# The Same Chromosome 9p21.3 Locus Is Associated With Type 2 Diabetes and Coronary Artery Disease in a Chinese Han Population

Xiang Cheng,[1,2,3] Lisong Shi,[2,3] Shaofang Nie,[1,3] Fan Wang,[2,3] Xiuchun Li,[2,3] Chengqi Xu,[2,3] Pengyun Wang,[2,3] Baofeng Yang,[4] Qingxian Li,[6] Zhenwei Pan,[4] Yue Li,[5] Hao Xia,[7] Chenhong Zheng,[8] Yuhe Ke,[8] Yanxia Wu,[8] Tingting Tang,[1,3] Xinxin Yan,[1,3] Yan Yang,[1,3] Ni Xia,[1,3] Rui Yao,[1,3] Binbin Wang,[9] Xu Ma,[9] Qiutang Zeng,[1,3] Xin Tu,[2,3] Yuhua Liao,[1,3] and Qing K. Wang[2,3]

**OBJECTIVE**—Recent genome-wide association studies (GWAS) revealed that a 9p21.3 locus was associated with type 2 diabetes. In this study, we carried out a large-scale case-control study in the GeneID Chinese Han population to *1*) further replicate the association of 9p21.3 type 2 diabetes GWAS single nucleotide polymorphisms (SNPs) and *2*) assess the association of these SNPs with coronary artery disease.

**RESEARCH DESIGN AND METHODS**—Three SNPs (rs2383208, rs10811661, and rs10757283) were genotyped in two GeneID cohorts of 3,167 Chinese Han individuals. Case-control association design was used to determine the association of the SNPs with type 2 diabetes and coronary artery disease. Gensini scores were calculated in the coronary artery disease subjects and were tested for association with the variants. Multivariate logistic regressions were performed on association studies.

**RESULTS**—The association between two of the three SNPs and type 2 diabetes was replicated in the GeneID population (rs2383208, $P = 0.936$; rs10811661-T, $P = 0.02$, odds ratio [OR] = 1.23; rs10757283-C, $P = 0.003$, OR = 1.30). The same two SNPs also contributed to the risk of coronary artery disease (CAD) (rs10811661-T, $P = 0.002$, OR = 1.19; rs10757283-C, $P = 0.003$, OR = 1.18). In addition, rs10757283 was associated with severity of coronary atherosclerosis estimated by the Gensini scoring system (risk allele C, quantitative-trait regression adjusted $P = 0.002$).

**CONCLUSIONS**—For the first time to our knowledge, our results indicated that the same 9p21.3 locus, represented by SNPs rs10811661 and rs10757283, contributed to the risk of type 2 diabetes and coronary artery disease in our GeneID Chinese Han population. ***Diabetes*** **60:680–684, 2011**

From the [1]Institute of Cardiology, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; the [2]Key Laboratory of Molecular Biophysics of Ministry of Education, College of Life Science and Technology, Center for Human Genome Research, Huazhong University of Science and Technology, Wuhan, China; the [3]Cardio-X Institute, Huazhong University of Science and Technology, Wuhan, China; the [4]Department of Pharmacology, Harbin Medical University, Harbin, China; the [5]Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China; the [6]Department of Cardiology, Jining Medical College Affiliated Hospital, Jining, China; the [7]Renmin Hospital of Wuhan University, Wuhan, China; the [8]Wuhan No.1 Hospital, Wuhan, China; and the [9]Research Institute of the National Population and Family Planning Commission, Beijing, China.

Corresponding authors: Xin Tu, xtu@mail.hust.edu.cn; Yuhua Liao, liaoyh27@163.com; or Qing K. Wang, qkwang@mail.hust.edu.cn.

Received 6 February 2010 and accepted 29 October 2010.

DOI: 10.2337/db10-0185

This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db10-0185/-/DC1.

X.C., L.S., and S.N. contributed equally to this work.



