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# Review of KCNQ1 rs2237895 gene polymorphism increases susceptibility to type 2 diabetes mellitus in Asian populations

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**Abstract**

BACKGROUND

The association of single nucleotide polymorphism of KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) gene rs2237895 with type 2 diabetes mellitus (T2DM) is currently controversial. Meanwhile, it is unknown whether this association is generalizable across different populations.

AIM

We aimed to determine the association of the KCNQ1 gene rs2237895 with T2DM and to provide reliable evidence for genetic susceptibility to T2DM.

METHODS

Nine electronic databases were searched in PubMed, Embase, Web of Science, Cochrane Library, Medline, Baidu Academic, China National Knowledge Infrastructure (CNKI), CBM, and Wanfang to investigate the association between KCNQ1 gene rs2237895 and the risk of T2DM up to January 12, 2022. Review Manager 5.4 was used to analyze the association of the KCNQ1 gene rs2237895 locus polymorphism with T2DM and to evaluate the publication bias of the selected literature.

RESULTS

Twelve case-control studies (including 11,273 cases and 11,654 controls) met our inclusion criteria. In the full population, allelic model (OR: 1.19; 95% CI: 1.09-1.29; P<0.0001), recessive model (OR: 1.20; 95% CI: 1.11-1.29; P<0.0001), dominant model (OR: 1.27. 95% CI: 1.14-1.42; P<0.0001), and co-dominant model (OR: 1.36; 95% CI: 1.15-1.60; P=0.0003) (OR: 1.22; 95% CI: 1.10-1.36; P=0.0002) indicated that the KCNQ1 gene rs2237895 locus polymorphism was significantly correlated with the susceptibility of T2DM. In stratified analysis, this association was confirmed in Asian populations (allelic model (OR: 1.25; 95% CI: 1.13-1.37; P<0.0001), recessive model (OR: 1.29; 95% CI: 1.11-1.49; P=0.0007), dominant model (OR: 1.35; 95% CI: 1.20-1.52; P<0.0001), co-dominant model (OR: 1.49; 95% CI: 1.22-1.81; P<0.0001) (OR: 1.26; 95% CI: 1.16-1.36; P<0.0001)), while in non-Asian populations, this association was not significant (allelic model (OR: 1.06; 95% CI: 0.98-1.14; P=0.12), recessive model (OR: 1.04; 95% CI: 0.75-1.42; P=0.83) , dominant model (OR: 1.06; 95% CI: 0.98-1.15; P=0.15), co-dominant model (OR: 1.08; 95% CI: 0.82-1.42; P=0.60) (OR: 1.15; 95% CI: 0.95-1.39; P=0.14)).

CONCLUSION

This study demonstrated that the KCNQ1 gene rs2237895 was significantly associated with susceptibility to T2DM in an Asian population. Carriers of the C allele have a higher risk of developing T2DM compared to those who do not carry the C allele. However, this association was not significant in non-Asian populations.

**Keywords:** type 2 diabetes mellitus; KCNQ1; single nucleotide polymorphism

**Core tip:** There is no consensus on the association of the KCNQ1 gene rs2237895 single nucleotide polymorphism with T2DM. We demonstrated a significant association between rs2237895 and T2DM in Asian populations. However, this correlation was not significant in non-Asian populations.

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common multifactorial, metabolic disease whose pathogenesis is influenced by a combination of genetic and environmental factors. The rise and large-scale application of genome-wide association studies (GWAS) have contributed to the understanding of genetic factors related to T2DM. T2DM remains a health problem that plagues the world to this day. As of January 4, 2021, the number of people with diabetes worldwide had reached 537 million. Even more alarmingly, this number is expected to increase to 643 million by 2030. The various expenditures due to diabetes have exceeded $966 billion, and this figure is growing at an annual rate of 63% since 2006[1]. The etiology of T2DM is complex and has not yet been fully elucidated. T2DM is characterized by defective insulin secretion and reduced sensitivity, leading to chronic hyperglycemia and severe metabolic dysfunction in patients[2-3]. Hyperglycemia affects the physiological function of several tissues and organs in the body, among which the most common are neuropathy and vascular complications[1].

