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ORIGINAL ARTICLE

Association of *ABCG2* rs2231142-A allele and serum uric acid levels in male and obese individuals in a Han Taiwanese population

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Background/Purpose: Recent studies suggest that hyperuricemia is a potential risk factor for cardiovascular disease (CVD). Hyperuricemia is highly heritable and is associated with sex and body weight. Previous genome-wide association studies have found that the *ABCG2* single nucleotide polymorphism (SNP) rs2231142 is an important genetic factor for increased uric acid (UA) levels, and the degree of association between rs2231142 and hyperuricemia is affected by both sex and ethnicity. This investigation aimed to analyze the association between *ABCG2* polymorphisms and UA levels, as well as their interactions with sex and obesity in Taiwanese.
Methods: Two genetic polymorphisms around the *ABCG2* gene were genotyped in 459 patients.
Results: After adjusting for clinical covariates, the rs2231142 SNP was found significantly associated with UA levels using a dominant inheritance model. Patients carrying the rs2231142-A allele had a higher frequency of hyperuricemia than those with the rs2231142-CC allele. Subgroup analysis revealed an association of rs2231142 with UA levels in male or obese patients, and there was no association in nonobese female patients.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: The rs2231142 SNP is associated with serum UA levels and hyperuricemia in Taiwanese patients and it occurs predominantly in male or obese patients. Hyperuricemia might be controlled differently by sex and obesity.

Introduction

Hyperuricemia is commonly caused by overproduction or underexcretion of uric acid (UA).[1] As a result of evolution, humans and great apes are hyperuricemic.[2] This is due to a series of mutations in the uricase gene 20 to 15 million years ago.[3] In recent years, significant progress has been made, and UA is found to contribute to gouty arthritis, vascular damage, and cardiovascular disease (CVD).[4–8] Nevertheless, there are conflicting reports regarding the relationship between hyperuricemia and the risks of CVD.[9] In a Taiwanese cohort study, hyperuricemia is identified as a risk factor for stroke mortality in ethnic Han Chinese and high-risk subgroups.[10] The prevalence of hyperuricemia in Taiwanese males and females is 42.1% and 27.4%,[11] and is higher in Taiwanese compared with other ethnic groups.[12,13]

ABCG2 belongs to the G-family ABC transporters.[14,15] It is postulated to be a unidirectional secretory urate transporter in the proximal renal tubule[16] and gut.[17] Recent studies have shown association of the *ABCG2* single nucleotide polymorphisms (SNPs) with various phenotypes, including UA levels, gout, and low-density lipoprotein cholesterol levels.[18–25] A C-to-A mutation rs2231142, which results in a Q-to-K substitution at position 141, has been associated with hyperuricemia and gout.[5,25,26] Mutant ABCG2 protein with an engineered Q141K residue results in a 53% reduction of urate transporter activity.[16] Therefore, in people carrying the rs2231142-A allele, hyperuricemia is more likely to develop.

It is suggested that effect size of this SNP is greater in males.[22] Indeed, sexual differences in the regulation of serum UA levels have been reported.[8] Obesity is often accompanied by hyperuricemia,[27,28] but few studies have addressed the association between obesity and genetic variants involved in UA metabolism. The degree of association between *ABCG2* rs2231142 SNP and gout risk has been found to vary with ethnicity.[26] In this study, we examined whether association between the *ABCG2* SNPs and UA levels in a Taiwanese cohort is differentially regulated by sex and obesity.

Materials and methods

Patients

After obtaining written informed consent, we recruited study participants without history of major systemic diseases, CVDs, and medication for hypertension or hyperuricemia. In total, we recruited 459 participants of Han Chinese origin into this study.

