


Association Between *LIN28A* Gene Polymorphisms and Glioma Susceptibility in Chinese Children

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Abstract

Gliomas are the most prevalent brain tumors among children and adolescents. The occurrence and development of various malignant tumors is closely related with *LIN28A* gene, but its relationship with glioma susceptibility has not been widely discovered. In this case-control study, we conducted four single nucleotide polymorphisms (SNPs) (rs3811464 G>A, rs3811463 T>C, rs34787247 G>A, and rs11247957 G>A) of *LIN28A* gene to investigate whether they increase the risk of glioma. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate their relationship. There was no significant correlation between four SNPs and glioma risk in single polymorphism and conjoint analysis. However, in stratification analysis, we found that rs3811463 TC/CC may add to the risk of glioma with clinical stage III (adjusted OR = 3.16, 95% CI = 1.15–8.70, P = .026) or stage III+IV patients (adjusted OR = 2.05, 95% CI = 1.02–4.13, P = .044). Our research suggested that four SNPs of *LIN28A* gene have a weak relationship with the risk of glioma in Chinese children. *LIN28A* rs3811463 TC/CC may increase the possibility of glioma in clinical stage III or stage III+IV patients which need larger samples and further confirmation.

Keywords

LIN28A, polymorphism, glioma, susceptibility, Chinese

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Introduction

Glioma, one of the nervous system tumors, is the most prevalent and occurs in primary intracranial neoplasm among children.¹ Besides, the most common secondary primary neoplasms of childhood cancer survivors were central nervous system tumors of which 30% were glioma approximately.² The stages of glioma were classified by WHO as I to IV according to the degree of malignancy. With the exception of stage I or II (low-grade gliomas, LGGs), the stage III or IV (high-grade gliomas, HGGs) shows significant aggressiveness. Outcomes of LGGs are usually good with 5-year overall survival up to 95%.³ In contrast, owing to aggressive characteristic and limited therapeutic efforts, HGG patients still maintain poor prognosis.⁴

Many factors that contribute to the occurrence of glioma have been explored.^{5–10} Radiation is the only verified risk

factor for glioma, especially in childhood.¹¹ However, several genetic disorders have been linked to glioma in children including neurofibromatosis type 1 (NF1), Turcot syndrome, and Li-Fraumeni syndrome.¹² This indicates that genetic factors are particularly important for the pathogenesis of glioma and it is necessary to clarify the pathogenesis for treatment and observation of prognosis. Moreover, evidence shows that *P53*, *BRAF V600E*, and *H3-K27M* mutations are associated with malignancy of pediatric glioma.^{13–16} It is worth mentioning that genetic diversity and disease susceptibility show up to be connected with single nucleotide polymorphisms (SNPs). Margaret Wensch et al.¹⁷ confirmed that rs1412829, which is near *CDKN2B* in chromosome 9p21, may be a promoting element of glioma susceptibility. Marc Sanson et al.¹⁸ exhibited that *EGFR* rs11979158 and rs2252586 at 7p11.2 facilitated the transformation from benign glioma to malignant glioma. However, the discovery of



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these risks is only a small part of the etiological mechanism; further exploration of polymorphisms is needed.

LIN28 is a highly conserved RNA-binding protein in structure which was first found to be a timing controlling gene.¹⁹ *LIN28* can inhibit the synthesis of *let-7*, a tumor suppressor gene, to promote the occurrence and development of tumors.^{20,21} In mammals, there are two *LIN28* homologous, *LIN28A*, and *LIN28B*, respectively. *LIN28A* blocks *let-7* progressing using *Zcchc11* mechanism to promote tumor growth.²² A vast number of *LIN28A*-related cancers have been identified in recent years including breast cancer,²³ ovarian cancer,²⁴ colon cancer,²⁵ osteocarcinoma,²⁶ and pancreatic cancer.²⁷ In addition, a result of a multicenter study demonstrated that *LIN28A* polymorphisms, especially rs34787247 G>A, may add the risk of neuroblastoma.²⁸ Jinjing Lu et al.²⁹ verified that *LIN28A* impeded tumor suppressor gene *IRF6* to promote glycolysis and proliferation of glioma cells by stabilizing *SNHG14*.

