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Association of the genetic variant rs2000999 with haptoglobin and diabetic macrovascular diseases in Chinese patients with type 2 diabetes

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ABSTRACT

Aims: The common copy number variant (CNV) in the haptoglobin (Hp) gene may influence the susceptibility to diabetic macrovascular diseases. We aimed to investigate the relationship of the genetic variant rs2000999, located in the haptoglobin-related protein (HPR) gene, with serum Hp levels and diabetic macrovascular diseases in Chinese type 2 diabetes patients.

Methods: The Hp CNV and rs2000999 were genotyped in a group of 5457 Chinese patients with type 2 diabetes. Associations of rs2000999 with the common Hp CNV, susceptibility to diabetic macrovascular diseases and related metabolic traits were analysed. Furthermore, 886 patients were selected to detect serum Hp levels and to evaluate the correlation between rs2000999 and serum Hp levels.

Results: The genetic variant rs2000999 was not associated with diabetic macrovascular diseases ($P = 0.6109$), while subjects carrying the A allele had higher levels of low-density lipoprotein cholesterol ($P = 0.0578$) and a smaller inter-adventitial diameter of the common carotid artery ($P = 0.0266$). Additionally, rs2000999 exhibited strong association with serum Hp levels ($P = 2.03 \times 10^{-21}$).

Conclusions: The genetic variant rs2000999 was not associated with diabetic macrovascular diseases but showed an association with metabolic traits and serum Hp levels in Chinese patients with type 2 diabetes.

1. Introduction

Type 2 diabetes mellitus (T2DM) remains a concurrent public health problem worldwide, with considerably increased risk of coronary heart disease, stroke, and peripheral arterial diseases in affected patients.[1] As diabetic macrovascular diseases are the major causes of morbidity and mortality in patients with T2DM, the risk factors contributing to the accelerated atherosclerosis have long been a major focus.[2] The roles of abnormal lipid metabolism, including the reduction of high-density lipoprotein cholesterol (HDL-C) levels and increasing low-density lipoprotein cholesterol (LDL-C) levels, in diabetic macrovascular diseases have been fiercely debated.[3]

In recent years, genome-wide association studies (GWAS) have discovered several loci that are genetic determinants of dyslipidaemia, with relevance for diabetes and atherosclerosis.[4,5] A single nucleotide polymorphism (SNP) rs2000999 located in the haptoglobin-related protein (HPR) gene has been identified to influence serum cholesterol levels in the general European population.[6] The haptoglobin (Hp) gene, located adjacent to the HPR gene, encodes the Hp protein, which binds haemoglobin (Hb) and prevent Hb-induced oxidative tissue damage.[7,8] The common copy number variant (CNV) in the Hp gene (Hp1-1, Hp2-1 and Hp2-2) was reported as an independent risk factor for cardiovascular disease in T2DM.[9,10] Furthermore, the results of another GWAS demonstrated that SNP rs2000999 was a strong genetic determinant of serum Hp levels in children with European ancestry.[11] However, it is unknown whether SNP rs2000999 was correlated with diabetic macrovascular diseases through the influence of circulating Hp levels or serum lipids in Chinese populations.

Therefore, in the present study, we investigated the relationship of SNP rs2000999 with circulating Hp levels, lipid profiles and diabetic macrovascular diseases in Chinese patients with type 2 diabetes.

2. Methods

2.1. Ethical approval

Ethical approval of this research was granted by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's

Duality of interest: The authors have no conflicts of interest.

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Hospital according to the Helsinki Declaration II. We obtained oral and written informed consent from all patients.

