

Original Article

Serum uric acid levels are associated with polymorphisms in the *SLC2A9*, *SF1*, and *GCKR* genes in a Chinese population

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Aim: Genome-wide association studies have identified several novel loci associated with serum uric acid concentrations in individuals of European descent. In the current study, we aimed to evaluate the associations between these loci and serum uric acid concentrations in a Chinese population.

Methods: Fourteen single nucleotide polymorphisms (SNPs) mapped in or near 11 loci (*PDZK1*, *GCKR*, *LRP2*, *SLC2A9*, *ABCG2*, *LRR16A*, *SLC17A1*, *SLC17A3*, *SLC22A11*, *SLC22A12* and *SF1*) were genotyped in 2329 Chinese subjects in Shanghai. Serum biochemical parameters including uric acid concentrations were determined. All the variants were analyzed for gender differences since uric acid metabolism differed between genders.

Results: In males after adjustments for age and BMI, *GCKR* rs780094, *SLC2A9* rs11722228 and *SF1* rs606458 were associated with the uric acid concentrations, which were statistically significant ($P=0.016$, 0.001 and 0.03 , respectively), whereas *SLC2A9* rs3775948 was marginally associated with the uric acid concentrations ($P=0.071$). In females, *SLC22A12* rs506338 was also marginally associated with the uric acid concentrations ($P=0.057$). The meta-analysis for combined data from both males and females revealed that rs3775948 and rs606458 were associated with the uric acid concentrations ($P=0.036$ and 0.043 , respectively). Furthermore, the gender significantly affected the association of rs11722228 with serum uric acid levels ($P=0.012$).

Conclusion: The *SLC2A9* rs11722228, *SF1* rs606458 and *GCKR* rs780094 variants modulate uric acid concentrations in Chinese males, while *SF1* rs606458 and *SLC2A9* rs3775948 are associated with the uric acid concentrations in both Chinese males and females.

Keywords: uric acid; gout; single nucleotide polymorphisms; *SLC2A9*; *SF1*; *GCKR*; genome-wide association; Chinese

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Introduction

Elevated serum uric acid is a risk factor for gout and is independently associated with cardiovascular disease in the general population^[1, 2]. In addition, it is linked to insulin resistance, type 2 diabetes, metabolic syndrome and obesity^[3–6]. Although conventional factors, including age, body mass index (BMI), alcohol consumption and cigarette smoking, contribute greatly to variations in serum uric acid concentrations^[7–11], genetic determinants also play roles, and heritabili-

ties as high as 42% have been reported^[12]. Moreover, genetic studies facilitate the development of effective treatments for associated diseases^[13, 14]. Recently, advances have been made in identifying genes regulating serum uric acid through genome-wide association studies. The first wave of discovery of uric acid genes was conducted with European populations, identifying the associations of *SLC2A9*, *ABCG2*, and *SLC17A3* with uric acid concentrations^[15–17]. In addition, many genome-wide association studies focusing on serum uric acid concentrations in individuals of European descent have identified several novel associated loci mapped in or near *SLC17A1*, *SLC22A11*, *SLC22A12*, *SLC16A9*, *LRR16A*, *GCKR*, *R3HDM2-INHBC*, and *RREB1*^[18–20]. These studies have established the utility of the genome-wide association approach in elucidating complex genetic traits related to uric acid levels. However,

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because discrepancies exist in the allelic frequencies and effect sizes observed with individuals of different ethnicities, replication studies of the loci originally identified in individuals of European descent should be performed on individuals of other ethnicities to more comprehensively explore the impact of genetics on serum uric acid levels. To date, few genome-wide association studies have been conducted on individuals of East Asian descent. One novel loci mapped to *LRP2* has been reported in association with uric acid, and associations of *SLC2A9*, *SLC22A12*, *ABCG2*, and *MAF* with uric acid have also been demonstrated^[21–23]. However, the effects of the other European-derived loci in individuals of non-European descent populations remain unclear. In the present study, we aimed to test the associations of SNPs from eleven reported loci with uric acid in 2329 Shanghai Chinese individuals.

Materials and methods

Ethics statement

This study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital in accordance with the principle of the Helsinki Declaration II. Written informed consent was obtained from each participant.

