Original Article

Association of *LINC00673* rs11655237 polymorphism with pediatric glioma susceptibility in a Chinese population

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Background: Previous researches have suggested that *LINC00673* rs11655237 C>T polymorphism might be correlated to cancer susceptibility. However, its correlation with pediatric glioma is unknown. Therefore, this study aimed to determine whether *LINC00673* rs11655237 C>T polymorphism is correlated with pediatric glioma.

Methods: In total, we included 399 subjects from South China. The Student's *t*-test was performed to evaluate age differences between glioma cases and controls. Differences in the categorical variables between the two groups were assessed using the χ^2 test. A logistic regression was conducted to calculate the odds ratio (OR) and the 95% confidence interval (CI).

Results: We conducted this case-control study to investigate the association between *LINC00673* polymorphism and pediatric glioma susceptibility. Our results revealed that *LINC00673* rs11655237 C>T polymorphism was not correlated to pediatric glioma susceptibility in a Chinese population (CC/CT compared with TT: adjusted OR =2.49, 95% CI: 0.87–7.15, P=0.091). Furthermore, a stratified analysis also indicated *LINC00673* rs11655237 C>T polymorphism did not increase the risk of glioma in different subgroups.

Conclusions: Our study revealed that *LINC00673* rs11655237 C>T polymorphism was not correlated to pediatric glioma susceptibility in a Chinese population. In the future, further exploration of this genetic factor in relation to glioma susceptibility will require a larger sample size to verify the current findings.

Keywords: LINC00673; polymorphism; glioma; susceptibility

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Introduction

With the exception of leukemia, central nervous system (CNS) tumors are the most common tumors in children and adolescents. CNS tumors are difficult to treat, have a poor prognosis, and a high recurrence rate (1). With the rapid expansion in imaging technology, the diagnostic rate of new CNS tumors is increasing yearly. According to the latest statistics of United States, approximately 23,880 glioma cases are diagnosed, and 16,830 estimated new cases will die

from glioma (2). Despite recent advances in treatment, the prognosis for glioma patients remains poor, and the average overall survival (OS) for glioblastoma patients is less than 16 months (3-5). Therefore, there is an urgent need to explore the molecular pathological mechanisms and potential molecular biomarkers for glioma.

Long noncoding RNAs (lncRNAs) are a type of complex molecule with little or no protein-coding ability and are transcribed in most eukaryotic genomes. Initially, lncRNAs were considered to be merely transcriptional noise without any biological function (6). However, there is growing evidence that LncRNAs regulate gene expression at the epigenetic, transcriptional, and post-transcriptional processing levels by acting on nucleic acid molecules and proteins and play a key role in many of the biological processes associated with tumors (7). Of these, *LINC00673* is among the most thoroughly studied (8) and is located on chromosome 17q24.3, at approximately 275-kb telomeric of SOX9. Analysis of this lncRNA sequence has shown that it possesses an absolutely conserved region, which is remarkably similar to the SRA1 protein. Therefore, this lncRNA is also known as "SRA-like non-coding RNA" (SLNCR) (9). Notably, Childs *et al.* first reported in a genome-wide association study (GWAS) of 9925 pancreatic cancer cases and 11,569 controls that the single nucleotide polymorphisms (SNPs) in *LINC00673* were significantly associated with pancreatic cancer susceptibility in North America, Central Europe, and Australia (10). However, to date, the correlation between *LINC00673* polymorphism and pediatric glioma susceptibility has not been investigated. Therefore, this study focused on whether *LINC00673* polymorphism is associated with the risk of pediatric glioma by recruiting 399 subjects from South China. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tp-21-291).

