Genetic Variations of GWAS-Identified Genes and Neuroblastoma Susceptibility: a Replication Study in Southern Chinese Children

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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 > N, 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.

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 countries, the incidence is highest among Caucasians, while it is relatively lower in African-American and Hispanic children. In Asian countries, the incidence is much lower, with China reporting the lowest incidence [2]. Understanding the genetic factors contributing to neuroblastoma development is crucial for improving diagnosis and treatment strategies.

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1Novelty: 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.

2Conflict 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 also found that polymorphisms within the DUSP12 gene at 2q35 were associated with high-risk neuroblastoma [17]. Gene Polymorphism Allele Case (N = 256) Control (N = 531) Adjusted OR a (95% CI) P b Adjusted OR a (95% CI) P b HWE

| Gene | Polymorphism | Allele | Case | Control | Adjusted OR a (95% CI) | P b | Adjusted OR a (95% CI) | P b | HWE |
|------|--------------|--------|------|---------|------------------------|-----|------------------------|-----|-----|
| CASC15 | rs6939340 | G A | 155 | 81 | 19 | 232 | 247 | 52 | 0.50 (0.37-0.68) <0.0001 | 0.74 (0.43-1.40) | 0.286 | 0.239 |
| CASC15 | rs6939340 | T C | 151 | 96 | 15 | 285 | 209 | 57 | 0.57 (0.42-0.78) | 0.0014 | 0.84 (0.45-1.60) | 0.581 | 0.875 |
| CASC15 | rs9295336 | A C | 168 | 71 | 11 | 282 | 212 | 27 | 0.90 (0.65-1.25) | 0.562 | 1.19 (0.72-1.94) | 0.439 | 1.019 |
| BARD1 | rs7585356 | G A | 120 | 111 | 213 | 235 | 273 | 59 | 0.88 (0.65-1.2) | 0.414 | 0.71 (0.42-1.20) | 0.199 | 0.948 |
| BARD1 | rs6453862 | T G | 74 | 74 | 7 | 381 | 133 | 17 | 1.19 (0.86-1.65) | 0.291 | 0.85 (0.35-2.07) | 0.71 | 0.205 |
| BARD1 | rs3768716 | C A | 168 | 76 | 11 | 282 | 212 | 37 | 0.90 (0.67-1.22) | 0.497 | 1.19 (0.72-1.97) | 0.503 | 0.756 |
| LIN28B | rs221634 | A T | 74 | 113 | 60 | 163 | 274 | 93 | 1.04 (0.75-1.45) | 0.798 | 0.85 (0.45-1.60) | 0.581 | 0.875 |
| LIN28B | rs6435862 | T G | 176 | 64 | 7 | 345 | 168 | 17 | 0.74 (0.54-1.03) | 0.078 | 0.88 (0.36-2.14) | 0.771 | 0.205 |
| LIN28B | rs9295536 | A C | 168 | 76 | 11 | 282 | 212 | 37 | 0.90 (0.65-1.22) | 0.497 | 1.19 (0.72-1.97) | 0.503 | 0.756 |
| CASC15 | rs9295536 | C A | 120 | 111 | 213 | 235 | 273 | 59 | 0.88 (0.65-1.25) | 0.562 | 1.19 (0.72-1.94) | 0.439 | 1.019 |
| BARD1 | rs3768716 | C A | 168 | 76 | 11 | 282 | 212 | 37 | 0.90 (0.65-1.22) | 0.497 | 1.19 (0.72-1.97) | 0.503 | 0.756 |
| LMO1 | rs10840002 | A G | 166 | 81 | 8 | 364 | 148 | 19 | 1.18 (0.86-1.63) | 0.291 | 0.85 (0.35-2.07) | 0.71 | 0.205 |
| LIN28B | rs221635 | A T | 74 | 113 | 60 | 163 | 274 | 93 | 1.04 (0.75-1.45) | 0.798 | 0.88 (0.36-2.14) | 0.771 | 0.205 |

