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The association of two common polymorphisms in miRNAs with diabetes mellitus

A meta-analysis

Guixin Li, MD, Beibei Liu, PhD, Qianqian Jiang, MD, Junli Zhang, PhD, Shengliang Xin, MD, Keshu Xu, PhD*

Abstract

Background: MicroRNAs (miRNAs) are small noncoding single-stranded RNAs with a length of ~21 nucleotides. Single nucleotide polymorphisms (SNPs) may affect the function of miRNAs, resulting in a variety of disorders in vivo. Recently, diabetes mellitus (DM) has become a global healthcare problem, and several studies have reported that 2 common polymorphisms (miRNA 146a rs2910164 and miRNA 27a rs895819) are related to susceptibility to diabetes. Given that no consensus had been reached regarding the association of the 2 polymorphisms with diabetes, we conducted this meta-analysis.

Methods: Four databases (PubMed, EMBASE, Cochrane, and Web of Science) were searched up to January 9, 2019. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the association strength. Subgroup and sensitivity analyses were also performed.

Results: Six studies involving 2585 cases and 2435 controls for miR146a rs2910164 and 5 studies involving 2922 cases and 2781 controls for miR27a rs895819 were ultimately analyzed in our meta-analysis. Based on pooled results, no statistical significance in association between rs2910164 and diabetes in Caucasians, Asians, or type 2 diabetes was observed in any genetic models. Nevertheless, we found a significant correlation between miRNA27a rs895819 and diabetes in the homozygote model (CC vs TT: OR = 0.58, 95%CI [0.35,0.98]) and recessive model (CC vs CT + TT: OR = 0.59, 95%CI [0.36,0.97]). By performing subgroup analysis, we also observed that C allele conveyed a significant protective effect against diabetes development in Caucasians (C vs T: OR = 0.67, 95%CI [0.52,0.85]).

Conclusion: In conclusion, this meta-analysis indicated that miRNA27a rs895819 might play a protective role in diabetes, and miRNA146a rs2910164 likely had no association with diabetes.

Abbreviations: CI = confidence interval, DM = diabetes mellitus, HWE = Hardy–Weinberg equilibrium, miRNA = microRNA, NF-κB = nuclear factor-κB, OR = odds ratio, PPAR γ = peroxisome proliferator-activated receptor γ, SNP = single nucleotide polymorphism, T1D = type 1 diabetes, T2D = type 2 diabetes.

Keywords: diabetes mellitus, microRNA, single nucleotide polymorphism

1. Introduction

1.1. Background

Diabetes mellitus (DM) is becoming a global healthcare problem, which is no longer restricted in the United States. The dramatically increased disease incidence is also expected in developing countries such as China and India.[1] DM is considered as a disorder characterized by hyperglycemia, which is a result of insufficient insulin or insulin resistance. Although a new method of classification, based on the pathogenic mechanism,[2] was reported, the disease is traditionally classified in general categories including type 1, type 2, gestational diabetes mellitus, and other specific types associated with disorders affecting liver, pancreas, or endocrine glands.[3] Type 1 diabetes (T1D) once seemed like a simple autoimmune disorder resulting from the destruction of pancreatic β cells. Nowadays, it is recognized to result from a complex interaction among environmental factors, microbiome, genome, metabolism, and immune system.[4] It usually presents in childhood and accounts for 5% to 10% of all diabetes.[1] Type 2 diabetes (T2D) is characterized by relative insulin deficiency produced by β-cell and insulin resistance in target organs.[5] In 2015, more than 90% of 415 million diabetic patients were diagnosed as T2D.[5] Gestational diabetes is a special type of diabetes, that is first diagnosed or begins during pregnancy, and characterized by glucose intolerance of varying severity.[6] Some reports have suggested that pregnancy initiates metabolic imbalances, which lead to a continuous diabetic state in some women.[6]

MicroRNAs (miRNAs) are produced from stem-loop precursor RNAs generated from independent transcriptional units or from introns of protein-coding genes. These primary transcripts

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(pri-miRNAs) are initially processed to produce shorter RNA molecules (pre-miRNAs) and then transported to the cytosol where they are further cleaved to generate the mature forms of the miRNAs.[7,8] Mature miRNAs are small noncoding single-stranded RNAs with a length of ~21 nucleotides, exert biological effects via posttranscriptional regulation of protein-coding mRNAs and primarily through 2 recognized mechanisms: target transcript degradation/decay and arrest of target transcript translation.[9,10] It is estimated that about 45,000 miRNA-targeting sites in the human genome affect the expression of approximate 60% of genes.[9] Numerous studies have indicated that miRNAs are closely related to physiology and disease development, especially play a part in metabolic diseases via the impairment of glucose metabolism and lead to diabetes by interfering with the β cell membrane's electrical excitation, insulin synthesis, fate of β cells, pancreatic mass formation, and exocytosis process.[11]

Single nucleotide polymorphisms (SNPs) are single-base differences in the DNA sequence, and they are defined as the least common allele occurring in 1% or greater of the population.[12] SNPs located in the coding region can lead to nonsynonymous changes, which change the amino acid sequence or generate a stop codon, thereby affecting protein functions.[13] SNPs affect the miRNA binding efficiency, giving rise to increased or decreased miRNA regulation.[14] Identification of genetic variants that alter the levels of key miRNAs, aided by the increasing afford ability of personal genomic sequencing, may become a clinically powerful tool to identify at-risk individuals, to prompt patients to take preventive action, and, eventually, to prescribe tailored therapeutics.[15]

