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Original Article

Genetic associations between miR-146a/499 polymorphisms and tuberculosis: a meta-analysis

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Abstract: Polymorphisms in miR-146a and -499 are associated with a number of diseases. An association between these miRNAs and tuberculosis (TB) susceptibility has been detected in some studies, but not others. To clarify whether miR-146a and -499 are related to TB, which is widespread and potentially fatal, we performed a meta-analysis of these studies. The effect sizes were estimated based on pooled odds ratios (OR) with 95% confidence intervals (CIs). Six studies involving 1260/1261 cases and 1833/1670 controls (miR-146a/499, respectively) were identified. Overall, no significant association between miR-146a/499 polymorphisms and TB susceptibility was found for any genetic model (i.e., allelic, dominant, recessive, and additive genetic models). Anethnicity-stratified analysis showed that there is no significant association between miR-146a/499 polymorphisms and TB risk in Asian populations. Based on this meta-analysis, current data does not support an association between miR-146a/499 polymorphisms and genetic susceptibility to TB. Due to the small sample size and limited number of studies of Caucasian populations, additional large-scale analyses that include a wider range of ethnicities, as well as well-designed studies are needed to confirm this conclusion.

Keywords: Polymorphism, miR-146a, miR-499, tuberculosis, susceptibility

Introduction

Tuberculosis (TB) is an infectious disease caused by several strains of mycobacteria, especially *Mycobacterium tuberculosis* (MTB), and ranks first in infectious disease mortality worldwide. According to a report from the World Health Organization, approximately one-third of the current global population is infected with MTB, but only 10% will progress to active TB during their lifetime [1, 2]. Several factors could modulate the outcome of MTB infection, including MTB strain, physical condition, smoking history, socio-economic factors, and host genetic components [3, 4]. Accumulating evidence confirms that a number of genetic factors affect TB susceptibility [5-7].

MicroRNAs (miRNAs) are a family of endogenous, small, non-coding RNAs (~22 nucleotides in length) that negatively regulate gene expression via inhibiting translation or inducing mRNA degradation [8]. They are essential regulators involved in a variety of biological processes. Numerous diseases, including TB, are associated with the aberrant expression or dysfunction of miRNAs [9]. Single nucleotide polymorphisms (SNPs) in pre-miRNAs or miRNAs may affect miRNA properties, leading to phenotypic differences among individuals and influencing the risk of diseases [10]. Previous studies have revealed associations between miR-146a rs2910164 (G>C) and miR-499 rs3746444 (T>C) polymorphisms and various diseases, including rheumatoid arthritis, severe sepsis, and breast cancer [11-13]. Some studies have reported associations between miR-146a/499 polymorphisms and TB; however, the results of these studies are inconsistent [14-16]. Hence, we performed a meta-analysis to evaluate the association between miR-146a/499 polymorphisms and TB risk.

Methods

Publication search

A literature search of PubMed, Web of Science, Medline, and Embase databases up to Nov12, 2015 was conducted by using "(microRNA OR microRNAs) AND (polymorphism OR variation OR SNP) AND (tuberculosis OR TB)". Citations of all retrieved articles were also searched for relevant studies.

Table 1. Characteristics of the 6 studies included in this meta-analysis

Author	Year	Country	Ethnicity	TB type	Genotyping method	Sample size		Quality score
						Case	Control	
Zhang X	2015	China	Asian (Uygur)	PTB	PCR-RFLP	301	361	7
Zhang X	2015	China	Asian (Kazak)	PTB	PCR-RFLP	251	362	7
Zhang X	2015	China	Asian (Han)	PTB	PCR-RFLP	354	300	7
Naderi M	2015	Iran	Caucasian	PTB	T-ARMS-PCR	202	204	6
Li D	2011	China	Asian (Tibetan)	PTB	PCR-RFLP	147	171	7
Li D	2011	China	Asian (Han)	PTB	PCR-RFLP	190	567	7

PTB: pulmonary tuberculosis.

