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Original Article

Association Between miR-492 rs2289030 G>C and Susceptibility to Neuroblastoma in Chinese Children from Jiangsu Province

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Abstract

Background and objectives: Neuroblastoma is a heterogeneous solid tumor that originates extracranially from neuroblasts. Previous research has demonstrated that miR-492 polymorphisms can contribute to cancer susceptibility. However, their specific involvement in susceptibility to neuroblastoma has yet to be fully clarified.

Methods: To address this question, we used the TaqMan method to genotype miR-492 rs2289030 G>C in a cohort of 402 neuroblastoma children and 473 control individuals from Jiangsu Province, China.

Results: Our study showed that there was no significant association between miR-492 rs2289030 G>C and the risk of neuroblastoma in children, as assessed by combined odds ratios (ORs) and 95% confidence intervals ($P > 0.05$).

Conclusions: Further validation of these findings requires well-designed studies with large sample sizes.

Introduction

Neuroblastoma is a heterogeneous solid tumor that originates extracranially from neuroblasts. Approximately 90% of affected individuals are under the age of 10, with a median diagnosis age of 18 months, ultimately leading to the development of tumors in the adrenal glands and/or sympathetic ganglia.[1] The overall survival rate for children aged between 18 months and 12 years is 49%, whereas it decreases to less than 10% for adolescents and young adults (>12 years).[2] The prognosis of patients with neuroblastoma varies significantly. While some patients may recover spontaneously without any medical intervention (as observed in 4S neuroblastoma), others need to fight drug resistance throughout their lives.[3,4] Following disease staging, each patient is categorized into one of the four groups: very-low-risk, low-risk, intermediate-risk, or high-risk based on clinical and molecular risk factors. This approach helps clinicians determine the optimal treatment approach.[5] Despite advancements in overall survival rates, 36% of patients are diagnosed with metastatic, high-risk disease, which poses significant challenges for successful treatment.[6] The prognosis for high-risk neuroblastoma patients remains dismal, with an overall 5-year survival rate of less than 50%, even after aggressive surgery and multimodal cytotoxic therapies.[7]

The specific environmental risk factors associated with the de-

Keywords: miR-492; Susceptibility; Neuroblastoma; Polymorphism.

Abbreviations: CIs, confidence intervals; GWASs, genome-wide association studies; HWE, Hardy-Weinberg equilibrium; miRNAs, microRNAs; ORs, odds ratios; pre-miRNAs, precursor miRNAs; SNPs, single nucleotide polymorphisms; INSS, International Neuroblastoma Staging System.

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velopment of neuroblastoma are still undefined.[8] Multiple studies have suggested that genetic factors, including *ALK*[9,10] and *PHOX2B*[11,12] gene mutations, may have a significant impact on the development of neuroblastoma. Genome-wide association studies (GWASs) have additionally discovered polymorphisms within the *CASC15*, *HACE1*, *LMO1*, *LIN28B*, *BARD1*, and *TP53* genes that are associated with an increased risk of neuroblastoma.[5,13,14] The identification of microRNAs (miRNAs) has revealed a novel mechanism of gene regulation, shedding light on the complex pathophysiology of neuroblastoma and potentially offering solutions to unresolved issues. miRNAs are short, single-stranded RNA molecules consisting of 19–25 nucleotides in length.[15] miRNAs act by binding to a complementary sequence located in the 3′ untranslated region of mRNAs, thereby inhibiting gene expression, causing mRNA degradation, and preventing translation.[16] Dysregulation of miRNAs has been observed in various types of malignancies, where specific miRNAs can function either as tumor promoters or tumor suppressors.[17,18] Single nucleotide polymorphisms (SNPs) within the encoding sequences of precursor miRNAs (pre-miRNAs) can potentially impact the expression and maturation of miRNAs, consequently affecting susceptibility to neuroblastoma and other types of cancers.[19–22]

In this study, we focused on miRNA-492, which has been reported to be a regulator involved in several gastrointestinal cancers.[23] Previous studies have also suggested that the miRNA-492 G>C rs2289030 polymorphism could impact susceptibility to different types of liver cancers, such as hepatocellular carcinoma.[24]

However, to date, no study has investigated the role of miRNA-492 G>C rs2289030 in the risk of neuroblastoma. We conducted this case-control investigation using samples from Nanjing Children's Hospital, comprising 402 cases and 473 controls. The aim was to evaluate the potential link between miRNA-492 G>C rs2289030 and neuroblastoma susceptibility.

