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Original Article

Genetic effects on hypertriglyceridemic waist phenotype: *rs780094, rs10830963, rs151290, and rs972283* polymorphisms and the interactions between them and behavior risk factors

Jinjin Wang[1], Jianfeng Zhang[2], Jianna Li[3], Zichen Liu[3], Kaiping Gao[3]

[1]*Department of Traditional Chinese Medicine Prevention, Henan University of Chinese Medicine, Zhengzhou, People's Republic of China;* [2]*Henan Armed Police Corps Hospital, Zhengzhou, People's Republic of China;* [3]*School of Medicine, Shenzhen University, Shenzhen, People's Republic of China*

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Abstract: Backgrounds: We aimed to evaluate the association of SNPs in *GCKR*, *MTNR1B*, *KCNQ1*, and *KLF14* genes confirmed in previous studies and hapertriglyceridemic waist (HTGW) in Han Chinese, and assess the interactions between genes and behavior risk factors. Methods: We genotyped the single nucleotide polymorphisms (SNPs) for *GCKR*, *MTNR1B*, *KCNQ1*, and *KLF14* gene were genotyped in 373 patients with HTGW and 466 normal healthy subjects. We used logistic regression to investigate the gene-gene, gene-behavior interactions for the risk of HTGW. Results: Among the 4 SNPs, the AG genotype of rs780094 was protective factor, whereas the recessive model of rs151290 was risk factor after adjusting for confounders. Stratified by sex, only for women, the recessive model of rs151290 was still significance. The significant synergies interactions between SNPs were found between rs780094 in *GCKR* and rs972283 in *KLF14* and rs10830963 in *MTNR1B*, respectively; meanwhile, the antagonistic interaction was revealed for rs151290 and rs780094 only for women. For male, there were significant synergies interactions between rs780094, smoking and alcohol drinking; and antagonistic interaction was revealed between rs780094 and severe activity both for men and women. Conclusions: *GCKR* and *KLF14* genes play a significant role in risk of HTGW in a Han Chinese population.

Keywords: Polymorphisms, HTGW, Chinese, interaction

Introduction

As a marker of the atherogenic metabolic triad in man, hypertriglyceridemic waist (HTGW) was first proposed in 2000 [1]. A meta-analysis published in 2015 showed that the prevalence of HTGW ranged from 4% to 47% in different countries, and the pooled prevalence was 18% (95% CI, 13-23%) [2]. HTGW is a specific metabolic abnormality associated with type 2 diabetes, cardiovascular risk, impaired glucose tolerance and increased insulin resistance [3-6]. It is noteworthy that HTGW has spreading to schoolchildren and adolescents [7, 8]. However, the main reason for the non-effective implementation of prevention and control, the etiology and the mechanisms of HTGW remain uncertain. Through genetic analysis to discover the candidate gene associated with HTGW is and effective method to reveal the exact pathogenesis of this metabolic abnormal phenotype.

The genetic evidences for HTGW phenotype are relatively rare. One study published in 2015 investigated 19 fasting insulin-associated single nucleotide polymorphisms (SNPs), and the results showed that glucokinase regulatory protein (*GCKR*) was an independent risk factor because of its primary effect on body mass index (BMI), triglycerides (TG) and high-density lipoprotein-cholesterol (HDL-C). The *GCKR* variant is likely to affect glucose and lipid metabolism in the liver and is significantly associated with multiple liver-based phenotypes [9]. Recently, lots of studies have evaluated the associations between type 2 diabetes (T2DM) and HTGW, and obtained the positive answers [2, 3, 10-13]. Our previous meta-analysis

Table 1. The single nucleotide polymorphisms (SNPs) selected for study

Gene	SNPs	Alleles	Ancestral Allele	MAF*
GCKR	rs780094	A/G	G	0.366
MTNR1B	rs10830963	C/G	C	0.366
KCNQ1	rs151290	A/C	A	0.433
KLF14	rs972283	A/G	G	0.333

*MAF minor allele frequencies in Han Chinese people.