**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

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) | P* |
|-----------------|----------------|-------------------|-------------|-------|---------------------|----|
| AA/AT           |                |                   |             |       |                     |    |
| AG/AA           | 45 (17.58)     | 167 (31.45)       | 1.00        | 1.00  |                     |    |
| GG/AG           | 72 (28.13)     | 138 (25.99)       | 2.92 (1.24-6.86) | .014  | 2.88 (1.22-6.79) | .016 |
| AG/AA           | 11 (4.30)      | 14 (2.64)         | 1.94 (1.25-2.99) | .003  | 1.92 (1.24-2.97) | .003 |
| GG/AG           | 11 (4.30)      | 42 (7.91)         | 3.00 (1.80-4.98) | .0001 | 3.01 (1.81-5.01) | .0001 |
| AG/AA           | 25 (9.77)      | 25 (4.71)         | 3.71 (1.95-7.07) | .0001 | 3.66 (1.92-6.97) | .0001 |
| TT/AA           | 13 (5.08)      | 12 (2.26)         | 4.02 (1.72-9.41) | .001  | 4.11 (1.75-9.66) | .001 |

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 | Case  | Control |
|------------|------|--------|-------|---------|-------|---------|
| CASC15     |      |        |       |         |       |         |
| rs6939340  |      |        |       |         |       |         |
| A > G      |      |        |       |         |       |         |
| Diskin     | 2012 | Caucasians | 2101  | /       | 1959  | 2307    |
|            |      |         |       |         |       |         |
| Latorre    | 2012 | Africans | 365   | 12      | 103   | 248     |
|            |      |         |       |         |       |         |
| Capasso    | 2013 | Caucasians | 339   | 74      | 162   | 103     |
|            |      |         |       |         |       |         |
| Lu         | 2015 | Asians  | 244   | /       | 124   | 364     |
|            |      |         |       |         |       |         |
| He         | 2016 | Asians  | 255   | 19      | 81    | 155     |
|            |      |         |       |         |       |         |
| Total      | 3302 |         |       | 1853    | 2349  | 5.049   |
|            |      |         |       |         |       | .0001   |
|            |      |         |       |         |       |         |
| LMO1       |      |        |       |         |       |         |
| rs110419   |      |        |       |         |       |         |
| G > A      |      |        |       |         |       |         |
| Diskin     | 2012 | Caucasians | 2101  | /       | 1853  | 2349    |
|            |      |         |       |         |       | .0559   |
|            |      |         |       |         |       | .0001   |
| Latorre    | 2012 | Africans | 365   | 18      | 124   | 223     |
|            |      |         |       |         |       | .0781   |
|            |      |         |       |         |       | .00001  |
| Capasso    | 2013 | Caucasians | 325   | 84      | 152   | 87      |
|            |      |         |       |         |       | .0505   |
|            |      |         |       |         |       | .0001   |
| Lu         | 2015 | Asians  | 244   | /       | 125   | 363     |
|            |      |         |       |         |       | .0744   |
|            |      |         |       |         |       | .00001  |
| He         | 2016 | Asians  | 256   | 36      | 117   | 103     |
|            |      |         |       |         |       | .0631   |
|            |      |         |       |         |       | .00001  |
| Total      | 3289 |         |       | 8308    | 4294  | 4110    |
|            |      |         |       |         |       | .00001  |

* 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 χ²-based Q test. Random-effect modeling was used when I² < .1 [34].

Statistical Analysis
We applied χ² tests to compare categorical variables such as demographics and genotype frequencies. We used the goodness-of-fit χ² 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).
CI = 1.19−1.58, \( P = 1.97 \times 10^{-5} \)). 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, \( P = 3.15 \times 10^{-4} \)) (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

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**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.
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 the role of five polymorphisms in predicting 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 CDZ3 [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.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tranon.2017.09.008.

References

[1] Bao PP, Li K, Wu CX, Huang ZZ, Wang CF, Xiang YM, Peng P, Gong YM, Xiao XM, and Zheng Y (2013). Recent incidences and trends of childhood malignant solid tumors in Shanghai, 2002-2010. Zhonghua Er Ke Za Zhi 51, 288-294.
[2] Gatta G, Capocaccia R, Coleman MP, Ries LA, and Berrino F (2002). Childhood cancer survival in Europe and the United States. Cancer 95, 1677-1722.
[3] Spix C, Pastore G, Sankila R, Stiller CA, and Steliarova-Foucher E (2006). Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer 42, 2081-2091.
[4] Liu YL, Lo WC, Chiang CJ, Yang YW, Lu MY, Hsu WM, Ho WL, Li MJ, Miser JS, and Lin DT, et al (2015). Incidence of cancer in children aged 0-14 years in Taiwan, 1996-2010. Cancer Epidemiol 39, 21–28.
[5] Baade PD, Youlدن DR, Valery PC, Hassall T, Ward L, Green AC, and Atkin JF (2010). Trends in incidence of childhood cancer in Australia, 1983-2006. Br J Cancer 102, 620–626.
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[6] Swaminathan R, Rama R, and Shanta V (2008). Childhood cancers in Chennai, India, 1990-2001: incidence and survival. *Int J Cancer* 122, 2607–2611.