Type 2 diabetes mellitus and coronary artery disease (CAD) are both complex diseases that are caused by interactions among multiple genetic and environmental factors. Both of them reduce the quality of life and greatly increase mortality, and multiple approaches have been developed to understand the genetic basis of these complex disorders (1,2). Recently, several genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in a chromosome 9p21.3 region that contributed to risk of coronary heart disease/myocardial infarction (MI) (3–7) and type 2 diabetes (5,8–10). The 9p21.3 genetic variants associated with these two diseases seem to reside on two adjacent haplotype blocks in this region (44-kb CAD block from rs10116277 to rs1333049 and 4-kb type 2 diabetes block from rs10965243 to rs10757283) (11). Two recent studies with European populations suggested that these two blocks may be associated with the two diseases independently (12,13). One SNP, rs10811661, has been replicated of type 2 diabetes risk in East Asian populations (14–19) including Chinese (20,21). It was thought that type 2 diabetes and CAD may share common genetic and environmental antecedents (22,23). Whether this diabetic region contributes to both type 2 diabetes and CAD risk needs to be studied. In this study, we carried out a large-scale case-control study in our GeneID Chinese Han population to assess the association of three type 2 diabetes GWAS SNPs—rs2383208, rs10811661, and rs10757283—with type 2 diabetes and CAD.

## RESEARCH DESIGN AND METHODS

**Study subjects.** All participants in this study were selected from the GeneID database (24), which enrolls study subjects with the same Han ethnic origin from several hospitals in Central China (individuals enrolled in hospitals in Wuhan city were from Hubei province, Hunan province, Anhui province, and Henan province) and Northern China (individuals enrolled in hospitals in Jining, Harbin, and Beijing cities were from Shandong province, Heilongjiang province, and Beijing city). The study followed the principals outlined in the Declaration of Helsinki and has been approved by the local institutional review boards. Written informed consents were acquired from all participants. The GeneID-Central-China cohort was used as the discovery sample to test the association of the 9p21.3 locus with type 2 diabetes and CAD. The GeneID-Northern-China cohort was used as the replication population. Blood samples were drawn from the peripheral vein, and genomic DNA was isolated by using Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI).

**Diagnostic criteria of type 2 diabetes and CAD.** Type 2 diabetes was diagnosed as features of diabetes with a plasma glucose level of ≥200 mg/dL (11.1 mmol/L), or a fasting plasma glucose concentration of ≥126 mg/dL (7.0 mmol/L) after at least 8 h fasting, or a 2-h plasma glucose level of ≥200 mg/dL

(11.1 mmol/L) during an oral glucose tolerance test (OGTT) (25). Each glucose test was performed again at the subsequent day to confirm the diagnosis. CAD was defined as angiographically demonstrated stenosis of more than 70% in a major or a main branch of the coronary artery (26). All participants had undertaken both an OGTT and coronary angiography. Each subject was classified into one of the following groups: *1*) type 2 diabetes group, which comprised type 2 diabetes patients without stenosis in coronary arteries. Patients who had a MI record were also excluded from the type 2 diabetes group (27); *2*) CAD group, which comprised CAD patients without abnormal blood glucose levels; and *3*) control group, which comprised individuals who had neither abnormal blood glucose levels nor stenosis in any coronary artery. Individuals older than 80 years or younger than 30 years were excluded from this study.

**Other clinical data.** Data on age, sex, smoking, and smoking history were collected from the participants' medical records or by direct interviews. Hypertension was diagnosed as a blood pressure of higher than 140/90 mmHg, which was measured according to guidelines (28). Fasting concentrations of the total cholesterol (Tch), triglyceride (TG), LDL cholesterol (LDL-c), and HDL cholesterol (HDL-c) were measured using standard methods (29).

**Gensini scores.** Severity of coronary atherosclerosis was calculated according to the Gensini scoring system (30). In each segment, the narrowing of the coronary artery lumen is rated 1 for 0–25% stenosis, 2 for 26–50%, 4 for 51–75%, 8 for 76–90%, 16 for 91–99%, and 32 for 100%. Each stenosis score is multiplied by a factor, which is assigned to each coronary segment depending on vessel size and importance (ranging from 0.5 to 5.0). Each patient's Gensini index is the sum of the total weights for each segment. The association between Gensini scores and the three SNPs was assessed by treating the Gensini scores as a quantitative trait or using quartile case-control methods (31).

