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Association between miRNA polymorphisms and susceptibility to brain tumors

A meta-analysis

Fu'an Gao, MM[a], Yuntao Zhu, MM[b,*]

Abstract

Background: Previous studies have demonstrated that single-nucleotide polymorphisms (SNPs) in miRNAs are related to the susceptibility to brain tumors, but the conclusions remain controversial. This study was to perform a meta-analysis to re-assess the associations between miRNA SNPs and brain tumor risk.

Methods: Relevant studies were identified in the databases of PubMed and the Cochrane Library databases. Pooled odds ratio (OR) and 95% confidence interval (95% CI) were calculated to assess the relationships between SNPs and the risk of brain tumors under various genetic models by the STATA software.

Results: Five studies, containing 2275 cases, and 2323 controls, were included, 4 of which evaluated miR-196a2 (rs11614913), 3 for miR-146a (rs2910164) and 2 for miR-499 (rs3746444) and miR-149 (rs2292832), respectively. The meta-analysis indicated that the GG genotype carriers of miR-146a were more susceptible to brain tumors compared with GC genotype carriers (OR = 1.19, 95% CI = 1.01–1.41, $P = .036$). No significant associations were observed between the SNPs of other miRNAs and the risk of brain tumors. Furthermore, all miRNA polymorphisms did not show significant associations with the risk of glioma subgroup in any genetic models, while meta-analysis of non-glioma subgroup could not be performed due to low statistical power and analysis of only 1 study.

Conclusion: Our study suggests that miR-146a polymorphism may modify the risk for brain tumors, but which type (glioma or benign non-glioma tumors) should be verified with large sample size.

Abbreviations: 3'-UTR = 3'-untranslated region, CI = confidence interval, HWE = Hardy-Weinberg equilibrium, microRNAs = miRNAs, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PCR-LDR = polymerase chain reaction–ligation detection reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, PRISMA = the Preferred Reporting Items for Systematic Review and Meta-analysis, SNPs = single-nucleotide polymorphisms.

Keywords: brain tumor, glioma, meta-analysis, miRNAs, polymorphism

1. Introduction

Brain tumors are one of the leading causes of cancer-related mortality, accounting for approximately 20% of all cancer deaths.[1] Brain tumors are a heterogeneous group, including several subtypes, such as glioma, meningioma, schwannomas et al, among which glioma is the common type, contributing to about 70% of all brain tumors.[2] In addition to environmental factors (ionizing radiation, dietary, and occupational exposure), accumulating evidence has demonstrated that genetic predisposition also plays important roles in the development of brain tumors.[3–5] Thus, investigation of crucial genetic variants underlying brain tumors may be of significance in order to develop new diagnostic and therapeutic strategies.

Although the molecular mechanism of brain tumors is complex, microRNAs (miRNAs), 25-nucleotide long noncoding RNAs, have been believed to be important by negatively regulating the expression of target genes at the posttranscriptional level through binding to their 3'-untranslated regions (3'-UTRs). For example, Yang et al observed the expression of miR-196a was upregulated in glioma specimens and its high expression level was significantly associated with poor prognosis of patients. In vitro study proved miR-196a promoted the proliferation and suppressed the apoptosis of glioma cells by interacting with the 3'-UTR of IκBα to suppress its expression and then activate NF-κB-mediated pathways. Inhibition of miR-196a could ameliorate tumor growth in vivo.[6] miR-146b-5p was shown to be significantly downregulated in gliomas. Overexpression of miR-146b-5p dramatically suppressed glioma cell proliferation, migration and invasion and induced apoptosis, ultimately improving the prognostic outcomes of glioma patients.[7–9] The mechanisms studies revealed miR-146b-5p may exert tumor suppressor effects by influencing the expressions of matrix metalloproteinase 16,[7] tumor necrosis factor receptor-associated factor 6[8] and epidermal growth factor receptor.[9]

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Hereby, genetic variants in miRNAs may be underlying risk factors for the development of brain tumors by causing the expression changes of miRNAs or the binding capacity with targeted genes.

Recently, there have several studies to investigate the associations between single-nucleotide polymorphisms (SNPs) of miRNAs and the risk of brain tumors.[10–13] However, the conclusions seem inconsistent. For example, Dou et al showed the genotype CC of miR-196a (rs11614913) polymorphism was associated with a decreased risk of glioma [$P = .035$; odds ratio (OR) = 0.74, 95% confidence interval (CI) = 0.56–0.98).[13] Sibin et al did not find any association between rs11614913 polymorphism and glioma risk.[12] Hu et al found miR-196a2 was associated with an increased risk of glioma (high grade: $P = .01$; OR = 1.27, 95%CI = 1.06–1.52; low grade: $P = .03$; OR = 1.23, 95%CI = 1.02–1.48).[14] These controversial conclusions may be attributed to small sample size of individual studies. Therefore, it is necessary to reevaluate the true association of these miRNA polymorphisms and the susceptibility to brain tumors.