Table 2. Behavior risk factors' distributions for cases with HTGW and controls

Behavior	Controls (%)	Cases (%)	*P* value
Smoking			
Non-smoking	277 (74.3)	321 (68.9)	0.092
Smoking	96 (25.7)	145 (31.1)	
Drinking			
Non-alcohol	312 (83.6)	406 (87.3)	0.138
Drinking	61 (16.4)	59 (12.7)	
Activity			
Mild	159 (34.1)	213 (57.1)	< 0.001
Moderate	74 (15.9)	39 (10.5)	
Severe	233 (50.0)	121 (32.4)	

including 6 studies showed that the rs151290 in voltage-gated channel KQT-like subfamily, member 1 (*KCNQ1*) and rs972283 in Krüppel-like factor 14 (*KLF14*) were both associated with increased risk of type 2 diabetes, and another meta-analysis also proved the association between rs10830963 in melatonin receptor 1B (*MTNR1B*) and rs780094 in *GCKR* and type 2 diabetes [14].

To sum up, we hypothesized that these four genes are associated with HTGW. Therefore, we aimed to evaluate the association of SNPs in *GCKR*, *MTNR1B*, *KCNQ1*, and *KLF14* genes confirmed in previous studies (**Table 1**, all SNPs' MAF was above 0.05 in Han Chinese based on the International HapMap Project) and HTGW in Han Chinese, and assess the interactions between genes and behavior risk factors.

Materials and methods

We used the case-control design to investigate the associations with HTGW.

All participants signed the informed consents, and the study was approved by the Ethics Committees of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine.

Patients and controls

All participants were from local inhabitants of Henan Province shared the same Han Chinese ancestry (confirming by People's Republic of China resident identity card). A total of 373 cases first diagnosed with HTGW were recruited from the outpatient clinics in four different hospitals. HTGW was diagnosed based on the International Diabetes Federation criteria for metabolic syndrome and the WHO criteria for central obesity for Asian populations, which were defined as a waist circumference (WC) of 85 cm or more in men, a WC of 80 cm or more in women, and a triglyceride level of 1.70 mmol/L or more [15, 16]. 466 healthy controls were recruited from the same clinics. We used the PGA package, for the condition: Disease prevalence in China, 2.8 [17]; the lowest MAT in Chinese among these four SNPs, 0.333; $\alpha = 0.05$; $1/\beta = 0.85$; case to control ratio, 1:4. The exclusion criteria for participants in our study included pregnant women; handicapped; or mentally disturbed; cancer patients; obesity caused by other diseases or drugs intake; and unable or unwilling to participate.

Biochemical and anthropometry measurements

All blood samples were combined after a minimum 8-hour fasting with disodium non-EDTA for measuring total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C) by using an automatic biochemical analysis instrument. Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Freidwald formula [18]. Body weight, height, WC (The study object to keep upright, arms naturally drooping, relax the abdomen, the weight will be evenly distributed in the legs, legs were merged state, to maintain normal breathing, breathing should be measured smoothly, do not intentionally breath or abdomen; Measurement of the position above the navel 1 cm, the level of measurement, the measurement tape to be in direct contact with the skin, banned underwear or single clothing across the measurement. Record the readings at the end of each inspiration and accurate to 0.5 cm), and blood pressure (systolic and diastolic: SBP

Table 3. Characteristics of patients with HTGW and controls in a Han Chinese population

Characteristics	Control (n = 466)	Case (n = 373)	*P* value
Sex			
Male	270 (57.90)	164 (44.00)	< 0.001
Female	196 (42.10)	209 (56.00)	
Age (years)	47.62±12.229	52.98±11.252	< 0.001
Body mass index (kg/m^2)	22.82±3.075	29.14±4.255	< 0.001
Waist circumference (cm)	76.34±6.408	99.05±14.506	< 0.001
SBP (mmHg)	121.25±17.521	132.34±18.211	< 0.001
DBP (mmHg)	71.39±10.581	77.65±11.941	< 0.001
Fasting plasma glucose (mmol/l)	5.78±1.941	7.30±3.095	< 0.001
HDL-C (mmol/l)	1.21±0.262	1.07±0.210	< 0.001
LDL-C (mmol/l)	2.55±0.690	3.00±0.995	< 0.001
TG (mmol/l)	1.08±0.320	2.98±1.478	< 0.001
TC (mmol/l)	4.22±0.798	5.18±1.112	< 0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TG: triglycerides; TC: total cholesterol.

