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Genetic analysis of *ABCG2* and *SLC2A9* gene polymorphisms in gouty arthritis in a Korean population

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Background/Aims: Gout is a common inflammatory arthritis triggered by the crystallization of uric acid in the joints. Serum uric acid levels are highly heritable, suggesting a strong genetic component. Independent studies to confirm the genetic associations with gout in various ethnic populations are warranted. We investigated the association of polymorphisms in the *ABCG2* and *SLC2A9* genes with gout in Korean patients and healthy individuals.

Methods: We consecutively enrolled 109 patients with gout and 102 healthy controls. The diagnosis of gout was based on the preliminary criteria of the America College of Rheumatology. Genomic DNA was extracted from whole blood samples. We identified single nucleotide polymorphism (SNP) changes in the *ABCG2* and *SLC2A9* genes using a direct sequencing technique. rs2231142 in *ABCG2* and rs6449213 and rs16890979 in *SLC2A9* and nearby regions were amplified by polymerase chain reaction.

Results: Patients with gout had significantly higher A/A genotype (29.3% vs. 4.9%, respectively) and A allele (52.8% vs. 26.5%, respectively) frequencies of rs2231142 in *ABCG2* than did controls (χ^2 = 29.42, p < 0.001; odds ratio, 3.32; 95% confidence interval, 2.11 to 5.20). We found novel polymorphisms (c.881A>G and c.1002+78G>A) in the *SLC2A9* gene. The univariate logistic regression analysis revealed that the c.881A>G and c.1002+78G>A SNPs were significantly higher in patients than in controls.

Conclusions: We demonstrated a significant association between rs2231142 in the *ABCG2* gene and gout and identified novel SNPs, c.881A>G and c.1002+78G>A, in the *SLC2A9* gene that may be associated with gout in a Korean population.

Keywords: Gout; ABCG2; SLC2A9

INTRODUCTION

Gout is a common form of inflammatory arthritis triggered by the crystallization of uric acid within the joints [1]. The condition is characterized by painful joint inflammation, destructive tophi and can result in joint destruction and disability if untreated. A strong genetic predisposition to gout has been recognized for centuries; however, our understanding of the roles of specific genes was limited to families with uncommon mutations. These rare familial forms of gout and hyperuricemia include mutational defects in purine metabolic pathway constituents (e.g., X-linked superactivity of PRPS1 and deficiency of hypoxanthine-guanine phos-

phoribosyl transferase [HGPRT]) and those associated with hereditary renal disorders (e.g., autosomal dominant familial juvenile hyperuricemic nephropathy, medullary cystic kidney disease type 1 and 2) [2]. Recent genome-wide association studies (GWAS) have rapidly advanced understanding of the genetics underlying hyperuricemia and gout [3]. Recent GWAS have identified substantial associations between the single nucleotide polymorphisms (SNPs), rs2231142 in the *ABCG2* gene and rs6449213 and rs16890979 in the *SLC2A9* gene and uric acid concentration and gout in various ethnic groups [4,5]. We assessed the genetic associations of these SNPs and nearby regions with gout in a Korean population.

METHODS

Patient selection

A total of 109 patients with gout and 102 gout-free control subjects were recruited from the Chosun University Hospital and Daegu Catholic University Medical Center. The normal control subjects had selected by self-reported history of no arthritis, diabetes, and hypertension. All participants were interviewed using a structured questionnaire to obtain their personal history and demographic characteristics (age, sex, height, weight, and body mass index [BMI]). The gout diagnosis was made according to the 1977 preliminary criteria for the classification of gout published by the American College of Rheumatology for use in clinical settings and population-based epidemiological studies [6] and confirmed by experienced rheumatologists. The both ethics committees of the Institutional Review Board approved the study protocol and all participants provided written informed consent prior to participation in the study. The study was conducted in accordance with the principles of the current version of the Declaration of Helsinki.

Identification of single nucleotide polymorphisms

Serum was separated from peripheral venous blood samples obtained from each participant and stored at –70°C for the clinical chemistry assays. Polymerase chain reaction (PCR)-direct sequencing was performed to detect SNPs. rs2231142, rs6449213, rs16890979 and nearby regions were amplified by PCR, and the products were sequenced using the ABI 3730XL DNA sequencer

(Applied Biosystems, Foster City, CA, USA) for mutational analysis. Genotype and allele frequencies were compared in patient and control samples.

