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RESEARCH ARTICLE

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CYP2D6 polymorphism rs1065852 significantly increases the risk of type 2 diabetes

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ABSTRACT

Background: Genetic variations within the cytochrome P450 (CYP) gene family are significant determinants of type 2 diabetes mellitus (T2DM) susceptibility. This study aimed to investigate the association between *CYP2C8* and *CYP2D6* gene variants and the risk of T2DM.

Methods: We conducted a case-control study involving 512 individuals with T2DM and 515 controls. Genotyping of *CYP2C8* and *CYP2D6* polymorphisms was performed using the Agena MassARRAY system. Logistic regression analysis was employed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), thereby assessing the relationship between these genetic variants and T2DM risk. Additionally, multifactor dimensionality reduction (MDR) was utilized to assess the potential interaction effects of SNPs on T2DM risk.

Results: The study found a strong correlation between rs1065852 and increased risk of T2DM in overall (A vs. G: OR = 1.22, 95% CI: 1.03–1.45, p = .024; AA vs. GG: OR = 1.46, 95% CI: 1.04–2.06, p = .031; AA–AG vs. GG: OR = 1.36, 95% CI: 1.04–1.79, p = .026; additive: OR = 1.21, 95% CI: 1.02–1.44, p = .027), males and age < 59 subgroups. However, there is no significant association between the *CYP2C8* polymorphisms (rs1934953, rs1934951, rs2275620 and rs17110453) and T2DM risk. MDR analysis results showed that the best model was the one locus model (rs1065852, testing accuracy = 0.534; OR = 1.39; 95% CI: 1.05–1.85; p = .023; CVC = 10/10), indicating that rs1065852 is an independent risk factor for T2DM.

Conclusions: This study suggests that rs1065852 (*CYP2D6*) is an independent risk factor for T2DM. Further research is warranted to validate these results and explore their clinical implications.

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by insulin insufficiency or impaired insulin action [1]. The global prevalence of DM has risen significantly, with an estimated 9.3% (463 million people) in 2019 and projections of 10.9% (700 million) by 2045 [2]. A nationally representative cross-sectional study indicated that the estimated prevalence of DM in China increased from 10.9% in 2013 to 12.4% in 2018 [3]. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of all DM patients, which develops later in life. Unlike T1DM, T2DM is a non-autoimmune, relatively heterogeneous, complex and involving polygenic disease. While unhealthy eating habits and sedentary lifestyles have been reported to play important roles in the development of T2DM [4,5], genetic factors play a critical role in predisposing individuals to T2DM [6,7].

Numerous studies have identified various single nucleotide polymorphisms (SNPs) in cytochrome P450 (CYP) genes are associated with the risk of T2DM, such as *CYP2R1* [8], *CYP17A1* [9] and *CYP19A1* [10]. CYP enzymes play a central role in the oxidative metabolisms of a diverse number of drugs and chemicals [11]. Among these, *CYP2C8* and *CYP2D6* are particularly notable due to their involvement in the metabolism of numerous drugs and their reported associations with various diseases. The enzyme encoded by the *CYP2C8* gene belongs to the human CYP2C subfamily and converts endogenous compounds, such as arachidonic acid into biologically active epoxide metabolites [12]. Recently, studies have reported that *CYP2C8* polymorphisms are associated with susceptibility to many

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diseases, such as essential hypertension [13], breast cancer [14] and tuberculosis [15]. Similarly, the *CYP2D6* gene encodes a highly polymorphic enzyme, which catalyses the biotransformation of about 20–25% of the clinically used drugs [16]. *CYP2D6* polymorphisms have been reported to be associated with a risk of autoimmune diseases [17], lung cancer [18] and coronary heart disease [19].

However, there are very few reports of the relationships between *CYP2C8* and *CYP2D6* polymorphisms and T2DM risk in the Chinese Han population. Given their roles in drug metabolism and their reported associations with other diseases, we hypothesized that polymorphisms in these genes may also contribute to T2DM susceptibility. Therefore, to determine whether the five polymorphisms in *CYP2C8* (rs1934953, rs1934951, rs2275620 and rs17110453) and *CYP2D6* (rs1065852) are associated with susceptibility to T2DM, we designed a case-control study including 512 T2DM patients and 515 controls. The findings from this study may provide insights into the underlying genetic mechanisms of T2DM and contribute to the development of personalized approaches for risk assessment and intervention.

Materials and methods

Sample size determination

We used G*Power (3.1.9.7) software to estimate the sample size [20]. First, we select the statistical method: *t*-test, difference between two independent means (two groups). Then, we set parameters: tail: two; effect size *d*: 0.2; significance level (*α*): 0.05; statistical power: 0.89; allocation ratio: 1. The sample size of both the case group and the control group was 516.