2.2. Participants

A total of 5457 type 2 diabetes patients, including 2953 males and 2504 females from the Shanghai Diabetes Institute Inpatient Database of Shanghai Jiao Tong University Affiliated Sixth People's Hospital were enrolled in the present study from May 2013 to December 2015. Type 2 diabetes was diagnosed according to the 1999 WHO criteria.[12] All populations underwent a series of vascular examinations, including ultrasound of the bilateral common carotid artery to measure intima-media thickness (IMT), inter-adventitial diameter (IAD) and bilateral lower limb arteries and computed tomography or magnetic resonance imaging to evaluate cerebrovascular diseases. Diabetic macrovascular diseases were diagnosed by the evidence of atherosclerosis from cerebrovascular, carotid arteries, myocardial infarction and lower limb arteries.[13]

2.3. Clinical measurements

The anthropometric parameters of all the participants were collected. Body mass index (BMI) was assessed by weight (kg)/height^2 (m^2). Systolic and diastolic blood pressures were measured by skilled medical workers. Fasting venous blood samples were obtained from all the participants to test the clinical metabolic parameters. HbA1c levels were measured via Bio-Rad VARIANT™ high-performance liquid chromatography methods (Bio-Rad Laboratories, Hercules, CA). Blood lipids, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol and triglycerides, were tested via a 7600-020 Automated Analyser (Hitachi, Tokyo, Japan). We measured Hp levels in a group of 886 serum samples (468/418 cases/controls of diabetic macrovascular diseases, respectively) via enzyme-linked immunosorbent (ELISA) assay by using commercially available ELISA kits (R&D Systems, Inc., Minneapolis, USA).

2.4. Genotyping

DNA was extracted from the blood specimens. The SNP rs2000999 was genotyped by primer extension of the multiplex products with detection through matrix-assisted laser desorption ionisation–time of flight mass spectrometry via a MassARRAY Compact Analyser (Sequenom, San Diego, CA, USA). After genotyping, the data were assessed for quality control, and 5457 individuals were selected for further analysis. The CNVs of the Hp gene were genotyped by TaqMan assays using a 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA) according to a previously described classical method.[14,15]

2.5. Statistical analysis

SAS for Windows (version 8.0; SAS Institute, Cary, NC, USA) was utilized to perform the statistical analyses. Statistical significance was defined as a two-tailed P value <0.05. The variables were subjected to normal distribution tests, and the skewness distribution data were applied for further analysis after logarithm transition. Data are shown as n or the means ± standard deviation (SD) or median (interquartile range). IMT and IAD were defined as the average values of the bilateral common carotid artery.

The Hardy–Weinberg equilibrium test of rs2000999 was performed prior to the statistical analysis among patients without Hpdel (a two-tailed P value >0.05 was considered statistically significant).[16] The Wilcoxon test was conducted to compare the clinical characteristics among three genotypes of rs2000999. The association between rs2000999 and diabetic macrovascular diseases was analysed via multivariate logistic regression after adjusting for confounding factors, and ORs with 95% CIs are presented. The correlation of rs2000999 with diabetic macrovascular disease-related quantitative traits, clinical traits and serum Hp levels were preformed using multiply linear regression under additive models.

3. Results

3.1. Clinical characteristics

The genotyping results of Hp CNV were as follows: 6.60% Hp1-1 (N = 360), 35.75% Hp2-1 (N = 1951), 50.10% Hp2-2 (N = 2734), 2.36% Hp1-del (N = 129), 5.19% Hp2-del (N = 283). Considering the interruption of the Hpdel allele, we further examined those patients with common Hp CNVs (N = 5045). The genotypes of rs2000999 were in Hardy-Weinberg equilibrium (P = 0.0777) and distributed as follows: AA, 7.51% (N = 379); AG, 38.00% (N = 1917); and GG, 54.49% (N = 2749). After further analysis, rs2000999 A was in low linkage disequilibrium with Hp2 in patients without Hpdel ($|D'| = 0.93$, $r^2 = 0.11$).

The clinical characteristics of the 5045 patients grouped by rs2000999 genotypes are shown in Table 1. There was a significant difference in systolic blood pressure (P = 0.0315) among different genotypes. The trend of the difference in LDL-C levels was observed (P = 0.0834). After adjusting for age, sex, BMI and blood pressure, LDL-C was marginally associated with rs2000999 genotypes (P = 0.0578, β ± SE = 0.0060 ± 0.0032 for the A allele) (Table 2). However, this association was no longer statistically significant after adjusting for the common Hp CNV (P = 0.6189). Contrarily, the correlation between Hp CNV and LDL-C levels was significant after adjusting for SNP rs2000999 (P = 0.0003, β ± SE = 0.0124 ± 0.0034 for Hp2 allele).