1.2. Importance of this meta-analysis

In recent years, some clinical studies have been carried out to illuminate the association of rs2910164 and rs895819 with diabetes,[16–23] but the agreement has not been reached. Although the etiology of T2D differs from that of T1D, some causative mechanisms such as immune-cell infiltration and decrease in functional-cell mass are observed in both types.[24] Besides, another study showed that SNPs in miRNA-binding sites in T2D might be associated with gestational diabetes.[25] Combining with above evidences, we intend to explore the role of the 2 common miRNA SNPs in patients with type 1, type 2, or gestational diabetes. Whether SNPs in miRNAs play a similar role in susceptibility to diabetes in different ethnicities has also been emphasized and further explored in this meta-analysis.

2. Methods

2.1. Ethical review and protocol

Data of this work were drawn from eligible studies and we proposed ideas by extracting, integrating, and analyzing the information. Thereby ethical approval is not necessary as the work is not an experimental study. In addition, we conducted the meta-analysis conforming to the protocol registered in PROSPERO (NO. CRD42019117137).

2.2. Strategy of search

In order to identify as many relative reports as possible, 4 online databases including PubMed, EMBASE, Cochrane, and Web of Science were searched. The search had no restriction and was last performed on January 9, 2019. The strategy was based on the combination of the following terms: (diabetes mellitus (MeSH terms) OR diabet* (Title/Abstract)) AND (microRNAs (MeSH terms) OR microRNA* (Title/Abstract) OR miRNA* (Title/Abstract) OR small temporal RNA (Title/Abstract) OR stRNA (Title/Abstract)) AND (polymorphism* (All fields) OR variant* (All fields)).

2.3. Inclusion and exclusion criteria

Studies were selected according to the following inclusion criteria: case–control studies; studies investigating the association of miR146a rs2910164 and miR27a rs895819 with DM; diabetes clearly diagnosed and classified; and studies providing sufficient genotype frequencies. The following studies were excluded: studies not focused on human beings; studies without available data; and case report, summary, review, or meta-analysis. Two reviewers (Li and Liu) independently extracted the data in accordance with the inclusion and exclusion criteria listed above. The disagreements between the 2 reviewers were discussed with another reviewer (Zhang) until consensus was reached.

2.4. Data extraction

We extracted the data from eligible studies independently with a data extraction sheet. The following information was recorded: the first author's name, publication year, country, ethnicity, Hardy–Weinberg equilibrium (HWE), diabetes definition, the type of diabetes, sample size, and distribution of genotype frequency in cases and controls.

2.5. Statistical analysis

In each study, the HWE was assessed using the Chi-square test in control groups. $P > .05$ means the frequency of genotypes in the control group conforms to the HWE. Odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of the association between miR146a rs2910164 and miR27a rs895819 polymorphisms and diabetes. Pooled ORs were computed for different genetic models: allele model, heterozygote model, homozygote model, dominant model, and recessive model. The ancestral alleles of rs2910164 and rs895819 were G and T, respectively. The significance of pooled ORs was evaluated by Z-test, and $P < .05$ means statistically significant. Statistical heterogeneity was determined by Q-test. If $P > .10$ for Q-test, no heterogeneity was found among studies, and the fixed effect model (the Mantel–Haenszel method) was chosen to calculate the pooled ORs. Otherwise, subgroup analysis and the random effect model (the DerSimonian and Laird method) were applied. Publication bias was assessed by Begg funnel plot and Egger test. $P < .05$ indicated significant publication bias. The above-mentioned statistical analysis was performed with STATA 12.0 (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of inclusive studies

The study selection procedure is shown as a flow chart (Fig. 1). Based on the inclusion criteria, a total of 8 articles were included in our meta-analysis. Seven articles were written in English and 1 in Chinese. In the studies of Ciccacci et al,[16] Li et al,[17] and Wang et al,[18] genotype frequencies of miR146a rs2910164 and

