric acid levels in humans by contributing to either secretion or reabsorption of urate in the proximal renal tubules have not been fully elucidated (10). We have previously shown that the heritability of serum uric acid (UA) levels is 63% (11), suggesting that genetic variation may contribute to UA levels through regulation of UA synthesis, excretion, or reabsorption. Several recent genome-wide association studies (GWAS) identified significant associations between single nucleotide polymorphisms (SNPs) in the gene *SLC2A9* with UA levels and gout (12–16). The gene product of *SLC2A9* had not previously been implicated in UA metabolism, highlighting the power of GWAS to identify unknown physiologic mechanisms contributing to disease.

The objective of this study was to identify genetic loci related to UA using GWAS in two population-based studies (11847 participants) and subsequently replicate them in a third

population-based study (14867 participants). Moreover, a meta-analysis of replicated SNPs was performed for UA and gout across studies to combine the results in whites. Finally the association of a genetic risk score summarizing the number of risk alleles was tested with both UA levels and gout risk.

Methods

Phenotype and genotype data for the present study was made available through the GWAS initiatives of the Framingham Heart Study, the Rotterdam Study (RS), and the ARIC Study, which are three large population-based studies initiated to study cardiovascular disease and its risk factors, aging, neurologic disease, locomotion, and eye disease.

Framingham Heart Study (FHS)

Subjects

The FHS started in 1948 when 5209 participants began undergoing biannual examinations to identify cardiovascular disease and its risk factors (17,18). In 1971, 5124 participants were enrolled into the Framingham Offspring Study. Offspring subjects underwent examinations approximately every 4 years; the design and methodology have been previously described (19,20). In 2002, the Third Generation, representing the children of the Offspring cohort, was recruited (n=4095) (21). Nearly all FHS participants are self-identified white (of European descent). The Original Cohort consisted of 1644 spouse pairs; the Offspring cohort consisted of 2632 individuals with two parents in the Original cohort, 916 with at least one parent in the Original Cohort, and 1576 spouse pairs. The Third Generation consisted of 2944 individuals with both parents in the Offspring cohort, and 1146 individuals with at least one parent in the Offspring Cohort. By protocol, spouses were not recruited into the Third Generation Cohort (20). A broad range of phenotypes have been collected, and are publically available at the dbgap website (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v2.p1). The study was approved by the Institutional Review Board of the Boston University Medical Center. All subjects provided written informed consent.

Genotyping and Study Subjects Included

The SHARe project (22) genotyped 9274 FHS participants, using the Affymetrix 500K mapping array and the Affymetrix 50K supplemental array. Of those, 8508 samples were genotyped successfully (sample call rate ≥97%). Exclusion of individuals with missing UA measurements (n = 623) or covariates (n=186) resulted in a final sample size of 7699 (Original Cohort n=572, Offspring n=3377, Third Generation n=3750). SNPs were excluded for SNP call rate <95% or Hardy-Weinberg equilibrium p-value $<10^{-6}$, resulting in a final number of 503551 SNPs.

Outcomes

UA was measured at the first examination cycle of each cohort using an autoanalyzer with a phosphotungstic acid reagent (23). Gout was ascertained via self-report in the Offspring subjects during exam cycles 3–7, and the first exam of the Third Generation. Information on UA and gout was available for 7699 and 7386 subjects, respectively.

The Rotterdam Study (RS)

Subjects

The RS is a prospective, population-based cohort study on determinants of several chronic diseases among subjects aged ≥55 years (24,25). In brief, all inhabitants of Ommoord, a district

of Rotterdam in the Netherlands, who were 55 years or over, were invited to participate in this study. Of all 10275 eligible individuals, 7983 agreed to participate (78%). For the baseline examination (1990 – 1993), participants completed an interview at home and visited the research center for blood sampling and examination. Follow-up started at baseline and examinations were carried out periodically. In addition, participants were continuously monitored for major events through automated linkage with files from general practitioners and pharmacies working in the study district of Ommoord. Written informed consent was obtained from all participants and the Medical Ethics Committee of Erasmus Medical Center approved the study.

Genotyping and Study Subjects Included

Plated DNA was available for 6680 (83.7%) of 7129 participants who visited the research center. Genotyping was conducted using the Illumina 550K array among self-reported Caucasian individuals, and succeeded in 6240 individuals (sample call rate ≥ 97.5%). We excluded subjects for excess autosomal heterozygosity, mismatch between called and phenotypic gender, or being outliers identified by the IBS clustering analysis. The final population for analysis comprised 5974 subjects. SNPs were excluded for minor allele frequency ≤1%, Hardy-Weinberg equilibrium p-value<10^{-5}, or SNP call rate ≤90% resulting in data on 530683 SNPs.

Population stratification

The RS data was examined for potential population stratification after excluding outliers detected by the IBS clustering analysis (26,27). The genomic inflation factor (based on median chi-squared) was 1.014 for UA analyses, providing evidence against the presence of significant population stratification affecting the results.