The goal of our present study was to perform a meta-analysis to investigate the correlations of all the included miRNA polymorphisms (miR-146a, miR-149, miR-196a2, and miR-499) with the risk of brain tumors, which, to our knowledge, had not been reported previously.

2. Materials and methods

2.1. Search strategy

A comprehensive literature search in the PubMed and the Cochrane Library databases was performed by 2 independent investigators before December, 2018. The used keywords were as follows: ("glioma" OR "glioblastoma" OR "brain tumors") AND ("microRNA" OR "miRNA" OR "miR") AND ("polymorphism" OR "SNP" OR "mutation" OR "variant"). The references of retrieved articles were also manually searched to acquire other potentially relevant studies.

This meta-analysis was conducted based on the Guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. All results were collected from previous published studies; thus, no ethical approval and patient consent were required.

2.2. Selection criteria

Eligible studies were selected according to the following inclusion criteria:

(1) case-control design;
(2) research on the associations between miRNA polymorphisms and the risk of glioma by at least 2 studies;

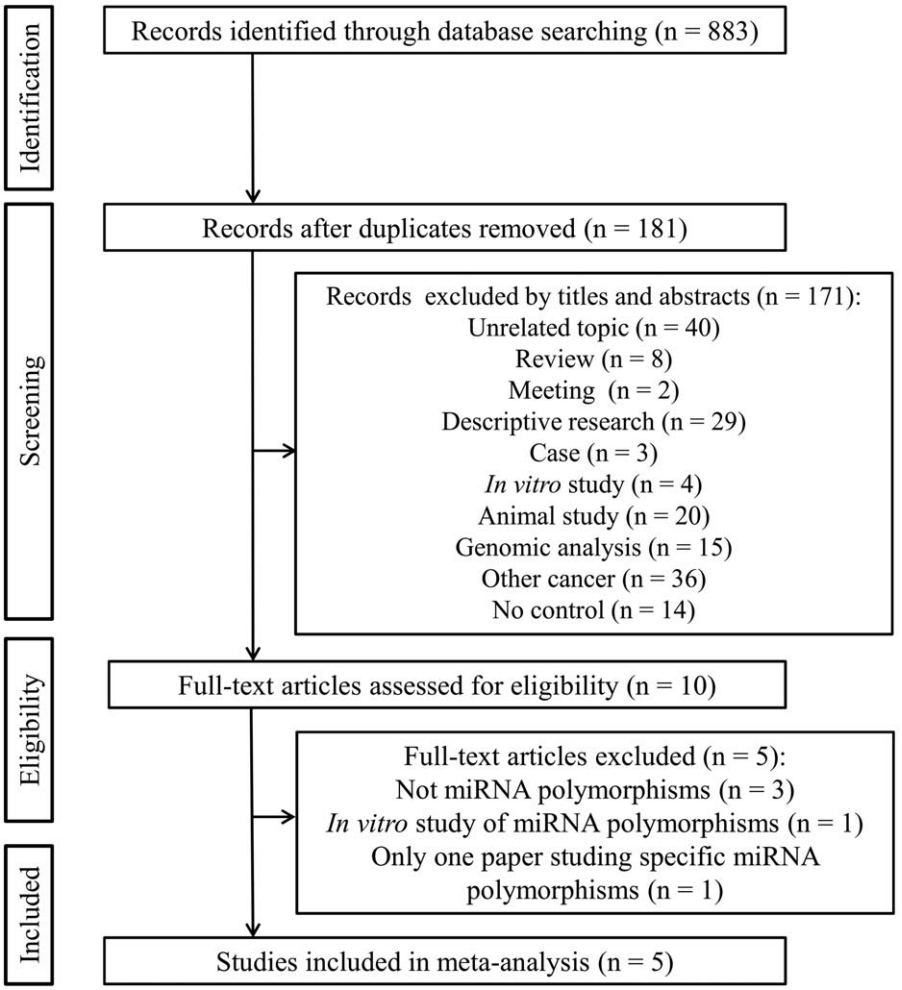

Figure 1. Flow diagram of study identification.

(3) providing genotype frequency data for computing the ORs with 95%CIs; and
(4) published in the English or Chinese language.