Methods

Subjects

In this case-control study, 399 subjects (171 cases and 228 controls) were included from South China as we reported before (Table S1) (11). All glioma patients were pathologically confirmed. We collected clinical information including patients' age, gender, and clinical stage. Before collecting blood samples, written informed consent was obtained from the parents or legal guardians of each child. This investigation protocol was approved by the Ethics Committee of Guangzhou Women (No.: 2016021650) and Children's Medical Center. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Polymorphism analysis

LINC00673 rs11655237 C>T was selected based on previous publications (12,13). Blood was collected in an EDTA test tube from 399 participants. Details of the blood draw, DNA extraction, and storage status have been described in a previous study (14). *LINC00673* genotyping was conducted with TaqMan real-time quantitative PCR (QPCR). For quality control, the obtained variants of *LINC00673* rs11655237 C>T polymorphism were confirmed by genotype in 10% of randomly selected genomic DNA samples, and the results of the quality control were in accord with the first assays.

Statistical analysis

Statistical analyses were performed with SAS software (version 9.4; SAS institute in United States). The Hardy-Weinberg equilibrium (HWE) of all SNPs in the controls was tested by the goodness-of-fit χ^2 test. The Student's *t*-test was used to assess age differences between glioma cases and controls. Differences in categorical variables between the two groups were determined by the χ^2 test. A multiple logistic regression model was used to calculate the odds ratio (OR) and the 95% confidence interval (CI). All P values were two-sided, and $P<0.05$ was considered statistically significant.

Results

Patient characteristics

In this case-control study, to explore the correlation between *LINC00673* rs1165237 C>T polymorphism and glioma susceptibility, we recruited 339 age- and gender-matched subjects (171 glioma cases and 228 non-tumor controls) from South China. The clinicopathological characteristics of all 339 subjects are listed in Table S1. The average ages of the glioma patients and controls were 63.40±47.72 months (range, 4.00–168.00 months) and 52.41±32.65 months (range, 4.00–168.00 months), respectively. Overall, there were less females (174, 43.6%)

Table 1 Association between LINC00673 rs11655237 C>T polymorphism and glioma risk

Genotype	Cases (N=171)	Controls (N=228)	P[a]	Crude OR (95% CI)	P	Adjusted OR (95% CI)[b]	P[b]
rs11655237 (HWE=0.289)							
CC	105 (61.40)	146 (64.04)		1.00		1.00	
CT	56 (32.75)	76 (33.33)		1.03 (0.67–1.57)	0.911	0.98 (0.64–1.52)	0.941
TT	10 (5.85)	6 (2.63)		2.32 (0.82–6.58)	0.114	2.49 (0.87–7.15)	0.091
Additive			0.309	1.20 (0.85–1.70)	0.309	1.19 (0.84–1.69)	0.340
Dominant	66 (38.60)	82 (35.96)	0.590	1.12 (0.74–1.69)	0.590	1.09 (0.72–1.65)	0.683
Recessive	161 (94.15)	222 (97.37)	0.105	2.30 (0.82–6.45)	0.114	2.50 (0.88–7.12)	0.086

[a], χ^2 test for genotype distributions between glioma patients and cancer-free controls. [b], adjusted for age and gender. OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

than males (225, 56.4%). No significant differences in age and gender were identified between the case and control groups (P=0.623 and P=0.190, respectively). In the case group, patients with WHO grade I–II were in the majority (131, 76.61%), with only 40 patients classified with high grade gliomas (23.39%) (Table S1).

Association of LNIC00673 rs11655237 C>T variants with pediatric glioma susceptibility

All 399 subjects underwent genotype testing for LINC006773 rs11655237 C>T polymorphism. The genotype frequencies and percentage of *LINC00673* rs11655237 C>T polymorphism are summarized in *Table 1*. All genotypes were checked for quality control and were consistent with HWK in control subjects (P=0.289). Next, we investigated the association of LINC006773 rs11655237 C>T polymorphism and glioma susceptibility. *LINC00673* rs11655237 C>T polymorphism showed no correlation with glioma susceptibility (CC *vs.* TT: adjusted OR =2.49, 95% CI: 0.87–7.15, P=0.091). A possible reason for this finding is a lack of statistical power due to our small sample size.

