Lack of associations between AURKA gene polymorphisms and neuroblastoma susceptibility in Chinese children

Jue Tang1,*, Yuanmin Qian2,*, Jinhong Zhu3, Jiao Zhang4, Feng-Hua Wang5, Jia-Hang Zeng1, Jiang-Hua Liang1, Hui Wang1, Huimin Xia1, Jing He1 and Wei Liu1

1Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangzhou Women and Children’s Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China; 2Department of Gynecology and Obstetrics, Guangzhou Women and Children’s Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China; 3Department of Clinical Laboratory, Molecular Epidemiology Laboratory, Harbin Medical University Cancer Hospital, Harbin 150040, Heilongjiang, China; 4Department of Pediatric Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, China

Correspondence: Wei Liu (liuwei19610624@126.com) or Jing He (hejing198374@gmail.com, hejing@gwcmc.org)

Previous studies have demonstrated that polymorphisms in the AURKA gene are associated with various types of cancer. In neuroblastoma, AURKA protein product regulates N-myc protein levels and plays a critical role in tumorigenesis. To investigate the association between three AURKA polymorphisms (rs1047972 C>T, rs2273535 T>A, and rs8173 G>C) and neuroblastoma susceptibility in Chinese populations, we performed this two-center case–control study including 393 neuroblastoma cases and 812 controls. Two study populations were recruited from two different regions in China. No significant associations were identified amongst any of the three AURKA polymorphisms and the risk of neuroblastoma. Similar observations were found in the stratified analysis. In conclusion, our results indicate that none of the AURKA polymorphisms are associated with neuroblastoma susceptibility in two distinct Chinese populations. Further studies with larger sample sizes and different ethnicities are warranted to validate our results.

Introduction

Neuroblastoma is a neuroendocrine tumor that originates from the developing sympathetic nervous system. It is the most common solid malignancy in the first year of life, accounting for approximately 15% of pediatric cancer deaths [1]. Despite remarkable advances in multimodality treatment, the survival rate for patients with high-risk tumors remains approximately 50% [1,2]. At present, the etiology of neuroblastoma remains far from clear. Genetic variations have been shown to be important factors in the origin and development of neuroblastoma [3-5]. A previous genome-wide association study (GWAS) demonstrated that common genetic variations in the BARD1 gene may contribute to the etiology of the aggressive neuroblastoma [6]. Moreover, polymorphisms in the CDKN1B gene were found to associate with neuroblastoma susceptibility [7]. Over the past years, several GWASs have identified a number of genetic alterations that not only influence neuroblastoma formation but also contribute to malignant transformation [8-10]. Single nucleotide polymorphisms (SNPs) within DDX4, HSD17B12, and DUSP12 are recurrent in low-risk neuroblastoma [11,12]. SNPs in CASC15, LMO1, and LIN28B are enriched in high-risk neuroblastoma and are correlated with neuroblastoma tumor aggressiveness [10,13,14]. Previous study demonstrated that LIN28B promotes AURKA expression via inhibition of let-7, further driving neuroblastoma oncogenesis [15].

AURKA, located at chromosome region 20q13.2, encodes a serine/threonine kinase (Aurora-A) that has been shown to play a crucial role in regulating mitosis. Overexpression of Aurora-A contributes to centrosomal duplication abnormalities, genomic instability, and the promotion of tumorigenesis [16,17].
Over the past decade, Aurora-A overexpression has been demonstrated in multiple human cancers, including primary colorectal carcinoma, esophageal squamous cell carcinoma, and breast and ovarian cancers [17-19]. And overexpression of Aurora-A is associated with advanced clinical states, worse overall survival, and shorter event-free survival in patients with neuroblastoma [20]. In addition, several studies confirmed that AURKA polymorphisms were associated with the risk of several human cancers [21-24]. To date, no study has assessed the associations between AURKA SNPs and the risk of neuroblastoma.

To evaluate the associations between the SNPs in the AURKA gene and neuroblastoma susceptibility, we conducted this case–control study with 393 neuroblastoma cases and 812 control subjects from the Chinese population.