Exclusion criteria included:

(1) duplicated studies;
(2) abstracts, case reports/series, reviews, meta-analysis, comments, or editorial articles;
(3) animal model or cell-lines research; and
(4) lack of available data.

2.3. Data extraction

Two investigators independently extracted the following data, including first author, year of publication, country of the study, sample size as well as age of cases and controls, genotyping method, source of controls, Hardy-Weinberg equilibrium (HWE) for controls, alleles and genotypes of each polymorphism. Any disagreement was resolved by discussion to reach a consensus.

2.4. Quality assessment

Two independent investigators assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS).[15] The NOS evaluated a study based on 3 aspects: selection, comparability, and exposure/outcome. The full score was 9 stars. Study with a score of ≥7 stars was defined as high quality.

2.5. Statistical analysis

STATA software (version 13.0; STATA Corporation, College Station, TX) was used to perform the meta-analysis. The association of miRNA polymorphisms with the risk of brain tumors (or glioma, country subgroups) was estimated by calculating the pooled ORs and 95%CIs. Heterogeneity among studies was evaluated using Cochran's Q (Chi-squared) statistic and the I^2 statistic. A random-effects (significant heterogeneity, $P<.10$ and $I^2>50\%$) or fixed-effects (no heterogeneity, $P>.10$ and $I^2<50\%$) model was utilized for OR calculation. The significance of the pooled ORs was determined by the Z test, with $P<.05$ set as the statistical threshold. Publication bias was evaluated with funnel plots and the Egger linear regression test ($P<.05$). Sensitivity analysis was performed to assess the robustness of the results by omitting each study at a time.

3. Results

3.1. Characteristics of included studies

Figure 1 shows the flow chart for the study selection process. Five case-control studies, including 2275 cases and 2323 controls, were finally suggested to be eligible according to the inclusion and exclusion criteria.[11–14,16] The basic characteristics of these selected studies are summarized in Table 1. Four studies investigated the association of miR-196a2 polymorphism (rs11614913) with brain tumor risk,[11–14] three focused on the miR-146a (rs2910164)[11,14,16] and 2 analyzed miR-499 (rs3746444) and miR-149 (rs2292832),[11,14] respectively. The study of Lim et al analyzed 3 types of brain tumors, including glioma, meningioma, and schwannoma;[11] the glioma samples were only collected in other studies.[12–14,16] The eligible studies were published from 2010 to 2018. Genotyping methods included polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), TaqMan, polymerase chain reaction–ligation detection reaction (PCR-LDR), SNaPshot assay and Illumina GoldenGate technology. Three papers were population-based case-control studies, while the other 2 were hospital-based case-control studies. Most of the included studies were conducted in Asians (including 2 in China, 1 in Korea, 1 in India), and only 1 was for the Caucasians population (USA). The frequencies of the alleles and genotypes among cases and controls are shown in Table 2. The score of NOS was 7 or 8 for each study, indicating they were of high quality (Table 3).

3.2. Quantitative synthesis

The association between each miRNA polymorphism and brain tumor risk was estimated in 6 genetic models. For miR-146a polymorphism, the GG carriers were found to be significantly at a higher risk for brain tumors (OR=1.19, 95%CI=1.01–1.41, $P=.036$) compared with the GC genotype carriers (Table 4; Fig. 2). However, no significant association was found in other

Table 1

Characteristics of included studies in the meta-analysis.

Study	Year	Country	Control source	Sample size		Age (years, mean ± SD)		Genotype method	SNP	HWE
				Cases	Controls	Cases	Controls			
Lim J	2018	Korea	PB	79 (gliomas) 69 (meningiomas) 31 (schwannomas)	183	51.9±14.7	45.9±16.6	PCR-RFLP	miR-146a (rs2910164), miR-149 (rs2292832), miR-196a2 (rs11614913), miR-499 (rs3746444)	Yes
Hu E	2013	China	HB	680 (gliomas)	690	53.2±12.9	53.0±12.2	SNaPshot assay	miR-146a (rs2910164), miR-149 (rs2292832), miR-196a2 (rs11614913)	Yes
Permuth-Wey J	2011	USA	PB	593 (gliomas)	614	55 (19–89)	58 (19–89)	Illumina GoldenGate	miR-146a (rs2910164)	Yes
Sibin MK	2017	India	PB	180 (gliomas)	180	34.6±11.5	40.4±13.3	Taqman	miR-196a2 (rs11614913)	Yes
Dou T	2010	China	HB	643 (gliomas)	656	NA	NA	PCR–LDR	miR-196a2 (rs11614913)	Yes

HB = hospital-based, HWE = Hardy-Weinberg equilibrium, PB = population-based, PCR-LDR = polymerase chain reaction–ligation detection reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

Table 2

Genotype and allele distribution in cases and controls.