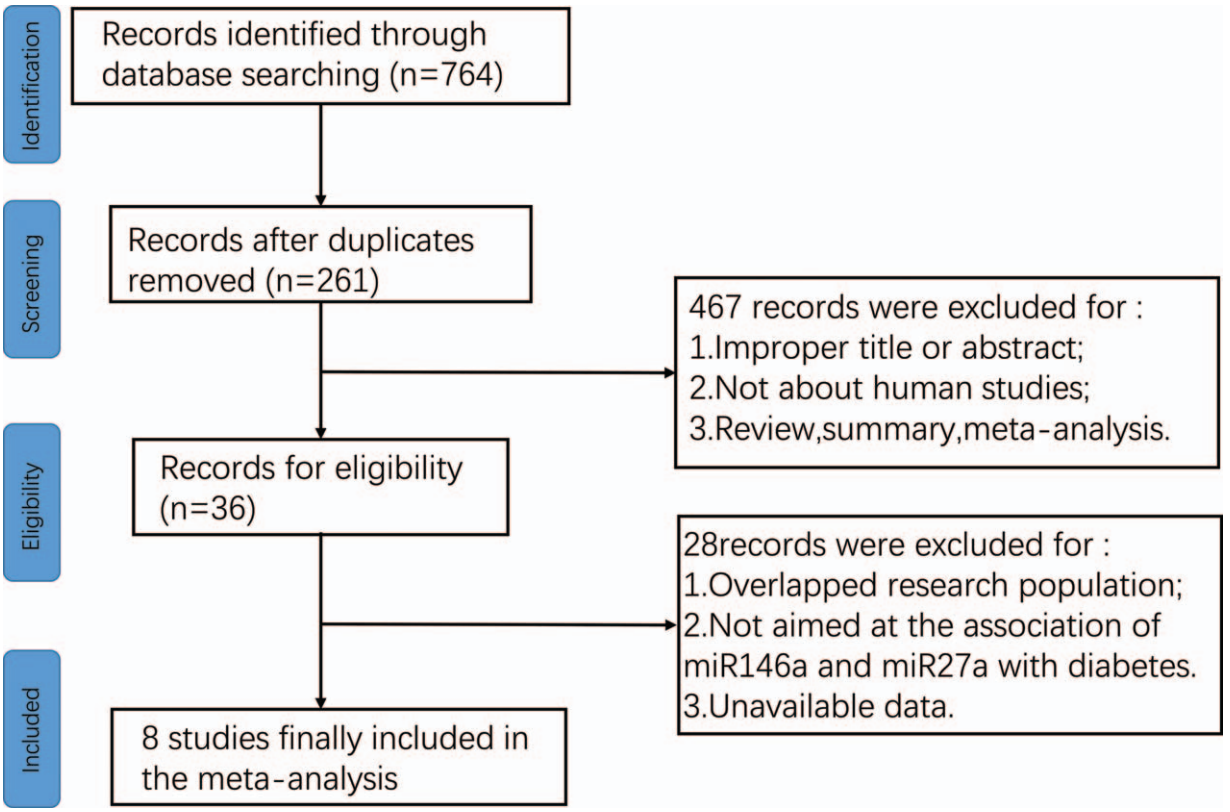

Figure 1. Flow chart of study selection.

miR27a rs895819 were presented separately, so we respectively extracted data of each SNP. Therefore, 6 studies involving 2585 cases and 2435 controls for miR146a rs2910164 and 5 studies involving 2922 cases and 2781 controls for miR27a rs895819 were ultimately analyzed. For rs2910164, 4 articles were consisted of Caucasians and 2 were about Asians. For rs895819, 2 articles were based on Caucasians, and 3 were based on Asians. Several genotyping methods such as PCR-RFLP, PCR-TaqMan, directing sequencing, and SNPscan were used. Blood samples were used for genotyping in all studies. All studies were evaluated by the NOS scale. The details of these studies are summarized in Table 1.[16–23]

3.2. Quantitative synthesis of the association between miR146a rs2910164 polymorphism and diabetes

The pooled results of the association between miR146a rs2019164 and susceptibility to diabetes are summarized in

Table 1

Characteristics of studies included in the meta-analysis[16–23].

Author	Year	Country	Ethnicity	Diabetes type	HWE* (control)	Case/control	Case			Control		
rs2910164												
							GG	GC	CC	GG	GC	CC
Ciccacci et al	2013	Italy	Caucasian	Type2	0.68	153/181	90	49	14	101	67	13
Li et al	2015	China	Asian	Type2	0.08	738/610	78	296	364	104	270	236
Wang et al	2015	China	Asian	Type2	0.70	995/967	176	506	313	168	477	322
Alipoor et al	2016	Iran	Caucasian	Type2	0.21	183/192	92	62	29	112	65	15
Assmann et al	2017	Brazil	Caucasian	Type1	>0.05	431/405	257	142	32	192	161	52
Abo-Elmatty et al	2018	Egypt	Caucasian	GDM	0.88	85/80	49	30	6	46	29	5
rs895819												
							TT	TC	CC	TT	TC	CC
Ciccacci et al	2013	Italy	Caucasian	Type2	0.53	148/147	101	45	2	83	53	11
Ghaedi et al	2016	Iran	Caucasian	Type2	0.31	204/209	108	85	11	97	86	26
Li et al	2015	China	Asian	Type2	0.68	738/610	371	322	45	330	240	40
Wang et al	2015	China	Asian	Type2	0.17	995/967	554	361	80	526	363	78
Wang et al	2014	China	Asian	GDM	0.57	837/848	482	329	26	469	319	60

* Hardy–Weinberg equilibrium (HWE) was evaluated using the Chi-square test. $P > .05$ means the frequency of genotypes in control group conforms to HWE.

Table 2

Subgroup analysis of miR146a rs2019164.

