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Genetic Variations of GWAS-Identified Genes and Neuroblastoma Susceptibility: a Replication Study in Southern Chinese Children[1,2,3]

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Abstract

Neuroblastoma is one of the most commonly diagnosed solid cancers for children, and genetic factors may play a critical role in neuroblastoma development. Previous genome-wide association studies (GWASs) have identified nine genes associated with neuroblastoma susceptibility in Caucasians. To determine whether genetic variations in these genes are also associated with neuroblastoma susceptibility in Southern Chinese children, we genotyped 25 polymorphisms within these genes by the TaqMan method in 256 cases and 531 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strength of the associations. We performed a meta-analysis to further evaluate the associations. Furthermore, we calculated the area under the receiver-operating characteristic curves (AUC) to assess which gene/genes may better predict neuroblastoma risk. We confirmed that *CASC15* rs6939340 A > G, rs4712653 T > C, rs9295536 C > A, *LIN28B* rs221634 A > T, and *LMO1* rs110419 A > G were associated with significantly altered neuroblastoma susceptibility. We also confirmed that rs6939340 A > G (G versus A: OR = 1.30, 95% CI = 1.13-1.50) and rs110419 G > A (A versus G: OR = 1.37, 95% CI = 1.19-1.58) were associated with increased neuroblastoma risk for all subjects. We also found that the combination of polymorphisms in *CASC15*, *LIN28B*, and *LMO1* may be used to predict neuroblastoma risk (AUC = 0.63, 95% CI = 0.59-0.67). Overall, we verified five GWAS-identified polymorphisms that were associated with neuroblastoma susceptibility alteration for Southern Chinese population; however, these results need further validation in studies with larger sample sizes.

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Introduction

Neuroblastoma is one of the most frequently occurring childhood tumors worldwide, affecting approximately 7.7 children per million in the Chinese population and accounting for approximately 9.8% of solid tumors in children [1]. Ethnic differences may influence the incidence of neuroblastoma. In the United States and most European

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[1] Novelty: In this study of 256 neuroblastoma cases and 531 controls, we evaluated the association of polymorphisms in nine GWAS-identified genes with neuroblastoma susceptibility and confirmed associations with five polymorphisms. We also found that risk genotype carriers have a significantly increased neuroblastoma risk of 4.11-fold. By analyzing data from all available publications, we further confirmed that the *CASC15* rs6939340 G>A and *LMO1* rs110419 A>G polymorphisms are significantly associated with neuroblastoma risk.

[2] Conflict of Interest: None.

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countries, neuroblastoma accounts for approximately 7% to 10% of all childhood cancers with a standardized incidence rate of 8 to 14 neuroblastoma cases per million [2,3]. In the Taiwan area, the incidence is approximately 7.8 children per million, which is quite similar to mainland China [4]. As for other countries, the incidence rate in children is approximately 9.6 per million for Australia [5], 4.5 per million for India [6], 9.1 per million for Uruguay, 4.7 per million for Chile, 3.8 per million for Mexico, 5.9 per million for Brazil, and 8.3 per million for Argentina [7]. To date, no environmental factors have been found to lead to the occurrence of neuroblastoma [8,9], suggesting that genetic factors may play a crucial role in the occurrence of neuroblastoma [10–13].

Because of the increased human genome knowledge and advancements in genotyping technology developed in the past decade, genome-wide association studies (GWASs) of human diseases became possible and have been widely utilized to study diseases such as cancer [14,15]. In 2008, the first GWAS for neuroblastoma was conducted by Maris et al. [16], which included 1032 neuroblastoma patients and 2043 controls of European descent and was then confirmed with an additional 720 cases and 2128 controls. They confirmed that three polymorphisms (rs6939340 A > G, rs4712653 T > C, and rs9295536 C > A) within the *CASC15* (also known as *LINC00340*) gene at the 6p22 chromosomal region were significantly associated with neuroblastoma susceptibility. When focusing on a high-risk subset, they found that common variations in the *BARD1* gene at 2q35 were associated with high-risk neuroblastoma [17]. They also found that polymorphisms within *DUSP12* at 1q23.3, *DDX4* and *IL31RA* at 5q11.2, and *HSD17B12* at 11p11.2 were associated with low-risk neuroblastoma [18]. In the fourth GWAS, by enlarging the sample size to 2251 cases and 6097 controls of European descent from four case series, Wang et al. [19] confirmed that four polymorphisms, especially the rs110419 A > G polymorphism within the *LMO1* gene at 11p15.4 region, were significantly associated with altered susceptibility to neuroblastoma. In addition, Diskin et al. [20] analyzed data from 2817 neuroblastoma patients and 7473 controls and found that polymorphisms in the *LIN28B* and *HACE1* genes at 6q16 were associated with neuroblastoma susceptibility.