Study			No of cases			Allele of cases, n (%)		No of controls			Allele of cases, n (%)	
miR-146a	Year	Sample size (cases/controls)	GG	GC	CC	G	C	GG	GC	CC	G	C
Lim J	2018	79/183	15	34	30	64 (40.5)	94 (59.5)	25	88	70	138 (37.7)	228 (62.3)
		69/183	9	32	28	50 (36.2)	88 (63.8)					
		31/183	4	17	10	23 (40.3)	37 (59.7)					
Hu E	2013	680/690	205	330	145	740 (54.4)	620 (45.6)	151	359	180	661 (48.6)	719 (51.4)
Permuth-Wey J	2011	593/614	345	198	50	888 (74.9)	298 (25.1)	375	214	25	964 (78.5)	264 (21.5)
miR-149		CC	CT	TT	C	T	CC	CT	TT	C	T	
Lim J	2018	79/183	12	37	30	61 (38.6)	97 (61.4)	14	72	97	100 (27.3)	266 (72.7)
		69/183	7	27	35	41 (29.7)	97 (70.3)					
		31/183	2	11	18	15 (24.2)	47 (75.8)					
Hu E	2013	680/690	70	297	313	437 (32.1)	923 (67.9)	78	302	310	458 (33.2)	922 (66.8)
miR-196a2		CC	CT	TT	C	T	CC	CT	TT	C	T	
Lim J	2018	79/183	13	44	22	70 (44.3)	88 (55.7)	45	92	46	182 (49.7)	184 (50.3)
		69/183	17	32	20	66 (47.8)	72 (52.2)					
		31/183	6	15	10	27 (43.5)	35 (56.5)					
Sibin MK	2017	180/180	86	82	12	254 (70.6)	106 (29.4)	92	76	12	260 (72.2)	100 (27.8)
Hu E	2013	680/690	185	314	181	684 (50.3)	676 (49.7)	138	342	210	618 (45.4)	762 (54.6)
Dou T	2010	643/656	111	343	189	565 (43.9)	721 (56.1)	143	305	208	591 (45.0)	721 (55.0)
miR-499		AA	AG	GG	A	G	AA	AG	GG	A	G	
Lim J	2018	79/183	58	19	2	135 (85.4)	23 (14.6)	112	64	7	288 (78.7)	78 (21.3)
		69/183	44	24	1	112 (81.2)	26 (18.8)					
		31/183	20	10	1	50 (80.6)	12 (19.4)					
Hu E	2013	680/690	449	206	25	1104 (81.2)	256 (18.8)	476	188	26	1140 (82.6)	240 (17.4)

Table 3

Quality of included studies evaluated according to the Newcastle–Ottawa Scale (NOS).

	Selection (score)				Comparability (score)	Exposure (score)			
Study	Adequate definition of patient cases	Representativeness of patients cases	Selection of controls	definition of controls	Control for important factor or additional factor	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non-response rate	Total score
Li J	1	1	1	1	1	0	1	1	7
Lim J	1	1	1	1	1	0	1	1	7
Sibin MK	1	1	1	1	1	0	1	1	7
Hu E	1	1	1	1	2	0	1	1	8
Permuth-Wey J	1	1	1	1	2	0	1	1	8
Dou T	1	1	1	1	2	0	1	1	8

genetic models (Table 4). Furthermore, the subgroup analysis was also performed for the glioma type. The results showed no statistical correlation between the miR-146a polymorphism and the susceptibility to glioma in any models (Table 5).

miR-196a2 polymorphism did not show significant associations with overall brain tumor (Table 4) or glioma (Table 5) risk in any of the genetic models. Moreover, the subgroup analysis was also carried out for the subtypes of glioma or stratification by country. The results showed the TT genotype carriers of Chinese population may have a relative lower risk for the development of glioma compared with the TC + CC genotype carriers only at the marginal significance threshold ($P < .1$; OR = 0.86, 95%CI = 0.07–0.94) (Table 5). No significantly elevated or reduced risk of the development of glioma was present in other subgroups (Table 5).

For miR-149 and miR-499 polymorphisms, no significant risk associations were observed when all the eligible studies were pooled into the analysis under various models, indicating they were not genetic-related risk factors with overall brain tumor (Table 4) or glioma (Table 5).

3.3. Publication bias and sensitivity analysis

As shown in Tables 4 and 5, there was no noticeable heterogeneity in the overall comparison of miR-146a (GG vs GC) and subgroup analysis of miR-196a (TT vs TC + CC in China), indicating no potential publication bias. Egger test was also performed to further confirm that no statistical evidence for publication bias of miR-146a analysis (GG vs GC, $P = .595$) (Fig. 3).

