

Examining an Association of Single Nucleotide Polymorphisms with Hyperuricemia in Chinese Flight Attendants

Jianpin Ye^{1,*}, Zhiwei Zeng^{2,*}, Yuxian Chen³, Zhenkun Wu³, Qingwei Yang⁴, Tao Sun²

¹Outpatient Department Laboratory, Xiamen Aviation, Xiamen, Fujian, People's Republic of China; ²Center for Precision Medicine, School of Medicine and School of Biomedical Sciences, Huaqiao University, Xiamen, Fujian, People's Republic of China; ³Taokang Institute of Neuro Medicine, Xiamen, Fujian, People's Republic of China; ⁴Department of Neurology, Zhongshan Hospital, School of Medicine, Xiamen University, Xiamen, Fujian, People's Republic of China

*These authors contributed equally to this work

Correspondence: Tao Sun, Center for Precision Medicine, School of Medicine and School of Biomedical Sciences, Huaqiao University, Xiamen, Fujian, People's Republic of China, Email taosun@hqu.edu.cn

Background: Both genetic and environmental factors strongly affect serum uric acid (SUA) concentrations. The incidence of hyperuricemia tends to be younger in the Chinese population. In particular, we have found a high prevalence of hyperuricemia among Chinese flight attendants, aged from 20 to 40, in our survey. This study aims to evaluate whether there is an association between gene polymorphisms and hyperuricemia among Chinese flight attendants.

Methods: A total of 532 flight attendants with high and normal serum uric acid levels were recruited. Allele-specific polymerase chain reaction (AS-PCR) was performed using blood samples of enrolled subjects.

Results: Previous studies have reported single nucleotide polymorphisms (SNPs) that are tightly associated with uric acid levels. Among them, six SNPs that are strongly associated with SUA or gout in Asians, for instance *ABCG2* (rs2231142, rs72552713 and rs2231137), *GCKR* (rs780094), *SLC2A9* (rs1014290) and *SLC17A1* (rs1183201), were selected for AS-PCR analyses. We found that SNPs such as *ABCG2* rs2231142, *GCKR* rs780094 and *SLC2A9* rs1014290 are strongly associated with hyperuricemia in male flight attendants, and *SLC2A9* rs1014290 among female flight attendants.

Conclusion: Our study provides evidences of an association between SNPs and hyperuricemia in the Chinese flight attendants, and highlights the significance of improving diagnostics and prevention of disease development in uric acid metabolism disorders and gout using these SNPs.

Keywords: serum uric acid, hyperuricemia, single nucleotide polymorphisms, flight attendants

Introduction

Hyperuricemia is mainly caused by elevated purine metabolism or abnormal uric acid excretion, which is related to diet, environment and heredity.^{1,2} Uric acid (UA) is the final product of purine metabolism. Hyperuricemia is usually diagnosed when the concentration of serum uric acid (SUA) is higher than 420 $\mu\text{mol/L}$ (7.0 mg/dL) in men and 360 $\mu\text{mol/L}$ (6.0 mg/dL) in premenopausal women.^{3,4} Hyperuricemia has been considered closely related to the development of gout, kidney disease, cardiovascular disease, diabetes and other disorders.^{1,3-8} Gout is a chronic disease characterized by acute arthritis symptoms such as pain, swelling, heat, redness in the affected joint, which can cause difficulty of walking and other activities.⁹ Moreover, renal underexcretion of urate is a major contributor to hyperuricemia.¹⁰ In mainland China, the prevalence of hyperuricemia is about 13.3%, with a significantly higher prevalence in men (19.4%) than that in women (7.9%).¹¹

In recent years, precision medicine has drawn a significant attention. Precision medicine is the practice of providing tailored and efficient diagnostics and treatments for patients based on individual genetic characteristics, including single-nucleotide polymorphisms (SNPs).^{12,13} Studies have shown that the genetic effect on uric acid levels is estimated to

account for 40–70%.¹⁴ Genetic variations such as SNPs can lead to differential uric acid excretion through altering the functions of urate transporters.^{2,15} Some dysfunctional SNP variants increase the risk of hyperuricemia and gout, affect the age of onset of hyperuricemia/gout, and are highly associated with a familial hyperuricemia/gout history.¹⁶

In particular, studies have indicated that the SUA concentration is affected by gene-environmental interactions, and the genetic effect on uric acid levels is different in different regions of the population.^{2,17–19} For instance, a genome-wide association study identified two genetic loci (*SLC2A9* and *ABCG2*) affecting SUA concentrations in the Chinese population.¹⁹ *GCKR* ($P = 5.12 \times 10^{-6}$) and *SLC17A1* ($P = 1.73 \times 10^{-3}$) genetic variants associated with serum uric acid levels were detected in a genome-wide association study in the Japanese population.²⁰ A case-control study replicated and confirmed that *GCKR* and *SLC17A1* are associated with SUA and gout in Chinese.²¹ In particular, the most common dysfunction variant *ABCG2* rs2231142 increases the risk of gout and hyperuricemia in different regions including Asia.^{22–26} *ABCG2* rs72552713 has been widely studied in Asian populations, and 1–2 alleles (A) of rs72552713 have been proved to be associated with an increased risk of hyperuricemia and gout in Asian populations.^{4,26–28} The *ABCG2* rs2231137 variant is identified as a protective effect from gout with high probability²⁹ and reduces the risk of gout by approximately 36–57% in Asians.²⁶ The protective effect of *GCKR* rs780094 polymorphism on SUA concentration and hyperuricemia was first found in a GWAS of European ancestry³⁰ and was subsequently confirmed in Japanese and Chinese populations.^{19,20} The SNP rs1014290 G allele of *SLC2A9* has been reported to protect against gout and hyperuricemia in Asian populations,^{31–33} and homozygous loss-of-function mutations in *SLC2A9* cause massive renal hypouricemia via total loss of uric acid absorption.³⁴ In a GWAS and a case-control study, *SLC17A1* rs1183201 polymorphism was confirmed to be associated with SUA concentrations in Japanese population and Han Chinese.^{20,21} Therefore, revealing SNPs associated with serum uric acid levels in a specific population will help better understanding the prevalence of hyperuricemia and gout.

Noticeably, recent studies have shown that the incidence of hyperuricemia tends to be younger in the Chinese population.^{35,36} Interestingly, we have found a high prevalence of hyperuricemia among Chinese flight attendants, aged from 20 to 40, in our survey. The demanding tasks and unique working environment such as exposing in cosmic radiation, poor cabin air quality, hypoxia and vibrations make flight attendants become more prone to poor health conditions, for instance fatigue, musculoskeletal disorders, cancer, heart disease, depression and sleep disorders.^{37–42} Thus, we questioned whether it is a coincidence or there is a genetic reasoning of high prevalence of hyperuricemia in Chinese flight attendants.