3.2. Association between rs2000999 and diabetic macrovascular diseases

There was no significant difference in the minor allele frequency of SNP rs2000999 between diabetic macrovascular cases and controls (P = 0.5066) among 5045 patients without Hpdel (Fig. 1a). After adjusting for age, sex, BMI, blood pressure, duration of diabetes, HbA1c, LDL-C and HDL-C levels, we still failed to detect a significant association between the variant rs2000999 and diabetic macrovascular diseases (P = 0.6109, OR = 0.968 [0.854, 1.097] for the A allele) (Fig. 1b). Furthermore, we analysed the association of rs2000999 with IMT and IAD of the common carotid artery. A significant association was identified between variant rs2000999 and IAD after adjusting for age, sex, BMI and blood pressure (P = 0.0266, β ± SE = −0.0378 ± 0.0170 for the A allele).

3.3. Association between rs2000999 and serum Hp levels

Among patients tested for serum Hp levels, 817 individuals carried the common Hp CNV without Hpdel. After adjusting for age, sex, BMI, smoking and Hb levels, there was a significant correlation between the variant rs2000999 and serum Hp levels by multiple linear regression analysis for both the additive model ($P = 2.03 \times 10^{-21}$, β ± SE = −0.1517 ± 0.0155 for the A allele) (Fig. 2a) and the recessive model ($P = 6.84 \times 10^{-9}$, β ± SE = −0.2346 ± 0.0401 for the A allele) (Fig. 2b).

4. Discussion

The present study investigated the association between a genetic variant of rs2000999 in the HPR gene and diabetic macrovascular diseases in Chinese patients with type 2 diabetes. We did not provide enough evidence to demonstrate that rs2000999 was associated with diabetic macrovascular diseases in our samples. However, rs2000999 was correlated with the parameters of IAD and LDL-C, which play key roles in the occurrence and development of atherosclerosis. In addition, SNP rs2000999 was associated with the levels of serum Hp in Chinese diabetes.

Table 1
Clinical characteristics grouped by rs2000999 in the present study.

Genotypes	GG	GA	AA	*P* value
Male/female (n)	1462/1287	1050/867	203/176	–
Age (years)	59.83 ± 12.14	59.43 ± 12.33	59.76 ± 12.70	0.5557
BMI (kg/m^2)	24.84 ± 5.09	24.78 ± 3.66	24.42 ± 3.49	0.3125
Diastolic blood pressure (mm Hg)	80 (75, 88)	80 (74, 88)	80 (76, 86)	0.6256
Systolic blood pressure (mm Hg)	130 (120, 140)	130 (120, 140)	130 (120, 145)	**0.0315**
Duration of diabetes (years)	8.00 (3.00, 13.00)	8.00 (3.00, 13.00)	8.00 (4.00, 12.00)	0.8048
HbA1c (%)	8.6 (7.2, 10.5)	8.7 (7.3, 10.4)	8.7 (7.2, 10.4)	0.7970
HDL-C (mmol/L)	1.09 (0.91, 1.30)	1.07 (0.90, 1.29)	1.08 (0.91, 1.30)	0.3007
LDL-C (mmol/L)	2.90 (2.38, 3.49)	2.96 (2.38, 3.57)	3.00 (2.49, 3.57)	**0.0834**
Total cholesterol (mmol/L)	4.67 (4.00, 5.40)	4.70 (4.03, 5.40)	4.80 (4.10, 5.40)	0.6019
Triglycerides (mmol/L)	1.40 (0.97, 2.14)	1.46 (1.00, 2.13)	1.48 (1.01, 2.12)	0.6297

Data are shown as n or the mean ± standard deviation or median (interquartile range). BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. *P* values <0.05 are shown in bold.