Allele frequency was defined as the percentage of the individuals carrying the allele among the total number of the individuals. The SNP nomenclature used in this study was based on the Human Genome Variation Society recommendations and the National Center for Biotechnology Information SNP database.

Haplotype analysis

Linkage disequilibrium (LD) was measured using Lewontin's D' (|D'|) and r^2 [7,8]. The haplotype of each individual was inferred using the expectation maximization (EM) algorithm (PHASE v 2.0) developed by Stephens et al. [9].

Statistical analysis

Statistical analyses were performed using the SPSS version 17 (SPSS Inc., Chicago, IL, USA). The data are expressed as mean ± standard deviation (SD). The chi-square test, *t* test, and multivariate logistic regression analysis were used for between-group comparisons. The associations of five polymorphisms and haplotypes (rs2231142 in *ABCG2*, and rs16890979, c.813-18A>G, c.881A>G, and c.1002+78G>A in *SLC2A9*) with the risk of gouty arthritis were assessed using logistic regression models with age (continuous value), sex, and BMI (continuous value) as covariates. The chi-square test was used to estimate the Hardy-Weinberg equilibrium. All statistical tests were conducted using SAS version 9.1 (SAS Institute, Cary, NC, USA) and SPSS version 17 was used to calculate the LD. In all analyses, *p* values < 0.05 were deemed to indicate statistical significance.

RESULTS

Participant demographic and clinical characteristics

The majority of the study participants (98.8%) were male. Mean uric acid levels were not significantly different between the patients with gout (5.8 ± 1.9 mg/dL) and controls (6.1 ± 1.2 mg/dL), possibly because most of the patients were likely to have received a uric acid-lowering agent such as allopurinol, febuxostat, or benzbromarone. Furthermore, we found no significant differences

in age, height, weight, and BMI between the patient and control groups (Table 1).

Identification of single nucleotide polymorphisms

Table 2 shows nine SNPs, three of which (rs2231142, rs6449213, and rs16890979) are associated with serum urate levels in patients with gout. rs2231142, also known as Q141K and C421A, is an SNP in the *ABCG2* gene and, thus, a missense variant. The A allele of rs2231142 is associated with an increased risk of gout. The percentage of the A/A genotype (29.3% vs. 4.9%, respectively) and A allele (52.8% vs. 26.5%, respectively) frequency in the rs2231142 (c.421C>A) SNP were significantly higher in patients with gout than in control subjects and was significantly associated with gout (χ^2 = 29.42, p < 0.001; odds ratio [OR], 3.32; 95% confidence interval [CI], 2.11 to 5.20) (Table 3). These findings are similar to those reported previously. Conversely, the genotype distributions of

rs6449213 and rs16890979 did not differ significantly between patients and control subjects. rs6449213 is a surrogate for rs7442295 which is in a fairly tight linkage (r^2 = 0.88) and, thus, associated with high serum urate levels. We found a high distribution of the A/A genotype in the rs6449213 SNPs of both patients and controls (98.2% vs. 99.0%, respectively). We identified the A/G genotype in two patients with gout and in one control subject (Table 4). Several previous independent studies have shown an association between rs16890979 and gout. rs16890979 may be a variation in the SLC2A9 gene, which is more commonly known as *GLUT9*. Furthermore, the distribution of the A/A genotype was high in the rs16890979 polymorphism in patients (100%) and controls (98.1%) (Table 5).

We identified novel polymorphisms in regions near rs16890979. The genotype frequencies of the c.881A>G and c.1002+78G>A SNPs in the *SLC2A9* gene were signifi-

Table 1. Demographic and clinical characteristics of the study population

Characteristic	Patients with gout (n = 109)	Control subjects (n = 102)	p value
Age, yr	55.0 ± 12.1	51.8 ± 6.7	0.018[a]
Height, cm	168.3 ± 6.4	169.4 ± 5.4	0.18
Weight, kg	69.9 ± 8.6	69.1 ± 8.7	0.54
Body mass index, kg/m^2	24.6 ± 2.7	24.0 ± 2.7	0.12
Serum uric acid, mg/dL	5.8 ± 1.9	6.1 ± 1.2	0.17

Values are presented as mean ± SD.
[a]p < 0.05.