**SNP selection and genotyping.** We analyzed three GWAS suggestive SNPs—rs2383208, rs10811661, and rs10757283—covering the previously reported type 2 diabetic-risk region. They were selected according to type 2 diabetes GWAS reported by Scott et al. (rs2383208 and rs10811661) (8), Takeuchi et al. (rs2383208) (18), and Zeggini et al. (rs10811661 and rs10757283) (9).

All study individuals were genotyped for these three SNPs using a Rotor-Gene 6000 High-Resolution Melt (HRM) system (Corbett Life Science, Concorde, NSW, Australia). Genotyping was performed in a total of 25 μL PCR volume containing 1 μL of LC Green dye, 5 pmol of each primer, 25 ng of genomic DNA, 2.5 μL of 10× PCR buffer with 1.5 mmol/L $MgCl_2$, 5 mmol deoxynucleotide triphosphates, and 1 unit of Taq polymerase. Two positive controls for each genotype were included in each run. For each SNP, a total of 48 cases and controls were randomly selected for verification of genotyping results using direct DNA sequencing analysis. DNA sequence analysis was performed with forward and/or reverse primers using the BigDye Terminator v3.1 Cycle Sequencing Kits on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA).

**Statistical analysis.** A statistical power analysis was performed using PS software version 3.0.2 for a case-control design (32). Hardy-Weinberg equilibrium tests were carried out for each SNP among control groups by using PLINK software version 1.05 (33). Allelic and genotypic associations of SNPs with a binary disease trait were assessed using Pearson's $2 \times 2$ and $2 \times 3$ contingency table $\chi^2$ tests (PLINK). Odds ratios (ORs) and 95% confidence intervals (CI) were estimated using $\chi^2$ tests (PLINK). Multivariate analysis was performed by incorporating age, sex, hypertension, smoking history, Tch, TG, HDL-c, and LDL-c level as covariates by using multivariate logistic regression (PLINK). Gensini scores P-P plot was generated by SPSS v13.0 to test for normal distribution. The quantitative trait association of Gensini scores was calculated after $\log_e$-transformation (PLINK). All CAD patients were classified into quartiles of Gensini score levels. The first (lowest) and the fourth (highest) quartile were selected to carry out a case-control SNP association analysis. Linkage disequilibrium (LD) block patterns were constructed by Haploview software version 4.0 based on $r^2$ values.

## RESULTS

**Population characteristics and power analysis.** Two cohorts of study subjects were studied, and they are the GeneID-Central-China cohort and GeneID-Northern-China cohort. Table 1 shows the detailed clinical features of the two cohorts. Among a total of 1,724 individuals in the GeneID-Central-China cohort, 379 were diagnosed as type 2 diabetic cases, 496 as CAD cases, and 849 as controls. Mean ages (with standard deviations) of the three groups were 55.3 ± 11.4, 60.6 ± 10.7, and 54.6 ± 13.2, respectively. Proportions of men were 57.0, 64.9, and 46.6%, respectively. The GeneID-Northern-China cohort consisted of 1,443 individuals, of whom 597 were CAD cases and 846 were controls. Mean ages (with standard deviation) were 60.8 ± 11.3 for the CAD group and 55.4 ± 14.0 for the control group.

Under the population parameter settings of the effect size (OR of 1.3 for type 2 diabetes and 1.2 for CAD) (17,18,34–36), an allelic frequency of 0.37 (HapMap CHB data, the minimum minor allele frequency (MAF) among the three SNPs was 0.37 for rs10757283) and nominal Type I error of 0.05, our sample size for type 2 diabetes can provide 83.8% of statistical power and the CAD samples size can provide 90.7% power. The power analysis indicated that our GeneID sample sizes were sufficient to test the association between the 9p21.3 locus and type 2 diabetes and CAD.

