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Original Article

Lack of associations between rs2910164 and rs11614913 polymorphisms and the risk of ischemic stroke

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Abstract: Emerging evidence suggests that single nucleotide polymorphisms (SNPs) in microRNA genes may play a role in the development of cerebrovascular diseases including ischemic stroke through functionally modulating the expression of microRNA target genes. However, the current studies regarding the associations of the common microRNA polymorphisms with susceptibility to ischemic stroke have obtained discrepant results, which prompted us to perform a meta-analysis for a more precise estimation of the concerned associations. Relevant studies evaluating the associations between two common polymorphisms (miR-146a rs2910164 and miR-196a2 rs11614913) and the risk of ischemic stroke were retrieved from the PubMed, Embase, Cochrane Library, Google Scholar, Chinese Wanfang, Chinese Biomedical Database, and Chinese National Knowledge Infrastructure databases. The odds ratio (OR) with its 95% confidence interval (95% CI) were pooled to assess the strength of the associations using RevMan 5.2 and Stata 12.0 software. A total of 5 case-control studies with 2069 cases and 2061 controls on rs2910164, 4 case-control studies with 1873 cases and 1856 controls on rs11614913 polymorphisms were enrolled in the meta-analysis. Overall, neither allele frequency nor genotype distribution of the two common polymorphisms was found to be associated with risk for ischemic stroke in all genetic models. The subgroup analysis revealed a significant association between miR-146a rs2910164 polymorphism and increased risk of ischemic stroke in large sample size group and in Koreans under homozygous, allele, dominant and recessive models. The present meta-analysis suggests that the two common polymorphisms (rs2910164, rs11614913) may not contribute to the susceptibility to ischemic stroke. However, more well-designed studies with large sample size are warranted to further validate the results in different ethnicities.

Keywords: miR-146a rs2910164, miR-196a2 rs11614913, susceptibility, ischemic stroke, meta-analysis

Introduction

With high morbidity, disability, and mortality, ischemic stroke approximately accounting for 80% of all strokes is considered as an economic and health burden for the patients and society worldwide [1]. Etiologically, ischemic stroke is supposed to be a highly complex disease influenced by multiple genetic and environmental risk factors. However, efforts focusing the pathophysiologic mechanism of ischemic stroke make us more cognitive about the etiology that several identified single-nucleotide polymorphisms (SNPs) in microRNAs may serve as susceptibility loci for ischemic stroke risk in addition to the traditional risk factors including age, smoking, hypertension, diabetes mellitus and et al. over the past decades [2, 3].

microRNAs are a class of noncoding RNAs of ~22 nucleotides functionally modulating the expression of target genes at the post-transcriptional level through binding to the 3'-untranslated region of the target mRNAs [3]. Altered expression of microRNAs has been observed in ischemic stroke, both in animals and patients, suggesting a potential role in predicting the diagnosis and prognosis of ischemic stroke [4, 5]. Estimates suggest that a single microRNA is able to bind to hundreds of target mRNAs with various capabilities, and thereby functions diversely in ischemic stroke-related

