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ORIGINAL ARTICLE

Mutational Screening of miR-17-92 Cluster and miR-34a by DNA Sequencing in Childhood High-Grade Brain Tumors

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OBJECTIVE

The miR-17-92 cluster and miR-34a are short non-coding RNAs, which are important in tumorigenesis as they regulate numerous oncogenes and tumor suppressor genes. This study aimed to investigate the associations of mutations/polymorphisms of the miR-17-92 cluster and miR-34a coding sequences with high-grade central nervous system malignancies in pediatric patients.

METHODS

This study included 53 children with central nervous system malignancies and age- and gender-matched 27 healthy volunteers. Genomic DNAs were extracted from the paraffin-embedded tumor tissues (n=53) and peripheral blood samples (n=15) in the patient group and from the peripheral blood samples in the control group and were analyzed for mutations/polymorphisms of the miR-17-92 cluster and miR-34a coding sequences by DNA sequencing method.

RESULTS

There were no copy number alterations, amplifications, deletions, insertions, duplications, rearrangements, single nucleotide polymorphisms or mutations in the miR-17-92 cluster and miR-34a coding sequences of tumor tissue or blood samples in the patient group and of blood samples in the control group.

CONCLUSION

In children with high-grade brain tumors, no mutation was detected, leading to failures in regulations of miRNA coding DNA sequences of miR-17-92 and miR-34a. Further studies are needed to elucidate extremely complicated mechanisms underlying oncogenesis in high-grade central nervous system tumors.

Keywords: Cancer; central nervous system; miRNAs; oncogene; tumor.

Introduction

MicroRNAs (miRNAs) are short non-coding RNAs that regulate gene expression either by post-transcriptional regulation leading to mRNA degradation or repression of mRNA translation or by up-regulation of their targets.[1-3] miRNAs may control genes playing important roles in cell proliferation and apoptosis and

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are important in tumorigenesis as they regulate a significant number of oncogenes and tumor suppressor genes.[1-3] Approximately 50% of all annotated human miRNA genes reside in the regions of the genome that are commonly related to cancer.[4] While transcriptional activation or amplification of the miRNA encoding gene can upregulate mature miRNA, deletion of a particular chromosomal region, epigenetic silencing, or defects in their biogenesis can lead to silencing or reduced expression.[3,5]

Several miRNAs have been identified as mediators of tumor suppression regulated by p53 gene; miR-34a and miR-34-b/c, both of which have tumor-suppressive activity, were the first reported ones.[5,6] miR-34a is mapped in the region of chromosome 1p36, the deletion of which is frequently associated with MYCN-amplified neuroblastoma.[6,7] In addition, expression of miR-34a in glioma and medulloblastoma (MB) cells lead to inhibition of proliferation, G1/S cell cycle progression, survival, migration, and invasion of these cells.[8-10] Studies suggested that miR-34a inhibits glioblastoma cell growth and that allelic losses at 1p36 region may cause glioma formation due to loss of tumor-suppressive effect in glioma stem cells.[8-10]

The miR-17-92 cluster, a prototypical example of a polycistronic miRNA gene, encodes six miRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92-1) and is located on chromosome 13q31 in the human genome.[11] Several studies have shown that miRNAs of the mir-17-92 cluster are highly expressed in cancer cells and subjected to frequent amplification and overexpression.[11,12] The miR-17-92 cluster has pleiotropic effects on normal development and malignant transformation by promoting cell proliferation, inhibiting cell differentiation, sustaining cell survival, and decreasing apoptosis.[13] The miR-17-92 cluster is located in a region of DNA that is amplified in human B-cell lymphomas, is the first miRNA found to have oncogenic potential, and is called as oncomiR-1.[14] c-Myc has been shown to activate expression of the miR-17-92 cluster;[15] moreover, the miR-17-92 cluster has been found to collaborate with the Sonic Hedgehog (Shh) signaling pathway in MBs where the high-level focal amplification of the miR-17-92 cluster was identified on chromosome 13q31.3.[16,17]

Pediatric high-grade central nervous system (CNS) tumors have a very aggressive behavior and a low cure rate despite multimodal therapeutic regimens. The development of effective therapeutic agents targeting genetic pathways of CNS tumors depends on better understanding of the molecular features and biology of these malignancies.[18] Currently, studies on DNA microarrays and DNA-based genomic studies classify CNS tumors according to their phenotypes, clinical courses and prognosis. The present study aims to investigate the associations of mutations/polymorphisms of the miR-17-92 cluster and miR-34a coding sequences with high-grade CNS malignancies and thus to further elucidate the pathogenesis of these tumors in pediatric patients.