Study subjects

The case group included 516 patients who had been recently diagnosed with T2DM in the First Affiliated Hospital of Xi'an Jiaotong University according to the World Health Organization (WHO) diagnostic criteria [21], fasting plasma glucose (FPG) >126 mg/dL (70 mmol/L), or 2 h plasma glucose of oral glucose tolerance test (2hPG-OGTT) ≥200 mg/dL (11.1 mmol/L), or glycated haemoglobin (HbA1c) ≥6.5%. The control group consisted of age and gender-matched 516 healthy individuals who were recruited from the medical centre of the First Affiliated Hospital of Xi'an Jiaotong University during the same period. Subjects who had been diagnosed with cancer, kidney disease, myocardial infarction or acute infections were excluded from this study. Among 1032 subjects, four T2DM patients and one control were excluded, and ultimately 512 cases and 515 controls were included in this study. The flowchart of this study is shown in Figure 1.

We collected the basic information (sex and age) and clinical testing information from the clinical charts, including FPG, HbA1c, lipid levels (total cholesterol (TC), triglyceride (TG), high-density lipoproteins cholesterol (HDL-C) and low-density lipoproteins cholesterol (LDL-C)) and biochemical indicators of renal function (urea, creatinine (Cr), cystatin C (Cys-C) and glomerular filtration rate (GFR)).

DNA extraction

Peripheral blood sample (5 mL) from each participant was collected in ethylene diamine tetraacetic acid (EDTA) tubes and stored at −20 °C until the experiments. Genomic DNA (gDNA) was extracted from whole blood samples using the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag. Co. Ltd., Xi'an, China) according to the manufacturer's directions. We used a Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA) to detect the concentration and purity of extracted DNA. The DNA yield at optical density (OD) 260 nm/OD280 nm between 1.8 and 2.0 was considered qualified. The isolated DNA was stored at −20 °C for further experiment use.

SNPs genotyping

We selected five SNPs in *CYP2C8* (rs1934953, rs1934951, rs2275620 and rs17110453) and *CYP2D6* (rs1065852) for genotyping based on previously published articles [13,15,18,22–26]. These SNPs were chosen due to their established associations with various diseases and their relevance to drug metabolism, particularly in the context of *CYP2C8* and *CYP2D6* enzymes, which are known to influence glucose homeostasis and T2DM risk. Additionally, the 1000 Genome Project database indicated that the minor allele frequency (MAF) of all selected SNPs is greater than 0.05 in the global population, ensuring that these variants are sufficiently common to have a potential impact on the studied traits. The primers of polymerase chain reaction (PCR) and single nucleotide extension were designed by the Agena Bioscience Assay Design Suite Version 2.0. We used the Agena MassARRAY platform (Agena Bioscience, San Diego, CA) to genotype five SNPs in *CYP2C8* and *CYP2D6* following the manufacturer's instructions [25]. The Agena Bioscience TYPER software (version 4.0) was used to manage and analyse the genotyping results.