Methods

Study subjects

This study involved a sample of 402 cases of neuroblastoma and 473 healthy control subjects enrolled from Jiangsu province (Table S1). This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (revised in 2013). The study protocol (202112141-1) was approved by the institutional review board of the Children's Hospital of Nanjing Medical University. Prior to participation, all individuals involved in the study, including minors, provided written informed consent. For participants who were minors, the consent form was signed by their parent or legal guardian. Details of the participant selection process have been provided in our previous publication.[14,25,26]

Genotyping of the miR-492 rs2289030 G>C SNP

Based on our previously established criteria,[27] we chose to investigate the potential association of the miR-492 rs2289030 G>C polymorphism in this case-control study. We extracted genomic DNA from peripheral blood donated by subjects using the TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd., Beijing, China). The genotyping of all selected SNP was performed using a commercially available TaqMan real-time PCR assay (ID C_15880380_10) according to standard protocols. We programmed the instrument for PCR using the following conditions: pre-read stage at 60°C for 30 seconds, holding stage at 95°C for 10 minutes, and 45 cycles of denaturation at 95°C for 15 seconds, annealing and extension at 60°C for 1 minute. Then, we selected standard run mode and added the reaction mixture (5 μL for each well in a 384-well reaction plate). The reaction plate was loaded into the instrument, and the run was started. Additional methodological details can be found in the referenced literature.[27–29] Eight negative controls with water and eight replicate samples were included in each 384-well plate as a quality control measure. In addition, 10% of the samples were randomly selected for a second run. All duplicate sets were found to have a concordance rate of 100%.

Statistical analysis

The demographic characteristics and distribution of genotype frequencies between patients with neuroblastoma and controls were compared using the bilateral χ^2 test. The goodness-of-fit χ^2 test was used to assess whether there were deviations from Hardy-Weinberg equilibrium for the selected polymorphisms in the control group. Then, we used a two-sided chi-square test to assess the differences in demographic variables and allele frequencies between all cases and controls. Logistic regression analysis was used to evaluate the relationship between the miR-492 SNP and neuroblastoma susceptibility, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All statistical analyses were carried out using SAS software version 9.4 (SAS Institute, Cary, NC). The level of statistical significance was predetermined at $P < 0.05$.

Results

Characteristics of the participants

This study included a total of 402 neuroblastoma cases and 473 healthy controls from Jiangsu province. All of the cases included in this study were newly confirmed neuroblastoma patients who underwent histopathological diagnosis and had no progressive disease or previous treatments. The location of the patients' neuroblastoma was mainly in the retroperitoneal region (41.54%), mediastinum (29.85%) and adrenal gland (23.13%). International Neuroblastoma Staging System (INSS) staging consisted primarily of stage I (26.87%) and stage IV (25.87%). The clinical characteristics and demographics of neuroblastoma cases and controls are summarized in Table S1. No significant associations were detected between cases and controls in terms of age ($P = 0.100$) and gender ($P = 0.987$).

Association of the miR-492 SNP with susceptibility to neuroblastoma

As shown in Table 1, the genotype frequency distribution of miR-492 rs2289030 G>C was in accordance with the Hardy-Weinberg equilibrium (HWE) in the control group ($P = 0.056$). Our findings revealed that the genotype distribution among neuroblastoma patients did not show significant differences when compared with those among the control group. Consequently, none of the rs2289030 genotypes were found to be associated with susceptibility to neuroblastoma.

Discussion

In this case-control study involving children from Jiangsu province, China, we examined the association between a miR-492 SNP and susceptibility to neuroblastoma. To the best of our knowledge, miR-492 rs2289030 G>C has not been investigated in any previous studies regarding neuroblastoma. As a result, our study found

Table 1. ***miR-492*** **rs2289030 G>C polymorphism and neuroblastoma risk 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
rs2289030 (HWE = 0.056)							
GG	248 (61.69)	286 (60.47)		1.00		1.00	
GC	134 (33.33)	154 (32.56)		1.00 (0.75–1.34)	0.981	1.00 (0.75–1.34)	0.982
CC	20 (4.98)	33 (6.98)		0.70 (0.39–1.25)	0.227	0.70 (0.39–1.25)	0.227
Additive			0.434	0.92 (0.74–1.14)	0.433	0.92 (0.74–1.14)	0.433
Dominant	154 (38.31)	187 (39.53)	0.711	0.95 (0.72–1.25)	0.711	0.95 (0.72–1.25)	0.711
GG/GC	382 (95.02)	440 (93.03)		1.00		1.00	
CC	20 (4.98)	33 (6.98)	0.216	0.70 (0.39–1.24)	0.218	0.70 (0.39–1.24)	0.218

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

no significant association between miR-492 rs2289030 G>C and the risk of neuroblastoma in children.