Table 4. Genotypic and allelic distributions of SNPs for cases with HTGW and controls in a Han Chinese population

SNPs	Controls (%)	Cases (%)	*P* value
rs780094			
GG	129 (27.7)	86 (23.1)	0.111
AG	208 (44.6)	193 (51.7)	
AA	129 (27.7)	94 (25.2)	
G	466 (50.0)	365 (48.9)	0.694
A	466 (50.0)	381 (51.1)	
rs10830963			
CC	174 (37.3)	131 (36.1)	0.302
GC	214 (45.9)	164 (44.0)	
GG	78 (16.7)	78 (20.9)	
C	562 (60.3)	426 (57.1)	0.194
G	370 (39.7)	320 (42.9)	
rs151290			
AA	59 (12.7)	47 (12.6)	0.153
CA	208 (44.6)	190 (50.9)	
CC	199 (42.7)	136 (36.5)	
A	606 (65.0)	462 (61.9)	0.202
C	326 (35.0)	284 (38.1)	
rs972283			
GG	234 (50.2)	193 (51.7)	0.889
GA	190 (40.8)	146 (39.1)	
AA	42 (9.0)	34 (9.1)	
G	658 (70.6)	532 (71.3)	0.787
A	274 (29.4)	214 (28.7)	

Data are number (%).

and DBP) were collected as anthropometric data. The behavioral risk factors (including smoking, alcohol drinking, and physical activity) were collected by interviewer-administered questionnaire. Smoking was divided into two smoking group by collecting information about cigarettes and hand-rolled cigarettes: smoking cessation groups (those who have quit for more than one year) and non-smoking group. The subjects were divided into two groups, including non-alcohol and drinking group who are drinking liquor in the past 12 months. Physical activity was divided into three groups according to the nature of the work mainly engaged in, including mild physical activity group (to sit or station-based: exp. the sale of the store) and moderate physical activity group (motorists, electricians, fitters, metal-workers, carpenters, etc.), and severe physical activity groups (manual handling, construction, construction, repair, etc.) (**Table 2**).

Genotyping

We extracted genomic DNA from whole blood by using the blood genome DNA extraction kit (Laifeng BIO, Zhengzhou, China). Genotyping was performed by using TaqMan SNP Genotyping Fluorescence quantitative assays (Applied Biosystems, Foster City, CA, USA) in 2014. PCR was carried out on a GeneAmp PCR system 7000, and fluorescence was detected on an ABI PRISM 7000 sequence detector (Applied Biosystems). The TaqMan Fluorescence SNP probes were synthesized by Life Technologies Biotech Co. (Foster, CA, USA). Overall, genotyping success rate was 100%. To verify the reproducibility, we repeated 20% of samples at random as a quality control for genotyping, and the concordance rate was 100% (data not shown).

Statistical analysis

Statistical analyses were performed with SPSS v21.0 for Windows (SPSS Inc., Chicago, IL,

Table 5. Association of SNPs and HTGW in Han Chinese

SNPs	Genotypes	Unadjusted OR (95% CI)	*P* value	Adjusted OR* (95% CI)	*P** value
rs780094	GG	1	-	1	-
	AG	1.392 (0.995-1.947)	0.054	0.655 (0.446-0.962)	0.031
	AA	1.093 (0.747-1.600)	0.647	1.078 (0.605-1.922)	0.798
	AA vs. AG+GG	0.880 (0.646-1.199)	0.419	0.722 (0.454-1.148)	0.169
	AA+AG vs. GG	1.277 (0.932-1.750)	0.128	1.524 (0.952-2.439)	0.080
rs10830963	CC	1	-	1	-
	GC	1.018 (0.751-1.380)	0.909	0.785 (0.502-1.227)	0.289
	GG	1.328 (0.902-1.956)	0.151	1.187 (0.687-2.051)	0.539
	GG vs. GC+CC	1.315 (0.928-1.864)	0.123	1.356 (0.831-2.211)	0.223
	GG+GC vs. CC	1.101 (0.829-1.462)	0.507	0.895 (0.593-1.351)	0.598
rs151290	AA	1	-	1	-
	CA	1.147 (0.745-1.764)	0.533	1.191 (0.610-2.328)	0.609
	CC	0.858 (0.552-1.333)	0.496	0.752 (0.377-1.501)	0.419
	CC vs. CA+AA	0.770 (0.582-1.018)	0.067	1.089 (0.676-1.752)	0.739
	CC+CA vs. AA	1.005 (0.667-1.515)	0.979	1.528 (1.107-2.109)	0.010
rs972283	GG	1	-	1	-
	GA	0.932 (0.699-1.242)	0.630	0.824 (0.544-1.249)	0.362
	AA	0.981 (0.601-1.603)	0.941	1.011 (0.480-2.129)	0.977
	AA vs. GA+GG	1.013 (0.630-1.627)	0.959	1.097 (0.533-2.261)	0.801
	AA+GA vs. GG	0.941 (0.716-1.235)	0.660	0.853 (0.575-1.266)	0.430

*Adjusted for sex, age, FPG, SBP, DBP, and behavior risk factors.