Although abundant studies have suggested the significance of gene polymorphism in glioma, the effect of the *LIN28A* polymorphisms on pediatric glioma has not been discovered. In the present study, we investigated whether *LIN28A* gene polymorphisms are associated with the risk of glioma in Chinese children.

Material and Methods

Patients and Controls

In this study, totally 191 cases with newly diagnosed glioma and 248 controls were enrolled belonging to the Chinese

population. The included 191 children were examined at the medical center and pathologically typed and staged as WHO classification. All cases with other cancers or exposure to chemotherapy in the last 6 months were excluded. The non-cancer controls only were examined and matched on sex and age from the same residing areas as patients. The controls were confirmed without nervous system diseases, congenital genetic diseases, and infectious diseases. None of the subjects had blood relationship. Approval for this study was obtained from the institutional review board of Guangzhou Women and Children's Medical Center (2016021650). The patients provided their necessary written informed consent for the research use of their blood sample according to relevant laws and regulations. The protocol of this study was complied with ethical guidelines.

SNP Selection and Genotyping

Four *LIN28A* polymorphisms (rs3811464 G>A, rs3811463 T>C, rs34787247 G>A, and rs11247957 G>A) were selected through the dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>) and SNPinfo software (<http://snpinfo.niehs.nih.gov/snfunc.htm>). Selection criteria are briefly described below: (1) the minor allele frequency (MAF) reported in HapMap was > 5% for Chinese Han subjects; (2) putative functional potential SNPs located in the 5'-flanking region, exon, 5'-untranslated region (5' UTR), and 3' UTR, which might affect transcription activity or binding capacity of the microRNA binding site; (3) SNPs in low linkage disequilibrium with each other ($R^2 < .8$). rs3811464 G>A is located in transcription factor binding sites (TFBS); rs3811463 T>C and rs34787247 G>A are located in transcription factor binding sites (TFBS) and also affect binding capacity of the microRNA binding site; rs11247957 G>A is located in TFBS, affects binding capacity of the miRNA binding site, and affects splicing regulation activity. There was no significant LD ($R^2 < .8$) among these 4 SNPs of *LIN28A* ($R^2 = .183$ between rs3811464 and rs3811463, $R^2 = .009$ between rs3811464 and rs34787247, $R^2 = .054$ between rs3811464 and rs11247957, $R^2 = .03$ between rs3811463 and rs34787247, $R^2 = .052$ between rs3811463 and rs11247957, $R^2 = .002$ between rs34787247 and rs11247957). We used a standard commercial TaqMan real-time PCR kit to genotype the DNA samples.^{30,31} About 10% samples were randomly chosen and re-genotyped for accuracy of genotyping results and quality control. We acquired 100% concurrence for the quality control samples.

Statistical Analysis

We utilized χ^2 test to estimate the dissimilarity of gender, subtypes, and clinical stages between cases and cancer-free controls. The goodness-of-fit test was applied to check Hardy-Weinberg equilibrium (HWE) in controls. The strength between the selected polymorphisms and risk of glioma was counted by odds ratio (ORs) and 95% confidence intervals (CIs). We adjusted age and gender as adjusted ORs, neglecting

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corresponding stratify factor. Besides, stratification analysis was accomplished to validate the connection of age, gender, clinical stages, and subtypes. *P*-value <.05 was considered as statistically significant.

Results

Association Between *LIN28A* Polymorphisms and Glioma Susceptibility

Supplementary Table S1 gives information on the baseline characteristics of the included cases and controls. Similar distributions of age (*P* = .997) and gender (*P* = .329) were

observed between cases and controls. Of the included subjects, we successfully genotyped 191 cases and 248 controls. Distributions of *LIN28A* genotype rs3811464 G>A, rs3811463 T>C, rs34787247 G>A, and rs11247957 G>A polymorphisms in glioma patients and cancer-free controls are summarized in Table 1. All the selected SNPs were followed by HWE genetic balance in controls (HWE = .217 for rs3811464 G>A, HWE = .514 for rs3811463 T>C, HWE = .980 for rs34787247 G>A, and HWE = .847 for rs11247957 G>A). Unfortunately, no significant association was discovered between all of these *LIN28A* polymorphisms and glioma susceptibility. Furthermore, combined analysis of four SNPs failed to show any notable result.

Table 1. Association Between *LIN28A* Gene Polymorphisms and Glioma Susceptibility in Chinese Children.