The associations between polymorphisms within these GWAS-identified genes and neuroblastoma susceptibility have been validated in African-Americans [21], Italians [22], and Northern [23] and Southern Chinese children [24–29]. Genetic background may differ among Europeans, African-Americans, and Chinese subjects, even among different regions of China. In the present study, we describe the relationship between genetic variations of the nine GWAS-identified genes and neuroblastoma susceptibility in Southern Chinese children including 256 cases and 531 controls. We also performed a meta-analysis to assess the association of the *CASC15* rs6939340 A > G and *LMO1* rs110419 G > A polymorphisms with neuroblastoma susceptibility for Southern Chinese children. We also calculated the area under the receiver-operating characteristic curves (AUC) to assess which gene/genes can best predict neuroblastoma susceptibility.

Materials and Methods

Study Subjects

This study consists of 256 neuroblastoma patients and 531 cancer-free controls that were matched by age, gender, and ethnicity as we described previously (Supplemental Table 1) [26,30,31]. Briefly, histopathologically confirmed neuroblastoma cases were recruited mainly between February 2010 and November 2015 with written, informed consent by their guardians. All the controls were collected in the same period from the Guangzhou Women and Children's Medical Center. This study was approved by the Institutional Review Board of Guangzhou Women and Children's Medical Center.

Table 1. Association between Polymorphisms in GWAS-Identified Genes and Neuroblastoma Risk in Southern Chinese Children

