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ORIGINAL RESEARCH

HSD17B12 gene rs11037575 C>T polymorphism confers neuroblastoma susceptibility in a Southern Chinese population

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Zhuorong Zhang,[1,2] Yan Zou,[2] Jinhong Zhu,[3] Ruizhong Zhang,[2] Tianyou Yang,[2] Fenghua Wang,[2] Huimin Xia,[1,2] Jing He,[2] Zhichun Feng[1,4–6]

[1]Southern Medical University, Guangzhou, Guangdong, [2]Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, [3]Molecular Epidemiology Laboratory, Department of Laboratory Medicine, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, [4]Division of Neonatology, Affiliated BaYi Children's Hospital, Clinical Medical College in PLA Army General Hospital, Southern Medical University, [5]National Engineering Laboratory for Birth Defects Prevention and Control of Key Technology, [6]Beijing Key Laboratory of Pediatric Organ Failure, Beijing, People's Republic of China

Correspondence: Zhichun Feng
Division of Neonatology, Affiliated BaYi Children's Hospital, Clinical Medical College in PLA Army General Hospital, Southern Medical University, No 5 Nanmen Cang Hutong, Dongcheng District, Beijing 100700, People's Republic of China
Tel +86 10 6672 1786
Fax +86 10 6406 3099
Email bzfengzc@yahoo.com

Jing He
Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou 510623, Guangdong, People's Republic of China
Tel/fax +86 20 3807 6560
Email hejing198374@gmail.com

Abstract: A previous genome-wide association study (GWAS) identified four genetic polymorphisms (rs1027702 near *DUSP12*, rs10055201 in *IL31RA*, rs2619046 in *DDX4*, and rs11037575 in *HSD17B12* gene) that were associated with neuroblastoma susceptibility, especially for low-risk subjects. The aim of this study was to examine the association between these four polymorphisms and neuroblastoma susceptibility in a Southern Chinese population composed of 256 cases and 531 controls. Overall, among all the polymorphisms, single-locus analysis only revealed significant association between the *HSD17B12* rs11037575 C>T polymorphism and neuroblastoma susceptibility (CT vs CC: adjusted odds ratio [OR] =0.71, 95% confidence interval [CI] =0.51–0.97, *P*=0.030). Moreover, stratified analysis indicated that the rs11037575 T allele was associated with decreased neuroblastoma risk among the children aged 0–18 months (adjusted OR =0.60, 95% CI =0.37–0.97, *P*=0.036); regarding the tumor site, this polymorphism protected against tumor in the mediastinum (adjusted OR =0.59, 95% CI =0.37–0.94, *P*=0.025). When risk genotypes were combined, we found that girls with two to four risk genotypes were at a significantly increased risk of neuroblastoma (adjusted OR =1.65, 95% CI =1.03–2.64, *P*=0.039). In terms of clinical stages, individuals with two to four risk genotypes had a tendency toward the development of stage III/IV diseases (adjusted OR =1.69, 95% CI =1.12–2.54, *P*=0.012). In conclusion, we verified that the *HSD17B12* rs11037575 T allele might negatively associate with neuroblastoma risk. These findings need further validation by prospective studies with larger sample size and different ethnicities.

Keywords: GWAS, *HSD17B12*, polymorphism, neuroblastoma, susceptibility

Introduction

Neuroblastoma is a pediatric cancer originating from the developing sympathetic nervous system. It is the most frequent peripheral nervous system tumor of infancy and childhood,[1,2] which constitutes of approximately 7%–10% of all childhood cancers.[3] Neuroblastoma is the third leading cause of cancer-related death in children.[3] Despite of remarkable advances in the treatments of many childhood cancers, neuroblastoma remains a serious clinical problem, causing 15% of childhood cancer mortality.[4] The median age at diagnosis of this disease is around 17 months.[5] Neuroblastoma may occur throughout the sympathetic nervous system, mostly within the abdomen and adrenal medulla.[6] The incidence rate of neuroblastoma is about 1 in 7000 live newborns worldwide.[7] It is also one of the most commonly diagnosed solid tumors in the Chinese infants, with an incidence rate of ~7.7 per million.[8] The majority of neuroblastomas are sporadic, and only about 1% of patients have a family history of this type of disease.[9] Thus far, the etiology of neuroblastoma remains largely unidentified, especially for

