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Original Article

Association of single nucleotide polymorphism rs10757274 A/G with coronary heart disease in the presence and absence of diabetes in a Chinese population

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Abstract: Background: A recent genome wide association study in Chinese Han Population has implicated rs10757274 A/G polymorphism on chromosome 9p21.3 was associated with coronary heart disease (CHD), and diabetes may have a modifying role. In this study, we aimed to evaluate the association of the SNP with CHD in the presence and absence of type 2 diabetes mellitus (T2D) in a Chinese population. Methods and Results: SNP of rs10757274 at 9p21.3 locus was genotyped in 1,168 CHD patients and 294 controls, among which all cases were diagnosed through angiography. We compared subjects using a dominant model for the risk allele G; AG (n = 735), GG (n = 302) vs. AA (n = 425), multivariate liner regression was used with adjustment for age, sex, ethnicity, smoking status, alcohol intake, hypertension, hyperlipidemia and diabetes. In addition, we evaluated diabetes-specific genetic effect on CHD. There was a significant association between rs10757274 A/G polymorphism and CHD, both for AG (OR = 1.40, 95% CI: 1.03-1.91) and GG (OR = 2.48, 95% CI: 1.64-3.76) genotypes vs. AA genotype. While further diabetes-specific analysis showed different results between AG and GG vs. AA genotypes for the association of rs10757274 with CHD in the presence and absence of T2D. GG is associated with CHD in both with and without diabetes while AG is associated with CHD only in diabetes. Conclusions: The rs10757274 A/G polymorphism was associated with greater risk of CHD, and this association may be modified by diabetes status.

Keywords: Coronary heart disease, single nucleotide polymorphism, 9p21, rs10757274

Introduction

Coronary heart disease (CHD) is a complex multifactorial disorder for which genetic factors, environmental factors, and their interaction have been identified to be responsible for the etiology. As for genetic factors, the genome wide scanning has discovered several loci were associated with CHD. To date, the 9p21.3 locus CHDS8 is the most consistently replicated genetic locus for CHD [1-6]. It consists of 58-kbs and contains no annotated genes and is not associated with established CHD risk factors such as hyperlipidemia, hypertension, or diabetes. A single nucleotide polymorphism (SNP) in this locus, rs10757274 A/G has been replicated to be associated with CHD in some Caucasian populations [1, 7, 8], most excitingly, it was also replicated in Chinese population recently [9]. Since then, studies performed in Chinese population have shown that rs10757274 A/G polymorphism is not only associated with CHD [10], but also associated with stroke [11], and peripheral artery disease [12]. But obviously, more studies are needed to replicate and confirm its relationship with CHD.

Type 2 diabetes mellitus (T2D) is a CHD equivalent, and once CHD is concomitant with T2D, it usually representing itself as diffused, calcified, 3-vessel disease. Thus, T2D amplified the risk of complications in CHD. Genetic determinant for T2D is also located on human chromosome 9p21.3, which is located adjacent to CHDS8. This pattern of location has raised a research interest, and it's important to investigate the association of genetic variation with CHD, in the presence, and absence of T2D.

So, the current study was undertaken to evaluate the association of rs10757274 A/G polymorphism and risk of CHD, and whether this association will be modified by the concomitant status of diabetes.

Material and methods

Study population

The study participants were patients undergoing coronary angiography for suspected or known coronary atherosclerosis at Peking University First Hospital (Beijing, China) who consented to participate the study. Between June 2012 and May 2013, we selected a total of 1,462 consecutive patients (951 men and 511 women), who were all angiographically ascertained to have CHD or not. The criteria for diagnosis of CHD is 1) a ≥ 50% stenosis of at least one segment of a major coronary artery or their main branches confirmed by coronary angiography with typical angina; or 2) a history of documented myocardial infarction; or 3) a history of revascularization. Control subjects were those without coronary stenosis ≥ 50% at angiography, without a history of documented myocardial infarction, or a history of revascularization. All enrolled participants provided written consents. This study had been approved by the Ethics Committee of the Peking University First Hospital prior to commencement.