Materials and methods

Study subjects

In the present study, a total of 393 neuroblastoma cases and 812 controls were recruited from two different regions of China [25-28]. The first population was composed of 275 neuroblastoma cases and 531 controls from the Guangzhou Women and Children’s Medical Center [29-31]. The second population consisted of 118 neuroblastoma cases and 281 controls from The First Affiliated Hospital of Zhengzhou University [32,33]. Both the cases and controls were of Chinese Han ethnicity and were genetically unrelated. The cases and controls were matched according to age, gender, and ethnicity. Neuroblastoma patients were diagnosed by biopsy and staged according to the International Neuroblastoma Staging System (INSS) [34]. The present study was approved by the Institutional Review Board of each institution. Written informed consent was acquired from the parents or guardians of each participant.

Polymorphism selection and genotyping

Polymorphisms were chosen based on the following criteria: (i) minor allele frequency >5% for CHB subjects; (ii) potentially functional as predicted by SNPinfo (http://snpinfo.niehs.nih.gov/) software; (iii) not investigated for the association with neuroblastoma susceptibility. We searched the potentially functional polymorphisms located in the 5′-flanking region, 5′ UTR, 3′ UTR, and exon of AURKA gene. Three SNPs (rs1047972 C>T, rs2273535 T>A, and rs8173 G>C) in the AURKA gene were selected (Supplementary Table S1). These three SNPs can capture additional fourteen SNPs. As shown in Supplementary Figure S1, there was no significant linkage disequilibrium between paired polymorphisms (R² = 0.119 between rs8173 and rs1047972; R² = 0.527 between rs8173 and rs2273535; and the R² = 0.291 between rs1047972 and rs2273535). These SNPs were genotyped using TaqMan real-time PCR following a published protocol [35-38]. To ensure credible genotyping results, 10% of the samples were randomly selected for repeated genotyping assays, and the results were 100% concordant.

Statistical analysis

Differences in genotype frequencies as well as in demographic variables between cases and controls were compared by two-sided χ² tests. Hardy–Weinberg equilibrium (HWE) for the genotype frequencies in controls was calculated by a goodness-of-fit χ² test. Associations between AURKA SNPs and neuroblastoma were estimated using adjusted odds ratios (ORs) and 95% confidence intervals (CIs). We also performed analyses stratified by age, gender, tumor sites, and clinical stages. P <0.05 was considered statistically significant. All statistical tests were performed using SAS software (version 9.4; SAS Institute, Cary, NC, U.S.A.).

Results

AURKA gene polymorphisms and neuroblastoma susceptibility

In the present study, 393 cases and 812 controls were successfully genotyped. The genotype frequencies of the three AURKA polymorphisms and their associations with neuroblastoma susceptibility are summarized in Table 1. The observed genotype frequencies among the control subjects were in HWE (P =0.337 for the rs1047972 C>T polymorphism, P =0.174 for the rs2273535 T>A polymorphism, and P =0.506 for the rs8173 G>C polymorphism). No significant associations were identified between any of the three AURKA SNPs and the risk of neuroblastoma.

Stratification analysis

We then divided participants into subgroups according to age, gender, clinical stage, and site of origin. The effects of the selected polymorphisms on the risk of neuroblastoma were assessed in this stratified analysis (Table 2). The effects of combined risk genotypes on neuroblastoma risk were also assessed. However, no significant association was discovered for any of the selected polymorphisms.
### Table 1 The correlation of AURKA gene polymorphisms with neuroblastoma risk