**9p21.3 SNPs were associated with type 2 diabetes in a Chinese Han GeneID population.** The call rate was 100% for three SNPs in all samples. All three SNPs gained quality control results of 100% according to 48 random selected DNA samples direct sequencing verification of HRM genotyping for each SNP. There was no deviation from the Hardy-Weinberg equilibrium for the three 9p21.3

TABLE 1
Clinical characteristics of the study populations

| | GeneID-Central-China | | | GeneID-Northern-China | |
|---|---|---|---|---|---|
| Characteristics | Type 2 diabetes | CAD | Control | CAD | Control |
| *n* | 379 | 496 | 849 | 597 | 846 |
| Age (years)* | 55.3 ± 11.4 | 60.6 ± 10.7 | 54.6 ± 13.2 | 60.8 ± 11.3 | 55.4 ± 14.0 |
| Sex (% men) | 57.0 | 64.9 | 46.6 | 60.6 | 48.1 |
| Smoking (%) | 28.2 | 34.8 | 11.7 | 47.6 | 16.1 |
| Fasting plasma glucose (mmol/L) | | 5.0 ± 0.8 | 4.9 ± 0.6 | 4.8 ± 0.7 | 4.8 ± 0.8 |
| 2-Hour plasma glucose (mmol/L) | | 6.0 ± 1.3 | 5.8 ± 1.5 | 5.6 ± 1.6 | 5.7 ± 1.1 |
| BMI ($kg/m^2$) | 24.6 ± 4.3 | 24.0 ± 3.2 | 23.5 ± 3.5 | 24.3 ± 3.5 | 23.8 ± 3.0 |
| Hypertension (%) | 66.0 | 56.7 | 4.6 | 61.7 | 7.0 |
| Tch (mmol/L) | 4.63 ± 1.16 | 4.31 ± 1.15 | 4.20 ± 1.12 | 4.86 ± 0.98 | 4.60 ± 0.92 |
| TG (mmol/L) | 1.94 ± 1.03 | 1.89 ± 1.28 | 1.72 ± 1.28 | 2.05 ± 1.12 | 1.98 ± 1.52 |
| HDL-c (mmol/L) | 1.11 ± 0.37 | 1.17 ± 0.60 | 1.22 ± 0.31 | 1.08 ± 0.38 | 1.12 ± 0.32 |
| LDL-c (mmol/L) | 2.71 ± 0.83 | 2.60 ± 0.87 | 2.37 ± 0.73 | 3.11 ± 0.90 | 2.92 ± 0.86 |
| Gensini score | | 30.2 ± 28.9 | | 28.5 ± 25.2 | |

Data are presented as means ± SD or percent. *Age for the case group refers to age at diagnosis; age for the control group refers to age at which the study subject was enrolled.

SNPs in all control groups. Two of these three SNPs showed significant association with type 2 diabetes in the GeneID-Central population (rs10811661-T, $P = 0.02$, OR = 1.23, 95% CI 1.03–1.47; rs10757283-C, $P = 0.003$, OR = 1.30, 95% CI 1.09–1.54) (Table 2). Significant genotypic association was also found between these two variants and type 2 diabetes (additive model $P$ values after adjustment for covariates of 0.006 for both SNPs) (Supplementary Table 1). Association of rs2383208 was not significant in neither allelic ($P = 0.936$) nor genotypic association (additive model $P = 0.468$) with disease (Table 2 and Supplementary Table 1). All $P$ values retained their initial significance status after multivariate logistic regression (adjustive $P$ values in Table 2 and Supplementary Table 1).

**The three 9p21.3 SNPs were associated with CAD in Chinese GeneID cohorts.** In GeneID-Central-China cohort, rs10811661 and rs10757283 showed significant allelic association with CAD ($P = 0.030$ and 0.026, respectively), whereas no allelic association was detected for SNP rs2383208 ($P = 0.259$) (Table 2). The CAD association was replicated in our GeneID-Northern-China cohort with $P$ values of 0.028 and 0.039 for rs10811661 and rs10757283, respectively (Table 2). Association for rs2383208 did not reach the significant level ($P = 0.108$) (Table 2). In the combined population of the two GeneID Chinese cohorts, the CAD association remained significant for rs10811661 (T allele, $P = 0.002$, OR = 1.19, 95% CI 1.06–1.33) and rs10757283 (C allele, $P = 0.003$, OR = 1.18, 95% CI 1.06–1.32) (Table 2). SNP rs2383208 gained a near significant allelic $P$ value of 0.058 (Table 2). For rs10811661 and rs10757283, significant genotypic association was also found assuming an additive model ($P = 5.72 \times 10^{-4}$ and 0.005, respectively) (Supplementary Table 1). All $P$ values retained their initial significance status after multivariate logistic regression (adjustive $P$ values in Table 2 and Supplementary Table 1).

