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Research Paper

Association between *NEFL* Gene Polymorphisms and Neuroblastoma Risk in Chinese Children: A Two-Center Case-Control Study

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Abstract

Neuroblastoma is a lethal tumor that mainly occurs in children. To date, the genetic etiology of sporadic neuroblastoma remains obscure. A previous study identified three neuroblastoma susceptibility loci (rs11994014 G>A, rs2979704 T>C, rs1059111 A>T) in *neurofilament light* (*NEFL*) gene. Here, we attempted to evaluate the contributions of these three single nucleotide polymorphisms to neuroblastoma susceptibility in Chinese children. We genotyped these three polymorphisms using subjects from Guangdong province (256 cases and 531 controls) and Henan province (118 cases and 281 controls). Logistic regression models were performed to generate odds ratios and 95% confidence intervals to access the association of these three polymorphisms with neuroblastoma risk. Overall, we failed to provide any evidence supporting the association between these three polymorphisms and neuroblastoma susceptibility, either in single center population or in the combined population. Moreover, such null association was also observed when the samples were stratified by age, gender, tumor sites, and clinical stages. In the future, larger samples from different ethnicities are needed to clarify the role of *NEFL* gene polymorphisms in neuroblastoma risk.

Key words: neuroblastoma; *NEFL*; polymorphism; susceptibility

Introduction

Neuroblastoma, one the most common solid cancer in children, is characterized by various clinical phenotypes [1]. It accounts for about 7% of all cancer types in children under 15 years of age [2, 3]. The prevalence of neuroblastoma is higher in the United States [4] than that in China [5] (8-14 cases per million versus about 7.7 per million). Neuroblastoma can be categorized into three different groups, low-risk, intermediate-risk, and high-risk groups. A large proportion of the affected patients have a favorable prognosis, as they bear localized benign tumors that can regress spontaneously [6]. The survival rate for low-risk patients is generally greater than 95%, no matter treated with minimal chemotherapy or not. Patients with intermediate-risk neuroblastoma constitute about 15% of all neuroblastoma patients, and their survival rate is larger than 80% after multimodal therapy. Moreover, nearly 50% of

patients are classified as high-risk neuroblastoma, with survival rate approximately less than 35% even after` receiving comprehensive treatments [7, 8]. Such poor prognosis might be attributed to the widespread dissemination of tumor to bone and bone marrow at the time of diagnosis.

By now, the etiology of familial neuroblastoma is mainly attributed to the *ALK* [9, 10] and *PHOX2B* [11, 12] gene mutations. However, familial neuroblastoma only accounts for 1% of all neuroblastoma cases [13]. The explicit causes of most common sporadic neuroblastoma still remain obscure. Previous studies have paid attention to the role of environmental risk factors in influencing susceptibility to neuroblastoma [14, 15]. However, environmental etiology alone cannot explain the fact that only a small portion of children finally developed neuroblastoma after parental exposure to risk environmental factors [16]. Mounting evidence has suggested that genetic factors and gene-environmental interactions might influence the susceptibility to neuroblastoma [17, 18].

Early genome-wide association studies (GWASs) of neuroblastoma have identified a number of neuroblastoma susceptibility loci in the genes including *BARD1* [19], *DUSP12* [20], *DDX4* [20], *HSD17B12* [20], *IL31RA* [20], *LIN28B* [21], *HACE1* [21], and *LMO1* [22]. Moreover, several single nucleotide polymorphisms (SNPs) in lncRNA also contributed to the susceptibility to neuroblastoma and other cancers [23, 24]. However, these gene loci only account for a small fraction of neuroblastoma heritability. Some potential functional gene loci might be ruled out as a result of the introduction of the multiple testing corrections in GWAS [25]. To discover more hidden true-positive loci, a variety of novel methods have been presented. The methods include but not limit to: adopting gene- or pathway-based approaches, using larger GWAS samples, replicating previously reported GWAS signals in a larger cohort, conducting a meta-analysis of GWAS datasets, and performing imputation and epistasis analysis [26]. For instance, using larger GWAS samples, rare variants of *TP53* were found to be associated with neuroblastoma predisposition [27].

In a previous proteomic study on differentiated neuroblastoma cell line, Capasso et al. [28] found that eight proteins were differentially expressed during neuroblastoma differentiation. To discover more variants predisposing to neuroblastoma, Capasso et al. [29] further investigated whether the genes encoding these eight proteins were related to neuroblastoma development. Using the discovery set (2,101 patients and 4,202 control subjects) and the replication set (459 cases and 809 controls), they successfully identified three common neuroblastoma predisposing variants in the *neurofilament light* (*NEFL*) gene (rs11994014 G>A, rs2979704 T>C, rs1059111 A>T).

