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META-ANALYSIS

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Association Between Single-Nucleotide Polymorphism (SNP) in miR-146a, miR-196a2, and miR-499 and Risk of Ischemic Stroke: A Meta-Analysis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The association between 3 well known SNPs – miR-146a C/G (rs2910164), miR-196a2 T/C (rs11614913), and miR-499 A/G (rs3746444) – in pre-miRNA sequences and ischemic stroke (IS) are still conflicting and inconclusive. This meta-analysis aimed to pool previous studies get a more precise assessment of the association between these 3 SNPs and the risk of IS.

Material/Methods: Relevant studies were searched in online databases. The strength of the association between the SNPs and IS were estimated by pooling odds ratios (OR) and 95% confidence intervals (CI) using Review Manager (version 5.3).

Results: Rs2910164 C allele was associated with lower IS risk. But this trend was only observed in Koreans under the allele model (OR=0.81, 95% CI=0.68-0.95, p=0.009), dominant model (OR=0.68, 95% CI=0.50–0.93, p=0.02), recessive model (OR=0.79, 95% CI=0.63–1.00, p=0.05), and homozygous model (OR=0.63, 95%CI=0.45–0.88, p=0.007). Rs11614913 T allele might be associated with higher IS risk under the dominant model (OR=1.45, 95% CI=1.19–1.78, p=0.0003), while rs3746444 A allele might be associated with decreased IS risk under the homozygous model (OR=0.48, 95% CI=0.23–0.98, p=0.04) only in Chinese, but not in Koreans.

Conclusions: Although the 3 SNPs might be associated with IS, the association varied significantly in different countries.

MeSH Keywords: MicroRNAs • Polymorphism, Single Nucleotide • Stroke

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Background

Stroke causes about 11% of all death across the world and is the most common cause of adult-acquired disability [1]. Ischemic stroke (IS) and intracerebral hemorrhage (ICH) constitute about 80-85% and 15-20% of all stroke cases, respectively [1]. IS is a highly complex disease caused by multiple genetic and environmental risk factors [2]. Several susceptible genes associated with increased risk of IS have been recognized, such as ACE, F5, MTHFR, and APOE [3]. But these findings only revealed a part of the inherited risk of IS. It is necessary to further study the genetic background and disease susceptibility genes to better understand this disease.

MicroRNAs (miRNAs) are a group of small (~22-nucleotide) and conserved endogenous non-coding RNA. They can bind to the 3'-untranslated region (3'-UTR) of target mRNAs, thereby regulating gene expression through translational repression or mRNA degradation [4]. Single-nucleotide polymorphisms (SNPs) were the most frequent variation in the human genome. SNPs or mutations in mature miRNAs may affect the maturation process or target selection, thus influencing the downstream physiological processes [5,6]. Three well-known SNPs in pre-miRNA sequences – miR-146a C/G (rs2910164), miR-196a2 T/C (rs11614913), and miR-499 A/G (rs3746444) – have been widely studied and were associated with the risk of several diseases [7,8]. In fact, miR-146a is closely related to regulation of tumor necrosis factor-α (TNF-α) [9]. MiR-146a were significantly downregulated in patients with IS in the acute phase but upregulated in the subacute phase [10], exerting a neuroprotective effect through astrocytes [11]. MiR-196a2 can target annexin A1 [12]. MiR-499 can affect the inflammatory reaction through modulating C-reactive protein (CRP) [13]. Therefore, these 3 miRNAs may play important roles in regulating thrombosis or inflammation pathways in the circulation system. Considering the important role of the SNPs in the expression or targeting of the miRNAs, several recent studies tried to explore the influence of the SNPs on IS risk [14–17]. However, the results were conflicting and inconclusive. The present meta-analysis aimed to pool previous studies to get a more precise assessment of the association between the 3 SNPs and the risk of IS.