In this study, to investigate the association of genetic variants with the risk of hyperuricemia among Chinese flight attendants, we selected and examined variants of six SNPs in *ABCG2*, *GCKR*, *SLC2A9* and *SLC17A1* genes, which have been reported to be strongly associated with SUA or gout in Asians. We have found that SNPs such as *ABCG2* rs2231142, *GCKR* rs780094 and *SLC2A9* rs1014290 are associated with hyperuricemia in male flight attendants. Our study has highlighted potential genetic variants that may help early prevention of hyperuricemia and gout, in particular among flight attendants.

Materials and Methods

Participants

We recruited 4114 Chinese flight attendants, including 867 males and 3247 females, for basic physical examinations from the Xiamen Aviation, Xiamen, Fujian, China from May 2020 to September 2021. Serum uric acid (SUA) levels of the participants under normal purine diet were measured after fasting. Hyperuricemia was determined when the concentration of SUA is higher than 420 $\mu\text{mol/L}$ (7.0 mg/dL) in males and higher than 360 $\mu\text{mol/L}$ (6.0 mg/dL) in females. Demographic characteristics and medical history of the participants were collected by questionnaires.

To explore the association of gene polymorphisms with hyperuricemia, 532 subjects were selected from the 4114 flight attendants for genotyping analyses. Among the 532 subjects, 276 subjects with high SUA levels, including 160 males and 116 females, were grouped as a hyperuricemia group. 256 subjects with normal SUA levels, including 138 males and 118 females, were randomly selected and grouped as a control group. These subjects were selected according to the following inclusion criteria: (1) no history of gout or acute onset of gouty arthritis. (2) no history of significant liver or renal dysfunction. (3) no history of cardiovascular disease, hypertension, diabetes and active malignancy. (4) no treatment with an anti-hyperuricemia agent or diuretics within 4 weeks before the start of the study (Table 1). Physical conditions of enrolled subjects, including age, body mass index (BMI), uric acid, fasting serum glucose, ratio of aspartate

Table 1 Information of 532 Selected Subjects

| | 532 Selected Subjects |
|-----------------------------|---|
| Age range, years | 20–40 |
| Sex ratio, males/females | 298/234 |
| BMI rang, Kg/m ² | 15.00–27.00 |
| Medical history | (1) No history of gout or acute onset of gouty arthritis. (2) No history of significant liver or renal dysfunction. (3) No history of cardiovascular disease, hypertension, diabetes and active malignancy. (4) No treatment with an anti-hyperuricemia agent or diuretics within 4 weeks before the start of the study. |

Abbreviation: BMI, body mass index.

aminotransferase/alanine aminotransferase (AST/ALT), direct bilirubin (DBIL), albumin, cholesterol, blood urea nitrogen (BUN) and lactate dehydrogenase (LDH) were examined.

The study was in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethical Committee of the Xiamen Aviation and the Quanzhou First Hospital (20162016). Each subject provided written informed consent before participating.

Processes

Peripheral blood samples were collected from 532 enrolled subjects. Physical examinations were conducted and plasma samples were used for standard biochemical tests.

Blood sample DNA was extracted using the blood genomic DNA Midi kit (Jiangsu Conway Century Biotechnology Co., Ltd., China), according to the manufacturer's instructions. Polymorphisms of the six SNPs including *ABCG2* (rs2231142, rs72552713 and rs2231137), *GCKR* (rs780094), *SLC2A9* (rs1014290) and *SLC17A1* (rs1183201) were examined using allele-specific polymerase chain reaction (AS-PCR). The Primer Premier 5 software was used, and specific wild-type (W) and mutant (M) primers were designed according to the principles of base complementary pairing and mismatch (Table 2).

PCR amplification was performed in a 20 µL volume reaction, containing 10 µL 2 × STBR Green PCR Master Mix (Beijing Biterbo Biotechnology Co., Ltd., Beijing, China), 7.6 µL DNase-free water, 0.4 µL ROX Reference, 0.5 µL primers and 50 ng DNA. DNA was denatured at 95°C for 30s, followed by 40 cycles of denaturation at 95°C for 5s, annealing and extension at 60°C for 30s, running in an Applied Biosystems Quant Studio 6 (Applied Biosystems, USA). The results were analyzed using the QuantStudio 6 Flex Real-Time PCR system (Applied Biosystems, USA). The genotypes were interpreted according to ΔC_t calculation and analysis. Some genotypes were further verified using the Sanger sequencing.

Statistical Analysis

The SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The biochemical baseline characteristics of the two groups were analyzed using Student's *t*-test. A one-way analysis of variance (ANOVA) was used to evaluate differences in SUA levels within each genotype. Data were presented as mean ± standard deviation (SD). Categorical variables, including Hardy-Weinberg equilibrium (HWE), differences in single gene frequency and genotype distribution between two groups were estimated by Chi-Square test. Moreover, the HWE, odds ratio (OR) values, 95% confidence intervals (95% CI) and differences of genotypes and allele frequency between the two groups were analyzed to verify SNPs by using the SHEsis platform (<http://analysis.bio-x.cn/myAnalysis.php>).⁴³ Logistic regression analysis was applied to adjust for covariates differentially distributed in case-control cohorts. *P* value <0.05 was considered to be statistically significant (double tail).

Table 2 Six SNPs and Primer Sequences for PCR Analyses

| SNP | Loci Gene | Chr | Position | Variant | Alleles | PCR Primer Sequences (5'-3') | Length of PCR Product |
|--------------------|-----------|-----|----------|-------------|---------|---|-----------------------|
| rs2231142 (Q141K) | ABCG2 | 4 | 88131171 | Missense | G > T | W-F: CCGAAGAGCTGCTGACAACTG M-F: GCCGTAGAGCTGCTGAGAACTT R: TTATAGCAGGCTTTGCAGACATC | 247 bp |
| rs72552713 (Q126X) | ABCG2 | 4 | 88131805 | Stop Gained | G > A | F: AGATTCTCCCTGCCTTTTCACA W-R: AAATGTAATCCGGTTACGTGGTAC M-R: AAATGTAATCCGGTTACGTGGTAT | 204 bp |
| rs2231137 (V12M) | ABCG2 | 4 | 88139962 | Missense | C > T | W-F: ATTGGCGTTTCCTTGTGACAC M-F: CCATTGGTGTTTCCTTGTGTCAT R: ATGTTCTTATCACAAATGGTATGGGC | 226 bp |
| rs780094 | GCKR | 2 | 27518370 | Intron | T > C | W-F: TCAGCAAATGTATTGATCAGCAAAT M-F: TCAGCAAATGTATTGATCAGCAAAC R: GATTCAATCCACTAAACCACAGGC | 120 bp |
| rs1014290 | SLC2A9 | 4 | 10000237 | Intron | G > A | W-F: AGTGCACAAGATACTGATCTGCG M-F: AAGTGCACAAGATACTGATCGACA R: GTTCTGTAGGTGTCCTCATTGTTC | 228 bp |
| rs1183201 | SLC17A1 | 6 | 25823216 | Intron | A > T | F: ATATGCTGCCTGTCGCTGTAAC W-R: AGCCAAAAAAGTGAACCTAT M-R: AGCCAAAAAAGTGAACCTAA | 257 bp |

Abbreviations: Chr, chromosome; PCR, polymerase chain reaction; W, wide type; M, mutant; F, forward primer; R, reverse primer; bp, base pair.