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predisposing factors for neuroblastoma.[10,11] Family studies and case–control studies have been often adopted to discover neuroblastoma susceptibility genetic variants.[12–15] For instance, Diskin et al[16] conducted a case–control study with 2,817 neuroblastoma cases and 7,473 controls. They recognized two loci at 6q16 region associated with the neuroblastoma susceptibility, one within the *HACE1* (rs4336470), and the other within the *LIN28B* (rs17065417) gene.

Over the past years, at least five genome-wide association studies (GWASs) have been accomplished mainly in North American patients of European descent, and several loci were proven to be related with the risk of neuroblastoma, such as *CASC15* in 2008, *BARD1* in 2009, and *LMO1* in 2011.[11,16–19] A two-stage neuroblastoma GWAS by Nguyen et al[18] included 1,627 cases and 2,575 controls at the first stage, as well as 398 cases and 1,507 controls in the replication stage. They found that dual-specificity phosphatase 12 (*DUSP12*) gene polymorphisms, at chromosome band 1q23.3, significantly conferred neuroblastoma susceptibility. When they limited the analysis to 574 low-risk neuroblastoma cases and 1,722 controls, *DUSP12* and three novel genes were validated to be associated with low-risk neuroblastoma. They were *IL31RA* and *DDX4* located on chromosome band 5q11.2 and *HSD17B12* on chromosome band 11p11.2. Among all the significant polymorphisms in the four genes, the rs1027702 T>C, rs10055201 A>G, rs2619046 G>A, and rs11037575 C>T are most noteworthy. The association between these polymorphisms and neuroblastoma susceptibility has been replicated in the Italians[20] and a Northern Chinese population.[15] To scrutinize the association between the four most significant polymorphisms and neuroblastoma susceptibility in Southern Chinese population, we conducted this study including 256 neuroblastoma cases and 531 cancer-free controls.

Materials and methods

Study subjects

To investigate the association between chosen genetic polymorphisms and the risk of neuroblastoma, we included 256 neuroblastoma cases having received treatments from the Guangzhou Women and Children's Medical Center as reported previously,[21–25] and 531 age-, gender-, and race-matched cancer-free controls were randomly picked from children who visited the same hospital for a routine physical examination.[26–28] This study received the approval of the Institutional Review Board of Guangzhou Women and Children's Medical Center. Written informed consent was acquired from each participant or his/her guardian.

Polymorphism analysis

DNA samples were processed as we described elsewhere.[29–32] Briefly, DNA samples were diluted to a stock concentration of 10 ng/μL and added to the 96-well plates. Genotyping for the four GWAS-identified gene single-nucleotide polymorphisms (SNPs) (rs1027702 T>C, rs10055201 A>G, rs2619046 G>A, and rs11037575 C>T)[20] was carried out in the 384-well plate using Taqman method following a published protocol.[29] Moreover, for the purpose of quality control and validation of the accuracy of genotyping results, ~10% of the samples were randomly selected for sequencing. The results were 100% concordant.

Statistical analysis

Differences in the demographics and genotypes between neuroblastoma cases and controls were compared by χ^2 test. Hardy–Weinberg equilibrium for control subjects was calculated by goodness-of-fit χ^2 test. Unconditional univariate and multivariate logistic regression analyses were performed. Odds ratios (ORs) and 95% confidence intervals (CIs), with adjustment for age and gender, were used to quantify the strength of associations between these four polymorphisms and neuroblastoma susceptibility. Stratified analysis was performed regarding age, gender, tumor sites, and clinical stages. A $P<0.05$ was considered as statistically significant.[33] All statistical tests were two-sided, and were calculated using SAS software (Version 9.1; SAS Institute, Cary, NC, USA).

