

## Research Paper

# Functional Polymorphisms in *hOGG1* Gene and Neuroblastoma Risk in Chinese Children

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## Abstract

Neuroblastoma is a lethal tumor of the sympathetic nervous system. 8-Hydroxydeoxyguanine (8-OH-dG) formation is a common seen type of oxidative DNA damage, which could be repaired by human oxoguanine glycosylase I (*hOGG1*). To explore the contributing role of *hOGG1* gene single nucleotide polymorphisms (SNPs) in neuroblastoma risk, we performed a case-control study by genotyping three SNPs (rs1052133 G>C, rs159153 T>C, rs293795 A>G) in *hOGG1* gene. A total of 512 neuroblastoma cases and 1076 cancer-free controls were enrolled from three medical centers in China. The *hOGG1* gene polymorphisms were determined using TaqMan real-time PCR. The results showed that only the rs1052133 G>C polymorphism was associated with neuroblastoma risk [GC vs. GG: adjusted odds ratio (OR)=0.64, 95% confidence interval (CI)=0.51-0.81,  $P=0.0002$ ; dominant model: adjusted OR=0.71, 95% CI=0.57-0.88,  $P=0.002$ ]. Moreover, subjects carrying 1, 2, or 1-3 protective genotypes have less opportunity to develop neuroblastoma, in comparison to those without protective genotypes. Stratified analysis revealed that rs1052133 GC/CC carriers were less likely to develop neuroblastoma in subgroups of age >18 months, males, tumor that develops from retroperitoneal, mediastinum and clinical stage I+II+4s. Our results indicate that *hOGG1* rs1052133 G>C polymorphism is associated with decreased risk of neuroblastoma. However, the exact biological mechanism awaits further research.

Key words: neuroblastoma, *hOGG1*, polymorphism, susceptibility, DNA repair

## Introduction

Neuroblastoma, a malignancy mainly diagnosed before age 5, is the most common extracranial solid tumor in infants [1]. It is a cancer that mainly develops from the adrenal medulla and the sympathetic ganglia [2]. Neuroblastoma presents approximately 7% of all pediatric malignancies and 15% of all childhood cancer deaths [2, 3]. Neuroblastoma is remarkable for its widely variable clinical heterogeneity [1]. Intermediate- or low- risk neuroblastoma is highly curable, which might spontaneously regress

without chemotherapy. However, high-risk neuroblastoma succumbs to therapy-resistant disease [4]. The 5-year survival rate of high-risk neuroblastoma, which accounts for nearly 50% of all cases, still less than 40% despite intensive, multi-modal therapy [4-7].

The factors that impact the neuroblastoma risk are only partially defined. Several environmental factors have been implicated in the initiation of neuroblastoma, yet still lack strict associations [8, 9].

Growing evidence indicated that neuroblastoma results from the combination of genetic factors and environmental factors. The etiology of familial neuroblastoma is mainly attributed to the mutations of *PHOX2B* [10] and *ALK* [11, 12] genes. Genome-wide association studies (GWASs) have revealed that risk alleles within genes *TP53*, *HACE1*, *BARD1*, *LIN28B*, *LMO1*, and *CASC15* are associated with sporadic neuroblastoma risk [13-17]. As neuroblastoma is a heterogeneous and complex disease, identification of more genetic variants in influencing neuroblastoma risk could help to better managing this disease.

Human genome is continuously exposed to the assaults by different exogenous and endogenous carcinogens or mutagens [18]. Sustained oxidative stress, such as exposure to smoke, induces oxidative DNA adducts [19]. 8-hydroxy-2-deoxyguanine (8-OH-dG) is a major form of oxidative DNA damage with highly mutagenic character [20]. It would cause GC to TA transversions, if not excised on DNA replication [21]. An increase in 8-OH-dG content in DNA is associated with tumor initiation and progression [22]. Thus, it is important to preserve genome integrity through the repair of damaged DNA. Human 8-oxoguanine glycosylase 1 (*hOGG1*) is a multifunctional DNA glycosylase that participates in the repair of DNA oxidative damage [23]. This enzyme could specifically recognize the 8-OH-dG damage and then efficiently catalyze and remove the damage [24].

*hOGG1* gene is located to chromosome 3p25 with eight exons. Several single nucleotide polymorphisms (SNPs) of the *hOGG1* gene have been identified, and their contributing roles in cancer risk have been evaluated in many studies [25-27]. However, few studies have been conducted to evaluate the association of *hOGG1* gene polymorphisms and neuroblastoma risk. To determine whether common genetic variants of *hOGG1* gene confer risk for neuroblastoma, we performed a case-control study in a Chinese Han population from three regions.

