Association of polymorphisms in *CYP2C8* and *CYP2C9* with susceptibility to type 2 diabetes mellitus in a Chinese population

Li Jin
Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Yan Huang
Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Yangyang Li
Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Cinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Bo Xu
Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Cheng Hu
Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People's Hospital https://orcid.org/0000-0003-4314-2386

Rong Zhang (rongzhang11@hotmail.com)
Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People's Hospital

Research article

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Abstract

Background: *CYP2C8* and *CYP2C9* are cytochrome P450 epoxygenases that metabolize arachidonic acid into epoxyeicosatrienoic acids (EETs). EETs are important lipid mediators with many beneficial effects in type 2 diabetes mellitus. In this study, we aimed to investigate the association of *CYP2C8* and *CYP2C9* variants with type 2 diabetes in a Chinese population.

Methods: We genotyped 9 tag single nucleotide polymorphisms (SNPs) in *CYP2C8* and 10 tag SNPs in *CYP2C9* based on HapMap Chinese and Japanese data. Then, we genotyped the SNPs in a Chinese population that included 3410 type 2 diabetes patients and 3401 normal controls. The association between the SNPs and type 2 diabetes was analysed.

Results: In the study population, we found that rs1819173 in the *CYP2C9* gene region was associated with type 2 diabetes and the A allele was protective against type 2 diabetes (odds ratio: 0.840, 95% confidence interval (CI): 0.780-0.904, P=3.04×10^{-6}). Haplotypes GT and AT (rs2071426-rs6583967) in *CYP2C8* were associated with type 2 diabetes (P=0.049 and 0.038, respectively). On the other hand, an interaction effect between rs1819173 in *CYP2C9* and rs12766752 in *CYP2C8* on type 2 diabetes was found (P=0.003). What's more, rs1819173 showed significant association with HDL-C (high-density lipoprotein cholesterol).

Conclusions: Our results suggested that common SNPs in the *CYP2C8* and *CYP2C9* regions were associated with T2DM in a Chinese Han population.

Background

Type 2 diabetes mellitus (T2DM), a form of diabetes mellitus (DM), is one of the most well-known chronic diseases in the world. It is a metabolic disorder characterised by increased insulin resistance and impaired insulin secretion [1]. According to a recent report in the International Diabetes Federation Diabetes Atlas [2], the prevalence of DM in adults is 9.1%, accounting for 415 million adults with DM. Furthermore, 318 million adults suffer from impaired glucose regulation, and their risk of developing DM in the future is high. China has the largest number of people with DM, and since approximately 90% of diabetic patients have T2DM, this disease should receive more attention [3]. The risk factors associated with the development of DM are increased insulin resistance, visceral fatty deposits, westernisation of the diet, unhealthy lifestyle and genetic background [4]. Urbanisation and environmental toxicity also play a role in increasing the risk of developing DM. Increased environmental pollutants, including those in air, food and water, are closely associated with the incidence of metabolic disorders, but different individuals have different capabilities for metabolising toxins, depending on their genetic backgrounds [5, 6]. Hence, polymorphisms in the genes involved in metabolising xenobiotics may be part of the key to resolving the genetic architecture of T2DM.