Information collection

Demographic and medical history data were obtained from each participant, including age, sex, ethnicity, body mass index (BMI), smoking status, alcohol intake, hypertension, hyperlipidemia and diabetes. Smoking status was defined as current active smokers or those with smoking history at least 10 pack-year, while alcohol intake was defined as consuming alcohol more than 50 g per week for at least 6 months. Weight and height were measured when the subjects lightly clothed and barefooted, and BMI was calculated as weight divided by the square of height (kg/m^2). Overnight fasting blood samples were obtained from all participants, and measurements of the plasma concentrations of glucose, total cholesterol (TCHO), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were conducted in the clinical laboratory of the Peking University First Hospital according to the standard biochemical methods. D2M was diagnosed according to the WHO criteria in 1999 [13]; hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg based on the average of two separate measurements, or antihypertensive treatment currently; hyperlipidemia was diagnosed as fasting total cholesterol ≥ 200 mg/dL or low-density lipoprotein cholesterol ≥ 130 mg/dL, or lipid lowering therapy currently.

Determination of genotypes

Genomic DNA was extracted from each participant's peripheral blood leucocytes by using the method of protein precipitation following standard procedures. All the DNA samples were quantified using Nanophotometer (Implen, Germany) and were diluted to a final concentration of 50 ng/uL. SNP genotyping was performed using the single base primer extension genotyping technology with the GenomeLab SNPstream genotyping system (Beckman Coulter Inc, Fullerton, CA, USA) following the manufacturer's protocol [14]. 10% of blind duplicate samples were genotyped repeatedly and the rate of consistency was 100%.

Statistical analysis

Data were analyzed using Statistics Package for Social Sciences software (SPSS, version 16.0; Chicago, IL, USA). The continuous variables were presented in the form of Mean ± SD, two-sample t test was adopted to compare their means. The comparison of categorical variables and the test of Hardy-Weinberg Equilibrium (HWE) among all participants were conducted using Pearson's χ^2 test. Unconditional logistic regression (ULR) was performed to estimate the association (Odds ratios (ORs) and 95% confidence intervals (CIs) between rs10757274 polymorphisms and CHD, adjusting for potential confounders, including age, sex, ethnicity, smoking status, alcohol intake, hypertension, hyperlipidemia and diabetes. Gene-environmental interactions were examined by using the generalized multifactor dimensionality reduction (GMDR, version 0.7, obtained from http://www.healthsystem.virginia.edu/internet/Addiction-Genomics/software/) method [14], adjusting for age, gender, ethnicity as covariates. GMDR is a nonparametric method reducing the high-dimensional data into one dimension. In this study, one to five factor mod-

Table 1. Baseline characteristics

	Controls	CHD patients	*P* value
N	294	1168	
Age (years)	61.98 ± 10.70	64.23 ± 10.81	0.002
Male subjects (%)	47.6	69.4	< 0.001
BMI (kg/m^2)	22.5 ± 2.9	23.6 ± 3.6	< 0.001
Han people (%)	94.2	96.7	0.045
Cigarette smoking (%)	35.7	54	< 0.001
Alcohol drinking (%)	26.2	35.5	< 0.001
Hypertension (%)	64.6	73.1	0.004
Diabetes (%)	24.1	40.8	< 0.001
Hyperlipidemia (%)	39.8	44.6	0.138

Data shown in the table: body mass index (BMI, kg/m^2).

