Associations of *miR-146a*C>G, *miR-149*C>T, *miR-196a2*C>T and *miR-499*A>G polymorphisms with brain tumors

JAEJOON LIM[1*], JUNG OH KIM[2*], HAN SUNG PARK[2], IN BO HAN[1], KYUBUM KWACK[2], NAM KEUN KIM[2] and KYUNGGI CHO[1]

[1]Department of Neurosurgery, CHA University, CHA Bundang Medical Center, Seongnam 134-96; [2]Department of Biomedical Science, College of Life Science, CHA University, Seongnam 134-88, Republic of Korea

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Abstract. MicroRNAs (miRNAs/miRs) are short, non-coding RNAs that are implicated in tumorigenesis, functioning as tumor suppressors and oncogenes. However, the clinical significance of miRNA expression profiles for brain tumors remains unclear. Therefore, the present study was designed to investigate the associations between miRNA genetic variants and brain tumor risk. A total 362 participants were recruited, including 179 who were healthy subjects and 183 who were patients with brain tumors confirmed as gliomas, meningiomas or schwannomas. This study investigated the single nucleotide polymorphisms *miR-146a*C>G, *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G by polymerase chain reaction-restriction fragment length polymorphism. It was found that the dominant *miR-149* and CC genotypes were significantly more frequent in patients with glioma. The odds ratios for the C-C-C-G, C-T-C-G and G-C-T-G haplotypes (*miR-146a*C>G-*miR-149*T>C-*miR-196a2*T>C-*miR-499*A>G) were significantly increased in glioma, as were the odds ratios for the GCT haplotype of *miR-146a*C>G, *miR-149*T>C and *miR-196a2*T>C, and for the C-C-G haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G. In meningioma, the odds ratios were increased in the G-T-C-G haplotype of *miR-146a*C>G, *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G. The odds ratios were also increased in the G-C-G haplotype of *miR-146a*C>G, *miR-196a2*T>C and *miR-499*A>G, and in the C-C-G haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G. The odds ratios for schwannoma were increased in the G-C-T-G haplotype of *miR-146a*C>G, *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G, and in the C-C-G haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G. In conclusion, these results suggested that the miR-149 polymorphism may be involved in the development of gliomas, and the C-C-G haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G showed increased odds ratios for all types of brain tumors.

Correspondence to: Professor Nam Keun Kim, Department of Biomedical Science, College of Life Science, CHA University, 335 Pangyo-ro, Bundang, Seongnam 134-88, Republic of Korea
E-mail: nkkim@cha.ac.kr

Professor Kyunggi Cho, Department of Neurosurgery, Bundang CHA Medical Center, CHA University College of Medicine, Yatap-ro 59, Seongnam 134-96, Republic of Korea
E-mail: sandori50@gmail.com

*Contributed equally

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Introduction

MicroRNAs (miRNAs/miRs) regulate mRNA expression through RNA interference and are known to be associated with various diseases (1-3). Abnormal miRNA expression is a well-known and crucial factor that is associated with the initiation and progression of various tumors, including brain tumors and breast cancer (1,4,5). The term brain tumor describes an inhomogeneous collection of tumors of the brain, which can be either malignant or benign and either originate in the central nervous system or represent metastases from other tumors (4,6). Among these various types of brain tumors, studies have been conducted on miRNAs in gliomas, meningiomas and schwannomas (6-10). Notably, certain previous studies have focused on the expression profiles of miRNAs in cancerous tissues and their associations with target genes involved in cancer cell formation and metastasis.

Abnormal expression of miRNAs in glioma tissues was previously reported, and miRNAs, including *miR-34a*, *146a*, *7*, *128* and *195*, were downregulated in cancer tissues compared with those in normal tissues, suggesting dysregulation of tumor suppressor genes (6). However, the expression of certain miRNAs (*miR-21*, *26a*, *10b*, *30e* and *221/222*) was increased, suggesting that miRNAs act not only as tumor suppressors, but also, dependent on the function of the targeted mRNA, as oncogenes (6,7). The miRNA expression profiling of meningiomas has shown a reduction in *miR-29c* and *miR-219* depending on the tumor grade and has indicated that high expression of *miR-190a* in meningiomas correlates with tumorigenic risk. In addition, the expression pattern of *miR-190a* is a prognostic predictor of postoperative outcome (8). In addition, the expression patterns of miRNAs, including *miR-200a* and *miR-145*, are reportedly associated with the progression of meningiomas (9).

A schwannoma study also showed altered miRNA expression patterns in tumor tissues, with 8 miRNAs showing increased expression and 4 miRNAs showing decreased expression in tumor tissues compared with that in normal tissues (10).

Numerous studies have found a correlation between *miR-146a*, *149*, *196a2* and *499* and tumorigenesis and tumor suppression. These miRNAs are associated with tumor initiation, invasion, metastasis and proliferation through a variety of mechanisms, and can also function as tumor suppressor genes (4,11-13). Thus, previous studies of miRNA have focused on miRNA regulation and its influence on tumorigenesis. Nevertheless, the reasons for the widespread differential expression of miRNAs in malignant cells compared with that in normal cells are not fully elucidated.