Results

Population characteristics

The demographic characteristics of participants are reviewed in Table S1. No statistically significant differences were detected between cases and controls with respect to age (P=0.239) and gender (P=0.333). Based on International Neuroblastoma Staging System criteria,[2] 54 (21.09%), 65 (25.39%), 44 (17.19%), 77 (30.08%), and 9 (3.52%) patients were diagnosed with clinical stage I, II, III, IV, and 4s neuroblastoma, respectively. Regarding tumor sites, 46 (17.97 %) neuroblastomas were found in the adrenal glands, 87 (33.98%) in retroperitoneal regions, 90 (35.16%) in the mediastinum, and 25 (9.77%) in other regions.

Association between selected polymorphisms and neuroblastoma susceptibility

The genotype counts of the polymorphisms and their associations with neuroblastoma susceptibility are presented

Table 1 Associations between selected polymorphisms and risk of neuroblastoma

Genotype	Cases (N=256), n (%)	Controls (N=531), n (%)	*P*-value[a]	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)[b]	*P*-value[b]
***DUSP12* rs1027702 T>C (HWE =0.534)**							
TT	137 (53.52)	282 (53.11)		1.00		1.00	
TC	98 (38.28)	206 (38.79)		0.98 (0.71–1.34)	0.896	0.98 (0.71–1.34)	0.887
CC	21 (8.20)	43 (8.10)		1.01 (0.57–1.76)	0.985	1.01 (0.58–1.78)	0.961
Additive			0.990	0.99 (0.79–1.25)	0.950	0.99 (0.79–1.26)	0.962
Dominant	119 (46.48)	249 (46.89)	0.914	0.98 (0.73–1.33)	0.914	0.98 (0.73–1.33)	0.915
Recessive	235 (91.80)	488 (91.90)	0.960	1.01 (0.59–1.75)	0.960	1.02 (0.59–1.77)	0.932
***IL31RA* rs10055201 A>G (HWE =0.511)**							
AA	69 (26.95)	153 (28.81)		1.00		1.00	
AG	136 (53.13)	257 (48.40)		1.17 (0.83–1.67)	0.373	1.17 (0.82–1.67)	0.380
GG	51 (19.92)	121 (22.79)		0.94 (0.61–1.44)	0.760	0.92 (0.60–61.43)	0.719
Additive			0.442	0.98 (0.79–1.21)	0.851	0.97 (0.79–1.21)	0.810
Dominant	187 (73.05)	378 (71.19)	0.587	1.10 (0.79–1.53)	0.587	1.09 (0.78–1.53)	0.607
Recessive	205 (80.08)	410 (77.21)	0.362	0.84 (0.58–1.22)	0.363	0.83 (0.58–1.21)	0.333
***DDX4* rs2619046 G>A (HWE =0.499)**							
GG	57 (22.27)	151 (28.44)		1.00		1.00	
AG	132 (51.56)	257 (48.40)		1.36 (0.94–1.97)	0.103	1.36 (0.94–1.97)	0.101
AA	67 (26.17)	123 (23.16)		1.44 (0.94–2.21)	0.092	1.45 (0.95–2.22)	0.088
Additive			0.175	1.10 (0.97–1.48)	0.090	1.20 (0.97–1.49)	0.086
Dominant	199 (77.73)	380 (71.56)	0.066	1.39 (0.98–1.97)	0.067	1.39 (0.98–1.98)	0.065
Recessive	189 (73.83)	408 (76.84)	0.356	1.18 (0.83–1.66)	0.356	1.18 (0.84–1.67)	0.345
***HSD17B12* rs11037575 C>T (HWE =0.026)**							
CC	144 (56.25)	263 (49.53)		1.00		1.00	
CT	91 (35.55)	236 (44.44)		**0.70 (0.51–0.97)**	**0.030**	**0.71 (0.51–0.97)**	**0.030**
TT	21 (8.20)	32 (6.03)		1.20 (0.67–2.16)	0.545	1.19 (0.66–2.14)	0.565
Additive			0.049	0.89 (0.70–71.13)	0.334	0.89 (0.69–1.13)	0.327
Dominant	112 (43.75)	268 (50.47)	0.077	0.76 (0.57–1.03)	0.077	0.76 (0.57–1.03)	0.077
Recessive	235 (91.80)	499 (93.97)	0.254	1.39 (0.79–2.47)	0.255	1.38 (0.78–2.45)	0.270
Combined effect of risk genotypes							
0	2 (0.78)	5 (0.94)		1.00		1.00	
1	107 (41.80)	260 (48.96)		1.03 (0.20–25.39)	0.973	1.02 (0.19–5.33)	0.986
2	122 (47.66)	227 (42.75)		1.34 (0.26–27.03)	0.726	1.33 (0.25–26.94)	0.739
3	23 (8.98)	37 (6.97)		1.55 (0.28–8.68)	0.616	1.55 (0.28–8.66)	0.621
4	2 (0.78)	2 (0.38)		2.50 (0.19–32.19)	0.482	2.29 (0.18–29.69)	0.536
Trend			0.359	**1.26 (1.01–1.58)**	**0.042**	**1.26 (1.01–1.58)**	**0.043**
0–1	109 (42.58)	265 (49.91)		1.00		1.00	
2–4	147 (57.42)	266 (50.09)	0.054	1.34 (1.00–01.82)	0.054	1.34 (0.99–1.81)	0.055