[7] Moreno F, Lopez Marit J, Palladino M, Lobos P, Guaitieri A, and Cacciavillano W (2016). Childhood neuroblastoma: incidence and survival in Argentina. Report from the National Pediatric Cancer Registry, ROHA Network 2000-2012. *Pediatr Blood Cancer* 63, 1362–1367.

[8] De Roos AJ, Olshan AF, Teschke K, Poole C, Savitz DA, Blart J, Bondy ML, and Pollock BH (2001). Parental occupational exposures to chemicals and incidence of neuroblastoma in offspring. *Am J Epidemiol* 154, 106–114.

[9] De Roos AJ, Teschke K, Savitz DA, Poole C, Grufterman S, Pollock BH, and Olshan AF (2001). Parental occupational exposures to electromagnetic fields and radiation and the incidence of neuroblastoma in offspring. *Epidemiology* 12, 508–517.

[10] Capasso M and Diskin SJ (2010). Genetics and genomics of neuroblastoma. *Cancer Treat Res* 155, 65–84.

[11] Deyell RJ and Attiyeh EF (2011). Advances in the understanding of constitutional and somatic genomic alterations in neuroblastoma. *Cancer Genet* 204, 113–121.

[12] Capasso M, Diskin S, Cimmino F, Acigno G, Totaro F, Petrosino G, Pezone L, Diamond M, McDaniel L, and Hakonarson H, et al (2014). Common genetic variants in NEFL influence gene expression and neuroblastoma risk. *Cancer Res* 74, 6913–6924.

[13] Oldridge DA, Wood AC, Weichert-Leahey N, Crimmins I, Sussman R, Winter C, McDaniel LD, Diamond M, Hart LS, and Zhu S, et al (2015). Genetic predisposition to neuroblastoma mediated by a LMO1 super-enhancer polymorphism. *Nature* 528, 418–421.

[14] Stadler ZK, Thom P, Robson ME, Weitzel KE, Hurley KE, Devlin V, Gold B, Klein RJ, and Offit K (2010). Genome-wide association studies of cancer. *J Clin Oncol* 28, 4255–4267.

[15] Frazer KA, Murray SS, Schork NJ, and Topel EJ (2009). Human genetic variation and its contribution to complex traits. *Nat Rev Genet* 10, 241–251.

[16] Maris JM, Mosse YP, Bradfield JP, Hou C, Monni S, Scott RH, Asgharzadeh S, Attiyeh EF, Diskin SJ, and Luedenslager M, et al (2008). Chromosome 6p22 locus in African-Americans. *Cancer Genet* 179, 113–120.

[17] Capasso M, Diskin S, Cimmino F, Acigno G, Totaro F, Petrosino G, Pezone L, Diamond M, McDaniel L, and Hakonarson H, et al (2014). Common genetic variants in NEFL influence gene expression and neuroblastoma risk. *Cancer Res* 74, 6913–6924.

[18] Oldridge DA, Wood AC, Weichert-Leahey N, Crimmins I, Sussman R, Winter C, McDaniel LD, Diamond M, Hart LS, and Zhu S, et al (2015). Genetic predisposition to neuroblastoma mediated by a LMO1 super-enhancer polymorphism. *Nature* 528, 418–421.

[19] Stadler ZK, Thom P, Robson ME, Weitzel KE, Hurley KE, Devlin V, Gold B, Klein RJ, and Offit K (2010). Genome-wide association studies of cancer. *J Clin Oncol* 28, 4255–4267.

[20] Frazer KA, Murray SS, Schork NJ, and Topel EJ (2009). Human genetic variation and its contribution to complex traits. *Nat Rev Genet* 10, 241–251.

[21] Maris JM, Mosse YP, Bradfield JP, Hou C, Monni S, Scott RH, Asgharzadeh S, Attiyeh EF, Diskin SJ, and Luedenslager M, et al (2008). Chromosome 6p22 locus in African-Americans. *Cancer Genet* 179, 113–120.

[22] Capasso M, Diskin S, Cimmino F, Acigno G, Totaro F, Longo L, De Mariano M, Russo R, Cimmino F, Hakonarson H, Tonini GP, and Devoto M, et al (2013). Replication of GWAS-identified neuroblastoma risk loci strengthens the role of BARD1 and affirms the cumulative effect of genetic variations on disease susceptibility. *Carcinogenesis* 34, 605–611.

