Evaluation of the Relationship Between Cytochrome P450 Polymorphisms and T2DM Risk

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Research

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Abstract

Background: Recent studies have identified some genetic polymorphisms of *CYP2C8* and *CYP2D6* related to disease susceptibility. However, it has not been reported whether polymorphisms in *CYP2C8* and *CYP2D6* are associated with the risk of type 2 diabetes mellitus (T2DM). We designed a case-control study to evaluate the relationship between those CYP polymorphisms and T2DM risk.

Methods: Four single nucleotide polymorphisms (SNPs) of *CYP2C8* and *CYP2D6* were genotyped from 512 patients and 515 healthy controls using Agena MassARRAY. The chi-square test was used to compare the differences in allele and genotype frequencies between the two groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression analysis to evaluate the relationship between polymorphism and T2DM risk.

Results: The results found that the rs1065852 in *CYP2D6* was correlated with the T2DM risk in overall (A vs. G: OR = 1.22, 95% CI: 1.03–1.45, *P* = 0.024; AA vs.GG: OR = 1.46, 95% CI: 1.04–2.06, *P* = 0.031; AA-AG vs. GG: OR = 1.36, 95% CI: 1.04–1.79, *P* = 0.026; additive: OR = 1.21, 95% CI: 1.02–1.44, *P* = 0.027). Gender stratification analysis results demonstrated that the rs1065852 in *CYP2D6* was related with an increased the risk of T2DM in male and age < 59 years old. However, no statistical significance relation was found between *CYP2C8* SNPs and T2DM risk. **Conclusions:** This study revealed that *CYP2D6* (rs1065852) could be potential genetic markers of susceptibility to T2DM. Further studies are required to confirm our findings.

Background

Diabetes mellitus (DM) is one of the most common chronic disease, characterized by impaired glucose metabolism due to defective insulin secretion or action[1]. The global prevalence of DM has increased significantly over the past two decades, primarily due to the obesity epidemic. It has been estimated that approximately 451 million people worldwide suffering from DM in 2017 and it is expected to reach more than 693 million in 2045 [2]. Type 2 diabetes mellitus (T2DM) is the most common form of DM, which accounts for more than 90% of the all of DM patients. According to reports, the prevalence of T2DM among Chinese adults was approximately 11.6% in 2010 [3]. T2DM is a non-autoimmune, complex, heterogeneous, and polygenic metabolic disease. Environmental risk factors and genetic components have been reported to play important roles in the etiology and pathogenesis of T2DM [4]. This genetic factor for T2DM is likely to be due to single-nucleotide polymorphisms (SNPs) [5]. Studies have identified that several genes polymorphisms were associated with susceptibility to T2DM, such as *CYP3A4* [6], *CYP2C9* [7], and *CYP2D6* [8].

Cytochrome P450 (CYP) enzymes play a central role in the oxidative metabolisms of a diverse number of drugs and chemicals [9]. CYP2C8 enzyme encoded by the *CYP2C8* gene is a member of the human CYP2C enzyme family. CYP2C8 comprises 7% of the total hepatic CYP content and converts endogenous compounds such as arachidonic acid to biologically active epoxide metabolites [10, 11]. Recently, studies have reported that *CYP2C8* polymorphisms are associated with susceptibility to coronary artery disease [12], colorectal cancer [13], ischemic stroke[14]. CYP2D6 enzyme encoded by the *CYP2D6* gene is a highly polymorphic enzyme. CYP2D6 comprises a small percentage of the total hepatic CYP content and catalyzes the biotransformation of about 20–25% of the clinically used drugs[15]. Some polymorphisms of *CYP2D6* have been reported to be associated with risk of pemphigoid [16], Parkinson's disease [17], autoimmune Diseases [18].

However, there are very few reports of the relationship between *CYP2C8* and *CYP2D6* polymorphisms and T2DM risk in the Chinese Han population. Therefore, to exported whether the five polymorphisms in *CYP2C8* (rs1934953, rs1934951, rs2275620, and rs17110453) and *CYP2D6* (rs1065852) are associated with the risk of T2DM, we designed this study with 512 T2DM patients and 515 healthy controls. Understanding SNPs related with T2DM susceptibility may be helpful for providing personalized diagnosis and prevention.