Measurement of UA

We used uricase and peroxidase-catalyzed reactions to measure UA concentrations. In brief, reaction mix was freshly prepared by mixing four parts of solution I [59 mg/dL N-ethyl-N-(2-hydroxy-3-sulfopropyl)-m-toluidine sodium salt and 0.01% Triton X-100 (Sigma, St. Louis, MO, USA) in 0.1 mol/L phosphate buffer solution (PBS; 0.08 mol/L Na_2HPO_4 and 0.02 mol/L $NaH_2PO_4 \cdot H_2O$, pH 7.4; Merck, Germany)] with one part of solution II [480 U/L uricase (Sigma), 24 mg/dL 4-aminoantipyrine (Sigma) and 1300 U/L horseradish peroxidase (Fluka, Switzerland) in 0.1 mol/L PBS pH 7.4]. We then added 5 μL normal saline, international standard of UA (10 mg/dL; Wako, Japan) or serum/plasma samples into 200 μL of reaction mix, incubated for 20 minutes at room temperature, and measured absorbance at 545 nm using a 96-well plate reader (Spectra MAX190, Molecular Devices, Sunnyvale, CA, USA). UA concentrations were calculated using a colorimetric method. Intra-assay and interassay variabilities were controlled to be 1.6～1.8% and 1.7～2.5%, respectively.

Genomic DNA extraction and genotyping

Genomic DNA was extracted from leukocytes with proteinase K digestion, phenol/chloroform extraction, and isopropanol precipitation. Primers were generated to amplify fragments containing SNPs reported on GenePipe (http://genepipe.ncgm.sinica.edu.tw/) and GeneCards (http://www.genecards.org/). Genotyping for rs72552713 was performed with polymerase chain reaction and restriction enzyme digestions. Genotyping for rs2231142 was performed using TaqMan SNP Genotyping Assays (ABI, Foster City, CA, USA).

Statistical analysis

Chi-square test was used to examine categorical data. Characteristics of continuous variables were expressed as means ± standard deviations and tested by two-sample *t*-test or analysis of variance (ANOVA). A general linear model was applied to capture the major effect of each polymorphism on phenotypic variable, with body mass index (BMI), age, sex, and smoking status as confounding covariates. Triglyceride was logarithmically transformed to normality. A value of $p < 0.05$ using a two-sided test was considered statistically significant. Analysis of

deviation from Hardy–Weinberg equilibrium and estimation of linkage disequilibrium between polymorphisms were performed using THESIAS (http://ecgene.net/genecanvas/).[29] Genetic association analyses were performed using SPSS (IBM, USA) and Golden Helix (Bozeman, MT, USA). Interactions between each SNP and UA levels, sex, and obesity were tested with two-way ANOVA. When interaction terms were significant, stratified analyses of the interactive effects between genetic variants of the SNPs and UA levels were performed while controlling for confounding covariates. Statistical results were validated using a dominant model and multiple testing corrections using Golden Helix.

Results

Baseline characteristics

Table 1 summarizes basic demographic characteristics of the study participants. Although no difference in systolic blood pressure, total cholesterol concentrations, and frequency of hypertension or diabetes mellitus were observed, many variables were different between different sexes. Smokers were seen with a male predominance, and males also had higher diastolic blood pressure, BMI, low-density lipoprotein, triglycerides, and UA levels. In contrast, high-density lipoprotein levels were higher in females.

Association of the ABCG2 SNPs with UA levels and frequency of hyperuricemia

After adjusting for clinical covariates including age, sex, BMI, and smoking status, rs2231142 was found significantly associated with UA levels using a dominant inheritance model, whereas no evidence of association between rs72552713 and UA levels was found (Table 2). Carriers of the rs2231142-A allele had significantly higher UA levels compared with those carrying the CC allele. Patients carrying the rs2231142-A allele also had a higher frequency of hyperuricemia (Figure 1).

Table 2 Association between *ABCG2* genotypes and uric acid levels.

SNP number	Genotypes	UA levels Mean ± SD (*n*)	*p*	*p**
rs2231142	CC	6.02 ± 1.56 (208)		
	CA	6.58 ± 1.62 (202)	0.002	0.437
	AA	6.37 ± 1.65 (41)		
	CC		5.73×10^{-4}	0.009
	CA+AA	6.54 ± 1.63 (243)		
rs72552713	AG	6.80 ± 2.09 (6)	0.463	0.163
	GG	6.32 ± 1.61 (440)		

p, unadjusted; *p**, adjusted for age, sex, body mass index, and smoking status.
SD = standard deviation; SNP = single nucleotide polymorphism; UA = uric acid.