**SNP rs10757283 was associated with the Gensini scores in the Chinese GeneID population.** We estimated the severity of coronary atherosclerosis by the Gensini scoring system and found that the scores of GeneID CAD patients followed the normal distribution after natural log transformation (Supplementary Figs. 1 and 2). When analyzed as a quantitative trait, significant association for severity of atherosclerosis was found for SNP rs10757283 (observed $P = 2.48 \times 10^{-9}$, adjusted $P = 0.002$ after logistic regression with 11 clinical traits as covariates) but not for SNPs rs2383208 and rs10811661 (observed $P = 0.134$ and 0.263, adjusted $P = 0.567$ and 0.488, respectively, after logistic regression with 11 covariates) (Table 3).

When the distribution of the risk alleles in the highest and lowest Gensini score quartiles of patients was compared in a case-control design, significant association was obtained again with SNP rs10757283 (observed $P = 9.5 \times 10^{-10}$, adjusted $P = 0.006$ after logistic regression with 11 covariates, OR = 2.09, 95% CI 1.65–2.64) but not with SNPs rs2383208 and rs10811661 (Table 3).

## DISCUSSION

In this study, we carried out an extensional replication study for the association of a chromosome 9p21.3 locus tagged by rs2383208, rs10811661, and rs10757283 with type 2 diabetes in a Chinese population, and the results indicate that this locus confers a significant risk of type 2 diabetes in our GeneID Chinese population. For the first time to our knowledge, this study also demonstrated that this same diabetic locus was associated with CAD.

The association between rs2383208 and type 2 diabetes in GWAS reports (8,18) was not replicated in our GeneID Chinese population in neither allelic nor genotypic analysis. For rs10811661, we further confirmed its genetic risk on type 2 diabetes in the Chinese population, which was in accordance with previous studies in both risk allele (major allele T) and risk effect (OR = 1.2–1.3) (20,21). For SNP rs10757283, we replicated its association with type 2 diabetes for the first time in a Chinese Han population. It was noteworthy that the risk allele of this variant was C in our GeneID Chinese population instead of T in previously

TABLE 2
Allelic association of 9p21.3 SNPs rs2383208, rs10811661, and rs10757283 with type 2 diabetes and CAD in the Chinese GeneID population

| SNP (risk allele) | Risk AF | | $P$ | OR (95% CI) | $P$-adj* |
|---|---|---|---|---|---|
| | Case | Control | | | |
| Type 2 diabetes | | | | | |
| GeneID-Central-China (379 cases/849 controls) | | | | | |
| rs2383208(G) | 0.424 | 0.425 | 0.936 | 0.99 (0.84–1.18) | 0.806 |
| rs10811661(T) | 0.621 | 0.571 | 0.020 | 1.23 (1.03–1.47) | 0.021 |
| rs10757283(C) | 0.472 | 0.409 | 0.003 | 1.30 (1.09–1.54) | 0.004 |
| CAD | | | | | |
| GeneID-Central-China (496 cases/849 controls) | | | | | |
| rs2383208(G) | 0.448 | 0.425 | 0.259 | 1.10 (0.94–1.28) | 0.206 |
| rs10811661(T) | 0.614 | 0.571 | 0.030 | 1.19 (1.02–1.40) | 0.048 |
| rs10757283(C) | 0.453 | 0.409 | 0.026 | 1.20 (1.02–1.40) | 0.013 |
| GeneID-Northern-China (597 cases/846 controls) | | | | | |
| rs2383208(G) | 0.437 | 0.407 | 0.108 | 1.13 (0.97–1.31) | 0.121 |
| rs10811661(T) | 0.609 | 0.568 | 0.028 | 1.18 (1.02–1.38) | 0.031 |
| rs10757283(C) | 0.446 | 0.408 | 0.039 | 1.17 (1.01–1.36) | 0.035 |
| GeneID-combined (1,093 cases/1,695 controls) | | | | | |
| rs2383208(G) | 0.442 | 0.416 | 0.058 | 1.11 (1.00–1.24) | 0.061 |
| rs10811661(T) | 0.611 | 0.570 | 0.002 | 1.19 (1.06–1.33) | 0.004 |
| rs10757283(C) | 0.449 | 0.408 | 0.003 | 1.18 (1.06–1.32) | 0.001 |

AF, allele frequency. *Adjusted $P$ values were obtained using multivariate logistic regression analysis.