Participants

A total of 2329 participants were recruited from a community-based study. All subjects were derived from the same predominant genetic background with eastern Han Chinese ancestry and resided in Shanghai or nearby regions. Participants with cancer, hepatic disease, renal disease or other coexisting illness were excluded.

Clinical measurements

The phenotypes of the anthropometric and biochemical traits related to uric acid were extensively evaluated for all participants. Height (m) and weight (kg) were measured and BMI was calculated as weight/height². Systolic and diastolic blood pressures (mmHg) were also measured. Overnight fasting venous blood specimens were obtained. Serum concentrations of uric acid, creatinine and lipids, including total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were measured using a type 7600-020 automated analyzer (Hitachi, Tokyo, Japan). Plasma glucose concentrations were measured by the glucose oxidase-peroxidase method using commercial kits (Shanghai Biological Products Institution, Shanghai, China).

SNP selection, genotyping and quality control analysis

We selected 14 SNPs from 11 loci (*PDZK1* rs12129861, *GCKR* rs780094, *LRP2* rs2544390, *SLC2A9* rs11722228, rs16890979, rs3775948, and rs10489070, *ABCG2* rs2231142, *LRR16A* rs742132, *SLC17A1* rs1183201, *SLC17A3* rs1165205, *SLC22A11* rs17300741, *SLC22A12* rs506338, and *SF1* rs606458) that have been recently reported to be associated with serum uric acid levels. The SNPs were genotyped by multiplex primer extension with detection by matrix-assisted laser desorption ioniza-

tion-time of flight mass spectroscopy using the MassARRAY Compact Analyzer (Sequenom, San Diego, CA, USA). All fourteen SNPs passed quality control criteria with genotyping call rates of greater than 90%. Individuals with more than 10% missing genotypes were excluded. After all quality control checks, 2170 individuals and all fourteen SNPs were analyzed.

Statistical analysis

We performed the Hardy-Weinberg equilibrium test before the association analysis. Those SNPs that failed the Hardy-Weinberg equilibrium test ($P < 0.01$) were excluded. Tests of normality were conducted for all quantitative traits. The quantitative traits were analyzed by linear regression using the additive model with adjustments for age, gender and BMI using PLINK^[24], and the regression coefficients with 95% CIs were presented. The meta-analysis of serum uric acid levels in the males and females was performed using the Comprehensive Meta-analysis software (v2.2.057) with a fixed model or random effect model after testing for heterogeneity. Homogeneity was assessed by the Cochran Q test. The statistical analyses were performed using SAS for Windows (version 8.0; SAS Institute, Cary, NC, USA) unless otherwise specified. A two-tailed P value of < 0.05 was considered statistically significant.

The previously reported effect size of genetic loci on serum uric acid levels is approximately 8.5–30^[18, 20]. Based on this reported effect size and the allele frequency observed in our samples, the statistical power was calculated under an additive genetic model. For SNPs with minor allele frequencies greater than 0.2, we determined that the power was greater than 80% for detecting associations between genotypes and uric acid concentrations with a relative β value greater than 8.5 mmol/L per allele.

Results

The clinical characteristics of the participants are shown in Table 1. The genotype frequencies of all polymorphisms were in Hardy-Weinberg equilibrium. Because uric acid metabolism differs between genders^[25–27], we investigated the gender-specific impacts of all variants on serum uric acid levels. As shown in Table 2, *GCKR* rs780094 ($\beta = 9.154$, 95% CI 1.721–16.59 $P = 0.016$), *SLC2A9* rs11722228 ($\beta = 12.990$, 95% CI 5.246–20.730 $P = 0.001$) and *SF1* rs606458 ($\beta = 8.416$, 95% CI 0.813–16.020 $P = 0.030$) showed associations with serum uric acid levels in the males after adjustments for age and BMI as confounders; *SLC2A9* rs3775948 demonstrated marginally significant associations with uric acid ($P = 0.071$). In the females, no associations were observed with the exception of rs506338 in *SLC22A12*, which was potentially associated with uric acid ($P = 0.057$). After the meta-analysis combining the males and females, we detected that only *SLC2A9* rs3775948 and *SF1* rs606458 were associated with uric acid ($P = 0.036$ and 0.043, respectively).