Imputation of SNPs in the RS

We imputed two SNPs, rs16890979 on chromosome 4 and rs1165205 on chromosome 6, which were not on the Illumina Infinium II HumanHap550 SNP chip. Imputation was done using maximum likelihood method implemented in MACH 1.0 (28). HapMap release 22 CEU phased genotypes were used as a reference. The R square estimate of MACH was 0.96 for rs16890979 and 0.99 for rs1165205. This estimate is a ratio of observed variation to the expected variation under Hardy-Weinberg equilibrium and measures above 0.8 indicate acceptable quality of the imputation.

Outcomes

UA was measured at baseline with a Kone Diagnostica reagent kit and a Kone autoanalyzer (29). Data on medication prescription were obtained from a computer network of pharmacies in the study area that registers all prescriptions of drugs used from January 1, 1991, onward. Subjects receiving medication exclusively prescribed for gout (allopurinol, probenecid, benzbromarone and colchicine) were considered gout cases. Information on UA was available in 4148 individuals, and in 5741 individuals for gout.

Atherosclerosis Risk in Communities (ARIC) Study

Subjects

The ARIC Study is an ongoing, population-based, prospective study in four U.S. communities. From 1987–89, 15792 mostly Caucasian and African American study participants aged 45–64 years were recruited by probability sampling and underwent the baseline examination (visit 1) and three subsequent examinations scheduled approximately every three years (30). For the current study, participants were excluded for non-consent to genetic research (n=53) or if they

did not self-identify as "black" or "white" (n=47). Of the remaining 11,440 white and 4,252 black participants, 8,923 and 2,650, respectively, attended study visit 4. Further exclusion to the study samples were made for genotyping failure of all SNPs as well as missing outcomes or covariates. The final study sample for association analyses therefore consisted of 11,024 white and 3,843 black participants at visit 1, and 8,599 white and 2,392 black participants at visit 4. Institutional Review Boards of the participating institutions approved the study protocols, and each participant provided written informed consent.

Genotyping and Study Subjects Included

The ARIC Central DNA Laboratory genotyped SNPs rs16890979, rs2231142, and rs1165205 individually using TaqMan assays (Applied Biosystems). The percent agreement of 315 blind duplicate samples was >98.4% for all genotyped SNPs.

Outcomes

UA was measured using the uricase method (31) at study visit 1. Repeated measurements of UA in 40 individuals, taken at least one week apart, yielded a reliability coefficient of 0.91, and the coefficient of variation was 7.2% (32). Gout was defined by self-report at study visit 4.

Measurement of covariates

In all three studies, alcohol consumption was self-reported as drinks per week and converted to grams/week, and antihypertensive treatment was defined as self-reported intake of antihypertensive medication or medication reconciliation.

Statistical analysis

GWAS of UA

GWAS analyses used cohort- (FHS only) and sex-specific UA residuals, adjusted for age, body mass index (BMI), alcohol consumption, and hypertension treatment. In FHS, GWAS analysis was conducted as: 1) linear mixed effects models to account for familial correlation; 2) family-based association testing using FBAT to reduce the chance of false positive findings due to population stratification (33,34). In RS, linear regression was performed using PLINK ver.1.01 (26,27). Both studies used an additive genetic model.

Replication in ARIC and Association with Gout

The most significant SNP that reached genome-wide significance with UA for each region in either FHS ($p<0.5\times10^{-8}$) or RS ($p<1.0\times10^{-7}$) was selected *a priori* for follow-up genotyping in ARIC. This criterion was met by rs16890979, rs2231142, and rs1165205 (FHS), and rs6449213 and rs2231142 (RS). rs16890979 and rs6449213 are located in the same genetic region and in moderate linkage disequilibrium (LD) with each other ($r^2=0.66$ in HapMap CEU). Therefore, only rs16890979, rs2231142, and rs1165205 were genotyped in ARIC. In all studies, the association with gout was considered significant at $p<0.05$, as only SNPs consistently associated with UA across studies were examined in this setting.

Meta-analysis of UA and Gout

We combined the multivariable adjusted measures of beta and OR of replicated SNPs with UA and gout across studies. We used Cochran Q-test to detect heterogeneity across the studies. Since no significant heterogeneity was found with UA levels and gout (all p-values >0.07), a fixed-effect model was used for both traits. We used the "meta" (35) package running under R (36) to calculate the combined estimates and p-values.

Genetic Risk Score and Gene-by-Environment Interaction

A genetic risk score was generated for each individual by counting the number of alleles associated with higher UA levels (rs16890979 C, rs2231142 T, rs1165205 A; range 0–6). Gene-by-environment testing was performed for the three selected SNPs with five environmental factors; additional details can be found in the supplement. Additional secondary analyses including conditional analyses are described in the Supplementary methods.

Results

Study Sample Characteristics

Characteristics of 26714 participants are shown in Table 1. SNPs genotyped in all three studies met quality control standards (Supplementary Table 1).