Here, we tested the association between the three putative SNPs in *NEFL* gene and neuroblastoma risk in a two-center, case-control study in Chinese population. The aim of our study was to reveal the contribution of these SNPs to the neuroblastoma susceptibility in Chinese children.

Materials and methods

Study subjects

This study consisted of two populations, one including 256 cases and 531 controls from Guangdong province, and the other including 118 cases and 281 controls from Henan province (**Supplemental Table 1**) [30]. The selection details and criteria of the subjects were provided in our previously published articles [31-36]. At recruitment, informed written consent was obtained from all participants or their guardians. The study protocols were approved by the Institutional Review Boards of Guangzhou Women and Children's Medical Center and the First Affiliated Hospital of Zhengzhou University.

SNP selection and genotyping

Three SNPs (rs11994014 G>A, rs2979704 T>C, rs1059111 A>T) in the *NEFL* gene by Capasso et al. [29] were selected. Genomic DNA was mainly purified from venous blood collected from the subjects, using a TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd., Beijing, China). Genotyping was performed using TaqMan real-time PCR by standard methods, with details reported elsewhere [37-39]. For quality control, we randomly selected approximately 10% of the samples to perform duplicate analyses. 100% concordance rate was observed for each SNP among duplicate sets.

Statistical analysis

Deviation from Hardy-Weinberg equilibrium (HWE) for each SNP was assessed in the control subjects, using the goodness-of-fit χ^2 test. The chi-squared test was employed to evaluate differences in the demographic variables and allele frequencies between the cases and controls. Odds ratios and corresponding 95% confidence intervals were calculated to determine the relative cancer risk, adjusting for age and gender. A two-sided P value < 0.05 was set as the statistical significance level. All statistical analyses were conducted using SAS statistical package, version 9.1 (SAS Institute, Cary, NC).

Results

Association between NEFL gene polymorphisms and neuroblastoma susceptibility

Genotyping were successfully conducted in the Guangdong population (255 cases and 531 controls) and Henan population (118 cases and 281 controls). The genotype frequencies and association results of these three *NEFL* gene polymorphisms (rs11994014 G>A, rs2979704 T>C, and rs1059111 A>T) were presented for Guangdong, Henan, and combined population separately in **Table 1**. All of these three polymorphisms were agreed with HWE (P=0.513 for rs11994014 G>A, P=0.498 for rs2979704 T>C, and P=0.535 for rs1059111 A>T in the controls of combined population). No significant association between these three polymorphisms and neuroblastoma risk was observed in either study population. We then validated such association in the combined population, aiming to obtain a robust conclusion. Likely, no association were found between these three polymorphisms and neuroblastoma risk (**Table 1**).

Stratification analysis for the association between NEFL gene polymorphisms and neuroblastoma susceptibility for combined subjects

Stratified analysis was also performed in the combined population by age, gender, sites of origin, and clinical stages. Consistently, we found no significant associations for all these three polymorphisms (**Table 2**).

Discussion

Herein, we investigated the association of *NEFL* gene polymorphisms with neuroblastoma risk in Chinese population. To the best of our knowledge, this is the first study to replicate the previously reported associations between *NEFL* gene polymorphisms and neuroblastoma risk in a two-center case-control study of Chinese children.

NEFL gene is located at chromosome 8p21.2. This gene encodes the light subunit of neurofilaments, which play an important role in maintaining normal function of nerve cells [40, 41]. More than 10 mutations in the *NEFL* gene are found to be associated with Charcot-Marie-Tooth disease types 2, or distal nerve demyelination [42]. In addition to the definite role of *NEFL* gene in neuron disease, *NEFL* gene also has been implicated in cancer initiation and progression. First, the chromosome 8p21 is enriched for loss of heterozygosity (LOH), which was involved in various cancers, including breast cancer [43, 44], lung cancer [45], prostate cancer [46], head and neck cancer [47]. It was reported that more than 40% of head and neck cancer patients harbored LOH at the *NEFL* locus. Second, several functional molecular targets related to cancer-associated pathways have been shown to interact with *NEFL* gene [48]. Furthermore, *NEFL* could also alter the cancer cell resistance to chemotherapy. Previous study has pointed out that restoring expression of *NEFL* in head and neck cancer cell lines could increase sensitivity of the cells to the cisplatin [48]. Last, aberrant expression and methylation of *NEFL* gene was detected in several cancers [49-51].