Gene	Polymorphism	Allele		Case (*N* = 256)			Control (*N* = 531)			Adjusted OR[a]	*P*[a]	Adjusted OR[b]	*P*[b]	HWE
		A	B	AA	AB	BB	AA	AB	BB	(95% CI)		(95% CI)		
CASC15	rs6939340	G	A	155	81	19	232	247	52	**0.50 (0.37-0.68)**	**<.0001**	0.74 (0.43-1.28)	.286	0.239
CASC15	rs4712653	C	T	171	69	15	285	209	37	**0.57 (0.42-0.78)**	**.0004**	0.84 (0.45-1.56)	.581	0.875
CASC15	rs9295536	A	C	168	76	11	282	212	37	**0.59 (0.43-0.80)**	**.0008**	0.61 (0.30-1.21)	.154	0.739
BARD1	rs7585356	G	A	120	114	21	235	237	59	0.88 (0.65-1.19)	.414	0.71 (0.42-1.20)	.199	0.948
BARD1	rs6435862	T	G	174	74	7	381	133	17	1.19 (0.86-1.65)	.291	0.85 (0.35-2.07)	.717	0.205
BARD1	rs3768716	A	G	166	81	8	364	148	19	1.18 (0.86-1.63)	.298	0.86 (0.37-1.99)	.723	0.415
LIN28B [24]	rs221634	A	T	74	113	60	163	274	93	1.04 (0.75-1.45)	.798	**1.50 (1.04-2.17)**	**.030**	0.228
LIN28B [24]	rs221635	T	C	176	64	7	345	168	17	0.74 (0.54-1.03)	.078	0.88 (0.36-2.14)	.771	0.527
LIN28B [24]	rs314276	C	A	125	96	26	254	228	48	0.90 (0.67-1.22)	.497	1.19 (0.72-1.97)	.503	0.756
LIN28B [24]	rs9404590	T	G	130	100	17	286	205	39	1.06 (0.78-1.43)	.723	0.93 (0.52-1.69)	.819	0.786
LMO1 [26]	rs110419	A	G	103	117	36	159	275	97	**0.63 (0.46-0.86)**	**.004**	0.74 (0.49-1.12)	.152	0.248
LMO1 [26]	rs4758051	G	A	95	126	35	194	242	95	0.99 (0.73-1.35)	.942	0.73 (0.48-1.11)	.144	0.199
LMO1 [26]	rs10840002	A	G	90	124	42	182	240	109	0.97 (0.71-1.33)	.863	0.76 (0.51-1.13)	.174	0.070
LMO1 [26]	rs204938	A	G	164	83	9	354	165	12	1.12 (0.82-1.54)	.470	1.55 (0.64-3.73)	.330	0.153
DUSP12 [28]	rs1027702	T	C	137	98	21	282	206	43	0.98 (0.73-1.33)	.915	1.02 (0.59-1.77)	.932	0.534
IL31RA [28]	rs10055201	A	G	69	136	51	153	257	121	1.09 (0.78-1.53)	.607	0.83 (0.58-1.21)	.333	0.512
DDX4 [28]	rs2619046	G	A	57	132	67	151	257	123	1.39 (0.98-1.98)	.065	1.18 (0.84-1.67)	.345	0.499
HSD17B12 [28]	rs11037575	C	T	144	91	21	263	236	32	0.76 (0.57-1.03)	.077	1.38 (0.78-2.45)	.270	0.026
HACE1	rs6571212	A	T	137	102	17	310	185	36	1.22 (0.90-1.64)	.204	1.00 (0.55-1.82)	.995	0.246
HACE1	rs1316908	C	T	195	58	3	374	145	12	0.74 (0.52-1.04)	.080	0.51 (0.14-1.82)	.299	0.639
HACE1 [29]	rs2499667	A	G	90	118	41	181	248	101	0.91 (0.66-1.24)	.546	0.84 (0.56-1.25)	.394	0.330
HACE1 [29]	rs9404576	T	G	134	97	18	303	189	38	1.15 (0.85-1.55)	.380	1.03 (0.57-1.85)	.921	0.259
HACE1 [29]	rs2499663	T	C	93	115	41	189	243	98	0.92 (0.68-1.26)	.614	0.87 (0.59-1.30)	.508	0.204
HACE1 [29]	rs4336470	C	T	130	99	20	303	188	39	1.22 (0.90-1.65)	.197	1.13 (0.64-1.98)	.681	0.194
HACE1 [29]	rs4079063	A	G	92	116	41	189	242	99	0.94 (0.69-1.28)	.690	0.86 (0.58-1.29)	.466	0.169

HWE, Hardy-Weinberg equilibrium.

[a] Adjusted for age and gender for dominant model.

[b] Adjusted for age and gender for recessive model.

Table 2. Estimates of Neuroblastoma Risk by Genotypes at *CASC15* (rs6939340), *LIN28B* (rs221634), and *LMO1* (rs110419)

Genotypes			Case (*N* = 256)	Control (*N* = 531)	OR (95% CI)	*P*	Adjusted OR (95% CI) [a]	*P* [a]
rs6939340	rs221634	rs110419	*N* (%)	*N* (%)				
AG/AA	AA/AT	GG/AG	45 (17.58)	167 (31.45)	1.00		1.00	
AG/AA	AA/AT	AA	33 (12.89)	76 (14.31)	1.61 (0.95-2.72)	.075	1.59 (0.94-2.69)	.082
AG/AA	TT	GG/AG	11 (4.30)	42 (7.91)	0.97 (0.46-2.04)	.940	0.96 (0.46-2.02)	.913
AG/AA	TT	AA	11 (4.30)	14 (2.64)	**2.92 (1.24-6.86)**	**.014**	**2.88 (1.22-6.79)**	**.016**
GG	AA/AT	GG/AG	72 (28.13)	138 (25.99)	**1.94 (1.25-2.99)**	**.003**	**1.92 (1.24-2.97)**	**.003**
GG	AA/AT	AA	46 (17.97)	57 (10.73)	**3.00 (1.80-4.98)**	**<.0001**	**3.01 (1.81-5.01)**	**<.0001**
GG	TT	GG/AG	25 (9.77)	25 (4.71)	**3.71 (1.95-7.07)**	**<.0001**	**3.66 (1.92-6.97)**	**<.0001**
GG	TT	AA	13 (5.08)	12 (2.26)	**4.02 (1.72-9.41)**	**.001**	**4.11 (1.75-9.66)**	**.001**

[a] Adjusted for age and gender.