Table 2. Hardy-Weinberg equilibrium test for rs10757274 genotype frequencies among all patients (N = 1,462)

Comparator	rs10757274 genotype			Allele	
	GG n (%)	AG n (%)	AA n (%)	G n (%)	A n (%)
Observed frequencies	312 (21.2)	735 (49.9)	425 (28.9)	(46.16)	(53.84)
Expected frequencies	313.7	731.7	426.7	-	-

χ^2 = Σ (observed frequencies-expected frequencies)^2/expected frequencies = 0.382, df = 1, P = 0.537. Rs10757274 genotype information was available for 1,462 patients.

els were constructed and the highest prediction accuracy model was defined as the "best model", and sign statistical test $P < 0.05$ is considered that the model is significant, then 1000 times permutation test was performed to validate the results.

Results

A total of 1168 CHD patients and 294 controls were studied in the present study. Demographic characteristics of the study subjects are summarized in **Table 1**. There were more males, hypertensive, diabetes, cigarette smokers and alcohol drinkers in the CHD group than in the control group, and the differences between the two groups were significant. BMI in the CHD group was significantly higher than in the control group.

Genotype frequencies for the rs10757274 A/G polymorphism were AA: 33.3%, AG: 51.0%, GG: 15.6% in the control group, and AA: 28.0%, AG: 50.1%, GG: 21.9% in the CHD group. The genotype distribution was in Hardy-Weinberg equilibrium (**Table 2**).

The association of the rs10757274 A/G polymorphism with the risk of CHD was summarized in **Table 3**. As compared to subjects with AA genotype, subjects with AG genotype had slightly higher risk of CHD (OR = 1.4, 95% CI: 1.03-1.91), while subjects with GG genotype had significantly higher risk of CHD (OR = 2.48, 95% CI: 1.64-3.76), after adjusting for age, sex, ethnicity, smoking status, alcohol intake, hypertension, hyperlipidemia, and diabetes.

We further analyzed the association of the rs10757274 A/G polymorphism with the risk of CHD with the patients stratified by diabetes (**Table 4**). The subgroup analysis showed different results for the association of rs10757274 A/G polymorphism with CHD: compared to subjects in the absence of diabetes with AA genotype, subjects in the presence of diabetes with both AG and GG genotypes had significantly higher risk of CHD (OR = 3.93, 95% CI: 2.40-6.44, $P < 0.001$; OR = 4.66, 95% CI: 2.14-10.14, $P < 0.001$; respectively). However, compared to subjects in the absence of diabetes with AA genotype, subjects in the absence of diabetes with AG genotype turned out to be not significantly associated to the risk of CHD (OR = 1.35, 95% CI: 0.93-1.96, $P = 0.114$), while subjects with GG genotype were consistently associated with a significantly higher risk of CHD (OR = 2.66, 95% CI: 1.65-4.28, $P < 0.001$), which indicated that potential gene-environmental interaction was likely to exist between Diabetes and rs10757274 polymorphism with the risk of CHD.

Finally, we performed a GMDR analysis using CHD as an endpoint to show the interaction between rs10757274 A/G polymorphism, diabetes, smoking and etc. (**Table 5**). After 1000 permutation tests, we found that among all the two-comparator-models, diabetes and rs10757274 A/G polymorphism has the most significant and highest accuracy of the interaction (accuracy is 60.60%, $P < 0.001$), which confirmed that Diabetes is likely to have an interaction with rs10757274 polymorphism when contributing the increased risk of CHD.

Table 3. Associations of rs10757274 with coronary heart disease

	Control subjects (n = 294)	CHD patients (n = 1168)	OR (95 CI)	P	OR_{adj} (95 CI)*	P
AA	98 (33.3)	327 (28.0)	1.00		1.00	
AG	150 (51.0)	585 (50.1)	1.17 (0.88-1.56)	0.289	1.40 (1.03-1.91)	0.032
GG	46 (15.6)	256 (21.9)	1.67 (1.13-2.45)	0.010	2.48 (1.64-3.76)	< 0.001

*Adjusted for age, sex, ethnicity, smoking status, alcohol intake, hypertension, hyperlipidemia and diabetes.