Notes: The values are in bold if the 95% CIs excluded 1 or $P<0.05$. [a]χ^2 test for genotype distributions between neuroblastoma patients and controls. [b]Adjusted for age and gender.

Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.

in Table 1. We spotted significant association between the rs11037575 T allele and a decreased risk of neuroblastoma (CT vs CC: adjusted OR =0.71, 95% CI =0.51–0.97, *P*=0.030). However, we observed no significant association with neuroblastoma susceptibility for the rs1027702 T>C and rs10055201 A>G polymorphism. We then combined risk genotypes and found a significant trend toward an increased neuroblastoma risk with the accumulation of risk genotypes (adjusted OR =1.26, 95% CI =1.01–1.58, *P*=0.043). Participants harboring two to four risk genotypes had a borderline significantly increased neuroblastoma risk (adjusted OR =1.34, 95% CI =0.99–1.81, *P*=0.055) in comparison to those with zero to one risk genotype.

Stratified analysis of selected polymorphisms and neuroblastoma susceptibility

Next, participants were stratified in terms of age, gender, sites of origin, and clinical stages. We further assessed the effects of variant genotypes of polymorphisms on the risk of neuroblastoma among the different strata (Table 2). We found that the rs11037575 T allele was associated with a decreased neuroblastoma risk among the children aged ≤18 months (CT/TT vs CC: adjusted OR =0.60, 95% CI =0.37–0.97, *P*=0.036), and those with tumor in mediastinum (CT/TT vs CC: adjusted OR =0.59, 95% CI =0.37–0.94, *P*=0.025). In the combined analysis, it was shown that the accumulation of risk

Table 2 Stratification analysis for association of *HSD17B12* and combined genotypes with risk of neuroblastoma