Table 2. *ABCG2* and *SLC2A9* single nucleotide polymorphisms

Gene	Polymorphism (dbSNP no)	Polymorphism (HGVS nomenclature)	Genotype frequency in patients with gout (%)	Odds ratio
ABCG2	rs2231142	c.421C>A	AC (46.7)	3.32[a]
ABCG2	·	c.871+386A>G	AA (95.4)	
SLC2A9	rs6449213	c.410+4190A>G	AA (98.2)	
SLC2A9	·	c.410+4124C>T	CC (98.2)	
SLC2A9	·	c.410+4242G>A	GG (99.1)	
SLC2A9	rs16890979	c.844A>G	AA (100)	
SLC2A9	·	c.881A>G	AA (47.7)	1.54[a]
SLC2A9	·	c.1002 + 78G>A	GG (55.9)	1.64[a]
SLC2A9	·	c.813-18A>G	AA (99.1)	

dbSNP, single nucleotide polymorphism database; HGVS, Human Genome Variation Society.
[a]p < 0.05.

Table 3. Genotype distribution and relative allele frequencies of the c.421C>A (rs2231142) polymorphism of *ABCG2*

Group	No.	Genotype frequency, n (%)			Allele frequency, n (%)	
		C/C	C/A	A/A	C	A
Patient	109	26 (23.8)	51 (46.7)	32 (29.3)	103 (47.2)	115 (52.8)
Control	102	53 (51.9)	44 (43.1)	5 (4.9)	150 (73.5)	54 (26.5)
		$\chi^2 = 29.42$, df = 2, $p < 0.001$[a]			$\chi^2 = 30.32$, df =1, $p < 0.001$[a]	
		OR, 3.32; 95% CI, 2.11–5.20			OR, 3.10; 95% CI, 2.04–4.76	

OR, odds ratio; CI, confidence interval.

[a]$p < 0.05$.

Table 4. Genotype distribution and relative allele frequencies of the c.410+4190A>G (rs6449213) polymorphism in the *SLC2A9* gene

Group	No.	Genotype frequency, n (%)			Allele frequency, n (%)	
		A/A	A/G	G/G	A	G
Patient	109	107 (98.2)	2 (1.8)	0	216 (99.0)	2 (1.0)
Control	102	101 (99.0)	1 (1.0)	0	203 (99.5)	1 (0.5)
		$p > 0.05$			$p > 0.05$	

No significant difference in genotype distribution was found between patients with gout and control subjects.

Table 5. Genotype distribution and relative allele frequencies of the c.844A>G (rs16890979) polymorphism in the *SLC2A9* gene

Group	No.	Genotype frequency, n (%)			Allele frequency, n (%)	
		A/A	A/G	G/G	A	G
Patient	109	109 (100)	0	0	218 (100)	0
Control	102	100 (98.1)	2 (1.9)	0	202 (99.0)	2 (1.0)
		$p = 0.232$			$p = 0.232$	

No significant difference in genotype was found between the gout and control groups.

cantly different between patients with gout and controls. The c.881A>G variant in the patient group had significantly higher frequencies of the G/G genotype (20.1% vs. 5.8%, respectively) and G allele (36.2% vs. 25.0%, respectively) than did the control group ($\chi^2 = 9.36$, $p < 0.001$; OR, 1.54; 95% CI, 1.03 to 2.28) (Table 6). Moreover, the distribution of the A/A genotype (10.1% vs. 2.9%, respectively) and A allele frequency (27.1% vs. 17.2%, respectively) for c.1002+78G>A was significantly higher in the patient than in the control group ($\chi^2 = 5.93$, $p = 0.05$; OR, 1.64; 95% CI, 1.03 to 2.62) (Table 7). Conversely, the genotype frequencies of c.871+386A>G in the *ABCG2* gene and c.410+4124C>T and c.410+4242G>A in the *SCL2A9* gene were not significantly different between patients with gout and control subjects. c.813-18A>G, which is located

near rs16890979 in *SLC2A9*, had an A/A genotype distribution of 99.1%. Notably, none of the minor alleles of the four SNPs were observed in the patients with gout; thus, the OR could not be calculated.