Genotyping and Quality Control

We genotyped the 25 polymorphisms within the nine GWAS-identified genes by TaqMan real-time PCR [32,33]. To monitor quality control, eight negative controls (water) as well as eight replicate samples were included in each 384-well plate. Additionally, approximately 10% of the samples were randomly selected for further quality control, and the results were 100% concordant.

Meta-Analysis

We performed a meta-analysis by collecting data from all available publications on the *CASC15* rs6939340 A > G and *LMO1* rs110419 G > A polymorphisms. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were used to investigate the strength of the associations under an allele-comparing model. Heterogeneity was measured by a χ^2-based *Q* test. Random-effect modeling was used when $P_{het} < .1$ [34].

Statistical Analysis

We applied χ^2 tests to compare categorical variables such as demographics and genotype frequencies. We used the goodness-of-fit χ^2 test to assess the Hardy-Weinberg equilibrium for controls by using the observed genotypes for each polymorphism. Associations of the selected polymorphisms and the combined genotypes for the three most significant polymorphisms from each region with neuroblastoma susceptibility were estimated by ORs and 95% CIs were calculated using unconditional logistic regression with adjustment for age and gender. We adopted a nonparametric approach to compare the area under the receiver operating characteristic (ROC) curves (AUC) for the polymorphisms from the three most significant genes and the combined genes [35]. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). All the *P* values were two sided, and $P < .05$ was considered statistically significant.

Results

Associations between Selected Polymorphisms and Neuroblastoma Susceptibility

As shown in Table 1, of the 25 selected polymorphisms, we confirmed that five were associated with neuroblastoma susceptibility: *CASC15* gene polymorphisms rs6939340 G > A, rs4712653 C > T, and rs9295536 A > C; *LIN28B* gene polymorphism rs221634 A > T; and *LMO1* gene polymorphism rs110419 A > G. No significant associations were observed for other polymorphisms.

Estimates of Neuroblastoma Risk by Genotype

As shown in Table 2, we chose one of the most significant polymorphisms from each of the three regions (rs6939340, rs221634, and rs110419) to assess the joint impact on neuroblastoma risk. When the rs6939340 AG/AA, rs221634 AA/AT, and rs110419 GG/AG carriers were used as a reference, we found that risk genotype carriers may have increased neuroblastoma risk, particularly carriers of the rs6939340 GG, rs221634 TT, and rs110419 AA polymorphisms (adjusted OR = 4.11, 95% CI = 1.95-9.66).

Meta-Analysis Results

As shown in Table 3 and Figure 1, analysis of the rs6939340 G > A polymorphism in 3302 neuroblastoma cases and 8279 controls found that carrying the rs6939340 G allele is associated with increased neuroblastoma risk (G versus A: OR = 1.37, 95%

Table 3. Characteristics of Studies Included in This Meta-Analysis for *CASC15* rs6939340 A > G and *LMO1* rs110419 G > A Polymorphisms