Materials and Methods

This study included the paraffin-embedded tumor tissue materials available for adequate DNA extraction from 53 pediatric patients (0-18 years; 29 boys and 24 girls) with high-grade CNS tumors, the treatments and follow-ups of whom were performed in the Pediatric Oncology Department of Medical Faculty at the Gazi University within a 20-year period (1992-2012). This study also included a control group that consisted of age- and gender-matched 27 healthy volunteers. Informed consent was obtained from the families of all patients at the time of diagnosis, and this study was approved by the Institutional Ethics Committee of Gazi University University.

The paraffin-embedded tumor tissue samples were provided from the Pathology Department. A form was filled for each patient regarding information about demographics; age at the time of diagnosis; histopathological diagnosis; localization of primary tumor; presence of metastasis at the time of diagnosis; symptoms and their duration; neurological examination findings; extent of surgical resection; time, dose, and area of radiotherapy (RT), if applied; details of chemotherapy (CT), if applied; presence of recurrences; and outcomes. Surgical interventions were performed by a senior neurosurgeon (K.B.). Adjuvant CT and RT were decided by a joint commission, including pediatric oncologists, neurosurgeons, radiation oncologists, radiologists, and pathologists for each patient. The same procedure was repeated in case of recurrence or progressive disease. Cranial and spinal magnetic resonance imaging were performed in all patients at diagnosis, and postoperative computerized tomography or magnetic resonance imaging was performed within 48 h for the detection of residual mass. The follow-up imaging studies were performed every three months for the first two years, every six months for the next five years and yearly thereafter. The follow-up period was defined as the period from the date of prognosis up to the date of the last medical review or up to the date of death.

Genomic DNAs were extracted from the paraffin-embedded tumor tissues (n=53) and peripheral blood samples (only from 15 patients who were alive and available for blood sampling) in the patient group and from the peripheral blood samples in the control group. Genomic DNAs were analyzed for mutations/polymorphisms of the miR-17-92 cluster and mir-34a coding sequences by DNA sequencing method. Isolation of DNA from paraffin-embedded tissue samples was performed using DNeasy Blood & Tissue kit (Qiagen, UK) according to the instructions of the manufacturer. Isolation of DNA from the peripheral blood samples was performed using a commercial spin-column method (Qiagen, UK). The relevant regions were amplified using a polymerase chain reaction thermal cycler (Corbett Research, Ltd., Sydney, Australia) with the following primers: 1) F3-R3 primer: 5'-CCTCCCCACATTTCCTTCCTT-3' (forward) and 5'-CAAACTTCTCCCAGCCAAAA-3' (reverse) for miR-34a; 2) F1-R1 primer: 5'-AGGGATTATGCTGAATTTGTATGG-3' (forward) and 5'-TTGCTTGGCTTGAATTATTGG-3' (reverse) for the first region of miR-17-92; and 3) F2-R2 primer: 5'-CCAATAATTCAAGCCAAGCAA-3' (forward) and 5'-ACCGATCCCAACCTGTGTAG-3' (reverse) for the second region of miR-17-92. After the purification steps, these amplified regions were automatically sequenced by ABI Prism 3100 Genetic Analyzer (Thermo Fisher Scientific, USA) and analyzed for mutations.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) version 13.0. Kaplan-Meier analyses were performed for survival analysis, and the Analysis of Variance (ANOVA) test was used for comparing statistical data. A p-value of <0.05 was considered statistically significant.

Results

Among 53 paraffin-embedded tumor tissues included in this study, 44 were neuroepithelial tissue tumors, and nine were CNS tumors originating from different tissues. The most common histopathological diagnosis was MB (n=12), followed by astrocytic tumors (n=8) and primitive neuroectodermal tumors (PNETs; n=8). Spinal metastases at the time of diagnosis were observed in nine (17%) patients. The demographic characteristics, tumor localization, spinal metastases and diagnoses of the patients at the time of diagnosis are presented in Table 1.