Furthermore, a leave-one-out analysis was carried out to investigate the influence of each individual study on the pooled OR. The results indicated no obvious alteration in the pooled OR after removal of any study (Fig. 4).

Table 4

Meta-analysis results of brain tumors.

Comparison	Qualified studies	Test of association			Test of heterogeneity	
		OR (95%CI)	*P* value	Model	*P* value	I^2 (%)
miR-146a (G > C)						
G vs C	5	1.04 (0.82–1.33)	.730	R	.005	72.8
GG vs CC		1.02 (0.54–1.90)	.963	R	.001	79.4
GG vs GC		1.19 (1.01–1.41)	**.036**	F	.213	31.3
GC vs CC		0.89 (0.62–1.28)	.521	R	.041	60.0
GG+GC vs CC		0.93 (0.62–1.41)	.738	R	.007	71.6
GG vs GC+CC		1.16 (0.82–164)	.401	R	.024	64.5
miR-149 (T > C)						
T vs C	4	1.82 (0.82–4.06)	.141	R	.000	90.8
TT vs CC		0.95 (0.70–1.29)	.737	F	.110	50.2
TC vs CC		0.98 (0.72–1.34)	.899	F	.597	0.0
TT vs TC		0.97 (0.80–1.17)	.747	F	.356	7.3
TT+TC vs CC		0.96 (0.72–1.29)	.806	F	.248	27.3
TT vs TC+CC		0.96 (0.81–1.16)	.691	F	.149	43.7
miR-196a (T > C)						
T vs C	6	1.02 (0.87–1.19)	.844	R	.061	52.5
TT vs CC		1.05 (0.74–1.49)	.792	R	.044	56.1
TC vs TT		1.09 (0.93–1.28)	.283	F	.735	0.0
TC vs CC		1.10 (0.78–1.55)	.598	R	.006	69.3
TT+TC vs CC		1.09 (0.78–1.52)	.610	R	.005	70.4
TT vs TC+CC		0.91 (0.79–1.06)	.243	F	.667	0.0
miR-499 (A > G)						
G vs A	4	0.99 (0.84–1.17)	.923	F	.200	35.4
GG vs AA		0.95 (0.56–1.60)	.833	F	.479	0.0
GA vs AA		1.03 (0.84–1.25)	.778	F	.183	38.2
GG vs AG		0.83 (0.50–1.39)	.486	F	.902	0.0
GG+AG vs AA		1.01 (0.84–1.22)	.905	F	.160	42.0
GG vs GA+AA		0.85 (0.52–1.39)	.520	F	.789	0.0

CI = confidence interval, F = fixed-effects model, OR = odds ratios, R = random-effects model.