Material and Methods

Searching strategy

Relevant studies published before 1 June 2015 were systematically searched by 2 authors independently in the databases, including PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBLM) by using the following searching terms: "ischemic stroke (IS)" and ("single nucleotide polymorphism" or "polymorphism" or "mutation" or "variant" or "SNP") and ("microRNA" or "miRNA" or "miR"). No language restriction was applied for searching. Reference list of studies included and other relevant meta-analyses or reviews were manually searched to find other potentially qualified studies.

Studies meeting the following criteria were included in this meta-analysis: (1) Case-control design; (2) Studies assessed the association between SNP of miRNAs and the risk of IS; (3) the genotype distribution of the controls agreed with the Hardy-Weinberg equilibrium (HWE); (4) Detailed data of genotype frequency could be extracted from original studies. Repeat studies and studies without detailed data were excluded.

Data extraction

Two authors independently extracted data from the original studies. The information extracted included surname of the first author, year of publication, country, ethnicity, disease, numbers of subjects, age, sex, source of controls, genotyping methods, genotype frequency of case and control, and p value of Hardy-Weinberg equilibrium (HWE) in controls. Disagreement was resolved by referring to original studies in group discussion.

Quality assessment of studies included

The quality of included studies was assessed using the modified Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) quality score system. This system has 40 assessment items to assess a trial's quality by giving scores from 0 to 40. Based on the scoring, the quality is defined as low quality (0–19), moderate quality (20–29), or high quality (30–40).

Statistical analysis

Cochrane Review Manager (version 5.3, Cochrane Collaboration, Copenhagen, Denmark) was used for data integration and analysis. The χ^2 test was used to evaluate the HWE of the control group. The strength of the association between the SNPs and IS were estimated by pooling odds ratios (OR) and 95% confidence intervals (CI) under 5 genetic models, including allele model, homozygote model, heterozygote model, dominant model, and recessive model. Statistical heterogeneity among studies was assessed using the chi square-based Q test and I^2 [12]. χ^2 tests $p<0.1$ or I^2 >50% indicates significant heterogeneity [12]. If there was significant heterogeneity among the studies, the random-effects model (the DerSimonian and Laird method) was used to make estimates, otherwise the fixed-effects model (Mantel-Haenszel method) was used. Since only 5 original studies were involved, there was no need to assess the publication bias. The statistical significance of the pooled OR was

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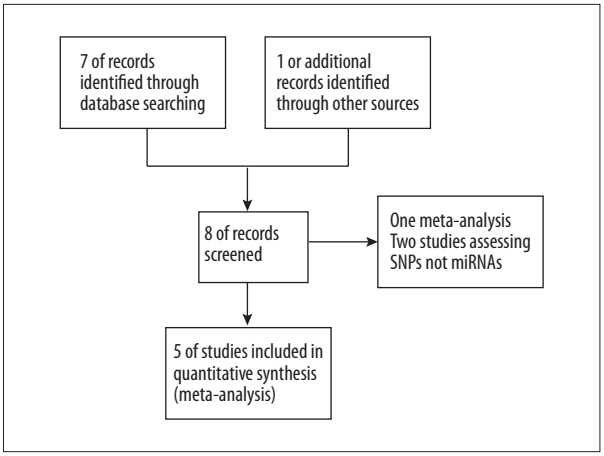

Figure 1. The flowchart of searching and screening process.

determined by Z test and p<0.05 was considered as a significant difference.

Results

Characteristics of studies included

A total of 8 studies were found through searching in the databases. Among them, 2 were excluded for irrelevance and 1 meta-analysis was excluded. Finally, 5 studies meeting the criteria were included [14–18], among which 2254 cases and 2506 controls were included. The flow chart summarizing the search process is shown in Figure 1 and the basic information of the included studies is given in Table 1. Among the 5 studies, 5 assessed the association between miR-146a (rs2910164) and IS risks, 4 assessed miR-196a2 (rs11614913), and 3 assessed miR-499 (rs3746444). The genotype distribution of rs2910164, rs11614913, and rs3746444 is presented in Table 2. All of the studies had genotype distribution in controls in agreement with Hardy-Weinberg equilibrium (HWE) expectation.