Haplotype association analysis

Of the four SNPs in the *SLC2A9* gene, c.881A>G and c.1002+78G>A showed tight linkage ($|D'| = 1$, $r^2 = 0.672$), whereas the linkage between rs16890979 and c.813-18A>G was low due to their extremely low frequencies (Fig. 1); thus, c.881A>G and c.1002+78G>A were used for haplotype construction. Haplotypes of *SLC2A9* were constructed using PHASE (v 2.1), and three haplotypes were used for further statistical analysis. We observed no linkage with rs2231142 in *ABCG2*.

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Table 6. Genotype distribution and relative allele frequencies of the c.881A>G polymorphism in the *SLC2A9* gene

| Group	No.	Genotype frequency, n (%)			Allele frequency, n (%)	
		A/A	A/G	G/G	A	G
Patient	109	52 (47.7)	35 (32.1)	22 (20.1)	139 (63.7)	79 (36.2)
Control	102	57 (55.8)	39 (38.2)	6 (5.8)	153 (75.0)	51 (25.0)
		$\chi^2 = 9.36$, df = 2, $p < 0.001$[a] OR, 1.54; 95% CI, 1.03–2.28			$\chi^2 = 6.24$, df =1, $p = 0.015$[a] OR, 1.70; 95% CI, 1.12–2.60	

OR, odds ratio; CI, confidence interval.
[a]$p < 0.05$.

Table 7. Genotype distribution and relative allele frequencies of the c.1002+78G>A polymorphism in the *SLC2A9* gene

Group	No.	Genotype frequency, n (%)			Allele frequency, n (%)	
		A/A	A/G	G/G	A	G
Patient	109	11 (10.1)	37 (33.9)	61 (55.9)	59 (27.1)	159 (72.9)
Control	102	3 (2.9)	29 (28.4)	70 (68.6)	35 (17.2)	169 (82.8)
		$\chi^2 = 5.93$, df = 2, $p = 0.011$[a] OR, 1.64; 95% CI, 1.03–2.26			$\chi^2 = 5.96$, df =1, $p = 0.015$[a] OR, 1.78; 95% CI, 1.11–2.86	

OR, odds ratio; CI, confidence interval.
[a]$p < 0.05$.
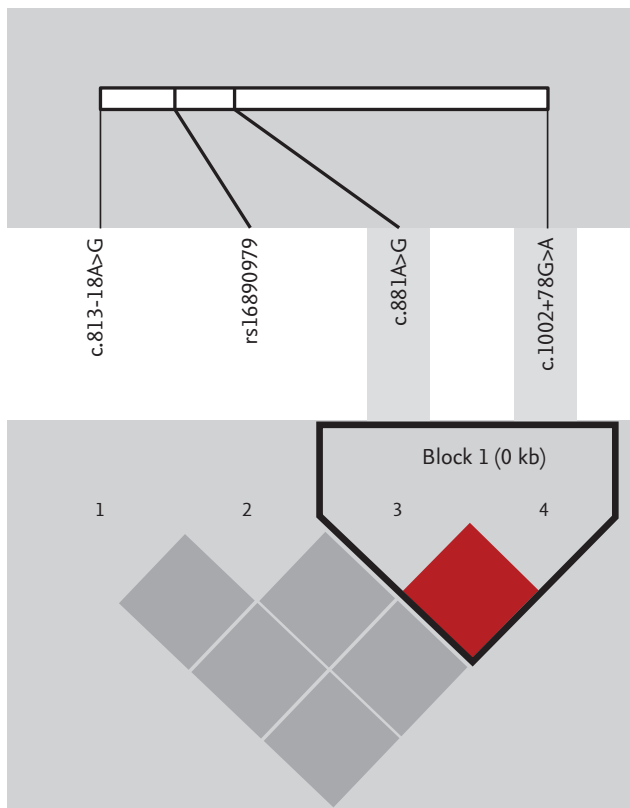
Figure 1. Among the four single nucleotide polymorphisms in the *SLC2A9* gene, c.881A>G and c.1002+78G>A showed a tight linkage ($|D'| = 1$, $r^2 = 0.672$).

In summary, we found a strong association of rs2231142 in the *ABCG2* gene with gouty arthritis. Moreover, we identified a novel association between the c.881A>G and c.1002+78G>A polymorphisms in the *SLC2A9* gene and gout. Thus, we compared the association of genotype and allele frequencies of three SNPs (rs2231142 in *ABCG2*, c.881A>G, and c.1002+78G>A in *SLC2A9*) in Korean patients with gout and healthy control subjects.