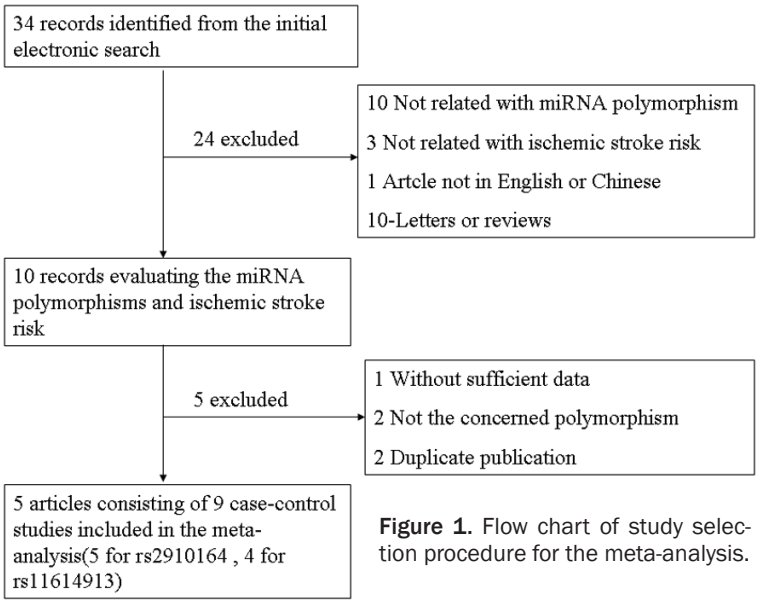

Figure 1. Flow chart of study selection procedure for the meta-analysis.

biologic processes possesses underlying atherosclerosis and plaque rupture, including macrophage inflammatory response to atherogenic lipids, inflammation, and extra-cellular matrix remodeling, which are responsible for the formation or progression of ischemic stroke [6-8]. Recently, the involvement of the alleles of two well-known microRNAs including miR-146a and miR-196a2 in the regulation of miRNA targets methylenetetrahydrofolate reductase, annexin A1 (ANXA1), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) which are closely associated with the thrombosis or inflammation pathways in the circulation system has been widely suggested, indicating the possible importance of variants in the three pre-miRNA sequences in the pathogenesis of cerebrovascular disease including ischemic stroke [9-11].

Growing evidence has already indicated that genetic variation such as SNPs in microRNAs is likely to have an influence on biogenesis or target selection of microRNAs, which may causally contribute to the altered susceptibility to diseases, including ischemic stroke [2, 12, 13]. Although the well-established polymorphisms in pre-microRNA sequences (miR-146a C>G, rs2910164 and miR-196a2 T>C, rs11614913) have been extensively investigated and reported to be associated with the altered risk of ischemic stroke [14, 15], discrepancy of conclusions from individual studies is retaining, which may be due to the limited sample size in a single study. Thus, to better assess the relationship between the well-established polymorphisms (rs2910164 and rs11614913) and the risk of ischemic stroke, we conducted a meta-analysis of all eligible published case-control studies relevant to the concerns.

Materials and methods

Search strategy

Relevant studies were electronically searched in the PubMed, Embase, Cochrane Library, Google Scholar, Chinese Wanfang, Chinese Biomedical Database, and Chinese National Knowledge Infrastructure databases to identify potentially eligible publications updated to July 2015 with the following limits: human study, article in English or Chinese. To perform a more comprehensive search, we developed a search strategy using the following terms variably combined by "Stroke", "microRNA", "miRNA", "polymorphism", "polymorphisms", "SNP", "single nucleotide polymorphism", "variant" and "genotype". The clearly irrelevant studies were excluded after reviewing the titles and abstracts of searched studies. The full texts of the remaining articles were read to identify the eligibility. Additionally, the reference lists of relevant reviews and eligible articles were also checked individually and manually for retrieving other possible eligible articles.

Selection criteria

To be eligible, all retrieved studies had to meet the specific inclusion criteria as follows: (1) Case-control studies investigating the association of the two polymorphisms (rs2910164 and rs11614913) with the risk of ischemic stroke. (2) Sufficient information for evaluating the Odds ratios (ORs) and their 95% confidence intervals (95% CIs). (3) All the diagnosis of ischemic stroke was based on the clinical manifestations, physical examination and neuroimaging data including computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, according to the International Classification of Disease (9th Revision, codes 430 to 438). (4) The extraction of the frequencies of