Table 2. Genotype frequencies of miR-146a rs2910164 in the 6 studies

Author	Year	Case			Control			MAF		HWE
		CC	GC	GG	CC	GC	GG	Case	Control	
Zhang X	2015	36	146	106	51	179	131	0.378	0.389	0.415
Zhang X	2015	53	92	65	55	174	124	0.471	0.402	0.639
Zhang X	2015	64	120	39	41	98	38	0.556	0.508	0.152
Naderi M	2015	16	70	116	15	80	109	0.252	0.270	0.951
Li D	2011	39	72	36	62	85	24	0.510	0.611	0.549
Li D	2011	76	93	21	141	297	129	0.645	0.511	0.252

Table 3. Genotype frequencies of miR-499 rs3746444 in the 6 studies

Author	Year	Case			Control			MAF		HWE
		CC	TC	TT	CC	TC	TT	Case	Control	
Zhang X	2015	22	103	176	4	79	171	0.244	0.171	0.127
Zhang X	2015	3	53	116	10	68	157	0.172	0.187	0.450
Zhang X	2015	5	67	177	9	74	156	0.155	0.192	0.951
Naderi M	2015	8	81	113	6	81	117	0.240	0.228	0.067
Li D	2011	9	43	95	5	32	134	0.207	0.123	0.086
Li D	2011	3	34	153	18	133	416	0.105	0.149	0.073

Inclusion and exclusion criteria

To be included, studies should meet the following criteria: (1) Case-control study in design, (2) Evaluation of miR-146a/499 polymorphisms and TB, (3) Detailed genotype data for calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Exclusion criteria: (1) Comment, review and editorial, (2) Study with no detailed genotype data, (3) Genotype of control group was not in accordance with Hardy-Weinberg equilibrium (HWE).

Data extraction

Two investigators (Yanjun Lu and Na Shen) independently screened initially identified articles, and reviewed full text for eligibility. Conflict was dissolved by discussion to reach consensus. If the dissent still existed, the third investigator (Xiong Wang) would be involved to adjudicate the disagreements. We extracted the following contents from original publications: name of the first author, publication year, country, ethnicity, genotyping method, sample size, genotype information in cases and controls.

Statistics analysis

HWE was evaluated for each study, and $P<0.05$ was considered as significant disequilibrium. The strength of the association between miR-146a/499 polymorphisms and TB was examined by pooled OR and 95% CI. Pooled ORs were performed for allelic comparison (miR-146a: C vs. G; miR-499: C vs. T), dominant model (miR-146a: CC + GC vs. GG; miR-499: CC + TC vs. TT), recessive model (miR-146a: CC vs. GC + GG; miR-499: CC vs. TC + TT), additive model (miR-146a: CC vs. GG; miR-499: CC vs. TT), respectively. The significance of the pooled OR was determined by Z test, and $P<0.05$ was considered as statistically significant. Heterogeneity was evaluated using a χ^2-based Q statistic and I^2 statistic tests. If $P_Q>0.10$ or $I^2<50\%$, the fixed-effect model was used for pooled ORs; if $P_Q<0.10$ or $I^2>50\%$, the random-effect model was applied. Sensitivity analysis was carried out by sequentially omitting individual study to estimate the stability of the