| Genotype | Cases (n=393) | Controls (n=812) | P 1 | Crude OR (95% CI) | P 2 | Adjusted OR (95% CI) |
|----------|---------------|-----------------|-----|-------------------|-----|----------------------|
| rs1047972 C>T (HWE = 0.337) |               |                 |     |                   |     |                      |
| CC       | 305 (77.61)   | 629 (77.46)     | 1.00 | 1.00              |     |                      |
| CT       | 87 (22.14)    | 168 (20.69)     | 1.07 (0.80–1.43) | 0.660 | 1.07 (0.80–1.43) | 0.671 |
| TT       | 1 (0.25)      | 15 (1.85)       | 0.14 (0.02–1.05) | 0.055 | 0.14 (0.02–1.04) | 0.055 |
| Additive |               |                 | 0.070 | 0.92 (0.70–1.20) | 0.535 | 0.92 (0.70–1.20) | 0.526 |
| Dominant | 88 (22.39)    | 183 (22.54)     | 0.955 | 0.99 (0.74–1.32) | 0.955 | 0.99 (0.74–1.32) | 0.943 |
| Recessive| 392 (99.75)   | 797 (98.15)     | 0.024 | 0.14 (0.02–1.03) | 0.053 | 0.14 (0.02–1.03) | 0.053 |
| rs2273535 T>A (HWE = 0.174) |               |                 |     |                   |     |                      |
| TT       | 182 (46.31)   | 377 (46.43)     | 1.00 | 1.00              |     |                      |
| TA       | 171 (43.51)   | 340 (41.87)     | 1.04 (0.81–1.35) | 0.753 | 1.04 (0.81–1.34) | 0.765 |
| AA       | 40 (10.18)    | 95 (11.70)      | 0.87 (0.58–1.31) | 0.513 | 0.87 (0.58–1.31) | 0.511 |
| Additive |               |                 | 0.699 | 0.97 (0.81–1.16) | 0.735 | 0.97 (0.81–1.16) | 0.728 |
| Dominant | 211 (53.69)   | 435 (53.57)     | 0.969 | 1.01 (0.79–1.28) | 0.969 | 1.00 (0.79–1.28) | 0.981 |
| Recessive| 353 (89.82)   | 717 (88.30)     | 0.433 | 0.86 (0.58–1.26) | 0.433 | 0.86 (0.58–1.27) | 0.435 |
| rs8173 G>C (HWE = 0.506) |               |                 |     |                   |     |                      |
| GG       | 164 (41.73)   | 314 (38.67)     | 1.00 | 1.00              |     |                      |
| GC       | 176 (44.78)   | 389 (47.91)     | 0.87 (0.67–1.12) | 0.278 | 0.86 (0.67–1.12) | 0.265 |
| CC       | 53 (13.49)    | 109 (13.42)     | 0.93 (0.64–1.36) | 0.711 | 0.93 (0.64–1.36) | 0.698 |
| Additive |               |                 | 0.555 | 0.94 (0.78–1.12) | 0.473 | 0.94 (0.78–1.12) | 0.458 |
| Dominant | 229 (58.27)   | 498 (61.33)     | 0.309 | 0.88 (0.69–1.13) | 0.309 | 0.88 (0.69–1.12) | 0.294 |
| Recessive| 340 (86.51)   | 702 (80.58)     | 0.978 | 1.01 (0.71–1.43) | 0.978 | 1.00 (0.71–1.43) | 0.981 |
| Combined effect of protective genotypes | 0 | 162 (41.22) | 312 (38.42) | 1.00 | 1.00 | 1.00 |
|         | 1–3 | 231 (58.78) | 500 (61.58) | 0.351 | 0.89 (0.70–1.14) | 0.351 | 0.89 (0.69–1.13) | 0.335 |

1Adjusted for age and gender.
2Protective genotypes were rs1047972 TT, rs2273535 AA, and rs8173 GC/CC.

### Discussion

We conducted the present case–control study with a total of 393 neuroblastoma patients and 812 control subjects to investigate the impact of three AURKA SNPs on the risk of neuroblastoma in Chinese populations. Our data indicated that none of the selected SNPs were associated with neuroblastoma susceptibility in two independent Chinese populations. To the best of our knowledge, this is the first study to investigate the association between neuroblastoma susceptibility and polymorphisms in the AURKA gene.

AURKA has been reported to be overexpressed in several human malignancies and encodes a serine/threonine kinase that is involved in the processes of proliferation, survival, invasion, and stemness in multiple types of cancer [17]. Several studies have demonstrated that AURKA SNPs were associated with the risk of cancer [21-23]. Lee et al. [39] identified an association between a genetic variant (rs2273535) in the AURKA gene and oral cancer. A recent study has demonstrated that AURKA SNPs (rs1047972 and rs2273535) increase the risk of oral squamous cell carcinoma [40]. In Malaysian Chinese, AURKA rs2273535 protected against breast cancer [41]. A meta-analysis suggested that AURKA rs1047972 is associated with a decreased breast cancer risk in Caucasians, while AURKA rs2273535 polymorphism is associated with an increased risk of breast cancer [23]. This finding indicates that the functions of AURKA SNPs may vary depending on the types of cancer and ethnic differences.

