Different Associations Between CDKAL1 Variants and Type 2 Diabetes Mellitus Susceptibility: A Meta-analysis

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Background: CDK5 regulatory subunit associated protein 1 like 1 (CDKAL1) is a major pathogenesis-related protein for type 2 diabetes mellitus (T2DM). Recently, some studies have investigated the association of CDKAL1 susceptibility variants, including rs4712523, rs4712524, and rs9460546 with T2DM. However, the results were inconsistent. This study aimed to evaluate the association of CDKAL1 variants and T2DM patients.

Methods: A comprehensive meta-analysis was performed to assess the association between CDKAL1 SNPs and T2DM among dominant, recessive, additive, and allele models.

Results: We investigated these three CDKAL1 variants to identify T2DM risk. Our findings were as follows: rs4712523 was associated with an increased risk of T2DM for the allele model (G vs A: OR = 1.172; 95% CI: 1.103–1.244; p < 0.001) and dominant model (GG + AG vs AA: OR = 1.464; 95% CI: 1.073–1.996; p = 0.016); rs4712524 was significantly associated with an increased risk of T2DM for the allele model (G vs A: OR = 1.146; 95% CI: 1.056–1.245; p = 0.001), additive model (GG vs AA: OR = 1.455; 95% CI: 1.265–1.673; p < 0.001) recessive model (GG vs AA + AG: OR = 1.343; 95% CI: 1.187–1.518; p < 0.001) and dominant model (GG + AG vs AA: OR = 1.221; 95% CI: 1.155–1.292; p < 0.001); and rs9460546 was associated with an increased risk of T2DM for the allele model (G vs T: OR = 1.215; 95% CI: 1.167–1.264; p = 0.023). The same results were found in the East Asian subgroup for the allele model.

Conclusions: Our findings suggest that CDKAL1 polymorphisms (rs4712523, rs4712524, and rs9460546) are significantly associated with T2DM.

Keywords: type 2 diabetes mellitus, CDKAL1, polymorphisms, susceptibility, meta-analysis
1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex disease characterized by insulin resistance in peripheral tissues and dysregulated insulin secretion by pancreatic β-cells (Li et al., 2020). The incidence of T2DM in adults has been increasing over recent decades (Yang et al., 2010; Tian et al., 2019) and is estimated to increase to over 700 million by 2045 (Saeedi et al., 2019; Li et al., 2020). T2DM is caused by genetic and environmental factors (Tian et al., 2019; Wu et al., 2014). Genetic variants are thought to be involved in the development of T2DM. Genome-wide association studies have indicated that some single nucleotide polymorphisms (SNPs) are critical risk factors for T2DM (Tian et al., 2019).

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**TABLE 1** | Characteristics of each study included in rs4712523 of meta-analysis.

| Author | Year | Ethnic | T2DM/NDM | ORs with 95% CI (G vs A) | Allele distribution | Genotype distribution |
|-------|------|-------|----------|--------------------------|---------------------|----------------------|
| Liu et al. | 2020 | India | 1183/1188 | 1.077 (0.983–1.300) | T2DM, n = 1640; NDM, n = 726; 1684; 692 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Tian et al. | 2019 | Chinese | 510/503 | 1.420 (1.190–1.690) | T2DM, n = 508; NDM, n = 512; 588; 418 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Qian et al. | 2019 | Chinese | 526/526 | 1.027 (0.956–1.103) | T2DM, n = 590; NDM, n = 462; 556; 496 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Rao et al. | 2016 | Chinese | 458/429 | 0.924 (0.766–1.114) | T2DM, n = 525; NDM, n = 391; 475; 383 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Ren et al. | 2013 | Chinese | 98/97 | 1.521 (1.018–2.273) | T2DM, n = 99; NDM, n = 97; 118; 76 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Li et al. | 2013 | Chinese | 192/190 | 1.654 (1.237–2.212) | T2DM, n = 202; NDM, n = 182; 246; 134 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Lu et al. | 2012 | Chinese | 2897/3259 | 1.225 (1.139–1.314) | T2DM, n = 3105; NDM, n = 2689; 3816; 2702 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Gong et al. | 2016 | Chinese | 91/186 | 1.380 (1.250–1.520) | T2DM, n = 91; NDM, n = 186 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Long et al. | 2012 | African Americans | 1549/2722 | 0.980 (0.870–1.070) | T2DM, n = 1549; NDM, n = 2722 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Takeuchi et al. | 2009 | Japanese | 5629/6406 | 1.270 (1.210–1.330) | T2DM, n = 5629; NDM, n = 6406 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Takeuchi et al. | 2009 | Europeans | 14586/17968 | 1.120 (1.080–1.160) | T2DM, n = 14586; NDM, n = 17968 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Rung et al. | 2009 | Caucasian | 180/165 | 1.200 (1.140–1.260) | T2DM, n = 180; NDM, n = 165 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |
| Scott et al. | 2007 | Finnish | 1161/1174 | 1.123 (1.032–1.222) | T2DM, n = 1161; NDM, n = 1174 | AA = 131; AG = 246; GG = 175; T2DM, n = 149; NDM, n = 159; 190; 119 |