GWAS Results with UA

Three loci manifested SNPs that reached genome-wide significance in FHS: for each locus, the most significant SNPs were rs16890979 (a missense SNP in *SLC2A9*, $p=1.6\times10^{-76}$), rs2231142 (a missense SNP in *ABCG2*, $p=9.0\times10^{-20}$), and rs1165205 (intron 1 of *SLC17A3*, $p=5.6\times10^{-10}$; Table 2). Likewise, two loci manifested genome-wide significant SNPs in the RS: rs6449213 (intron 4 of *SLC2A9*, $p=1.15\times10^{-29}$), and rs2231142 in *ABCG2* ($p=3.3\times10^{-9}$).

Exploration of Loci

All SNPs reaching genome-wide significance at 4p16-p15.3 (*SLC2A9*), 4q22 (*ABCG2)*, and 6p21.3 (*SLC17A3)* are presented in Supplementary Tables 2 (FHS) and 3 (RS). Figure 1 displays the results from *ABCG2* locus. The *SLC17A3* locus, detailed in Supplementary Figure 1, shows extensive LD in Caucasians extending downstream of *SLC17A3* to include *SLC17A1* and *SLC17A4*; the *SLC17A3/SLC17A1/SLC17A4* region will be referred to as the *SLC17A3* region for the remainder of the paper due to the location of the most associated variant.

Replication in ARIC

Both rs16890979 and rs2231142 were strongly associated with UA in whites ($p=2.3\times10^{-105}$ and 9.7×10^{-30}, respectively) and blacks ($p=2.9\times10^{-18}$ and 9.8×10^{-4}, respectively). rs1165205 was strongly associated with UA among whites only ($p=8.4\times10^{-11}$; Table 2).

Meta-analysis, Association with Gout, and Secondary Analyses

All meta-analysis p-values for UA reached genome-wide significance (Table 2); rs16890979 explained the largest variation in UA levels, ranging from 2.8%–5.3% of the variation in UA levels in white subjects across studies. The total R^2 for all 3 SNPs in explaining UA levels was 5.8% (ARIC whites), 2.4% (ARIC blacks); 7.1% (FHS); 3.7% (RS).

Conditional on the top SNPs, only SNPs in the *SLC2A9* region, one in FHS and two in RS, remained significant (Supplementary Results).

Study-specific results for gout were direction-consistent with the UA associations and are presented in Table 2. rs16890979 was associated with gout in whites from all three studies (meta-analysis odds ratio [OR] 0.58 per T allele, 95% CI 0.53–0.63, $p=1.2\times10^{-31}$). Significant results were also observed for rs2231142 and rs1165205, and for rs6449213 in FHS and RS. Among ARIC blacks, only rs2231142 in *ABCG2* showed a marginal association with gout (OR 1.71 per T allele, 95% CI 1.06–2.77, p=0.028). There were no genome-wide significant findings for gout in either FHS or RS.

Secondary analyses further adjusted UA results for diabetes, systolic blood pressure, and estimated glomerular filtration rate; results were not materially changed. Upon adjustment of gout results for UA, attenuation of the ORs for gout was observed, although most loci retained significance. In the FHS, only rs2231142 remained associated with gout upon adjustment for UA (OR 1.57, 95% CI 1.14–2.16, p=0.0053); all other loci lost significance. In RS, none of the SNPs remained significant after adjustment for serum UA. In the ARIC study, substantial attenuation of the genotypic effect for all three loci on gout risk was observed upon adjustment for UA. P-values decreased: for rs16890979 from 1.8×10^{-9} to 2.4×10^{-4}; for rs2231142 from 1.9×10^{-7} to 1.7×10^{-3}; and for rs1165205 from 3.0×10^{-3} to 0.015.

Genetic Risk Score for UA and Gout in Whites

The genetic risk score counting the number of high risk alleles from 0 to 6 showed common variation the population (Figure 2a). Mean UA levels increased linearly with the number of risk alleles (Figure 2b). For individuals with 0 risk alleles, the crude prevalence of gout was 1–2% across the studies and increased to 8–18% for those with 6 risk alleles (Figure 2c). The multivariable adjusted ORs of gout increased accordingly across the risk scores among the three studies (Figure 2d).

Gene-by-Environment Interactions for UA

Significant gene-by-sex interaction was observed for rs16890979 and rs2231142 (Supplementary Table 4). rs16890979 had a stronger relation with UA in women than men in all three studies; data are presented from ARIC in Figure 3 (p-value for interaction=5.4×10^{-11} in whites). Although this SNP was significantly associated with UA within each sex, it explained 7.6% of the variance in UA levels in women compared to 1.7% in men. Results were similar for FHS and RS and for rs6449213 the next most significant SNP in *SLC2A9*. For rs2231142, the T allele was associated with both higher UA levels and higher odds of gout in men compared to women (Figure 3); the SNP explained 0.6% of the variance in UA levels in women but 2.0% in men. We did not observe significant interactions of any tested SNP with age, BMI, alcohol intake, or hypertension treatment.