Genotype	Cases (N = 191)	Controls (N = 248)	<i>P</i> ^a	Crude OR (95% CI)	<i>P</i>	Adjusted OR (95% CI) ^b	<i>P</i> ^b
rs3811464 G>A (HWE = .217)							
GG	147 (76.96)	192 (77.42)		1.00		1.00	
GA	39 (20.42)	50 (20.16)		1.02 (.64–1.63)	.938	1.02 (.63–1.63)	.949
AA	5 (2.62)	6 (2.42)		1.09 (.33–3.64)	.890	1.08 (.32–3.64)	.899
Additive			.890	1.03 (.70–1.51)	.889	1.02 (.70–1.51)	.903
Dominant	44 (23.04)	56 (22.58)	.910	1.03 (.66–1.61)	.910	1.02 (.65–1.61)	.923
Recessive	186 (97.38)	242 (97.5)	.895	1.09 (.33–3.61)	.895	1.08 (.32–3.61)	.903
rs3811463 T>C (HWE = .514)							
TT	136 (71.20)	191 (77.02)		1.00		1.00	
TC	50 (26.18)	52 (20.97)		1.35 (.86–2.11)	.187	1.39 (.89–2.18)	.154
CC	5 (2.62)	5 (2.02)		1.40 (.40–4.95)	.597	1.29 (.36–4.57)	.699
Additive			.180	1.30 (.89–1.89)	.181	1.30 (.89–1.91)	.177
Dominant	55 (28.80)	57 (22.98)	.166	1.36 (.88–2.09)	.167	1.38 (.89–2.13)	.148
Recessive	186 (97.38)	243 (97.98)	.675	1.31 (.37–4.58)	.676	1.19 (.34–4.21)	.788
rs34787247 G>A (HWE = .980)							
GG	131 (68.59)	172 (69.35)		1.00		1.00	
GA	55 (28.80)	69 (27.82)		1.05 (.69–1.59)	.832	1.09 (.71–1.66)	.699
AA	5 (2.62)	7 (2.82)		.94 (.29–3.02)	.915	.98 (.30–3.18)	.971
Additive			.912	1.02 (.71–1.46)	.912	1.05 (.74–1.51)	.774
Dominant	60 (31.41)	76 (30.65)	.863	1.04 (.69–1.56)	.863	1.08 (.71–1.63)	.722
Recessive	186 (97.38)	241 (97.18)	.896	.93 (.29–2.96)	.897	.95 (.30–3.08)	.938
rs11247957 G>A (HWE = .847)							
GG	184 (96.34)	242 (97.58)		1.00		1.00	
GA	7 (3.66)	6 (2.42)		1.53 (.51–4.64)	.449	1.54 (.51–4.72)	.446
AA	0 (.00)	0 (.00)		/	/	/	/
Additive			.445	1.53 (.51–4.64)	.449	1.54 (.51–4.72)	.446
Dominant	7 (3.66)	6 (2.42)	.445	1.53 (.51–4.64)	.449	1.54 (.51–4.72)	.446
Combined effect of risk genotypes ^c							
0	5 (2.62)	7 (2.82)	.339	1.00		1.00	
1	114 (59.69)	162 (65.32)		.99 (.31–3.18)	.980	.96 (.29–3.11)	.939
2	45 (23.56)	45 (18.15)		1.40 (.41–4.74)	.589	1.34 (.39–4.58)	.639
3	20 (10.47)	28 (11.29)		1.00 (.28–3.61)	1.000	.99 (.27–3.61)	.992
4	7 (3.66)	6 (2.42)		1.63 (.34–7.95)	.544	1.59 (.32–7.86)	.566
0-1	119 (62.30)	169 (68.15)		1.00		1.00	
2-4	72 (37.70)	79 (31.85)	.202	1.29 (.87–1.92)	.202	1.29 (.87–1.93)	.206

Abbreviations: OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium.

^a χ^2 test for genotype distributions between glioma patients and cancer-free controls.

^bAdjusted for age and gender.

^cRisk genotypes were carriers with rs3811464 GA/AA, rs3811463 TC/CC, rs34787247 GA/GG, and rs11247957 GA genotypes.