Materials And Methods

Study Subjects

This case-control study was based on 1027 individuals of Chinese Han population. The case group included 512 patients who had been recently diagnosed with T2DM in the First Affiliated Hospital of Xi'an Jiaotong University according to the WHO guidelines, fasting plasma venous glucose more than 126 mg/dl, or plasma glucose more than 200 mg/dl after 2 h of oral glucose, or glycated hemoglobin level more than 6.5%. Subjects who had been diagnosed with cancer, acute infections, myocardial infarction, or kidney disease were excluded from this study. A total of 515 healthy controls were recruited from the medical center of the First Affiliated Hospital of Xi'an Jiaotong University. We collected the clinical and laboratory findings of each T2DM patient from the clinical charts, including fasting blood glucose, glycated hemoglobin, total cholesterol, high-density lipoproteins (HDL) cholesterol, low-density lipoproteins (LDL) cholesterol, triglyceride, urea, creatinine, cystatin C and glomerular filtration rate (GFR).

DNA extraction

We collected 5 mL of peripheral blood from each participant using Ethylene diamine tetraacetic acid (EDTA) tube, then stored at − 20 °C until analysis. Genomic DNA was isolated from whole blood samples using GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Co. Ltd., Xi'an, China). We used a Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) to detect the concentration and purityof extracted DNA. The DNA yield at optical density (OD) 260 nm/OD280nm between 1.8 and 2.0 was considered as pure. The isolated DNA was stored at − 20 °C for further experiment use.

SNP genotyping

We selected the five SNPs in *CYP2C8* (rs1934953, rs1934951, rs2275620, and rs17110453) and *CYP2D6* (rs1065852) based on previously published articles [19–24]. The HapMap database showed that the minor allele frequency (MAF) of all SNPs is more than 0.05 in global population. The polymerase chain reaction (PCR) primers were designed by the online software Agena Bioscience Assay Design Suite Version 2.0 (https://agenacx.com/online-tools/). We used the Agena MassARRAY platform (Agena Bioscience, San Diego, CA, USA) to genotype five *CYP2C8* and *CYP2D6* SNPs following the manufacturer's instructions. The Agena Bioscience TYPER software (version 4.0) was used to manage and analyze the genotyping results.

Statistical analysis

The data were analyzed using the SPSS 20.0 statistical software (SPSS, Chicago, IL, USA) and PLINK 1.07. The chi-square test was used to determine whether the genotype frequencies distributions of *CYP2C8* and *CYP2D6* genes SNPs in control group were in Hardy-Weinberg Equilibrium (HWE). The distributions of the alleles and genotypes frequencies of polymorphisms were compared between the case and control groups using chi-square test. The continuous variables were provided as mean ± standard deviation (SD). We used Student's t test to compare the numerical values of the continuous variables. The odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the association between the polymorphisms *CYP2C8* and *CYP2D6* and T2DM risk by logistic regression model. The threshold for significance was set at $P < 0.05$.

Results

In this study, we recruited a total of 512 T2DM patients and 515 healthy controls. The demographics and clinical parameters of all participants are shown in Table 1. The case group comprised 281(55%) male T2DM patients and 231(45%) female T2DM patients. The control group had 283 (55%) males and 232 (45%) females. The chi-square test result showed that no significant difference in gender distribution was observed between the case group and the control

group (P = 0.982). The average age of the case group and control group was 59.23 ± 9.592 and 59.27 ± 11.97, respectively. T test results showed no significant difference in age distribution between the two groups (P = 0.962). The clinical indicators including fasting blood glucose, glycated hemoglobin, total cholesterol, triglyceride, urea, creatinine and GFR were significantly different in cases compared with the controls (P < 0.05). However, no significant difference was observed between the two groups concerning LDL, HDL and Cystatin C.