All patients underwent surgical interventions, 41 patients received RT in the Radiation Oncology Department, and 42 patients were treated with combined adjuvant CT regimens in the Pediatric Oncology Department. Three patients died while receiving RT, and another three patients could not receive CT. The median follow-up period was 15 months (range, 0-180 months) in all patients (n=53). Four patients were referred to other cancer centers because of social reasons. One or more recurrences were encountered in 20 (41.7%) of 49 cases by August 2012. Most of the recurrences were observed in primary tumor localization. Seventeen patients died of disease progression. The outcomes of the patients are presented in Table 2. Overall and event-free survival rates of the patients were 42% and 17%, respectively (Fig. 1a and 1b).

There were no copy number alterations, amplifications, deletions, insertions, duplications, rearrangements, single nucleotide polymorphisms or mutations in the miR-17-92 cluster and miR-34a coding sequences of tumor tissue or blood samples in the patient group and of blood samples in the control group.

Discussion

MicroRNAs are small non-coding RNAs having important roles in gene expressions at translational levels. They have a role in the regulation of development, differentiation, proliferation, and apoptosis of the cells. MicroRNAs with oncogenic or tumor suppressor effects, i.e. having a role in cancer, are called oncogenic miRNAs (oncomiRs).[19-21] miRNAs are encoded in the genome and are generally transcribed by RNA polymerase II. They act via RNA-induced silencing complexes, targeting them to messenger RNAs where they either repress translation or direct destructive cleavage.[22] OncomiRs can be deregulated by several mechanisms, such as deletion, amplification, point mutation, and aberrant DNA methylation, leading to genetic or epigenetic alterations.[23] Different nucleotide polymorphisms and mutations are encountered on miRNAs coding DNA sequences and are associated with oncogenic transformations at the cellular level.[21] miRNAs specific to their origins and types have been reported to be differentially expressed in pediatric cancers.[24]

The first evidence of the connection between miRNAs and cancer was the association of chronic lymphocytic leukemia (CLL) with miR-15 and miR-16 coding DNA sequence deletions, which is a reference

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Table 1 General characteristics of the patients at the time of diagnosis

Characteristics	
Gender	
Boys	29 (55)
Girls	24 (45)
Age, months	90.9 (1-192)
Follow-up period, months	15 (0-180)
Tumor localization	
Cerebral hemispheres	16 (30.2)
Ventricles	15 (28.3)
Cerebellum	12 (22.6)
Suprasellar region	3 (5.7)
Thalamus	3 (5.7)
Basal ganglia	2 (3.8)
Brain stem	2 (3.8)
Spinal metastases	
Medulloblastoma	5 (9.4)
Primitive neuroectodermal tumor	2 (3.8)
Anaplastic ependymoma	1 (1.8)
Malignant mesenchymal tumor	1 (1.8)
Diagnosis	
Glial tumors	17 (32)
Anaplastic astrocytoma	5 (9.4)
Glioblastoma multiforme	3 (5.7)
Characteristics (continued)	
Malignant oligodendroglioma	1 (1.8)
Anaplastic ependymoma	6 (11.3)
Choroid plexus carcinoma	1 (1.8)
High-grade glial tumor- non otherwise specified	1 (1.8)
Mixed glial-neuronal tumors	
Anaplastic ganglioglioma	2 (3.8)
High-grade desmoplastic infantile astrocytoma	1 (1.8)
Embryonal tumors	
Medulloblastoma	12 (22.6)
PNET	8 (15.1)
High-grade embryonal tumor- non otherwise specified	1 (1.8)
Ependymoblastoma	1 (1.8)
Atypical teratoid rhabdoid tumor	2 (3.8)
Meningeal – mesenchymal tumors	
Malignant mesenchymal tumor	2 (3.8)
Malignant meningioma	1 (1.8)
Hemangiopericytoma	1 (1.8)
Congenital fibrosarcoma	1 (1.8)
Malignant peripheral nerve sheath tumor of CNS	
Germ cell tumor of CNS	2 (3.8)

Data are presented as number (%) and median (minimum-maximum), where appropriate; CNS: Central nervous system.