Stratification Analysis

As shown in Table 2, we further performed stratification analysis according to age, gender, subtypes, and clinical stages to investigate the connection of *LIN28A* gene and glioma risk. We found that rs3811463 TC/CC genotype in patients with clinical III stage (adjusted OR = 3.16, 95% CI = 1.15–8.70, P = .026) and clinical III+IV stage (adjusted OR = 2.05, 95% CI = 1.02–4.13, P = .044) carried higher risk to develop glioma compared with those who have rs3811463 TT genotype.

Discussion

Gliomas are thought to originate from neuroglial stem or oligodendroglial progenitor cells; despite various therapies, the median survival of malignant glioma is still less than 15 months.^{32,33} Although the rate of progression from LGGs to HGGs is much lower among children than adults, HGGs can be fatal in childhood. Unlike adults, there are relatively few high-grade gliomas in children and with differences in molecular genetics.¹²

Abundant explorations have been found that show variety of gene mutations could lead to glioma, and further study on the susceptibility of glioma is continuing. The most common somatic mutation in pediatric LGGs is *BRAF V600E* and it is often accompanied with deletion of *CDKN2A/B* in pleomorphic xanthoastrocytomas which shows a tendency of transformation.^{33,34} Carl Wibom et al.³⁵ confirmed that *EGFR* gene variations (rs17172430 and rs11979158) would lead to

the homozygous loss of *CDKN2A/B*. Isocitrate dehydrogenase (*IDH1*) mutation was generally considered to occur in children over 14 years old with HGGs,³⁶ yet there have been cases of mutation detected under the age of ten.³⁷ Interestingly, the prognosis of *IDH1* mutation is better than that of the wild type. After SNP detection, Robert B. Jenkins et al.³⁸ found that the variant rs55705857 located on 8q24.21 was strongly correlated with *IDH1* mutation glioma. In addition, gliomas with *H3-K27M* mutation are mostly classified as WHO grade IV, and usually occur together with *p53* gene.³⁹ *p53* gene is a suppresser gene and rs78378222 of *p53* gene susceptibility was detected to be connected with glioma (OR = 2.35) in a genome-wide association study.⁴⁰ *H3-K27M* mutation gliomas are deadly; more related mechanisms need to be discovered to treat patients.

Currently, the main view is that *LIN28A* regulates the occurrence and development of tumors by controlling *let-7* molecules. *Let-7*, a series of highly conserved miRNA sequence, is a tumor suppressor gene that acts by inhibiting proto-oncogenes such as *RAS* and *HMGA2*.^{41,42} *LIN28A* plays an inhibitory role to *let-7* by blocking the transformation of *pre-let-7* to *let-7*.⁴³ Meanwhile, the proliferation of tumor cells depends on glycolysis, a study demonstrated that *LIN28A* facilitated glycolysis in glioma cells by downregulating the suppressor gene *IRF6*.²⁹ Therefore, as a tumor-promoting factor, *LIN28A* abnormally expressed in numerous tumors and represents a poor prognosis. In a clinical trial, Ning Li et al.⁴⁴ found that cyclins such as *CDK2* and *CDKN1* could be controlled by *LIN28A* in tumor cells to support cell cycle

Table 2. Stratification Analysis of Risk Genotypes with Glioma Susceptibility.

Variables	rs3811463 (Cases/controls)		AOR (95% CI) ^a	P ^a	Risk Genotypes (Cases/controls)		AOR (95% CI) ^a	P ^a
	TT	TC/CC			0-1	2-4		
Age, month								
<60	68/96	29/30	1.41 (.77–2.57)	.268	59/88	38/38	1.55 (.88–2.72)	.130
≥60	68/95	26/27	1.35 (.72–2.51)	.347	60/81	34/41	1.11 (.63–1.95)	.716
Gender								
Females	68/82	21/22	1.11 (.56–2.19)	.774	60/72	29/32	1.02 (.55–1.89)	.953
Males	68/109	34/35	1.60 (.91–2.82)	.102	59/97	43/47	1.55 (.91–2.62)	.107
Subtypes								
Astrocytic tumors	98/191	38/57	1.35 (.83–2.20)	.230	85/169	51/79	1.27 (.81–1.98)	.299
Ependymoma	21/191	12/57	2.04 (.93–4.46)	.075	18/169	15/79	1.93 (.91–4.08)	.086
Neuronal and mixed	11/191	3/57	.89 (.24–3.35)	.865	10/169	4/79	.86 (.26–2.87)	.808
Embryonal tumors	6/191	1/57	.33 (.03–3.51)	.356	6/169	1/79	.22 (.02–2.21)	.197
Clinical stages								
I	83/191	27/57	1.09 (.64–1.86)	.751	73/169	37/79	1.06 (.65–1.71)	.825
II	27/191	11/57	1.36 (.64–2.92)	.427	23/169	15/79	1.39 (.69–2.81)	.359
III	9/191	8/57	3.16 (1.15–8.70)	.026	9/169	8/79	2.09 (.77–5.70)	.151
IV	17/191	8/57	1.48 (.57–3.83)	.416	14/169	11/79	1.50 (.62–3.62)	.369
I+II	110/191	38/57	1.17 (.73–1.88)	.519	96/169	52/79	1.16 (.75–1.89)	.510
III+IV	26/191	16/57	2.05 (1.02–4.13)	.044	23/169	19/79	1.69 (.86–3.31)	.128

