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RESEARCH ARTICLE

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Association between *GPC2* polymorphisms and neuroblastoma risk in Chinese children

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Abstract

Background: The cell surface glycoprotein glypican 2 (GPC2) has been shown to increase susceptibility to neuroblastoma, which is the most common malignancy in children. However, associations between single nucleotide polymorphism(s) of *GPC2* and neuroblastoma risk remain unclarified.

Methods: We conducted a case–control study to investigate two *GPC2* polymorphisms (rs1918353 G>A and rs7799441 C>T) in 473 healthy controls and 402 pediatric patients with neuroblastoma. Single nucleotide polymorphism (SNP) genotyping was conducted on the samples by the TaqMan technique, and the data were subsequently analyzed by the t test, chi-squared test, and logistic regression model. In addition, we further performed stratification analysis by age, sex, tumor site of origin, or clinical stage to control confounding factors.

Results: According to the data of dominant models (GA/AA vs. GG: adjusted OR = 0.99, 95% CI = 0.76–1.29, $p = 0.943$; CT/TT vs. CC: adjusted OR = 0.91, 95% CI = 0.70–1.19, $p = 0.498$) or other comparisons, as well as the conjoint analysis (adjusted OR = 1.22, 95% CI = 0.93–1.59, $p = 0.152$), we unfortunately proved that the analysis of single or multiple loci did not support any significant association of *GPC2* polymorphisms with susceptibility to neuroblastoma.

Conclusion: *GPC2* polymorphisms (rs1918353 G>A and rs7799441 C>T) are unable to statistically affect neuroblastoma risk in Chinese children. Therefore, more samples, especially from patients of various ethnic backgrounds, are required to increase the sample size and verify the effect of *GPC2* polymorphisms on neuroblastoma risk in the presence of ethnic factor.

KEYWORDS
glypican 2, neuroblastoma, polymorphism, susceptibility

Meng Li, Xinxin Zhang and Jiabin Liu contributed equally to this work.

1 | INTRODUCTION

Neuroblastoma is the most common extracranial solid tumor and is associated with various clinical manifestations and progressions, which generally occurs during the first decade of a child's life.[1] Neuroblastoma accounts for 5%–7% of child malignancies and nearly 15% of pediatric tumor-related deaths.[1–3] Based on the risk of death, neuroblastoma patients are classified into four groups: (I) very low risk, (II) low risk, (III) intermediate risk, and (IV) high risk.[4] It has been reported that the survival rate of patients in the first three risk groups is approximately 100%, while the 5-year survival rate is <50% for patients with high-risk neuroblastoma.[5–7]

Glypicans (GPCs) include six (GPC1-6) glycoproteins located on the cell membrane that are covalently bound to heparan sulfate (HS) glycosaminoglycan chains via glycosylphosphatidylinositol (GPI) anchors.[8] Acting as cell surface coreceptors that participate in signal transduction, GPCs play various roles in cancer cell proliferation by interacting with multiple growth factors and chemokines.[9–11] To date, several single nucleotide polymorphisms (SNPs) in *GPC* genes have been shown to contribute to the risk of cancer. For instance, a polymorphism (rs2267531) in the *GPC3* promoter region is significantly associated with hepatocellular carcinoma.[12] A polymorphism (rs1048369) in *GPC4* contributes to the risk of Epstein–Barr virus-associated gastric carcinoma.[13]

Interestingly, it was reported that the overexpression of GPC2 can be observed in most neuroblastoma samples, which is critical for neuroblastoma maintenance.[14] The *GPC2* gene was originally identified in brain tissues of rats, and it is located at locus 7q22.1.[15] This gene encodes a 579-amino acid protein bearing heparan sulfate, which works as a protein coreceptor and participates in Wnt, Notch, and Hedgehog signal transduction.[16–19] Moreover, GPC2 levels are nearly undetectable in normal pediatric tissue samples, which is more suitable for drug development than disialoganglioside (GD2). GD2 is highly expressed in nociceptor-containing peripheral nerves as well as neuroblastoma tissues.[14,20] Undoubtedly, *MYCN* amplification is the most popular marker of neuroblastoma, and it indicates a high risk of death and poor prognosis.[21,22] *GPC2* expression closely correlates with *MYCN* amplification in neuroblastoma.[14,23] Therefore, GPC2 is attracting more attention worldwide, and increasing evidence has demonstrated that GPC2 can act as a strong target with great potential for immunotherapy in neuroblastoma.[24–26]

Nevertheless, the influences of *GPC2* gene polymorphism(s) on susceptibility to neuroblastoma remain unexplored. Herein, we performed this case–control study to determine whether there is any association of *GPC2* polymorphism(s) with susceptibility to neuroblastoma in Chinese children.