Variables	rs11037575 (cases/controls)		Adjusted OR[a] (95% CI)	*P*-value[a]	Combined (cases/controls)		Adjusted OR[a] (95% CI)	*P*-value[a]
	CC	CT/TT			0–1	2–4		
Age, months								
≤18	63/117	38/116	**0.60 (0.37–0.97)**	**0.036**	46/118	55/115	1.22 (0.77–1.96)	0.399
>18	81/146	74/152	0.89 (0.60–61.31)	0.546	63/147	92/151	1.43 (0.96–2.12)	0.076
Gender								
Female	59/113	44/120	0.70 (0.44–1.11)	0.131	40/119	63/114	**1.65 (1.03–2.64)**	**0.039**
Male	85/150	68/148	0.81 (0.55–1.20)	0.297	69/146	84/152	1.17 (0.79–1.73)	0.440
Sites of origin								
Adrenal gland	25/263	21/268	0.83 (0.45–1.52)	0.545	17/265	29/266	1.71 (0.92–93.20)	0.091
Retroperitoneal	48/263	39/268	0.80 (0.51–1.26)	0.340	42/265	45/266	1.06 (0.68–1.68)	0.792
Mediastinum	56/263	34/268	**0.59 (0.37–0.94)**	**0.025**	41/265	49/266	1.19 (0.76–1.87)	0.443
Others	11/263	14/268	1.26 (0.56–2.82)	0.582	7/265	18/266	**2.55 (1.05–06.23)**	**0.039**
Clinical stages								
I + II +4s	73/263	53/268	0.71 (0.48–1.06)	0.092	58/265	68/266	1.17 (0.79–1.73)	0.433
III + IV	67/263	54/268	0.78 (0.53–1.17)	0.229	45/265	76/266	**1.69 (1.12–2.54)**	**0.012**

Notes: The values are in bold if the 95% CIs excluded 1 or $P<0.05$. [a]Adjusted for age and gender.
Abbreviations: CI, confidence interval; OR, odds ratio.

genotypes (two to four) statistically significantly increased neuroblastoma risk in girls (adjusted OR =1.65, 95% CI =1.03–2.64, *P*=0.039). Moreover, those with more than one risk genotype tended to develop tumor originated from others (adjusted OR =2.55, 95% CI =1.05–06.23, *P*=0.039), and were also more likely to have clinical stage III/IV disease (adjusted OR =1.69, 95% CI =1.12–2.54, *P*=0.012).

Discussion

In this study, we evaluated the association of four GWAS-identified polymorphisms (rs1027702 T>C, rs10055201 A>G, rs2619046 G>A, and rs11037575 C>T) with the risk of neuroblastoma in 256 patients and 531 cancer-free controls. Our results demonstrated that rs11037575 T allele protected against neuroblastoma. Moreover, stratified analysis showed that the rs11037575 variants reduced the risk of neuroblastoma among younger subjects (0–18 months of age), and decreased the risk of mediastinal neuroblastoma. When we collectively analyzed risk genotypes, we found that girls carrying two to four risk genotypes had a statistically significantly increased neuroblastoma risk, and patients with two to four risk genotypes tended to develop advanced disease (clinical stage III + IV). The results from the current study suggested that rs11037575 T allele alone had negative effect on neuroblastoma, while combined risk genotypes conferred increased neuroblastoma susceptibility. The rs2619046 allele A (frequency of 0.52 and 0.47 in cases and controls, respectively) showed a trend toward the association with risk of neuroblastoma development (*P*=0.087, OR =1.202, 95% CI =0.973–1.484) as previously reported in Italians and American Europeans.[18,20] These results were in accordance with the findings from previous GWAS study.[18] To the best of our knowledge, this is the first investigation to validate the association of neuroblastoma risk with GWAS-identified SNPs within the *DUSP12, IL31RA, DDX4*, and *HSD17B12* genes in a Southern Chinese population.