Abbreviations: OR, odds ratio; CI, confidence interval.

^aAdjusted for age and gender, omitting the corresponding stratify factor.

progression. It has been reported that *LIN28A* can interact with coiled-coil containing protein kinase2 to accelerate the malignant transformation of ovarian cancer.⁴⁵ Two case-control studies demonstrated that *LIN28A* polymorphisms changed susceptibilities of neuroblastoma and Wilms tumor.^{28,46} Despite evidence has shown that *LIN28A* increases the incidence of numerous tumors, there has been no previous study about the relationship between *LIN28A* polymorphisms and glioma susceptibility.

In this study, we estimated 191 pediatric glioma patients and 248 cancer-free controls to work out whether *LIN28A* gene polymorphisms are associated with the risk of glioma. Although the result implied that none of these picked polymorphisms were related to glioma susceptibility, the stratification analysis suggested that rs3811463 TC/CC may increase the risk of clinical stage III or III+IV patients with glioma. From what we know, this is the earliest study of assessing the association between *LIN28A* polymorphisms and glioma susceptibility. However, several limitations of our study should be noticed. First of all, due to insufficient sample size, there may exist some deviations between our study and real situation. More samples needed to be included in the future to obtain more accurate conclusions. Second, because specimens from other ethnic groups were not available, our findings do not apply to ethnic groups other than the Han. Third, the large differences exist in genetic variation between children and adults with glioma, thus our conclusions may not be applicable to the entire population. Moreover, our patients were recruited from hospital; many factors including environmental influence, diet background, and personality preference were not taken into account which may be led to bias eventually.

In conclusion, this study suggested that *LIN28A* polymorphisms have a weak relationship with glioma susceptibility and further investigation with larger samples is needed to proceed.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Approval for this study was obtained from the institutional review board of Guangzhou Women and Children's Medical Center (2016021650).

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Supplemental Material

Supplemental material for this article is available online.