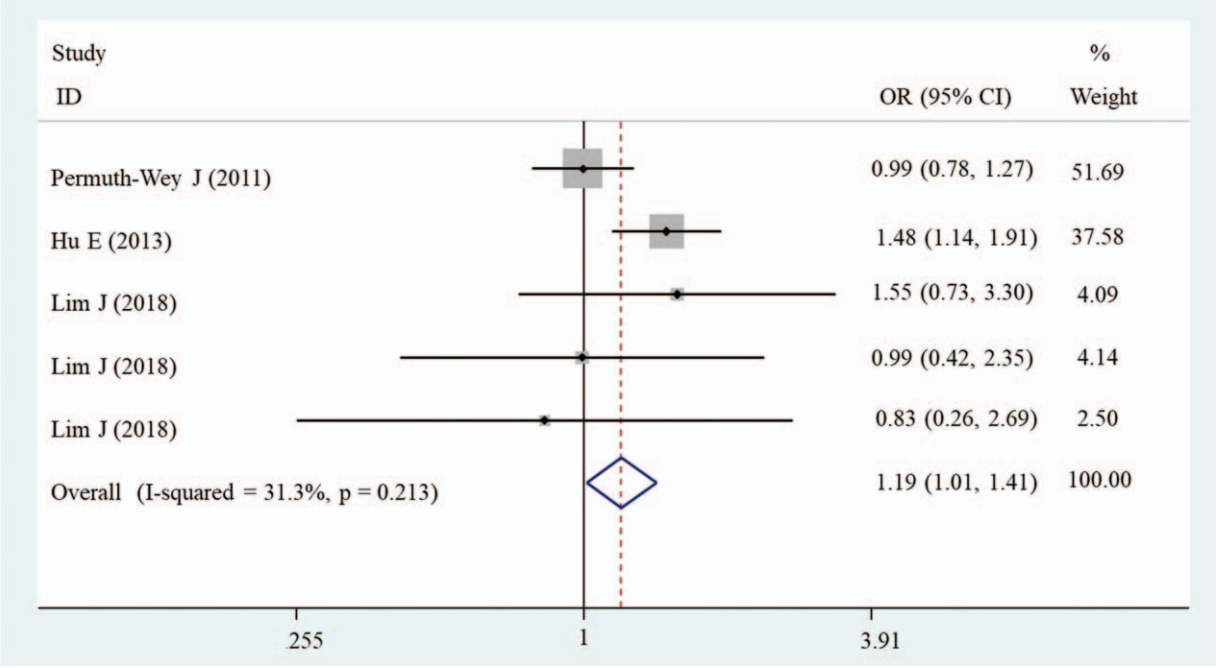

Figure 2. Forest plots of the association of miR-146a polymorphism (rs2910164) and brain tumor risk under GG vs GC model. CI = confidence interval, OR = odds ratio.

Table 5

Meta-analysis results of glioma.

Comparison	Qualified studies	Test of association			Test of heterogeneity	
		OR (95%CI)	*P* value	Model	*P* value	I^2 (%)
miR-146a (G>C)						
G vs C	3	1.06 (0.76–1.48)	.743	R	.001	86.0
GG vs CC		1.03 (0.42–2.49)	.439	R	.000	89.5
GG vs GC		1.25 (0.91–1.72)	.171	R	.010	78.5
GC vs CC		0.80 (0.46–1.40)	.437	R	.073	61.8
GG+GC vs CC		0.87 (0.46–1.63)	.653	R	.001	85.2
GG vs GC+CC		1.23 (0.79–1.90)	.363	R	.004	81.7
miR-149 (T>C)						
T vs C	2	0.82 (0.47–1.41)	.468	R	.010	85.1
TT vs CC		0.69 (0.23–2.07)	.502	R	.018	82.1
TC vs CC		1.00 (0.72–1.40)	.980	F	.208	36.9
TT vs TC		0.84 (0.51–1.39)	.501	R	.087	65.8
T+TC vs CC		0.78 (0.34–1.81)	.561	R	.054	73.2
TT vs TC+CC		0.79 (0.42–1.49)	.469	R	.027	79.6
miR-196a (T>C)						
T vs C	4	0.99 (0.82–1.21)	.943	R	.029	66.8
TT vs CC		1.00 (0.65–1.55)	.999	R	.019	69.9
TC vs TT		0.88 (0.75–1.04)	.139	F	.831	0.0
TC vs CC		1.13 (0.73–1.75)	.594	R	.001	81.4
TT+TC vs CC		1.09 (0.72–1.67)	.686	R	.001	81.8
TT vs TC+CC		0.88 (0.76–1.04)	.126	F	.769	0.0
Glioma subtype						
Glioblastoma						
T vs C	2	1.10 (0.90–1.35)	.346	F	.407	0.0
Others						
T vs C	2	1.03 (0.85–1.25)	.772	F	.424	0.0
Country						
Chinese						
T vs C	2	0.92 (0.71–1.19)	.505	R	.016	82.9
TT vs CC		0.87 (0.48–1.56)	.629	R	.007	86.3
TC vs TT		1.15 (0.96–1.37)	.126	F	.407	0.0
TC vs CC		0.99 (0.48–2.07)	.987	R	.000	92.7
TT+TC vs CC		0.94 (0.48–1.86)	.865	R	.000	92.4
TT vs TC+CC		0.86 (0.73–1.02)	.081	F	.645	0.0
Other	2					
T vs C		1.15 (0.90–1.47)	.263	R	.589	0.0
TT vs CC		1.35 (0.75–2.42)	.314	R	.464	0.0
TC vs TT		0.97 (0.59–1.61)	.919	F	.888	0.0
TC vs CC		1.27 (0.88–1.83)	.203	R	.396	0.0
TT+TC vs CC		1.26 (0.89–1.80)	.197	R	.363	0.0
TT vs TC+CC		1.10 (0.68–1.78)	.711	F	.789	0.0
miR-499 (A > G)						
G vs A	2	0.88 (0.51–1.50)	.631	R	.043	75.5
GG vs AA		0.95 (0.56–1.60)	.833	F	.479	0.0
GA vs AA		0.86 (0.44–1.71)	.674	R	.032	78.2
GG vs AG		0.89 (0.51–1.54)	.668	F	.918	0.0
GG+AG vs AA		0.85 (0.43–1.67)	.643	R	.029	79.1
GG vs GA+AA		0.91 (0.54–1.54)	.737	F	.544	0.0

CI = confidence interval, F = fixed-effects model, OR = odds ratios, R = random-effects model.