Surname	Year	Race	Case							Control						
CASC15 rs6939340 A > G			All	AA	AG	GG	A	G	G Freq	All	AA	AG	GG	A	G	G Freq
Diskin	2012	Caucasians	2101	/	/	/	1895	2307	0.549	4202	/	/	/	4404	4000	0.476
Latorre	2012	Africans	363	12	103	248	127	599	0.825	2480	82	677	1721	841	4119	0.830
Capasso	2013	Caucasians	339	74	162	103	310	368	0.543	761	196	390	175	782	740	0.486
Lu	2015	Asians	244	/	/	/	124	364	0.746	305	/	/	/	205	405	0.660
He	2016	Asians	255	19	81	155	119	391	0.767	531	52	247	232	351	711	0.669
Total			3302							8279						
LMO1 rs110419 G > A			All	GG	AG	AA	G	A	A Freq	All	GG	AG	AA	G	A	A Freq
Diskin	2012	Caucasians	2101	/	/	/	1853	2349	0.559	4202	/	/	/	4294	4110	0.489
Latorre	2012	Africans	365	18	124	223	160	570	0.781	2491	137	863	1491	1137	3845	0.772
Capasso	2013	Caucasians	323	84	152	87	320	326	0.505	774	271	370	133	912	636	0.411
Lu	2015	Asians	244	/	/	/	125	363	0.744	305	/	/	/	241	369	0.605
He	2016	Asians	256	36	117	103	189	323	0.631	531	97	275	159	469	593	0.558
Total			3289							8303						