Studies have not provided an accurate description of the etiology of T2DM, and a genome-wide scan of Japanese by Nawata *et al*. showed that KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) is a susceptibility gene for T2DM in Japan[4]. In addition, genes such as ADRA2A, KCNJ11 and CDKAL1 may be associated with the development of T2DM[4-5]. KCNQ1 is a potassium channel subunit that is mainly found in adipose and pancreatic tissues. It was found that KCNQ1 affects the process of islet β-cell depolarization by regulating potassium channel currents, thereby limiting insulin secretion from pancreatic β-cells and leading to the development of T2DM[6].

Previous studies have found that C allele carriers of the KCNQ1 gene rs2237895 may have an increased risk of developing T2DM[7]. The rs2237895 is present in three genotypes in the population, AA, AC, and CC. The A gene is wild type and the C gene is

mutant, and their gene frequencies in the population are approximately 66% and 34%[8]. A study by Cui *et al.* in Kazakhs living in China showed that single nucleotide polymorphism of KCNQ1 gene rs2237895 was not significantly associated with T2DM[7]. A study by Afshardoost *et al.* on Iranians also showed no significant association between the single nucleotide polymorphism of rs2237895 and T2DM[9]; while in a study by Khan *et al.* on Indians, they confirmed a significant association between the polymorphism of rs2237895 and T2DM[10]. Previously, a similar study has been conducted by Sun Q[11], but we consider that their inclusion criteria are more lenient and the strength of the proof may be weakened. Meanwhile, their work is more than ten years old and many new studies have been published during this period and this Meta-analysis is in urgent need of updating. To address the above issues, we performed this meta-analysis.

## MATERIALS AND METHODS

### *Literature search*

The following nine electronic databases were searched: PubMed, Embase, Web of Science, Cochrane Library, Medline, Baidu Academic, China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), and Wanfang Database, with the following search formulas: subject (T2DM) and keywords (KCNQ1) and keywords (rs2237895). The las
t search date was January 12, 2022. Chinese and English literature on the association of the rs2237895 single nucleotide polymorphism in the KCNQ1 gene with T2DM was collected. The inclusion criteria for the articles were (i) T2DM patients relevant studies in the case group met the diagnostic criteria for diabetes published by WHO in 1999 or ADA in 2010; (ii) the type of experiment was a case-

control study or a cohort study; (iii) there was sufficient information in the text to describe the genotype and allele frequencies of the case and control groups; (iv) the patients in the control group all met the H-W genetic equilibrium model; (v) patients were randomly selected with no special restrictions on age, sex, or family history; (vi) duplicate or data-identical literature, the one with the most complete information. Exclusion criteria were: (i) incomplete study data; (ii) exclusion of literature reviews; (iii) exclusion of studies with gestational diabetes as an endpoint; (iv) exclusion of studies with familial diabetes as a basis.

***Data extraction***

Two researchers independently performed literature screening and extraction of each information based on the above criteria. A third researcher was required to discuss and agree on the results when difficult differences were encountered. For each article, we collected the basic information that needed to be used for Meta-analysis, and the literature screening process is shown in Figure 1.

***Statistical analysis***

The data were processed using Review Manager 5.4 software. The strength of association between single nucleotide polymorphisms in the KCNQ1 gene rs2237895 and the risk of T2DM was assessed using the odds ratio (OR) and its corresponding 95% confidence interval (CI) as a criterion in the data statistics. The forest plots were used to show the OR and its 95% CI for each study. Meanwhile, the pooled results can be directly observed on the forest plots (significant differences were considered when the 95% CI did not include 1). Allelic model (C vs A), recessive model (CC vs AA+AC), dominant model (CC+AC vs AA) and co-dominant model (CC

vs AA and AC vs AA) were used to assess the genetic effects of the genes. The significance level was set at P<0.05. The random effect model was used to calculate the effect size when the heterogeneity $I^2$ > 50%, and the fixed effect model was used when $I^2$ < 50%. Publication bias assessed by Egger's test and funnel plot. In the funnel plot, the dashed line perpendicular to the horizontal axis indicates the combined effect size. It suggests that the studies are without publication bias when the distribution of studies in the funnel plot is approximately symmetrical.

**RESULTS**

According to the research strategy, a total of 323 relevant papers were retrieved from the databases. Some duplicates were found in these databases, and we removed the duplicates by Endnote software. We also screened the citations of the paper to ensure the comprehensiveness of the search. After a stepwise screening process, 12 eligible papers were finally included for Meta-analysis[10,12-22], which included 11273 patients with T2DM and 11654 controls. Ten of the datasets were studied from Asia, one from Europe, and one from Africa. The basic information of the studies is shown in Table 1.