Discussion

Principal Findings

First, we identified two new loci related to UA levels and gout, *ABCG2* and *SLC17A3*. A missense SNP in *ABCG2* (rs2231142; Q141K) was associated with UA levels and gout in both whites and blacks and may be a causal candidate variant. Second, we confirm the previously reported association of variation in *SLC2A9* with UA and gout in whites and extend the findings to blacks. Third, we demonstrate sex-specific effects of SNPs in *ABCG2* and *SLC2A9*. Fourth, we show that an additive genetic risk score has strong and graded associations with UA levels and gout in three population-based studies.

Biologic Mechanisms

SNPs in *SLC2A9* recently have been identified as associated with UA levels (12–15), and were associated with low renal fractional excretion of UA (15), the most common cause for hyperuricemia (37). We identified the missense SNP rs16890979 in *SLC2A9* as showing the strongest association with UA levels and gout. This SNP leads to a valine-to-isoleucine amino acid substitution (V253I); the valine residue is highly conserved across species. This association was also present in black ARIC participants, where the LD pattern differs. However, sequencing efforts in prior GWAS of UA did not support rs16890979 as the causal SNP in the region, as among 541 individuals from Sardinia, this SNP was minimally associated

with UA levels (p=0.02) (12). Therefore, the potential causal role of this missense SNP remains unclear.

The apparent importance of renal urate transport influencing UA concentrations and subsequently gout is supported by the other two genetic loci we identified. *ABCG2* encodes a transporter of the ATP-binding cassette (ABC) family (38). Like SLC2A9, ABCG2 is expressed in the apical membrane of human kidney proximal tubule cells (39), and transports purine nucleoside analogues, which resemble the molecular structure of UA (40). We observed the strongest association with UA levels and gout in both white and black individuals with the *ABCG2* missense SNP rs2231142. This SNP in exon 5 leads to a glutamine-to-lysine amino acid substitution (Q141K); the glutamine residue is highly conserved across species. Based on the FHS data, rs2231142 was not grouped into any LD block. Three other SNPs located downstream of and in disequilibrium with the Q141K variant were associated with UA, two of which are located in the *PKD2* gene. However, neither these SNPs nor other SNPs in the region were independently associated with UA conditional on the Q141K variant in either FHS or Rotterdam. Combining this evidence with the relatively weak LD pattern in the *ABCG2* region in the HapMap Yoruban sample and the significant association in ARIC blacks despite the low minor allele frequency of 3%, suggests that the *ABCG2* Q141K variant (rs2231142) could be causally related to UA levels.

SLC17A3 encodes a sodium phosphate (Na/Pi) transporter (NPT4), the rat homologue of which localizes to the apical membrane of renal proximal tubule cells (41). Several prior studies have investigated the role of *SLC17A1*, located directly downstream of *SLC17A3*. *SLC17A1* encodes NPT1, which is expressed in the human kidney and has been shown to transport urate in model systems (42). In our study, the association of rs1165205 in *SLC17A3* was weaker with UA levels compared to the other loci. In FHS, the missense SNP rs1165196 (T269I) in exon 7 of *SLC17A1* also showed genome-wide significant association with UA levels ($p=6.24\times10^{-10}$ in FHS; p=0.003 in Rotterdam). This SNP was not in the same LD block as rs1165205, but both SNPs were in high pair-wise LD ($r^2=0.9$ in FHS). Additionally, the observed non-replication of rs1165205 with UA and gout among the black ARIC participants may allow for some degree of fine-mapping of the observed association. It is therefore conceivable that one or more causal genetic variants may be located downstream of *SLC17A3*, possibly in *SLC17A1* or even further downstream in *SLC17A4* due to the extensive LD in this region.

Clinical Implications

Although the gout risk conferred by the individual common genetic variants was modest, their combination resulted in a large effect on UA and gout prevalence. Further, the minor allele frequencies were common, suggesting that variants with low effect sizes will impact a large proportion of the population. Individual risk variants were associated with up to a 70% increased risk of developing gout, with effect sizes similar to that of known environmental risk factors (1). Our genetic risk score was associated with up to a 40-fold increased risk of developing gout, substantially higher than environmental risk factors, suggesting that knowledge of genotype may help identify individuals at risk for developing gout long before the onset of clinical disease. This underscores the value of a one-time assessment of the genetic risk score, whereas the measurement of uric acid is subject to measurement error and physiologic variability over time.

In additional to risk prediction, knowledge of an individual's genotype or risk score could be used to help guide clinical decision making, especially with respect to the selection of medications known to increase uric acid levels and precipitate gout. Currently, gout prophylaxis for asymptomatic hyperuricemia is not recommended (43), but it is conceivable that our genetic risk score could be used to identify individuals in which asymptomatic hyperuricemia should be treated. Since treatment decisions are best guided by randomized

trials, stored specimens from existing trials should be tested to directly estimate how this discovery of an easily determined strong genetic risk gradient can lead to personalized medicine. It is also possible that the genetic risk score, or certain genes that comprise it, differentially associate with gout complications, particularly joint destruction or poor response to medications.