A. Results of subgroup analysis distinguished by ethnicity.

Genetic model	Population	Pooled OR	95%CI	*P* value	P_h
Allele model: C versus G	Overall	1.05	[0.80,1.38]	.75	<.01
	Caucasian	0.98	[0.65,1.47]	.91	<.01
	Asian	1.18	[0.78,1.78]	.44	<.01
Heterozygote model: CG versus GG	Overall	0.98	[0.76,1.26]	.88	.02
	Caucasian	0.84	[0.64,1.11]	.22	.19
	Asian	1.19	[0.84,1.71]	.33	.08
Homozygote model: CC versus GG	Overall	1.18	[0.70,1.98]	.54	<.01
	Caucasian	1.07	[0.46,2.53]	.87	<.01
	Asian	1.37	[0.63,2.99]	.43	<.01
Dominant model: CC + CG versus GG	Overall	1.04	[0.74,1.44]	.83	<.01
	Caucasian	0.91	[0.61,1.36]	.64	.01
	Asian	1.29	[0.74,2.27]	.37	<.01
Recessive model: CC versus CG + GG	Overall	1.14	[0.77,1.66]	.52	<.01
	Caucasian	1.13	[0.54,2.37]	.75	.01
	Asian	1.19	[0.72,1.97]	.51	<.01

B. Results of subgroup analysis distinguished by diabetes type.

Genetic model	Diabetes type	Pooled OR	95%CI	*P* value	P_h
Allele model: C versus G	Overall	1.05	[0.80,1.38]	.75	<.01
	Type2	1.19	[0.91,1.56]	.21	<.01
Heterozygote model: CG versus GG	Overall	0.98	[0.76,1.26]	.88	.02
	Type2	1.11	[0.88,1.38]	.38	.19
Homozygote model: CC versus GG	Overall	1.18	[0.70,1.98]	.54	<.01
	Type2	1.50	[0.89,2.54]	.13	<.01
Dominant model: CC + CG versus GG	Overall	1.04	[0.74,1.44]	.83	<.01
	Type2	1.20	[0.88,1.65]	.25	.01
Recessive model: CC versus CG + GG	Overall	1.14	[0.77,1.66]	.52	<.01
	Type2	1.35	[0.90,2.02]	.14	<.01

CI = confidence interval, OR = odds ratio, P_h = *P*-value for heterogeneity test.

Table 2. No significant association between rs2910164 and diabetes was identified in any genetic models (C vs G: OR = 1.05, 95%CI [0.80,1.38]; CG vs GG: OR = 0.98, 95%CI [0.76,1.26]; CC vs GG: OR = 1.18, 95%CI [0.70,1.98]; CC + CG vs GG: OR = 1.04, 95%CI [0.74,1.44]; CC vs CG + GG: OR = 1.14, 95% CI [0.77,1.66]). Considering the *P* value of heterogeneity < .10, the pooled ORs were calculated using the random effect model. We conducted subgroup analysis of ethnicity and diabetes type. No statistical significance in association between rs2910164 and diabetes in Caucasians, Asians, or T2D was found in any genetic models.

3.3. Quantitative synthesis of the association between miR27a rs895819 polymorphism and diabetes

The pooled results of the association between miR27a rs895819 and diabetes are displayed in Table 3. We found a significantly decreased risk of developing diabetes in the homozygote model (CC vs TT: OR = 0.58, 95%CI [0.35,0.98]; Fig. 2) and recessive model (CC vs CT + TT: OR = 0.59, 95%CI [0.36,0.97]; Fig. 3). Moreover, we carried out subgroup analysis and observed that C allele conveyed a significant protective effect against diabetes development in Caucasians (C vs T: OR = 0.67, 95%CI [0.52,0.85]; Fig. 4). Subgroup analysis was also conducted on the homozygote model (CC vs TT: OR = 0.31, 95%CI [0.14,0.67]), dominant model (CC + CT vs TT: OR = 0.70, 95%CI [0.52,0.94]), and recessive model (CC vs CT + TT: OR = 0.34, 95%CI [0.18,0.66]) in Caucasian. However, no statistical significance in association between rs895819 and T2D was found.

3.4. Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the stability of pooled ORs by deleting every single study. No qualitative change was found, indicating that the results of this meta-analysis were reliable. Begg funnel plot and Egger test were performed to evaluate potential publication bias. Egger test provided the statistical evidence of funnel plot asymmetry. Funnel plot and Egger test all demonstrated the absence of publication bias (rs2910164: C vs G: *P* > .99; CG vs GG: *P* = .86; CC vs GG: *P* = .89; CC + CG vs GG: *P* = .69; CC vs CG + GG: *P* = .92. rs895819: C vs T: *P* = .14; CT vs TT: *P* = .33; CC vs TT: *P* = .12; CC + CT vs TT: *P* = .21; CC vs CT + TT: *P* = .12). The Begg funnel plots are shown in Figures 5 and 6.

4. Discussion

DM is a global health issue that has attracted increasing research attention. Progressive diabetes can lead to adverse effects on target organs, such as cardiovascular, kidney, retina, and nervous system.[5,26] These complications account for DM-related mortality. MiRNA is a small endogenous and noncoding RNA that plays a vital part in gene regulation, tumorigenesis, proliferation, apoptosis, and metabolism. So far, dozens of

Table 3

Subgroup analysis of miR27a rs895819.