TABLE 3
Associations of LN-transformed Gensini score with the three SNPs of 1,093 cases

| | Quantitative trait association | | | | | Case-control association* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Quartile risk AF ($n$) | | | | |
| SNP (risk allele) | β | SE | $r^2$ | $P$ | $P$-adj† | 1st (304) | 4th (265) | $P$ | OR (95% CI) | $P$-adj† |
| rs2383208(G) | 0.053 | 0.047 | 0.001 | 0.134 | 0.567 | 0.428 | 0.381 | 0.111 | 1.21 (0.96–1.54) | 0.748 |
| rs10811661(T) | −0.066 | 0.044 | 0.002 | 0.263 | 0.488 | 0.378 | 0.406 | 0.345 | 0.89 (0.70–1.13) | 0.945 |
| rs10757283(C) | 0.267 | 0.045 | 0.032 | $2.48 \times 10^{-9}$ | 0.002 | 0.401 | 0.583 | $9.50 \times 10^{-10}$ | 2.09 (1.65–2.64) | 0.006 |

*The 1st and 4th quartiles of LN[Gensini score] distribution were used to carried out case-control association analysis. The 4th quartile was defined as the highest Gensini score quartile, which meant that patients in this quartile were in the worst condition of coronary atherosclerosis. †Adjusted $P$ values were obtained using multivariate logistic regression analysis with age, sex, hypertension, smoking history, BMI, glucose level, Tch, TG, HDL-c, and LDL-c level as covariates.

published European ancestry populations. This result may be false positive because of limited sample size, or 10757283 may be only a marker so that the two different risk alleles in distinct ethical populations are in LD with the unidentified causative SNP/gene allele. Thus future studies are needed in various populations to investigate the association of rs10757283 with type 2 diabetes.

The association between CAD and chromosome 9p21.3 has been reported and confirmed in various populations. Most of these CAD-associated SNPs lie in a 44-kb LD block (11). Our findings provided the evidence of extensional association of variants in an adjacent diabetic region with CAD phenotype. To our knowledge, it is the first report that the same SNPs confer to both type 2 diabetes and coronary heart disease. To investigate whether these newly found CAD SNPs are an extension of the previously reported CAD LD region, we constructed and compared the linkage disequilibrium pattern of a 150-kb 9p21.3 region (chromosome 9 from 22.05 to 22.20 Mb containing previously reported CAD associated locus and type 2 diabetic region) based on HapMap data and our GeneID SNP array data. The results showed that these disease risk SNPs were in LD in our control samples (Supplementary Fig. 3). Populations of different ancestry origin showed a highly consistent LD pattern: there exists a high recombination rate interval between these two disease-associated LD regions (Supplementary Fig. 4). When the nearest upstream CAD-risk SNP rs1333049 was compared with the strongest effect SNP rs10757283 in this study, we found that these two variants seemed to be totally independent from each other whether examined in HapMap CEU ($D'$ = 0.14, $r^2$ = 0.02), HapMap CHB ($D'$ = 0.28, $r^2$ = 0.05), or in our GeneID population ($D'$ = 0.11, $r^2$ = 0.01). These data suggested that these three SNPs might not be in linkage with the upstream CAD LD block and would contribute to CAD risk independently.

The Gensini scoring system is a well-used method for measuring the severity of coronary atherosclerosis, which is the primary pathophysiological process underlying CAD (37). Because our 1,093 Gensini scores were in accordance with normal distribution after $\log_e$-transformation (Supplementary Figs. 1 and 2), we performed quantitative trait association and quartile case-control association studies for the three 9p21.3 SNPs. For both analyses, rs10757283 gained significant observed $P$ values (risk allele C, quantitative trait $P = 2.48 \times 10^{-9}$, quartile case-control, $P = 9.50 \times 10^{-10}$). We also performed logistic regressions by incorporating as much clinical data as possible (age, sex, hypertension, smoking history, Tch, TG, HDL-c, and LDL-c level, BMI, fast glucose, and OGTT as covariates) (Table 3). The results showed that the association between Gensini scores and rs10757283 was still significant (risk allele C, quantitative trait $P$-adj = 0.002, quartile case-control, $P$-adj = 0.006, respectively) (Table 3). These suggested that SNP rs10757283 genotype might influence the coronary atherosclerosis degree and increase CAD risk in the Chinese Han population.