n, Number; T2DM, type 2 diabetes mellitus; NDM, Non-diabetic subject; OR, odds ratio; CI, confidence interval.
CDK5 regulatory subunit associated protein 1 like 1 (CDKAL1) is a crucial pathogenesis-related protein for T2DM. The CDKAL1 gene encodes cyclin-dependent kinase 5 regulatory subunit-associated protein 1 (CDK5RAP1)-like 1. Cyclin-dependent kinase 5 (CDK5) is a serine/threonine protein kinase that contributes to the glucose-dependent regulation of insulin secretion (Li et al., 2020); therefore, it plays a critical role in the pathophysiology of β-cell dysfunction and predisposition to T2DM (Li et al., 2020; Wei et al., 2005; Ubeda et al., 2006). The associations of many SNPs in CDKAL1 with T2DM have been examined in some meta-analyses, but no published meta-analysis has evaluated the role of CDKAL1 variants rs4712523, rs4712524 and rs9460546 variants in the susceptibility to T2DM. Several studies have examined the association between CDKAL1 polymorphisms (rs4712523, rs4712524 and rs9460546) and T2DM risk, but some findings were failed to replicate. Therefore, performing a meta-analysis is needed to evaluate the association between CDKAL1 polymorphisms (rs4712523, rs4712524, and rs9460546) and T2DM.

2 MATERIALS AND METHODS

This meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.
and I² test. Lower heterogeneity was defined as I² < 50% and p > 0.01, using the fixed effects model (Mantel–Haenszel) to calculate ORs with corresponding 95% CIs. Otherwise, the random effects model (Mantel–Haenszel) was used. The significance of the ORs was evaluated using the Z test. Begg’s and Egger’s tests were used to determine publication bias. STATA v.14.0 software (Stata Corporation, Texas, United States) was used to perform all statistical analyses.

3 RESULTS

3.1 Study Inclusion and Characteristics
A total of 179 potential studies were searched using the inclusion and exclusion criteria. Figure 1 shows a flow chart of the study selection process. Twelve articles, including 7 in English and 5 in Chinese, had rs4712523 data. Eight articles, including 5 in English, 2 in Chinese and 1 in Russian, had rs4712524 data. Five articles, including 5 in English, had rs9460546 data. The characteristics of each included study are shown in Tables 1–3.

3.2 Heterogeneity Analysis

3.2.1 rs4712523
High heterogeneity among studies (Scott et al., 2007; Rung et al., 2009; Takeuchi et al., 2009; Long et al., 2012; Lu et al., 2012; Gong, 2016; Li et al., 2013; Ren et al., 2013; Rao et al., 2016; Qian, 2019; Tian et al., 2019; Liju et al., 2020) was detected in the allele model (G vs A: I² = 84.4%; p < 0.001), additive model (GG vs AA: I² = 84.6%; p < 0.001), recessive model (GG vs AA + AG: I² = 73.8%; p = 0.002), and dominant model (GG + AG vs AA: I² = 86.1%; p < 0.001) (Figure 2).

3.2.2 rs4712524
High heterogeneity among studies (Unoki et al., 2008; Lu et al., 2012; Rao et al., 2016; Li, 2018; Tian et al., 2019; Azarova, 2020; Li et al., 2020; Liju et al., 2020) was detected in the allele model (G vs A: I² = 75.1%; p < 0.001). A moderate degree of heterogeneity among studies was detected under the additive model (GG vs AA: I² = 58.7%; p = 0.024) and recessive model (GG vs AA + AG: I² = 57.8%; p = 0.027). Low heterogeneity among studies was detected under the
dominant model (GG + AG vs AA: I² = 31.8%; p = 0.185) (Figure 3).