Table 1. The characteristics of included studies in the meta-analysis

First author	Year	Country	Ethnicity	Genotype-case	Genotype-control	Source of control	Genotype method	microRNA polymorphism	HWE test
				VR Ho/Ht/WT Ho*	VR Ho/Ht/WT Ho*				
Jeon [15]	2013	Korea	Asian	128/327/223	76/266/211	hospital	TaqMan	miR-146a rs2910164	0.589
	2013	Korea	Asian	139/352/187	105/292/156	hospital	TaqMan	miR-196a2 rs11614913	0.126
Hu [21]	2014	China	Asian	34/87/75	26/82/97	population	PCR-RFLP	miR-146a rs2910164	0.190
Liu [14]	2013	China	Asian	52/159/85	77/198/116	hospital	PCR-RFLP	miR-146a rs2910164	0.650
	2013	China	Asian	51/181/64	84/214/93	hospital	PCR-RFLP	miR-196a2 rs11614913	0.060
Huang [2]	2014	China	Asian	81/261/189	55/257/219	hospital	TaqMan	miR-146a rs2910164	0.106
	2014	China	Asian	100/265/166	112/266/153	hospital	TaqMan	miR-196a2 rs11614913	0.856
Zhu [20]	2014	China	Asian	50/173/145	64/185/132	hospital	PCR-LDR	miR-146a rs2910164	0.952
	2014	China	Asian	71/189/108	78/198/105	hospital	PCR-LDR	miR-196a2 rs11614913	0.384

*VR, variant; WT, wild-type; Ht, heterozygote; VR Ho, variant homozygote; WT Ho, wide-type homozygote; HWE, Hardy-Weinberg equilibrium.

alleles or genotypes in case and control was available. Articles were excluded when they were: (1) overlapped articles or data, (2) abstracts, comments, reviews and editorial letters; (3) studies without sufficient data of ORs and 95% CIs. In case of duplicate studies, we selected the study with the largest sample size.

Data extraction

Two reviewers independently assessed the eligibility of the identified studies and extracted data from all included studies using a standardized form. In case of a conflict, the disagreement between the reviewers would be resettled by discussion and consultation with a third reviewer. The following information was sought from every included study: first author, year of publication, country of origin, ethnicity, genotyping method, source of control groups, allele or genotype frequencies in cases and controls.

Statistical analysis

The ORs with their corresponding 95% CIs were pooled to calculate the strength of the associations using Review Manager version 5.2 software (provided by The Cochrane Collaboration, Oxford, UK; http://www.cochrane. org/software/revman.htm). The significance of the pooled ORs was determined by the Z test ($P<0.05$ was considered statistically significant). The heterogeneity among studies was assessed by Cocharan's chi-square based Q-test and I^2 test, *P* value <0.10 and $I^2>50\%$ suggested significant heterogeneity between studies [16]. In case of the presence of significant heterogeneity, the pooled analyses were performed using the random effects model (DerSimonian Laird) [17], otherwise, the fixed effects model (Mantel-Haenszel) was selected for the meta-analysis [18]. Moreover, the publication bias was evaluated by Begg's funnel plot and Egger's linear regression test ($P<0.05$ was considered significant) [19], which were both carried out using STATA 12.0 software (STATA Corp, College Station, TX, USA). Sensitivity analysis by removing a study at a time was performed to evaluate the stability of the results. The significance of pooled ORs was not materially affected, suggesting the reliability of the results of the meta-analysis. All *p*-values generated were two-tailed.

Results

Study characteristics

The flow chart of study selection procedure was shown in **Figure 1**. In brief, a total of 34 articles were obtained according to the search strategy. However, 24 apparently irrelevant articles were excluded after reading the titles and abstracts. 5 articles were further excluded after a full-text review. Finally, 9 case-control studies from 5 articles consisting of 4 reported in English and 1 reported in Chinese were included in the meta-analysis [2, 14, 15, 20, 21], resulting in 3942 cases and 3917 controls (rs2910164, 5 case-control studies with 2069 cases and 2061 controls; rs11614913, 4 case-control studies with 1873 cases and 1856 controls). Moreover, all the five studies were conducted in Asian populations, including 4 in Chinese population and 1 in Korean population. All polymorphisms in the controls subjects were in agreement with the Hardy-Weinberg equilibrium. Detailed characteristics of the included studies are displayed in **Table 1**.