Although novel agents for lowering UA such as febuxostat (44) are promising, allopurinol remains the mainstay of treatment for gout (45). The efficacy of allopurinol can be limited by drug dosing and intolerance, drug-drug interactions, and treatment failure (7). Errors are frequently made in allopurinol use (46), and only 21% of patients randomized to allopurinol in a clinical trial achieved optimal UA levels (44). The genes identified here may provide the opportunity for the identification of novel proteins and molecular mechanisms influencing UA levels, and the opportunity for the discovery of needed novel drug targets in order to ultimately improve the treatment of gout.

Study Limitations

Limitations to our study include the self-reported ascertainment of gout in FHS and ARIC, which could lead to misclassification and underestimation of the true magnitude of the genotype-phenotype association. We used slightly different definitions of gout across studies. Nonetheless, the findings remain consistent, highlighting their robustness. Hyperuricemia may have influenced the diagnosis of gout in our sample. However, gout was not ascertained at the same time that UA was measured; therefore, this is unlikely to account for the joint association of the SNPs with UA levels and gout. We note that the association between the SNPs and gout was not completely attenuated by adjustment for UA levels, which may be due to the fact that UA levels were measured before the onset of gout in the majority of cases. Due to the limited power for GWAS for gout in this setting, we focused our genetic analyses on UA levels and only related SNPs for UA to gout. Therefore, there are likely to be additional loci for gout that we have not detected. Finally, we assigned identical risk to each allele in creating the genetic risk score for ease of interpretation, as done previously (47).

Summary

UA levels and gout prevalence are related to genetic variation in *SLC2A9*, *ABCG2* and *SLC17A3*. The *ABCG2* Q141K variant identified is a potential causal candidate for a 70% elevation in gout risk among both whites and blacks with a stronger effect in men than women. Existing functional studies suggest that all three genes are involved with renal urate transport, and their protein products may ultimately be drug targets for uric acid-lowering therapeutics. Independent, moderate risks conferred by common genetic variations can result in a combined risk of substantial magnitude for gout, a common and debilitating form of arthritis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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policies for data sharing (http://www.cscc.unc.edu/ARIC/). Information about data sharing policies in the Rotterdam Study is available through the PI of the Rotterdam Study (a.hofman@erasmusmc.nl).

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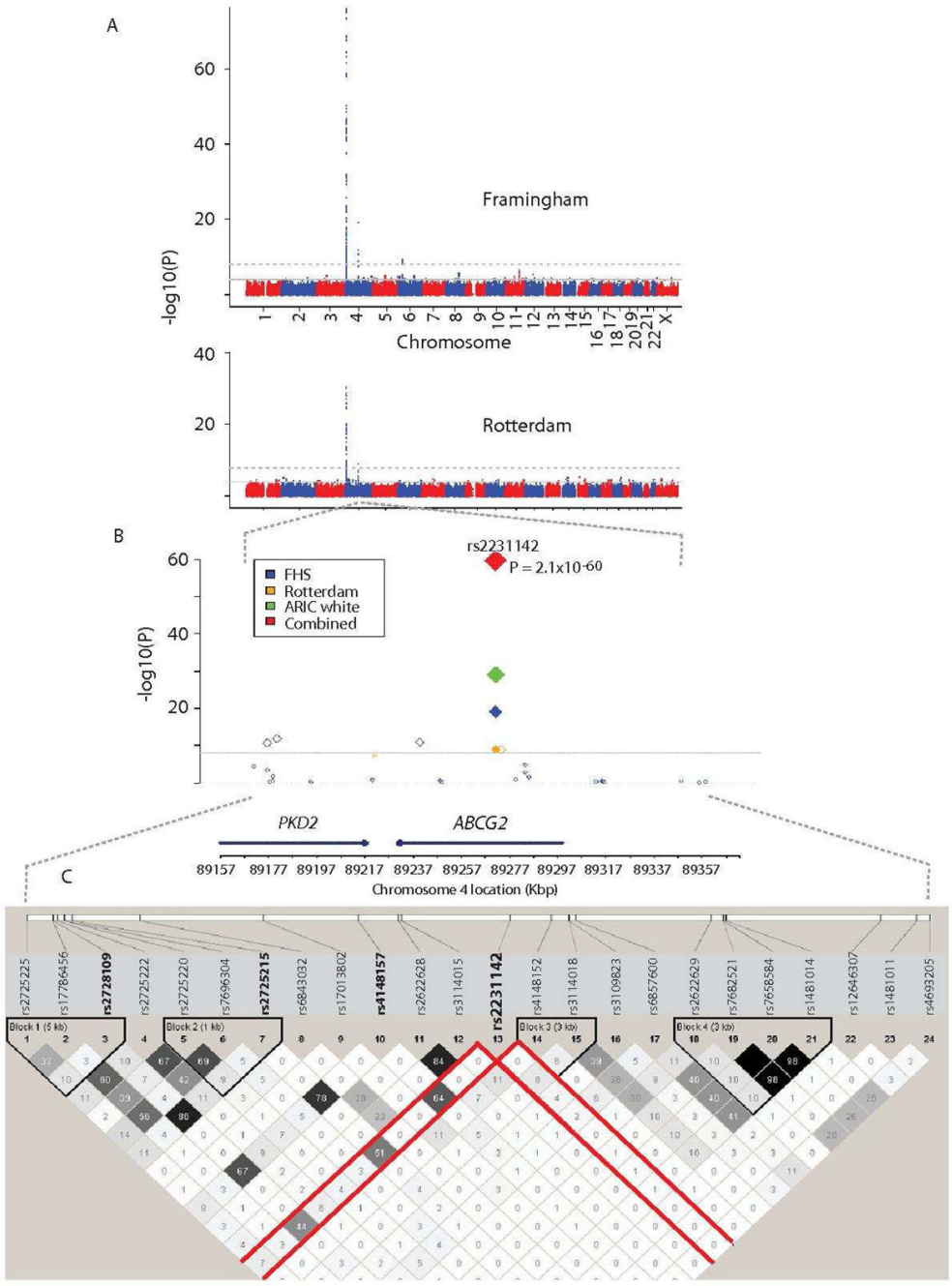