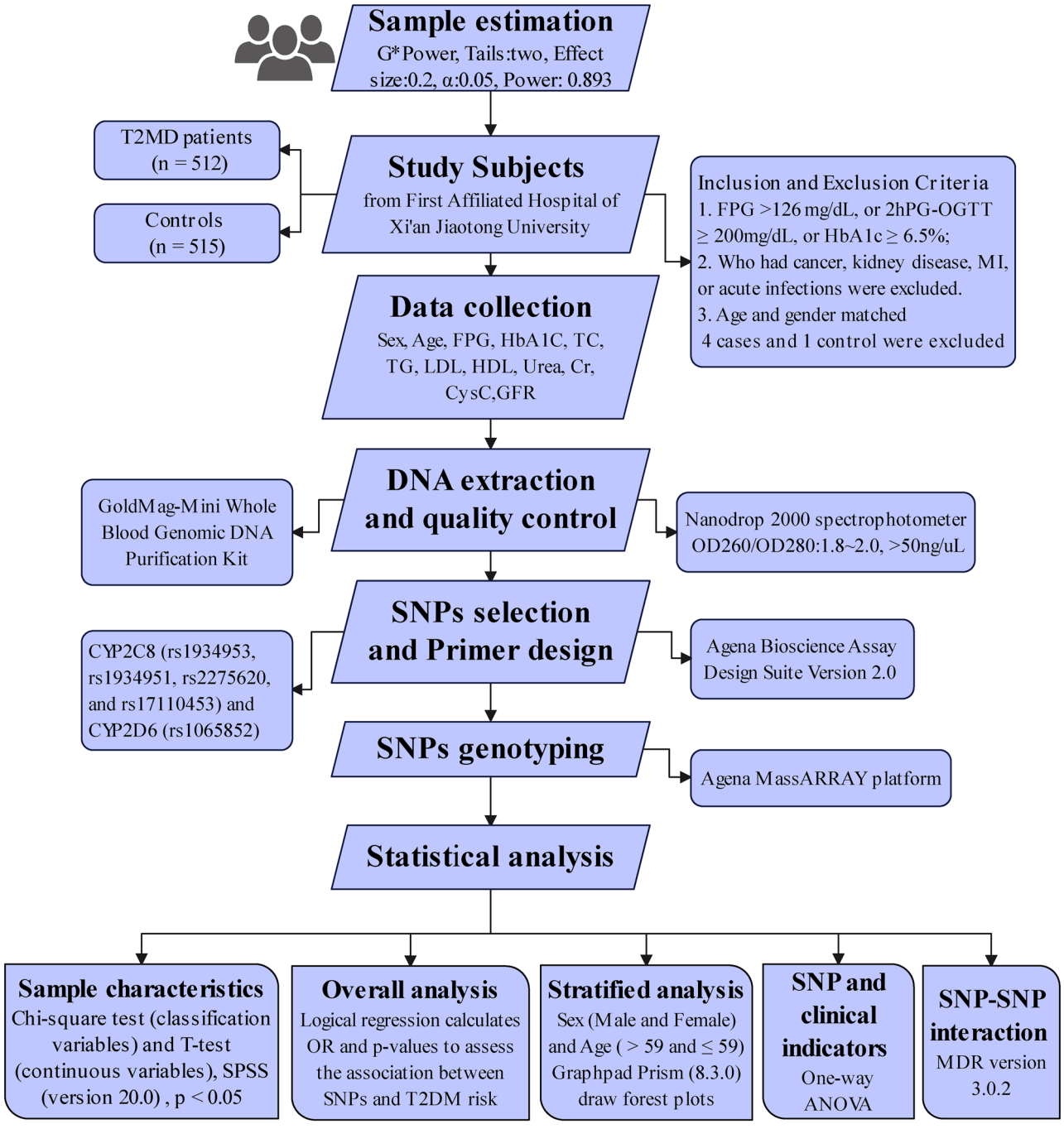

Figure 1. Flowchart of the study design.

Statistical analysis

The data were analysed using the SPSS 20.0 statistical software (SPSS, Chicago, IL) and PLINK 1.9. The continuous variables were provided as mean ± standard deviation (SD). The independent *t*-test was used to compare the differences between two groups of continuous variables. The Chi-square test was used to assess differences between two groups of categorical variables. Meanwhile, we used the Chi-square test to determine whether the genotype frequency distributions of *CYP2C8* and *CYP2D6* genes SNPs in the control group were following Hardy–Weinberg equilibrium (HWE). The odds ratio (OR) and 95% confidence interval (CI) were calculated using logistic regression adjusting confounding factors (age and gender) to evaluate the association between the polymorphisms *CYP2C8* and *CYP2D6* and T2DM risk under multiple genetic models (allele, co-dominant, dominant, recessive and additive) [27,28]. Specifically, the allele model (A vs. B):

Table 1. Characteristics of the study participants.

Variables		Cases (n = 512)	Controls (n = 515)	p
Gender	Male	281 (55%)	283 (55%)	.982
	Female	231 (45%)	232 (45%)	
Age	>59	264 (52%)	272 (53%)	.688
	≤59	248 (48%)	243 (47%)	
	Mean ± SD	59.23 ± 9.59	59.27 ± 11.97	.962
Fasting blood glucose (mM)		9.949 ± 4.687	5.674 ± 0.783	<.001
Glycated haemoglobin (%)		9.301 ± 2.472	5.878 ± 0.787	<.001
Total cholesterol (mM)		4.616 ± 1.319	4.940 ± 0.946	.002
Triglyceride (mM)		2.492 ± 2.255	1.761 ± 1.423	<.001
LDL-C (mM)		2.771 ± 0.949	2.685 ± 0.688	.271
HDL-C (mM)		1.223 ± 0.640	1.205 ± 0.244	.667
Urea (mM)		6.376 ± 3.332	5.053 ± 1.268	<.001
Creatinine (μM)		63.298 ± 19.908	60.259 ± 13.201	.044
Cystatin C (mg/L)		0.969 ± 2.170	0.876 ± 0.198	.904
GFR (mL/min)		122.78 ± 35.999	94.086 ± 15.927	<.001