Association of LINC00673 rs11655237 C>T variants with glioma susceptibility in different subgroups

To identify whether *LINC00673* rs11655237 C>T variants were correlated with the risk of glioma in different subgroups, we performed a stratified analysis of glioma patients based on their clinicopathological characteristics after adjustments for age and gender. *Table 2* shows the genotype frequencies of *LINC00673* rs11655237 C>T polymorphism in the different subgroups. The association of *LINC00673* rs11655237 C>T polymorphism and the risk of glioma did not reach statistical significance for any of the subgroups (*Table 2*). Therefore, in the present study, *LINC00673* rs11655237 C>T polymorphism did not demonstrate a significant correlation with pediatric glioma susceptibility in a Chinese population.

Discussion

A growing body of evidence shows that heredity plays a key role in cancer susceptibility. Over the past decade, scientists have published more than 1,300 GWAS, and identified nearly 6,500 gene loci associated with diseases (15). However, just 7% of these sites were located in protein-coding regions, while the remaining 93% were located mainly in non-coding regions. Presently, four different variants of SNPs have been identified: transformation, transposition, deletion, and insertion. Gene mutations in protein-coding regions often cause harmful or fatal outcomes, making it impossible for carriers to survive long enough for cancer to develop (16). However, mutations in regulated regions may cause small changes in the gene expression in cell types or in tissue-specific ways that may confer cancer susceptibility in the carrier (17,18). Currently, many SNPs have been correlated with cancer susceptibility, such as in gastric cancer, lung cancer, and other malignant tumors (19,20).

We conducted this case-control study to investigate the association between *LINC00673* polymorphism and pediatric glioma susceptibility. Our results suggested that *LINC00673* rs11655237 C>T polymorphism was not correlated with glioma susceptibility in a pediatric Chinese population, which is inconsistent with results

Table 2 Stratification analysis between LINC00673 rs11655237 C>T polymorphism and glioma risk

Variables	rs1042522 (cases/controls)		Crude OR	P	Adjusted OR[a]	P[a]
	CC	CT/TT	(95% CI)		(95% CI)	
Age, months						
<60	53/76	33/43	1.12 (0.63–1.99)	0.695	1.12 (0.63–1.98)	0.710
≥60	53/70	33/39	1.12 (0.63–2.01)	0.710	1.10 (0.61–1.99)	0.743
Gender						
Females	47/59	34/34	1.26 (0.68–2.31)	0.465	1.23 (0.66–2.29)	0.511
Males	58/87	32/48	1.00 (0.57–1.75)	1.000	0.99 (0.56–1.73)	0.963
Subtype						
Astrocytic tumors	75/146	50/82	1.19 (0.76–1.86)	0.454	1.16 (0.73–1.83)	0.536
Ependymoma	16/146	9/82	1.00 (0.42–2.37)	0.997	1.04 (0.44–2.47)	0.935
Neuronal and mixed	9/146	5/82	0.99 (0.32–3.05)	0.985	1.00 (0.32–3.10)	0.998
Embryonal tumors	5/146	2/82	0.71 (0.14–3.75)	0.689	0.61 (0.10–3.83)	0.595
Clinical stages						
I	59/146	44/82	1.33 (0.83–2.14)	0.242	1.33 (0.82–2.15)	0.248
II	17/146	11/82	1.15 (0.52–2.58)	0.730	1.15 (0.52–2.59)	0.727
III	11/146	4/82	0.65 (0.20–2.10)	0.469	0.66 (0.20–2.17)	0.497
IV	18/146	7/82	0.69 (0.28–1.73)	0.431	0.66 (0.25–1.75)	0.403
I+II	76/146	55/82	1.29 (0.83–2.00)	0.259	1.27 (0.81–1.97)	0.296
III+IV	29/146	11/82	0.68 (0.32–1.42)	0.302	0.66 (0.31–1.40)	0.276

[a], adjusted for age and gender, omitting the corresponding stratify factor. OR, odds ratio; CI, confidence interval.