References

1. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: A report from the childhood cancer survivor study. *J Natl Cancer Inst.* 2006;98(21):1528-1537. doi: [10.1093/jnci/djj411](https://doi.org/10.1093/jnci/djj411).
2. Reulen RC, Frobisher C, Winter DL, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA.* 2011;305(22):2311-2319. doi: [10.1001/jama.2011.747](https://doi.org/10.1001/jama.2011.747).
3. Stokland T, Liu JF, Ironside JW, et al. A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: A population-based cohort study (CCLG CNS9702). *Neuro Oncol.* 2010;12(12):1257-1268. doi: [10.1093/neuonc/noq092](https://doi.org/10.1093/neuonc/noq092).
4. Oberoi RK, Parrish KE, Sio TT, Mittapalli RK, Elmquist WF, Sarkaria JN. Strategies to improve delivery of anticancer drugs across the blood-brain barrier to treat glioblastoma. *Neuro Oncol.* 2016;18(1):27-36. doi: [10.1093/neuonc/nov164](https://doi.org/10.1093/neuonc/nov164).
5. Cordier D, Gerber M, Brand S. Effects of two types of exercise training on psychological well-being, sleep, quality of life and physical fitness in patients with high-grade glioma (WHO III and IV): Study protocol for a randomized controlled trial. *Cancer Commun (Lond).* 2019;39(1):46. doi: [10.1186/s40880-019-0390-8](https://doi.org/10.1186/s40880-019-0390-8).
6. Jiang Y, Zhou J, Zou D, et al. Overexpression of limb-bud and heart (LBH) promotes angiogenesis in human glioma via VEGFA-mediated ERK signalling under hypoxia. *EBioMedicine.* 2019;48:36-48. doi: [10.1016/j.ebiom.2019.09.037](https://doi.org/10.1016/j.ebiom.2019.09.037).
7. Zhou L, Dong S, Deng Y, et al. GOLGA7 rs11337, a polymorphism at the microRNA binding site, is associated with glioma prognosis. *Mol Ther Nucleic Acids.* 2019;18:56-65. doi: [10.1016/j.omtn.2019.08.006](https://doi.org/10.1016/j.omtn.2019.08.006).
8. Deng Y, Zhou L, Yao J, et al. Associations of lncRNA H19 polymorphisms at microRNA binding sites with glioma susceptibility and prognosis. *Mol Ther Nucleic Acids.* 2020;20:86-96. doi: [10.1016/j.omtn.2020.02.003](https://doi.org/10.1016/j.omtn.2020.02.003).
9. Lu JH, Li S, Zhang WJ, et al. DeltaNp63 drives epithelial differentiation in glioma. *Clin Transl Med.* 2020;10(4):e165. doi: [10.1002/ctm2.165](https://doi.org/10.1002/ctm2.165).
10. Wang J, Yang S, Ji Q, et al. Long non-coding RNA EPIC1 promotes cell proliferation and motility and drug resistance in glioma. *Mol Ther Oncolytics.* 2020;17:130-137. doi: [10.1016/j.omto.2020.03.011](https://doi.org/10.1016/j.omto.2020.03.011).
11. Vienne-Jumeau A, Tafani C, Ricard D. Environmental risk factors of primary brain tumors: A review. *Rev Neurol (Paris).* 2019;175(10):664-678. doi: [10.1016/j.neurol.2019.08.004](https://doi.org/10.1016/j.neurol.2019.08.004).
12. Braunstein S, Raleigh D, Bindra R, Mueller S, Haas-Kogan D. Pediatric high-grade glioma: Current molecular landscape and therapeutic approaches. *J Neuro Oncol.* 2017;134(3):541-549. doi: [10.1007/s11060-017-2393-0](https://doi.org/10.1007/s11060-017-2393-0).