Previous studies have reported miRNA polymorphisms in various cancer types. miRNA single nucleotide polymorphisms (SNPs) have been found to be associated with carcinogenesis, progression, development and prognosis (14,15). SNPs are known to affect miRNA expression and maturation (16). *miR-146a*C>G,*miR-149*C>T,*miR-196a2*C>T and *miR-499*A>G are well-known miRNA SNPs, and among these, three variants (*miR-146a*C>G, *miR-196a2*C>T and *miR-499*A>G) are located in the mature form of the sequence, and the remaining variant (*miR-149*C>T) is located in the precursor form of the sequence. A previous study (14) reported that increased expression of the *miR-196a2*C>T polymorphism was associated with a decreased survival rate in patients with lung cancer. In addition, other studies have reported significant associations between the *miR-196a2*C>T polymorphism and the prevalence of various cancer types and heart disease (17-22). Furthermore, previous studies have suggested that *miR-146a*C>G, *miR-149*C>T and *miR-499*A>G variants are associated with heart disease and esophageal cancer (18,19,22).

Recently, reports have found an association between miRNAs and brain tumors. However, the function of miRNA polymorphisms in brain tumors is unclear in terms of the pathogenesis, and the majority of studies have been limited to specific tumors. The results of these studies have been inconsistent (11,14-24). Thus, the present study sought to investigate the frequency of four miRNA polymorphisms (*146a*C>G, *149*C>T, *196a*C>T and *499*A>G) in brain tumors, specifically gliomas, meningiomas and schwannomas.

Materials and methods

Study population. A total of 362 patients were enrolled, including 179 with brain tumors and 183 healthy controls. Patients with brain tumors were diagnosed through imaging examinations, including computed tomography and magnetic resonance imaging, and were confirmed to have gliomas, meningiomas or schwannomas through histopathological studies following surgical resection. Adults who underwent a general health care examination at CHA Bundang Hospital (Seongnam, South Korea) and who had no history of tumors, brain diseases, including Alzheimer's disease, dementia, stroke or intracerebral hemorrhage, or other underlying diseases were selected for the control group. All study participants were fully informed and received an explanation of the study, and provided written informed consent; individuals who did not agree to the study were excluded.

Genetic analysis. Genomic DNA was extracted using the G-DEX blood kit (iNtRON Biotechnology, Inc., Seongnam, South Korea) from anticoagulated peripheral blood, as previously described (25). The four miRNA polymorphisms of interest (*miR-146a*, *149*, *196a2* and *499*) were identified by a literature search using the key words 'miRNA' and 'brain tumor' in Pubmed (https://www.ncbi.nlm.nih.gov/pubmed). The genotype examination conditions outlined in our previous study protocol were used (25). Samples underwent re-genotyping examination by an additional operator for confirmation. In addition, 20% of the total samples were randomly selected and the four miRNA polymorphisms were confirmed by sequencing (ABI3730xl DNA analyzer; Applied Biosystem; Thermo Fisher Scientific, Inc., Waltham, MA, USA). PCR was performed with conditions and primer and probe sequences as detailed in our previous study (25).

Statistical analysis. The genotype and allele frequencies for miRNA polymorphisms in the patients with brain tumors and the controls were determined. The differences in the genotypes and allele frequencies were analyzed using the χ^2 test and Fisher's exact test, respectively. Allelic frequencies included calculated deviations based on the Hardy-Weinberg equilibrium, using $P<0.05$ as a threshold (26). As the inferences of the present study were derived from multiple tests, the Benjamini and Hochberg strategy was adopted, which effectively reduced the potential impact of spurious significant results (27). Statistical analyses were performed that measured the efficacy of the association between brain tumor and genotype based on multivariable logistic regression and according to the statistical methods discussed by Kim and Hong (28). The multifactor dimensionality reduction method has been described in detail previously (29-33). In addition, all possible allele-allelic combinations were performed using HAPSTAT software (v.3.0; www.bios.unc.edu/~lin/hapstat/). Survival analysis estimated the adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs), with adjustment for age by multivariate Cox proportion hazards regression.

Results

Participant characteristics. A total of 362 participants whose aged from 21 to 85 years were enrolled in the present study, including 183 healthy controls (age range, 24-85 years) and 179 patients (age range, 21-78 years) with brain tumors. In the brain tumor group, 79 patients had gliomas, 69 had meningiomas and 31 had schwannomas. The male:female ratio for all participants was 1:1.48 (1:1.88 for the control group and 1:1.16 for the brain tumor group). The mean age of all participants was 48.8±15.9 years (control group mean, 45.9±16.6 years; brain tumor group mean, 51.9±14.7 years) (Table I).

Genetic analysis. The *miR-146a* rs2910164, *miR-149* rs4846049, *miR-196a2* rs11614913 and *miR-499* rs3746444 polymorphisms were compared between the brain tumor and control groups. Participant genotype and allelic frequencies of the four miRNA polymorphisms are detailed in Table II. Analysis by tumor type found that the frequencies of the dominant *miR-149* genotype [odds ratio (OR), 1.842; 95% CI, 1.074-3.159; P=0.02] and CC type of *miR-149* (OR, 2.771; 95% CI, 1.158-6.635;