3.2.3 rs9460546
Low heterogeneity among studies (Herder et al., 2008; Unoki et al., 2008; Hu et al., 2009; Maller et al., 2012; Li et al., 2020) was detected in the allele model (G vs T: I² = 37.0%; p = 0.174) (Figure 4).

3.3 Meta-Analysis Results
3.3.1 rs4712523
A significant difference was found between T2DM patients and NDM controls for the allele model (G vs A: OR = 1.172; 95% CI: 1.103–1.245; p < 0.001) and dominant model (GG + AG vs AA: OR = 1.464; 95% CI: 1.073–1.996; p = 0.016). No significant associations were found under the additive model (GG vs AA: OR = 1.495; 95% CI: 0.990–2.257; p = 0.056) and recessive model (GG vs AA + AG: OR = 1.188; 95% CI: 0.900–1.568; p = 0.223) using a random effects model (Figure 2).

3.3.2 rs4712524
A random effects model was used to analyze the allele, additive and recessive models, and the dominant model was analyzed using a fixed effects model. A significant difference was found between T2DM patients and NDM controls for the allele model (G vs A: OR = 1.146; 95% CI: 1.056–1.245; p = 0.001), additive model (GG vs AA: OR = 1.455; 95% CI: 1.265–1.673; p < 0.001) recessive model (GG vs AA + AG: OR = 1.343; 95% CI: 1.187–1.518; p < 0.001) and dominant model (GG + AG vs AA: OR = 1.221; 95% CI: 1.155–1.292; p < 0.001) (Figure 3).

3.3.3 rs9460546
A significant difference was found between T2DM patients and NDM controls for the allele model (G vs T: OR = 1.215; 95% CI: 1.167–1.264; p = 0.023) using a fixed effects model (Figure 4).
Figure 4: Meta-analysis using a fixed effects model for the association between the CDKAL1 rs9460546 polymorphism and T2DM susceptibility (Allele model, G vs T). OR: odds ratio, CI: confidence interval, I-squared: measure to quantify the degree of heterogeneity in meta-analyses.

Figure 5: Association between the CDKAL1 variants and T2DM susceptibility in the subgroup for the allele model (A) rs4712523: G vs A (random effects model) (B) rs4712524: G vs A (random effects model) (C) rs9460546: G vs T (fixed effects model). OR: odds ratio, CI: confidence interval, I-squared: measure to quantify the degree of heterogeneity in meta-analyses.
3.4 Subgroup Analyses

3.4.1 rs4712523
We performed subgroup analysis according to ethnicity to evaluate the association between rs4712523 and T2DM susceptibility in the allele model. Rs35767 was significantly related to the risk of T2DM in the East Asian (G vs A: OR = 1.241; 95% CI: 1.123–1.371; \( p < 0.001 \)) and others subgroup (G vs A: OR = 1.108; 95% CI: 1.039–1.180; \( p = 0.002 \)) using a random effects model (Figure 5A).

3.4.2 rs4712524
We performed subgroup analysis according to ethnicity to evaluate the association between rs4712524 and T2DM susceptibility in the allele model. Rs4712524 was significantly related to the risk of T2DM in the East Asian (G vs A: OR = 1.189; 95% CI: 1.134–1.247; \( p < 0.001 \)) and others subgroup (G vs A: OR = 1.071; 95% CI: 0.807–1.423; \( p = 0.634 \)) using a random effects model (Figure 5B).

3.4.3 rs9460546
We performed subgroup analysis according to ethnicity to evaluate the association between rs9460546 and T2DM susceptibility in the allele model. Rs9460546 was significantly related to the risk of T2DM in the East Asian (G vs T: OR = 1.189; 95% CI: 1.134–1.247; \( p < 0.001 \)) and others subgroup (G vs T: OR = 1.277; 95% CI: 1.188–1.373; \( p < 0.001 \)) using a fixed effects model (Figure 5C).