Table 4. Associations of rs10757274 A/G polymorphism with CHD in the presence and absence of diabetes

Comparator		CHD vs. Control			
	rs10757274	OR (95 CI)	P	OR_{adj} (95 CI)*	P
Absence of diabetes	AA	1.00		1.00	
	AG	1.30 (0.91, 1.85)	0.145	1.35 (0.93, 1.96)	0.114
	GG	2.14 (1.36, 3.37)	0.001	2.66 (1.65, 4.28)	< 0.001
Presence of diabetes	AG	3.21 (2.00, 5.15)	< 0.001	3.93 (2.40, 6.44)	< 0.001
	GG	3.58 (1.69, 7.57)	< 0.001	4.66 (2.14, 10.14)	< 0.001

*Adjusted for age, sex, ethnicity, smoking status, alcohol intake, hypertension and hyperlipidemia.

Table 5. GMDR models of gene-environmental interactions on MI risk

Models*	Prediction accuracy	CVC	P_{perm} †
Diabetes	58.84	10/10	< 0.001
Diabetes, rs10757274	60.60	10/10	< 0.001
Diabetes, Alcohol drinking, rs10757274	58.41	7/10	< 0.001
Diabetes, hyperlipidemia, Alcohol drinking rs10757274	54.29	4/10	0.022
Diabetes, hyperlipidemia, hypertension, Alcohol drinking, rs10757274	59.33	10/10	< 0.001

*Adjusting for age, gender, ethnicity as covariates. †*P* value from 1000 times permutation test.

Discussion

In the current study, we successfully replicated the association between risk of CHD and rs10757274 polymorphism, which had been identified by whole genome scan, and replicated in association studies, in both Caucasian populations and Chinese populations. We further discovered that there exists an interaction between the rs10757274 polymorphism and diabetes which is novel, but common in the etiology for complex disease.

Previous studies have shown that CHDS8 in which rs10757274 was located, was associated with a variety of phenotypes, like aortic aneurysm [15], stroke [16], glioma [17], and malignant melanoma [18]. However, the whole genome region is not responsible for coding any genes that has been proved to be related to CHD, indicating its potential role in regulation other genes. Animal studies have shown that deletion of the 70-kb noncoding interval on mouse chromosome 4 which is orthologous to human chromosome 9p21 could regulate cardiac expression of neighboring genes, and influence the proliferation properties of vascular cells [19]. It was shown that cardiac expression of 2 genes near the noncoding interval, Cdkn2a and Cdkn2b, was severely reduced in delta-70-kb homozygous mice, and primary cultures of aortic smooth muscle cells from homozygous delta-70-kb mice exhibited excessive proliferation and diminished senescence, a cellular phenotype consistent with accelerated CHD pathogenesis. So, we hypothesis that rs10757274 polymorphism, either directly altered the distant acting function of this interval, or indirectly associated with CHD risk by being linkage disequilibrium with another functional variation.

Our subgroup analyses showed that the association of rs10757274 A/G polymorphism with risk of CHD was modified by the concomitant

diabetes. For the homozygous GG genotype, its relationship with high risk of CHD was not affected by diabetes, but for heterozygote AG genotype, it was associated with high risk of CHD in subjects with diabetes, but not in subjects without diabetes. However, further interaction testing revealed that the interaction between rs10757274 A/G polymorphism and diabetes on CHD risk is statistical insignificant. Obviously, this novel discovery needs further confirmation, and once it could be conformed, more effort are needed to explore the gene-gene interaction in this chromosome region which contains both CHD susceptible locus and T2D susceptible locus.

There are several limitations of this study: firstly, the control group patients were suspicious of CHD undergoing angiography with no significant stenosis rather than the truly healthy people. Thus, the number of subjects are imbalanced in the two groups; secondly, we only genotyped the rs10757274 A/G polymorphism, which kept us from doing any haplotype analyses.

In conclusion, we confirmed in our study that the rs10757274 A/G polymorphism is associated with greater risk of CHD, and this association may be modified by diabetes.

Disclosure of conflict of interest

None.

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