Results

Prevalence of Hyperuricemia Among Recruited Flight Attendants

To investigate whether there is an association of genetic variants with the risk of hyperuricemia among Chinese flight attendants, we recruited 4114 flight attendants, including 867 males and 3247 females, for basic physical examinations. The average age of the participants was 27.14 ± 4.85 years old (26.60 ± 4.33 years old in males, 27.29 ± 4.98 in females). The mean levels of serum uric acid (SUA) were 322.12 ± 81.97 $\mu\text{mol/L}$ (424.99 ± 79.18 $\mu\text{mol/L}$ in males, 294.69 ± 57.15 $\mu\text{mol/L}$ in females), equivalent to 5.42 ± 1.38 mg/dL (7.15 ± 1.33 mg/dL in males, 4.96 ± 0.96 mg/dL in females).

The ages and SUA levels showed significant sex differences. Among 867 male flight attendants, 427 (49.25%) had higher SUA levels (above 420 $\mu\text{mol/L}$ (7.0 mg/dL)), and among 3247 female flight attendants, 381 (11.73%) displayed higher SUA levels (above 360 $\mu\text{mol/L}$ (6.0 mg/dL)) (Table 3). Our study indicates that among recruited flight attendants, male flight attendants show an elevated prevalence of hyperuricemia than females. Interestingly, both male and female

Table 3 Numbers of Hyperuricemia and Control Groups Among Recruited Flight Attendants

| | Males | Females | Total |
|--|--------|---------|--------|
| Hyperuricemia group | 427 | 381 | 808 |
| Control group | 440 | 2866 | 3306 |
| All subjects | 867 | 3247 | 4114 |
| Prevalence rate of hyperuricemia (Flight attendants) | 49.25% | 11.73% | 19.64% |
| Prevalence rate of hyperuricemia (Chinese populations) | 19.4% | 7.9% | 13.3% |

Note: Hyperuricemia is defined as the SUA level higher than 420 $\mu\text{mol/L}$ (7.0 mg/dL) in males and 360 $\mu\text{mol/L}$ (6.0 mg/dL) in females.

flight attendants display greatly higher prevalence of hyperuricemia than the overall Chinese population, which is 19.4% in men and 7.9% in women¹¹ (Table 3).

Physical Examinations of Recruited Flight Attendants

We further selected 276 subjects with high SUA levels as a hyperuricemia group. 256 subjects with normal SUA levels as a control group according to the inclusion criteria (Table 1).

Basic physical examinations were performed among selected 532 subjects (Table 4). In all subjects, individuals in the hyperuricemia group were younger in the age, had higher levels of cholesterol and lactate dehydrogenase (LDH), compared to the control group (Table 4). There was no significant difference in body mass index (BMI), in levels of fasting serum glucose, aspartate aminotransferase/alanine aminotransferase (AST/ALT), direct bilirubin (DBIL), albumin and blood urea nitrogen (BUN) between the two groups. Subjects in the male hyperuricemia group were younger in the age, and displayed a lower ratio of AST/ALT and a higher level of LDH, while those in the female group also were younger, and showed a higher ratio of AST/ALT and the level of cholesterol, compared to their respective controls ($P < 0.05$). These data suggest that flight attendants with hyperuricemia are overall in normal physical conditions.

Association of Genetic Variants with Hyperuricemia in Male Flight Attendants

Because male flight attendants showed a higher prevalence of elevated SUA than males of the Chinese population (Table 3), we examined whether there is a link of genetic variants with hyperuricemia in recruited male hyperuricemia and control groups. Previous studies have reported that polymorphisms of *ABCG2*, rs2231142 (Q141K), rs72552713 (Q126X) and rs2231137 (V12M); *GCKR*, rs780094; *SLC2A9*, rs1014290 and *SLC17A1*, rs1183201 might be associated with hyperuricemia,^{21,26,44,45} we thus decided to analyze these six SNPs among studied subjects by performing AS-PCR (Table 2). Except the SNP rs2231137 of *ABCG2* ($P < 0.05$ in controls), genotype distributions of other SNPs in the two groups were in accordance with the Hardy-Weinberg equilibrium (HWE) test ($P > 0.05$).²⁷ Therefore, we conducted SNP analyses only on the congruent 5 gene loci (Table 5).

Table 4 Physical Examinations of Hyperuricemia and Control Groups

| Physical Examinations | Males (n = 298) | | | Females (n = 234) | | | All Subjects (n = 532) | | |
|-------------------------------|-------------------------------|-------------------------|-------------------|-------------------------------|-------------------------|-------------------|-------------------------------|-------------------------|-------------------|
| | Hyperuricemia Group (n = 160) | Control Group (n = 138) | P value | Hyperuricemia Group (n = 116) | Control Group (n = 118) | P value | Hyperuricemia Group (n = 276) | Control Group (n = 256) | P value |
| Age, years | 26.11 ± 3.61 | 26.99 ± 3.37 | 0.007 | 26.82 ± 4.23 | 27.52 ± 3.16 | 0.020 | 26.40 ± 3.89 | 27.26 ± 3.29 | < 0.001 |
| BMI, Kg/m ² | 20.73 ± 2.46 | 20.51 ± 2.59 | 0.74 | 20.16 ± 2.60 | 20.87 ± 3.43 | 0.29 | 20.41 ± 2.54 | 20.74 ± 3.14 | 0.49 |
| Uric acid, μmol/L | 502.10 ± 56.58 | 362.07 ± 39.39 | < 0.001 | 419.33 ± 56.02 | 275.60 ± 45.76 | < 0.001 | 467.31 ± 69.56 | 322.21 ± 60.50 | < 0.001 |
| Fasting serum glucose, mmol/L | 5.30 ± 0.43 | 5.31 ± 0.36 | 0.56 | 5.18 ± 0.45 | 5.26 ± 0.37 | 0.14 | 5.25 ± 0.44 | 5.29 ± 0.36 | 0.18 |
| AST/ALT | 0.92 ± 0.39 | 1.06 ± 0.47 | 0.006 | 1.43 ± 0.49 | 1.24 ± 0.27 | 0.004 | 1.14 ± 0.50 | 1.14 ± 0.40 | 0.29 |
| DBIL, μmol/L | 6.96 ± 2.55 | 6.91 ± 2.31 | 0.84 | 5.85 ± 2.15 | 5.43 ± 2.03 | 0.13 | 6.49 ± 2.45 | 6.23 ± 2.31 | 0.24 |
| Albumin, g/L | 48.59 ± 2.20 | 48.27 ± 2.23 | 0.28 | 47.41 ± 2.55 | 47.14 ± 2.10 | 0.39 | 48.09 ± 2.42 | 47.75 ± 2.24 | 0.081 |
| Cholesterol, mmol/L | 4.85 ± 0.86 | 4.68 ± 0.85 | 0.061 | 4.84 ± 0.76 | 4.63 ± 0.76 | 0.018 | 4.85 ± 0.82 | 4.65 ± 0.81 | 0.003 |
| BUN, mmol/L | 4.86 ± 1.10 | 4.87 ± 1.01 | 0.81 | 4.36 ± 1.10 | 4.07 ± 0.98 | 0.052 | 4.65 ± 1.12 | 4.50 ± 1.08 | 0.21 |
| LDH, U/L | 163.65 ± 29.00 | 160.01 ± 45.41 | 0.029 | 152.91 ± 36.45 | 147.89 ± 20.50 | 0.069 | 159.13 ± 32.71 | 154.42 ± 36.57 | 0.003 |