The 12 datasets that met the inclusion criteria were pooled for Meta-analysis, and allelic, recessive, dominant, and co-dominant models were used to investigate the association of rs2237895 polymorphism with T2DM. Since the study population was predominantly Asian, we performed stratified analysis of Asian and non-Asian populations, and the results are shown in Figures 2-3.

In the full population, allelic model (OR: 1.19; 95% CI: 1.09-1.29; P<0.0001), recessive model (OR: 1.20; 95% CI: 1.11-1.29; P<0.0001),

dominant model (OR: 1.27. 95% CI: 1.14-1.42; P<0.0001), and co-dominant model (OR: 1.36; 95% CI: 1.15-1.60; P=0.0003) (OR: 1.22; 95% CI: 1.10-1.36; P=0.0002) all showed significant association between rs2237895 polymorphism and T2DM. In the subgroup of the Asian population, allelic model (OR: 1.25; 95% CI: 1.13-1.37; P<0.0001), recessive model (OR: 1.29; 95% CI: 1.11-1.49; P=0.0007), dominant model (OR: 1.35; 95% CI: 1.20-1.52; P<0.0001), co-dominant model (OR: 1.49; 95% CI: 1.22-1.81; P<0.0001) (OR: 1.26; 95% CI: 1.16-1.36; P<0.0001) also showed a significant association between rs2237895 polymorphism and T2DM, which was consistent with the whole population. The analysis shows that C allele carriers have an increased risk of developing T2DM. The CC and AC genotypes significantly increased the risk of T2DM compared to the AA genotype. However, in the non-Asian population subgroup, allelic model (OR: 1.06; 95% CI: 0.98-1.14; P=0.12), recessive model (OR: 1.04; 95% CI: 0.75-1.42; P=0.83), dominant model (OR: 1.06; 95% CI: 0.98-1.15; P=0.15), co-dominant model (OR: 1.08; 95% CI: 0.82-1.42; P=0.60) (OR: 1.15; 95% CI: 0.95-1.39; P=0.14) all showed no significant association between rs2237895 polymorphism and T2DM.

The funnel plots are shown in Figures 4-5, and no significant publication bias was found in the Meta-analysis. The results of Egger's test showed no significant publication bias for the allelic model (t=1.84, p=0.095), recessive model (t=-0.48, p=0.64), dominant model (t=1.44, p=0.18), and co-dominant model (t=1.33, p=0.21) (t=1.79, p=0.10).

We performed a sensitivity analysis. After sequentially excluding one study in the allelic model, recessive model, dominant model, and co-dominant model, we calculated the pooled effect sizes for the remaining studies. By calculation, no qualitative change occurred between the pooled results of the remaining studies and the original results. Sensitivity analysis proved that the results of the meta-analysis were reliable.

## DISCUSSION

Compared with previous studies, we increased the inclusion criteria of cases, excluded the interference of other factors (e.g., gestational diabetes), improved the strength of proof of the study, and made the results more reliable and stable. Our Meta-analysis supported the findings of Khan *et al.* suggesting that the rs2237895 single nucleotide polymorphism in the KCNQ1 gene is significantly associated with the development of T2DM in Asian populations[10]. In the study by Cui *et al*, their study population had an overall overweight problem[7], which increased the risk of T2DM prevalence and thus confounded the findings[23].

T2DM is a multifactorial, chronic, metabolic disease[24]. The idea that genetic factors have a significant role in the development of T2DM is now more widely accepted[24], although only a few genetic genes have been confirmed as risk genes for the development of T2DM. However, many genetic characteristics associated with T2DM, such as effect sizes and risk allele frequencies, need to be explored[25]. There is a need for researchers to identify risk genetic loci for T2DM and characterize the variation at the loci, thus providing a basis for elucidating the genetic pathogenesis of T2DM.