The cytochrome P450 (CYP) family is a group of enzymes responsible for phase I biotransformation, during which various endogenous and exogenous compounds are metabolised. On the other hand, CYP gene family have more variability than major regions in other genes [7]. As a result, they have the potential capacity to influence the susceptibility to drug metabolism, endogenous compound metabolism and toxin degradation. *CYP2C8* and *CYP2C9* are important genes in the CYP2C family, and their polymorphisms influence an individual's predisposition to various metabolic disorders and certain cancers [8-10]. Both genes are located on chromosome 10q24. The *CYP2C8* gene could influence the metabolism of anti-diabetic drugs, such as the thiazolidinedione class, including rosiglitazone and pioglitazone [11, 12]. The *CYP2C9* gene is one of the most common CYP enzymes in the liver, accounts for approximately 18% of the cytochrome P450 protein in liver microsomes and catalyses more than 100 therapeutic drugs, including thiazolidinediones and sulfonylureas [12-14]. Genetic polymorphisms in *CYP2C8* and *CYP2C9* can influence the catalytic activity of the enzyme and affect xenobiotic metabolism in the body. On the other hand, members of the CYP2C gene family are also known arachidonic acid (AA) epoxygenases that mediate the formation of epoxyeicosatrienoic acids (EETs) [8]. Animal studies have overwhelmingly and consistently shown a protective role of EETs in the aetiology and progression of DM [15, 16]. EETs can improve plasma glucose and insulin levels and improve glucose tolerance. They can also activate the PPAR-γ and MAPK pathways, as well as increase atrial natriuretic peptide production, and elevated EET levels are also accompanied by alleviated inflammatory responses and decreased dyslipidaemia [15, 17-19]. The abovementioned studies implicate the production of EETs in the prevention of DM and its cardiovascular consequences. Thus, polymorphisms in the CYP2C family genes may influence the production of EETs. Therefore, in this candidate gene study, we aimed to investigate the association of *CYP2C8* and *CYP2C9* polymorphisms with T2DM and provide genetic evidence for T2DM susceptibility.

Methods

Ethical approval

The Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital assured ethical approval according to the Helsinki Declaration II. All subjects provided written informed consent to participate.

Participants

We recruited a total of 6822 individuals in the study, including 3410 type 2 diabetic patients from endocrinology and metabolism department, and 3412 normal glucose metabolism controls from a community epidemiological survey. They were all unrelated subjects living in Shanghai and surrounding areas. Type 2 diabetic patients were diagnosed by World Health Organization criteria (fasting plasma glucose ≥ 7.0 mmol/L and/or 2-h post challenge plasma glucose ≥ 11.1 mmol/L) and individuals received treatment with oral hypoglycaemic drugs and/or insulin. The controls had normal oral glucose tolerance test（fasting plasma glucose ＜6.1 mmol/L and/or 2-h post challenge plasma glucose < 7.8 mmol/L）. Individuals with type 1 diabetes,

pregnancy, severe infection, drug or alcohol addiction, cancers, severe mental disorders or disabilities were excluded. Detailed information was mentioned before [20].

Clinical measurement

Anthropometric characteristics were collected, such as age, gender, height, weight, duration of diabetes, blood lipid level (Triglyceride, cholesterol, low density lipoprotein- cholesterol, high density lipoprotein-cholesterol). Body mass index (BMI) was defined as weight (kg) / height^2 (m^2). Plasma glucose and serum insulin level were measured after a standard 75 g oral glucose tolerance test. At 0 min, 30 min and 120 min, blood samples were obtained. Plasma glucose levels were analysed by the glucose oxidase method, insulin levels were analysed by radioimmunoassay (Linco Research, St. Charles, MO, USA). HbA1c levels were measured in Bio-Rad Variant II Hb testing system by high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA). We calculated the areas under the curve for glucose and insulin (GAUC and IAUC, respectively) using the trapezoidal rule and estimated the insulinogenic index. Homeostasis model assessment (HOMA) were used to estimated participants' insulin sensitivity and insulin secretion ability [21]. Furthermore, three indices proposed by Stumvoll et al. and Gutt et al. (Stumvoll first phase and second phase insulin secretion and the Gutt index) were also used [22, 23].

Single nucleotide polymorphism selection, genotyping and quality control

For the selection of tag single nucleotide polymorphisms (SNPs), Haploview 4.2 software was used. The SNPs were obtained from the HapMap phase III JPT+CHB database using a threshold of $r^2 \geq 0.5$. In addition, the SNPs were located in *CYP2C8* and *CYP2C9* gene regions including 30 kb upstream and 30 kb downstream. We selected 9 tag SNPs for *CYP2C8* and 10 tag SNPs for *CYP2C9*. The tag SNPs have a minor allele frequency (MAF)≥0.05. In order to cover the most part of the physical location of the genes, the SNP were located in intron or non-coding region part, so the classic variation in exome region like *CYP2C8**2 or *CYP2C8**3 were not analysis in our study. All SNPs were genotyped by MassArray Compact Analyzer (Agena Bioscience, San Diego, CA, USA) with matrix-assisted laser desorption ionisation-time of flight mass spectrometry. Then, we tested the data quality in our sample; all SNPs should have had a MAF more than 0.01. All of the SNPs passed quality control with call rates≥90% and concordance rates≥99%.