LDL-C: low-density lipoproteins cholesterol; HDL-C: high-density lipoproteins cholesterol; GFR: glomerular filtration rate.
Chi-square tests were used to analyse intergroup differences for categorical variables, while t-tests were used for continuous variables. $p < .05$ was considered to be significant.

this model evaluates the impact of the presence or absence of the A allele on hypertension risk, without distinguishing between specific genotype combinations. Co-dominant model (AA vs. BB and AB vs. BB): this model compares homozygous (AA), heterozygous (AB) and homozygous (BB) individuals to assess the specific effects of each genotype, accounting for both alleles in heterozygotes. Dominant model (AA + AB vs. BB): This model combines AA and AB into a single category and compares it with BB to evaluate the dominant effect of the minor allele A. Recessive model (AA vs. AB + BB): this model compares AA with the combined group of AB and BB to assess the recessive effect of the minor allele A. Additive model (BB vs. AB vs. AA): this model evaluates the dose–response relationship of alleles, where each additional minor allele (A) contributes independently to the phenotype, with effects being cumulative. We also used GraphPad Prism software (version 8.3.0, La Jolla, CA) to draw forest plots. One-way ANOVA analysis was used to estimate the association between SNPs and clinical indicators. The SNP–SNP interaction was analysed by open-source Java software multifactor dimensionality reduction (MDR) [29,30], version 3.0.2. p Value <.05 was considered significant.

Results

Sample characteristics

The demographics and clinical indicators of all participants are shown in Table 1. Chi-square test results indicated that no significant difference in gender distribution was observed between the case and control groups (p = .982). The average ages of the case and control groups were 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 = .962). These results indicate that gender and age were similarly distributed across both groups and could be considered comparable. Moreover, analysis of clinical indicators showed that the levels of FBG, HbA1c, TC, TG, urea, Cr and GFR were significantly different in cases compared with the controls ($p < .05$). However, no significant differences in HDL-C, LDL-C and Cys-C levels were observed between the two groups ($p > .05$). These findings suggest that diabetes may exert certain effects on blood glucose control, lipid metabolism and renal function.

Table 2. Basic information of SNPs in *CYP2C8* and *CYP2D6*.

SNP-ID	Chr	Position	Role	Allele A/B	Gene	HWE-p
rs1934953	10	95037713	Intron	T/C	*CYP2C8*	.374
rs1934951	10	95038791	Intron	T/C	*CYP2C8*	.574
rs2275620	10	95042841	Intron	T/A	*CYP2C8*	.590
rs17110453	10	95069772	Upstream transcript	C/A	*CYP2C8*	.159
rs1065852	22	42130692	Intron	A/G	*CYP2D6*	.210

SNP: single nucleotide polymorphism; Chr: chromosome; MAF: minor allele frequency; HWE: Hardy–Weinberg's equilibrium; OR: odds ratio; CI: confidence interval.
$p < .05$ was considered to be significant.

Assessment of HWE for SNPs

The detailed information and HWE-p values of the SNPs in *CYP2C8* and *CYP2D6* are shown in Table 2. Chi-square test results showed that the genotype frequencies of the five SNPs in the control group conformed to HWE ($p > .05$), suggesting that the genotype distribution in the control group is consistent with the expected genetic variation in a randomly mating population. The distribution differences of allele and genotype frequencies between the two groups of these five SNPs are shown in Supplement Table 1.

Overall association between SNPs and T2DM risk

We tested to evaluate the association between five SNPs in *CYP2C8* and *CYP2D6* and the risk of T2DM under genetics models (Figure 2). The allele A of rs1065852 in *CYP2D6* was found to be significantly related to an increased risk of T2DM compared to the G allele (OR = 1.22, 95% CI: 1.03–1.45, p = .024). The AA genotype of rs1065852 carriers had a 1.46-fold increased risk of T2DM compared with those having the GG genotype (OR = 1.46, 95% CI: 1.04–2.06, p = .031). Significant associations were also found between rs1065852 and the risk of T2DM under the dominant model (AA–AG vs. GG: OR = 1.36, 95% CI:

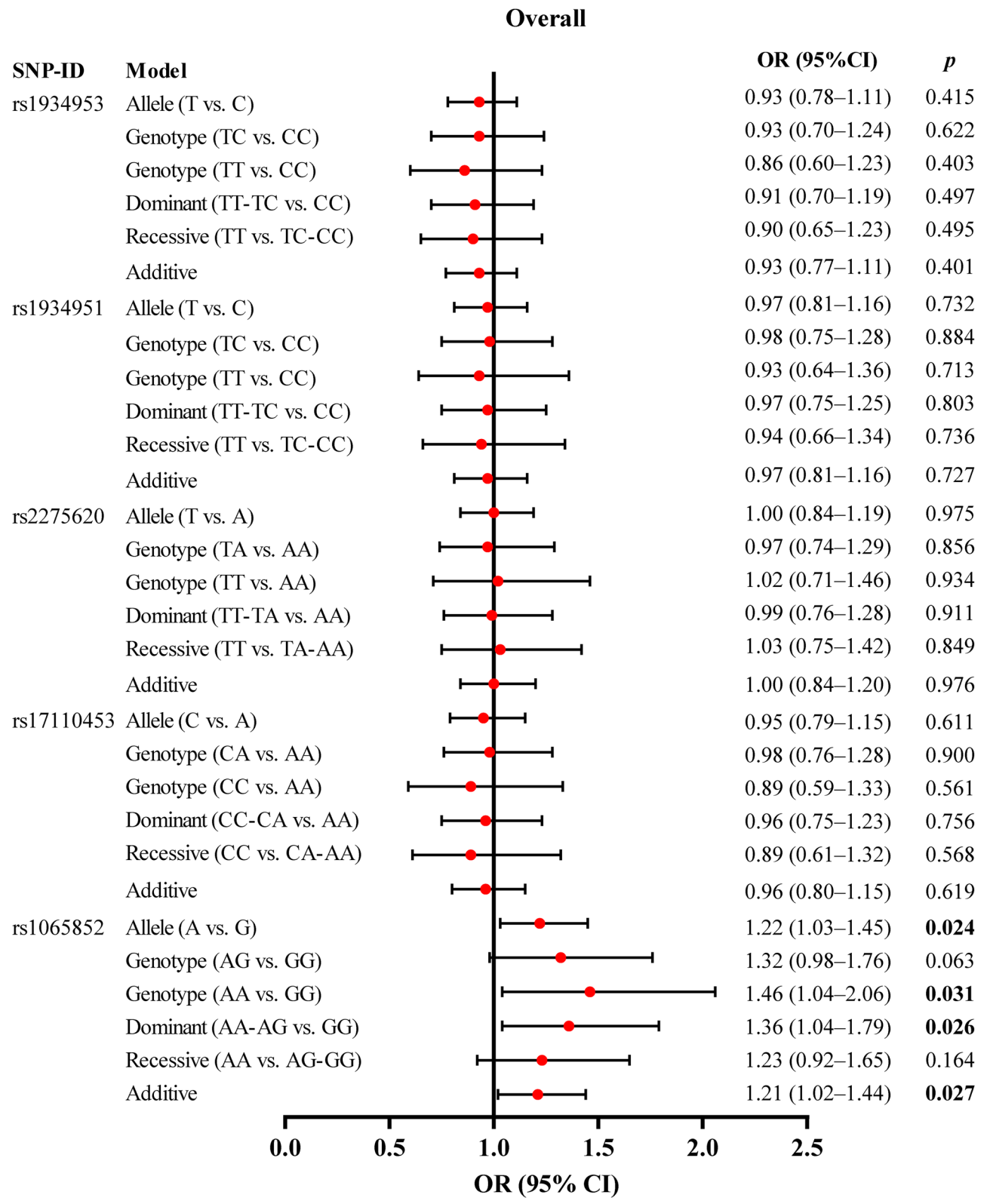

Figure 2. Forest plot of *CYP2C8* and *CYP2D6* polymorphisms and T2DM risk. The circle represents the OR value. The horizontal lines represented the study-specific 95% CI. OR (95% CI) calculated via logistic regression, adjusted for confounders. SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval. $p < .05$ was considered to be significant.

1.04–1.79, $p = .026$) and additive model (OR = 1.21, 95% CI: 1.02–1.44, $p = .027$), indicating that this SNP may play a role in the susceptibility to T2DM. However, no statistical significance association was found between the four SNPs (rs1934953, rs1934951, rs2275620 and rs17110453) in *CYP2C8* and

susceptibility to T2DM. This suggests that these particular SNPs in *CYP2C8* may not be major determinants of T2DM risk within the studied population.

Stratified analysis of age and gender

Furthermore, to minimize the impact of sex and age on our statistical results, we performed a stratified analysis. In males, the A allele of rs1065852 was associated with an increased risk of T2DM compared to the G allele (OR = 1.29, 95% CI: 1.02–1.64, p = .032); the AA genotype (OR = 1.63, 95% CI: 1.03–2.59, p = .039) and AA–AG (OR =1.47, 95% CI: 1.02–2.12, p = .041) of rs1065852 were associated with an increased risk of T2DM compared with the GG genotype; rs1065852 was found to be associated with an increased risk of T2DM under the additive mode (OR = 1.28, 95% CI: 1.02–1.62, p = .035) (Figure 3). These results highlight the potential influence of rs1065852 on T2DM susceptibility in males.