Type 2 diabetes and CAD have been thought to share common genetic and environmental antecedents, described as a common soil (22,23). In this study, our findings provided possible genetic evidences that the same genetic variants in a 9p21.3 locus contributed to risk of both type 2 diabetes and CAD. Despite these findings, our case-control association study has limitations that our results are difficult to reveal the underlying shared causative molecular mechanism on pathology of these two disorders. Further studies are needed to focus on the discovery of potential molecular and physiological pathways that involve the two disease development.

In conclusion, our results indicated that the same 9p21.3 locus, represented by SNPs rs10811661 and rs10757283, contributed to the risk of type 2 diabetes and CAD in our GeneID Chinese Han population.

## ACKNOWLEDGMENTS

This work was supported by the China National Basic Research Program (973 Program 2007CB512000), China National 863 Scientific Program (2006AA02Z476), National Natural Science Foundation of China (30800457, 30900803, 30971592, 30871067), Program for New Century Excellent Talents in University of China (NCET-09-0380), a Key Program of Hubei Province Natural Science Fund (2008CDA047), and an Academic Leader Project of Wuhan City (200951830560). This study had no relationship with any industry.

No potential conflicts of interest relevant to this article were reported.

X.C., L.S., S.N., F.W., X.L., C.X., P.W., B.Y., Q.L., Z.P., Y.L., H.X., C.Z., Y.K., Y.W., T.T., X.Y., Y.Y., N.X., R.Y., B.W., X.M., and Q.Z. researched data. X.C., L.S., and S.N. wrote the article. B.Y., X.T., Y.L., and Q.K.W. contributed to discussion. X.T., Y.L., and Q.K.W. reviewed and edited the article.

## REFERENCES

1. Watkins H, Farrall M. Genetic susceptibility to coronary artery disease: from promise to progress. Nat Rev Genet 2006;7:163–173
2. Prokopenko I, McCarthy MI, Lindgren CM. Type 2 diabetes: new genes, new understanding. Trends Genet 2008;24:613–621
3. Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 2007; 316:1491–1493