The effects of gender on the associations of all SNPs with serum uric acid levels were further explored in our samples. We found that gender significantly affected the association of rs11722228 in *SLC2A9* with uric acid levels ($P = 0.012$). Gen-

Table 1. Clinical characteristics of the study samples. Data are shown as mean±SD.

	Female	Male	P value
<i>n</i>	1455	874	-
Age (year)	49.203±14.086	51.006±16.012	0.005
Body mass index (kg/m ²)	23.282±3.155	23.621±3.132	0.006
Serum uric acid (μmol/L)	262.712±65.150	352.576±77.309	<0.0001
Blood urea nitrogen (mmol/L)	4.531±1.188	4.952±1.203	<0.0001
Serum creatinine (mmol/L)	58.201±11.986	78.513±13.928	<0.0001
Systolic blood pressure (mmHg)	120.337±17.169	125.543±17.062	<0.0001
Diastolic blood pressure (mmHg)	76.315±9.788	80.003±10.134	<0.0001
Total cholesterol (mmol/L)	4.727±1.006	4.560±0.965	<0.0001
Triglyceride (mmol/L)	1.275±0.865	1.593±1.108	<0.0001
High-density lipoprotein cholesterol (mmol/L)	1.441±0.316	1.248±0.312	<0.0001
Low-density lipoprotein cholesterol (mmol/L)	2.935±0.794	2.908±0.780	0.413
Fasting glucose (mmol/L)	5.187±0.553	5.146±0.591	0.089

der had marginally significant effects on the associations of rs780094 in *GCKR* and rs606458 in *SF1* with uric acid levels ($P=0.057$ and 0.054). However, we failed to detect any other influences of gender on the associations of the other SNPs with uric acid levels.

Because *GCKR* rs780094 was associated with fasting glucose and triglyceride levels, we further analyzed its association with serum uric acid levels after adjusting for age, BMI, and fasting glucose and triglyceride levels in the males. The results indicated that *GCKR* rs780094 was strongly associated with uric acid independent of fasting glucose and triglyceride levels ($\beta=9.905$, 95%CI 2.498–17.310, $P=0.009$).

Finally, we analyzed the effects of *GCKR* rs780094, *SLC2A9* rs11722228, and rs3775948 on serum creatinine levels, which are related to uric acid metabolism. We found that *GCKR* rs780094, *SLC2A9* rs11722228, and rs3775948 were associated with serum creatinine levels in the males; in addition, *SLC2A9-WDR1* rs10489070 and *SF1* rs606458 demonstrated marginally significant correlations with creatinine concentrations. However, after the combined analysis, all SNPs lost their associations with serum creatinine levels (Table 3). Because the above SNPs showed significant associations with serum creatinine levels in the males, we performed further adjustments, including these levels as confounders in the association analysis of the SNPs with uric acid levels. After adjustments for age, BMI and serum creatinine levels, we showed that only rs11722228 was significantly associated with uric acid levels ($P=0.025$ for rs11722228; $P=0.108$ and 0.409 for rs780094 and rs3775948).

Discussion

In the current study, we attempted to replicate the effects of recently reported loci on serum uric acid levels in a Chinese population. We were able to confirm significant associations between serum uric acid and SNPs in *SLC2A9* rs3775948 and *SF1* rs606458. Gender impacts on the associations of *GCKR* rs780094 and *SLC2A9* rs11722228 with uric acid levels were also observed in our samples. However, no associations with uric acid concentrations were detected for the markers of the

other known loci in our study.