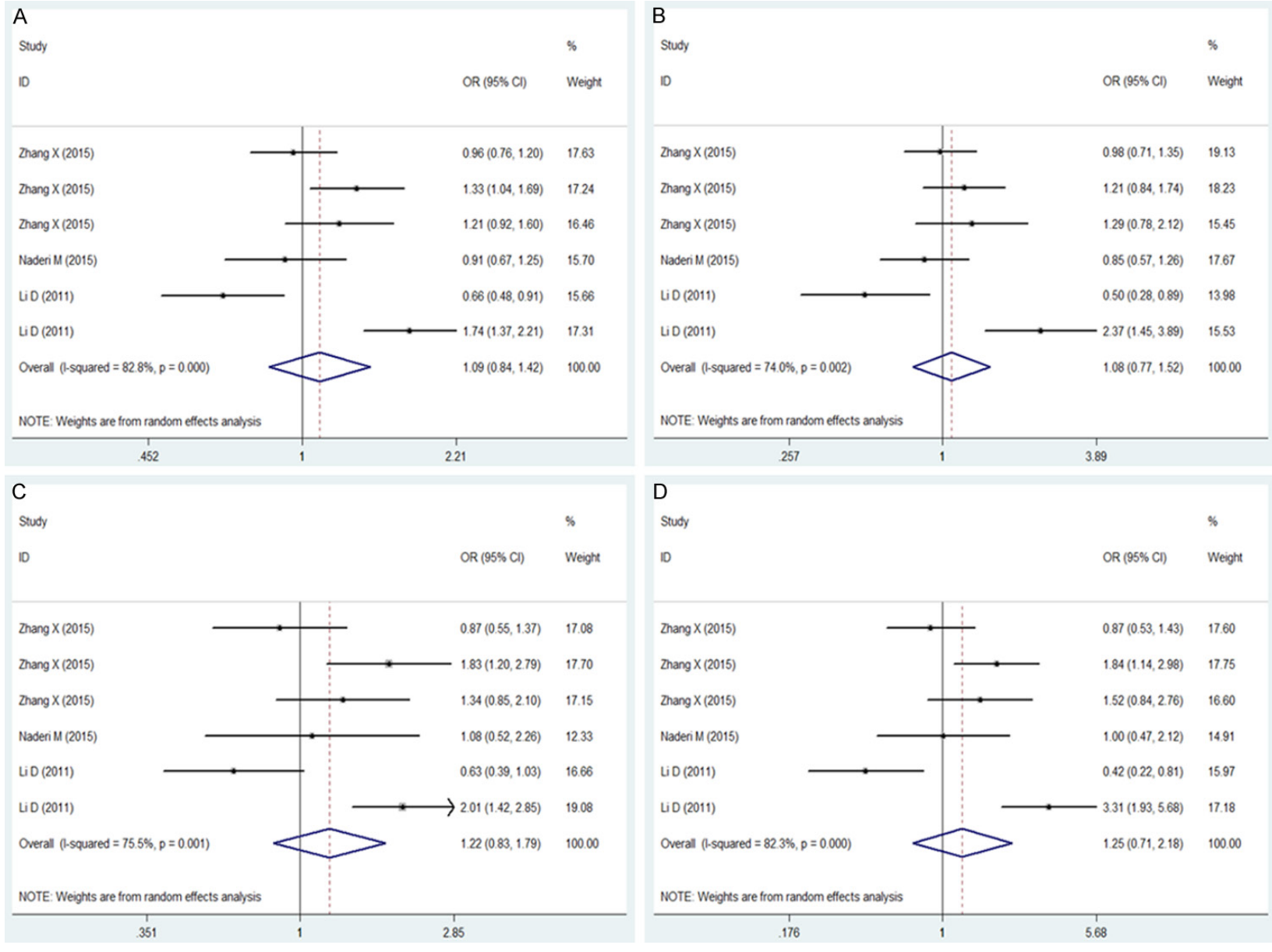

Figure 1. Forest plots for the overall association of miR-146a rs2910164 polymorphism and susceptibility of TB. A. Allelic; B. Dominant; C. Recessive; D. Additive.