Figure 1.

ABCG2 locus (Panel A): −log10 p-values of genome-wide association analysis of uric acid for FHS and Rotterdam; (Panel B): −log10 p-values vs. physical position based on NCBI build 36.2 for SNPs (minor allele frequency >0.01) within 60Kb of *ABCG2* (open diamonds) for uric acid association analysis for FHS (in blue), Rotterdam (in orange, only SNPs with $p<10^{-7}$ included), and ARIC whites (in green) (only SNPs with $p<10^{-7}$ included). The top associated SNP rs2231142 is plotted with solid diamonds with respective colors for the three studies, and the p-value from the meta-analysis combining the results of the three studies is plotted with a red solid diamond; (Panel C): Plot of linkage disequilibrium pattern in the *ABCG2* region with all minor allele frequency >0.01 of SNPs typed in FHS. Each diamond

contains a pair-wise r^2 value (no value means $r^2=1$) between two SNPs, with a darker shade representing higher correlation. The relative locations of the SNPs are marked on the top panel. SNPs with p-value $<10^{-8}$ in FHS are in bold font, and the r^2 tracks with top associated SNP are outlined by red lines. The LD plot was generated using the program Haploview; haplotype blocks are defined using the method by Gabriel *et al*.(48,49)

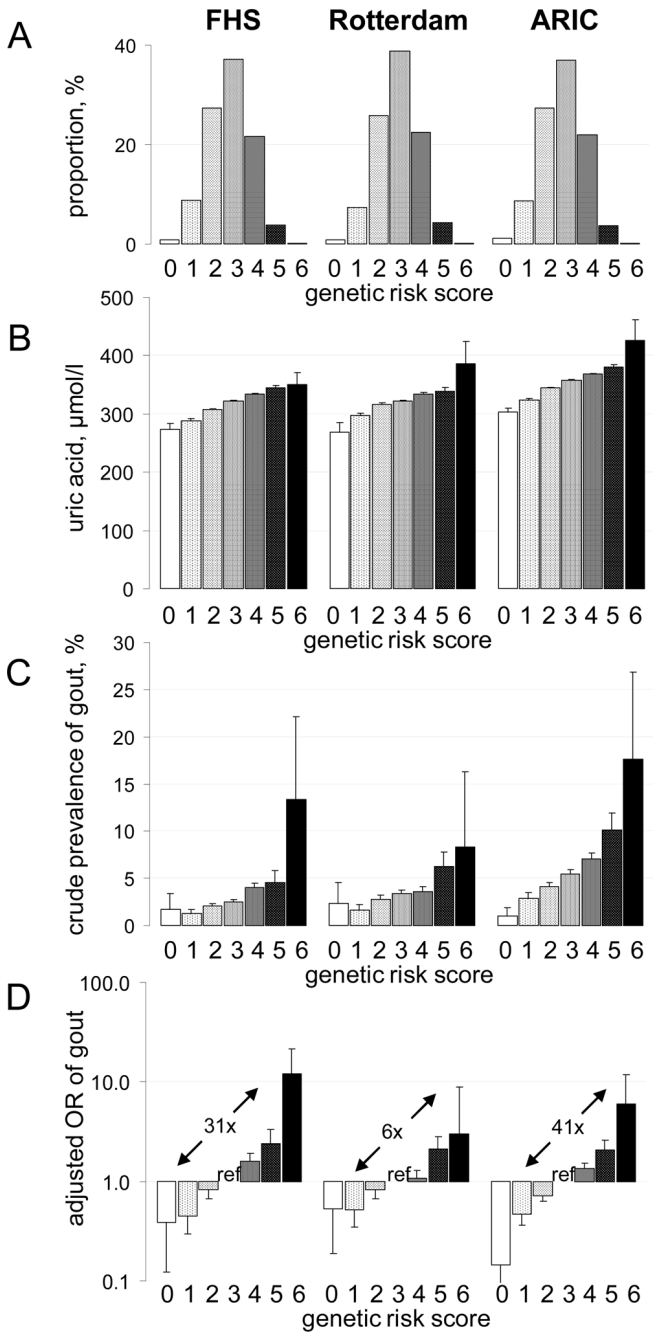

Figure 2.