found in other solid tumors. This different outcome may be related to variations in sample populations, differing research protocols, and the small sample size in the present study. In other solid tumors, current research has focused on the association of the SNPs of *LINC00673* (rs11655237 C>T polymorphism) and cancer risk. Zheng *et al.* reported that rs11655237 is located on exon 4 of *LINC00673* and six SNPs are involved in the high-linkage disequilibrium with rs11655237 (21). *LINC00673* rs11655237 C>T polymorphism may increase the risk of many solid cancers in an allele-specific manner (12,21,22). One possible reason is that rs11655237 could be recognized and complemented with the miR-1231 domain, which further regulates the expression level of *LINC00673* (23). In fact, the formation of this miR-1231-recognition region is caused by the single-base substitution of the G allele to the A allele at rs11655237, and miR-1231 may bind to the recognition region and further reduce the expression level of *LINC00673*. Previous studies have reported that *LINC00673* acts as a tumor suppressor gene in a variety of tumors, and downregulation of *LINC00673* could increase the risk of tumor susceptibility in subjects (21,24). Zhu *et al.* (24) found that cervical cancer patients with the A allele of rs116552337 had a poorer prognosis than those with the G allele of rs11655237. These findings suggest that *LINC00673* plays an important role in maintaining cell homeostasis, and its polymorphisms could increase the risk of cancer susceptibility. However, how SNPs affect *LINC00673* binding to transcription factors remains unclear.

This case-control study has several limitations. Firstly, the sample size was not large enough to obtain statistically significant results. Thus, a larger sample size is needed in future studies to verify the above results. Secondly, a much higher number of SNP loci should be considered in any further research. We cannot rule out the influence of other

loci polymorphisms on pediatric glioma susceptibility. Thirdly, more studies are needed to consider the role of other potentially confounding variables, such as environmental factors.

In conclusion, as far as we know, this is the first case-control study focusing on the possible association of *LINC00673* rs11655237 C>T polymorphism and glioma risk. In contrast to other *LINC00673* rs11655237 C>T polymorphism studies, we found that *LINC00673* rs11655237 C>T polymorphism was not correlated with pediatric glioma susceptibility in a Chinese population.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tp-21-291

Data Sharing Statement: Available at https://dx.doi.org/10.21037/tp-21-291

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tp-21-291). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangzhou Women (No. 2016021650) and Children's Medical Center and informed consent was taken from all the patients.

References

1. Ostrom QT, Gittleman H, Truitt G, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro Oncol 2018;20:iv1-86.
2. Siegel RL, Miller KD, Jemal A, et al. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
3. Fan CD, Fu XY, Zhang ZY, et al. Selenocysteine induces apoptosis in human glioma cells: evidence for TrxR1-targeted inhibition and signaling crosstalk. Sci Rep 2017;7:6465.
4. Gomez GA, Oksdath M, Brown MP, et al. New approaches to model glioblastoma in vitro using brain organoids: implications for precision oncology. Transl Cancer Res 2019;8:S606-11.
5. Qu S, Chen Z, Liu B, et al. N6-methyladenine-related genes affect biological behavior and the prognosis of glioma. Cancer Med 2021;10:98-108.
6. Jing L, Gong M, Lu X, et al. LINC01127 promotes the development of ovarian tumors by regulating the cell cycle. Am J Transl Res 2019;11:406-17.
7. Chen Y, Zitello E, Guo R, et al. The function of LncRNAs and their role in the prediction, diagnosis, and prognosis of lung cancer. Clin Transl Med 2021;11:e367.
8. Li N, Cui Z, Huang D, et al. Association of LINC00673 rs11655237 polymorphism with cancer susceptibility: A meta-analysis based on 23,478 subjects. Genomics 2020;112:4148-54.
9. Zhu K, Gong Z, Li P, et al. A review of linc00673 as a novel lncRNA for tumor regulation. Int J Med Sci 2021;18:398-405.
10. Childs EJ, Mocci E, Campa D, et al. Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. Nat Genet 2015;47:911-6.
11. He J, Li Y, Lin HR, et al. Genetic variants in m 6 A modification core genes are associated with glioma risk in Chinese children. Mol Ther Oncolytics. 2021 ;20:199-208.
12. Li Y, Zhuo ZJ, Zhou H, et al. Additional data support the role of LINC00673 rs11655237 C>T in the development of neuroblastoma. Aging (Albany NY) 2019;11:2369-77.
13. Zhang Z, Chang Y, Jia W, et al. LINC00673 rs11655237