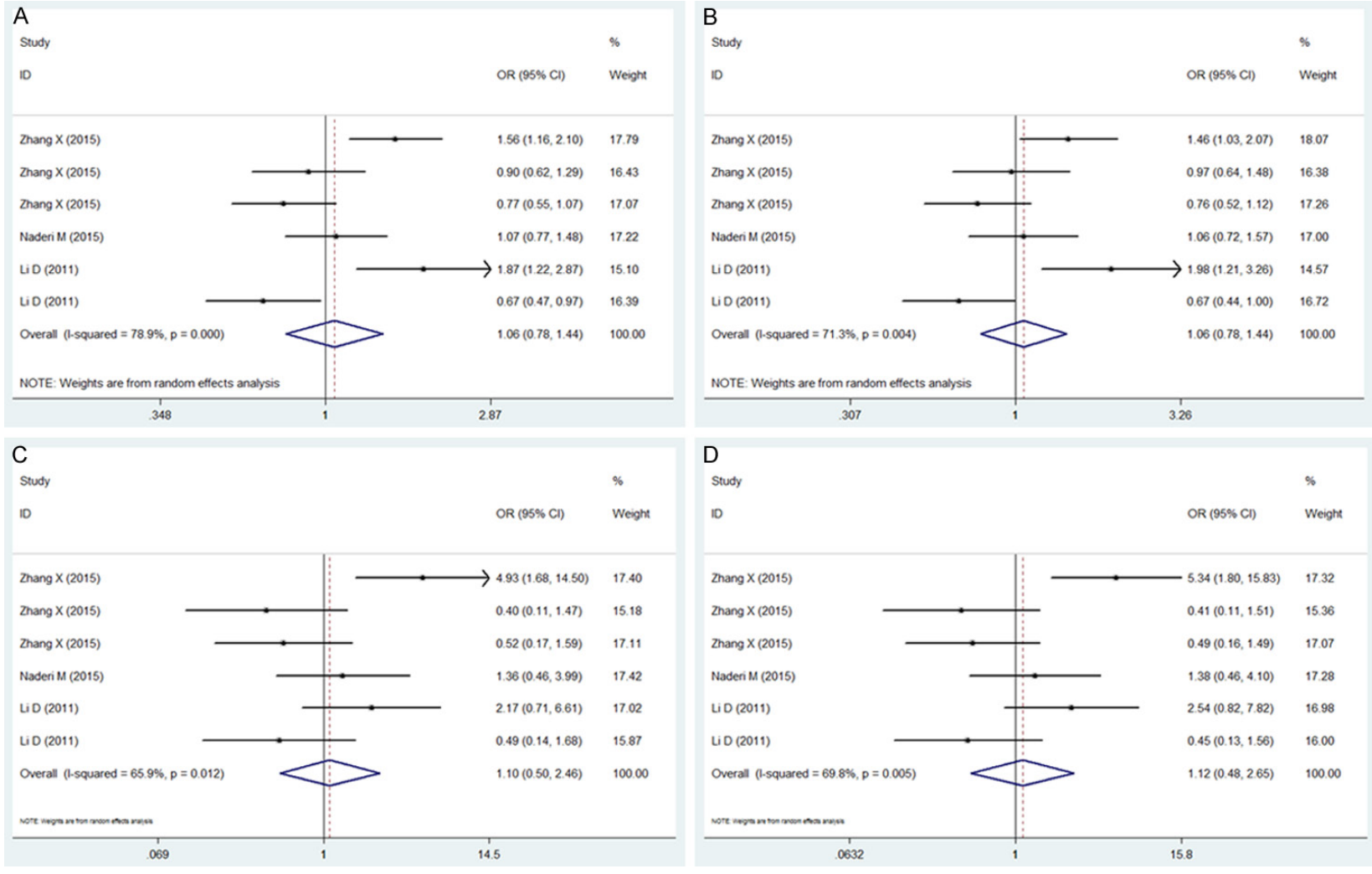

Figure 2. Forest plots for the overall association of miR-499 rs3746444 polymorphism and susceptibility of TB. A. Allelic; B. Dominant; C. Recessive; D. Additive.