In the age < 59 subgroup, the A allele of rs1065852 was correlated with an increased risk of T2DM compared with the G allele (OR = 1.44, 95% CI: 1.12–1.85, p = .005). The AA genotype (OR = 1.98, 95% CI: 1.20–3.29, p = .008), AG genotype (OR = 1.66, 95% CI: 1.07–2.55, p = .035) and AA–AG genotype (OR = 1.76, 95% CI: 1.17–2.64, p = .007) were also associated with an increased risk of T2DM compared with the GG genotype. Meanwhile, rs1065852 was also found to be associated with an increased risk of T2DM under the additive mode in age < 59 subgroup (OR = 1.41, 95% CI: 1.10–1.82, p = .007) (Figure 3). These findings underscore the significant role of rs1065852 in T2DM risk, particularly in younger individuals. However, no statistically significant association was found between the four SNPs (rs1934953, rs1934951, rs2275620 and rs17110453) in *CYP2C8* and the risk of T2DM in subgroups (Supplement Table 2). This suggests that these SNPs may not be major contributors to T2DM risk within the studied population. Moreover, no significant association was found between rs1065852 and clinical indicators (Supplement Table 3), indicating that while rs1065852 is associated with T2DM risk, it may not have a direct impact on clinical markers of the disease.

SNP–SNP interactions on T2DM risk

The results of the MDR analysis examining SNP–SNP interactions on T2DM risk are demonstrated in Table 3. The MDR analysis results identified the one-locus model (rs1065852) as the best-performing model, with a testing accuracy of 0.534, an OR of 1.39 (95% CI: 1.05–1.85), and a p value of .023. Moreover, the cross-validation consistency (CVC) of 10/10 indicates that the model's predictive accuracy was consistently high across all cross-validation folds, and generalizability, reinforcing the conclusion that rs1065852 plays a role in T2DM susceptibility.

Discussion

This study investigated the association between polymorphisms of *CYP2C8* and *CYP2D6* and susceptibility to T2DM in the Chinese Han population. The results of this study indicated that rs1065852 in *CYP2D6* was significantly associated with an increased risk of T2DM in overall, males and age < 59 years old subgroup. However, no association was found between the four SNPs (rs1934953, rs1934951, rs2275620 and rs17110453) in *CYP2C8* and T2DM risk in the Chinese Han population.

CYP2C8 mapped in chromosome 10q23 encodes a significant enzyme in the oxidative metabolism of numerous drugs and chemicals [12]. Previous studies have reported associations between specific SNPs in *CYP2C8* and various diseases. For example, rs1934953 is significantly associated with susceptibility to essential hypertension [13] and bladder cancer [25], while no significant correlation is found between rs1934953 and the risk of coronary heart disease in the Russian population [22]. The SNP rs1934951 is associated with the development of medication-related osteonecrosis of the jaw (MRONJ) in patients treated with bisphosphonates [24] and is significantly associated with an increased risk of bladder cancer [25]. The two-locus interaction (rs17110453 and rs751141) [31] and three-locus interaction (rs17110453, rs751141 and rs9333025) [32] confer significantly higher risk for ischemic stroke. Additionally, the TA genotype of rs2275620 is associated with an increased risk of tuberculosis in the northwest Chinese Han population [15], while it is associated with a decreased risk of bladder cancer [25]. Despite these prior associations, this study reported for the first time that four SNPs in *CYP2C8* (rs1934953, rs1934951, rs2275620 and rs17110453) were not significantly associated with the risk of T2DM in the Chinese Han population. Therefore, further studies are needed to confirm our findings.*CYP2D6* genetic polymorphisms may influence the enzymatic activity of *CYP2D6*, an enzyme responsible for the metabolism of numerous drugs, including tricyclic antidepressants, antipsychotics, beta-blockers, antiarrhythmics and anti-diabetics [33]. The SNP rs1065852 has been associated with an increased risk of lung cancer in the Northwestern Chinese Han population [18]. Furthermore, under multiple genetic models, rs1065852