Table 1
Characteristics of the study participants

Variables		Case	Control	*P*
Total		512	515	
Gender	Male	281 (55%)	283 (55%)	0.982
	female	231 (45%)	232 (45%)	
Age	> 59	264 (52%)	272 (53%)	
	≤ 59	248 (48%)	243 (47%)	
	Mean ± SD	59.23 ± 9.59	59.27 ± 11.97	0.962
Fasting blood glucose(mM)		9.949 ± 4.687	5.674 ± 0.783	< 0.001
Glycated hemoglobin (%)		9.301 ± 2.472	5.878 ± 0.787	< 0.001
Total cholesterol (mM)		4.616 ± 1.319	4.940 ± 0.946	0.002
Triglyceride (mM)		2.492 ± 2.255	1.761 ± 1.423	< 0.001
LDL-C (mM)		2.771 ± 0.949	2.685 ± 0.688	0.271
HDL-C (mM)		1.223 ± 0.640	1.205 ± 0.244	0.667
Urea (mM)		6.376 ± 3.332	5.053 ± 1.268	< 0.001
Creatinine (μM)		63.298 ± 19.908	60.259 ± 13.201	0.044
Cystatin C (mg/L)		0.969 ± 2.17	0.876 ± 0.198	0.904
GFR (mL/min)		122.78 ± 35.999	94.086 ± 15.927	< 0.001
LDL-C: low-density lipoproteins cholesterol, HDL-C: high-density lipoproteins cholesterol, GFR: glomerular filtration rate				
P < 0.05 was considered to be significant.				

The detailed information and allelic frequencies of the *CYP2C8* and *CYP2D6* genes SNPs in case and control groups are shown in Table 2. Chi-square test results showed that the genotype frequencies of the five *CYP2C8* and *CYP2D6* SNPs in control group conformed to HWE (P > 0.05). As presented, there is no statistically significant difference in the allelic frequencies of the *CYP2C8* gene SNPs between the T2DM patients and healthy controls (P > 0.05). However, the rs1065852 in *CYP2D6* was found to be related with an increased the risk of T2DM (A vs. G: OR = 1.22, 95% CI: 1.03–1.45, P = 0.024).

Table 2
Basic information of SNPs and association with T2DM risk

SNP-ID	Chr	Position	Role	Allele A/B	Gene	HWE	MAF-case	MAF-control	OR (95%CI)	*P*
rs1934953	10	95037713	intron	C/A	*CYP2C8*	0.374	0.435	0.452	0.93 (0.78–1.11)	0.415
rs1934951	10	95038791	intron	C/T	*CYP2C8*	0.574	0.370	0.377	0.97 (0.81–1.16)	0.732
rs2275620	10	95042841	intron	A/C	*CYP2C8*	0.590	0.429	0.428	1.00 (0.84–1.19)	0.975
rs17110453	10	95069772	upstream transcript	A/C	*CYP2C8*	0.159	0.313	0.324	0.95 (0.79–1.15)	0.611
rs1065852	22	42130692	intron	G/A	*CYP2D6*	0.210	0.496	0.446	1.22 (1.03–1.45)	0.024

SNP: single nucleotide polymorphism, Chr: chromosome, MAF: minor allele frequency, HWE: Hardy-Weinberg equilibrium, OR: odds ratio, CI: confidence interval.

P < 0.05 was considered to be significant.

Four genetics models were tested to evaluate the relationships between five *CYP2C8* and *CYP2D6* SNPs and the risk of T2DM (Table 3). The results found that the genotype AA of rs1065852 carriers had a 1.46-fold increased risk of T2DM compared with the genotype GG (OR = 1.46, 95% CI: 1.04–2.06, *P* = 0.031). Significant associations were also found under the dominant model (AA-AG vs. GG: OR = 1.36, 95% CI: 1.04–1.79, *P* = 0.026) and additive model (OR = 1.21, 95% CI: 1.02–1.44, *P* = 0.027) before and after adjusting with age and gender. However, no statistical significance relation was found between *CYP2C8* SNPs and the risk of T2DM.