13. Pollack IF, Finkelstein SD, Burnham J, et al. Age and TP53 mutation frequency in childhood malignant gliomas: Results in a multi-institutional cohort. *Cancer Res.* 2001;61(20):7404-7407.
14. Pollack IF, Finkelstein SD, Woods J, et al. Expression of p53 and prognosis in children with malignant gliomas. *N Engl J Med.* 2002;346(6):420-427. doi: [10.1056/NEJMoa012224](https://doi.org/10.1056/NEJMoa012224).
15. Mistry M, Zhukova N, Merico D, et al. BRAF mutation and CDKN2A deletion define a clinically distinct subgroup of childhood secondary high-grade glioma. *J Clin Oncol.* 2015;33(9):1015-1022. doi: [10.1200/JCO.2014.58.3922](https://doi.org/10.1200/JCO.2014.58.3922).
16. Larson JD, Kasper LH, Paugh BS, et al. Histone H3.3 K27M accelerates spontaneous brainstem glioma and drives restricted changes in bivalent gene expression. *Canc Cell.* 2019;35(1):140-155.e147. doi: [10.1016/j.ccell.2018.11.015](https://doi.org/10.1016/j.ccell.2018.11.015).
17. Wrensch M, Jenkins RB, Chang JS, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nat Genet.* 2009;41(8):905-908. doi: [10.1038/ng.408](https://doi.org/10.1038/ng.408).
18. Sanson M, Hosking FJ, Shete S, et al. Chromosome 7p11.2 (EGFR) variation influences glioma risk. *Hum Mol Genet.* 2011;20(14):2897-2904. doi: [10.1093/hmg/ddr192](https://doi.org/10.1093/hmg/ddr192).
19. Ambros V, Horvitz HR. Heterochronic mutants of the nematode *Caenorhabditis elegans*. *Science.* 1984;226(4673):409-416. doi: [10.1126/science.6494891](https://doi.org/10.1126/science.6494891).
20. Nam Y, Chen C, Gregory RI, Chou JJ, Sliz P. Molecular basis for interaction of let-7 microRNAs with Lin28. *Cell.* 2011;147(5):1080-1091. doi: [10.1016/j.cell.2011.10.020](https://doi.org/10.1016/j.cell.2011.10.020).
21. Viswanathan SR, Daley GQ, Gregory RI. Selective blockade of microRNA processing by Lin28. *Science.* 2008;320(5872):97-100. doi: [10.1126/science.1154040](https://doi.org/10.1126/science.1154040).
22. Piskounova E, Polytarchou C, Thornton JE, et al. Lin28A and Lin28B inhibit let-7 microRNA biogenesis by distinct mechanisms. *Cell.* 2011;147(5):1066-1079. doi: [10.1016/j.cell.2011.10.039](https://doi.org/10.1016/j.cell.2011.10.039).
23. Shen H, Yang Y, Zhao L, Yuan J, Niu Y. Lin28A and androgen receptor expression in ER-/Her2+ breast cancer. *Breast Cancer Res Treat.* 2016;156(1):135-147. doi: [10.1007/s10549-016-3744-9](https://doi.org/10.1007/s10549-016-3744-9).
24. He Y, Wang H, Yan M, et al. High LIN28A and PLK4 co-expression is associated with poor prognosis in epithelial ovarian cancer. *Mol Med Rep.* 2018;18(6):5327-5336. doi: [10.3892/mmr.2018.9562](https://doi.org/10.3892/mmr.2018.9562).
25. Wang T, He Y, Zhu Y, et al. Comparison of the expression and function of Lin28A and Lin28B in colon cancer. *Oncotarget.* 2016;7(48):79605-79616. doi: [10.18632/oncotarget.12869](https://doi.org/10.18632/oncotarget.12869).
26. Wang Z, Pang J, Ji B, et al. RNA binding protein Lin28A promotes osteocarcinoma cells progression by associating with the long noncoding RNA MALAT1. *Biotechnol Lett.* 2018;40(3):493-500. doi: [10.1007/s10529-017-2489-9](https://doi.org/10.1007/s10529-017-2489-9).
27. Xu M, Bian S, Li J, et al. MeCP2 suppresses LIN28A expression via binding to its methylated-CpG islands in pancreatic cancer cells. *Oncotarget.* 2016;7(12):14476-14485. doi: [10.18632/oncotarget.7507](https://doi.org/10.18632/oncotarget.7507).
28. Hua RX, Zhuo Z, Ge L, et al. LIN28A gene polymorphisms modify neuroblastoma susceptibility: A four-centre case-control study. *J Cell Mol Med.* 2020;24(1):1059-1066. doi: [10.1111/jcmm.14827](https://doi.org/10.1111/jcmm.14827).
29. Lu J, Liu X, Zheng J, et al. Lin28A promotes IRF6-regulated aerobic glycolysis in glioma cells by stabilizing SNHG14. *Cell Death Dis.* 2020;11(6):447. doi: [10.1038/s41419-020-2650-6](https://doi.org/10.1038/s41419-020-2650-6).
30. Zhuo ZJ, Liu W, Zhang J, et al. Functional polymorphisms at ERCC1/XPF genes confer neuroblastoma risk in Chinese children. *EBioMedicine.* 2018;30:113-119. doi: [10.1016/j.ebiom.2018.03.003](https://doi.org/10.1016/j.ebiom.2018.03.003).
31. Zhuo Z, Zhou C, Fang Y, et al. Correlation between the genetic variants of base excision repair (BER) pathway genes and neuroblastoma susceptibility in eastern Chinese children. *Cancer Commun (Lond).* 2020;40(11):641-646. doi: [10.1002/cac2.12088](https://doi.org/10.1002/cac2.12088).
32. Weller M, Wick W, Aldape K, et al. Glioma. *Nat Rev Dis Primers.* 2015;1:15017. doi: [10.1038/nrdp.2015.17](https://doi.org/10.1038/nrdp.2015.17).
33. Thorne AH, Meisen WH, Russell L, et al. Role of cysteine-rich 61 protein (CCN1) in macrophage-mediated oncolytic herpes simplex virus clearance. *Mol Ther.* 2014;22(9):1678-1687. doi: [10.1038/mt.2014.101](https://doi.org/10.1038/mt.2014.101).
34. Frazao L, do Carmo Martins M, Nunes VM, et al. BRAF V600E mutation and 9p21: CDKN2A/B and MTAP co-deletions—Markers in the clinical stratification of pediatric gliomas. *BMC Canc.* 2018;18(1):1259. doi: [10.1186/s12885-018-5120-0](https://doi.org/10.1186/s12885-018-5120-0).
35. Wibom C, Ghasimi S, Van Loo P, et al. EGFR gene variants are associated with specific somatic aberrations in glioma. *PLoS One.* 2012;7(12):e47929. doi: [10.1371/journal.pone.0047929](https://doi.org/10.1371/journal.pone.0047929).
36. Pollack IF, Hamilton RL, Sobol RW, et al. IDH1 mutations are common in malignant gliomas arising in adolescents: A report from the children's oncology group. *Childs Nerv Syst.* 2011;27(1):87-94. doi: [10.1007/s00381-010-1264-1](https://doi.org/10.1007/s00381-010-1264-1).
37. Ferris SP, Goode B, Joseph NM, et al. IDH1 mutation can be present in diffuse astrocytomas and giant cell glioblastomas of young children under 10 years of age. *Acta Neuropathol.* 2016;132(1):153-155. doi: [10.1007/s00401-016-1579-4](https://doi.org/10.1007/s00401-016-1579-4).
38. Jenkins RB, Xiao Y, Sicotte H, et al. A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendroglial tumors and astrocytomas with IDH1 or IDH2 mutation. *Nat Genet.* 2012;44(10):1122-1125. doi: [10.1038/ng.2388](https://doi.org/10.1038/ng.2388).
39. Solomon DA, Wood MD, Tihan T, et al. Diffuse midline gliomas with histone H3-K27M mutation: a series of 47 cases assessing the spectrum of morphologic variation and associated genetic alterations. *Brain Pathol.* 2016;26(5):569-580. doi: [10.1111/bpa.12336](https://doi.org/10.1111/bpa.12336).
40. Stacey SN, Sulem P, Jonasdottir A, et al. A germline variant in the TP53 polyadenylation signal confers cancer susceptibility. *Nat Genet.* 2011;43(11):1098-1103. doi: [10.1038/ng.926](https://doi.org/10.1038/ng.926).
41. Yu F, Yao H, Zhu P, et al. let-7 regulates self renewal and tumorigenicity of breast cancer cells. *Cell.* 2007;131(6):1109-1123. doi: [10.1016/j.cell.2007.10.054](https://doi.org/10.1016/j.cell.2007.10.054).
42. Sempere LF, Christensen M, Silaharoglu A, et al. Altered MicroRNA expression confined to specific epithelial cell