A. Results of subgroup analysis distinguished by ethnicity.

Genetic model	Population	Pooled OR	95%CI	*P* value	P_h
Allele model: C versus T	overall	0.87	[0.74,1.03]	.10	.01
	Caucasian	0.67	[0.52,0.85]	.001	.39
	Asian	0.96	[0.84,1.10]	.55	.10
Heterozygote model: CT versus TT	overall	0.99	[0.87,1.13]	.91	.27
	Caucasian	0.81	[0.59,1.10]	.18	.46
	Asian	1.03	[0.90,1.18]	.65	.28
Homozygote model: CC versus TT	overall	0.58	[0.35,0.98]	.04	<.01
	Caucasian	0.31	[0.14,0.67]	.003	.28
	Asian	0.76	[0.45,1.27]	.29	.01
Dominant model: CC+CT versus TT	overall	0.92	[0.78,1.09]	.33	.08
	Caucasian	0.70	[0.52,0.94]	.02	.44
	Asian	0.99	[0.86,1.15]	.94	.21
Recessive model: CC versus CT+TT	overall	0.59	[0.36,0.97]	.04	<.01
	Caucasian	0.34	[0.18,0.66]	.002	.32
	Asian	0.74	[0.45,1.24]	.25	.01

B. Results of subgroup analysis distinguished by diabetes type.

Genetic model	Diabetes type	Pooled OR	95%CI	*P* value	P_h
Allele model: C versus T	Overall	0.87	[0.74,1.03]	.10	.01
	Type2	0.86	[0.69,1.08]	.19	.01
Heterozygote model: CT versus TT	Overall	0.99	[0.87,1.13]	.91	.27
	Type2	0.98	[0.81,1.18]	.79	.16
Homozygote model: CC versus TT	Overall	0.58	[0.35,0.98]	.04	<.01
	Type2	0.65	[0.37,1.15]	.14	.02
Dominant model: CC+CT versus TT	Overall	0.92	[0.78,1.09]	.33	.08
	Type2	0.91	[0.72,1.14]	.41	.05
Recessive model: CC versus CT+TT	Overall	0.59	[0.36,0.97]	.04	<.01
	Type2	0.67	[0.40,1.13]	.14	.02

CI = confidence interval, OR = odds ratio, P_h = *P*-value for heterogeneity test.

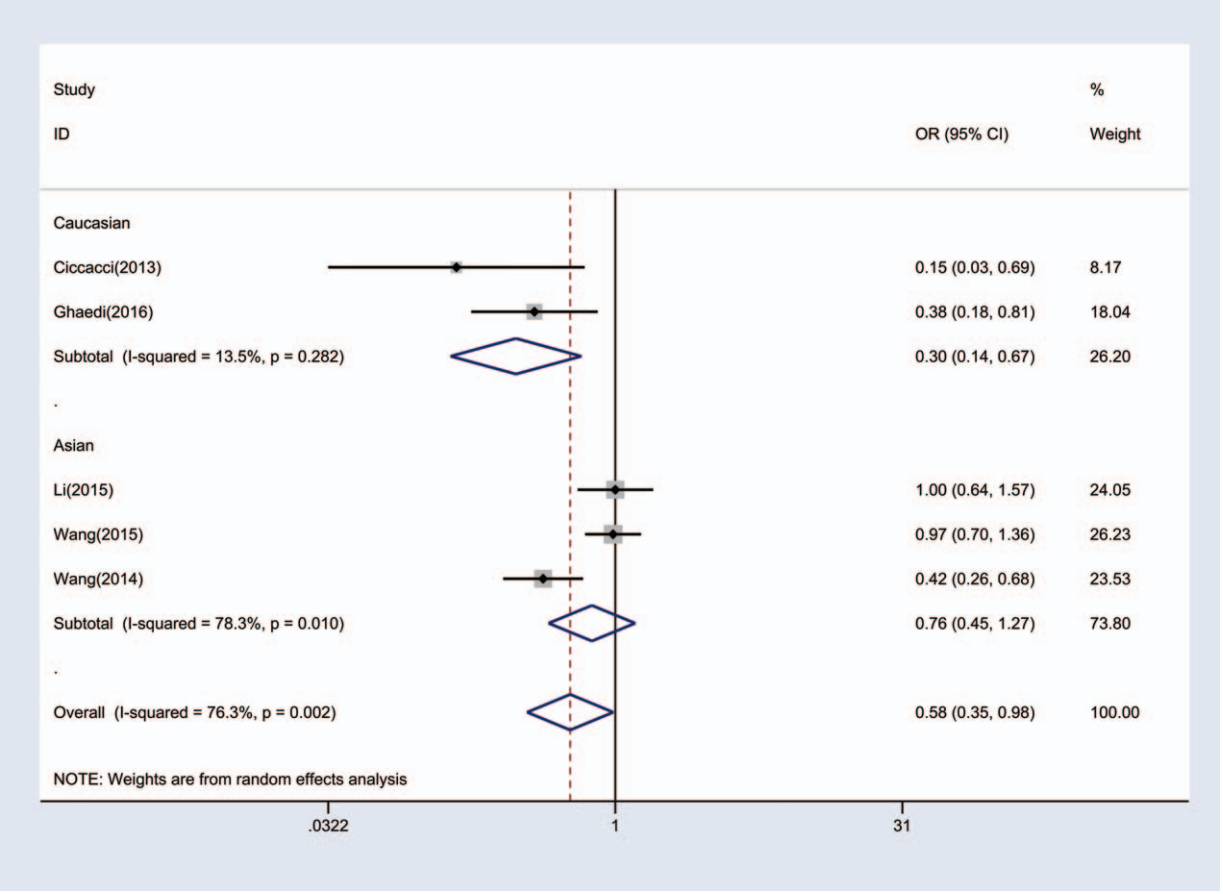

Figure 2. Forest plot of diabetes with the rs895819 polymorphism in the homozygote model (CC vs TT).