Statistical analysis

Hardy-Weinberg equilibrium was assessed by the chi-square test for each tag SNP to verify the normal genotype distributions (*P*-value ≥0.05 was considered indicative of statistical significance). Haploview 4.2 was used to perform pairwise linkage disequilibrium (LD) analysis. Genotype distribution between cases and controls was analysed by logistic regression, we use a genetic additive model to analyse the association between SNP genotype and the occurrence of T2DM, Odds ratios (ORs) with Standard errors or 95% confidence intervals (CIs) are shown, ORs were given accorded by minor allele. Permutation test under 10000 permutations was used to multiple hypothesis test correction (empirically *P* value), pointwise empirically *P* value were calculated under 10000 permutations considering of LD level in the local genome region. Haplotype analysis was used to calculated the relationship between haplotype block and disease occurrence. Genotype interactions was calculated under logistic regression. The effect of genotype on quantitative traits was tested by linear regression under an additive model. Quantitative traits with a skewed distribution were logarithmically transformed before linear regression analysis. All of these analyses were performed using PLINK and SAS 9.3 software (SAS Institute, Cary, NC, USA). A two-tailed *P*-value ≤ 0.05 was considered to indicate statistical significance.

Results

Association analysis of SNPs with T2DM

All the tag SNPs in *CYP2C8* and *CYP2C9* were in Hardy-Weinberg equilibrium. The clinical characteristics of T2DM case-control group were shown in Table 1. We tested the association between tag SNPs and T2DM. As shown in Table 2, rs1819173 in *CYP2C9* was significantly associated with decreased susceptibility to T2DM, and individuals with A allele were protected against T2DM (odds ratio: 0.840, 95% CI: 0.780-0.904, $P=3.04\times10^{-6}$). The distribution of rs2071426 in *CYP2C8* differed between T2DM patients and normal controls, and the frequency of the minor allele G was higher in controls (P=0.042). However, after adjusting for confounding factors (age, sex and BMI), the significant association disappeared (*P*=0.055). After adjustment for multiple comparisons, only rs1819173 showed a significant association with T2DM. Based on 10,000 permutations, the empirical *P*-value and the empirical *P*-value (pointwise) consider of LD were 3×10^{-4} and 2×10^{-4}, respectively.

Table 1. Clinical characteristics of the study samples

	Case	Control	*P*-Value
Sample (n)	3410	3412	-
Male (%)	53.14%	39.95%	<0.01
Age (years)	60.24±12.58	51.37±14.36	<0.01
BMI (kg/m^2)	24.19 (22.00,26.60)	23.24 (21.27,25.51)	0.04
Fasting plasma glucose (mmol/L)	12.77 (9.00,16.00)	5.02 (4.70,5.40)	<0.01
2 h plasma glucose (mmol/L)	17.00 (13.00,22.00)	5.39 (4.60,6.30)	<0.01
Total cholesterol (mmol/L)	4.70 (4.00,5.50)	4.70 (4.03,5.35)	0.99
Triglyceride (mmol/L)	1.51 (1.01,2.19)	1.27 (0.89,1.84)	<0.01
HDL-C (mmol/L)	1.13 (0.96,1.35)	1.35 (1.15,1.53)	<0.01
LDL-C (mmol/L)	2.99 (2.44,3.59)	3.06 (2.51,3.63)	<0.01

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Data are shown as the mean ± SD or median (interquartile range).