Association of the ABCG2 SNPs with UA levels and frequency of hyperuricemia in obese and nonobese patients

Hyperuricemia is associated with obesity.[27,28] The effect of obesity on UA levels in the rs2231142-CC carriers was similar to that in the other two variant carriers, in general and in either sex (Table 3). Obese patients carrying the rs2231142-A allele had higher UA levels than that with the homozygous rs2231142-CC allele (Table 3). In contrast, difference in UA levels was not significant in nonobese patients carrying the aforementioned alleles. In terms of frequency of hyperuricemia, the rs2231142-A allele also exerted more effects on obese patients (Figure 1).

Sexually dimorphic association of the ABCG2 SNPs with UA levels

Our data showed a sexual difference in effects of rs2231142 on UA levels and frequency of hyperuricemia. The SNP

Table 1 Baseline characteristics of the study patients.

	Total	Male	Female	*p*
Number of patients	459	241	218	
Age, y	45.0 ± 9.5	44.2 ± 9.4	45.8 ± 9.6	0.067
Hypertension, %	8.5	7.1	10.1	0.159
Systolic BP, mm Hg	112.6 ± 15.4	113.1 ± 12.6	112.0 ± 17.9	0.428
Diastolic BP, mm Hg	74.8 ± 9.7	76.7 ± 9.3	72.7 ± 9.8	<0.001
Cholesterol, mg/dL	198.8 ± 35.8	201.7 ± 34.3	195.7 ± 37.1	0.073
HDL cholesterol, mg/dL	55.6 ± 14.0	50.0 ± 12.0	61.6 ± 13.5	<0.001
LDL cholesterol, mg/dL	116.2 ± 32.1	119.2 ± 32.0	112.9 ± 32.1	0.037
Triglycerides, mg/dL	140.5 ± 115.0	171.9 ± 142.7	106.4 ± 57.5	<0.001
BMI, kg/m^2	24.2 ± 3.4	24.7 ± 3.0	23.6 ± 3.6	<0.001
Diabetes mellitus, %	3.7	4.1	3.2	0.390
Smokers, %	20.5	35.3	4.1	<0.001
UA, mg/dL	6.3 ± 1.6	7.1 ± 1.4	5.4 ± 1.3	<0.001

Continuous variables are presented as mean ± standard deviation. Triglyceride values were logarithmically transformed before statistical testing to meet the assumption of normal distributions; however, the untransformed data are shown.
BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

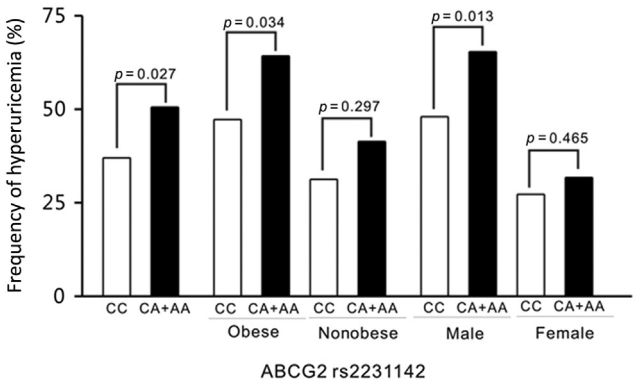

Figure 1 The rs2231142-A allele of the *ABCG2* gene is significantly associated with hyperuricemia in general, obese, and male population samples. Hyperuricemia was diagnosed according to the following criteria: male high:UA $\geq$ 7 mg/dL, male low:UA $<$ 7 mg/dL, female high:UA $\geq$ 6 mg/dL, female low:UA $<$ 6 mg/dL.

rs2231142 influenced UA levels more strongly in males (Table 3). In males with the rs2231142-A allele, hyperuremic conditions were also more likely to develop (Figure 1).