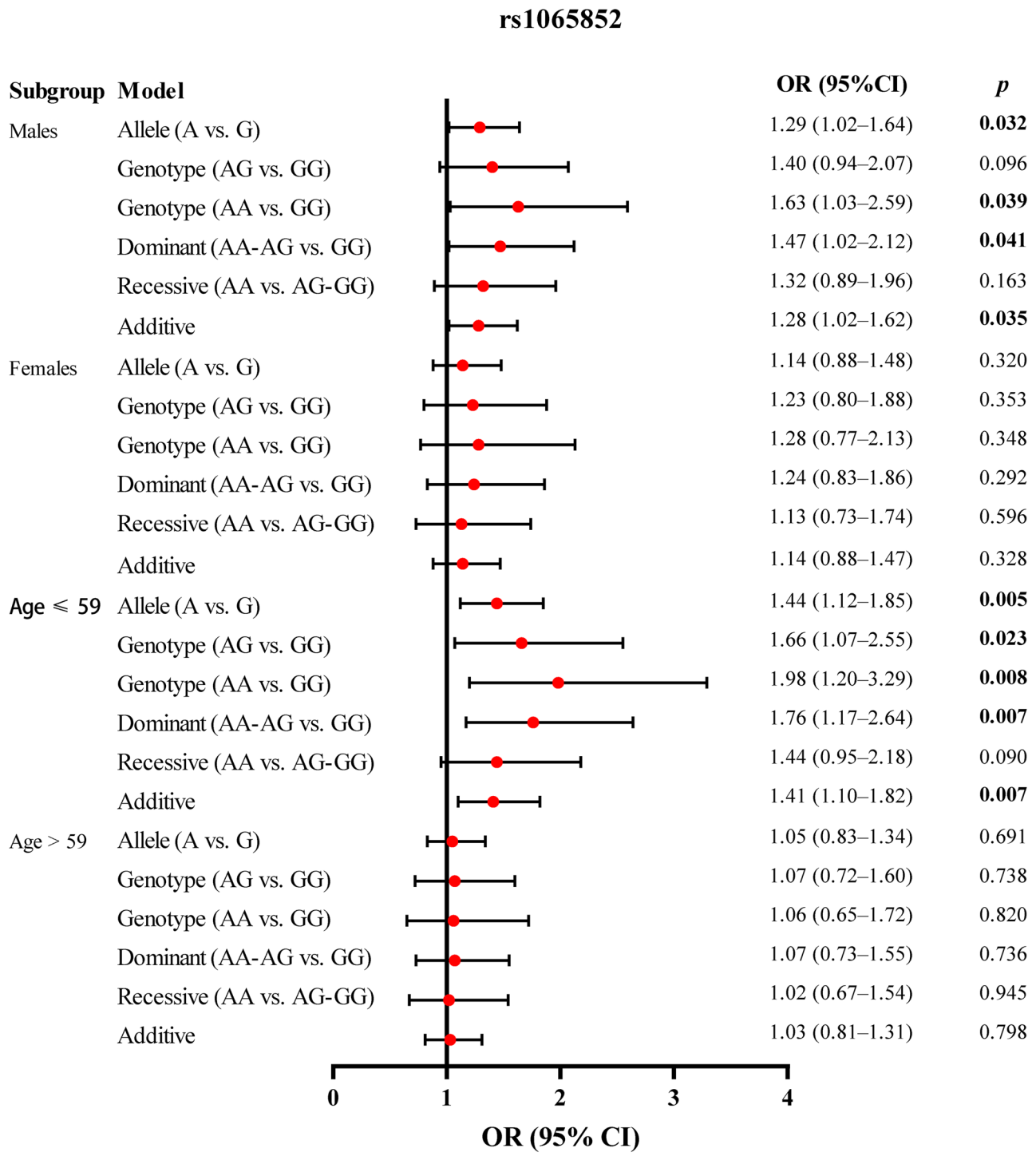

Figure 3. Forest plot of *CYP2D6* rs1065852 and T2DM risk stratified by sex and age. The circle represents the OR value. The horizontal lines represented the study-specific 95% CI. OR (95% CI) calculated via logistic regression, adjusted for confounders. SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval. $p < .05$ was considered to be significant.

was found to significantly increase the risk of coronary heart disease in participants who were ≤60 years old, smokers or had a family history [19]. In addition, rs1065852 has been shown to impact the prognosis of patients with non-small cell lung cancer treated with gefitinib [34]. In this study, rs1065852 in *CYP2D6* was identified as significantly risk factor for T2DM in the overall population. This finding underscores the potential utility of rs1065852 in genetic risk assessment and the development of targeted interventions for high-risk populations. However, to fully understand the role of rs1065852 in T2DM further research is needed to explore its biological mechanisms, particularly its functional impact on enzyme activity, insulin resistance

Table 3. SNP–SNP interactions on the risk of T2DM analysed by MDR.