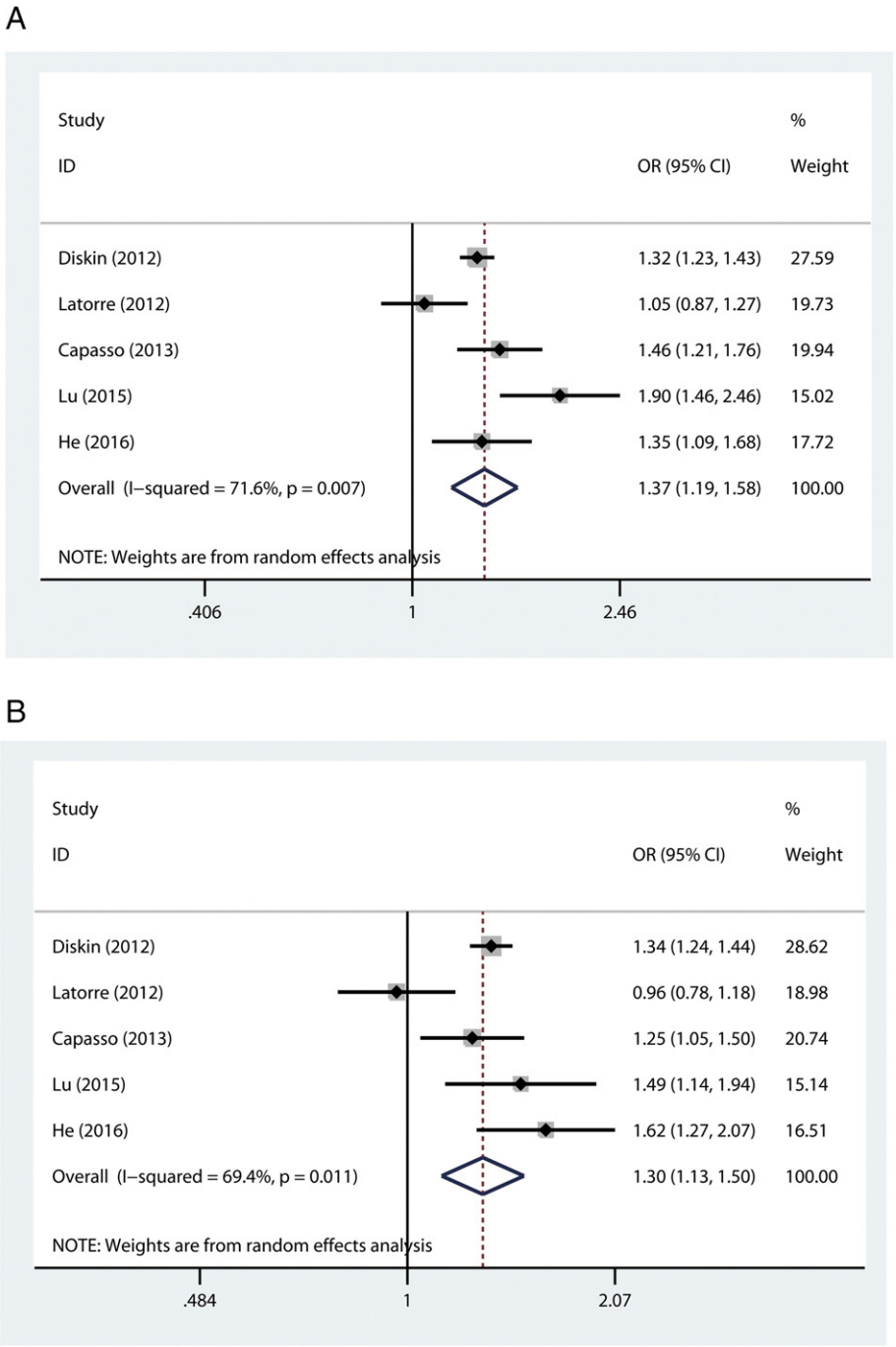

Figure 1. Forest plots for the correlation of the (A) *CASC15* rs6939340 G > A and (B) *LMO1* rs110419 A > G polymorphisms with neuroblastoma susceptibility under the allele-comparing model. The horizontal line represents the OR and 95% CI for each investigation. The diamond represents the pooled OR and 95% CI.

CI = 1.19-1.58, $P = 1.97*10^{-5}$). Similarly, for the rs110419 A > G polymorphism, a total of 3289 cases and 8303 controls were analyzed, and the combined results indicated that this polymorphism was significantly associated with neuroblastoma susceptibility (A versus G: OR = 1.30, 95% CI = 1.13-1.50, $P = 3.15*10^{-4}$) (Figure 1).

AUC for GWAS-Identified Genes

As shown in Figure 2, when all the polymorphisms for each gene are compared, the *CASC15* gene (AUC = 0.59, 95% CI = 0.55-0.63) is a better predictor of neuroblastoma risk than the *LMO1* gene (AUC = 0.56, 95% CI = 0.52-0.60) or *LIN28B* gene (AUC = 0.54, 95% CI = 0.51-0.58). However, these three genes combined have an AUC of 0.63 (95% CI = 0.59-0.67). When all the polymorphisms from the nine genes were combined, the AUC was further improved to 0.66 (95% CI = 0.61-0.70).

Discussion

In the described hospital-based case-control study with 256 neuroblastoma cases and 531 cancer-free controls from south China, we systematically evaluated the associations between

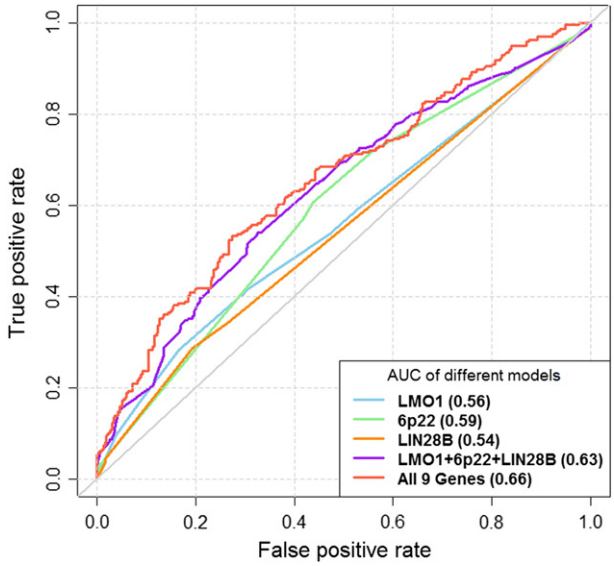

Figure 2. ROC analysis for single and combined genes identified from GWAS for neuroblastoma. The areas under the ROC curves (AUCs) were calculated to measure the predictive power of risk-assessment models based on polymorphisms within gene/genes.

polymorphisms derived from nine GWAS-identified genes and confirmed the role of five polymorphisms in predicting neuroblastoma susceptibility. We also found that risk genotype carriers have a significantly increased neuroblastoma risk, as high as 4.11-fold. By analyzing data from all available publications, we further confirmed that the *CASC15* rs6939340 G > A and *LMO1* rs110419 A > G polymorphisms were significantly associated with neuroblastoma risk.