2 | MATERIALS AND METHODS

2.1 | Research subjects

We determined the required sample size by POWER Program V.3.0.0 with the following parameters. The ratio of control to case was 1:1. The minor allele frequency (MAF) ranged from 0.10 to 0.50. The type I error was 0.05. The prevalence of neuroblastoma was 7.7 per million. Given that neuroblastoma is a very rare pediatric tumor, the odds ratio for the highest risk level of onset was 1.50. The power was 0.80. Thus, the calculated sample size required the recruitment of at least 383.4 cases and controls. In this study, 473 healthy controls and 402 neuroblastoma patients were recruited from Jiangsu Province (Table S1). The specific selection criteria and details about these participants were described in our previously published articles.[27–29] Briefly, children diagnosed with neuroblastoma by biopsy or histology were included in the case group. Moreover, cancer-free participants who visited the hospitals during the same period were randomly selected into the control group, and this group was matched to the case group in terms of population characteristics such as age and gender. Guardians of controls and patients were informed at recruitment and signed written consent forms. The protocols of this study were approved by the Institutional Review Boards of Children's Hospital of Nanjing Medical University and Guangzhou Women and Children's Medical Center.

2.2 | Polymorphisms selection and genotyping

Functional candidate SNPs were retrieved from the NCBI dbSNP database and SNPinfo Web Server. Briefly, the selection strategy of *GPC2* polymorphisms was as follows: The polymorphisms should be located in the 5′ flanking region, 5′ untranslated region, 3′ untranslated region, or the exon; the MAF among the Han Chinese population (Beijing) was higher than 5%; and low linkage disequilibrium was shown ($R^2 < 0.8$). Consequently, two SNPs (rs1918353 G>A and rs7799441 C>T) in the *GPC2* gene were considered candidates for subsequent analyses. The TIANamp Blood DNA Kit (TIANGEN Biotech Co. Ltd.) was used to extract genomic DNA from peripheral blood collected from the donors. Then, TaqMan real-time PCR was used for genotyping according to the standard method.[30–32] For quality control, we randomly selected approximately 10% of the specimens for duplicate analyses. A 100% concordance rate was observed for each SNP among the duplicate sets.

2.3 | Statistical analyses

The goodness-of-fit chi-squared test was performed to assess the deviation from Hardy–Weinberg equilibrium (HWE) for each SNP in the control subjects. Then, we conducted a two-sided chi-squared test to determine the differences in the demographic variables and genotypic frequencies between all the controls and neuroblastoma patients. Logistic regression analysis was applied to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs), which were subsequently used to estimate the strength of association between *GPC2* polymorphism(s) and neuroblastoma risk, adjusting for sex and age. SAS statistical package (version 9.4, SAS Institute, Cary, NC) was used for statistical analyses. All p values are two-sided, and $p < 0.05$ indicates significance.

3 | RESULTS

3.1 | Association between *GPC2* gene polymorphisms and susceptibility to neuroblastoma

In total, 473 controls and 402 patients were enrolled in the research (Table S1). Both polymorphisms (rs1918353 G>A and rs7799441 C>T) were in accordance with HWE in the control samples (rs1918353: P_{HWE} = 0.430; rs7799441: P_{HWE} = 0.062). In fact, neither rs1918353 G>A nor rs7799441 C>T in the *GPC2* gene showed a pronounced relationship with neuroblastoma risk according to the dominant models (GA/AA vs. GG: adjusted OR = 0.99, 95% CI = 0.76–1.29, p = 0.943; CT/TT vs. CC: adjusted OR = 0.91, 95% CI = 0.70–1.19, p = 0.498) or other comparisons (Table 1). Then, the two risk genotypes were used for conjoint analysis, and we found no significant association (adjusted OR = 1.22, 95% CI = 0.93–1.59, p = 0.152) between *GPC2* SNPs and susceptibility to neuroblastoma.

3.2 | Stratification analysis

To obtain more details, we further performed stratification analysis by age, sex, tumor site of origin, or clinical stage (Table 2). Unfortunately, we were unable to identify a significant association between both polymorphisms (rs1918353 G>A and rs7799441 C>T) and neuroblastoma risk.