Interaction of the ABCG2 SNPs with both sex and obesity on UA levels

It became evident from our previous analyses that effects of the rs2231142-A allele on UA levels were affected by sex and obesity. As a result, we sought to elucidate possible interactions between sex and obesity on UA levels among carriers of different rs2231142 alleles. For females, significant interactions were found between rs2231142 and obesity on UA levels (Table 3). In contrast, no significant differences of UA levels were observed in nonobese females with different rs2231142 genotypes (Table 3). Because the effects of rs2231142 on UA levels were not observed in female and nonobese patients, we then sought to examine the interaction term between nonobese females and the other patients. When obese females were grouped with the other male patients and compared with nonobese females, we still noted significantly higher UA levels for patients carrying the rs2231142-A allele in this large group (Figure 2). Moreover, a significant interaction was noted between the two groups (Figure 2, others vs. nonobese females, interaction $p = 0.0189$), indicating that the ability of rs2231142 in regulating UA levels could be greatly attenuated in nonobese females.

Table 3 The association between the *ABCG2* single nucleotide polymorphism rs2231142 and uric acid levels in subgroups of sex and obesity.

ABCG2 rs2231142	UA levels		UA levels		Interaction
	Means $\pm$ SD (*n*)		Means $\pm$ SD (*n*)		$p^{\#}$ value
	Obese	p^{**} value	Nonobese	p^{**} value	
CC	6.46 $\pm$ 1.65 (74)		5.78 $\pm$ 1.45 (134)		
CA	7.07 $\pm$ 1.44 (81)	0.374	6.25 $\pm$ 1.67 (121)	0.712	0.554
AA	6.98 $\pm$ 1.75 (17)		5.94 $\pm$ 1.46 (24)		
CC					
CA+AA	7.06 $\pm$ 1.49 (98)	0.018	6.20 $\pm$ 1.63 (145)	0.185	0.229
	Man	p^{*} value	Woman	p^{*} value	
CC	6.86 $\pm$ 1.49 (98)		5.28 $\pm$ 1.19 (110)		
CA	7.34 $\pm$ 1.33 (116)	0.707	5.55 $\pm$ 1.40 (86)	0.393	0.87
AA	7.25 $\pm$ 1.64 (20)		5.54 $\pm$ 1.19 (21)		
CC					
CA+AA	7.33 $\pm$ 1.38 (136)	0.023	5.54 $\pm$ 1.36 (107)	0.123	0.477
	Obese (Woman)	p^{*} value	Nonobese (Woman)	p^{*} value	
CC	5.48 $\pm$ 1.19 (30)		5.20 $\pm$ 1.19 (80)		
CA	6.50 $\pm$ 1.59 (30)	0.565	5.03 $\pm$ 0.97 (56)	0.588	
AA	6.04 $\pm$ 1.30 (7)		5.29 $\pm$ 1.09 (14)		
CC					
CA+AA	6.42 $\pm$ 1.53 (37)	0.01	5.08 $\pm$ 0.99 (70)	0.75	
	Obese (Man)	p^{*} value	Nonobese (Man)	p^{*} value	
CC	7.13 $\pm$ 1.59 (44)		6.63 $\pm$ 1.38 (54)		
CA	7.41 $\pm$ 1.25 (51)	0.447	7.30 $\pm$ 1.40 (65)	0.861	
AA	7.64 $\pm$ 1.78 (10)		6.85 $\pm$ 1.47 (10)		
CC					
CA+AA	7.44 $\pm$ 1.34 (61)	0.302	7.24 $\pm$ 1.41 (75)	0.038	

N: number of subjects; p* value: adjusted for age, BMI and smoking status; p^{**} value: adjusted for age, sex, BMI and smoking status; $p^{\#}$ value: interaction *p*.