Results of meta-analysis

The results of meta-analysis for the association between the 3 SNPs (rs2910164, rs11614913, and rs3746444) and the IS risks are shown in Table 3.

MiR-146a rs2910164 C/G and the risk of IS

There was no significant association between this SNP and the IS risk under all genetic models. When performing a subgroup analysis by country, a similar trend was observed in the Chinese population. However, significant associations were observed in the Korean population under the allele model (OR=0.81, 95% CI=0.68-0.95, p=0.009), dominant model (OR=0.68, 95% CI=0.50–0.93, p=0.02), recessive model (OR=0.79, 95% CI=0.63–1.00, p=0.05), and homozygous model (OR=0.63, 95%CI=0.45-0.88, p=0.007) (Table 3), suggesting there might be some protective effect of the C allele in Koreans.

MiR-196a2 rs11614913 T/C and the risk of IS

For rs11614913, a significant association between T allele and increased IS risk was observed under the dominant model (OR=1.35, 95% CI=1.15–1.59, p=0.0003), but not under other models. Subgroup analysis showed this association was only significant in Chinese (OR=1.45, 95% CI=1.19–1.78, p=0.0003), but not in Koreans (Table 3).

MiR-499 rs3746444 A/G and the risk of IS

For rs3746444, there was no significant association between this SNP and the IS risk under all genetic models, but subgroup analysis showed homozygote AA was associated with decreased IS risk under the homozygous model (OR=0.48, 95% CI=0.23–0.98, p=0.04) (Table 3) in Chinese.

Discussion

In this study, we found that, although the 3 SNPs might be associated with IS, the association varied significantly in different countries. rs2910164 C allele was associated with lower IS risk, but this trend was only observed in Koreans under the allele model, dominant model, recessive model, and homozygous model. rs11614913 T allele might be associated with higher IS risk under the dominant model (OR=1.45, 95% CI=1.19–1.78, p=0.0003), while rs3746444 A allele might be associated with decreased IS risk under the homozygous model (OR=0.48, 95% CI=0.23–0.98, p=0.04) only in Chinese. These results suggest that the effect of the SNPs might be significantly related to genetic background of a population.

Some recent studies found some miRNAs are dysregulated in IS. For example, miR-497 can directly bind to the 3'UTR of B-cell lymphoma 2 (Bcl-2) and Bcl-w mRNAs, whose proteins play an important role in attenuating stroke-induced apoptotic cell death [19]. MiR-29b expression was significantly increased in rat brains by focal ischemia. It can also directly bind to the Bcl-2 mRNA and thereby promote neuronal cell death [20]. The miR-146a/rs2910164, miR-196a2/rs11614913, and miR-499/rs3746444 were all in the 3p strand of mature miRNA regions. The G allele of rs2910164 and T allele of rs11614913 are associated with decreased mature miRNA levels [21,22]. This might help to explain why these 2 alleles were associated with increased risk of IS in Koreans and Chinese. In fact, miR-146a can regulate the expression of TNF-α and also inhibit the pro-inflammatory MAP kinase pathway and NF-κB pathway [23], which are closely related to occurrence of IS. A

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Table 1. The basic characteristics of studies included.

Study	Country	Ethnicity	Disease	Source of control	No. participants		Age (mean ±SD)		Male, n (%)		SNP	Genotype method	Quality score
					Control	Case	Control	Case	Control	Case			
Sun 2011	China	Asian	IS	HB	650	381	62 ±13	63 ±12	347 (53.4)	236 (61.9)	rs2910164	PCR-RFLP	30
Jeon 2013	China	Asian	IS	HB	553	678	63.14 ±10.19	64.16 ±11.90	244 (44.1)	336 (49.6)	rs2910164; rs2292832 rs11614913; rs3746444	Taqman	36
Liu 2014	China	Asian	IS	HB	391	296	66.34 ±11.07	67.52 ±10.29	227 (58.06)	180 (60.81)	rs2910164; rs11614913; rs3746444	PCR-RFLP	34
Zhu 2014	China	Asian	IS	HB	381	368	62.05 ±0.98	61.62 ±0.97	261 (68.50)	253 (68.75)	rs2910164; rs11614913	PCR-LDR	33
Huang 2015	China	Asian	IS	HB	531	531	61 (54, 68)*	63 (54, 70)*	327 (61.6)	327 (61.6)	rs2910164; rs11614913; rs3746444	Taqman	34

IS – ischemic stroke; HB – hospital based; PCR-RELP – polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR – polymerase chain reaction-ligation detection reaction; SNP – single nucleotide polymorphism. * data are expressed as median (25th, 75th quartiles).