4 | DISCUSSION

Aiming to investigate the relationship between *GPC2* polymorphisms and susceptibility to neuroblastoma, we performed this hospital-based case–control study in Chinese children. This is the first study to reveal the association between these two *GPC2* polymorphisms and neuroblastoma risk.

The overexpression of GPC2 was found in various cancers, including colon adenocarcinoma,[18] medulloblastomas,[33] prostate

TABLE 1 Associations between *GPC2* gene polymorphisms and neuroblastoma susceptibility in children from Jiangsu province.

Genotype	Cases (N = 402)	Controls (N = 473)	p[a]	Crude OR (95% CI)	p	Adjusted OR (95% CI)[b]	p[b]
rs1918353 (P_{HWE} = 0.430)							
GG	199 (49.50)	233 (49.26)		1.00		1.00	
GA	161 (40.05)	203 (42.92)		0.93 (0.70–1.23)	0.605	0.93 (0.70–1.23)	0.604
AA	42 (10.45)	37 (7.82)		1.33 (0.82–2.15)	0.246	1.33 (0.82–2.15)	0.245
Additive			0.589	1.06 (0.86–1.30)	0.588	1.06 (0.86–1.30)	0.587
Dominant	203 (50.50)	240 (50.74)	0.943	0.99 (0.75–1.29)	0.943	0.99 (0.76–1.29)	0.943
GG/GA	360 (89.55)	436 (92.18)		1.00		1.00	
AA	42 (10.45)	37 (7.82)	0.177	1.38 (0.87–2.19)	0.178	1.38 (0.87–2.19)	0.178
rs7799441 (P_{HWE} = 0.062)							
CC	174 (43.28)	194 (41.01)		1.00		1.00	
CT	189 (47.01)	232 (49.05)		0.91 (0.69–1.20)	0.502	0.91 (0.69–1.20)	0.502
TT	39 (9.70)	47 (9.94)		0.93 (0.58–1.48)	0.746	0.93 (0.58–1.48)	0.747
Additive			0.567	0.94 (0.77–1.16)	0.567	0.94 (0.77–1.16)	0.568
Dominant	228 (56.72)	279 (58.99)	0.498	0.91 (0.70–1.19)	0.498	0.91 (0.70–1.19)	0.498
CC/CT	363 (90.30)	426 (90.06)		1.00		1.00	
TT	39 (9.70)	47 (9.94)	0.907	0.97 (0.62–1.52)	0.907	0.97 (0.62–1.52)	0.909
Risk genotypes[c]							
0	187 (46.52)	243 (51.37)		1.00		1.00	
1	214 (53.23)	229 (48.41)		1.21 (0.93–1.59)	0.153	1.21 (0.93–1.59)	0.153
2	1 (0.25)	1 (0.21)		1.30 (0.08–20.91)	0.853	1.30 (0.08–20.91)	0.854
1–2	215 (53.48)	230 (48.63)	0.152	1.22 (0.93–1.59)	0.152	1.22 (0.93–1.59)	0.152

Note: Additive model was defined as GG versus GA versus AA (rs1918353); CC versus CT versus TT (rs7799441). Dominant model was defined as AA/GA versus GG (rs1918353); TT/CT versus CC (rs7799441). Recessive model was defined as GG/GA versus AA (rs1918353); CC/CT versus TT (rs7799441).

[a]Chi-squared test for genotype distributions between neuroblastoma cases and cancer-free controls.

[b]Adjusted for age and gender.

[c]Risk genotypes were carriers with rs1918353 AA and rs7799441 CC genotypes.

TABLE 2 Stratification analysis for the relevance of *GPC2* gene polymorphisms with neuroblastoma susceptibility.