## Materials and Methods

### Study populations

A total of 512 neuroblastoma cases and 1076 healthy controls from three centers (Guangzhou Women and Children's Medical Center, The First Affiliated Hospital of Zhengzhou University, and Anhui Provincial Children's Hospital) were included in this study. To be specific, 275 cases and 531 controls were enrolled from Guangzhou, Guangdong; 118 cases and 281 controls were recruited from Zhengzhou, Henan [28-30]; and 119 cases and 264 controls were enrolled from Hefei, Anhui. We

obtained signed informed consent before the study from every participant or his/her parents. The study protocol was approved by the Institutional Review Board of the above three hospitals. More details of the enrollment procedure were provided in our previous publication [31-33].

### SNP selection and genotyping

The included potentially functional candidate SNPs were selected as follows: located in the 5' untranslated region, 3' untranslated region, 5' flanking region, and exon of *hOGG1* gene. NCBI dbSNP database (<http://www.ncbi.nlm.nih.gov/projects/SNP>) and SNPinfo (<http://snpinfo.niehs.nih.gov/snpfunc.htm>) online software were used to perform the above selection. We chose three potentially functional SNPs in the *hOGG1* gene (rs1052133 G>C, rs159153 T>C, and rs293795 A>G) for analysis. The rs1052133 G>C and rs293795 A>G are located within miRNA binding sites, and the rs159153 T>C is located in transcription factor binding sites (TFBS). Genomic DNA was derived from EDTA-peripheral blood by using TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd., Beijing, China). The genotyping of all the subjects was carried out using TaqMan real-time PCR (Applied Biosystems), according to the manufacturer's protocols [34-36]. In each plate, eight negative controls with water were used for quality control. Investigators were blinded to the status of all case and control samples. 10% of samples were randomly selected for a second genotyping, and the genotype concordance rate was 100%.

### Statistical analysis

Departures from Hardy-Weinberg equilibrium were assessed for each SNP in controls by goodness-of-fit  $\chi^2$  test. Two-sided chi-square test and *t* test were conducted, as appropriate to compare the demographic variables and allele frequencies between the two groups. The odds ratio (OR), and the corresponding 95% confidence interval (CI) for each SNP were calculated. Logistic regression analysis was performed to determine the correlation between SNPs and neuroblastoma risk. Statistical adjustment for age and gender was performed. The version 9.4 SAS software (SAS Institute, Cary, NC) was used to perform analyses. The significant threshold was  $P < 0.05$ .

## Results

### Population characteristics

A detailed description of the study sample from Guangzhou and Zhengzhou was presented previously [33, 37, 38]. The population demographics of the cases and controls from Hefei, Anhui province were presented in **Table 1**. No significant differences

were observed in terms of age ( $P=0.507$ ) and gender ( $P=0.941$ ) between the case and the control groups. Of them, 45, 52, 14, and 8 patients were classified as clinical stages I, II, III, and IV neuroblastoma, respectively. Among these cases, 43 lesions occurred in adrenal gland, 41 in retroperitoneal region, 26 in mediastinum, and 9 in other region.

### Correlation of *hOGG1* gene polymorphisms with neuroblastoma susceptibility

The genotype frequencies of *hOGG1* associated with neuroblastoma risk were shown in **Table 2**. Overall, we found an inverse association between rs1052133 C allele and neuroblastoma risk (GC vs. GG: adjusted OR=0.64, 95% CI=0.51-0.81,  $P=0.0002$ ; dominant model: adjusted OR=0.71, 95% CI=0.57-0.88,  $P=0.002$ ). No statistically significant associations were detected regarding the rs159153 T>C, rs293795 A>G polymorphisms and neuroblastoma risk. We also presented the combined effects of protective genotypes on neuroblastoma risk. We found that individuals carrying 1 or 2 protective genotypes have a significant decreased neuroblastoma risk in comparison to those without protective genotypes with adjusted OR=0.78, 95% CI=0.61-0.99,  $P=0.039$ ; or adjusted OR=0.69; 95% CI=0.50-0.95,  $P=0.024$ , respectively. Similarly, individuals with 1-3 combined protective genotypes of *hOGG1* were also less likely to develop neuroblastoma (adjusted OR=0.75; 95% CI=0.60-0.94,  $P=0.012$ ), compared with those with 0 protective genotypes.