USA). Chi-square test was used to analyze the categorical variables which are presented as the number and percentage. Student t-test was used to analyze the continuous variables which are presented by mean and standard deviation. The Hardy_Weinberg equilibrium was calculated in controls using Haploview 4.2. The odds ratios (ORs), 95% confidence intervals (95% CIs) and corresponding *P* values for risk of HTGW were evaluated by logistic regression analysis after adjusting for gender, age, blood pressure, and behavioral risk factors (including smoking, alcohol consumption, and physical activity). The interaction terms between two variables were assessed by logistic regression models to evaluate the interactions between these 4 SNP and behavioral risk factors (involving alcohol, smoking, and physical activity) by adjusting gender, age and blood pressure. $P < 0.05$ was considered statistically significant. Power calculation was performed by PGA software (http://dceg.cancer.gov/bb/tools/pga).

Quality control

Investigators and laboratory operators were trained. All biochemical tests are performed in the same laboratory, and 20% of the samples at random were repeated.

Results

Clinical characteristics of the study participants

Totally, our study recruited 839 participants including 373 HTGW cases (164 males and 209 females) and 466 controls (270 males and 196 females). Compared with controls, HTGW patients had significantly greater anthropometric and metabolic values ($P < 0.001$; **Table 3**).

Association of four SNPs with HTGW

Among these four SNPs, the frequencies had no differences between cases and controls (**Table 4**). All genotypes were in Hardy-Weinberg equilibrium in controls ($P > 0.05$). By logistic regression analysis, the AG genotype of rs780094 and the recessive model of rs151290 was associated with HTGW; and the AG genotype of rs780094 was protective factor, whereas the recessive model of rs151290 was risk factor after adjusting for confounders such as sex, age, FPG, SBP, DBP, and behavior risk fac-

Table 6. Association of SNPs and HTGW stratified analysis by sex

Sex	SNPs	Genotypes	OR (95% CI)	*P* value
Male	rs780094	GG	1	-
		AG	0.410 (0.423-1.192)	0.195
		AA	0.838 (0.541-1.297)	0.428
		AA vs. AG+GG	0.911 (0.558-1.486)	0.709
		AA+AG vs. GG	1.333 (0.827-2.150)	0.238
	rs10830963	CC	1	-
		GC	0.903 (0.568-1.435)	0.666
		GG	1.908 (0.611-1.971)	0.755
		GG vs. GC+CC	1.162 (0.686-1.966)	0.577
		GG+GC vs. CC	0.957 (0.622-1.472)	0.841
	rs151290	AA	1	-
		CA	1.083 (0.556-2.110)	0.814
		CC	0.777 (0.390-1.550)	0.474
		CC vs. CA+AA	0.728 (0.474-1.119)	0.148
		CC+CA vs. AA	1.556 (0.996-2.433)	0.052
	rs972283	GG	1	-
		GA	0.964 (0.621-1.495)	0.869
		AA	1.164 (0.551-2.459)	0.691
		AA vs. GA+GG	1.182 (0.572-2.442)	0.651
		AA+GA vs. GG	0.999 (0.660-1.510)	0.995
Female	rs780094	GG	1	-
		AG	0.545 (0.296-1.003)	0.051
		AA	1.343 (0.699-2.578)	0.376
		AA vs. AG+GG	0.884 (0.531-1.474)	0.638
		AA+AG vs. GG	1.640 (0.938-2.867)	0.083
	rs10830963	CC	1	-
		GC	0.827 (0.492-1.390)	0.474
		GG	1.093 (0.563-2.123)	0.793
		GG vs. GC+CC	1.211 (0.664-2.208)	0.531
		GG+GC vs. CC	0.898 (0.554-1.455)	0.661
	rs151290	AA	1	-
		CA	1.382 (0.653-2.923)	0.397
		CC	0.711 (0.330-1.532)	0.383
		CC vs. CA+AA	0.550 (0.337-0.900)	0.017
		CC+CA vs. AA	1.730 (1.053-2.843)	0.031
	rs972283	GG	1	-
		GA	1.027 (0.627-1.682)	0.915
		AA	0.755 (0.331-1.723)	0.505
		AA vs. GA+GG	0.746 (0.337-1.654)	0.471
		AA+GA vs. GG	0.968 (0.608-1.542)	0.891

Adjusted for age, FPG, SBP, DBP, and behavior risk factors.

tors (**Table 5**). The power for them was about 98% and 96%, respectively. Stratified by sex, the recessive model of rs151290 was still significance for women, with a power about 95% (**Table 6**).