SLC2A9 encodes glucose transporter 9 (GLUT9), which can serve as a facilitative transporter of glucose and fructose as well as uric acid. Several genome-wide association studies have identified genetic variants of *SLC2A9* that are robustly associated with serum uric acid levels, with explained variance reaching 3.4%–8.8% in women and 0.5%–2.0% in men^[15–17, 28–30]. The rs11722228 variant in *SLC2A9* has been previously reported to be highly associated with uric acid levels in Japanese individuals^[22]. In the present study, we successfully confirmed the association of this variant with uric acid concentrations in males from a Chinese population. Moreover, gender was demonstrated to affect the association of this variant with uric acid concentrations in our study. This indicated that *SLC2A9* (rs11722228), together with gender, participated in the regulation of uric acid concentrations and confirmed the sex-specific role of *SLC2A9* in regulating uric acid levels, which is in accordance with a previous study^[15]. Because rs11722228 explained 1.03% of the total variation in serum uric acid levels in the Chinese population compared with 1.33% of the variation in individuals of Japanese descent, the detailed underlying biological mechanisms require further investigation^[4, 22]. Another variant in *SLC2A9* rs3775948 has been previously reported to be greatly correlated with uric acid levels in East Asians^[21]. This variant was not in linkage disequilibrium with rs11722228 (Supplementary Figure 1). In accordance with this finding, we also observed a relationship between this variant and uric acid levels. Because the association between rs3775948 and uric acid levels was observed only in the combined analysis of the males and females, it may have been caused by the increased sample size and/or gender effects. Thus, this association between rs3775948 and uric acid needs to be further investigated using a larger sample size. The association of rs11722228 and rs3775948 in this study together with the large number of SNPs in *SLC2A9* that have been previously identified and have been replicated to be associated with uric acid in multiple populations highlight the genetic pathways that are important in the regulation

Table 2. Association between SNPs from eleven loci and serum uric acid levels in the Chinese subjects.

Loci	SNP	Chr*	Position (bp)	Effect Allele	Other Allele	MAF	Males			Females			Combined			
							β	P value	[95% CI]	β	P value	[95% CI]	β	P value	[95% CI]	
PDK1	rs12129861	1	145725689	A	G	0.189	3.960	0.393	0.125	0.967	1.277	0.967	1.277	0.967	1.277	0.615
GOKR	rs780094	2	27741237	G	A	0.451	9.154	0.016	0.543	0.816	2.899	0.816	2.899	0.816	2.899	0.144
LRP2	rs2544390	2	170204846	T	C	0.456	-5.199	0.157	0.960	0.679	-0.796	0.679	-0.796	0.679	-0.796	0.684
SLC2A9	rs11722228	4	9915741	T	C	0.293	12.990	0.001	0.481	0.854	6.384	0.854	6.384	0.854	6.384	0.307
SLC2A9	rs16890979	4	9922167	T	C	0.015	3.232	0.844	-3.280	0.722	-1.716	0.722	-1.716	0.722	-1.716	0.831
SLC2A9	rs3775948	4	9995182	G	C	0.410	-6.737	0.071	-3.205	0.184	-4.245	0.184	-4.245	0.184	-4.245	0.036
SLC2A9-WDR1	rs10489070	4	10276352	C	G	0.138	-6.403	0.229	0.875	0.800	-1.282	0.800	-1.282	0.800	-1.282	0.658
ABCG2	rs2231142	4	89052323	A	C	0.312	0.022	0.996	-0.032	0.990	-0.015	0.990	-0.015	0.990	-0.015	0.994
LRR16A	rs742132	6	25607571	C	T	0.257	2.659	0.506	2.504	0.362	2.554	0.362	2.554	0.362	2.554	0.259
SLC17A1	rs1183201	6	25823444	T	A	0.157	-3.332	0.495	1.849	0.571	0.251	0.571	0.251	0.571	0.251	0.926
SLC17A3	rs1165205	6	25870542	A	T	0.160	-4.776	0.323	1.120	0.730	-0.709	0.730	-0.709	0.730	-0.709	0.792
SLC22A11	rs17300741	11	64331462	G	A	0.057	2.190	0.785	3.308	0.516	2.988	0.516	2.988	0.516	2.988	0.487
SLC22A12	rs506338	11	64440920	C	T	0.261	5.006	0.231	-4.965	0.057	-0.514	0.057	-0.514	0.057	-0.514	0.917
SF1	rs606458	11	64546391	G	A	0.354	8.416	0.030	2.505	0.310	4.206	0.310	4.206	0.310	4.206	0.043

* Chromosome.

P values were adjusted for age, gender, and BMI. P values <0.05 were shown in bold. Position is given for GRCh37.p10. The effect allele is the allele to which the β estimate refers.**Table 3.** Association between SNPs from eleven loci and serum creatinine levels in the Chinese subjects.