Table 2. The genotype distribution of rs2910164, rs11614913 and rs3746444.

Study	miRNA	SNP	Control			Cases			P.HWE
			CC	CG	GG	CC	CG	GG	
Huang 2015	miR-146a	rs2910164 C/G	219	257	55	189	261	81	0.106
Jeon 2013	miR-146a	rs2910164 C/G	211	266	76	223	327	128	0.589
Liu 2014	miR-146a	rs2910164 C/G	116	198	77	85	159	52	0.650
Sun 2011	miR-146a	rs2910164 C/G	228	304	118	146	170	65	0.345
Zhu 2014	miR-146a	rs2910164 C/G	132	185	64	145	173	50	0.952
			TT	TC	CC	TT	TC	CC	
Huang 2015	miR-196a2	rs11614913 T/C	153	266	112	166	265	100	0.856
Jeon 2013	miR-196a2	rs11614913 T/C	156	292	105	187	352	139	0.126
Liu 2014	miR-196a2	rs11614913 T/C	93	214	84	64	181	51	0.060
Zhu 2014	miR-196a2	rs11614913 T/C	105	198	78	108	189	71	0.384
			AA	AG	GG	AA	AG	GG	
Huang 2015	miR-499	rs3746444 A/G	403	128	0	398	133	0	0.002
Jeon 2013	miR-499	rs3746444 A/G	365	170	18	460	195	23	0.740
Liu 2014	miR-499	rs3746444 A/G	278	99	14	181	96	19	0.170

recent study found stroke acutely activates the Toll-like receptor (TLR) signaling pathway in cerebral vasculature. Upregulation of miR-146a contributes to neuroprotection, partly through inactivation of the TLR signaling pathway [24]. MiR-196a2 can regulate annexin A1, which has significant repressing effects on both neutrophil and monocyte migration and adhesion in atherosclerosis. Annexin A1, as an important endogenous anti-inflammatory mediator, can also repress the expression and activation of inflammatory enzymes, such as inducible cyclooxygenase 2 (COX2), inducible nitric oxide synthase (iNOS), and phospholipase A2 [25]. Therefore, through regulating annexin A1, miR-196a2 might exert some effect in IS. MiR-499 can

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Table 3. Overall and stratified analyses of association between the three SNPs and the IS risk.