Quantitative synthesis

miR-146a rs2910164: The aggregated ORs and heterogeneity test results for the associa-

Table 2. Meta-analysis results of the associations between miR-146a and miR-196a2 polymorphisms and the risk of bladder cancer

microRNA polymorphisms	Study group	Sample size (case/control)	Allele contrast		VR Ho vs. WT Ho*		Ht vs. WT Ho*		Dominant model		Recessive model	
			OR [95% CI]	P_h/I^2	OR [95% CI]	P_h/I^2	OR [95% CI]	P_h/I^2	OR [95% CI]	P_h/I^2	OR [95% CI]	P_h/I^2
miR-146a rs2910164	overall	2069/2061	1.11 [0.94, 1.31]	0.01/70%	1.36 [0.86, 2.15]	<0.01/83%	1.11 [0.97, 1.27]	0.40/1%	1.14 [0.95, 1.37]	0.09/50%	1.17 [0.88, 1.57]	0.03/64%
	Chinese	1391/1508	1.08 [0.87, 1.33]	0.01/73%	1.16 [0.75, 1.81]	0.01/73%	1.09 [0.93, 1.28]	0.28/22%	1.11 [0.87, 1.41]	0.07/58%	1.10 [0.77, 1.57]	0.03/65%
	Korean	678/553	**1.24 [1.06, 1.46]**	-	**2.35 [1.69, 3.27]**	-	1.16 [0.91, 1.49]	-	**1.26 [1.00, 1.59]**	-	**1.46 [1.07, 1.99]**	-
	Large	1209/1084	**1.25 [1.11, 1.41]**	0.94/0%	**2.06 [1.60, 2.65]**	0.22/32%	1.17 [0.98, 1.40]	0.95/0%	**1.26 [1.07, 1.50]**	0.96/0%	**1.50 [1.18, 1.90]**	0.79/0%
	Small	860/977	0.99 [0.86, 1.13]	0.04/70%	1.00 [0.63, 1.58]	0.07/62%	1.04 [0.85, 1.27]	0.19/39%	1.05 [0.77, 1.44]	0.07/62%	0.92 [0.72, 1.18]	0.19/39%
miR-196a2 rs11614913	overall	1873/1856	1.02 [0.93, 1.12]	0.63/0%	0.93 [0.77, 1.13]	0.66/0%	1.00 [0.86, 1.16]	0.63/0%	0.98 [0.85, 1.13]	0.69/0%	0.93 [0.79, 1.09]	0.46/0%
	Chinese	1195/1303	1.01 [0.90, 1.13]	0.44/0%	0.86 [0.68, 1.08]	0.96/0%	0.99 [0.82, 1.19]	0.43/0%	0.95 [0.80, 1.13]	0.55/0%	0.86 [0.70, 1.04]	0.75/0%
	Korean	678/553	1.04 [0.89, 1.22]	-	1.10 [0.79, 1.54]	-	1.01 [0.77, 1.31]	-	1.03 [0.80, 1.33]	-	1.10 [0.83, 1.46]	-
	Large	1209/1084	1.07 [0.95, 1.20]	0.66/0%	0.96 [0.76, 1.22]	0.23/31%	0.96 [0.80, 1.17]	0.64/0%	0.96 [0.80, 1.15]	0.42/0%	0.98 [0.80, 1.21]	0.26/21%
	Small	664/772	0.95 [0.82, 1.10]	0.91/0%	0.88 [0.65, 1.21]	0.99/0%	1.05 [0.82, 1.35]	0.27/17%	1.00 [0.79, 1.27]	0.39/0%	0.85 [0.65, 1.10]	0.46/0%

*VR, variant; WT, wild-type; Ht, heterozygote; VR Ho, variant homozygote; WT Ho, wide-type homozygote. The results were in bold, if the 95% CI excluded 1 or P<0.05; P_h, *P* value of Q-test for heterogeneity test, and Random effects model was used when *P* value for heterogeneity test <0.1; otherwise, fixed effects model was used in the analysis. I^2.