Table 2. Associations of *CYP2C8* and *CYP2C9* single nucleotide polymorphisms (SNPs) with T2DM

Gene	SNP	Chr. Position (Build 37)	Major/ minor allele	Overall MAF	Case MAF	Control MAF	OR for minor allele (95%CI)	*P*-value for minor allele	OR for genotype (95%CI)	*P*-value for genotype	Empirical *P*-value	Empirical *P*-value (pointwise)
CYP2C9	rs1819173	96680265	G/A	0.405	0.378	0.426	0.832(0.777,0.891)	**7.51×10^{-8}**	0.840(0.780,0.904)	**3.04×10^{-6}**	**3.00×10^{-4}**	**2.00×10^{-4}**
	rs1358894	96681133	C/T	0.044	0.043	0.044	0.989(0.843,1.161)	0.896	1.007(0.847,1.197)	0.941	1.000	0.854
	rs12782374	96695351	G/A	0.327	0.322	0.331	0.962(0.900,1.032)	0.282	0.957(0.887,1.033)	0.259	0.991	0.340
	rs2860905	96702295	G/A	0.088	0.086	0.089	0.963(0.858,1.080)	0.509	0.958(0.846,1.085)	0.497	0.999	0.448
	rs10509679	96708226	G/A	0.329	0.326	0.331	0.981(0.914,1.053)	0.598	0.977(0.905,1.054)	0.542	1.000	0.634
	rs2475376	96712400	C/T	0.390	0.391	0.389	1.011(0.945,1.082)	0.755	1.004(0.933,1.080)	0.922	1.000	0.935
	rs9332146	96722244	G/A	0.025	0.025	0.025	1.001(0.810,1.238)	0.991	0.950(0.756,1.193)	0.658	1.000	0.621
	rs1934967	96741426	C/T	0.174	0.176	0.172	1.025(0.939,1.119)	0.578	1.045(0.952,1.149)	0.354	0.999	0.445
	rs1934975	96769769	T/C	0.063	0.065	0.062	1.052(0.919,1.205)	0.459	1.051(0.908,1.217)	0.503	0.996	0.395
	rs11188133	96772015	G/A	0.439	0.435	0.442	0.973(0.910,1.041)	0.427	0.981(0.913,1.055)	0.610	1.000	0.580
CYP2C8	rs7899038	96772412	C/T	0.063	0.064	0.062	1.035(0.903,1.186)	0.619	1.031(0.890,1.194)	0.687	1.000	0.517
	rs12766752	96778531	T/C	0.375	0.370	0.378	0.958(0.894,1.026)	0.225	0.969(0.900,1.043)	0.403	0.993	0.345
	rs11572162	96803877	G/A	0.120	0.118	0.121	0.969(0.875,1.074)	0.554	0.964(0.863,1.077)	0.514	1.000	0.646
	rs11572133	96809376	A/T	0.397	0.394	0.399	0.977(0.913,1.046)	0.499	0.987(0.918,1.062)	0.731	1.000	0.697
	rs6583967	96814475	T/C	0.048	0.046	0.050	0.925(0.793,1.078)	0.313	0.918(0.778,1.083)	0.309	0.996	0.382
	rs2071426	96828323	A/G	0.073	0.069	0.077	0.877(0.773,0.990)	**0.042**	0.875(0.763,1.003)	0.055	0.636	0.083
	rs10882526	96828501	A/G	0.094	0.091	0.097	0.927(0.827,1.038)	0.188	0.936(0.828,1.058)	0.290	0.984	0.308
	rs10882532	96851496	C/A	0.440	0.442	0.438	1.018(0.952,1.089)	0.607	0.993(0.924,1.068)	0.858	1.000	0.758
	rs7921420	96854541	G/A	0.157	0.160	0.153	1.059(0.966,1.160)	0.219	1.051(0.953,1.160)	0.317	0.982	0.298

P-values < 0.05 are shown in bold. The additive model was used in the association analyses between genotype and T2DM. Empirical *P*-values for the genotypes were based on 10 000 permutations; empirical *P*-value corrected for all tests, and empirical *P*-value (pointwise) was per region. The odds ratios (ORs) with 95% confidence interval (CI) shown are for the minor allele. MAF: minor allele frequencies.