Interaction of four SNPs with HTGW

The logistic regression was used to analyze the interactions between pairs of SNPs after adjusting for confounders (such as age, SBP, DBP, and behavior risk factors for all participants and men and women, respectively). The results showed that the significant synergistic interactions between SNPs were genotype AG and AA of rs780094 in *GCKR,* GA of rs972283 in *KLF14*, GG genotype of rs10830963 in *MTNR1B*, respectively. Meanwhile, the antagonistic interaction was revealed for the genotype CC of rs151290 in *KCNQ1* and AA of rs780094 in *GCKR* only for women (**Table 7** listed all statistically significant results).

Interaction of SNPs with behavior risk factors and HTGW

The logistic regression was used to analyze the interactions between SNPs and behavior risk factors and HTGW after adjusting for confounders (such as age, SBP, DBP, and behavior risk factors including drinking, smoking, and activity for men, and for women only analyzing activity because of the data of drinking and smoking too little), respectively. The results showed that for total there were antago nistic interactions between AA genotype of rs780094 and alcohol drinking, and GA genotype of rs972283 and severe activity. For males, there were significant synergistic interactions between AA genotype of rs780094 and smoking, and AA, AG genotypes of rs780094 and alcohol drinking, while antagonistic interactions were revealed between AA genotype of rs780094 and severe activity. For females, there was antagonistic interaction between AA genotype of rs780094 and severe activity (**Table 8**). A preliminary discussion was performed about interactions in this study, and further study will be needed to verify.

Table 7. Interactions of genotypes of four single nucleotide polymorphisms (SNPs) for Women HTGW

Group		Beta	S.E.	OR	95% CI	*P*
rs780094	rs10830963					
AG	GG	2.258	1.034	9.568	1.261-72.573	0.029
AA	GG	2.518	1.116	12.409	1.393-110.564	0.024
rs151290	rs780094					
CC	AA	-2.752	1.355	0.064	0.004-0.908	0.042
rs780094	rs972283					
AG	GA	1.686	0.736	5.398	1.275-22.853	0.022
AA	GA	1.742	0.804	5.708	1.181-27.579	0.030

Adjusted for age, FPG, SBP, DBP, and behavior risk factors.

Discussion

Waist measurement is the main method for evaluating abdominal obesity estimating the accumulation of visceral adipose tissue [19]. Whereas, triglycerides concentration can indirectly reflect low-density lipoprotein cholesterol level [20]. When both measurements are increasing, it indicates that the body functions for processing residual energy and subcutaneous fat stored are damaged, followed by impaired glucose and lipid metabolism disorders. Some studies have shown that HTGW is associated with increased insulin resistance and excessive activation of beta cell function, and higher HTGW is useful for identifying and early intervention type 2 diabetes [21]. HTGW is the result of environmental factors and genetic factors interaction, and the genetic factors determine the different susceptibility to diabetes between individuals. Under certain environmental triggers action, individuals with high risk genetic variants have more susceptible HTGW. Combined with environmental factors to found and confirm susceptibility loci of HTGW play an important role in preventive measures and reducing the incidence of HTGW. Currently, researches about HTGW are main focusing the relationships between HTGW and cardiovascular and type 2 diabetes. However, evidence about susceptibility genes is rare. Our study provided new evidence indicating that that rs780094 and rs151290 genotypes are associated with HTGW in Han Chinese, especially in women.

In our study, stronger associations of SNPs and HTGW and the interactions between SNPs and HTGW were found in women than in men. This result suggested that gender factor may play important role in estimating the effect of genetic factors on HTGW. In the analysis of metabolism-related indicators, sex differences exist in the relationships among abdominal obesity, obesity related metabolic abnormalities [22]. Our results showed that the interactions between SNPs and HTGW were only found in women. Since women in this survey had less smoking and drink-ing, physical activity showed more significant antagonistic interaction with AA genotype rs780094.