sample of linkage between malignant transformation and miRNA mutations. miR-15 and miR-16, which negatively regulate the anti-apoptotic BCL2 protein at the translational level, are located in a 30 kb region at chromosome 13q14, and the deletion of this region has been reported in more than half of B-cell CLLs.[25,26] Nowadays, next-generation microarrays allow the analysis of miRNAome, and to date, alterations in the expressions of miRNA have been reported in several types of cancer. Polymorphisms and mutations in miRNA, which arise from insertions, deletions, amplifications, and chromosomal translocations, may be heterozygous or homozygous.[27-31] Single nucleotide polymorphisms (SNPs), which are found in pri-, pre- and mature-miRNA, may affect the expression of multiple genes and pathways and thereby the function of miRNAs. SNPs of miRNAs may alter the biological structure of miRNAs, expression levels of mature miRNA, and base pairing in the target region. This results in gene dysregulation, which can be important for susceptibility to cancer and for estimating the prognosis and treatment response. Distinct SNPs at different steps of miRNA biogenesis have been identified in several malignancies.[3,20,21,28,30,31]

Alterations and dysregulation in the expressions of miRNA may also have potential roles in malignant proliferation in CNS tumors and other cancers. Among innumerable candidates of oncomiRs, we hypothesized that possible mutations of miR-17-92 and/or miR-34a coding DNA sequences might be associated with CNS tumorigenesis. Hence, in this study, we aimed to investigate the presence of any mutations in miRNA coding DNA sequences of our pediatric patients with high-grade CNS malignancies. Embryonal tumors (WHO grade IV) and high-grade glial tumors (WHO grade III and IV) are often the subjects of investigational studies due to their potential for genetic aberration and their high incidence in childhood. Our study group of high-grade CNS tumors was heterogeneous to some extent; the most common diagnoses were MB (n=12), supratentorial PNETs (n=8), anaplastic astrocytoma (n=5) and glioblastoma multiforme (GBM, n=3).

Mechanisms underlying the development of MB -the most common malignant pediatric brain tumor- have been widely investigated. Genomic and gene expression studies have revealed the molecular heterogeneity of MBs and have classified the disease into distinct subtypes using risk stratification other than clinical status and anaplasia.[32-34] Recently, at a consensus meeting held in Boston, it has been agreed that there are four core molecular subgroups in MBs,[35] namely WNT, SHH,

Table 2 The outcome of the patients with high-grade central nervous system tumor

Outcomes	n/n (%)
Recurrent disease*	20/49 (40.8)
Primary tumor localization	10/20 (20.5)
Primary tumor localization+widespread dissemination	7/20 (14.3)
Medulla spinalis	1/20 (2.0)
Primary tumor localization+medulla spinalis	1/20 (2.0)
Distant region	1/20 (2.0)
Survived in remission	12/53 (22.6)
Lost to follow-up	5/53 (9.4)
With disease	4/53 (7.5)
Without disease	1/53 (1.9)
Survived with disease	15/53 (28.3)
Referred to another center	4/53 (7.5)
Death	17/53 (32.0)
Reasons for death	
Progressive disease	10/17 (58.8)
Progressive disease+toxicity of RT/CT	3/17 (17.6)
Toxicity of RT/CT	2/17 (11.8)
Post-operative complications	2/17 (11.8)

*Percentages of recurrences were calculated according to 49 patients who were alive in August 2012; RT: Radiotherapy; CT: Chemotherapy.

Group 3, and Group 4, which are actually the same subgroups as previously proposed by Northcott et al.[36] and Remke et al.[37] The miR-17-92 cluster has been found to be amplified in MBs repeatedly, particularly in the Shh-associated MBs.[16,17] Northcott et al.[16] performed profiling of 201 primary human MBs using Affymetrix SNP arrays and identified two MBs with high-level amplification of the miR-17-92 cluster. They subsequently performed interphase fluorescence in situ hybridization on an MB tissue microarray and found low-level amplification of miR17-92 cluster in five (6%) of their 80 cases. In the same study, the expression of 427 mature miRNAs was profiled in a series of 90 primary human MBs. Accordingly, they reported that the components of miR-17-92 (miR-18a, miR-19b, and miR-20a and also the paralogous miR-106a) clustered together, and their expression levels were considerably higher in most MBs than in the normal cerebella samples. They also found that miR-17-92 was highly expressed in the Shh subgroup, followed by group C (subsequent group 3) and WNT subgroup. This overexpression was found to be associated with high levels of MYC family proto-oncogenes MYC and MYCN, both of which were reported to transcriptionally regulate miR-17-92 cluster. While high MYCN expression was found in the Shh-associated MBs, high MYC expression was observed in Group 3 and WNT group. Thus, they concluded that overexpression of miR-17-92 synergized with exogenous Shh in promoting cerebellar granule neuron precursors proposed cells-of-origin for the Shh-associated MBs, and was able to drive proliferation even in the absence of Shh signaling.[16] In their study, in which mRNA transcriptome of 194 MBs was profiled, as well as their high-density, SNP array (n=115) and miRNA analysis (n=98) were performed, Cho et al.[38] described six molecular subgroups of MBs. They also revealed distinct