Haplotype analysis

LD analysis revealed that SNPs in *CYP2C8* formed two haplotype blocks (Figure 1). We compared the distribution of haplotypes between T2DM patients and controls and found that the frequency of the haplotype rs2071426-rs6583967 GT in the T2DM patients was lower than that in normal controls (P=0.049), while haplotype rs2071426-rs6583967 AT was higher in T2DM (*P*=0.038). The associations existed after adjustment for multiple comparisons (Table 3).

Table 3. Associations of two haplotypes in the *CYP2C8* region with T2DM

Haplotype	Haplotype frequencies		*P*-value	Empirical *P*-value	Empirical *P*-value (pointwise)
	Case	Control			
Block 1 (rs12766752-rs11572133)					
CT	0.369	0.379	0.249	0.727	0.257
TT	0.026	0.022	0.163	0.527	0.153
TA	0.605	0.600	0.481	0.915	0.446
Block 2 (rs2071426-rs6583967)					
GC	0.046	0.05	0.276	0.753	0.279
GT	0.023	0.028	**0.049**	0.205	**0.048**
AT	0.931	0.922	**0.038**	0.173	**0.041**

P-values < 0.05 are shown in bold. Empirical *P*-values for the haplotypes were based on 10000 permutations; empirical *P*-value corrected for all tests, and empirical *P*-value (pointwise) was per region.

Gene-gene interactions based on SNPs

To avoid overlooking the heritability of T2DM due to unknown interactions between *CYP2C8* and *CYP2C9* variants, we analysed the gene-gene interaction. The results showed that rs12766752 in *CYP2C8* and rs1819173 in *CYP2C9* had a significant gene-gene interaction on T2DM (*P*=0.003) (Figure 2).

Quantitative traits analysis

Since rs1819173 was the most significant T2DM related SNP in our study, we explored the association between diabetes-related traits with the SNP. For eliminating the interference of anti-diabetes medicine, we just calculated the association in normal controls (Supplemental Table 1). However, no significant result was found. As the number of rs1819173 A alleles increased, there was just a decreasing trend of 30 min plasma glucose levels after oral glucose tolerance test and GAUC from 0 to 120 min (*P*=0.074, *P*=0.056).

Considering the effect of lipid metabolism on diabetes, we further explored the association of serum lipid-related traits with rs1819173 in overall individuals (Table 4). It was shown that HDL-C was significantly associated with rs1819173 (*P*=0.031-0.048). The A allele of rs1819173 could increase the level of serum HDL-C.

Table 4. Association analyses of the rs1819173 genotype with obesity-related trait and serum lipid-related traits in overall individuals

	Unadjusted			*Model 1*			*Model 2*		
	β	s.e.	*P*	β	s.e.	*P*	β	s.e.	*P*
Total cholesterol (mmol/L)	0.004	0.020	0.828	0.012	0.020	0.557	0.019	0.020	0.356
Triglyceride (mmol/L)	0.032	0.027	0.239	0.033	0.027	0.228	0.041	0.027	0.130
HDL-C (mmol/L)	0.016	0.008	**0.036**	0.016	0.007	**0.031**	0.014	0.007	**0.048**
LDL-C (mmol/L)	0.003	0.016	0.878	0.008	0.016	0.632	0.012	0.016	0.469

HDL-C high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; s.e., standard error. Data are shown as the mean ± SD or median (interquartile range). *Model 1*: adjusted for age, sex; *Model 2*: were adjusted for age, sex and BMI. *P*-values < 0.05 are shown in bold.