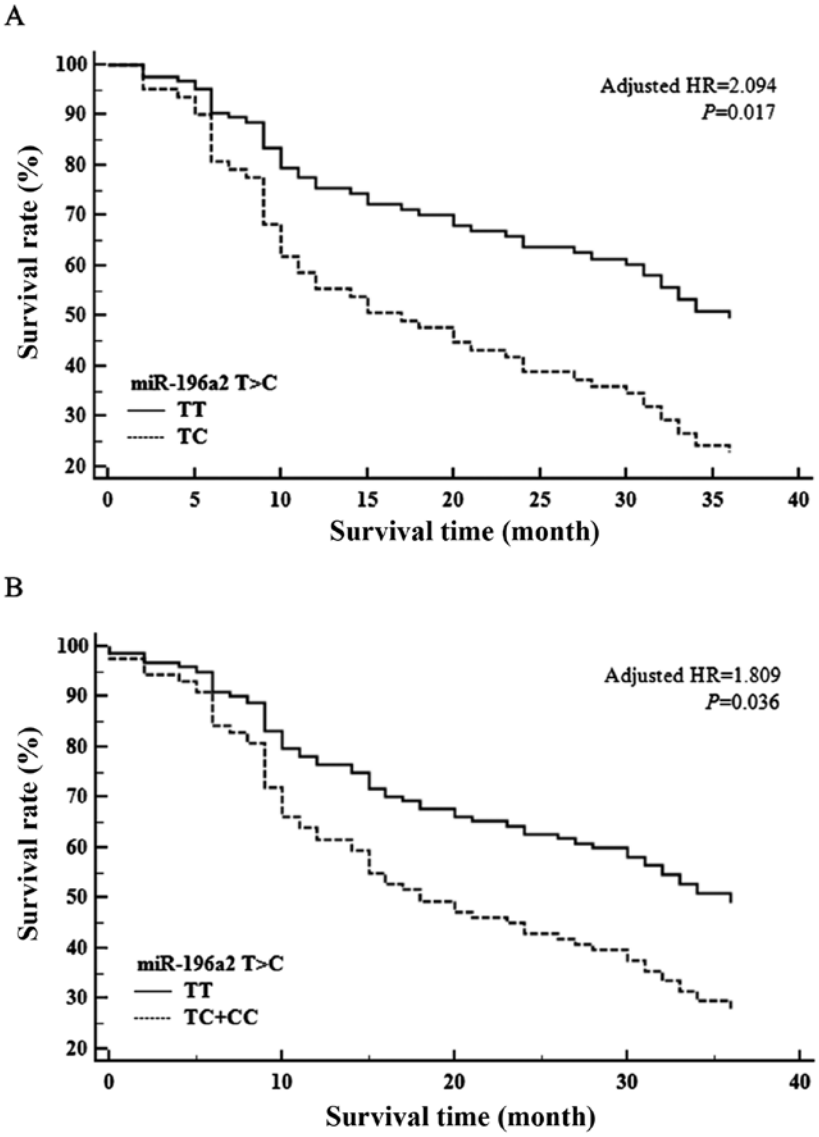

Figure 1. Survival analysis for the *miR-196a2* polymorphism in patients with brain tumors. OS was analyzed by Cox proportional-hazards regression for the patients with brain tumors based on *miR-196a2* genotype. (A) OS curve of patients with *miR-196a2* TT vs. TC genotype. (B) OS curve of patients with *miR-196a2* TT vs. TC+CC genotype. miRNA/miR, microRNA; HR, hazard ratio; OS, overall survival.

P=0.02) were significantly increased compared with those of the TT and TC genotypes for gliomas. The frequencies of the *miR-146a*, *miR-149*, *miR-196a2* and *miR-499* genotypes were not significantly different between the control group and the meningioma or schwannoma patient groups.

Allele combination analysis according to subgroup. ORs for gliomas, meningiomas and schwannomas are detailed in Tables III, IV and V, respectively. The ORs for glioma were increased in the following combinations: i) CCCG, CTCG and GCTG haplotypes of *miR-146a*C>G, *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G; ii) GCT haplotype of *miR-146a*C>G, *miR-149*T>C and *miR-196a2*T>C; iii) CCG haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G; iv) GC haplotype of *miR-146a*C>G and *miR-149*T>C; and v) CA haplotype of *miR-149*T>C and *miR-499*A>G (Table III). For meningiomas, the ORs were increased in the following combinations: i) GTCG haplotype of *miR-146a*C>G, *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G; ii) GCG haplotype of *miR-146a*C>G, *miR-196a2*T>C and *miR-499*A>G; and iii) CCG haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G (Table IV). The ORs for schwannomas were increased in the following combinations: i) GCTG haplotype of *miR-146a*C>G, *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G; and ii) CCG haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G (Table V).

Multivariate survival analysis according to genotypes. Fig. 1 shows the association between the overall survival (OS) of patients with brain tumors and the four pre-miRNA SNPs. No significant association was found between OS and *miR-146a*, *miR-149* or *miR-499*; however, *miR-196a2*T>C was associated with a significantly shorter OS time (adjusted HR, 2.094; 95% CI, 1.147-3.823; P=0.017; Fig. 1). Additionally, when OS was analyzed according to the dominant genotype (TT vs. TC+CC), a poorer OS time was associated with the *miR-196a2* C allele (HR, 1.809; 95% CI, 1.043-3.137; P=0.036; Fig. 1).

Table I. Demographic characteristics of patients with brain tumor and control subjects.