[23] Lu J, Chu P, Wang H, Jin Y, Han S, Han W, Tai J, Guo Y, and Ni X (2015). Candidate gene association analysis of neuroblastoma in Chinese children strengthens the role of LMO1. *PLoS One* 10, e0127856.

[24] He J, Yang T, Zhang R, Zhu J, Wang F, Zou Y, and Xia H (2016). Potentially functional polymorphisms in the LIN28B gene contribute to neuroblastoma susceptibility in Chinese children. *J Cell Mol Med* 20, 1534–1541.

[25] He J, Zhang R, Zou Y, Zhu J, Yang T, Wang F, and Xia H (2016). Evaluation of GWAS-identified SNPs at 6p22 with neuroblastoma susceptibility in a Chinese population. *Tumour Biol* 37, 1635–1639.

[26] He J, Zhong W, Zeng J, Zhu J, Zhang R, Wang F, Yang T, Zou Y, and Xia H (2016). LMO1 gene polymorphisms contribute to decreased neuroblastoma susceptibility in a Southern Chinese population. *Onco Targets Ther* 9, 2277–22778.

[27] Zhang R, Zou Y, Zhu J, Zeng X, Yang T, Wang F, He J, and Xia H (2016). The association between GWAS-identified BARD1 gene SNPs and neuroblastoma susceptibility in a Southern Chinese population. *Int J Med Sci* 13, 133–138.

[28] Zhang Z, Zou Y, Zhu J, Zhang R, Yang T, Wang F, Xia H, He J, and Feng Z (2017). HSD17B12 gene rs1037575 C>T polymorphism confers neuroblastoma susceptibility in a Southern Chinese population. *Onco Targets Ther* 10, 1969–1975.

[29] Zhang Z, Zhang R, Zhu J, Wang F, Yang T, Zou Y, He J, and Xia H (2017). Common variations within HACE1 gene and neuroblastoma susceptibility in a Southern Chinese population. *Onco Targets Ther* 10, 703–709.

[30] He J, Wang F, Zhu J, Zhang R, Yang T, Zou Y, and Xia H (2016). Association of potentially functional variants in the XPG gene with neuroblastoma risk in a Chinese population. *J Cell Mol Med* 20, 1481–1490.

[31] He J, Wang F, Zou J, Zhang Z, Zou Y, Zhang R, Yang T, and Xia H (2017). The TP53 gene rs1042522 C>G polymorphism and neuroblastoma risk in Chinese children. *Aging (Albany NY)* 9, 852–859.

[32] He J, Qi LX, Wang MY, Hua RX, Zhang RX, Yu HP, Wang YN, Sun MH, Zhou XY, and Yang YJ, et al (2012). Polymorphisms in the XPG gene and risk of gastric cancer in Chinese populations. *Hum Genet* 131, 1235–1244.

[33] Lou J, Gong J, Ke J, Tian J, Zhang Y, Li J, Yang Y, Zhu Y, Gong Y, and Li L, et al (2017). A functional polymorphism located at transcription factor binding sites, rs6695837 near LAMC1 gene, confers risk of colorectal cancer in Chinese populations. *Carcinogenesis* 38, 177–183.

[34] He J, Shi TY, Zhu ML, Wang MY, Li QX, and Wei QY (2013). Associations of Lys939Gln and Ala499Val polymorphisms of the XPC gene with cancer susceptibility: a meta-analysis. *Int J Cancer* 133, 1765–1775.

[35] Ruan HL, Qin HD, Shugart YY, Bei JX, Luo FT, Zeng YX, and Jia WH (2013). Developing genetic epidemiological models to predict risk for nasopharyngeal carcinoma in high-risk population of China. *PLoS One* 8, e56128.

[36] Li J, Zou L, Zhou Y, Li L, Zhu Y, Yang G, Gong Y, Lou J, Ke J, and Zhang Y, et al (2017). A low-frequency variant in SMAD7 modulates TGF-beta signaling and confers risk for colorectal cancer in Chinese populations. *Mol Carcinog* 56, 1798–1807.

[37] McDaniel LD, Conkrite KL, Zhang X, Capasso M, Vakszman Z, Oldridge DA, Zachariau A, Horn M, Diamond M, and Hou C, et al (2017). Common variants upstream of MLF1 at 3q25 and within CPZ at 4p16 associated with neuroblastoma. *PLoS Genet* 13, e1006787.