Additive genetic risk score in the FHS, Rotterdam, and ARIC Studies. (A): prevalence of the genetic risk score; (B): mean serum uric acid, µmol/l; (C): prevalence of gout, %; (D) Odds ratio (OR) of gout, adjusted for age, sex, BMI, alcohol intake, antihypertensive medication, cohort in FHS and study center in ARIC. Results are presented for white ARIC participants only. Error bars present standard errors. Prevalence is period prevalence in the Rotterdam Study.

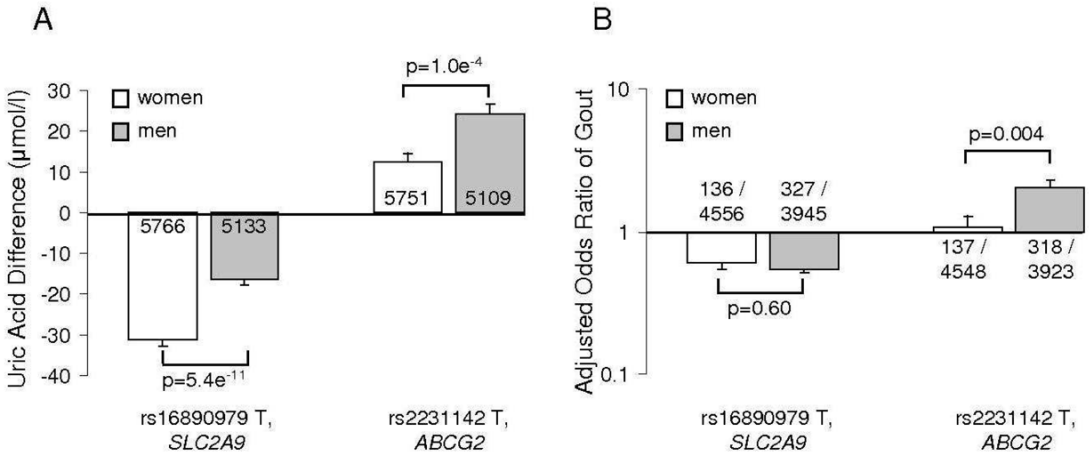

Figure 3.

Interaction of Sex with *SLC2A9* rs16890979 and *ABCG2* rs2231142 on Uric Acid Levels and Gout Risk. Multivariable adjusted (A) difference in mean uric acid levels; (B) odds ratio of gout. Results are presented for ARIC whites, results from FHS and Rotterdam are presented in Supplementary Table 5. Error bars represent standard errors. Numbers inside/next to bars present sample size (uric acid) and number of gout cases/sample size (gout). The sex-specific R^2 (proportion of variance explained, [men/women]) was for rs16890979: 2.0%/8.8% [FHS], 1.4%/4.1% [Rotterdam], 1.7%/7.6% [ARIC white], 0.5%/3.4% [ARIC black]; for rs2231142: 2.1%/0.8% [FHS], 1.6%/0.5% [Rotterdam], 2.0%/0.6% [ARIC white], 0.4%/0.3% [ARIC black].

Table 1

Characteristics of 26714 Study Participants from the Framingham Heart Study, Rotterdam Study, and ARIC Study. Data shown are mean (standard deviation) unless otherwise indicated.

	Study Sample			
	FHS	**Rotterdam**	**ARIC white**	**ARIC black**
Samples for serum uric acid	**Exam 1 (1948, 1971, 2002)[§]**	**visit 1 (1990 – 1993)**		**visit 1 (1987–89)**
Number	7699	4148	11024	3843
Uric Acid (μmol/l)[*]	315.2 (89.2)	321.2 (80.9)	350.9 (89.8)	374.7 (99.3)
Female (%)	53	61	53	62
Body Mass Index (kg/m^2)	25.9 (4.9)	26.3 (3.7)	27.0 (4.9)	29.6 (6.1)
Age (y)	37.9 (9.4)	69.7 (9.0)	54.3 (5.7)	53.5 (5.8)
Alcohol drinking (g/week)[**]	48 (12, 120)	43 (3,85)	30 (0, 93)	53 (15, 125)
Current Drinker (%)	81	79	65	32
Hypertension treatment (%)	8	33	26	43
Samples for gout	Offspring and Third Generation[£]	During follow up (1990 – 2006)		visit 4 (1996–98)
Number	7386	5741	8599	2392
Gout (%,n)	2.7 (197)	3.3 (190)	5.4 (467)	8.8 (210)
Female (%)	53	59	54	64
Body Mass Index (kg/m^2)	27.0 (6.5)	26.3 (3.7)	26.9 (4.7)	29.6 (5.9)
Age (y)	50.0 (13.9)	69.0 (8.8)	54.1 (5.7)	52.9 (5.7)
Alcohol drinking (g/week)[**]	33 (12, 60)	47 (3, 86)	28 (0, 91)	26 (0, 76)
Current Drinker (%)	51	79	56	26
Hypertension treatment (%)	21	32	39	59