Notes: The Student's t-test was used to evaluate differences of physical examinations in two groups. Variables are summarized as mean ± standard deviation (SD). P values < 0.05 were shown in bold and were considered to be statistically significant.

Abbreviations: BMI, body mass index; AST/ALT, aspartate aminotransferase/alanine aminotransferase; DBIL, direct bilirubin; BUN, blood urea nitrogen; LDH, lactate dehydrogenase.

Table 5 Allele Frequencies and Genotype Distributions of Six SNPs Among Flight Attendants

| SNP | Variants | | Males (n = 298) | | | | | Females (n = 234) | | | | | All Subjects (n = 532) | | | | |
|-------------------------|--------------------|-------|-------------------------------|-------------------------|------|-----------|---------|-------------------------------|-------------------------|------|-----------|---------|-------------------------------|-------------------------|------|------------|---------|
| | | | Hyperuricemia Group (n = 160) | Control Group (n = 138) | OR | 95% CI | P value | Hyperuricemia Group (n = 116) | Control Group (n = 118) | OR | 95% CI | P value | Hyperuricemia Group (n = 276) | Control Group (n = 256) | OR | 95% CI | P value |
| ABCG2 rs2231142 (Q141K) | Allele, n (freq) | G | 210 (65.6%) | 215 (77.9%) | 1.85 | 1.28–2.66 | 0.001 | 146 (62.9%) | 159 (67.4%) | 1.22 | 0.83–1.78 | 0.31 | 356 (64.5%) | 374 (73.0%) | 1.49 | 1.15–1.94 | 0.0027 |
| | | T | 110 (34.4%) | 61 (22.1%) | | | | 86 (37.1%) | 77 (32.6%) | | | | 196 (35.5%) | 138 (27.0%) | | | |
| | Genotype, n (freq) | GG | 69 (43.1%) | 83 (60.1%) | - | - | 0.0044 | 47 (40.5%) | 51 (43.2%) | - | - | 0.33 | 116 (42.0%) | 134 (52.3%) | - | - | 0.008 |
| | | GT | 72 (45.0%) | 49 (35.5%) | | | | 52 (44.8%) | 57 (48.3%) | | | | 124 (44.9%) | 106 (41.4%) | | | |
| | | TT | 19 (11.9%) | 6 (4.4%) | | | | 17 (14.7%) | 10 (8.5%) | | | | 36 (13.0%) | 16 (6.3%) | | | |
| | | HWE P | 0.97 | 0.71 | | | | | | | | | 0.67 | 0.28 | | | |
| ABCG2 rs2231137 (Q126X) | Allele, n (freq) | G | 318 (99.4%) | 274 (99.3%) | 0.86 | 0.12–6.16 | 0.88 | 230 (99.1%) | 236 (100%) | - | - | 0.15 | 548 (99.3%) | 510 (99.6%) | 1.86 | 0.34–10.21 | 0.47 |
| | | A | 2 (0.6%) | 2 (0.7%) | | | | 2 (0.9%) | 0 (0.0%) | | | | 4 (0.7%) | 2 (0.4%) | | | |
| | Genotype, n (freq) | GG | 158 (98.7%) | 136 (98.5%) | - | - | 0.99 | 114 (98.3%) | 118 (100%) | - | - | 0.36 | 272 (98.5%) | 254 (99.2%) | - | - | 0.77 |
| | | GA | 2 (1.3%) | 2 (1.5%) | | | | 2 (1.7%) | 0 (0.0%) | | | | 4 (1.5%) | 2 (0.8%) | | | |
| | | AA | 0 (0.0%) | 0 (0.0%) | | | | 0 (0.0%) | 0 (0.0%) | | | | 0 (0.0%) | 0 (0.0%) | | | |
| | | HWE P | 0.94 | 0.93 | | | | | | | | | 0.92 | - | | | |
| ABCG2 rs2231137 (V12M) | Allele, n (freq) | C | 222 (69.4%) | 169 (61.2%) | 0.70 | 0.50–0.98 | 0.037 | 172 (74.1%) | 156 (66.1%) | 0.68 | 0.46–1.01 | 0.058 | 394 (71.4%) | 325 (63.5%) | 0.70 | 0.54–0.90 | 0.006 |
| | | T | 98 (30.6%) | 107 (38.8%) | | | | 60 (25.9%) | 80 (33.9%) | | | | 158 (28.6%) | 187 (36.5%) | | | |
| | Genotype, n (freq) | CC | 76 (47.5%) | 45 (32.6%) | - | - | 0.032 | 65 (56.0%) | 50 (42.4%) | - | - | 0.11 | 141 (51.1%) | 95 (37.1%) | - | - | 0.0051 |
| | | CT | 70 (43.7%) | 79 (57.3%) | | | | 42 (36.2%) | 56 (47.5%) | | | | 112 (40.6%) | 135 (52.7%) | | | |
| | | TT | 14 (8.8%) | 14 (10.1%) | | | | 9 (7.8%) | 12 (10.2%) | | | | 23 (8.3%) | 26 (10.2%) | | | |
| | | HWE P | 0.70 | 0.016 | | | | | | | | | 0.55 | 0.52 | | | |