C>T confers neuroblastoma susceptibility in Chinese population. Biosci Rep 2018;38:BSR20171667.
14. He J, Zhang R, Zou Y, et al. Evaluation of GWAS-identified SNPs at 6p22 with neuroblastoma susceptibility in a Chinese population. Tumour Biol 2016;37:1635-9.
15. Visscher PM, Wray NR, Zhang Q, et al. 10 Years of GWAS Discovery: Biology, Function, and Translation. Am J Hum Genet 2017;101:5-22.
16. Collins FS, Brooks LD, Chakravarti A, et al. A DNA polymorphism discovery resource for research on human genetic variation. Genome Res 1998;8:1229-31.
17. Zhang X, Li J, Yang Q, et al. Tumor mutation burden and JARID2 gene alteration are associated with short disease-free survival in locally advanced triple-negative breast cancer. Ann Transl Med 2020;8:1052.
18. Castellanos-Rubio A, Ghosh S, et al. Disease-Associated SNPs in Inflammation-Related lncRNAs. Front Immunol 2019;10:420.
19. Sung H, Yang HH, Hu N, et al. Functional annotation of high-quality SNP biomarkers of gastric cancer susceptibility: the Yin Yang of PSCA rs2294008. Gut 2016;65:361-4.
20. O'Brien TD, Jia P, Caporaso NE, et al. Weak sharing of genetic association signals in three lung cancer subtypes: evidence at the SNP, gene, regulation, and pathway levels. Genome Med 2018;10:16.
21. Zheng J, Huang X, Tan W, et al. Pancreatic cancer risk variant in LINC00673 creates a miR-1231 binding site and interferes with PTPN11 degradation. Nat Genet 2016;48:747-57.
22. Zhao K, Zhang R, Li T, et al. Functional variants of lncRNA LINC00673 and gastric cancer susceptibility: a case-control study in a Chinese population. Cancer Manag Res 2019;11:3861-8.
23. Wang Y, Luo T, et al. LINC00673 rs11655237 Polymorphism Is Associated With Increased Risk of Cervical Cancer in a Chinese Population. Cancer Control 2018;25:1073274818803942.
24. Zhu W, Li L, Li D, et al. Rs11655237 polymorphism of LINC00673 affects the prognosis of cervical cancer by interfering with the interaction between LINC00673 and microRNA-1231. J Cell Physiol 2020;235:8155-66.

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Supplementary

Table S1 Frequency distribution of selected variables in glioma patients and cancer-free controls

Variables	Cases (N=171)		Controls (N=228)		P[a]
	No.	%	No.	%	
Age range, months	4.00–168.00		4.00–168.00		0.623
Mean ± SD	63.40±47.72		52.41±32.65		
<60	85	49.71	119	52.19	
≥60	86	50.29	109	47.81	
Gender					0.190
Female	81	47.37	93	40.79	
Male	90	52.63	135	59.21	
Subtypes					
Astrocytic tumors	125	73.10	–	–	
Ependymoma	24	14.62	–	–	
Neuronal and mixed neutonal-glial tumours	14	8.19	–	–	
Embryonal tumors	7	4.09	–	–	
WHO stages					
I	103	60.23	–	–	
II	28	16.37	–	–	
III	15	8.77	–	–	
IV	25	14.62	–	–	

[a], two-sided χ^2 test for distributions between glioma patients and cancer-free controls. SD, standard deviation.

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