Characteristics	Control (n=183)	Brain tumor (n=179)
Sex (male:female)	1:1.88	1:1.16
Age, years (mean ± SD)	45.9±16.6	51.9±14.7
Hypertension, n	-	43
Diabetes mellitus, n	-	21
FBS, mg/dl (mean ± SD)	-	168.0±70.8
Dyslipidemia, n	-	21
T. chol, mg/dl (mean ± SD)	-	197.9±57.3
Triglyceride, mg/dl (mean ± SD)	-	153.9±145.5
HDL-C, mg/dl (mean ± SD)	-	46.4±16.0
LDL-C, mg/dl (mean ± SD)	-	106.5±43.9
BUN, mg/dl (mean ± SD)	-	22.3±19.7
Creatinine, mg/dl (mean ± SD)	-	0.8±0.5
Platelets, 10^3 cell/μl (mean ± SD)	-	346.5±854.0
Antithrombin, % (mean ± SD)	-	85.2±27.5
aPTT, sec (mean ± SD)	-	34.2±21.5
Prothrombin time, sec (mean ± SD)	-	12.5±2.7
D-dimer, ng/ml (mean ± SD)	-	2925.8±2907.5
Fibrinogen, mg/dl (mean ± SD)	-	477.8±195.9
Hematocrit, % (mean ± SD)	-	28.9±6.1
Hemoglobin, mg/dl (mean ± SD)	-	9.5±2.6

FBS, fasting blood sugar; T. chol, total cholesterol; HDL-C, high dendity lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BUN, blood urea nitrogen; aPTT, activated partial thromboplastin time; SD, standard deviation.

Discussion

Brain tumors can cause severe impairment and impose a decreased quality of life, often resulting in mortality (34,35). The overall incidence rate of all brain tumors is 10.82 per 100,000 person-years (36). In the 2013 Central Brain Tumor Registry of the United States report, the average annual age-adjusted incidence rate of glioblastoma was 3.19 per 100,000 individuals, which was the highest incidence among all types of brain and central nervous system (CNS) tumors. Meningioma is the second most common type of brain tumor (37). Sex and age standardized incidence rates range from 1.28 per 100,000 individuals to 7.80 per 100,000 individuals for cerebral meningioma. The overall incidence rate of schwannomas was 1.2 per 100,000 individuals per year in the United States in the period between 2004 and 2009 (38).

Studies on the pathogenesis of brain tumors are ongoing. For several decades, studies have identified molecular alterations characterizing gliomas and reported decreased expression of tumor suppressor genes, such as retinoblastoma transcriptional corepressor 1 and p53, or alterations of genes in pathways associated with tumor suppressors (39). In addition, genetic variants, including isocitrate dehydrogenase 1 and phosphatase and tensin homolog (PTEN), have been reported in gliomas (40-42). Chromosomal anomalies, aberrant cellular pathways and alterations in tumor suppressor genes are associated with meningioma pathogenesis (43-46). Schwannomas are directly associated with genetic changes in neurofibromin 2 gene inactivation (47). However, no clear mechanism of the pathogenesis for all brain tumors has been identified.

miRNAs regulate target gene expression at the post-transcriptional level. miRNAs control key physiological processes, including cell growth, differentiation and apoptosis, which suggests that miRNA gene abnormality could be involved in tumorigenesis (1-3,48). The correlation between cancer and miRNAs was established in 2002 (49). Certain miRNA abnormalities have been associated with cancer types, and with carcinogenesis and progression (1,3-5). The results reported in the present study suggest that identifying miRNAs and their targets may provide potential diagnostic and prognostic tumor biomarkers and novel cancer therapeutic strategies. Studies of miRNAs associated with brain tumors are ongoing. miRNAs are associated with regulation of tumorigenic cells in CNS tumors, and certain miRNAs are oncogenes (4,50,51). miRNAs also regulate tumor invasion, metastasis and cell apoptosis, and are involved in tumor chemoresistance and radioresistance (52-54).

Recent epidemiological studies have demonstrated that miRNA variants cause altered expression and are associated with the risk of cancer (55). For example, miRNA-146a antagonizes the expression of interleukin (IL)-1β, tumor necrosis factor-α and nuclear factor-κB (56). *miR-146a* is known to be important for tumor proliferation and metastatic ability (23). In addition, certain studies have suggested that miR-196a dysfunction is associated with tumor abnormality (13). m*iR-196a2* has a double mature strand containing a 5'-end strand (*hsa-miR-196a2-5p*) and a 3'-end strand (*hsa-miR-196a2-3p*), and the *miR-196a2* rs11614913 T>C polymorphism is located in the hsa-miR-196a-3p sequence. The rs11612913 SNP may influence the maturation of *hsa-miR-196a*. In other words, this polymorphism may affect or alter the expression of the target, which may be involved in regulating carcinogenesis. Several studies have identified *miR-499*A>G as a potential marker for a number of cancer types, including breast cancer, gastric cancer, squamous cell carcinoma and hepatocellular carcinoma (11,14,24). The *miR-499* rs3746444 A>G polymorphism is located in the stem loop. To date, few studies have investigated rs2292932 in *miR-149* compared with the three other genes. Li *et al* (12) suggested that *miR-149* inhibits associated fibroblasts by regulating prostaglandin E2 and IL-6 in tumor cells (12).

The present study identified the genotypic distribution of the four most common miRNAs associated with tumors (i.e., *miR-146a*, *miR-149*, *miR-196a2* and *miR-499*) in patients with glioma, meningioma or schwannoma. In this Korean population, the frequencies of the dominant *miR-149* genotype and the CC genotype were significantly increased compared with those of the TT and TC genotypes in the patients with glioma. However, the frequency of the *miR-146a* rs2910164 C>G, *196a2* rs11614913 T>C and *499* rs3746444 A>G polymorphisms were not significantly different between the control group and the tumor group. To date, there have been considerably fewer studies on *miR-149* than on other miRNAs,

Table II. Genotype frequencies of miRNA polymorphisms between patients with three different brain tumor subtypes [glioma (n=79), meningioma (n=69) and schwannoma (n=31)] and control subjects (n=183).