Discussion

CYP2 gene family are responsible for metabolizing endogenous substances such as steroids, vitamins, and fatty acids, as well as exogenous substances such as drugs and environmental pollutants [24]. Among these, AA is an important fatty acid metabolised by cytochrome P450 epoxygenases into

epoxyeicosatrienoic acids. It is a class of important lipid metabolites with beneficial effects in obesity, hypertension, diabetes and cardiovascular disease [15-17]. Genetic variants may change the production and function of the CYP2 enzyme to influence the genetic susceptibility to diseases. Several studies have shown the role of CYP2 enzyme and related signalling pathways in diabetes and anti-diabetic drugs. Genetic variants in *CYP2C8* and *CYP2C9* are associated with a better response to anti-diabetic drugs in T2DM patients [12, 25], it also associated with risk of hypoglycaemia, increasing the possibility of pharmacogenetic interaction [14, 19]. Notably, EETs produced by CYP2 enzymes can directly induce the release of insulin secretion in isolated rat islets [26]. Luo et al. also determined that soluble epoxide hydrolase (sEH) blockade can stimulate insulin secretion in mice. SEH blockade can promote glucose-stimulated insulin secretion by increasing the intracellular Ca^{2+} concentration in islets [15, 27, 28]. As mentioned above, studying polymorphisms in candidate genes such as CYP enzymes is expected to improve our understanding of T2DM.

In the present study, we investigated the effects of *CYP2C8* and *CYP2C9* variants on T2DM and identified an association between rs1819173 in *CYP2C9* and T2DM in a Chinese population. The allele A in rs1819173 is protective against T2DM. In addition, we found that both the haplotypes GT and AT (rs2071426-rs6583967) in *CYP2C8* were associated with T2DM, which also suggested a relationship between *CYP2C8* and T2DM. Moreover, we found that rs1819173 in *CYP2C9* and rs12766752 in *CYP2C8* were interactive on T2DM. The results indicated that these two genes played a synergistic role in the pathogenesis of diabetes, consistent with the physiological and pathological functions of CYP enzyme epoxygenases. We also analysed the diabetes-related traits based on the rs1819173 genotype in normal controls, but we did not find a significant difference in related traits. Just the 30 min plasma glucose levels measurement and GAUC from 0 to 120 min showed a decreasing trend as the number of rs1819173 A alleles increased. Considering the impact of lipid metabolism on diabetes, we further explored whether rs1819173 was associated with serum lipid-related traits. And we found that rs1819173 was significantly associated with HDL-C.

In a previous study of the CYP2 gene family and diabetes, the authors mainly focused on pharmacogenomics. Genetic variants in *CYP2C9* were associated with blood sulfonylurea clearance, while variants in *CYP2C8* were found to influence the efficacy of repaglinide and rosiglitazone [12]. According to our data, genetic variants in *CYP2C9* were also associated with the occurrence of T2DM, and we identified a novel SNP in *CYP2C9* associated with occurrence of T2DM.

Previous epidemiological evidence suggested that low HDL levels are correlated with an increased risk of diabetes [29-31]. In our research, individuals with A allele in rs1819173 had lower risk to develop T2DM and higher level of HDL-C, which were consistent with epidemiological results mentioned above. We speculate that rs1819173 may modifies type 2 diabetes risk through modulation of HDL-C levels.

Some limitations of the study should be noted. First, lifestyle factors such as cigarette smoking and alcohol consumption were not included in the genotype-disease analysis. Whether interactions existed between lifestyle factors and genetic variants remains unknown. Second, all of the variants tested in our study were in non-coding regions, and the potential relationship between CYP2C enzyme activity and EET levels should be investigated in future studies. Moreover, false positives should not be excluded due to the modest effects of *CYP2C8* and *CYP2C9* variants.

Conclusions

Our results suggested that common SNPs in the *CYP2C8* and *CYP2C9* regions were associated with T2DM in a Chinese Han population. The mechanisms of how the *CYP2C8* and *CYP2C9* influenced T2DM should be further explored.

List Of Abbreviations

EET: epoxyeicosatrienoic acids; AA: arachidonic acid; CYP: cytochrome P450; SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; T2DM: type 2 diabetes mellitus; DM: diabetes mellitus; BMI: body mass index; GAUC: areas under the curve for glucose; IAUC: areas under the curve for insulin; HOMA: homeostasis model assessment; MAF: minor allele frequency.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital assured ethical approval according to the Helsinki Declaration II. All subjects provided written informed consent to participate.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Data was collected by LJ, YH, YYL and BX. The study was designed by RZ and CH. LJ and YH analyzed the data. LJ and YH wrote the manuscript. YYL and BX reviewed the manuscript. All authors read and approved the final manuscript.