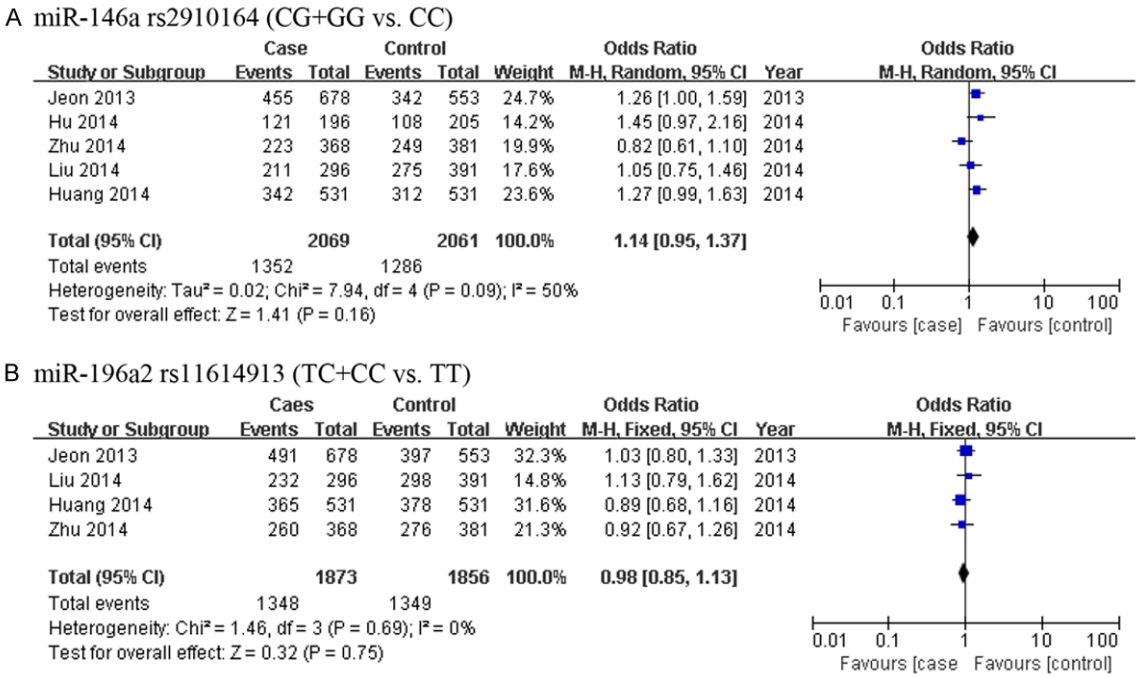

Figure 2. Forest plots for the associations between two polymorphisms and ischemic stroke risk.

tion between the rs2910164 polymorphism and the risk of ischemic stroke are presented in **Table 2** and **Figure 2**. Finally, 5 case-control studies involving 2069 cases and 2061 controls including 4 in Chinese population and 1 in Korean population were pooled into the meta-analysis. As a result, no significant association was found in any genetic model. However, a significant association between miR-146a rs2910164 polymorphism and increased risk of ischemic stroke in large sample size group and in Koreans, under homozygous, allele, dominant and recessive models was revealed.

miR-196a2 rs11614913: The association of rs11614913 polymorphism and the risk of ischemic stroke was investigated in 4 case-control studies including 1873 cases and 1856 controls. There were 3 case-control studies of Chinese population and 1 case-control study in Korean population. However, no significant association was suggested by all the genetic models (**Table 2** and **Figure 2**). With respect to the subgroup analysis based on ethnicity and sample size, we also failed to show any significant association.

Sensitivity analysis and publication bias

We performed sensitivity analysis by sequential omission of individual studies, and the results showed that the significance of the pooled ORs for miR-196a2 rs11614913 polymorphism was not excessively influenced, suggesting the stability and reliability of the results in the present meta-analysis. However, the significance of the pooled ORs was substantially altered by excluding the study of Zhu et al. [20] in all genetic models (all $P<0.05$), indicating a significant association for miR-196a2 rs11614913 polymorphism. Publication bias of the literature was evaluated by Begg's funnel plot and Egger's linear regression test (**Figure 3**). No visual asymmetry was found in the graphical funnel plots for the two studied SNPs, indicating no evidence of publication bias, which was also supported by the Egger's linear regression test (dominant model: $P=0.86$ for rs2910164 and $P=0.63$ for rs1161491).