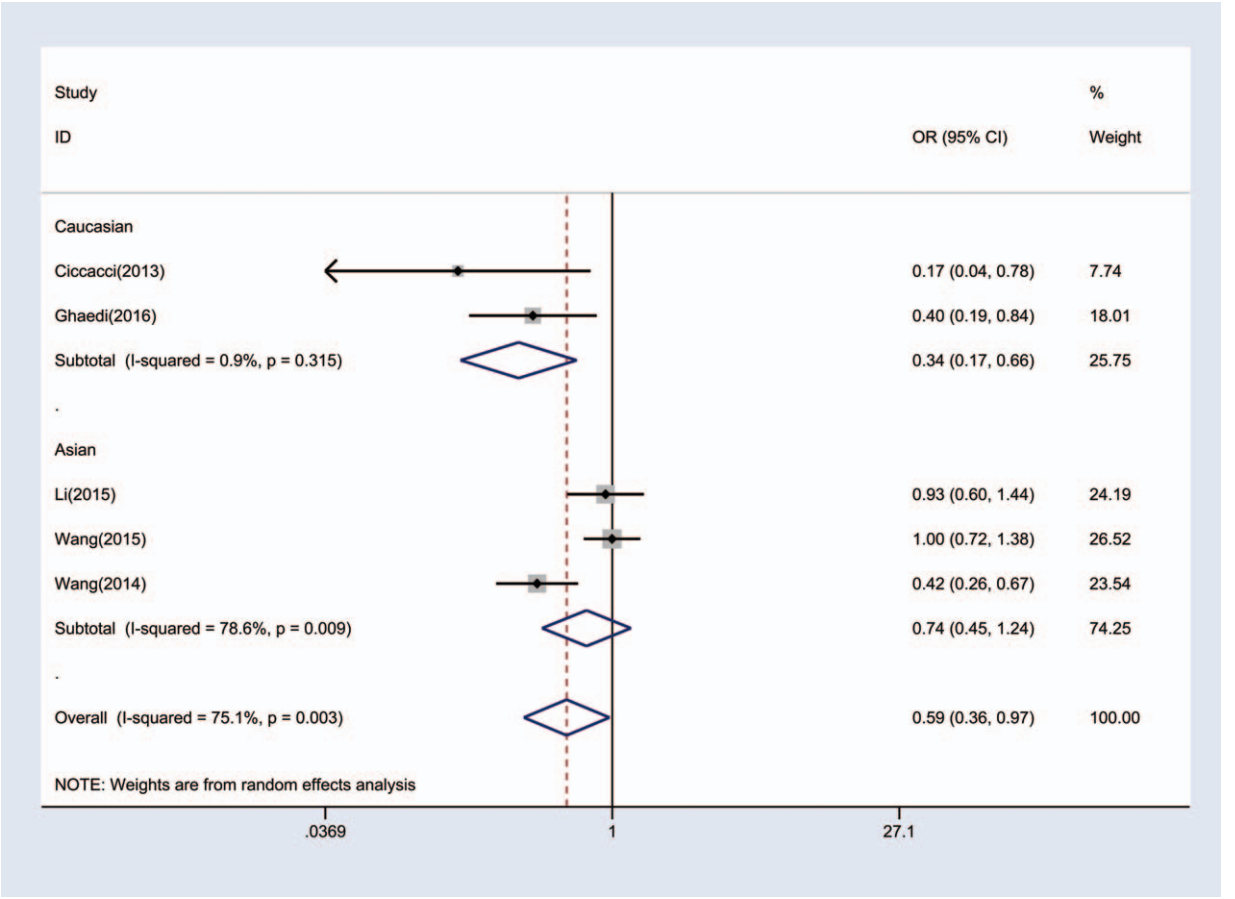

Figure 3. Forest plot of diabetes with the rs895819 polymorphism in the recessive model (CC vs CT+TT).

miRNAs have been identified as components of pathways contributing to the pathology of both T1D and T2D.[15] Sequence variation in miRNAs affects the process and target selection of miRNA,[27] thereby inducing the effects in physiology and pathology. Because of the complexity and high genetic predisposition of diabetes, and the increased interests in miRNAs, it likely seems that many more polymorphisms of miRNAs will be considered as factors in diabetes. Therefore, it is of great significance to explore the association of miRNA polymorphisms with diabetes, which contributes to improve understanding of the genetic basis of the disease and provides novel prognostic, diagnostic, and treatment alternatives.