We analyzed the interactions among four SNPs and behavioral factors in two directions, involving synergy which means two or more factors combine greater than additively in relation to risk and antagonism which to the contrary. Among these four SNPs, rs780094 in *GCKR* gene showed significant association with HTGW both in genetic effect and interactions analyses. *GCKR* belongs to an isomerase family, and locates on chromosome 2p23 mainly in the liver and pancreatic cells [23]. In liver cells, *GCKR* gene regulates GCK, and competitively inhibit the binding of glucose and GCK [24]. The results of some researches show that homozygous AA of rs780094 in *GCKR* gene had lower risk of developing diabetes [25]; A allele showed low risk in the performance of type 2 diabetes, and indicating low levels of fasting blood glucose and high triglycerides [26, 27]. Our results showed that AG genotype of rs780094 can reduce the risk of HTGW in independent analysis. Furthermore, AG and AA genotypes of rs780094 combined with GG genotype of rs10830963 in *MTNR1B* gene and GA genotype of rs972283 in *KLF14* gene can significant increased the risk of HTGW (OR: 5.398~12.409). Our data suggests that A allele in rs780094 is associated with increased risk of abnormal lipid metabolism through genetic- interactions' manner.

Recently, rs972283 in *KLF14* was found to be associated with T2DM in an European genome-wide association study. T2DM risk allele at rs972283 in *KLF14* was associated with higher fasting insulin, consistent with a primary effect on insulin action [28]. Our previous meta-analy-

Table 8. Interaction of behavioral factors and genotypes of single nucleotide polymorphisms (SNPs) for HTGW

Sex	Group		Beta	S.E.	OR	95% CI	*P*
Total	AA in rs780094	Alcohol	-1.883	0.684	0.152	0.040-0.581	0.006
	GA in rs972283	Severe Activity	-0.811	0.363	0.444	0.218-0.905	0.025
Male	AA in rs780094	Cig	1.213	0.597	3.365	1.045-10.834	0.042
	AA in rs780094	Alcohol	1.565	0.721	4.783	1.164-19.657	0.030
	AA in rs780094	Severe Activity	-0.746	4.519	0.474	0.238-0.943	0.034
	AG in rs780094	Alcohol	2.307	0.835	10.040	1.955-51.575	0.006
Female	AA in rs780094	Severe Activity	-0.701	0.324	0.496	0.263-0.937	0.031

Adjusted for age, FPG, SBP, DBP, and behavior risk factors.

sis suggested that rs972283 in *KLF14* was associated with increased risk of T2DM [29]. Given the close association between type 2 diabetes and HTGW, we hypothesized that rs972283 may also associated with HTGW. However, our data did not find any evidence of association between C allele of rs972283 and the risk of HTGW. We considered that the ethnicity may be the main reason for the differences, and it is widely known that the MAF of the SNPs change from one group to another, and the structure of LD also changes between different populations.

For chronic non-communicable diseases, lifestyle interventions play a crucial role. The research published in 2016 showed that exercise training has positive effect for maximal fat oxidation intensity on body composition and lipid metabolism in overweight middle-aged women [30]. Our results showed that activity had a positive effect on reducing the risk of HTGW.

Limitations should be pointed out in our study. First, some ORs in our study had very wide 95% CI this may be attributable to a relatively small sample size. Further studies with larger sample sizes are required to confirm the results from the present study. Second, our results did not exclude the possibility of an association between other SNPS in these four genes and the HTGW phenotype, a more detailed tagging SNPs analysis is needed to exclude the influence of other genetic variants on the results. In conclusion, *GCKR* and *KLF14* genes and gene-environment interactions play a significant role in the risk of HTGW in Han Chinese population, especially in women. Further studies in people of different ethnic backgrounds are needed to clarify the mechanisms and underlying genetic effects of HTGW.

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Disclosure of conflict of interest

None.

Authors' contribution

K. Gao and J. Wang designed the study, analyzed data, and drafted the manuscript. J. Wang, J. Li, Z. Liu, and K. Gao conducted data analyses. J. Wang, K. Gao, and J.Li extracted data and performed statistical analyses. J. Wang wrote the manuscript. All authors approved the final manuscript. We sincerely thank all of the authors for their work in this study.

Address correspondence to: Kaiping Gao, School of Medicine, Shenzhen University, 3688 Nanhai Avenue, Nanshan District, Shenzhen 518060, Guangdong, People's Republic of China. Tel: 0086-755-86671909; Fax: 0086-755-86671906; E-mail: gao_kp@szu.edu.cn

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