| | | | | | | | | | | | | | | | | | |
|----------------------|-----------------------|----------|-------------|-------------|------|---------------|--------|-------------|-------------|------|---------------|-------|-------------|-------------|------|---------------|--------|
| GCKR rs780094 | Allele, n (freq) | T | 191 (59.7%) | 134 (48.6%) | 0.64 | 0.46– 0.88 | 0.0065 | 133 (57.3%) | 122 (51.7%) | 0.80 | 0.55– 1.15 | 0.22 | 324 (58.7%) | 256 (50.0%) | 0.70 | 0.55– 0.89 | 0.0044 |
| | | C | 129 (40.3%) | 142 (51.4%) | | | | 99 (42.7%) | 114 (48.3%) | | | | 228 (41.3%) | 256 (50.0%) | | | |
| | Genotype, n (freq) | TT | 62 (38.7%) | 32 (23.2%) | - | - | 0.015 | 35 (30.2%) | 28 (23.7%) | - | - | 0.43 | 97 (35.1%) | 60 (23.4%) | - | - | 0.0099 |
| | | TC | 67 (41.9%) | 70 (50.7%) | | | | 63 (54.3%) | 66 (55.9%) | | | | 130 (47.1%) | 136 (53.3%) | | | |
| | | CC | 31 (19.4%) | 36 (26.1%) | | | | 18 (15.5%) | 24 (20.3%) | | | | 49 (17.8%) | 60 (23.4%) | | | |
| | | HWE P | 0.10 | 0.86 | | | | 0.23 | | | | | 0.19 | 0.63 | | | |
| SLC2A9 rs1014290 | Allele, n (freq) | A | 198 (61.9%) | 158 (57.2%) | 0.82 | 0.59– 1.14 | 0.25 | 158 (68.1%) | 136 (57.6%) | 0.64 | 0.44– 0.93 | 0.019 | 356 (64.5%) | 294 (57.4%) | 0.74 | 0.58– 0.95 | 0.018 |
| | | G | 122 (38.1%) | 118 (42.8%) | | | | 74 (31.9%) | 100 (42.4%) | | | | 196 (35.5%) | 218 (42.6%) | | | |
| | Genotype, n (freq) | AA | 56 (35.0%) | 50 (36.2%) | - | - | 0.027 | 52 (44.8%) | 40 (33.9%) | - | - | 0.048 | 108 (39.1%) | 90 (35.2%) | - | - | 0.0046 |
| | | AG | 86 (53.8%) | 58 (42.0%) | | | | 54 (46.6%) | 56 (47.5%) | | | | 140 (50.7%) | 114 (44.5%) | | | |
| | | GG | 18 (11.2%) | 30 (21.7%) | | | | 10 (8.6%) | 22 (18.6%) | | | | 28 (10.1%) | 52 (20.3%) | | | |
| | | HWE P | 0.078 | 0.097 | | | | 0.44 | | | | | 0.76 | 0.074 | | | |
| SLC17A1 rs1183201 | Allele, n (freq) | A | 53 (16.6%) | 52 (18.8%) | 1.17 | 0.77– 1.78 | 0.47 | 38 (16.4%) | 34 (14.4%) | 0.86 | 0.52– 1.42 | 0.55 | 91 (16.5%) | 86 (16.8%) | 1.02 | 0.74– 1.41 | 0.89 |
| | | T | 267 (83.4%) | 224 (81.2%) | | | | 194 (83.6%) | 202 (85.6%) | | | | 461 (83.5%) | 426 (83.2%) | | | |
| | Genotype, n (freq) | AA | 4 (2.5%) | 6 (4.3%) | - | - | 0.65 | 4 (3.4%) | 5 (4.2%) | - | - | 0.59 | 8 (2.9%) | 11 (4.3%) | | | 0.61 |
| | | AT | 45 (28.1%) | 40 (29.0%) | | | | 30 (25.9%) | 24 (20.3%) | | | | 75 (27.2%) | 64 (25.0%) | | | |
| | | TT | 111 (69.4%) | 92 (66.7%) | | | | 82 (70.7%) | 89 (75.4%) | | | | 193 (69.9%) | 181 (70.7%) | | | |
| | | HWE P | 0.82 | 0.53 | | | | 0.55 | | | | | 0.057 | 0.82 | | | |

Notes: Differences in allele frequency and genotype distributions between two groups were analyzed by using the Chi-square test. *P* values < 0.05 were shown in bold and were considered to be statistically significant.

Abbreviations: OR, odds ratio; CI, confidence intervals; n, number of subjects; Freq, frequency; HWE *P*, Hardy-Weinberg equilibrium *P* value.

Among male flight attendants, the frequency of the minor T allele of the *ABCG2* rs2231142 (Q141K) variant reached 34.4% in the hyperuricemia group and 22.1% in the control. The genotype frequencies of the SNP rs2231142 were 43.1% for GG, 45.0% for GT, and 11.9% for TT in the hyperuricemia group, and were 60.1% for GG, 35.5% for GT, and 4.4% for TT in the control (Table 5). Genotyping results of *ABCG2* rs2231142 were further verified using Sanger sequencing (Figure 1). Moreover, the frequency of the minor A allele in the rs72552713 (Q126X) of *ABCG2* was 0.6% in the hyperuricemia group and 0.7% in controls. No significant difference in the distribution of genotypes and allele in rs72552713 ($P > 0.05$) was observed between the two groups. These results indicate that the T allele, GT and TT genotypes in rs2231142 of *ABCG2* have a significantly higher frequency in the male hyperuricemia group than in the male control.

Furthermore, a logistic regression analysis was performed using variants of *ABCG2* rs2231142 and each of the confounding factors associated with the hyperuricemia in males (Table 6). After adjustments for ages, AST/ALT and LDH, we found that the T allele of *ABCG2* rs2231142 increases the risk of hyperuricemia, and the GT and TT genotypes have significantly higher probability of suffering from hyperuricemia than the ones with GG genotype. These analyses further suggest that carrying the T allele in rs2231142 of *ABCG2* could be a risk factor of hyperuricemia among male flight attendants (Figure 2A).

For the *GCKR* gene, the frequency of the C allele of *GCKR* rs780094 exhibited 40.3% in the hyperuricemia group and 51.4% in the control group (Table 5). The genotype frequencies were 38.7% for TT, 41.9% for TC, and 19.4% for CC in the hyperuricemia group, and were 23.2% for TT, 50.7% for TC, and 26.1% for CC in controls. These data indicate that the C allele, TC and CC genotypes of rs2231142 have a higher frequency in the male control than in the male hyperuricemia group. After adjustments for ages, AST/ALT and LDH, we found that the C allele in rs780094 is likely a protective factor for hyperuricemia development, the TC and CC genotypes exhibit a lower tendency toward hyperuricemia compared to those with the TT genotype (Table 6). However, SUA levels did not show significant differences among the three genotyping groups (Figure 2B). These results suggest that the C allele of *GCKR* rs780094 might have a protective effect on developing hyperuricemia among male flight attendants.