Table 1. Association between *NEFL* gene polymorphisms and neuroblastoma susceptibility

Genotype	Guangdong province				Henan province				Combined subjects			
	Cases (N=255)	Controls (N=531)	Adjusted OR (95% CI) [a]	P [a]	Cases (N=118)	Controls (N=281)	Adjusted OR (95% CI) [a]	P [a]	Cases (N=373)	Controls (N=812)	Adjusted OR (95% CI) [a]	P [a]
rs11994014 G>A (HWE=0.513 for combined subjects)												
GG	83 (32.55)	186 (35.03)	1.00		47 (39.83)	115 (40.93)	1.00		130 (34.85)	301 (37.07)	1.00	
AG	127 (49.80)	267 (50.28)	1.06 (0.76-1.48)	0.747	60 (50.85)	127 (45.20)	1.13 (0.72-1.79)	0.595	187 (50.13)	394 (48.52)	1.10 (0.84-1.44)	0.496
AA	45 (17.65)	78 (14.69)	1.28 (0.81-2.00)	0.287	11 (9.32)	39 (13.88)	0.70 (0.33-1.48)	0.351	56 (15.01)	117 (14.41)	1.11 (0.76-1.62)	0.597
Additive			1.12 (0.90-1.39)	0.324			0.92 (0.67-1.28)	0.632			1.06 (0.89-1.27)	0.510
Dominant	172 (67.45)	345 (64.97)	1.11 (0.81-1.52)	0.533	71 (60.17)	166 (59.07)	1.03 (0.66-1.60)	0.890	243 (65.15)	511 (62.93)	1.10 (0.85-1.42)	0.465
Recessive	210 (82.35)	453 (85.31)	1.24 (0.83-1.85)	0.302	107 (90.68)	242 (86.12)	0.65 (0.32-1.33)	0.240	317 (84.99)	695 (85.59)	1.05 (0.74-1.48)	0.784
rs2979704 T>C (HWE=0.498 for combined subjects)												
TT	83 (32.55)	184 (34.65)	1.00		48 (40.68)	115 (40.93)	1.00		131 (35.12)	299 (36.82)	1.00	
CT	126 (49.41)	268 (50.47)	1.04 (0.74-1.45)	0.835	60 (50.85)	127 (45.20)	1.11 (0.70-1.75)	0.670	186 (49.87)	395 (48.65)	1.07 (0.82-1.41)	0.602
CC	46 (18.04)	79 (14.88)	1.28 (0.82-2.00)	0.286	10 (8.47)	39 (13.88)	0.62 (0.29-1.34)	0.225	56 (15.01)	118 (14.53)	1.08 (0.74-1.58)	0.680
Additive			1.11 (0.89-1.39)	0.338			0.89 (0.64-1.23)	0.465			1.05 (0.88-1.26)	0.609
Dominant	172 (67.45)	347 (65.35)	1.09 (0.79-1.50)	0.592	70 (59.32)	166 (59.07)	0.99 (0.64-1.54)	0.968	242 (64.88)	513 (63.18)	1.08 (0.83-1.39)	0.574
Recessive	209 (81.96)	452 (85.12)	1.25 (0.84-1.86)	0.275	108 (91.53)	242 (86.12)	0.59 (0.28-1.22)	0.155	317 (84.99)	694 (85.47)	1.04 (0.74-1.47)	0.827
rs1059111 A>T (HWE=0.535 for combined subjects)												
AA	84 (32.94)	185 (34.84)	1.00		48 (40.68)	115 (40.93)	1.00		132 (35.39)	300 (36.95)	1.00	
AT	122 (47.84)	267 (50.28)	1.00 (0.72-1.40)	0.999	60 (50.85)	127 (45.20)	1.11 (0.70-1.75)	0.670	182 (48.79)	394 (48.52)	1.05 (0.80-1.37)	0.729
TT	49 (19.22)	79 (14.88)	1.35 (0.87-2.10)	0.181	10 (8.47)	39 (13.88)	0.62 (0.29-1.34)	0.225	59 (15.82)	118 (14.53)	1.14 (0.78-1.65)	0.501
Additive			1.13 (0.91-1.41)	0.256			0.89 (0.64-1.23)	0.465			1.06 (0.89-1.27)	0.506
Dominant	171 (67.06)	346 (65.16)	1.08 (0.79-1.48)	0.634	70 (59.32)	166 (59.07)	0.99 (0.64-1.54)	0.968	241 (64.61)	512 (63.05)	1.07 (0.83-1.38)	0.608
Recessive	206 (80.78)	452 (85.12)	1.35 (0.91-2.00)	0.134	108 (91.53)	242 (86.12)	0.59 (0.28-1.22)	0.155	314 (84.18)	694 (85.47)	1.11 (0.79-1.55)	0.560

OR, odds ratio; CI, confidence interval. [a] Adjusted for age and gender.