[*] to convert to mg/dl, divide by 59.48

[**] median (1st and 3rd quartile), among current drinkers

[§] Exam 1 of the Original Cohort (1948), Offspring (1971), and Third Generation (2002–2005)

[f] Exams 3–7 of Offspring (1987–1999) and exam 1 of the Third Generation (2002–2005)

Table 2

Association of Four SNPs in Three Loci with Uric Acid and Gout

SNP Information	Phenotype		FHS[§]	Rotterdam	ARIC white	ARIC black	All Whites
rs16890979 Chr 4: 9531265 Gene: ***SLC2A9*** Alleles: C/T V253I		Minor Allele Frequency	0.23	0.21	0.23	0.42	
	Uric acid	p-value	1.6×10^{-76}	4.7×10^{-27}	2.3×10^{-105}	2.9×10^{-18}	7.0×10^{-168}
		beta[**](se)	−0.36 (0.02)	−0.29 (0.03)	−0.34 (0.02)	−0.20 (0.02)	−0.34 (0.02)
		R^2	5.3%	2.8%	4.3%	2.0%	-
	Gout	p-value	1.3×10^{-3}	6.0×10^{-3}	1.8×10^{-9}	0.14	1.2×10^{-31}
		OR[***]	0.63	0.67	0.56	0.85	0.58
		95% C.I.	0.47–0.84	0.50–0.89	0.47–0.68	0.69–1.05	0.53–0.63
rs6449213 Chr 4: 9603313 Gene: ***SLC2A9*** Alleles: T/C		Minor Allele Frequency	0.19	0.18	n/a	n/a	n/a
	Uric acid	p-value	2.9×10^{-68}	1.15×10^{-29}			2.2×10^{-104}
		beta[**](se)	−0.37 (0.02)	−0.32 (0.03)	n/a	n/a	−0.35 (0.02)
		R^2	4.5%	3.0%			-
	Gout	p-value	1.1×10^{-2}	0.06			0.001
		OR[***]	0.66	0.75	n/a	n/a	0.69
		95% C.I.	0.49–0.91	0.55–1.01			0.55–0.86
rs2231142 Chr 4: 89271347 Gene: ***ABCG2*** Alleles: G/T Q141K		Minor Allele Frequency	0.11	0.12	0.11	0.03	-
	Uric acid	p-value	9.0×10^{-20}	3.3×10^{-9}	9.7×10^{-30}	9.8×10^{-4}	2.5×10^{-60}
		beta[**](se)	0.25 (0.03)	0.20 (0.03)	0.25 (0.02)	0.22 (0.07)	0.24 (0.02)
		R^2	1.3%	0.8%	1.2%	0.3%	-
	Gout	p-value	1.5×10^{-6}	1.5×10^{-4}	2.0×10^{-7}	0.03	3.3×10^{-15}

SNP Information	Phenotype		FHS[§]	Rotterdam	ARIC white	ARIC black	All Whites
		OR***	1.97	1.71	1.68	1.71	1.74
		95% C.I.	1.49–2.59	1.30–2.25	1.38–2.04	1.06–2.77	1.51–1.99
rs1165205 Chr 6: 25978521 Gene: ***SLC17A3***[£] Alleles: A/T		Minor Allele Frequency	0.46	0.47	0.47	0.13	-
	Uric acid	p-value	5.6×10^{-10}	0.01	8.4×10^{-11}	0.33	3.8×10^{-29}
		beta**(se)	−0.11 (0.02)	−0.06 (0.02)	−0.09 (0.01)	−0.03 (0.03)	−0.09 (0.01)
		R^2	0.7%	0.2%	0.4%	<0.1%	-
	Gout	p-value	0.10	0.86	3.0×10^{-3}	0.33	2.0×10^{-3}
		OR***	0.83	0.98	0.81	1.16	0.85
		95% C.I.	0.67–1.04	0.80–1.21	0.71–0.93	0.86–1.56	0.77–0.94

* Major/minor alleles on forward strand of human genome reference sequence of NCBI build 36.2, the minor allele was modeled.

** Beta coefficient represents 1 standard deviation change in the standardized residual of uric acid per copy increment in the minor allele, adjusting for age, sex, BMI, alcohol consumption, hypertension treatment, (cohort status in FHS, study center in ARIC)

*** OR is the odds ratio for gout per per copy increment of the allele modeled

adjusting for age, sex, BMI, alcohol consumption, hypertension treatment, (cohort status in FHS, study center in ARIC)

se is the standard error of the beta coefficient

§ FHS results generated using linear mixed effects models; FBAT results in FHS: rs16890979 (p=8.3×10-23), rs6449213 (p=1.9×10-24), rs2231142 (p=5.6×10-11), rs1165205 (7.1×10-03)

£ SLC17A3 refers to the entire SLC17A4/SLC17A1/SLC17A3 gene cluster