For the SNP *SLC2A9* rs1014290, the frequency of the G allele showed 38.1% in the hyperuricemia group and 42.8% in the control group. The allele distribution of *SLC2A9* rs1014290 did not show a significant difference between the two groups ($P = 0.25$). Genotype frequencies were 35.0% for AA, 53.8% for AG, and 11.2% for GG in the hyperuricemia group, and were 36.2% for AA, 42.0% for AG, and 21.7% for GG in controls (Table 5). After adjustments for ages, AST/ALT and LDH, we showed that the GA and AA genotypes have a higher tendency toward hyperuricemia compared to those with the GG genotype (Table 6). Because subjects with the GG genotype of *SLC2A9* rs1014290 had lower uric acid concentration than those with AA or AG genotypes (Figure 2C), our results suggest that the GG genotype of *SLC2A9* rs1014290 might play a protective role in hyperuricemia development among male flight attendants.

Moreover, for the SNP site of *SLC17A1* rs1183201, the frequency of the T allele showed 83.4% and 81.2% in the hyperuricemia and control group, respectively (Table 5). The frequency distributions of alleles and genotypes did not show statistic differences between the two groups in male flight attendants, suggesting a subtle link of the *SLC17A1* rs1183201 with hyperuricemia.

In summary, our analyses indicate that SNPs such as *ABCG2* rs2231142, *GCKR* rs780094 and *SLC2A9* rs1014290 are likely associated with hyperuricemia in male flight attendants.

Association of Genetic Variants with Hyperuricemia in Female Flight Attendants

We next analyzed whether the above genetic variants are as well associated with hyperuricemia among female flight attendants. We found that for the *ABCG2* gene, the frequencies of the allele and genotypes of SNPs rs2231142 and rs72552713 do not show significant differences between the hyperuricemia and control groups among female flight attendants (Table 5). Similarly, the frequencies of the allele and genotypes of *GCKR* rs780094 and *SLC17A1* rs1183201 did not exhibit significant differences in female flight attendants. These analyses indicate that the genetic variants of *ABCG2*, *GCKR* and *SLC17A1* are unlikely linked with hyperuricemia among female flight attendants.

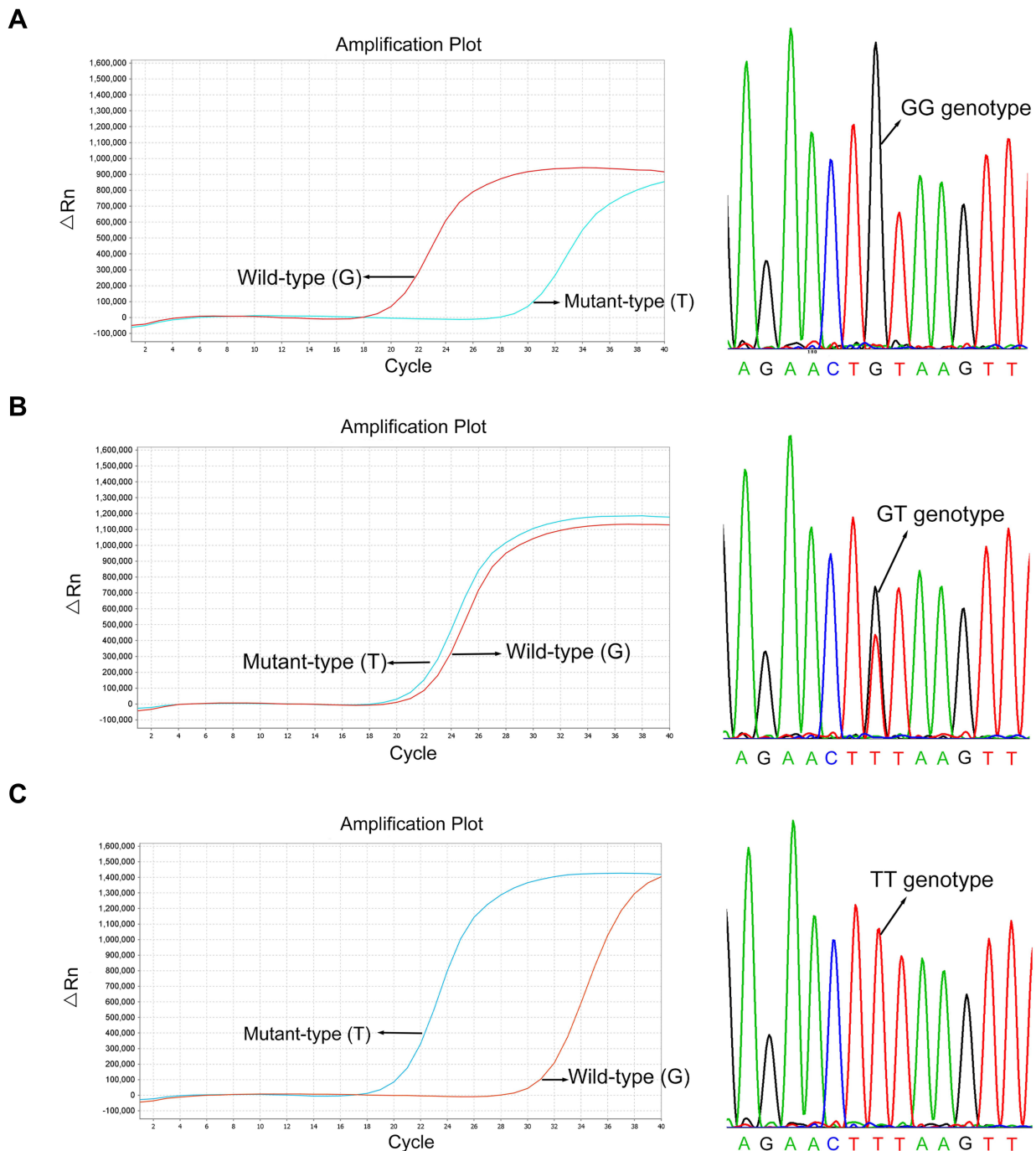


Figure 1 Detection of variants of the *ABCG2* rs2231142 using allele-specific polymerase chain reaction (AS-PCR) and sanger sequencing (right panel). Real-time PCR amplification plots (left panel) and genotype verifications using sequencing were presented in GG genotype (**A**), GT genotype (**B**) and TT genotype (**C**) of the rs2231142. The same set of DNA samples were used for AS-PCR and DNA sequencing.