With the progress in research and technology, an increasing number of researchers support the significant involvement of genetic factors in the pathogenesis of neuroblastoma. In recent years, GWASs have identified a number of genetic variants located in various genes that are linked to neuroblastoma risk.[30–34] The majority of the SNPs identified by GWAS as contributing to neuroblastoma risk have been verified through replication case-control studies.[25,26,35–37] It is necessary to further identify gene polymorphisms that are associated with susceptibility to neuroblastoma, which will aid in comprehending the etiology of this disease.

miRNAs can negatively regulate gene expression at the post-transcriptional level, thereby impacting various cellular processes, such as cell proliferation, carcinogenesis, apoptosis, metabolism, and differentiation.[38] miR-492 is derived from both the KRT19 pseudogene 2 and the KRT19 transcript.[39,40] It exerts its influence by targeting 11 genes and playing a role in multiple signaling pathways, governing crucial cellular processes such as invasion, epithelial-mesenchymal transition, cell proliferation, migration, and apoptosis.[41] However, miR-492 exhibits increased expression in multiple cancer types, while in certain others, its expression is decreased.[42–45] Neither the GG, GC, nor CC risk genotypes in our study showed any correlation with neuroblastoma risk. The reasons for the differential expression of miR-492 in various cancers are not fully understood, and further studies with larger sample sizes are needed. Consistent with our results, studies exploring miR-492 rs2289030 G>C genotype and susceptibility to colorectal cancer[46] and gastric cancer[47] failed to find an association, as did Hirschsprung disease[48] and high-risk atrophic gastritis.[47] The participants in these studies were European or southern Chinese. Polymorphisms may have varying genetic effects on cancer susceptibility contingent on factors such as the type of cancer, ethnicity, and geographical location.

This study has several limitations that should be acknowledged. Firstly, the statistical power of this study might be compromised due to the relatively small sample size. Secondly, as a hospital-based case-control study, the inclusion of non-representative subjects could lead to inherent selection bias. Thirdly, the conclusions drawn from this study may lack generalizability, as the subjects solely consisted of individuals of Chinese descent. Fourthly, the selection of the SNP was based on prior knowledge of potentially functional SNPs, probably resulting in the omission of other crucial tagging SNPs. Finally, in the current study, assessments of environmental factors and gene-environment interactions were not possible due to the lack of available environmental data.

Conclusions

We present initial evidence indicating that polymorphisms in the miR-492 rs2289030 G>C genotype may not have an impact on the risk of neuroblastoma in individuals from Jiangsu province, China. Additional validation of this evidence with larger samples is required. Ultimately, our study may shed light on the role of miR-492 in this aggressive pediatric tumor.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/CSP.2023.00025S.

Table S1. Demographic characteristics of neuroblastoma patients and cancer-free controls from Jiangsu province.

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Conflict of interest

One of the authors, Prof. Jing He, has been an editorial board member of *Cancer Screening and Prevention* since April 2023. The authors have no conflict of interests related to this publication.

Author contributions

Contributed to study concept and design (ZJZ and JH), acquisition of the data (WJW and CLZ), assay performance and data analysis

(WJW, CLZ, XXZ, YMZ, CMD, and HYW), drafting of the manuscript (WJW and CLZ), critical revision of the manuscript (ZJZ and JH), and supervision (ZJZ and JH).

Ethical statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (revised in 2013). The study protocol (202112141-1) was approved by the institutional review board of the Children's Hospital of Nanjing Medical University. Prior to participation, all individuals involved in the study, including minors, provided written informed consent. For participants who were minors, the consent form was signed by their parent or legal guardian.

Data sharing statement

The corresponding author will provide access to the datasets generated and utilized during the study upon reasonable request.

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