4. Discussion

Our current study, for the first time, investigated the association of miRNA polymorphisms with the risk of brain tumors based on 5 case–control studies. The pooled results indicated that the subjects carrying GG genotype of miR-146a had a higher risk of developing brain tumors compared with GC genotype carriers (OR = 1.19, $P = .036$). No significant associations were observed between the SNPs of miR-196a2, miR-499 and miR-149, and the risk of brain tumors or glioma alone.

There have meta-analysis studies to focus on the associations of miRNA polymorphisms with the risk of other cancers. For example, the study of Wang et al showed the C allele of miR-146a rs2910164 was a protective factor of urological cancers (C vs G: OR = 0.87, $P < .01$; GC vs GG: OR = 0.81, $P < .01$; CC vs GG: OR = 0.73, $P < .01$; CC + GC vs GG: OR = 0.80, $P < .01$; CC vs GC + GG: OR = 0.87, $P < .02$), especially for bladder cancer.[17] Mi et al identified the rs2910164 CC genotype of miR-146a polymorphism was associated with decreased prostate cancer

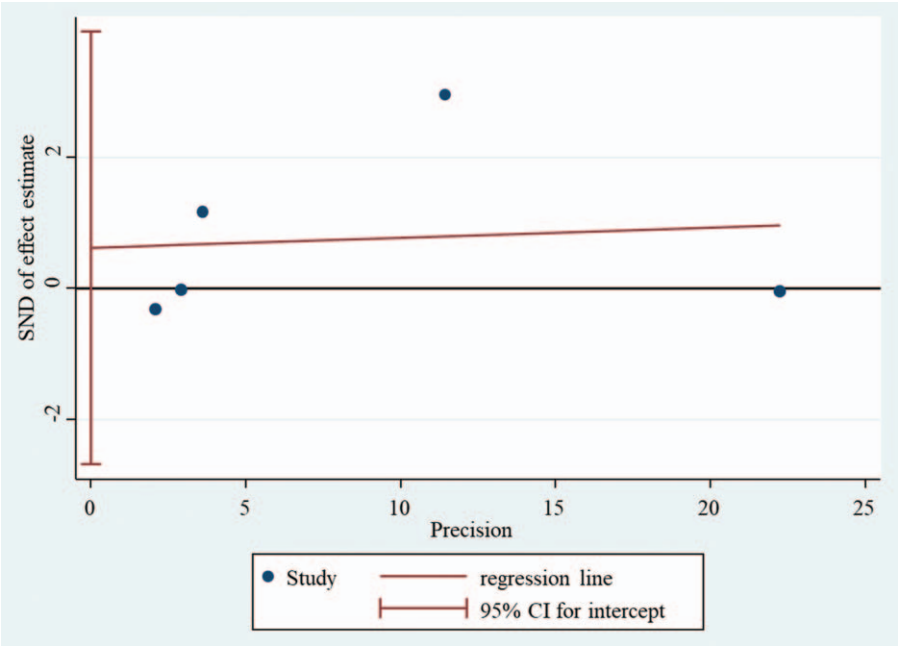

Figure 3. Egger funnel plot assessing evidence of potential publication bias of miR-146a polymorphism (rs2910164) and brain tumor risk under GG vs GC model. CI = confidence interval, SND = standard normal deviation.