Noticeably, for the SNP *SLC2A9* rs1014290, the frequencies of A allele showed 68.1% and 57.6% in the hyperuricemia and control groups, respectively (Table 5). Genotype frequencies were 44.8% for AA, 46.6% for AG, and 8.6% for GG in the hyperuricemia group, and were 33.9% for AA, 47.5% for AG, and 18.6% for GG in controls, indicating that distributions of allele and genotypes of rs1014290 are significantly different in female hyperuricemia and control groups (Table 5). After adjustments for ages, AST/ALT and cholesterol, we found that the A allele of *SLC2A9* rs1014290 increases the risk of hyperuricemia, the AA and AG genotypes are associated with an increased risk of hyperuricemia

Table 6 Associations Between the Variants of Three SNPs and Hyperuricemia After Exclusion of Confounders

| SNP | Variants | Males | | | Females | | | All Subjects | | |
|-----------------------------------|----------|-------|-----------|--------------|---------|-----------|--------------|--------------|-----------|--------------|
| | | OR | 95% CI | P value | OR | 95% CI | P value | OR | 95% CI | P value |
| <i>ABCG2</i> rs2231142 (Q141K) | G>T | 1.97 | 1.35–2.89 | 0.001 | 1.13 | 0.76–1.68 | 0.56 | 1.45 | 1.11–1.89 | 0.007 |
| | GG>GT+TT | 2.10 | 1.30–3.40 | 0.003 | 0.96 | 0.55–1.65 | 0.87 | 1.44 | 1.01–2.04 | 0.042 |
| | TT>GG+GT | 0.28 | 0.10–0.75 | 0.012 | 0.53 | 0.22–1.25 | 0.14 | 0.44 | 0.24–0.83 | 0.011 |
| <i>GCKR</i> rs780094 | T>C | 0.61 | 0.44–0.86 | 0.004 | 0.78 | 0.53–1.14 | 0.20 | 0.69 | 0.54–0.88 | 0.003 |
| | TT>TC+CC | 0.48 | 0.28–0.80 | 0.006 | 0.64 | 0.35–1.18 | 0.15 | 0.55 | 0.37–0.81 | 0.002 |
| | CC>TT+TC | 1.66 | 0.94–2.94 | 0.082 | 1.28 | 0.64–2.58 | 0.49 | 1.45 | 0.94–2.23 | 0.09 |
| <i>SLC2A9</i> rs1014290 | G>A | 1.15 | 0.82–1.62 | 0.42 | 1.16 | 1.09–2.39 | 0.018 | 1.32 | 1.03–1.70 | 0.031 |
| | GG>GA+AA | 2.05 | 1.07–3.95 | 0.031 | 2.57 | 1.11–5.96 | 0.028 | 2.20 | 1.33–3.64 | 0.002 |
| | AA>GG+GA | 1.14 | 0.69–1.87 | 0.61 | 0.61 | 0.35–1.06 | 0.081 | 0.87 | 0.60–1.24 | 0.43 |

Notes: Logistic regression analysis was used to exclude confounding factors, *P* value was adjusted for age, AST/ALT and LDH in male flight attendants, AST/ALT and cholesterol in female flight attendants, and cholesterol and LDH in all subjects. *P* values < 0.05 were shown in bold and were considered to be statistically significant.

Abbreviations: OR, odds ratio; CI, confidence intervals.

compared to those with the GG genotype (Table 6). Furthermore, subjects with the AA genotype of *SLC2A9* rs1014290 showed a significantly higher SUA concentration than those carrying AG or GG genotypes (Figure 2D), suggesting that the AA genotype in *SLC2A9* rs1014290 might be a risk factor of hyperuricemia among female flight attendants.

Discussion

Accumulating studies have reported SNPs associated with serum uric acid levels in a specific population. In this study we have detected a higher prevalence rate of hyperuricemia in Chinese flight attendants, and examined variants in six SNPs including *ABCG2* (rs2231142, rs72552713 and rs2231137), *GCKR* (rs780094), *SLC2A9* (rs1014290) and *SLC17A1* (rs1183201). We have provided genetic support of associations between SNPs and the occurrence of hyperuricemia in Chinese flight attendants. Our work should help develop potential SNPs for early diagnostics and prevention of diseases related to specific occupations such as flight attendants.

ABCG2, located on human chromosome 4q22, encodes an ATP-binding cassette transporter, which is responsible for transport and excretion of uric acid in the kidney and intestine.^{46,47} GWAS and meta-analyses have shown the association of *ABCG2* polymorphisms with SUA and hyperuricemia.^{14,17,24,26,30} The link between *ABCG2* variants and hyperuricemia has been shown in populations of different ethnic backgrounds including Asians, Europeans, African Americans, and American Indians.^{48–50} Among common variants of the *ABCG2* gene, rs2231142 (Q141K), rs72552713 (Q126X) and rs2231137 (V12M) are in the uric-acid-related loci. While variants Q141K and Q126X were reported as risk factors that are associated with hyperuricemia and gout, V12M also was identified as a protective variant with high probability in different ethnic groups.²⁹ In particular, the *ABCG2* Q141K minor allele (T) was confirmed to increase the risk of hyperuricemia and promote development of gout.^{22–26} Knock-in mouse model of the human Q141K variant of *ABCG2* showed significant hyperuricemia, which further supports the important role of *ABCG2* in urate excretion.⁴⁷ The minor allele (T) of *ABCG2* rs2231142 had a weaker effect on uric acid level in females.³⁰ In a GWAS study of the Chinese population, the T allele of rs2231142 in *ABCG2* displayed a gender difference with its higher effect on serum uric acid level in males than in females.¹⁹ Moreover, the dysfunctional variants of Q141K and Q126X of *ABCG2* increase the risk of gout and hyperuricemia.^{44,51,52}

In agreement with previous studies, we have found that the variant (carrying minor allele T) of rs2231142 (Q141K) in the *ABCG2* gene is significantly correlated with hyperuricemia among male flight attendants, indicating rs2231142 (Q141K) a risk factor of hyperuricemia among flight attendants. However, the significant association was not found among females. Causal mechanisms of sex-specific differences with the effect of *ABCG2* variants on hyperuricemia or