MiR146a is reported to suppress interleukin-1 receptor-associated kinase 1 (IRAK-1) and tumor necrosis factor receptor-associated factor 6 (TRAF-6), resulting in the inhibition of nuclear factor-κB (NF-κB) via the Toll-like receptor pathway.[28–30] A variety of cell and animal studies suggested activation of NF-κB was a key event in the pathobiology of diabetes. In pancreatic-cells, activation of NF-κB pathway can lead to cell death.[31] Sustained activation of NF-κB has been observed in the mononuclear cells from the patients with T1D and T2D.[32] Therefore, the downregulation of miR146a may increase expression of NF-κB target genes, such as interleukin-6 and tumor necrosis factor-α, by increasing the expression levels of TRAF-6 and IRAK-1. Subsequently inflammatory responses are associated with the metabolic defects of β-cell insufficiency and insulin resistance.[32] However, several studies concluded upregulation of miR146 in the cell line and pancreatic islets after exposure to palmitate, and elevated levels of this miRNA in islets of diabetic db/db mice, might contribute to increased apoptosis.[31,33] Rs2910164 downregulates the expression of pre- and mature miR146a.[28,34] According to the above findings, the genetic variant of miR146a is involved in a key biological process of the initiation and development of diabetes.

MiR27a has been linked to hyperglycemia and metabolic syndrome in T2D patients. Upregulation of this miRNA has been observed in hyperglycemic T2D rats and its potential role in the early-phase hyperglycemia has been reported.[35,36] And considering that miR27a has a potential angiogenic function, its downregulation in diabetes patients may reduce the angiogenic potential of endothelial progenitor cells in diabetes.[37] In a related study, miR27a was highly expressed in T1D followed by T2D and gestational diabetes mellitus.[38] Although available information was scarce, the study proposed miRNA27a might be involved in shared mechanisms for hyperglycemia control in the major types of diabetes.[38]

A previous study reported that miRNA polymorphisms conferred high level of miR27a.[39] The expression of miR27a increases, whereas expression of peroxisome proliferator-activated receptor γ (PPAR γ) decreases during adipogenesis, and miR27a is regarded as a negative regulator of PPAR γ.[40] Thus, some experts hypothesized that elevated amounts of miR27a due to the genetic variant downregulated the synthesis of PPAR γ and suppressed adipocyte differentiation in T2D.[16] MiR27a also

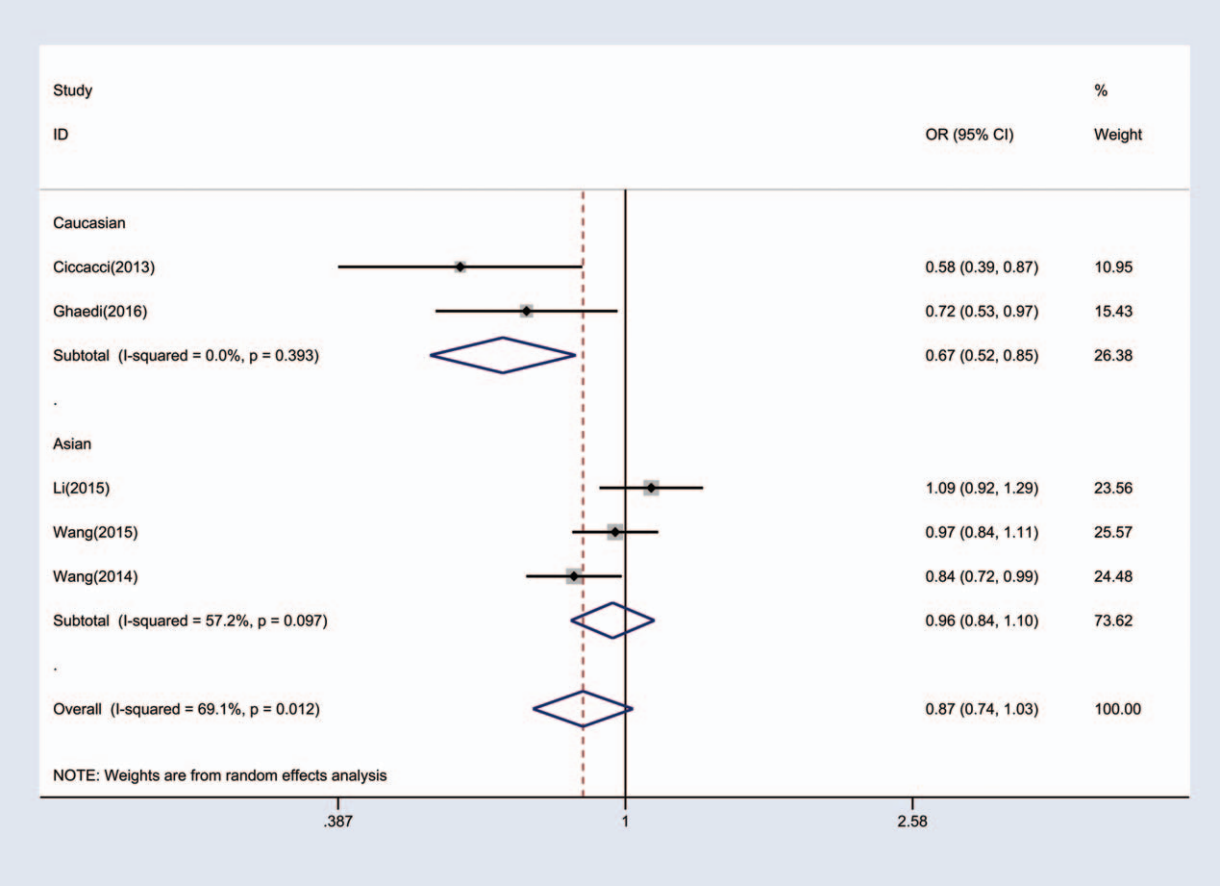

Figure 4. Results of subgroup analysis distinguished by ethnicity in the allele model (C vs T).