miRNAs and SNP	No. studies	Cases/ controls	Genetic models														
			C *vs.* G (allele model)			CC+CG *vs.* GG (dominant model)			CC *vs.* GG+CG (recessive model)			CC *vs.* GG (homozygous model)			CC *vs.* CG (heterozygous model)		
			OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2
Overall miR-146a rs2910164 C/G	5	2254/ 2506	0.96 (0.82–1.13)	0.63	73%	0.92 (0.70–1.21)	0.56	67%	0.96 (0.79–1.15)	0.64	57%	0.91 (0.64–1.28)	0.58	74%	0.96 (0.85–1.09)	0.57	17%
China	4	1576/ 1953	1.01 (0.85, 1.20)	0.92	69%	1.00 (0.74, 1.35)	1.00	62%	1.01 (0.82, 1.24)	0.93	54%	1.00 (0.69, 1.47)	0.98	70%	1.00 (0.87, 1.16)	0.96	18%
Korea	1	678/ 553	0.81 (0.68, 0.95)	**0.009**	–	0.68 (0.50, 0.93)	**0.02**	–	0.79 (0.63, 1.00)	**0.05**	–	0.63 (0.45, 0.88)	**0.007**	–	0.86 (0.67, 1.10)	0.23	–
			T *vs.* C (allele model)			TT+TC *vs.* CC (dominant model)			TT *vs.* TC+CC (recessive model)			TT *vs.* CC (homozygous model)			TT *vs.* TC (heterozygous model)		
			OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2
Overall miR-196a2 rs11614913 T/C	4	1873/ 1856	1.03 (0.94–1.13)	0.48	0%	1.35 (1.15–1.59)	**0.0003**	0%	1.02 (0.89–1.18)	0.75	0%	1.07 (0.89–1.30)	0.46	0%	1.00 (0.86–1.17)	0.95	0%
China	3	1195/ 1303	1.07 (0.96, 1.20)	0.22	0%	1.45 (1.19, 1.78)	**0.0003**	0%	1.05 (0.88, 1.25)	0.58	0%	1.17 (0.93, 1.47)	0.19	0%	1.01 (0.84, 1.22)	0.91	0%
Korea	1	678/ 553	0.96 (0.82, 1.12)	0.6	–	1.17 (0.88, 1.55)	0.29	–	0.97 (0.75, 1.24)	0.81	–	0.91 (0.65, 1.26)	0.56	–	0.99 (0.76, 1.29)	0.97	–
			A *vs.* G (allele model)			AA+AG *vs.* GG (dominant model)			AA *vs.* GG+AG (recessive model)			AA *vs.* GG (homozygous model)			AA *vs.* AG (heterozygous model)		
			OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2
Overall miR-499 rs3746444 A/G	3	1505/ 1475	0.88 (0.67–1.16)	0.38	73%	0.75 (0.47–1.19)	0.22	29%	0.88 (0.66–1.19)	0.42	71%	0.70 (0.35–1.42)	0.33	54%	0.91 (0.69–1.19)	0.47	63%
China	2	827/ 922	0.80 (0.56, 1.14)	0.22	73%	0.54 (0.27, 1.10)	0.09	–	0.79 (0.53, 1.16)	0.22	70%	0.48 (0.23, 0.98)	**0.04**	–	0.81 (0.58, 1.14)	0.22	59%
Korea	1	678/ 553	1.06 (0.86, 1.30)	0.59	–	0.96 (0.51, 1.79)	0.89	–	1.09 (0.86, 1.38)	0.49	–	0.99 (0.52, 1.86)	0.97	–	1.10 (0.86, 1.41)	0.46	–

OR – odds ratios; 95%CI – 95% confidence interval; "–" – not available. Bold indicates significant p values.

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regulate CRP, a protein closely related to cerebral ischemia. In addition, mi-499 can also regulate cell apoptosis and cell death in anoxia and ischemia conditions by targeting calcineurin and dynamin-related protein-1 [26]. Since rs3746444 A/G mutation might affect binding of targeting mRNAs and maturation of pre-miRNA, it is possible that this SNP might significantly affect downstream biological functions.

This study also has several limitations. Firstly, due to the limited number of original studies, the number of patients included was relatively small. After a comprehensive literature search, only 5 eligible studies were included. Secondly, the information on clinicopathological characteristics or disease subtypes was poorly provided in original studies, making it difficult to perform more subgroup meta-analysis. Thirdly, IS is a disease influenced by both genetic and environmental factors. The gene-gene and gene-environment interactions may significantly affect function of a single SNP. Therefore, the exact effect of the SNPs may vary in different populations with different genetic backgrounds. In addition, a SNP might be in linkage disequilibrium with other genetic variations of stroke susceptibility genes, which may present stronger effect when considered together with other variations. These hypotheses need to be tested in future studies.

Conclusions

The current meta-analysis suggests that rs2910164 C allele might be associated with lower IS risk in Koreans. rs11614913 T allele might be associated with higher IS risk under the dominant model, while rs3746444 A allele might be associated with decreased IS risk under the homozygous model in Chinese. However, these findings should be further verified in studies with large sample sizes.

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