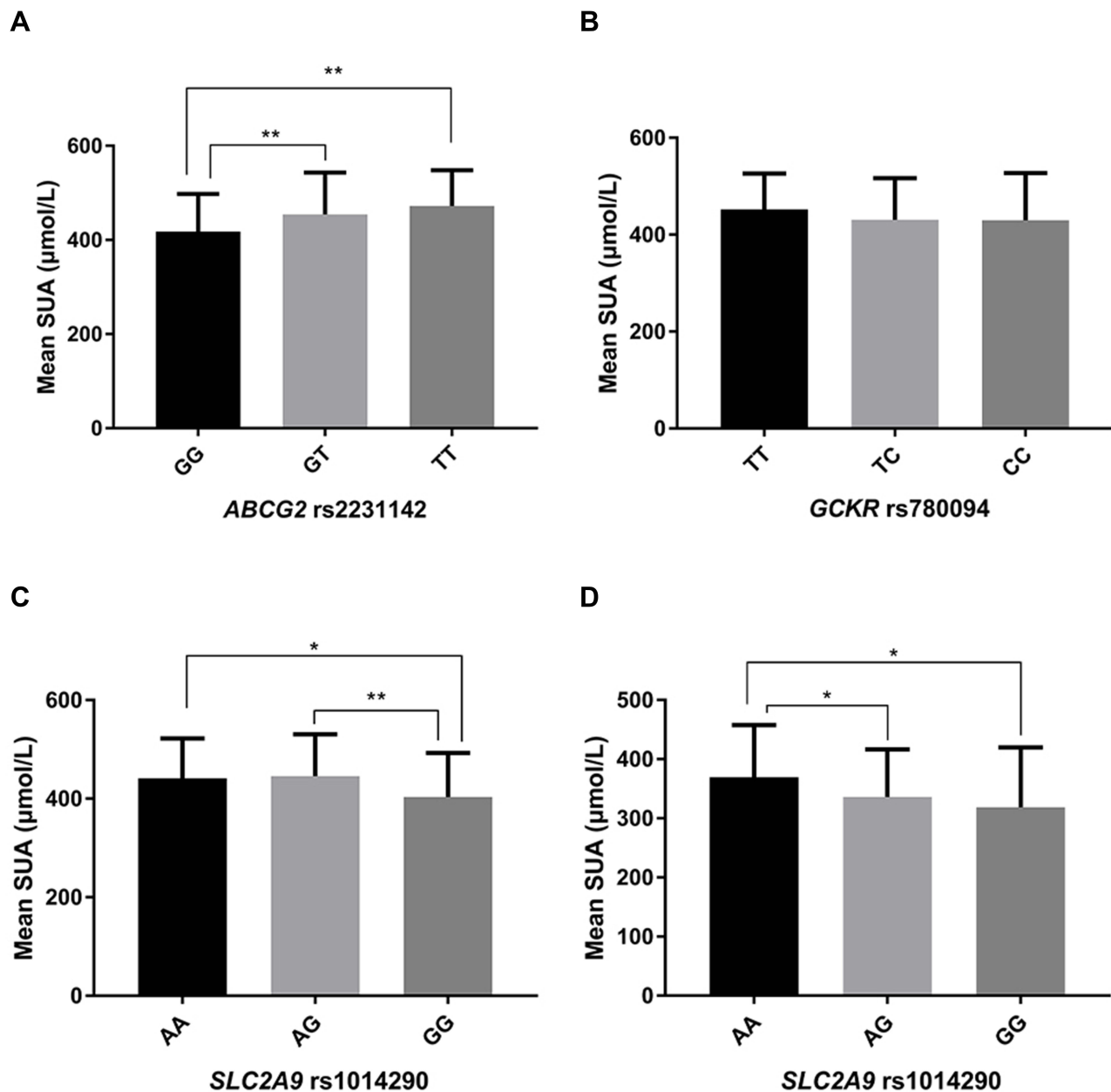


Figure 2 Average levels of serum uric acid (SUA) among different genotypes of SNPs, including *ABCG2* rs2231142 (**A**), *GCKR* rs780094 (**B**), and *SLC2A9* rs1014290 (**C**) in male flight attendants, and *SLC2A9* rs1014290 (**D**) in female flight attendants. Statistical differences between groups were determined by a one-way analysis of variance. $P < 0.05$ was considered to be statistically significant. * $P < 0.05$ and ** $P < 0.01$.

gout are unclear.²³ Studies have suggested that intervene of some hormones (oestrogen and progesterone) might contribute to differences in the regulation of SUA balance between males and females.^{53,54} Moreover, studies have shown that carrying 1–2 minor-allele-genotypes and allele C of rs72552713 (Q126X), and carrying rs2231137 (V12M) are associated with increased risk of hyperuricemia and gout in Asians.^{4,26–28} However, we have not detected significant differences in the distributions of genotypes and allele of these two SNPs between the hyperuricemia and control groups among both male and female flight attendants in this study. This different finding might be caused by the relatively small sample size.

Moreover, the *GCKR* gene, located on chromosome 2p23.2–3, encodes a glucokinase regulatory protein that is involved in regulating glucose metabolism and balance.⁵⁵ Studies have reported that while the frequency of C (G) allele

of *GCKR* rs780094 is high in normal controls, the variant of *GCKR* rs780094 is significantly associated with the development of gout in the male Han and Uyghur Chinese populations and in Caucasians.^{21,45,56–58} In consistence with previous studies, we have found that the C allele of rs780094 is highly detected in the control group than the hyperuricemia group in male flight attendants, which hints a protective effect of CT and CC genotypes from developing hyperuricemia. Functional experiments are required to explore mechanisms of the protective role of the C allele of rs780094 in hyperuricemia and gout in the future.²¹

In addition, the *SLC2A9* gene (4p16.1) is expressed in renal epithelial cells and encodes Glucose transporter 9 (GLUT9), which is a protein of the facilitative glucose transporter family and a transporter for both fructose and urate.³² The SNP rs1014290 of the *SLC2A9* gene has been reported to protect subjects from the development of gout and hyperuricemia.^{31,32} Individuals with rs1014290 GG (CC) genotypes had the lowest uric acid levels among the Han Chinese population.³³ Similarly, we here have found that the rs1014290 GG genotype has a lower uric acid level among both male and female flight attendants, suggesting a protective role of polymorphisms of *SLC2A9* in hyperuricemia development. Moreover, *SLC17A1* encodes sodium phosphate transport protein 1 (NPT1) and mediates sodium and inorganic phosphate co-transport. The SNP rs1183201 in *SLC17A1* has been shown to be associated with gout arthritis and uric acid concentrations in New Zealand Caucasians and Han Chinese.^{21,59} However, we did not detect a significant link of rs1183201 variants with hyperuricemia among Chinese flight attendants in this study.

Conclusion

In summary, our study has identified a higher prevalence of hyperuricemia in Chinese flight attendants, in particular in males. We have provided evidence of a strong association of three SNPs including *ABCG2* rs2231142, *GCKR* rs780094 and *SLC2A9* rs1014290, with hyperuricemia in Chinese flight attendants. We also have noticed the gender difference of genetic variations in hyperuricemia, with a higher prevalence and stronger genetic association in men than in women, which has as well been observed in previous studies. Identifying SNPs associated with diseases can help diagnose and prevent disease development such as uric acid metabolism disorders and gout. Evaluating health issues of flight attendants can help improve the quality of passenger service and the safety of aviation operation.

Ethics Approval and Consent to Participate

The study was in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethical Committee of the Xiamen Aviation and the Quanzhou First Hospital (20162016). Each subject provided written informed consent before participating.

Funding

This work was supported by the Scientific Research Funds of Huaqiao University (Z16Y0017, T.S.), and the National Natural Science Foundation of China (31771141).

Disclosure

The authors report no conflicts of interest in this work.

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