4. Samani NJ, Erdmann J, Hall AS, et al, WTCCC and the Cardiogenics Consortium. Genomewide association analysis of coronary artery disease. N Engl J Med 2007;357:443–453
5. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661–678
6. Helgadottir A, Thorleifsson G, Magnusson KP, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet 2008;40:217–224
7. Kathiresan S, Voight BF, Purcell S, et al; Myocardial Infarction Genetics Consortium; Schunkert H, Erdmann J, Linsel-Nitschke P, et al; Wellcome Trust Case Control Consortium. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet 2009;41:334–341
8. Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 2007;316:1341–1345
9. Zeggini E, Weedon MN, Lindgren CM, et al.; Wellcome Trust Case Control Consortium (WTCCC). Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 2007;316:1336–1341
10. Saxena R, Voight BF, Lyssenko V, et al.; Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 2007;316:1331–1336
11. Silander K, Tang H, Myles S, et al. Worldwide patterns of haplotype diversity at 9p21.3, a locus associated with type 2 diabetes and coronary heart disease (Abstract). Genome Med 2009;1:51
12. Broadbent HM, Peden JF, Lorkowski S, et al.; PROCARDIS consortium. Susceptibility to coronary artery disease and diabetes is encoded by distinct, tightly linked SNPs in the ANRIL locus on chromosome 9p. Hum Mol Genet 2008;17:806–814
13. Gori F, Specchia C, Pietri S, et al.; GISSI Prevenzione Investigators; SIBioC-GISSI Prevenzione Group. Common genetic variants on chromosome 9p21 are associated with myocardial infarction and type 2 diabetes in an Italian population. BMC Med Genet 2010;11:60
14. Cho YM, Kim TH, Lim S, et al. Type 2 diabetes-associated genetic variants discovered in the recent genome-wide association studies are related to gestational diabetes mellitus in the Korean population. Diabetologia 2009;52:253–261
15. Lee YH, Kang ES, Kim SH, et al. Association between polymorphisms in SLC30A8, HHEX, CDKN2A/B, IGF2BP2, FTO, WFS1, CDKAL1, KCNQ1 and type 2 diabetes in the Korean population. J Hum Genet 2008;53:991–998
16. Omori S, Tanaka Y, Takahashi A, et al. Association of CDKAL1, IGF2BP2, CDKN2A/B, HHEX, SLC30A8, and KCNJ11 with susceptibility to type 2 diabetes in a Japanese population. Diabetes 2008;57:791–795
17. Horikawa Y, Miyake K, Yasuda K, et al. Replication of genome-wide association studies of type 2 diabetes susceptibility in Japan. J Clin Endocrinol Metab 2008;93:3136–3141
18. Takeuchi F, Serizawa M, Yamamoto K, et al. Confirmation of multiple risk Loci and genetic impacts by a genome-wide association study of type 2 diabetes in the Japanese population. Diabetes 2009;58:1690–1699
19. Tabara Y, Osawa H, Kawamoto R, et al. Replication study of candidate genes associated with type 2 diabetes based on genome-wide screening. Diabetes 2009;58:493–498
20. Ng MC, Park KS, Oh B, et al. Implication of genetic variants near TCF7L2, SLC30A8, HHEX, CDKAL1, CDKN2A/B, IGF2BP2, and FTO in type 2 diabetes and obesity in 6,719 Asians. Diabetes 2008;57:2226–2233
21. Wu Y, Li H, Loos RJ, et al. Common variants in CDKAL1, CDKN2A/B, IGF2BP2, SLC30A8, and HHEX/IDE genes are associated with type 2 diabetes and impaired fasting glucose in a Chinese Han population. Diabetes 2008;57:2834–2842
22. Wagenknecht LE, Bowden DW, Carr JJ, Langefeld CD, Freedman BI, Rich SS. Familial aggregation of coronary artery calcium in families with type 2 diabetes. Diabetes 2001;50:861–866
23. Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes 1995;44:369–374
24. Shi L, Li C, Wang C, et al. Assessment of association of rs2200733 on chromosome 4q25 with atrial fibrillation and ischemic stroke in a Chinese Han population. Hum Genet 2009;126:843–849
25. American Diabetes Association. Standards of medical care in diabetes—2008. Diabetes Care 2008;31(Suppl. 1):S12–S54
26. Shen GQ, Li L, Rao S, et al. Four SNPs on chromosome 9p21 in a South Korean population implicate a genetic locus that confers high cross-race risk for development of coronary artery disease. Arterioscler Thromb Vasc Biol 2008;28:360–365
27. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432–440
28. Mancia G, De Backer G, Dominiczak A, et al.; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–1187
29. Ye S, Willeit J, Kronenberg F, Xu Q, Kiechl S. Association of genetic variation on chromosome 9p21 with susceptibility and progression of atherosclerosis: a population-based, prospective study. J Am Coll Cardiol 2008;52:378–384
30. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51:606
31. Roman MJ, Devereux RB, Kizer JR, et al. High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. J Am Coll Cardiol 2009;54:1730–1734
32. Dupont WD, Plummer WD Jr. Power and sample size calculations. A review and computer program. Control Clin Trials 1990;11:116–128
33. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–575
34. Zhou L, Zhang X, He M, et al. Associations between single nucleotide polymorphisms on chromosome 9p21 and risk of coronary heart disease in Chinese Han population. Arterioscler Thromb Vasc Biol 2008;28:2085–2089
35. Yang XC, Zhang Q, Chen ML, et al. MTAP and CDKN2B genes are associated with myocardial infarction in Chinese Hans. Clin Biochem 2009;42:1071–1075
36. Ding H, Xu Y, Wang X, et al. 9p21 Is a shared susceptibility locus strongly for coronary artery disease and weakly for ischemic stroke in Chinese Han population. Circ Cardiovasc Genet 2009;2:338–346
37. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481–3488