	rs1918353 (cases/controls)		Adjusted OR[a]		rs7799441 (cases/controls)		Adjusted OR[a]		Risk genotypes (cases/controls)		Adjusted OR[a]	
Variables	**GG/GA**	**AA**	**(95% CI)**	***p*[a]**	**CC**	**CT/TT**	**(95% CI)**	***p*[a]**	**0**	**1–2**	**(95% CI)**	***p*[a]**
Age, month												
≤18	124/131	15/8	1.98 (0.81–4.83)	0.134	65/57	74/82	0.79 (0.49–1.27)	0.332	59/74	80/65	1.55 (0.96–2.48)	0.072
>18	236/305	27/29	1.20 (0.69–2.09)	0.513	109/137	154/197	0.98 (0.71–1.36)	0.912	128/169	135/165	1.08 (0.78–1.49)	0.638
Gender												
Females	172/203	19/22	1.02 (0.53–1.95)	0.952	81/88	110/137	0.87 (0.59–1.29)	0.496	91/116	100/109	1.17 (0.80–1.72)	0.427
Males	188/233	23/15	1.92 (0.97–3.79)	0.061	93/106	118/142	0.95 (0.65–1.38)	0.781	96/127	115/121	1.26 (0.87–1.82)	0.223
Sites of origin												
Adrenal gland	84/436	9/37	1.26 (0.59–2.72)	0.553	41/194	52/279	0.89 (0.57–1.39)	0.597	43/243	50/230	1.22 (0.78–1.91)	0.378
Retroperitoneal	150/436	17/37	1.33 (0.73–2.44)	0.351	67/194	100/279	1.04 (0.72–1.49)	0.845	83/243	84/230	1.07 (0.75–1.52)	0.707
Mediastinum	105/436	15/37	1.69 (0.89–3.20)	0.106	55/194	65/279	0.82 (0.55–1.23)	0.343	51/243	69/230	1.43 (0.95–2.14)	0.084
Others	18/436	0/37	/	/	11/194	7/279	0.44 (0.17–1.15)	0.092	7/243	11/230	1.69 (0.64–4.45)	0.286
Clinical stages												
I + II + 4s	156/436	15/37	1.11 (0.59–2.08)	0.748	74/194	97/279	0.91 (0.64–1.29)	0.583	82/152	89/321	1.15 (0.81–1.63)	0.444
III + IV	148/436	15/37	1.22 (0.65–2.29)	0.543	75/194	88/279	0.82 (0.58–1.18)	0.287	74/152	89/321	1.27 (0.89–1.81)	0.196

[a]Adjusted for age and gender, omitting the correspondence factor.

cancer,[34] and so on. Moreover, GPC2 levels are relatively high in growing nervous tissues.[35-37] It has been widely shown that GPC2 overexpression also occurs in neuroblastoma.[14,24] However, no reports have demonstrated any association between *GPC2* polymorphism and susceptibility to neuroblastoma.

In light of the common indication of *GPC* SNPs in carcinogenesis and the close relationship between *GPC2* and neuroblastoma, we were motivated to study the association of *GPC2* polymorphism(s) with susceptibility to neuroblastoma. Unfortunately, after overall and stratified analyses, we proved that there is no noteworthy association between *GPC2* polymorphisms (rs1918353 G>A and rs7799441 C>T) and neuroblastoma risk in the studied donors. To date, we have not found any report that provided evidence of an association of *GPC2* polymorphism with cancer risk. Intriguingly, the rs12705073 polymorphism, located in the first intron of the *GPC2* gene, was shown to have a genome-wide statistical association with Alzheimer's disease.[38,39] Gene polymorphisms may exert a variety of effects on modifying tumor susceptibility, and these effects depend on diverse tumor types, ethnicities, and geographical regions.

While this research has some advantages, several shortcomings were inevitable. First, in this case–control study, we were unable to eliminate inherent bias since all the controls and patients were recruited from hospitals. Second, the moderate sample size, including 473 controls and 402 patients, might be the reason for the limited statistical power. Third, the statistical results of Chinese children are unsuitable for generalizing these conclusions to other populations. Fourth, we were unable to obtain details about environmental factors, such as parental exposures, dietary intake, and living environments, which are helpful for analyzing gene–environment interactions.

5 | CONCLUSION

In summary, we present the first report of data indicating that *GPC2* polymorphisms (rs1918353 G>A and rs7799441 C>T) have no significant association with susceptibility to neuroblastoma. In the future, it is essential to conduct more epidemiological studies in different ethnic groups to adequately understand the contribution of *GPC2* polymorphism(s) to neuroblastoma risk.

AUTHOR CONTRIBUTIONS

Meng Li: Investigation, Methodology, Writing & editing. Xinxin Zhang: Investigation, Resources. Jiabin Liu: Methodology, Resources. Chunlei Zhou: Data curation. Lei Miao: Formal analysis. Jing He: Funding acquisition, Conceptualization. Haiyan Wu: Investigation. Ruizhong Zhang: Funding acquisition, Project administration, Supervision, Investigation, Formal analysis, Data curation, Review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study may be requested from the corresponding author.

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SUPPORTING INFORMATION

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