Previous studies have shown that the KCNQ1, miR-21, and Arg972 gene may be risk genes for T2DM[26-27]. Among them, the KCNQ1 gene has now been shown to be located on chromosome 11p15.5, which is approximately 400 kb in length and consists of 17 exons ranging from 47 bp to 112 2 bp in length[28]. KCNQ1 is associated with voltage-gated K+ channels, and mutations in the KCNQ1 gene lead to dysfunction of K+ channels, which would cause diseases such as QT syndrome and familial atrial fibrillation. KCNQ1 is expressed in many tissues in vivo[28-29], and the more studied KCNQ1 gene is expressed in cardiac and pancreatic tissues[30]. Current

studies suggested that the main mechanisms of T2DM development were insulin resistance and islet β-cell dysfunction[2,24]. And research suggested that variants in the KCNQ1 gene would lead to increased susceptibility to T2DM in the population by altering insulin secretion from pancreatic β-cells[31-32]. It was hypothesized that variants in the KCNQ1 gene would lead to increased expression of KCNQ1 protein on pancreatic β-cells, which in turn would alter the open state of voltage-gated potassium channels, decrease insulin secretion, and impair glucose storage and utilization[33].

In this Meta-analysis of the KCNQ1 gene rs2237895 single nucleotide polymorphism and T2DM association study involved 12 papers including 11273 T2DM patients and 11654 controls. This analysis showed that the rs2237895 polymorphism was significantly associated with an elevated risk of developing T2DM in an Asian population, which is consistent with previous Khan *et al.*'s findings[10]. In Asian population, C allele carriers have an increased risk of developing T2DM. The risk of T2DM is also increased in people with the CC and AC genotypes compared to the AA genotype. This is consistent with the previous findings of Hu *et al*. Also, their findings showed that rs2237895 was associated with hypertension, BMI, and hypertriglyceridemia[34]. While in non-Asian populations, this association was not significant. A 2015 study by Ríos *et al*. in Europeans also showed that the KCNQ1 gene rs2237895 single nucleotide polymorphism was not significantly associated with T2DM (OR: 0.91; 95% CI: 0.77-1.08; P=0.28)[35], which is consistent with our findings. Our work provided strong evidence for the genetic pathogenesis of T2DM and helped to fully reveal the pathogenesis of T2DM.

This study showed that the rs2237895 polymorphism of the KCNQ1 gene was differentially associated with T2DM in different populations. The reasons for this variation may be mutations in the regulatory region of the KCNQ1 gene in a certain population[35],

which interfere with the expression of the KCNQ1 gene; or it may be due to the existence of different genotypes and allele frequencies in populations with different clinical characteristics, geographical distribution and ethnic origin; or differences in the external influences associated with T2DM, such as lifestyle and behavior, in different populations[4,23-25]; in addition, the possibility of false-negative results in non-Asian populations with small study sample sizes cannot be excluded.

## CONCLUSION

In the Asian population, there was a significant association between the KCNQ1 gene rs2237895 single nucleotide polymorphism and T2DM onset. C allele carriers are at increased risk of T2DM, and the CC and AC genotypes significantly increased the susceptibility to T2DM; whereas in the non-Asian population, the association between rs2237895 polymorphism and T2DM onset was not significant.

## ARTICLE HIGHLIGHTS

### *Research background*

The association between the rs2237895 single nucleotide polymorphism in the KCNQ1 gene and the prevalence of T2DM has been controversial in different studies.

### *Research motivation*

The topic of this study is to investigate the association between the KCNQ1 gene rs2237895 and the prevalence of T2DM, and to provide help in revealing the pathogenesis of T2DM.

***Research objectives***

Demonstration of the association of the rs2237895 single nucleotide polymorphism in the KCNQ1 gene with the prevalence of T2DM. Also, to explore whether this relationship differs in different populations.

***Research methods***

We searched the literature in nine databases. Two authors independently screened the literature according to the established inclusion and exclusion criteria. Finally, data extraction was performed and the data were meta-analyzed.

***Research results***

Twelve case-control studies met our inclusion criteria. After analysis, the rs2237895 single nucleotide polymorphism in the KCNQ1 gene is associated with T2DM prevalence in Asian populations. However, this association was not significant in non-Asian populations

***Research conclusions***

In Asian populations, carriers of the rs2237895 C allele of the KCNQ1 gene are highly susceptible to T2DM compared to those who do not carry the C allele. However, in non-Asian populations, the association between the rs2237895 polymorphism and T2DM was not significant.

***Research perspectives***

We should continue to search for T2DM susceptibility genes through advanced technologies (e.g., genome-wide association strategy) and gradually reveal the pathogenesis of T2DM.

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