The SNP rs2000999 was first identified by GWAS in intron 2 of the HPR gene, which was reported as a novel locus affecting classical blood lipid levels.[6] The product encoded by the HPR gene, haptoglobin-related protein, was part of apolipoprotein L1, which plays a key role in lipid metabolism.[17] Strictly speaking, the entire Hp gene contains a 16 kb tandemly repeated segmental duplication, with another repeated fragment sharing 94% DNA sequence identity and containing the HPR gene.[18] There is a 1.7 kb intragenic duplication in the generalized defined Hp gene, including the CNV of the Hp 1 and Hp 2 alleles, producing three common Hp genotypes, Hp1-1, Hp2-1 and Hp2-2.[19] Furthermore, a less common allele, Hpdel, lacking a 28-kb fragment that extends from the promoter region of the Hp gene to exon 5 of the HPR gene was identified.[20] Therefore, the genetic variant rs2000999 was interrupted when Hpdel appeared. According to this law, we performed an association analysis in patients without Hpdel. In the present study, the SNP rs2000999 was not in strong linkage disequilibrium with the common Hp CNV among Chinese T2DM patients, consistent with the data reported in the European and Japanese population.[21,22]

It was reported that rs2000999 A was in positive correlation with total cholesterol levels and LDL-C levels in individuals of European ancestry.[6] However, another study conducted in Chinese women recently revealed that this association was no longer statistically significant after adjusting for the common Hp CNV.[23] In contrast, the correlation between the common Hp CNV and LDL-C levels was still significant after adjusting for the SNP rs2000999. Notably, we obtained the same results in the present study. This phenomenon might provide evidence that Hp CNV plays a more important role in the regulation of blood lipids than the SNP rs2000999.[24] In addition, a significant relationship of rs2000999 and serum Hp levels was observed as previously reported.[11,22]

Oxidative stress plays a key role in the process of diabetic macrovascular complications.[25] The main biological function of the Hp protein involves the capture of free Hb released in circulation to form an Hp-Hb complex. This complex is removed mainly by the monocyte and macrophage CD163 Hp-Hb receptors expressed on Kupffer cells in the liver to prevent the tissue and organ damage resulting from the oxidative stress of iron.[26] The Hp protein is encoded by the Hp gene located on chromosome 16 and is characterized by a molecular heterogeneity with three major genotypes (Hp1-1, Hp2-1 and Hp2-2).[8] The mechanism for classification of three common Hp genotypes was based on the electrophoretic mobility of different phenotypes, with oligomers formed by Hp2, and monomers formed by Hp1. It was reported that an Hb-Hp2-2 complex exhibited a greater functional affinity for binding to the scavenger receptor CD163 than an Hb-Hp1-1 complex do.[27] However, a higher clearance rate of an Hb-Hp1-1 complex by CD163 than that of an Hb-Hp2-2 complex was observed in another research.[28] In view of this, functional studies of Hp proteins with different phenotypes in vivo and in vitro are needed to reveal the underlying mechanisms.

Many studies have shown that the Hp CNV is an independent risk factor for the susceptibility of diabetic macrovascular diseases.[29,30] However, few studies have investigated the relationship between SNP rs2000999 and diabetic macrovascular diseases. In the present study, no significant evidence was provided to support this association; however, we identified a significant correlation between rs2000999 and the IAD of the common carotid artery. It means that the effect of this SNP rs2000999 on the susceptibility to diabetic macrovascular diseases might be limited, compared to other established loci.[31] We speculated that a direct effect of SNP rs2000999 on IAD was stronger than that on diabetic macrovascular disease. As previously reported, IAD might serve as a surrogate for left ventricular mass and show predictive value for the origin and development of cardiovascular outcomes.[32] Further basic functional studies are needed to reveal the underlying mechanism of how this SNP plays a part in the atherosclerosis of the common carotid artery.

There are several limitations in the present study. First, the negative finding of the association between rs2000999 and diabetic macrovascular diseases in these Chinese diabetes samples was based on cross-sectional research. A prospective cohort study is needed to provide more powerful evidence. Second, the sample sizes of serum

Table 2
Association between rs2000999 and clinical traits.