DISCUSSION

Gout is a common inflammatory joint disease that may lead to joint destruction and disability if untreated [10]. Estimates indicate that up to 2% of males over the age of 30 years and females over the age of 50 years will develop gout at some time [1]. Hyperuricemia is associated with a variety of adverse health risks including gout. Emerging evidence suggests that gout is strongly associated with metabolic syndrome and may lead to cardiovascular disease, diabetes, and premature death [11-14].

GWAS have emerged as a comprehensive and powerful approach for identifying genetic variants related to complex diseases. Since 2007, several systematic,

well-powered, GWAS have been performed worldwide to explore the relationships between common sequence variations and disease predisposition [15]. These genetic data have considerably advanced our understanding of the pathogenesis of hyperuricemia and gout. Several recent GWAS have identified genes that may be causally associated with uric acid levels, including *SLC2A9/GLUT9*, *ABCG2* (BCRP), *SLC13A3*, *SLC17A1* (NPT1), *SLC17A3* (NPT4), *SLC17A4* (named as NPT5 provisionally), *SLC22A11* (OAT4), *SLC22A12* (URAT1), and *SLC16A9* (MCT9) as well as the urate transport-related scaffolding protein *PDXK1* [16-23]. Given the urate transporter activity of *SLC2A9* and *ABCG2* and the strong associations between their genetic variants and serum uric acid levels, these genes appear to be important modulators of uric acid levels and potential determinants of the risk of developing gout [17,19]. Several recent studies have found that the rs6449213, rs16890979, rs7442295, rs6855911, and rs734553 SNPs in the *SLC2A9* gene are highly associated with gout [17,24-26]. Furthermore, rs2231142, the missense SNP in *ABCG2* (Q141K) has been associated with hyperuricemia and gout in Caucasian, African-American, Japanese, and Han Chinese samples [27-29]. The investigation of the *ABCG2* variant (rs2231142) in Asian populations such as Han Chinese and Japanese [29-31] was particularly noteworthy.

We conducted a replication study of the associations of the rs6449213 and rs16890979 SNPs in *SLC2A9* and rs2231142 in *ABCG2* with gout. Our findings for the rs2231142 variant are similar to those reported previously. However, in contrast to previous studies, we found no differences in the distribution of the rs6449213 and rs16890979 genetic variants between the gout and control groups and no association with gout. This disparity may be explained by differences in the genetic variant among the various ethnic groups. In the search for novel SNPs, we compared allele and genotype distributions in regions near the target SNPs in the *ABCG2* and *SLC2A9* genes in the 109 Korean patients with gout and 102 gout-free controls. The genotype frequency of the c.881A>G and c.1002+78G>A variants differed significantly between gout and control groups. Moreover, c.881A>G and c.1002+78G>A showed a high LD in the haplotype analysis.

Our study had several limitations. First, the sample size was not sufficient to detect a potential correlation between the genetic associations of the SNPs and gout in a Korean population. Second, because only 2% of our participants were female, we were unable to perform a statistical analysis according to sex. Thus, the generalizability of our findings is limited to male patients with gout. Third, uric acid levels were not significantly different between the patient and control groups, possibly because the majority of patient with gout would have received a uric acid-lowering agent such as allopurinol, febuxostat, or benzbromarone. Despite these limitations, our study is the first to show an association between gout and SNPs (rs2231142 in *ABCG2*, and rs6449213 and rs16890979 in *SLC2A9*) among Koreans. Although previous studies have investigated *ABCG2* and *SLC2A9* variants in various ethnic populations, our study is the first to investigate the presence and effects of these SNPs in a Korean population.

In conclusion, rs2231142 in the *ABCG2* gene and c.881A>G, c.1002+78G>A in the *SLC2A9* gene are potential candidate variants underlying the pathogenesis of gout in Korean individuals. In-depth investigations of these SNPs in functional experiments are warranted to elucidate the precise mechanisms underlying the pathogenesis of gout.

KEY MESSAGE

1. Our study in a Korean population demonstrated a strong association of rs2231142 in the *ABCG2* gene with gout. Furthermore, we identified novel single nucleotide polymorphisms, c.881A>G and c.1002+78G>A, in the *SLC2A9* gene that are associated with gout.

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