Table 4. Meta-analysis of miR-146a/499 polymorphisms and TB

Genetic model	P_Q	I^2 (%)	95% CI	P_z
miR-146a rs2910164				
Overall				
Allelic model	0.000	82.8	1.09 (0.84, 1.42)	0.502
Dominant model	0.002	74.0	1.08 (0.77, 1.52)	0.650
Recessive model	0.001	75.5	1.22 (0.83, 1.79)	0.303
Additive model	0.000	82.3	1.25 (0.71, 2.18)	0.437
Asian				
Allelic model	0.000	85.5	1.13 (0.84, 1.53)	0.425
Dominant model	0.002	77.2	1.14 (0.76, 1.71)	0.533
Recessive model	0.000	80.1	1.24 (0.81, 1.91)	0.326
Additive model	0.000	85.5	1.29 (0.68, 2.46)	0.433
miR-499 rs3746444				
Overall				
Allelic model	0.000	78.9	1.06 (0.78, 1.44)	0.714
Dominant model	0.004	71.3	1.06 (0.78, 1.44)	0.705
Recessive model	0.012	65.9	1.10 (0.50, 2.46)	0.808
Additive model	0.005	69.8	1.12 (0.48, 2.65)	0.789
Asian				
Allelic model	0.000	83.1	1.06 (0.72, 1.56)	0.773
Dominant model	0.002	77.0	1.06 (0.73, 1.55)	0.748
Recessive model	0.006	72.6	1.05 (0.39, 2.83)	0.925
Additive model	0.002	75.7	1.07 (0.37, 3.09)	0.901

Table 5. Publication bias

Genetic model	Begg's test		Egger's test	
	z	Pr>|z|	t	P>|t|
miR-146a rs2910164				
Allelic model	1.13	0.260	-1.29	0.267
Dominant model	0.00	1.000	0.06	0.957
Recessive model	1.88	0.060	-1.33	0.255
Additive model	0.75	0.452	-0.90	0.419
miR-499 rs3746444				
Allelic model	0.75	0.452	-0.05	0.961
Dominant model	0.00	1.000	0.48	0.658
Recessive model	1.13	0.260	-1.91	0.129
Additive model	1.13	0.260	-1.82	0.143

result. Publication bias was assessed by Begg's and Egger's tests. All data were analysed with Stata 12.0 software (StataCorp, College Station, TX, USA).

Results

Study characteristics

In total, 48 studies were identified in the PubMed, Web of Science, Medline, and Embase databases using the general search terms (PubMed: 6, Web of Science: 10, Medline: 10, Embase: 22). After an independent review based on the exclusion criteria, a total of 6 studies in 3 publications that evaluated the association between miR-146a/499 polymorphisms and TB risk between 2011 and 2015, comprising 1260/1261 TB cases and 1833/1670 controls (miR-146a and -499, respectively), were included in the meta-analysis [14-16]. Zhang et al. examined 3 cohorts from Chinese Uygur, Kazak, and Southern Han populations, and these results were treated as 3 independent studies [14]. A publication by Li et al. included 2 cohorts' from Chinese Tibetan and Han populations, which were divided into 2 independent studies [16]. The study characteristics and patient genotypes included in the current meta-analysis are listed in **Tables 1**-**3**.

Meta-analysis of miR-146a/499 polymorphisms and TB

For the 4 genetic models, the estimates of heterogeneity among studies were P_Q<0.10 and I^2>50%. Thus, a random-effect model was used to calculate the pooled OR (**Figures 1**, **2**). Overall, the combined results showed that miR-146a/499 was not significantly associated with TB risk for any genetic model (miR-146a: allele model: OR = 1.09, 95% CI 0.84-1.42, *P* = 0.502; dominant model: OR = 1.08, 95% CI 0.77-1.52, *P* = 0.650; recessive mode: OR = 1.22, 95% CI 0.83-1.79, *P* = 0.303; additive model: OR = 1.25, 95% CI 0.71-2.18, *P* = 0.437. miR-499: allele model: OR = 1.06, 95% CI 0.78-1.44, *P* = 0.714; dominant model: OR = 1.06, 95% CI 0.78-1.44, *P* = 0.705; recessive mode: OR = 1.10, 95% CI 0.50-2.46, *P* = 0.808; additive model: OR = 1.12, 95% CI 0.48-2.65, *P* = 0.789). An ethnicity-stratified analysis showed that there was no significant association between miR-146a/499 polymorphisms and TB susceptibility in Asian populations (**Table 4**).