Genotypes	Controls, n (%)	Glioma					Meningioma					Schwannoma				
		n (%)	AOR (95% CI)	P-value[a]	FDR-P-value	Statistical power, %	n (%)	AOR (95% CI)	P-value[a]	FDR-P-value	Statistical power, %	n (%)	AOR (95% CI)	P-value[a]	FDR-P-value	Statistical power, %
*miR-146a*C>G																
CC	70 (38.3)	30 (38.0)	1.000 (reference)				28 (40.6)	1.000 (reference)				10 (32.3)	1.000 (reference)			
CG	88 (48.1)	34 (43.0)	0.902 (0.503-1.615)	0.727	0.969	5.1	32 (46.4)	0.909 (0.501-1.651)	0.754	0.898	5.7	17 (54.8)	1.352 (0.583-3.138)	0.482	0.749	7.6
GG	25 (13.7)	15 (19.0)	1.400 (0.648-3.023)	0.392	0.467	12.6	9 (13.0)	0.900 (0.374-2.168)	0.814	0.814	4.2	4 (12.9)	1.120 (0.322-3.895)	0.859	0.859	3.8
Dominant (CC vs. CG+GG)			1.012 (0.5881.742)	0.966	0.966	4.1		0.907 (0.515-1.597)	0.735	0.747	5.5		1.301 (0.579-2.924)	0.524	0.726	8.2
Recessive (CC+CG vs. GG)			1.481 (0.733-2.992)	0.273	0.364	17.5		0.948 (0.418-2.148)	0.898	0.994	3.9		0.936 (0.302-2.903)	0.909	0.909	3.0
*miR-149*T>C																
TT	97 (53.0)	30 (38.0)	1.000 (reference)				35 (50.7)	1.000 (reference)				18 (58.1)	1.000 (reference)			
TC	72 (39.3)	37 (46.8)	1.662 (0.940-2.938)	0.081	0.162	49.3	27 (39.1)	1.039 (0.578-1.870)	0.898	0.898	4.2	11 (35.5)	0.823 (0.366-1.850)	0.638	0.749	6.3
CC	14 (7.7)	12 (15.2)	2.771 (1.158-6.635)	0.022	0.088	67.4	7 (10.1)	1.386 (0.517-3.715)	0.517	0.814	8.7	2 (6.5)	0.770 (0.161-3.681)	0.743	0.859	1.8
Dominant (TT vs. TC+CC)			1.842 (1.074-3.159)	0.026	0.104	68.1		1.096 (0.630-1.907)	0.747	0.747	5.9		0.815 (0.377-1.760)	0.602	0.726	5.9
Recessive (TT+TC vs. CC)			2.162 (0.951-4.916)	0.066	0.264	48.8		1.363 (0.526-3.534)	0.524	0.994	8.6		0.833 (0.180-3.857)	0.815	0.909	1.9
*miR-196a2*T>C																
TT	46 (25.1)	22 (27.8)	1.000 (reference)				20 (29.0)	1.000 (reference)				10 (32.3)	1.000 (reference)			
TC	92 (50.3)	44 (55.7)	1.000 (0.537-1.863)	1.000	1.000	4.1	32 (46.4)	0.800 (0.413-1.550)	0.508	0.898	8.9	15 (48.4)	0.750 (0.313-1.799)	0.519	0.749	8.9
CC	45 (24.6)	13 (16.5)	0.604 (0.272-1.344)	0.216	0.432	22.6	17 (24.6)	0.869 (0.404-1.869)	0.719	0.814	4.6	6 (19.4)	0.613 (0.206-1.829)	0.380	0.859	9.6
Dominant (TT vs. TC+CC)			0.870 (0.480-1.577)	0.646	0.861	6.4		0.823 (0.443-1.526)	0.536	0.747	8.6		0.705 (0.309-1.607)	0.406	0.726	12.0
Recessive (TT+TC vs. CC)			0.604 (0.305-1.196)	0.148	0.296	27.4		1.003 (0.527-1.907)	0.994	0.994	4.1		0.736 (0.284-1.908)	0.528	0.909	6.1
*miR-499*A>G																
AA	112 (61.2)	58 (73.4)	1.000 (reference)				44 (63.8)	1.000 (reference)				20 (64.5)	1.000 (reference)			
AG	64 (35.0)	19 (24.1)	0.573 (0.314-1.047)	0.070	0.162	42.1	24 (34.8)	0.955 (0.532-1.713)	0.876	0.898	4.3	10 (32.3)	0.875 (0.386-1.985)	0.749	0.749	4.6

Table II. Continued.