Table 3
Genetic model analysis of *CYP2C8* and *CYP2D6* polymorphisms and T2DM risk

SNP_ID	Model	Genotype	Case (%)	Control (%)	OR (95% CI)	*P*	Adjust OR (95% CI)	*P*
rs1934953	Codominant	CC	158 (30.9)	149 (28.9)	1		1	
		TC	263 (51.4)	266 (51.7)	0.93 (0.70–1.24)	0.626	0.93 (0.7–1.24)	0.622
		TT	91 (17.8)	100 (19.4)	0.86 (0.60–1.23)	0.407	0.86 (0.6–1.23)	0.403
	Dominant	CC	158 (30.9)	149 (28.9)	1		1	
		TT-TC	354 (69.1)	366 (71.1)	0.91 (0.70–1.19)	0.500	0.91 (0.7–1.19)	0.497
	Recessive	TC-CC	421 (82.2)	415 (80.6)	1		1	
		TT	91 (17.8)	100 (19.4)	0.90 (0.65–1.23)	0.499	0.9 (0.65–1.23)	0.495
	Additive	–	–	–	0.93 (0.78–1.11)	0.405	0.93 (0.77–1.11)	0.401
rs1934951	Codominant	CC	205 (40.1)	202 (39.4)	1		1	
		TC	234 (45.8)	235 (45.8)	0.98 (0.75–1.28)	0.888	0.98 (0.75–1.28)	0.884
		TT	72 (14.1)	76 (14.8)	0.93 (0.64–1.36)	0.720	0.93 (0.64–1.36)	0.713
	Dominant	CC	205 (40.1)	202 (39.4)	1		1	
		TT-TC	306 (59.9)	311 (60.6)	0.97 (0.75–1.25)	0.809	0.97 (0.75–1.25)	0.803
	Recessive	TC-CC	439 (85.9)	437 (85.2)	1		1	
		TT	72 (14.1)	76 (14.8)	0.94 (0.67–1.34)	0.742	0.94 (0.66–1.34)	0.736
	Additive	–	–	–	0.97 (0.81–1.16)	0.734	0.97 (0.81–1.16)	0.727
rs2275620	Codominant	AA	166 (32.4)	165 (32.1)	1		1	
		TA	253 (49.4)	258 (50.2)	0.97 (0.74–1.29)	0.856	0.97 (0.74–1.29)	0.856
		TT	93 (18.2)	91 (17.7)	1.02 (0.71–1.46)	0.932	1.02 (0.71–1.46)	0.934

SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval.

Adjust OR (95%CI) were adjusted with age and gender.

P < 0.05 was considered to be significant.

SNP_ID	Model	Genotype	Case (%)	Control (%)	OR (95% CI)	*P*	Adjust OR (95% CI)	*P*
	Dominant	AA	166 (32.4)	165 (32.1)	1		1	
		TT-TA	346 (67.6)	349 (67.9)	0.99 (0.76–1.28)	0.913	0.99 (0.76–1.28)	0.911
	Recessive	TA-AA	419 (81.8)	423 (82.3)	1		1	
		TT	93 (18.2)	91 (17.7)	1.03 (0.75–1.42)	0.848	1.03 (0.75–1.42)	0.849
	Additive	–	–	–	1.00 (0.84–1.20)	0.974	1.00 (0.84–1.20)	0.976
rs17110453	Codominant	AA	246 (48)	242 (47.1)	1		1	
		CA	211 (41.2)	211 (41.1)	0.98 (0.76–1.28)	0.902	0.98 (0.76–1.28)	0.900
		CC	55 (10.7)	61 (11.9)	0.89 (0.59–1.33)	0.562	0.89 (0.59–1.33)	0.561
	Dominant	AA	246 (48)	242 (47.1)	1		1	
		CC-CA	266 (52)	272 (52.9)	0.96 (0.75–1.23)	0.757	0.96 (0.75–1.23)	0.756
	Recessive	CA-AA	457 (89.3)	453 (88.1)	1		1	
		CC	55 (10.7)	61 (11.9)	0.89 (0.61–1.32)	0.569	0.89 (0.61–1.32)	0.568
	Additive	–	–	–	0.96 (0.80–1.15)	0.621	0.96 (0.80–1.15)	0.619
rs1065852	Codominant	GG	132 (25.8)	164 (32.1)	1		1	
		AG	252 (49.2)	238 (46.6)	1.32 (0.98–1.76)	0.064	1.32 (0.98–1.76)	0.063
		AA	128 (25)	109 (21.3)	1.46 (1.04–2.06)	0.031	1.46 (1.04–2.06)	0.031
	Dominant	GG	132 (25.8)	164 (32.1)	1		1	
		AA-AG	380 (74.2)	347 (67.9)	1.36 (1.04–1.79)	0.026	1.36 (1.04–1.79)	0.026
	Recessive	AG-GG	384 (75)	402 (78.7)	1		1	

SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval.

Adjust OR (95%CI) were adjusted with age and gender.

P < 0.05 was considered to be significant.

SNP_ID	Model	Genotype	Case (%)	Control (%)	OR (95% CI)	*P*	Adjust OR (95% CI)	*P*
		AA	128 (25)	109 (21.3)	1.23 (0.92–1.65)	0.165	1.23 (0.92–1.65)	0.164
	Additive	–	–	–	1.21 (1.02–1.44)	0.027	1.21 (1.02–1.44)	0.027
SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval.								
Adjust OR (95%CI) were adjusted with age and gender.								
P < 0.05 was considered to be significant.								

Gender stratification analysis results demonstrated that the rs1065852 in *CYP2D6* was related with an increased the risk of T2DM in male under the allele model (A vs. G: OR = 1.29, 95% CI: 1.02–1.64, *P* = 0.032), codominant model (AA vs. GG: OR = 1.63, 95% CI: 1.03–2.59, *P* = 0.039), dominant model (AA-AG vs. GG: OR = 1.47, 95% CI: 1.02–2.12, *P* = 0.041) and additive model (OR = 1.28, 95% CI: 1.02–1.62, *P* = 0.035) (Table 4). Age stratification analysis indicated that the rs1065852 was correlated with an increased the risk of T2DM in age < 59 years old under the allele model (A vs. G: OR = 1.44, 95% CI: 1.12–1.85, *P* = 0.005), codominant model (AG vs. GG: OR = 1.66, 95% CI: 1.07–2.55, *P* = 0.035; AA vs. GG: OR = 1.98, 95% CI: 1.20–3.29, *P* = 0.008), dominant model (AA-AG vs. GG: OR = 1.76, 95% CI: 1.17–2.64, *P* = 0.007) and additive model (OR = 1.41, 95% CI: 1.10–1.82, *P* = 0.007) (Table 4).

Table 4
Stratified analysis between *CYP2D6* rs1065852 and T2DM risk

Variables	Model	Genotype	Case (%)	Control (%)	OR (95%CI)	*P*	Case (%)	Control (%)	OR (95%CI)	*P*
Gender			Male				Female			
	Allele	G	278 (49.5)	314 (55.9)	1		238 (51.5)	252 (54.8)	1	
		A	284 (50.5)	248 (44.1)	1.29 (1.02–1.64)	0.032	224 (48.5)	208 (45.2)	1.14 (0.88–1.48)	0.320
	Codominant	GG	70 (24.9)	92 (32.7)	1		62 (26.8)	72 (31.3)	1	
		AG	138 (49.1)	130 (46.3)	1.40 (0.94–2.07)	0.096	114 (49.4)	108 (47)	1.23 (0.80–1.88)	0.353
		AA	73 (26)	59 (21)	1.63 (1.03–2.59)	0.039	55 (23.8)	50 (21.7)	1.28 (0.77–2.13)	0.348
	Dominant	GG	70 (24.9)	92 (32.7)	1		62 (26.8)	72 (31.3)	1	
		AA-AG	211 (75.1)	189 (67.3)	1.47 (1.02–2.12)	0.041	169 (73.2)	158 (68.7)	1.24 (0.83–1.86)	0.292
	Recessive	AG-GG	208 (74)	222 (79)	1		176 (76.2)	180 (78.3)	1	
		AA	73 (26)	59 (21)	1.32 (0.89–1.96)	0.163	55 (23.8)	50 (21.7)	1.13 (0.73–1.74)	0.596
	Additive	–	–	–	1.28 (1.02–1.62)	0.035	–	–	1.14 (0.88–1.47)	0.328
Age			≤ 59				> 59			
	Allele	G	232 (46.8)	269 (55.8)	1		284 (53.8)	297 (55)	1	
		A	264 (53.2)	213 (44.2)	1.44 (1.12–1.85)	0.005	244 (46.2)	243 (45)	1.05 (0.83–1.34)	0.691
	Codominant	GG	54 (21.8)	79 (32.8)	1		78 (29.5)	85 (31.5)	1	0.944
		AG	124 (50)	111 (46.1)	1.66 (1.07–2.55)	0.023	128 (48.5)	127 (47)	1.07 (0.72–1.60)	0.738
		AA	70 (28.2)	51 (21.2)	1.98 (1.20–3.29)	0.008	58 (22)	58 (21.5)	1.06 (0.65–1.72)	0.820

SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval.

P < 0.05 was considered to be significant.

Variables	Model	Genotype	Case (%)	Control (%)	OR (95%CI)	*P*	Case (%)	Control (%)	OR (95%CI)	*P*
	Dominant	GG	54 (21.8)	79 (32.8)	1		78 (29.5)	85 (31.5)	1	
		AA-AG	194 (78.2)	162 (67.2)	1.76 (1.17–2.64)	0.007	186 (70.5)	185 (68.5)	1.07 (0.73–1.55)	0.736
	Recessive	AG-GG	178 (71.8)	190 (78.8)	1		206 (78)	212 (78.5)	1	
		AA	70 (28.2)	51 (21.2)	1.44 (0.95–2.18)	0.090	58 (22)	58 (21.5)	1.02 (0.67–1.54)	0.945
	Additive	–	–	–	1.41 (1.10–1.82)	0.007	–	–	1.03 (0.81–1.31)	0.798
SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval.										
P < 0.05 was considered to be significant.										

No relationship between genotypes of the rs1065852 and clinical characteristics (fasting blood glucose, glycated hemoglobin, total cholesterol, HDL, LDL, triglyceride, urea, creatinine, Cystatin C and GFR) (Table 5).

Table 5
Association between *CYP2D6* rs1065852 and clinical traits

Variables	Genotype (mean ± SD)			*P*
	AA	GA	GG	
Fasting blood glucose(mM)	10.396 ± 6.119	9.672 ± 3.622	9.972 ± 4.656	0.518
Glycated hemoglobin (%)	9.303 ± 2.306	9.218 ± 2.168	9.448 ± 3.108	0.803
Total cholesterol (mM)	4.547 ± 1.45	4.655 ± 1.413	4.614 ± 0.943	0.837
Triglyceride (mM)	2.121 ± 1.844	2.707 ± 2.564	2.483 ± 1.974	0.167
LDL-C (mM)	2.757 ± 1.122	2.742 ± 0.952	2.845 ± 0.715	0.732
HDL-C (mM)	1.23 ± 0.721	1.222 ± 0.652	1.216 ± 0.519	0.991
Urea (mM)	6.091 ± 1.958	6.492 ± 4.377	6.457 ± 1.982	0.664
Creatinine (μM)	63.36 ± 15.015	63.018 ± 22.345	63.73 ± 19.922	0.967
Cystatin C (mg/L)	0.812 ± 0.209	1.08 ± 3.121	0.932 ± 0.735	0.670
GFR (mL/min)	122.853 ± 33.857	122.542 ± 34.588	123.138 ± 40.978	0.993
LDL-C: low-density lipoproteins cholesterol, HDL-C: high-density lipoproteins cholesterol, GFR: glomerular filtration rate				
P < 0.05 was considered to be significant.				