### Stratification analysis

**Table 3** showed results from stratification

analyses of association between *hOGG1* genotypes and neuroblastoma risk, stratified by age, gender, tumor sites of origin and clinical stages. For age, *hOGG1* rs1052133 GC/CC genotype was significantly associated with decreased neuroblastoma risk among those >18 months (GC/CC vs. GG: adjusted OR=0.66; 95% CI=0.50-0.87). Significant inverse associations were also detected in subgroups of males (GC/CC vs. GG: adjusted OR=0.63; 95% CI=0.47-0.85), tumor that develops from retroperitoneal (GC/CC vs. GG: adjusted OR=0.58; 95% CI=0.40-0.85), tumor that develops from mediastinum (GC/CC vs. GG: adjusted OR=0.66; 95% CI=0.46-0.96) and clinical stage I+II+4s (GC/CC vs. GG: adjusted OR=0.64; 95% CI=0.48-0.85). In the stratified analysis of cumulative effects of protective genotypes, we found that the presence of 1-3 protective genotypes were protected from neuroblastoma in subgroups of age >18 months (adjusted OR=0.71; 95% CI=0.53-0.93), males (adjusted OR=0.71; 95% CI=0.53-0.96), tumor that develops from retroperitoneal (adjusted OR=0.63; 95% CI=0.43-0.92), and clinical stage I+II+4s (adjusted OR=0.71; 95% CI=0.54-0.95).

### Discussion

To the best of our knowledge, this study was the largest-scale case-control study to date to investigate the impact of *hOGG1* gene SNPs on the neuroblastoma risk in Chinese population. Our data demonstrated that a functional polymorphism rs1052133 G>C in *hOGG1* gene presented significant associations with decreased neuroblastoma risk.

**Table 1.** Demographic characteristics for neuroblastoma patients and cancer-free controls (Anhui and combined subjects)

Variables	Anhui province				$P^a$	Combined subjects				$P^a$
	Cases (N=119)		Controls (N=264)			Cases (N=512)		Controls (N=1076)		
	No.	%	No.	%		No.	%	No.	%	
Age range, month	0.001-108		0.001-96		0.507	0-132		0.001-156		0.937
Mean $\pm$ SD	26.86 $\pm$ 23.19		29.67 $\pm$ 27.52			33.82 $\pm$ 26.96		33.70 $\pm$ 28.68		
$\leq 18$	52	43.70	125	47.35		178	34.77	430	39.96	
$> 18$	67	56.30	139	52.65		334	65.23	646	60.04	
<b>Gender</b>										
Female	50	42.02	112	42.42	0.941	218	42.58	454	42.02	0.885
Male	69	57.98	152	57.58		294	57.42	622	57.98	
<b>Clinical stages</b>										
I	45	37.82				114	22.31			
II	52	43.70				145	28.38			
III	14	11.76				82	16.05			
IV	8	6.72				151	29.55			
4s	0	0.00				11	2.15			
NA	0	0.00				8	1.57			
<b>Sites of origin</b>										
Adrenal gland	43	36.13				196	38.28			
Retroperitoneal region	41	34.45				128	25.00			
Mediastinum	26	21.85				135	26.37			
Other region	9	7.56				45	8.79			
NA	0	0.00				8	1.56			

SD, standard deviation, NA, not available. <sup>a</sup> Two-sided  $\chi^2$  test for distributions between neuroblastoma patients and controls.