Genotypes	Controls, n (%)	Glioma					Meningioma					Schwannoma				
		n (%)	AOR (95% CI)	P-value[a]	FDR-P-value	Statistical power, %	n (%)	AOR (95% CI)	P-value[a]	FDR-P-value	Statistical power, %	n (%)	AOR (95% CI)	P-value[a]	FDR-P-value	Statistical power, %
GG	7 (3.8)	2 (2.5)	0.552 (0.111-2.741)	0.467	0.467	4.4	1 (1.4)	0.364 (0.044-3.042)	0.351	0.814	3.5	1 (3.2)	0.800 (0.093-6.858)	0.839	0.859	1.3
Dominant (AA vs. AG+GG)			0.571 (0.320-1.021)	0.059	0.118	45.2		0.896 (0.505-1.591)	0.708	0.747	5.5		0.868 (0.392-1.919)	0.726	0.726	5.4
Recessive (AA+AG vs. G)			0.653 (0.133-3.216)	0.600	0.600	2.9		0.370 (0.045-3.062)	0.356	0.994	3.6		0.838 (0.100-7.058)	0.871	0.909	1.4

[a]Adjusted for age. AOR, adjusted odds ratio; CI, confidence interval; miR/miRNA, microRNA; FDR, false discovery rate.

particularly concerning the association of *miR-149* with brain tumors. One previous study of the association between *miR-149* and brain tumors reported that increased *miR-149* levels downregulate tumor proliferation and metastasis in glioblastoma (57). *miR-149* regulates cell cycle-related genes and controls potential proliferation and invasion activity of glioma cells through a mechanism that induces arrest at the G_0/G_1 phase (58). However, the manner in which miRNAs affect tumorigenesis or suppression of brain tumors is not yet known, and the results differ by study and participant ethnicity. Analysis of haplotype frequencies according to brain tumor type showed that odds ratios were higher in certain haplotypes in the present study. In particular, the GCTG haplotype of *miR-146a*C>G, *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G had increased the ORs for gliomas and schwannomas. The CCG haplotype of *miR-149*T>C, *miR-196a2*T>C and *miR-499*A>G showed increased ORs for all three types of brain tumors. However, the mechanism by which certain haplotypes simultaneously increase the risk for various tumors has not been determined.

The *miR-196a2* rs11614913C allele has been reported to be associated with the risk of various cancer types in several studies. Hu *et al* (14) showed that the *miR-196a2* rs11614913C allele was associated with a significant risk of breast cancer. In addition, Tian *et al* (17) demonstrated that the *miR-196a2* rs11614913 CC type posed a significant risk of lung cancer in Chinese individuals. Moreover, several studies suggested the association of the *miR-196a2*C allele with an elevated risk of various cancer types, including hepatoma, gastric cancer and esophageal squamous cell carcinoma (20-22). To date, there have been only two reports on the effects of an association between *miR-196a2* and brain tumor prognosis (59,60). The present study showed that the *miR-196a2*T>C polymorphism was a significant factor for mortality in Korean patients with brain tumors. However, as the survival analysis included the entire brain tumor group, care must be taken when interpreting these results.

The present study had several limitations. First, the way in which miRNA genetic variants affect brain tumor progression remains unclear. Second, in this study, the expression patterns of the four miRNAs in gliomas, meningiomas and schwannomas samples could not be identified as the biopsy samples were in poor condition and the number of tissue samples was insufficient. Therefore, the acquisition of tissue samples is currently being attempted and further studies are being planned. Third, the sample size of this study is limited in number. Lastly, the analysis was performed in a solely Korean population. Although the results present the first evidence for utilization of miRNA polymorphisms as diagnostic and prognostic markers of brain tumor risk, further research in large and diverse cohorts is necessary. Based on the results from this study, a future large-population study is required to identify the association between brain tumors and miRNAs beyond the four miRNAs tested here. In addition, the expression patterns of miRNAs in brain tumors and normal tissues require further study, as does the function of cultured cell lines derived from brain tumors, including gliomas, meningiomas and schwannomas. Additional studies will also be necessary to determine the mechanism by which miRNAs affect carcinogenesis and tumor progression. In conclusion, the

Table III. Allele combination of miRNA polymorphisms between glioma patients (2n=158) and control subjects (2n=366).