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Authors' information

[1] Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China.

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Figures

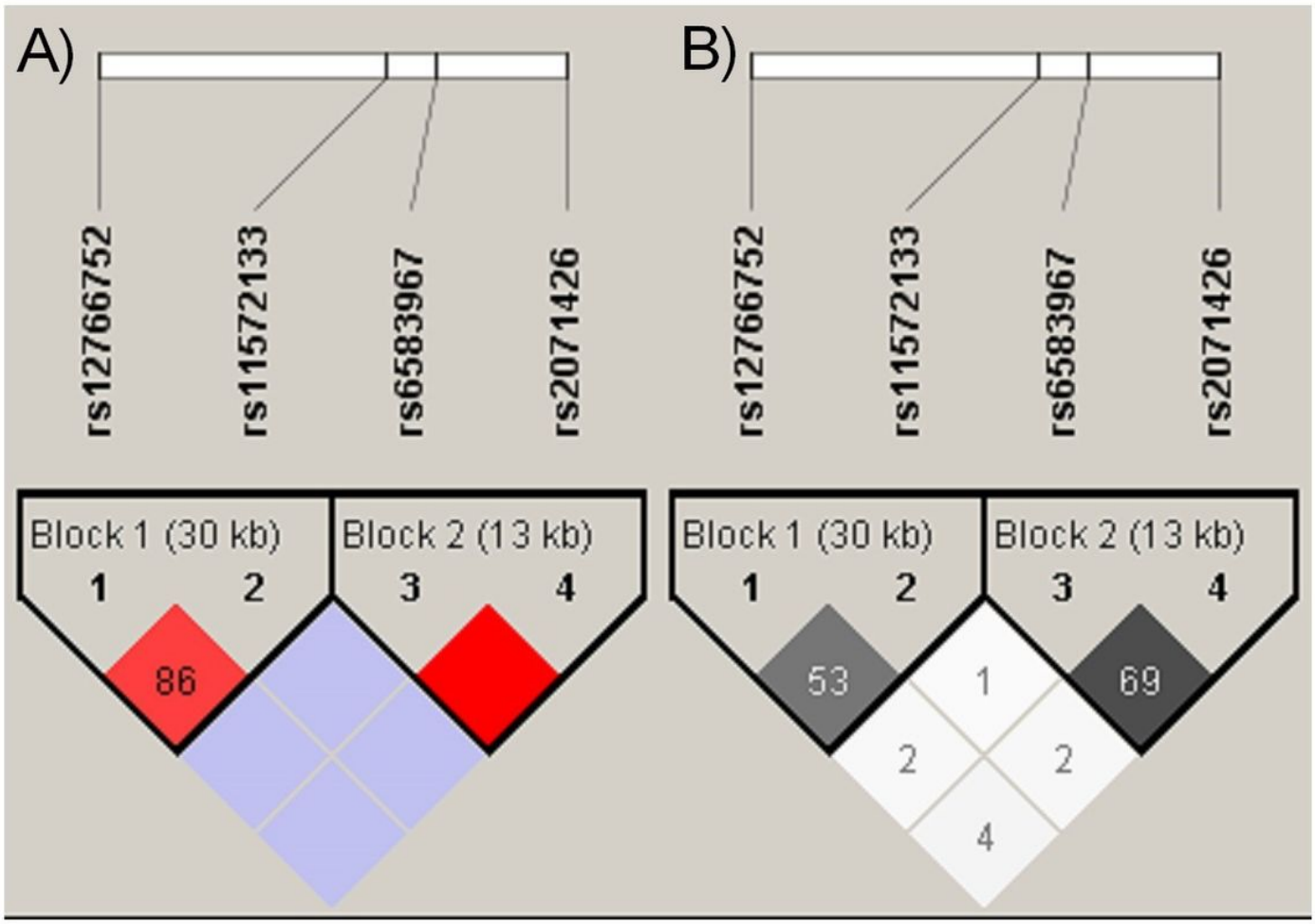

Figure 1

LD maps of tag single nucleotide polymorphisms (SNPs) in CYP2C8 region. Two measures of pairwise LD are shown: A) The value of D' was expressed as percentage; B) The value of r2 was expressed as percentage.