Discussion

The present meta-analysis including a total of 9 case-control studies from 5 individual researches involving 3942 cases and 3917 controls provided the most comprehensive quantitative assessment of the associations between the two well-known polymorphisms in the microRNAs and ischemic stroke risk to date. The overall analyses showed that there was no evidence of associations between ischemic stroke risk and the miR-146a rs2910164 and miR-196a2 rs11614913 polymorphisms.

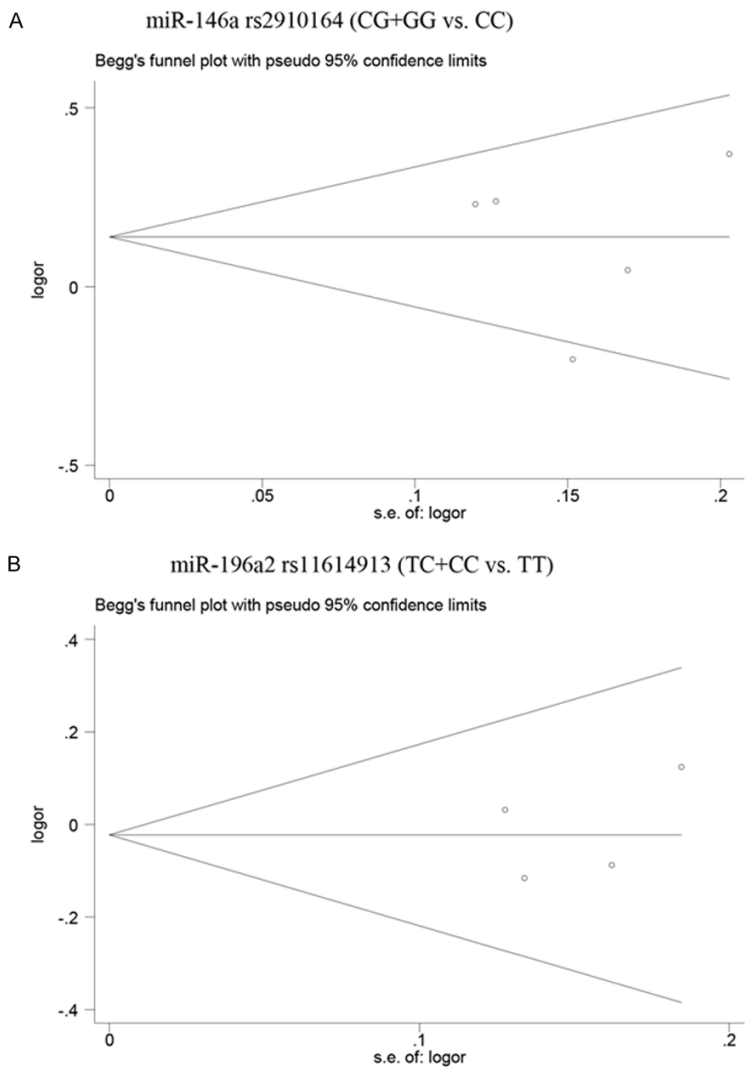

Figure 3. Begg's funnel plots for publication bias test on the associations of the two polymorphisms with ischemic stroke risk.

The investigations on microRNAs have shed lights on the molecular mechanism of ischemic stroke development in recent years. On the basis of growing evidence that specific microRNA profiles observed in peripheral blood of patients and rats with cerebrovascular disease may exhibit its potential as novel biomarkers [22, 23], microRNAs are recently found to be implicated in the development of ischemic stroke by providing sequence specificity to RNA silencing pathways related to atherosclerosis and plaque rupture [24], however, considering the pivotal role of each microRNA in the regulation of its various target genes, a minor inherited variation in microRNAs may present profound impact on the expression of target genes involved in the pathogenesis of ischemic stroke, and thus contribute to individual's susceptibility [2].