Allele combination	Controls, n (%)	Glioma, n (%)	Reference vs. Allele combination			Overall vs. Allele combination		
			OR (95% CI)	P-value[a]	FDR-P-value	OR (95% CI)	P-value[a]	FDR-P-value
*miR-146a*C>G/*miR-149*T>C/*miR-196a2*T>C/*miR-499*A>G								
C-T-T-A	51 (14.0)	28 (17.8)	1.000 (reference)			1.272 (0.773-2.091)	0.361	0.525
C-T-C-G	26 (7.0)	3 (1.7)	0.210 (0.058-0.757)	0.015	0.045	0.267 (0.080-0.896)	0.021	0.048
C-C-T-G	16 (4.4)	0 (0.0)	0.055 (0.003-0.948)	0.003	0.015	0.070 (0.004-1.176)	0.005	0.020
C-C-C-G	0 (0.0)	4 (2.6)	16.260 (0.844-313.200)	0.020	0.050	20.810 (1.113-389.100)	0.009	0.024
G-T-C-A	53 (14.6)	6 (4.0)	0.206 (0.079-0.540)	0.001	0.015	0.262 (0.110-0.623)	0.001	0.008
G-T-C-G	0 (0.0)	6 (3.8)	23.490 (1.275-432.700)	0.003	0.015	30.060 (1.682-537.200)	0.001	0.008
G-C-T-A	14 (3.8)	17 (10.9)	2.212 (0.951-5.146)	0.085	0.159	2.813 (1.353-5.847)	0.008	0.024
G-C-T-G	0 (0.1)	5 (2.9)	19.880 (1.060-372.900)	0.008	0.030	25.440 (1.397-463.100)	0.003	0.016
*miR-146a*C>G/*miR-149*T>C/*miR-196a2*T>C								
C-T-T	77 (21.0)	33 (20.7)	1.000 (reference)			0.993 (0.634-1.555)	1.000	1.000
G-T-C	53 (14.5)	10 (6.5)	0.440 (0.200-0.970)	0.045	0.158	0.437 (0.217-0.881)	0.018	0.072
G-C-T	14 (3.7)	17 (10.6)	2.833 (1.252-6.412)	0.018	0.126	2.813 (1.353-5.847)	0.008	0.064
*miR-146a*C>G/*miR-149*T>C/*miR-499*A>G								
C-T-A	116 (31.8)	57 (36.1)	1.000 (reference)			1.138 (0.788-1.645)	0.507	0.579
C-T-G	51 (13.9)	9 (5.5)	0.359 (0.165-0.781)	0.008	0.056	0.409 (0.196-0.851)	0.015	0.120
*miR-146a*C>G/*miR-196a2*T>C/*miR-499*A>G								
C-T-A	81 (22.2)	45 (28.2)	1.000 (reference)			1.287 (0.855-1.938)	0.240	0.384
C-T-G	42 (11.3)	6 (3.8)	0.257 (0.102-0.652)	0.003	0.021	0.331 (0.138-0.794)	0.008	0.064
G-C-A	72 (19.8)	20 (12.7)	0.500 (0.270-0.925)	0.035	0.123	0.644 (0.379-1.093)	0.106	0.212
*miR-149*T>C/*miR-196a2*T>C/*miR-499*A>G								
T-T-A	93 (25.3)	45 (28.3)	1.000 (reference)			1.121 (0.750-1.675)	0.604	0.690
C-C-G	0 (0.0)	8 (5.0)	34.930 (1.971-619.100)	0.0002	0.001	39.310 (2.254-685.700)	<0.0001	0.001
*miR-146a*C>G/*miR-149*T>C								
C-T	167 (45.8)	66 (41.6)	1.000 (reference)			0.916 (0.651-1.287)	0.666	0.804
G-C	39 (10.8)	33 (20.8)	2.141 (1.242-3.690)	0.009	0.027	1.960 (1.189-3.231)	0.010	0.040
*miR-146a*C>G/*miR-499*A>G								
C-A	163 (44.4)	81 (51.6)	1.000 (reference)			1.151 (0.831-1.594)	0.404	0.539
C-G	65 (17.9)	13 (7.9)	0.403 (0.210-0.773)	0.006	0.018	0.463 (0.248-0.865)	0.015	0.060
*miR-149*T>C/*miR-499*A>G								
T-A	206 (56.2)	83 (52.6)	1.000 (reference)			0.933 (0.681-1.280)	0.689	0.830
C-A	82 (22.5)	52 (32.9)	1.574 (1.023-2.422)	0.044	0.132	1.469 (0.990-2.179)	0.062	0.124
*miR-196a2*T>C/*miR-499*A>G								
T-A	134 (36.7)	78 (49.3)	1.000 (reference)			1.348 (0.964-1.887)	0.082	0.164
T-G	50 (13.6)	10 (6.4)	0.344 (0.165-0.716)	0.003	0.009	0.463 (0.229-0.937)	0.034	0.136
C-A	154 (42.0)	57 (36.2)	0.636 (0.421-0.961)	0.037	0.056	0.857 (0.600-1.225)	0.421	0.561

[a]P-value calculated by Fisher's exact test. OR, odds ratio; CI, confidence interval; miR/miRNA, microRNA; FDR, false discovery rate.

Table IV. Allele combination of miRNA polymorphisms between patients with meningioma (2n=138) and control subjects (2n=366).

Allele combination	Controls, n (%)	Meningioma, n (%)	Reference vs. Allele combination			Overall vs. Allele combination		
			OR (95% CI)	P-value[a]	FDR-P-value	OR (95% CI)	P-value[a]	FDR-P-value
*miR-146a*C>G/*miR-149*T>C/*miR-196a2*T>C/*miR-499*A>G								
C-T-T-A	51 (14.0)	26 (18.7)				1.352 (0.811-2.255)	0.277	0.462
C-T-C-G	26 (7.0)	0 (0.0)	0.037 (0.002-0.626)	0.0002	0.003	0.050 (0.003-0.826)	0.0002	0.003
G-T-C-A	53 (14.6)	6 (4.7)	0.222 (0.084-0.584)	0.002	0.014	0.300 (0.126-0.714)	0.004	0.030
G-T-C-G	0 (0.0)	4 (2.8)	17.490 (0.907-337.500)	0.017	0.079	23.820 (1.273-445.600)	0.006	0.030
*miR-146a*C>G/*miR-149*T>C/*miR-196a2*T>C								
C-T-T	77 (21.0)	41 (29.5)	1.000 (reference)			1.412 (0.922-2.164)	0.115	0.308
C-T-C	89 (24.3)	23 (16.9)	0.485 (0.268-0.880)	0.019	0.112	0.685 (0.416-1.128)	0.154	0.308
C-C-T	46 (12.7)	10 (7.3)	0.408 (0.187-0.892)	0.032	0.112	0.577 (0.283-1.174)	0.151	0.308
*miR-146a*C>G/*miR-149*T>C/*miR-499*A>G								
C-T-A	116 (31.8)	54 (39.3)	1.000 (reference)			1.235 (0.846-1.801)	0.281	0.664
C-T-G	51 (13.9)	10 (7.4)	0.421 (0.199-0.893)	0.029	0.203	0.520 (0.257-1.053)	0.066	0.528
*miR-146a*C>G/*miR-196a2*T>C/*miR-499*A>G								
C-T-A	81 (22.2)	36 (25.8)	1.000 (reference)			1.179 (0.760-1.828)	0.493	0.789
G-C-G	4 (1.2)	7 (5.2)	3.938 (1.084-14.300)	0.042	0.186	4.641 (1.337-16.110)	0.014	0.112
*miR-149*T>C/*miR-196a2*T>C/*miR-499*A>G								
T-T-A	93 (25.3)	47 (34.0)	1.000 (reference)			1.340 (0.897-2.003)	0.170	0.496
C-C-G	0 (0.0)	5 (4.0)	21.650 (1.172-400.200)	0.005	0.035	29.110 (1.598-530.300)	0.002	0.016
*miR-149*T>C/*miR-196a2*T>C								
T-T	126 (34.4)	58 (41.9)	1.000 (reference)			1.221 (0.845-1.763)	0.295	0.295
T-C	140 (38.3)	39 (28.4)	0.605 (0.378-0.970)	0.044	0.096	0.739 (0.493-1.108)	0.165	0.264