Variable	β for minor allele (A)	SE	*P* value
Duration of diabetes	−0.0004	0.0025	0.8854
HbA1c	−0.00006	0.0023	0.9795
High-density lipoprotein cholesterol	−0.0043	0.0026	0.0947
Low-density lipoprotein cholesterol	0.0060	0.0032	**0.0578**
Total cholesterol	0.0023	0.0023	0.3139
Triglycerides	0.0036	0.0060	0.5497

All skewed quantitative traits were logarithmically transformed for analysis with adjustment for age, sex, body mass index, and diastolic and systolic blood pressures. *P* value closed to 0.05 is shown in bold.

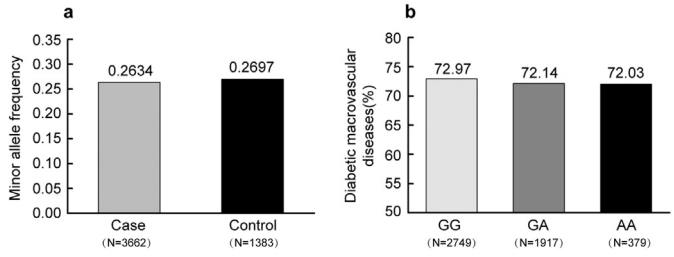

Fig. 1. Minor allele frequency and prevalence rate in diabetic macrovascular case-control population. Panel a represents the difference in the minor allele frequency of rs2000999 in case-control groups, $P = 0.5066$. The histograms represent the frequency of rs2000999 [A]. Panel b represents the difference of prevalence rate in different genotypes for the additive model, $P = 0.6109$, OR = 0.968 [0.854, 1.097]. The histograms represent the prevalence rate for the A allele of rs2000999.

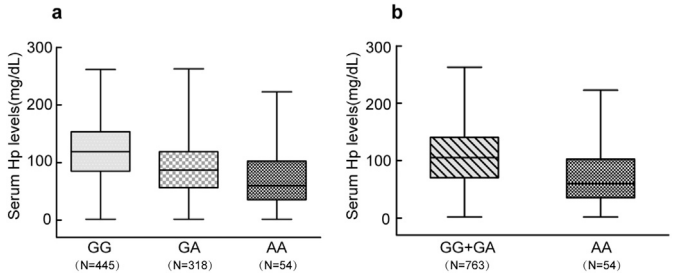

Fig. 2. Serum haptoglobin levels grouped by rs2000999. Box plot a shows the association of rs2000999 with serum haptoglobin for the additive model. $P = 2.03 \times 10^{-21}$, $\beta \pm SE = -0.1517 \pm 0.0155$. Box plot b shows the association of rs2000999 with serum haptoglobin for the recessive model. $P = 6.84 \times 10^{-9}$, $\beta \pm SE = -0.2346 \pm 0.0401$. *P* values and β values were determined by multiple linear regression adjusting for age, sex, body mass index, smoking and haemoglobin levels.

Hp measurement were relatively small, and a large sample size is required to validate these results. Third, lipid-lowering therapy was not be fully adjusted for in this study. As reported in the general European population,[6] the correlation of SNP rs2000999 with total cholesterol level and LDL-C were stronger in the whole subjects adjusted for the confounding effect of treatment with statins compared to participants who did not receive any lipid-lowering treatment. By that analogy, we speculated that the marginal correlation of LDL-C levels and rs2000999 genotypes observed in our study might be stronger if adjusting for this confounding factor. Finally, environmental influences, such as daily intake of food and physical activity at work and at leisure, which might influence the correlation of SNP rs2000999 with blood lipids, were not considered in the present study. It was reported that, the correlation between rs2000999 and LDL-C was improved after adjusting for those environmental covariates, suggesting that the genetic effect might be moderated by diet and physical activity.[6] Thus, we should take the environmental effects into consideration in future studies to understand the underlying mechanisms.

In conclusion, the results of the present study suggest that the genetic variant rs2000999 was not associated with diabetic macrovascular diseases but showed a correlation with metabolic traits and serum Hp levels in Chinese type 2 diabetes patients.

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