Table 2. Stratification analysis for the association between *NEFL* gene polymorphisms and neuroblastoma susceptibility for combined subjects

Variables	rs11994014 G>A				rs2979704 T>C				rs1059111 A>T			
	GG	AG/AA	Adjusted OR[a]	*P*[a]	TT	CT/CC	Adjusted OR[a]	*P*[a]	AA	AT/TT	Adjusted OR[a]	*P*[a]
	(Cases/Controls)		(95% CI)		(Cases/Controls)		(95% CI)		(Cases/Controls)		(95% CI)	
Age, month												
≤18	48/120	76/185	1.03 (0.67-1.58)	0.903	48/117	76/188	0.99 (0.64-1.51)	0.947	48/118	76/187	1.00 (0.65-1.53)	0.997
>18	82/181	167/326	1.13 (0.82-1.56)	0.451	83/182	166/325	1.12 (0.81-1.54)	0.487	84/182	165/325	1.10 (0.80-1.51)	0.559
Gender												
Females	50/135	107/207	1.40 (0.94-2.09)	0.099	50/131	107/211	1.33 (0.89-1.99)	0.161	50/132	107/210	1.35 (0.90-2.01)	0.143
Males	80/166	136/304	0.93 (0.66-1.30)	0.662	81/168	135/302	0.93 (0.66-1.30)	0.657	82/168	134/302	0.91 (0.65-1.27)	0.574
Sites of origin												
Adrenal gland	49/301	85/511	1.02 (0.70-1.49)	0.918	50/299	84/513	0.98 (0.67-1.43)	0.918	50/300	84/512	0.98 (0.67-1.44)	0.933
Retroperitoneal	24/301	63/511	1.53 (0.93-2.50)	0.092	24/299	63/513	1.52 (0.93-2.48)	0.098	25/300	62/512	1.44 (0.89-2.34)	0.142
Mediastinum	39/301	70/511	1.07 (0.70-1.62)	0.764	39/299	70/513	1.05 (0.69-1.59)	0.822	39/300	70/512	1.06 (0.70-1.60)	0.797
Others	14/301	21/511	0.88 (0.44-1.76)	0.719	14/299	21/513	0.87 (0.44-1.74)	0.696	14/300	21/512	0.88 (0.44-1.75)	0.709
Clinical stages												
I+II+4s	53/301	111/511	1.25 (0.87-1.78)	0.230	55/299	109/513	1.16 (0.81-1.65)	0.412	55/300	109/512	1.17 (0.82-1.66)	0.392
III+IV	70/301	119/511	1.01 (0.72-1.40)	0.978	70/299	119/513	1.00 (0.72-1.39)	0.985	70/300	119/512	1.00 (0.72-1.39)	0.998

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

Given the common implication of *NEFL* in carcinogenesis as well as the relative paucity of investigation into its role in neuroblastoma risk, we were motivated to explore the association between the three *NEFL* polymorphisms and neuroblastoma risk in a two-center case-control study of Chinese children. Unexpectedly, both overall analysis and stratified analysis indicated that there was no significant association of these studied *NEFL* polymorphisms with neuroblastoma risk in the study populations. Such negative association results might be ascribed to the following possible reasons. First, relatively small sample size might result in inadequate power to detect moderate effects. Second, most of the common SNPs only have weak effects on cancer risk [24, 52]. Thus, effects of *NEFL* polymorphisms might be overridden by environmental factors or other genetic variations. Third, lack of association between these three *NEFL* polymorphisms and neuroblastoma in Chinese children may be attributed to ethnic differences in allele frequencies of the SNPs (**Supplemental Table 2**).

Although this study has some merits, limitations are inevitable. First, inherent bias could not be avoided in this case-control study, since all participants were enrolled from hospitals. Second, statistical power might be limited due to the moderate sample size. It is challenging to recruit more cases, due to the relatively low morbidity rate of neuroblastoma in China. Third, we only replicated three SNPs in *NEFL* gene in this study. There are other potentially functional SNPs that might modify neuroblastoma susceptibility. Thus, more SNPs are needed to be explored in the future. Fourth, details on environmental factors, including dietary intake, living environment, and parental exposures, were not accessible, which disables us to analyze gene-environmental interaction. Fifth, though this is a two-center study, all the subjects were unrelated Chinese Han ethnicity. It should be cautious to extrapolate the results to other ethnic groups.

In all, we for the first time replicated the association between the *NEFL* gene polymorphisms and neuroblastoma risk using two independent populations in China. No significant association with neuroblastoma risk was detected. More epidemiological studies in different ethnic group are warranted before fully ascertaining the contribution of the *NEFL* gene polymorphisms to neuroblastoma susceptibility.

Abbreviations

GWAS, genome-wide association study; SNP, single nucleotide polymorphism; NEFL, neurofilament light; LOH, loss of heterozygosity.

Supplementary Material

Supplementary tables.
http://www.jcancer.org/v09p0535s1.pdf

Acknowledgments

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Competing Interests

The authors have declared that no competing interest exists.

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