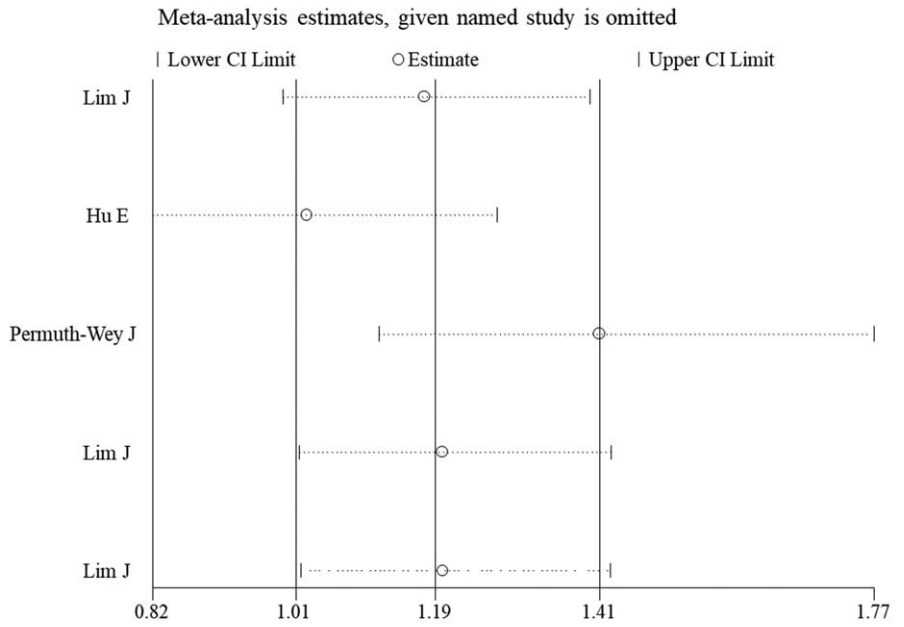

Figure 4. Sensitivity analysis for the assessment of influence of each study for miR-146a polymorphism (rs2910164) and brain tumor risk under GG vs GC model. CI = confidence interval.

risk in Asian population in homozygote comparison (OR = 0.64, $P = .04$).[18] Tian et al also found miR-146a rs2910164 increased hepatitis virus-related hepatocellular cancer risk in overall analysis under G vs C (OR = 1.13, $P = .006$), GG vs CC (OR = 1.28, $P = .01$), CG vs CC (OR = 1.20, $P = .01$) and CG + GG vs CC (OR = 1.22, $P = .004$) models.[19] All these studies suggested the allele G or genotype with G of miR-146a may be a risk factor for cancers. In line with these studies, we also confirmed GC genotype may contribute to an elevated risk of brain tumors.

miRNA SNP rs2910164 is located in the 3p strand of miR-146a. This G-C polymorphism leads to a mispairing in the hairpin of miR-146a precursor, which may subsequently

influence the production of mature miR-146a. Thus, miRNA SNP rs2910164 may be involved in cancer development (including brain tumors) by changing the expression of miR-146a itself and its target genes. This hypothesis has been validated in several cancers. For example, Iguchi et al observed colorectal cancer cell lines with the pre-miR-146a GG genotype exhibited significantly lower expression of miR-146a compared with those with the GC/CC genotype.[20] Yamashita et al proved proliferation, migration, and invasion abilities were significantly higher in human melanoma cell lines with the G allele than those with the C allele.[21] The study of Wang et al showed that individuals carrying the C allele had increased expression levels of miR-146a compared with those carrying the G allele. Further functional analysis revealed that miR-146a rs2910164 C allele inhibited the proliferation of bladder cancer cells by downregulating the expression of IRAK1 and TRAF6.[22] The GC and GG genotypes were also found to be associated with a higher risk of recurrence and a poorer survival rate compared with the CC genotype.[22,23] These findings seemed to be in accordance with the tumor suppressor roles of miR-146b-5p in brain tumors.[7–9] However, the functions of miR-146b-5p rs2910164 remain not well understood. Even, some showed the miR-146a was high expressed, while its target genes[24] was low expressed in the GG/GC group compared with that of the CC genotype group,[25–27] indicating the proto-oncogene functions of miR-146a for carcinogenesis, which seemed also to be observed in glioblastoma.[28] Accordingly, further investigation should be performed to confirm the association of miR-146a SNPs and the risk of brain tumors and their roles.

There are several limitations in this meta-analysis. First is the small sample size. This may be an underlying cause to result in negative associations between variants in miR-196a2, miR-499 and miR-149, and susceptibility to brain tumors or glioma subgroup. Furthermore, it may be also the reason not to confirm the association of miR-146a polymorphism with the specific type of brain tumors. The SNPs in the miR-146a do not show any statistical difference in the risk of acquiring glioma brain tumors (which is an important negative finding), while the risk of acquiring non-glioma brain tumors specifically schwannomas and meningiomas remains inconclusive due to low statistical power and analysis of only 1 study. Second is the lack of original data (such as genotype for subgroup analysis,[14] gene-to-gene, and gene-to-environment interactions) in eligible studies and some related analyses may be impossibly performed. Third, most studies included in this meta-analysis were from Asia and only 1 study was based on Caucasian descendants. Thus, the ethnic difference could not be investigated. Fourth, exclusion of papers published in languages other than English and Chinese may give some bias for our results. Hereby, more papers with large sample sizes and well data displayed were required to further confirm the associations between miRNA gene polymorphisms and brain tumor risk in the future.

In conclusion, our study suggests that miR-146a polymorphism may modify the risk for brain tumors, but which type of brain tumors should be verified with large sample size.

Author contributions

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