**Table 2.** Associations between hOGG1 polymorphisms and neuroblastoma susceptibility

Genotype	Cases (N=512)	Controls (N=1076)	P <sup>a</sup>	Crude OR (95% CI)	P	Adjusted OR (95% CI) <sup>b</sup>	P <sup>b</sup>
<b>rs1052133 G&gt;C</b>							
GG	197 (38.48)	330 (30.67)		1.00		1.00	
GC	217 (42.38)	567 (52.70)		<b>0.64 (0.51-0.81)</b>	<b>0.0002</b>	<b>0.64 (0.51-0.81)</b>	<b>0.0002</b>
CC	98 (19.14)	179 (16.64)		0.92 (0.68-1.24)	0.576	0.92 (0.68-1.24)	0.583
Additive			0.0005	0.90 (0.77-1.04)	0.155	0.90 (0.77-1.04)	0.157
Dominant	315 (30.67)	746 (69.33)	0.002	<b>0.71 (0.57-0.88)</b>	<b>0.002</b>	<b>0.71 (0.57-0.88)</b>	<b>0.002</b>
Recessive	414 (80.86)	897 (83.36)	0.219	1.19 (0.90-1.56)	0.219	1.19 (0.90-1.56)	0.216
<b>rs159153 T&gt;C</b>							
TT	415 (81.05)	858 (79.74)		1.00		1.00	
TC	94 (18.36)	211 (19.61)		0.92 (0.70-1.21)	0.550	0.92 (0.70-1.21)	0.553
CC	3 (0.59)	7 (0.65)		0.89 (0.23-3.44)	0.861	0.89 (0.23-3.46)	0.866
Additive			0.827	0.92 (0.72-1.19)	0.540	0.92 (0.72-1.19)	0.544
Dominant	97 (18.95)	218 (20.26)	0.539	0.92 (0.71-1.20)	0.539	0.92 (0.71-1.20)	0.543
Recessive	509 (99.41)	1069 (99.35)	0.879	0.90 (0.23-3.50)	0.881	0.91 (0.23-3.52)	0.886
<b>rs293795 A&gt;G</b>							
AA	462 (90.23)	955 (88.75)		1.00		1.00	
AG	49 (9.57)	116 (10.78)		0.87 (0.61-1.24)	0.450	0.87 (0.61-1.24)	0.451
GG	1 (0.20)	5 (0.46)		0.41 (0.05-3.55)	0.421	0.42 (0.05-3.57)	0.423
Additive			0.538	0.85 (0.61-1.18)	0.319	0.85 (0.61-1.18)	0.321
Dominant	50 (9.77)	121 (11.25)	0.374	0.85 (0.60-1.21)	0.374	0.86 (0.60-1.21)	0.376
Recessive	511 (99.80)	1071 (99.54)	0.414	0.42 (0.05-3.60)	0.428	0.42 (0.05-3.62)	0.430
<b>Combined effect of protective genotypes</b>							
0	180 (35.16)	311 (28.90)		1.00		1.00	
1	230 (44.92)	512 (47.58)		<b>0.78 (0.61-0.99)</b>	<b>0.039</b>	<b>0.78 (0.61-0.99)</b>	<b>0.039</b>
2	74 (14.45)	186 (17.29)		<b>0.69 (0.50-0.95)</b>	<b>0.024</b>	<b>0.69 (0.50-0.95)</b>	<b>0.024</b>
3	28 (5.47)	67 (6.23)		0.72 (0.45-1.16)	0.182	0.72 (0.45-1.17)	0.184
1-3	332 (64.84)	765 (71.10)	0.012	<b>0.75 (0.60-0.94)</b>	<b>0.012</b>	<b>0.75 (0.60-0.94)</b>	<b>0.012</b>

OR, odds ratio; CI, confidence interval. <sup>a</sup>  $\chi^2$  test for genotype distributions between neuroblastoma patients and controls. <sup>b</sup> Adjusted for age and gender. <sup>c</sup> Protective genotypes were rs1052133 GC/CC, rs159153 TC/CC, rs293795 AG/GG.

**Table 3.** Stratification analysis for association between hOGG1 genotypes and neuroblastoma susceptibility

Variables	rs1052133 (cases/controls)		AOR (95% CI) <sup>a</sup>	P <sup>a</sup>	Protective genotype (cases/controls)		AOR (95% CI) <sup>a</sup>	P <sup>a</sup>
	GG	GC/CC			0	1-3		
<b>Age, month</b>								
≤18	65/136	113/294	0.80 (0.56-1.16)	0.238	60/128	118/302	0.83 (0.57-1.21)	0.331
>18	132/194	202/452	<b>0.66 (0.50-0.87)</b>	<b>0.003</b>	120/183	214/463	<b>0.71 (0.53-0.93)</b>	<b>0.015</b>
<b>Gender</b>								
Females	81/149	137/305	0.83 (0.59-1.16)	0.279	77/139	141/315	0.81 (0.58-1.14)	0.230
Males	116/181	178/441	<b>0.63 (0.47-0.85)</b>	<b>0.002</b>	103/172	191/450	<b>0.71 (0.53-0.96)</b>	<b>0.026</b>
<b>Sites of origin</b>								
Adrenal gland	68/330	128/746	0.84 (0.61-1.15)	0.275	66/311	130/765	0.81 (0.58-1.12)	0.192
Retroperitoneal	55/330	73/746	<b>0.58 (0.40-0.85)</b>	<b>0.005</b>	50/311	78/765	<b>0.63 (0.43-0.92)</b>	<b>0.017</b>
Mediastinum	54/330	81/746	<b>0.66 (0.46-0.96)</b>	<b>0.029</b>	46/311	89/765	0.79 (0.54-1.15)	0.213
Others	15/330	30/746	0.88 (0.47-1.67)	0.703	13/311	32/765	1.00 (0.52-1.93)	0.991
<b>Clinical stages</b>								
I+II+4s	106/330	153/746	<b>0.64 (0.48-0.85)</b>	<b>0.002</b>	94/311	165/765	<b>0.71 (0.54-0.95)</b>	<b>0.020</b>
III+IV	83/330	150/746	0.81 (0.60-1.09)	0.155	79/311	154/765	0.80 (0.59-1.08)	0.145

AOR, Adjusted odds ratio; CI, confidence interval.