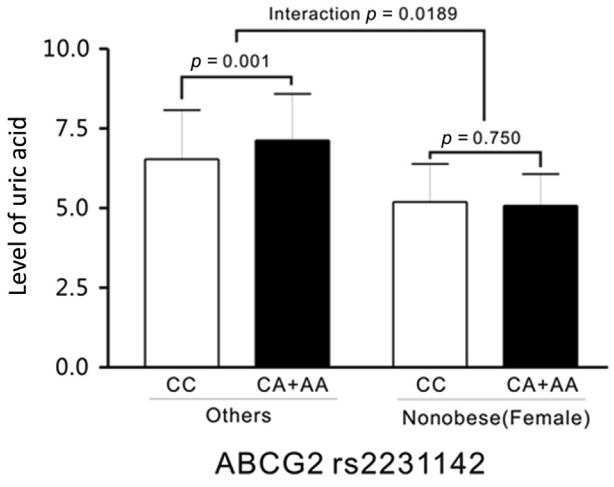

Figure 2 The rs2231142-A allele is not associated with UA levels in nonobese female patients.

Discussion

We confirmed association of the SNP rs2231142 with UA levels and hyperuricemia in a Taiwanese cohort, and found it predominantly in males. Furthermore, obesity alone determined serum UA levels regardless of *ABCG2* genotypes or sex, and we were the first to find an association between the rs2231142-A allele and hyperuricemia in obese patients.

A previous study shows that serum UA concentration has a 63% heritability.[9] Indeed, a meta-analysis identifies *ABCG2* among nine loci associated with UA concentration.[22] In these studies, rs2231142 is the only SNP consistently associated with both hyperuricemia and gout. We confirmed the association with hyperuricemia except in nonobese females.

Previous studies show substantial interaction between genotypes and sex on UA levels. For instance, rs2231142 is consistently associated with UA concentration and gout in males.[5,16,22] Our data showed a similar interaction, as we found significant association between rs2231142 and UA levels in males.

We found significant association between rs2231142 and hyperuricemia in obese patients. In a mouse model of obesity, concentration of both ABCG2 and urate reabsorption transporter URAT1 increases significantly,[30] suggesting a link between enhanced urate reabsorption and obesity-associated hyperuricemia. Although we did not measure ABCG2 or URAT1 concentration, UA concentration was higher in obese patients and was further enhanced in those carrying the rs2231142-A allele. We hypothesized that obesity readily reveals effect of rs2231142 on hyperuricemia.

We uncovered an extra layer of interaction between sex, obesity, and rs2231142 on UA levels. Our data showed rs2231142-A was not associated with UA levels in nonobese females. This difference might be due to specific physiological characteristics of the nonobese females other than that of estrogen, because it has been reported that estrogen does not increase renal clearance of serum UA in adult women.[31] Regarding the female hormonal effect on UA levels, we did not observe significant differences between premenopausal and menopausal female subgroups (Supplementary Table 1). Alternatively, nonobesity may have ameliorated hyperuricemia in rs2231142-A-carrying females by compensating for reduced ABCG2 activities. Whether it is due to metabolic or additional hormonal effect awaits further investigation, and a larger sample size is needed to clarify the role of sex hormones on UA levels and hyperuricemia in female patients.

Limitation

Because of the relatively small sample size and high minor allele frequency of rs2231142 in this study (Supplementary Table 2), it might have had limited power to detect associations between rs2231142 and UA. Still, we were able to validate our results independently using multiple regressions adjusted for confounding factors (Supplementary Table 3). In addition, we also validated our results using multiple testing corrections including full scan permutations ($p = 0.001$ for 1000 permutations), Bonferroni adjustment and false discovery rate (FDR) calculations (rs2231142-C allele; both regression Bonferroni P and regression FDR $= 5.7 \times 10^{-4}$), thus strengthening the conclusion that rs2231142 is indeed associated with serum UA levels.

Conclusion

A reduction-of-function SNP rs2231142 in the *ABCG2* gene is associated with hyperuricemia in a Taiwanese cohort. The genetic determinants for hyperuricemia differ according to sex and obesity status. The rs2231142-A allele has significantly stronger association with hyperuricemia in male and obese patients.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2015.12.002.

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