- subpopulations in breast cancer. *Cancer Res.* 2007;67(24):11612-11620. doi: [10.1158/0008-5472.CAN-07-5019](https://doi.org/10.1158/0008-5472.CAN-07-5019).
43. Heo I, Ha M, Lim J, et al. Mono-uridylation of pre-microRNA as a key step in the biogenesis of group II let-7 microRNAs. *Cell.* 2012;151(3):521-532. doi: [10.1016/j.cell.2012.09.022](https://doi.org/10.1016/j.cell.2012.09.022).
44. Li N, Zhong X, Lin X, et al. Lin-28 homologue A (LIN28A) promotes cell cycle progression via regulation of cyclin-dependent kinase 2 (CDK2), cyclin D1 (CCND1), and cell division cycle 25 homolog A (CDC25A) expression in cancer. *J Biol Chem.* 2012;287(21):17386-17397. doi: [10.1074/jbc.M111.321158](https://doi.org/10.1074/jbc.M111.321158).
45. Zhong Y, Yang S, Wang W, et al. The interaction of Lin28A/Rho associated coiled-coil containing protein kinase2 accelerates the malignancy of ovarian cancer. *Oncogene.* 2019;38(9):1381-1397. doi: [10.1038/s41388-018-0512-9](https://doi.org/10.1038/s41388-018-0512-9).
46. Zhuo Z, Fu W, Liu J, et al. LIN28A gene polymorphisms confer Wilms tumour susceptibility: A four-centre case-control study. *J Cell Mol Med.* 2019;23(10):7105-7110. doi: [10.1111/jcmm.14561](https://doi.org/10.1111/jcmm.14561).