Loci	SNP	Chr*	Position (bp)	Effect Allele	Other Allele	MAF	Males			Females			Combined			
							β	P value	[95% CI]	β	P value	[95% CI]	β	P value	[95% CI]	
PDK1	rs12129861	1	145725689	A	G	0.189	3.960	0.561	0.154	0.784	0.468	0.784	0.468	0.784	0.582	
GOKR	rs780094	2	27741237	G	A	0.451	9.154	0.049	0.062	0.885	0.428	0.885	0.428	0.885	0.243	
LRP2	rs2544390	2	170204846	T	C	0.456	-5.199	0.125	0.029	0.946	-0.279	0.946	-0.279	0.946	0.440	
SLC2A9	rs11722228	4	9915741	T	C	0.293	12.990	0.016	-0.184	0.703	0.705	0.703	0.705	0.703	0.464	
SLC2A9	rs16890979	4	9922167	T	C	0.015	3.232	0.770	0.697	0.687	0.305	0.687	0.305	0.687	0.839	
SLC2A9	rs3775948	4	9995182	G	C	0.410	-6.737	0.046	0.086	0.847	-0.349	0.847	-0.349	0.847	0.350	
SLC2A9-WDR1	rs10489070	4	10276352	C	G	0.138	-6.403	0.080	0.404	0.528	-0.232	0.528	-0.232	0.528	0.663	
ABCG2	rs2231142	4	89052323	A	C	0.312	0.022	0.725	0.655	0.172	0.530	0.172	0.530	0.172	0.530	0.183
LRR16A	rs742132	6	25607571	C	T	0.257	2.659	0.540	0.203	0.689	0.283	0.689	0.283	0.689	0.497	
SLC17A1	rs1183201	6	25823444	T	A	0.157	-3.332	0.725	0.655	0.172	0.530	0.172	0.530	0.172	0.530	0.594
SLC17A3	rs1165205	6	25870542	A	T	0.160	-4.776	0.143	0.081	0.832	-0.266	0.832	-0.266	0.832	0.517	
SLC22A11	rs17300741	11	64331462	G	A	0.057	2.190	0.819	0.578	0.539	0.312	0.539	0.312	0.539	0.694	
SLC22A12	rs506338	11	64440920	C	T	0.261	5.006	0.907	-0.844	0.080	-0.629	0.080	-0.629	0.080	-0.629	0.123
SF1	rs606458	11	64546391	G	A	0.354	8.416	0.060	-0.037	0.934	0.365	0.934	0.365	0.934	0.365	0.342

* Chromosome.

P values were adjusted for age, gender, and BMI. P values <0.05 were shown in bold. Position is given for GRCh37.p10. The effect allele is the allele to which the β estimate refers.

of serum uric acid levels. Recently, *SLC2A9* was reported to act as a high capacity and possibly electrogenic uric acid transporter that can mediate the efflux of uric acid from cells by exchanging extracellular hexoses for intracellular uric acid. It has also been reported to be involved in the reabsorption of uric acid in the basolateral membrane of the human proximal convoluted tubule. Because *SLC2A9* can be partially inhibited by drugs, including probenecid, losartan, and benzbromarone, and considering that it affects serum uric acid levels, it may be a potentially novel target for pharmacologic intervention to prevent or treat disorders related to serum uric acid.

The *SF1* rs606458 polymorphism was previously reported in a genome-wide association study of African Americans in 2011 and was also found in individuals of European ancestry^[31]. However, in East Asians, and particularly in Chinese populations, there is no evidence confirming the association between *SF1* (rs606458) and uric acid. In our study, this SNP demonstrated obvious correlations with uric acid. However, in the two populations (African American and East Asian), a reciprocal relationship between rs606458 and uric acid was observed ($\beta=4.206$ in Chinese and $\beta=-0.180$ in African American individuals). Because the allele frequencies of rs606458 (0.354 in Chinese vs 0.650 in African Americans for G allele) as well as the linkage disequilibrium patterns differ between the African American and Chinese populations, rs606458 is only the genetic marker that may be directly linked to uric acid concentrations in the Chinese population specifically.