3.5 Publication Bias
According to Begg’s and Egger’s tests, no significant publication bias was found in each of the genetic models (all \( p > 0.05 \), data not shown), and the funnel plots are shown in Figures 6–9.

4 DISCUSSION
CDKAL1 is a key pathogenesis-related protein for T2DM (Tian et al., 2019). Genetic variants may play an essential role in T2DM...
susceptibility. In this meta-analysis, three SNPs (rs4712523, rs4712524, and rs9460546) from previous studies were evaluated to determine the association of CDKAL1 polymorphisms with T2DM. CDKAL1 polymorphisms (rs4712523, rs4712524, and rs9460546) showed a significant association with T2DM. Our results were consistent with some previous study findings.

The results revealed that the G allele and GG + AG genotypes of rs4712523 were associated with an increased risk of T2DM. Nine of the thirteen previous studies investigated rs4712523 showed an association between the G allele and T2DM (Scott et al., 2007; Rung et al., 2009; Takeuchi et al., 2009; Long et al., 2012; Lu et al., 2012; Gong, 2016; Li et al., 2013; Ren et al., 2013; Tian et al., 2019), and four studies found an association between the GG + AG genotypes and T2DM (Lu et al., 2012; Li et al., 2013; Ren et al., 2013; Tian et al., 2019). In addition, the rs4712524 G allele, GG and GG + AG genotypes were associated with an increased risk of T2DM susceptibility. That have been confirmed previous observations (Unoki et al., 2008; Lu et al., 2012; Tian et al., 2019; Azarova, 2020; Li et al., 2020). Additionally, the
results showed that rs9460546 G allele was associated with T2DM susceptibility. Markedly, all five studies found that the rs9460546 G allele was associated with T2DM in various populations (Herder et al., 2008; Unoki et al., 2008; Hu et al., 2009; Maller et al., 2012; Li et al., 2020). Moreover, rs4712523, rs4712524, and rs9460546 showed a significant association with T2DM in the East Asian subgroup for the allele model. In general, our results have confirmed previous observations suggesting that CDKAL1 may play a role in T2DM. But it is worth noting that high heterogeneity among studies was detected in rs4712523 and rs4712524 likely because of the difference in country, ethnicity, genetic background and environmental factors. Subgroup analyses were performed by ethnicity in the allele model, and the subgroup still had high heterogeneity. Importantly, the high heterogeneity among studies might have affected our data.

CDKAL1 expression in human pancreatic β-cells increases insulin secretion by inhibiting CDK5 (Li et al., 2020; Wei et al., 2005; Ubeda et al., 2006; Ching et al., 2002). Subsequently, several studies have shown the association of genetic variants in CDKAL1 with defects in proinsulin conversion and the insulin response following glucose stimulation (Pascoe et al., 2007; Steinthorsdottir et al., 2007; Tian et al., 2019). Thus, CDKAL1 is involved in the development of T2DM. Genome-wide association studies have identified several SNPs in the CDKAL1 gene associated with T2D (Saxena et al., 2007; Scott et al., 2007; Tian et al., 2019). Our results confirmed the significant association between CDKAL1 SNPs and T2DM susceptibility. However, the mechanisms must be verified in functional studies. Our association results provide reference data to identify new biomarkers of T2DM that could contribute to the diagnosis of T2DM.

This meta-analysis has a few limitations. First, because of the limited examination of CDKAL1 variants in T2DM, the included studies had comparatively small sample sizes, which might affect the results of the meta-analysis because of insufficient statistical power. Thus, studies must be performed across different geographical and ethnic groups. Additionally, the factors of T2DM might be complex, with the contribution of genetic, environmental and dietary habits. Therefore, further study is...
required to evaluate whether other risk factors together with the CDKAL1 gene influence T2DM susceptibility.

5 CONCLUSION

To our knowledge, this study is the first to assess the role of CDKAL1 polymorphisms (rs4712523, rs4712524, and rs9460546) in T2DM. Significant associations were found between the CDKAL1 rs4712523, rs4712524, and rs9460546 polymorphisms and susceptibility to T2DM.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

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AUTHOR CONTRIBUTIONS

QZ, DZ and SG were responsible for the study design, statistical analysis, and manuscript preparation. QZ and FH managed the literature searches and analyses. The study was supervised by SC, YW and RG.

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