<sup>a</sup> Adjusted for age and gender, without the corresponding factor.

Herein, we for the first time investigated whether hOGG1 gene SNPs could affect the risk of neuroblastoma in Chinese children. The rs1052133 G>C, also referred as Ser326Cys, was located in exon 7. This genetic variant could result in an amino acid substitution of serine (Ser) with cysteine (Cys) at codon 326. It was reported by Kohno et al. that the substitution of amino acid affects hOGG1 function and further reduces DNA repair activity in an *in vitro* functional complementation assay [25]. Our results showed that the rs1052133 GC (Cys/Ser) was

associated with decreased neuroblastoma risk, when comparing to GG (Cys/Cys) genotype. The protective role of rs1052133 C (Ser) allele was also detected in other cancer types. For example, Xing et al. found that rs1052133 CC homozygotes confer to decreased risk for developing esophageal squamous cell carcinoma in a Chinese population [39]. Chen et al. observed that subjects possessing the hOGG1 rs1052133 C allele were less likely to develop prostate cancer in comparison with those carrying the G allele [40]. To note, our results failed to verify the hypothesis that

the CC genotype is associated with decreased risk to neuroblastoma. This may be potentially attributed to relatively moderate sample size. Besides, the final effect of *hOGG1* gene SNPs on neuroblastoma risk could be influenced by other exposure factors such as smoking status. Null relationship between SNP rs1052133 G>C and cancer risk was also observed. In a population-based (245 cases and 222 controls) and family-based (159 hereditary prostate cancer families) study, Xu et al. failed to detect the association between *hOGG1* rs1052133 G>C and prostate cancer risk [41]. Wikman et al. did not find statistical differences in rs1052133 genotype distribution between lung cancer cases and normal controls [42].

The current study failed to establish a relationship between rs159153 T>C, rs293795 A>G polymorphisms and neuroblastoma risk. This could be explained by that some weak impact single polymorphism in each gene might not be strong enough to influence the risk of cancer. Individual analysis of rs1052133 G>C, rs159153 T>C, rs293795 A>G revealed that only rs1052133 G>C polymorphism may be associated with decreased risk of neuroblastoma significantly. However, rs159153 TC/CC, rs293795 AG/GG genotypes may be associated with decreased risk of neuroblastoma, but not in significant level. Thus, we considered rs1052133 GC/CC, rs159153 TC/CC, and rs293795 AG/GG as protective genotypes, and further analyzed their combined effect. We found that individuals carrying 1, 2, 1-3 protective genotypes have a significant decreased neuroblastoma risk in comparison to those without protective genotypes.

In the stratified analysis, the significant association between rs1052133 genotype and neuroblastoma susceptibility was observed in neuroblastoma originating from retroperitoneal and mediastinum. However, the association of 1-3 protective genotypes with neuroblastoma susceptibility was detected only in neuroblastoma originating from retroperitoneal. Such discrepancy might be attributed to the small sample size in the stratified analysis.

Advantages of our study include the relatively large sample size as well as our analysis of three independent populations. Several limitations should be noted. First, although this is a multi-center study, the sample size is relatively moderate. Therefore, statistical power was impaired, especially for the stratification analysis. Second, only genetic factors were investigated; other environmental factors and genetic-environmental factors should also be included in the further study. Third, as this is a retrospective study, information bias and selection bias were inevitable. We have reduced these biases by frequency matching of cases and controls by age and

gender. However, other important information such as parental exposures, living environment, and dietary intake was unavailable. Thus, this information should be included in the further prospective studies. Last, although the participants were enrolled from three regions, they were all Han Chinese. The conclusions should be interpreted with caution when extrapolated to other ethnic groups.

In conclusion, our results suggest that polymorphism rs1052133 G>C in *hOGG1* gene was significantly associated with decreased neuroblastoma risk, in the Chinese population studied. Further functional studies are warranted to elucidate the biological role of *hOGG1* gene SNPs in the etiology of neuroblastoma.

## Abbreviations

GWAS: genome-wide association study; 8-OH-dG: 8-hydroxy-2-deoxyguanine; hOGG1: human 8-oxoguanine glycosylase 1; SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; Ser: serine; Cys: cysteine.

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## Competing Interests

The authors have declared that no competing interest exists.

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