In addition to environmental factors, genetic factors may also play a crucial role in the occurrence of neuroblastoma [13]. GWAS is a powerful tool in identifying disease-related loci. It has significantly improved our understanding of the genetic basis of cancer, providing the basis for discovering new options for targeted prevention and therapy [14]. To date, nine susceptibility genes have been discovered [16–20], and among them, polymorphisms within the *CASC15*, *LMO1*, *LIN28B*, and *HCAE1* genes are significantly associated with neuroblastoma risk, including but not limited to high-risk and low-risk subtypes. The first identified and most prominent polymorphism associated with neuroblastoma was *CASC15* rs6939340 G > A ($P = 9.33 \times 10^{-15}$) at 6p22 region. Two additional *CASC15* gene polymorphisms (rs4712653 with $P = 5.50*10^{-13}$ and rs9295536 with $P = 1.24*10^{-11}$) were also associated with neuroblastoma susceptibility [16]. Following this discovery, using data from 1627 cases and 3254 controls in the discovery stage and 624 cases and 2843 controls in the replication stage, Wang et al. [19] discovered four *LMO1* gene polymorphisms (rs110419 A > G, rs4758051 G > A, rs10840002 A > G, and rs204938 A > G) that were associated with neuroblastoma susceptibility. Among these polymorphisms, the rs110419 A > G was the most noteworthy one. In 2012, Diskin et al. [20] found that five polymorphisms in the *HACE1* gene and one polymorphism in the *LIN28B* gene were associated with neuroblastoma susceptibility including a total of 10,290 subjects. It is also worth noting that *BARD1* gene polymorphisms have been reported to be associated with high-risk neuroblastoma [17].

In their replication study consisting of African-Americans with 391 cases and 2500 controls, Latorre et al. [21] analyzed a total of 12 polymorphisms from the *CASC15*, *BARD1*, and *LMO1* genes and confirmed that all of the five polymorphisms in the *BARD1* gene were associated with neuroblastoma risk. However, they failed to confirm the effects of the *CASC15* and *LMO1* genes. In a replicated study in an Italian population with 370 cases and 809 controls, Capasso et al. [22] investigated 16 polymorphisms from the nine GWAS-identified genes and successfully confirmed the association of the *CASC15*, *BARD1*, *LMO1*, and *HSD17B12* genes. As for Northern Chinese subjects, Lu et al. [23] analyzed a total of 244 cases and 305 controls and found that polymorphisms in the *CASC15*, *LMO1*, and *HSD17B12* genes were associated with neuroblastoma susceptibility. In this study of Southern Chinese children, we confirmed that five polymorphisms within the nine GWAS-identified genes were associated with neuroblastoma susceptibility. Our meta-analysis also confirmed that the *CASC15* rs6939340 G > A and *LMO1* rs110419 A > G polymorphisms were significantly associated with increased neuroblastoma risk. Our failure to confirm an association with the additional polymorphisms may be due to the weak effect of SNPs, limited sample size, and ethnicity differences.

Several limitations should be mentioned. First, the sample size (256 neuroblastoma cases) is relatively small despite us including all the samples available. More samples from other regions of China should be investigated and combined in future multicenter studies. Second, we only included 25 polymorphisms in these nine genes and nearly none of them was potential functional according to SNPinfo (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html); inclusion of more polymorphisms, in particular, the potential functional ones [33] as well as low-frequency variants [36], needs to be considered. Third, we only investigated nine genes by previous GWAS; the latest ones such as *MLF1* and *CPZ* [37] were not included in the current study. Fourth, relatively limited information was collected due to the nature of retrospective investigations. Other factors such as paternal exposures, living environment, and dietary intake were not available.

In summary, we provide an overview of the genetic variations within the GWAS-identified genes associated with neuroblastoma susceptibility in Southern Chinese children. Further investigations with larger samples and different ethnicities are needed to validate and confirm the effect of GWAS-identified genes for neuroblastoma susceptibility.

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