Discussion

In this study, we recruited 512 T2DM patients and 515 healthy controls to investigate the relationship between polymorphisms of *CYP2C8* and *CYP2D6* and the risk of T2DM. The analysis results demonstrated that the rs1065852 in

CYP2D6 was related with an increased the risk of T2DM in overall, male and age < 59 years old subgroup. However, no association was found between the four SNPs in *CYP2C8* and T2DM risk in the Chinese Han population.

CYP2C8 mapped in chromosome 10q23 encodes a significant enzyme in metabolism of numerous drugs and chemicals [11]. No association between the four SNPs in *CYP2C8* (rs1934953, rs1934951, rs2275620, and rs17110453) and T2DM risk was found in this study. However, studies on the correlation of these loci with other diseases have been reported. Previous study has reported no significant correlation between rs1934953 in *CYP2C8* and risk of coronary heart disease in Russian population [19]. However, the SNP rs1934953 showed significantly association with essential hypertension risk in Russians [20]. A genome-wide association study previously identified that rs1934951 and rs17110453 in *CYP2C8* were risk factors for the development of osteonecrosis of the jaw (ONJ) in multiple myeloma patients under bisphosphonate therapy [25]. English et.al [26] found that rs1934951 was not associated with the development of bisphosphonate-related ONJ in men with castrate-resistant prostate cancer. Esperanza et.al [21] verified the frequency of SNP rs193451 in 79 patients with multiple myeloma and found that there was no significant correlation between this polymorphism and the risk of ONJ. A meta-analysis indicated that AA and AG genotypes of rs1934951 might be predictors for multiple myeloma patients at high risk to develop bisphosphonate-related ONJ [27]. The two-locus interaction (rs17110453 and rs751141) [14] and three-locus interaction (rs17110453, rs751141, and rs9333025) [28] confer significantly higher risk for ischemic stroke. Therefore, further well-designed studies are needed to confirm this finding.

CYP2D6 genetic polymorphisms because may influence on the enzymatic activity of CYP2D6, which is responsible for the metabolism of numerous drug, including tricyclic antidepressants, antipsychotics, beta-blockers, anti-arrhythmics, anti-diabetics [29]. In present study, the results firstly indicated that rs1065852 in *CYP2D6* was correlated with an increased the risk of T2DM in overall, male and age < 59 years old subgroup. Several studies about the effect of rs1065852 on drug metabolism and disease susceptibility have been reported. Previous study suggested that rs1065852 was a favorable factor in escitalopram treatment for major depressive disorder [30]. The mutation rs1065852 affects the pharmacokinetics of iloperidone and its metabolites in Chinese schizophrenia patients [31]. The SNP rs1065852 was found to be associated with increased risk of lung cancer in the Northwestern Chinese Han population [24]. Our results suggest that rs1065852 may be a good genetic marker for susceptibility to T2DM.

Conclusion

In conclusion, this is the first study performed to investigate the relationship between polymorphisms in *CYP2C8* and *CYP2D6* and T2DM risk in the Chinese Han population. Our data have demonstrated that rs1065852 in *CYP2D*6 could be potential genetic markers of susceptibility to T2DM. Further studies are required to confirm our findings and better understand the pathogenesis of T2DM.

Abbreviations

CI
confidence interval;
CYP
cytochrome P450;
DM
diabetes mellitus;
EDTA
ethylene diamine tetraacetic acid;
GFR
glomerular filtration rate;
HDL

high-density lipoproteins;
HWE
Hardy-Weinberg Equilibrium;
LDL
low-density lipoproteins;
MAF
minor allele frequency;
OD
optical density;
OR
odds ratio;
PCR
polymerase chain reaction;
SNPs
single-nucleotide polymorphisms;
T2DM
type 2 diabetes mellitus

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Central Hospital of Xianyang and First Affiliated Hospital of Xi'an Jiaotong University. All the procedures involving human subjects were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent revisions. No animals were used for studies that are the basis of this research.

Consent for publication

Not applicable.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Qingbin Zhao contributed to the study design and drafted the manuscript. Huiyi Wei contributed to the information collection and critically revised the manuscript. Zhiying Li and Haoyang Wei contributed to the data analysis and

interpretation. All authors gave final approval and are accountable for all aspects of the work and its integrity and accuracy.

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