Sensitivity analysis and publication bias

We performed a sensitivity analysis to examine the effect of individual studies on the pooled results and did not observe remarkable differences with the corresponding pooled ORs.

Based on the results of Begg's and Egger's tests, no publication bias was observed for any genetic model (**Table 5**).

Discussion

The pathogenesis of TB includes a complex interaction between environmental and genetic factors. Therefore, the identification of the genetic basis for susceptibility to TB would facilitate the development of effective and preventive interventions to decrease the incidence of TB [17]. This meta-analysis clarified the associations between miR-146a/499 polymorphisms and TB, and the results suggest that miR-146a/499 polymorphisms are not associated with TB susceptibility based on data obtained from published studies.

Gene expression regulation via miRNAs is involved in various biological processes, and increasing evidence suggests that miRNAs play essential roles in the control of infectious diseases [18-20]. SNPs within pre-miRNAs or miRNAs could change miRNA characteristics and result in functional or phenotypic changes, and have been implicated in the pathogenesis of multiple disorders. Among these miRNAs, miR-146a/499 polymorphisms have been widely investigated in several diseases. miR-146a rs2910164 involves a G>C nucleotide replacement, leading to the replacement of G:U pair by a C:U mismatch in the stem structure of pre-miR-146a [5]. The miR-499 rs374644 T>C polymorphism occurred within the stem region of the miR-499 gene, resulting in an A:U to G:U mismatch in the stem structure of pre-miR-499 [6]. Epidemiological research has shown that miR-146a/499 polymorphisms are associated with a number of diseases, such as ankylosing spondylitis, breast cancer, and inflammatory bowel disease [7]. In ankylosing spondylitis, miR-146a regulates many target genes involved in inflammatory signalling, including *TRAF-6*, *IRAK-1*, and *IRAK-2*. Additionally, miR-499 targets a variety of genes, including *IL-2*, *IL-6*, *IL-21*, *IL-23a* [3].

Li et al. first reported associations between miR-146a/499 polymorphisms and TB in the Chinese Tibetan and Han populations. Subsequently, Zhang et al. and Naderi et al. investigated these associations and reported inconsistent results. In this meta-analysis, 6 studies including a total of 1260/1261 TB cases and 1833/1670 controls (miR-146a and -499 respectively) were analysed. Based on the observed heterogeneity among studies, the random-effect model was used to calculate the pooled OR.

The pooled OR showed that miR-146a rs2910164 is not associated with TB for any genetic model. The genotype distribution of the control group for all studies conformed to the HWE. A sensitivity analysis showed that our pooled OR was robust and stable. Furthermore, based on a subgroup analysis considering ethnicity, there was no significant association between miR-146a rs2910164 polymorphism and TB risk in Asians. No publication bias was observed. In the allelic genetic model, the Chinese Kazak population and the Chinese Han population showed associations between the rs2910164 C allele and an increased TB risk, while the Chinese Tibetan population showed an association between the rs2910164 C allele and a decreased TB risk. For the dominant genetic model, Li et al. showed that the Chinese Tibetan and Han populations showed different associations between miRNA and TB risk. In the recessive and additive genetic models, studies of the Chinese Kazak population and the Chinese Han population have shown that the rs2910164 C allele is associated with an increased TB risk. In the additive genetic model, the opposite pattern was observed for the Chinese Tibetan population and the Han population. Naderi et al. examined a population in Iran and did not detect any association for any genetic model. These results indicated that different genetic backgrounds in the Chinese Han, Kazak, and Tibetan populations influence the genetic associations. However, larger sample sizes and additional ethnicities should be examined.