Model	Bal. Acc. CV training	Bal. Acc. CV testing	CVC	Testing sensitivity	Testing specificity	OR (95% CI)	*p*
rs1065852	0.534	0.534	10/10	0.742	0.326	1.39 (1.05–1.85)	.0225
rs17110453, rs1065852	0.542	0.503	4/10	0.541	0.482	1.40 (1.08–1.82)	.0109
rs1934951, rs17110453, rs1065852	0.552	0.511	8/10	0.529	0.471	1.52 (1.17–1.97)	.0016
rs1934953, rs1934951, rs17110453, rs1065852	0.559	0.488	7/10	0.543	0.447	1.62 (1.25–2.11)	.0003
rs1934953, rs1934951, rs2275620, rs17110453, rs1065852	0.567	0.497	10/10	0.594	0.412	1.74 (1.34–2.27)	<.0001

T2DM: type 2 diabetes mellitus; MDR: multifactor dimensionality reduction; Bal. Acc.: balanced accuracy; CVC: cross-validation consistency; OR: odds ratio; CI: confidence interval.
$p < .05$ was considered to be significant.

and β-cell function. *In vitro* and *in vivo* studies could provide valuable insights into how rs1065852 influences drug metabolism and disease progression, as well as its potential interactions with environmental factors such as BMI, smoking and dietary habits.

Our stratified analysis revealed that rs1065852 was associated with T2DM risk in males and individuals under 59 years of age. These findings highlight the importance of considering sex and age in genetic studies of T2DM, as genetic susceptibility may vary across these subgroups. The steep rise of T2DM goes along with mounting evidence of clinically important sex differences [35]. The T2DM incidence rates continually increased in China, particularly among young individuals, and T2DM-related mortality increased in males [36], which may be due to the involvement of BMI, diet, physical activity, smoking, income levels, sex hormones and other factors [37]. Additionally, age-natural decline in β-cell function and increases in insulin resistance may further contribute to differences in T2DM susceptibility [38]. Understanding these subgroup differences is crucial for developing personalized prevention and treatment strategies, which could improve the management of T2DM in diverse populations.

Furthermore, TG and TC levels in both Chinese men and women might be used to decrease the incidence of T2DM [39]. The ratio of TG/HDL-C is positively associated with diabetes risk [40]. The level of HDL-C was independently and negatively associated with the risk of new-onset T2DM among middle-aged and elderly Chinese [41]. Glucose, HOMA-IR, TG, LDL-C and HDL-C are superior biomarkers for predicting T2DM in children and adolescents [42]. Reduced levels of serum Cr were found to be significantly associated with an increased risk of T2DM in males [43]. Almost 40% of patients with T2DM in a nationwide cross-sectional study in Thailand had impaired GFR [44]. In this study, we observed significant differences in TC, TG, urea, Cr and GFR levels between T2DM cases and controls. However, no significant differences were found in HDL-C, LDL-C and Cys-C levels. Importantly, rs1065852 was not significantly associated with any of these clinical indicators, suggesting its contribution to T2DM risk may not be mediated through direct effects on lipid profiles or renal function. Instead, rs1065852 may influence T2DM risk through mechanisms related to drug metabolism, insulin resistance and β-cell function, or through interactions with other genetic or environmental factors. This discrepancy warrants further investigation to clarify the underlying mechanisms.

This study has certain limitations. First, there may be different SNP effects in different ethnic groups, so it is necessary to study different ethnic groups to confirm our results. Second, although a strong association between rs1065852 and T2DM risk has been found, further research is needed on the impact of this SNP on gene and protein expression and how they contribute to the development of T2DM. Finally, lack of other environmental factors such as lifestyle (smoking and drinking), diet and BMI. Multiple factor analysis is needed to more accurately determine the role of *CYP2C8* and *CYP2D6* in T2DM.

Conclusions

In conclusion, this is the first study performed to investigate the relationships between *CYP2C8* and *CYP2D6* polymorphisms and the risk of T2DM in the Chinese Han population. This study demonstrated that rs1065852 in *CYP2D6* is an independent risk factor for T2DM. Further studies are required to confirm our findings and better understand the pathogenesis of T2DM.

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Author contributions

Qingbin Zhao designed the research study, collected the samples and analysed the data. Huiyi Wei wrote the manuscript and conducted experiments. All authors read and approved the final version of the manuscript.

Ethics approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Approval No.: XJTU1AF2019LSL-030). 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.

Consent form

All participants provided written informed consent to participate in this study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The raw genotyping data generated during this study have been deposited in the Zenodo repository and are publicly available under the following DOI:10.5281/zenodo.14498839. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

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