In the previous study, miR-146a rs2910164 polymorphism was suggested to be associated with an increased risk of ischemic stroke through decreasing the production of mature miR-146a [2]. The rs2910164 polymorphism resided at the stem region opposite to the mature miR-146a sequence and was presented as a change from G to C in the passenger strand, which resulted in a lower transcriptional activity of pre-miR-146a, decreased amount of mature miR-146a and abnormal target mRNA binding [25], and this reduced the inhibition of target genes involved in the Toll-like receptor and cytokine signaling pathway (TRAF6, IRAK1) and impaired nuclear factor (NF)-kB activity which were both involved in the process of atherosclerosis [20]. Surprisingly, the current meta-analysis suggested no significant association between rs2910164 polymorphism and the risk of ischemic stroke, which was in line with the results of the study by Liu et al. [14], Zhu et al. [20] and Hu et al. [21], but inconsistent with the individual study by Huang et al. [2] and Jeon et al. [15]. The potential explanation for this phenomenon may be that the role of this variant may differ in different stroke subtype as supported by Zhu et al. [20]. Besides, the current meta-analysis incorporating more studies revealed no significant association in the overall analyses in keeping with the previous meta-analysis with a relatively sample size [26, 27], but suggested a significant association in the large sample size with less heterogeneity and in Koreans in the subgroup analysis, indicating the importance of heterogeneity or geographical variation in the association studies, which was also supported

by the finding that a significant association between rs2910164 polymorphism and the risk of ischemic stroke was revealed with evidently deceased heterogeneity between studies by excluding the study by Zhu et al. [20] in the sensitivity analysis. Hence, the results of the present study should be interpreted with caution and need to be further confirmed.

For the miR-196a2 rs11614913 polymorphism, 4 case-control studies with a total of 1873 cases and 1856 controls were included in this meta-analysis. The rs11614913 polymorphism located in the 3p strand of mature miR-196a2 region with a T>C change was reported to be associated with increased expression of mature miR-196a2, which was capable of resulting in deregulation of target genes homeobox (HOX) and annexin A1 (ANXA1) involved in cerebral ischemia and atherosclerosis [20]. However, the present meta-analysis for the first time provides valid evidence supporting no significant association of rs11614913 polymorphism with ischemic stroke susceptibility, which was in accordance with the previous studies, suggesting that miR-196a2 rs11614913 polymorphism might not be a determinant in the development of ischemic stroke. Nevertheless, the study by Jeon et al. [15] showed that miR-146aG/-149T/-196a2C/-499G allele combination was significantly associated with ischemic stroke prevalence, indicating a possible role of rs11614913 polymorphism in the risk of ischemic stroke through gene-gene interaction, which remains to be further confirmed with a large sample size.

Despite the considerable efforts were made to explore the possible association between the common microRNA polymorphisms and ischemic stroke susceptibility, caution should be noted when explaining the results because of some defects existed in the meta-analysis. Firstly, possible publication bias may be inevitable because studies with negative findings were comparatively difficult to be published, though no evident publication bias was suggested by the test of publication bias in the meta-analysis. Secondly, we are unable to perform subgroup analysis based on stroke subtype which is likely to affect the associations due to the lack of original information. Thirdly, the results of current meta-analysis was based on unadjusted estimates and a more precise analysis was supposed to be conducted under the consideration of confounding factors relevant to ischemic stroke such as diabetes, smoking, alcohol drinking, et al. Fourthly, possible gene-gene and gene-environment interactions were not fully assessed in the concerned associations due to the lack of sufficient data. Moreover, all of the included studies were conducted in Asian population, which would limit the comprehensiveness and veracity of the results. Further studies are needed to explore the influence of ethnicity on these associations.

In conclusion, the present meta-analysis suggests that the two common microRNA polymorphisms (miR-146a rs2910164 and miR-196a2 rs11614913) may not be associated with the risk of ischemic stroke. However, in light of the limitations in this meta-analysis, more well-designed studies with large sample size considering the gene-gene and gene-environment interactions and stroke subtype in different ethnicities are warranted to clarify the concerned associations.

Disclosure of conflict of interest

None.

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