The pooled ORs of miR-499 rs374644 and miR-146a rs2910164 were similar for the four genetic models. Zhang's study of the Chinese Uygur population showed a significant association between rs374644 and an increased TB risk for all genetic models. In the Chinese Tibetan population, Li et al. showed a significant association between rs374644 and an increased TB risk for the allelic and dominant genetic models, while in the Chinese Han population; there was a significant association between rs374644 and a decreased TB risk for the allelic genetic model. No significant associ-

ation was found in the remaining populations for any genetic models. Collectively, these results suggest that miR-146a/499 polymorphisms are not associated with TB, though significant associations have been detected in some studies.

In addition to the effects of ethnicity on polymorphisms, there may be various other confounding factors, including the TB inclusion criteria, male/female ratio, and age of study participants. Both Zhang et al. and Li et al. recruited TB patients according to the diagnostic criteria for pulmonary tuberculosis published by the Ministry of Health of China. Accordingly, the inclusion criteria were consistent between the studies. Zhang et al. reported that the male/female ratios of Uygur, Kazak, and Han TB patients and the corresponding controls were 1.09:1.53, 1.59:1.43, and 1.15:1.19, respectively. In the studies of Li et al, the male/female ratios of Tibetan and Han TB patients and the corresponding controls were 2:1.44 and 1.24:0.96, respectively. In the study of Naderi et al, the male/female ratio between TB patients and controls was 0.55: 0.85. In the Chinese Han population, the sex ratio for TB patients and controls was different between the studies of Zhang et al. and Li et al. (1.15:1.19 and 1.24:0.96). For the allelic and dominant models, Li et al. detected a significant association between TB patients and controls in the Chinese Han population, while Zhang et al. did not detect a significant association. These data suggest that sex-specific effects may contribute to the observed association. Some studies support this inference. Salie found a sex bias when analysing the association between TLR8 polymorphism and TB susceptibility [17]. Similar results have been reported by Lee et al. in an investigation of the association between rs4331426 and susceptibility to TB among female Han Taiwanese [18]. Moreover, age was not consistent among groups. Therefore, a well-designed study including paired sex ratios and balanced ages may limit the effects of confounding variables.

Jazdzewski et al. reported that the C allele of rs2910164 might reduce the level of mature miR-146a and the inhibition of its target genes [19]. Liu et al. showed that miR-146a is decreased in alveolar macrophages of TB patients, and is negatively correlated with the degree of positive smears. They found that overexpression of miR-146a decreased PTGS2 levels and promoted the ability of THP-1 cells to kill *Mycobacterium bovis* BCG. Additionally, miR-146a negatively regulated TNF-α release in a feedback manner, indicating an essential role of miR-146a in BCG infection in the regulation of the inflammation response of MTB infections [20]. The roles of gene-environment interactions, gene-gene interactions, and the detailed functions of miR-146a in TB require further studies.

This meta-analysis has several limitations. First, it was limited by the relatively small number of available studies. We included 6 studies from 3 publications, for a total of fewer than 500 cases. Second, as only a single publication included a Caucasian population, we were not able to perform a subgroup analysis for this group. Third, the studies were limited to those published in English, and this restriction might result in a language bias. Thus, additional studies are needed to further examine the association between miR-146a/499 and TB risk, especially those that include different ethnic populations.

In summary, the results of the meta-analysis suggest that miR-146a/miR-499 polymorphisms are not associated with TB susceptibility, despite previous reports indicating associations. Additional studies with larger sample sizes and appropriate designs are needed to accurately characterize the relationship between miR-146a/499 polymorphisms and susceptibility to TB.

Disclosure of conflict of interest

None.

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