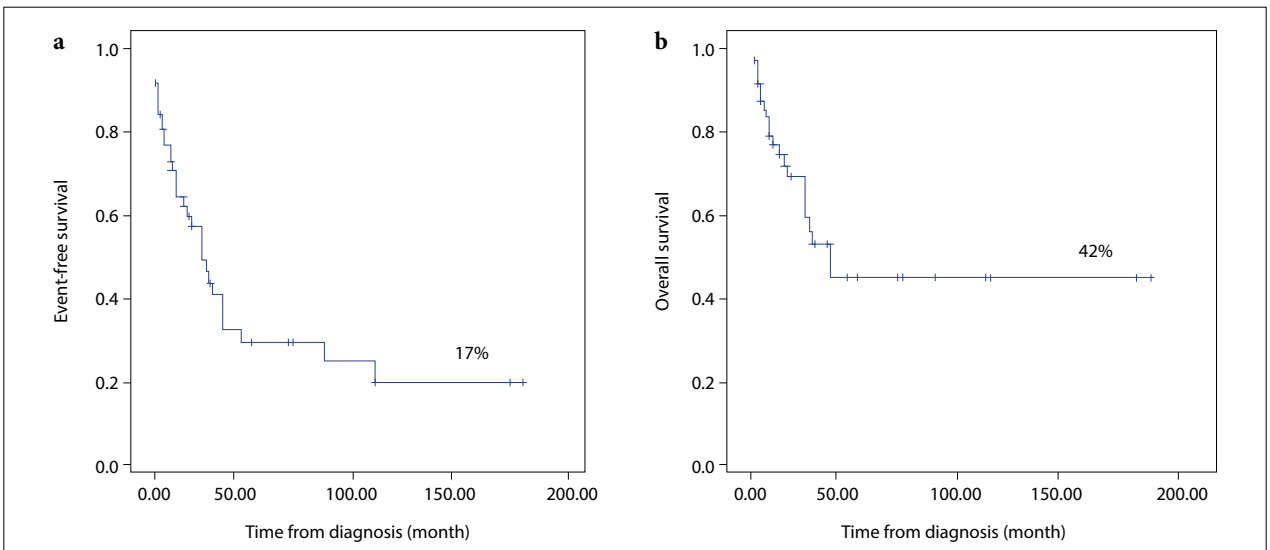

Fig. 1. (a) Event-free survival rate and (b) overall survival rate in the patient group.

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miRNA profiles in MB subgroups and upregulation of the miR-17-92 cluster across all MB samples relative to the normal cerebellum.[38] Uziel et al.[17] revealed the expression of miR-17-92 in the developing mouse cerebellum and proliferating cerebellar granule neuron precursors but not in postmitotic differentiated neurons.[17] Although MB is the most common CNS malignancy associated with the miR-17-92 cluster, it has been shown that this oncomiR might also play a role in the pathogenesis of malignant glial tumors. Lavon et al.[39] investigated the miRNA expression signatures of glial tumors, embryonic stem cells, neural precursor cells, and normal adult brains from human and mouse tissues. They reported that all gliomas showed neural precursor cell-like miRNA signatures and that nearly half of the miRNAs expressed in the shared profile clustered in seven genomic regions comprising a miR-17 family. They deduced that the mir-17 family had a role in gliomagenesis.[39] As the miR-17-92 cluster also plays a role in normal development and malignant transformation process, it may also be involved in the pathogenesis of other malignant CNS tumors.