regulated glucose homeostasis by inhibiting the insulin signaling pathway and mitogen-activated protein kinase signaling pathway.[41] In summary, published evidences indicated that rs895819 in miR27a decreased the risk of diabetes. Some case–control studies included in the meta-analysis were consistent with the conclusion.[16,22,23] However, the other 2 studies showed that rs895819 was not associated with diabetes.[17,18]

This study is the first meta-analysis committed to clarify the links between rs2910164, rs895819, and diabetes. In our meta-analysis, for rs2910164, we did not observe the significant association of rs2910164 with diabetes in any genetic models. And *P* values for heterogeneity were under .10 in all genetic models. Given high heterogeneity due to confounding factors, we performed the subgroup analysis distinguished by ethnicity and

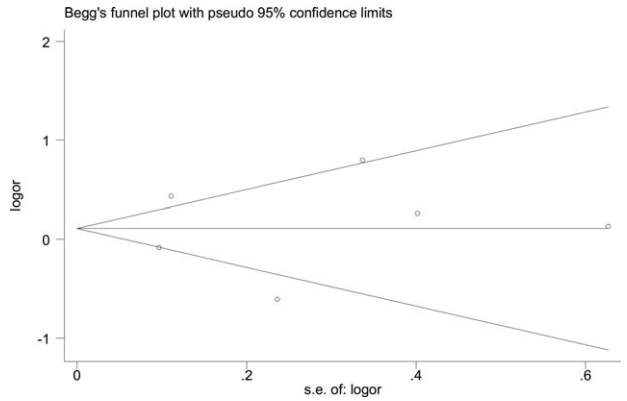

Figure 5. Begg funnel plot of the association between rs2910146 polymorphism and diabetes under the recessive model (CC vs CG + GG).

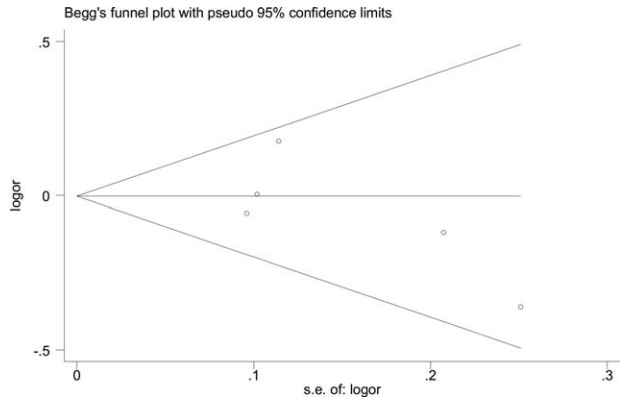

Figure 6. Begg funnel plot of the association between rs895819 polymorphism and diabetes under the heterozygote model (CT vs TT).

the diabetes type. However, there were slight changes in heterogeneity and no association was observed in any ethnicity and diabetes type. Sensitivity analysis showed that the results were stable. We speculated that high heterogeneity may come from other confounding factors whose data could not be fully extracted, such as condition of the patients, method of miRNA amplification, control resource, etc.

As for rs895819, the results showed that it had a potential association with diabetes in the homozygote model (CC vs TT) and recessive model (CC vs CT + TT). It is well-known that race is reflected in distinct sequencing of the human genome and the mapping of human genetic variation.[42] Subgroup analysis distinguished by ethnicity was performed and suggested that rs895819 decreased the risk of susceptibility to diabetes in Caucasians. In Asians, the association of rs895819 with diabetes was not observed.

Eight articles were included to strengthen the reliability of the conclusion. All the eligible articles were written in English or Chinese, so selection bias was absent. In addition, all studies conformed to the HWE.

However, due to several possible defects, the pooled results should be interpreted with caution. First, 8 articles included in this meta-analysis may not be sufficient to detect the minor effects of rs2910164 and rs895819 on the susceptibility of diabetes. In the future, numerous efforts should be put into identifying miRNA variants that regulate occurrence and development of diabetes. Second, 2 reviewers assessed the studies by NOS scale, which is known as criteria for the quality inspection of case–control studies, and the process might not totally conform to objectivity. Low-quality studies might be included. Third, even though we conducted subgroup analysis, owing to a limited number of references and excessive confounding factors, heterogeneity was still difficult to avoid and might distort the results. As one of confounders, for example, differences in sample preparation, RNA isolation, detection, and normalization methodologies may lead to mark inconsistencies in the findings and absence of standardized protocols, facilitating comparison in different studies, makes it difficult to reach a consensus about the miRNA variants' effects on diabetes. Beyond that, not all the confounding factors were presented in the included studies, such as family history, duration of diabetes, and BMI, which might affect the pooled results. Thus, we conducted funnel plot, Egger test, and sensitivity analysis to reduce the effects of above flaws on the final results.

In summary, the meta-analysis indicated that miRNA27a rs895819 might play a protective role in diabetes, and miRNA146a rs2910164 likely had no association with diabetes. Well-designed studies involving larger sample sizes need to be carried out to verify our conclusion in the future. In addition, it still needs further exploration whether the 2 common polymorphisms have the same effect on diabetes in different ethnicities.

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