[a]P-value calculated by Fisher's exact test. OR, odds ratio; CI, confidence interval; miR/miRNA, microRNA; FDR, false discovery rate.

Table V. Allele combination of miRNA polymorphisms between patients with Schwannoma (2n=62) and control subjects (2n=366).

Allele combination	Controls, n (%)	Schwannoma, n (%)	Reference vs. Allele combination			Overall vs. Allele combination		
			OR (95% CI)	P-value[a]	FDR-P-value	OR (95% CI)	P-value[a]	FDR-P-value
*miR-146a*C>G/*miR-149*T>C/*miR-196a2*T>C/*miR-499*A>G								
C-T-T-A	51 (14.0)	18 (28.6)	1.000 (reference)			2.083 (1.142-3.801)	0.021	0.135
C-T-C-A	63 (17.3)	3 (4.6)	0.135 (0.038-0.484)	0.001	0.013	0.281 (0.086-0.923)	0.029	0.135
C-C-T-G	16 (4.4)	0 (0.0)	0.084 (0.005-1.479)	0.019	0.095	0.178 (0.011-3.002)	0.144	0.504
G-T-T-A	39 (10.6)	4 (6.3)	0.291 (0.091-0.928)	0.049	0.127	0.606 (0.209-1.754)	0.490	0.858
G-C-T-A	14 (3.8)	0 (0.0)	0.096 (0.005-1.692)	0.033	0.107	0.202 (0.012-3.435)	0.235	0.632
G-C-T-G	0 (0.1)	3 (4.3)	19.490 (0.959-395.800)	0.022	0.095	41.050 (2.093-805.000)	0.003	0.042
*miR-146a*C>G/*miR-149*T>C/*miR-196a2*T>C								
C-T-T	77 (21.0)	20 (32.2)	1.000 (reference)			1.533 (0.875-2.687)	0.162	0.627
C-T-C	89 (24.3)	8 (12.5)	0.346 (0.144-0.830)	0.023	0.161	0.531 (0.245-1.148)	0.135	0.627
*miR-146a*C>G/*miR-196a2*T>C/*miR-499*A>G								
C-T-A	81 (22.2)	22 (36.0)	1.000 (reference)			1.603 (0.932-2.759)	0.098	0.302
C-C-A	81 (22.2)	7 (11.0)	0.318 (0.129-0.786)	0.014	0.084	0.510 (0.225-1.156)	0.122	0.302
G-T-A	53 (14.5)	4 (6.5)	0.278 (0.091-0.852)	0.024	0.084	0.446 (0.156-1.275)	0.151	0.302
*miR-149*T>C/*miR-196a2*T>C/*miR-499*A>G								
T-T-A	93 (25.3)	19 (31.4)	1.000 (reference)			1.206 (0.687-2.116)	0.552	0.877
T-C-G	27 (7.5)	0 (0.0)	0.087 (0.005-1.492)	0.024	0.084	0.107 (0.006-1.772)	0.037	0.148
C-C-G	0 (0.0)	3 (5.1)	33.560 (1.665-676.700)	0.006	0.042	41.050 (2.093-805.000)	0.003	0.024

[a]P-value calculated by Fisher's exact test. OR, odds ratio; CI, confidence interval; miR/miRNA, microRNA; FDR, false discovery rate.

present study analyzed the association between the *miR-149* rs2292832 C>T polymorphism and glioma susceptibility and found allele-allelic combinations in which miRNA polymorphisms were positively associated with glioma, meningioma and schwannoma susceptibility.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

KC and NKK conceived and designed the experiments. JOK and HSP performed the experiments. JL, JOK, HSP, IBH, KK, KC and NKK analyzed the data. JL, JOK, HSP, IBH, KC and NKK were responsible for reagents, materials and analysis tools. JL and JOK wrote the paper. KC and NKK performed the article editing.

Ethics approval and consent to participate

All study protocols were reviewed and approved by The Institutional Review Board of CHA Bundang Medical Center (Seongnam, South Korea) and followed the recommendations of the Declaration of Helsinki. All patients provided written informed consent.

Patient consent for publication

All patients provided written informed consent for publication.

Competing interests

The authors have no competing interests to declare.

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