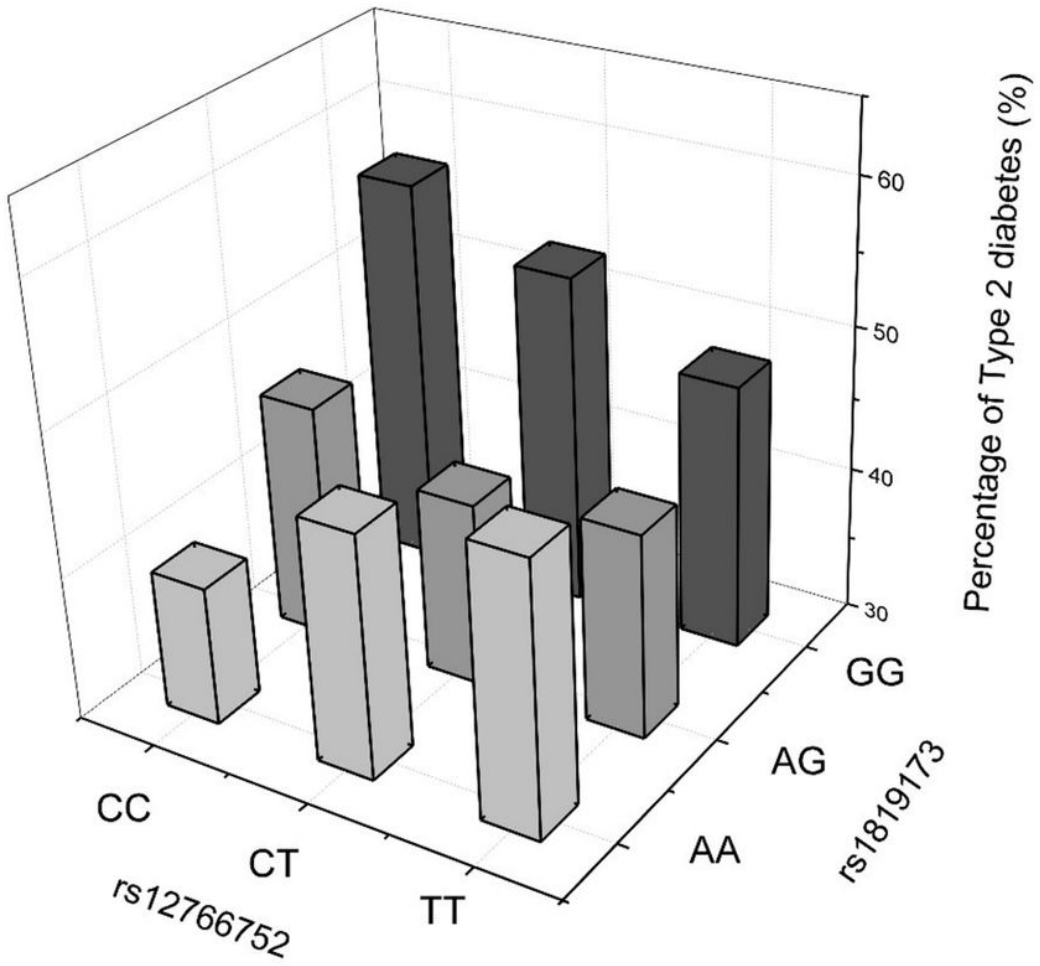

Figure 2

Interaction between rs1819173 of CYP2C9 and rs12766752 of CYP2C8 in T2DM. The percentage of T2DM patients for each genotype of rs1819173 of CYP2C9 and rs12766752 of CYP2C8 represent the mean values in total subjects

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