We found that the rs780094 variant in *GCKR* more substantially affected uric acid concentrations in males compared to females. This gender distinction in regulating uric acid levels was first reported in the Chinese population. The *GCKR* gene encodes a regulator of glucokinase, which is the first glycolytic enzyme responsible for glucose phosphorylation in the liver^[29]. Recently, genome-wide association studies focusing on type 2 diabetes and glucose-related traits have identified *GCKR* rs780094 polymorphisms to be associated with triglyceride, fasting plasma glucose levels and type 2 diabetes^[32-35]. However, its association with serum uric acid was independent of triglyceride and fasting plasma glucose levels in the men after adjusting age, BMI, and triglyceride and fasting plasma glucose levels as the confounding factors. In our study, no significant evidence of the existence of the influence of gender on the association of *GCKR* rs780094 with serum uric acid levels was found. The causative mechanisms underlying the effects of gender on the association of this variant with serum uric acid levels requires further investigation.

In females, only *SLC22A12* (rs506338) showed a marginally significant association with uric acid. This variant has been previously reported in Japanese individuals to be significantly correlated with uric acid levels, but gender differences were not detected. However, specific physiological characteristics of females may be related to the gender differences observed in the associations of the SNPs with uric acid levels. For example, estrogen levels may increase the renal clearance of serum uric acid^[25]. However, the underlying mechanism remains to be elucidated.

The concentrations of serum uric acid and creatinine levels are biochemical indicators of kidney function that are commonly used in clinical practice. Because the presence of elevated serum creatinine levels is a risk factor for cardiovascular disease, all-cause mortality, and end-stage renal disease^[36-38], it is equally important to identify and replicate genes associated with serum creatinine levels. However, few studies have explored the genetic heritability of serum creatinine levels to date. In this study, we also analyzed the association of uric acid-related SNPs with serum creatinine levels and found associations involving the variants in *GCKR* and *SLC2A9* in the males. Those SNPs identified by the genome-wide association study to be correlated with serum uric acid levels require further confirmation by large-scale association studies to determine whether they may play roles in regulating serum creatinine levels.

Although we showed that *SLC2A9*, *SF1*, and *GCKR* were associated with serum uric acid levels, there were limitations to our study. First, the small sample size may have caused the allele frequencies estimated in the population to be biased. In addition, because gender differences have been previously reported in the association of *GCKR* rs780094 with uric acid levels but were not observed in this study, a larger number of participants are needed to verify these findings in the Chinese population. Second, we did not adjust for lifestyle factors, such as alcohol consumption and cigarette smoking, as confounding factors. The interaction between lifestyle and these genetic variants on serum uric acid levels remains unknown. Third, only the reported SNP(s) from each locus was analyzed in the current study. Because differences exist in allele frequencies as well as linkage disequilibrium patterns between East Asians and Europeans, detailed analyses of additional SNPs from each locus in East Asians, and particularly in the Chinese population, may help to identify the causal variant. Fourth, because rs16890979 and rs17300741 are rare in the Chinese population, the present study had limited power to detect the effects of these SNPs on serum uric acid levels. Finally, the positive results in the present study need further replication because we did not perform multiple comparisons.

In conclusion, we showed that the *SLC2A9* rs11722228, *SF1* rs606458 and *GCKR* rs780094 variants modulated uric acid levels in Chinese males, while *SF1* rs606458 and *SLC2A9* rs3775948 were associated with uric acid levels in the combined group, which included both males and females. These findings suggest that genetic variation strongly influences the regulation of serum uric acid levels in humans.

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Author contribution

Cheng HU and Wei-ping JIA conceived and designed the experiments. Xue SUN, Dan-feng PENG, Feng JIANG, and Rong ZHANG performed the experiments. Xue SUN and Cheng HU analyzed the data. Cheng HU, Shan-shan TANG, Miao CHEN, Jing YAN, Tao WANG, Shi-yun WANG, and Yu-qian BAO contributed reagents/materials/analysis tools. Xue SUN and Cheng HU drafted the manuscript. All authors contributed to writing of this manuscript, and read and approved the final version.

Supplementary information

Supplementary Figures are available at the *Acta Pharmacologica Sinica's* web site.

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