DUSP12 belongs to the family of dual specificity phosphatases (DUSPs), which function to regulate multiple critical signaling pathways.[34] Misregulation of DUSPs contributes to the development of many diseases, including cancers.[35,36] DDX4 (VASA) is an ATP-dependent RNA helicase, which fundamentally regulates proliferation and differentiation of germ cell.[37] The mammalian HSD17B12 was originally recognized as a 3-ketoacyl-CoA reductase, engaged in the synthesis of long-chain fatty acid.[38] Interestingly, decreased expression of *HSD17B12* significantly inhibited breast cancer cell proliferation in vitro, which could be fully restored by the addition of arachidonic acid.[39] Combined with our findings, we believe that further functional experiments could validate whether rs11037575 C>T polymorphism has a role in *HSD17B12* expression. IL-31RA is a unique gp130-like receptor chain of interleukin-31 (IL-31). IL-31 is primarily synthesized by activated CD4 (+) T cells, and mediates activities of a wide spectrum of immune and nonimmune cells. Thus, this cytokine is potentially pleiotropic, which regulates hematopoiesis and immune response, and promotes the development of inflammatory bowel disease, airway hypersensitivity, and dermatitis.[40] Nguyen et al completed a two-stage GWAS on neuroblastoma, 574 low-risk cases and 1,722 controls in the first stage and 124 cases and

496 controls in the second stage.[18] They found that these four genes and their SNPs were associated with neuroblastoma susceptibility, especially for low-risk neuroblastoma.[18] In the previous replication study, comprising 370 neuroblastoma patients and 809 controls, Capasso et al[20] confirmed the association of neuroblastoma risk with two independent neuroblastoma-associated common genetic variants (rs1027702, rs11037575) in an Italian population.

Apparently, our findings were not totally consistent with the previous studies conducted among Caucasians, African-Americans, and Italians. The inconsistency may be ascribed to the environmental and genetic variations among different ethnicities. For instance, given the possible differences in the minor allele frequency[27] and pattern of linkage disequilibrium of SNPs among Asians, African-Americans, and Caucasians, the effects of the studied SNPs on genetic susceptibility to neuroblastoma may vary. Besides this, the relatively small sample size of this study might have limited the statistical power.

Limitations

There were several possible limitations that should be addressed in this study. First, although it was the largest study in Chinese children, there were only 256 neuroblastoma patients and 531 cancer-free controls included. As a result, the statistical power may be limited. Replication studies from other centers with more sample size were encouraged to validate the association. Second, only four most significant polymorphisms were investigated in the present study, and more polymorphisms, especially the potentially functional SNPs not contained in GWASs, remain to be studied. Third, due to the nature of the retrospective study design, information bias and selection bias might not be avoidable. We could only reduce these biases by frequency-matching of cases and controls by age and gender, due to lack of information on living environment, dietary intake, and parental exposures. Finally, as participants were recruited only from Chinese Han ethnicity residing in Southern China, the findings should be extrapolated to different ethnic groups with great caution.

Conclusion

In conclusion, we verified significant association between *HSD17B12* gene rs11037575 T allele and decreased neuroblastoma susceptibility in Southern Chinese children, especially for children aged ≤18 months, and those with tumor of mediastinum region. However, future well-designed prospective studies with larger sample size including different ethnic populations, detailed information (eg, parental exposures), and functional studies are warranted to strengthen our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 General characteristics in neuroblastoma cases and controls

Variables	Cases (n=256)	Controls (n=531)	*P*-value[a]
	N (%)	N (%)	
Age range, months	0–156	0.07–156	0.239
Mean ± standard deviation	30.87±26.45	29.73±24.86	
≤18	101 (39.45)	233 (43.88)	
>18	155 (60.55)	298 (56.12)	
Gender			0.333
Female	103 (40.23)	233 (43.88)	
Male	153 (59.77)	298 (56.12)	
Clinical stages			
I	54 (21.09)		
II	65 (25.39)		
III	44 (17.19)		
IV	77 (30.08)		
4s	9 (3.52)		
NA	7 (2.73)		
Sites of origin			
Adrenal gland	46 (17.97)		
Retroperitoneal region	87 (33.98)		
Mediastinum	90 (35.16)		
Other region	25 (9.77)		
NA	8 (3.13)		

Note: [a]Two-sided c^2 test for distributions between neuroblastoma cases and controls.
Abbreviation: NA, not available.