Being one of the most common CNS tumors in adulthood, high-grade gliomas (HGGs) only account for approximately 8-12% of all pediatric CNS tumors. HGGs in childhood are very aggressive and malignant lesions with a poor prognosis, as are in adults. However, pediatric gliomas differ from adult types not only by histological grade but also they differ concerning malignant transformation rate, site of presentation, molecular genetics, and biological features. As described in several studies, many molecular pathways may participate in gliomagenesis. Recent molecular profiling data have revealed major biological differences between pediatric high-grade gliomas and their adult counterparts.[40-44] While one of the most common genetic abnormalities is the epidermal growth factor receptor (EGFR) amplification in adult HGGs, platelet-derived growth factor receptor-A amplification and TP53 mutations are much more identified abnormalities in pediatric HGGs. Additionally, different studies have revealed gains of 1q and losses of 16q and 14q in pediatric HGGs. It is highly interesting that the deletion of the chromosome 1p36.23, including the miR-34a coding region, is commonly encountered in adult GBM. This frequent deletion of chromosome 1p36 has been suggested to be likely associated with the downregulation of miR-34a expression in GBM.[9,10] Moreover, Yin et al.[45] reported that miR-34a acted as a tumor suppressor by inhibiting GBM cell growth through decreasing cell-cycle protein and EGFR expressions. Although deletion of 1p is considered very rare in pediatric HGGs,[40,44] the deletion of 1p induced by ionizing radiation has been reported in 5/10 cases of pediatric HGGs.[42] TP53 gene encoding for the checkpoint protein -p53- normally acts as a tumor suppressor gene, and its mutations are common in pediatric and adult HGGs.[43] Interestingly, miR-34a, apart from being itself a transcriptional target of p53, inhibits the expression of silent information regulator 1 (SIRT1). Once SIRT1 is inhibited by miR-34a, elevation in acetylated p53, and also an increase in the expressions of p21 and PUMA, which are transcriptional targets of p53 regulating the cell cycle and apoptosis, respectively, are observed.[46] Moreover, overexpression of miR-34a causes a decrease in the level of MDM4 protein, which negatively regulates the p53 tumor suppressor gene.[47] Christoffersen et al.[48] reported the regulation of the miR-34a to be independent of the p53 and its upregulation to be mediated by ELK1, the ETS family transcription factor. Likewise, Wiggins et al.[49] reported that the role of miR-34a in the inhibition of cancer cell growth was also independent of the p53 status. According to these studies, it can be said that although miR-34a is independent of the p53, it exerts its tumor suppressor effect by regulating the p53 pathway. As the p53 pathway is frequently disrupted in pediatric HGG, it is obvious that miR-34a has a crucial role in gliomagenesis.

In the light of above-mentioned studies mainly on MB and GBM, in the present study, we investigated for any mutation leading to failures in the regulation of miRNA coding DNA sequences in our series of high-grade malignant tumors of the CNS. However, no mutation was found in the miR-17-92 cluster and miR-34a DNA sequences that might influence expression levels or functions of mature miRNAs.

Limitations of This Study

As the present study was performed at the DNA sequence levels, it was not possible to detect presumptive differences on the next steps of miRNA biogenesis underlying oncogenesis. Although no genomic alterations were found in the miR-17-92 and miR-34a genes, there might be still some mutations in the subclones of tumor cells. Since Sanger sequencing is not able to detect every clonal alteration at the DNA level, it would be more effective to reveal any genetic substitution in subclones of the tumor tissue through next-generation DNA sequencing, which is a robust technology to reveal genomic alterations in different subclones. Furthermore, any mutations in the gene control regions might have been missed since the gene control regions were not studied in the present study.

Conclusion

Several miRNAs were found to be deregulated in human cancers; however, which miRNAs are the real drivers of carcinogenesis should be determined. In our series of children with high-grade brain tumors, no mutation was detected, leading to failures in regulations of miRNA coding DNA sequences of miR-17-92 (acting as an oncogene) and miR-34a (acting as a tumor suppressor gene). Upregulation of the miR-17-92 cluster and downregulation of miR-34a reported by previous studies may reflect other undefined disturbances. Further studies are needed to elucidate extremely complicated mechanisms underlying oncogenesis in high-grade CNS tumors.

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