Aurora A is responsible for stabilizing N-myc in neuroblastoma. [17,42]. A previous study demonstrated that LIN28B-RAN-AURKA axis is implicated in neuroblastoma oncogenesis. Aurora A overexpression in neuroblastoma is associated with advanced clinical states, MYCN amplification, disease relapse, and progression [43]. As a transcriptional regulator, MYCN (encoding N-myc) plays a crucial role during embryonic development. In addition, MYCN amplification, which is involved in the inhibition of both cell-cycle exit and normal differentiation, contributes to neuroblastoma initiation and progression [44-46]. Knockdown of AURKA has been shown to decrease N-myc protein levels and neuroblastoma cell proliferation [47]. However, we failed to detect any significant association between these AURKA SNPs (rs1047972 C>T, rs2273535 T>A, and rs8173 G>C) and neuroblastoma susceptibility in the
### Table 2 Stratification analysis for association between AURKA gene genotypes and neuroblastoma susceptibility

| Variables                  | rs1047972 (case/control) | rs2273535 (case/control) | rs8173 (case/control) | AOR (95% CI) | P ¹ | AOR (95% CI) | P ² | AOR (95% CI) | P ³ |
|----------------------------|---------------------------|---------------------------|-----------------------|--------------|-----|--------------|-----|--------------|-----|
|                           | CC            | CT/TT                     | TT | TA/AA | CC        | CT/TT | TT | TA/AA | 0 | 1–3 |
| **Age, months**           |               |                           |               |               |           |       |     |       |          |     |
| ≤ 18                      | 103/241       | 23/64                     | 0.84          | 0.522        | (0.50–1.43)| 0.90  | 0.624 | (0.60–1.37) | 59/132 | 67/173 | 0.87 | 0.501 | (0.57–1.32) | 59/130 | 67/175 | 0.84 | 0.425 | (0.56–1.28) |
| > 18                      | 202/388       | 65/119                    | 1.05          | 0.789        | (0.74–1.48)| 1.05  | 0.759 | (0.78–1.41) | 105/182 | 162/325 | 0.86 | 0.344 | (0.64–1.17) | 103/182 | 164/325 | 0.89 | 0.458 | (0.66–1.21) |
| **Gender**                |               |                           |               |               |           |       |     |       |          |     |
| Female                    | 130/269       | 38/73                     | 1.09          | 0.715        | (0.70–1.70)| 1.06  | 0.773 | (0.73–1.53) | 67/139 | 101/203 | 1.05 | 0.821 | (0.72–1.53) | 66/138 | 102/204 | 1.06 | 0.772 | (0.72–1.55) |
| Male                      | 175/360       | 50/110                    | 0.93          | 0.711        | (0.64–1.36)| 0.97  | 0.834 | (0.70–1.33) | 97/175 | 128/295 | 0.78 | 0.123 | (0.56–1.07) | 96/174 | 129/296 | 0.78 | 0.136 | (0.57–1.08) |
| **Sites of origin**       |               |                           |               |               |           |       |     |       |          |     |
| Adrenal gland             | 118/629       | 35/183                    | 1.00          | 0.999        | (0.66–1.51)| 1.09  | 0.623 | (0.77–1.55) | 56/314 | 97/498 | 1.06 | 0.768 | (0.74–1.51) | 55/312 | 98/500 | 1.08 | 0.696 | (0.75–1.54) |
| Retroperitoneal           | 66/629        | 19/183                    | 0.96          | 0.894        | (0.57–1.65)| 1.02  | 0.941 | (0.75–1.59) | 38/314 | 49/498 | 0.82 | 0.381 | (0.62–1.28) | 37/312 | 50/500 | 0.85 | 0.476 | (0.54–1.33) |
| Mediastinum               | 87/629        | 22/183                    | 0.88          | 0.621        | (0.54–1.45)| 0.86  | 0.460 | (0.58–1.28) | 52/314 | 57/498 | 0.71 | 0.090 | (0.47–1.06) | 52/312 | 57/500 | 0.70 | 0.080 | (0.47–1.04) |
| Others                    | 27/629        | 9/183                     | 1.14          | 0.737        | (0.53–2.47)| 0.97  | 0.922 | (0.50–1.89) | 15/314 | 21/498 | 0.90 | 0.750 | (0.45–1.77) | 15/312 | 21/500 | 0.88 | 0.723 | (0.45–1.75) |
| **Clinical stage**        |               |                           |               |               |           |       |     |       |          |     |
| I + II + 4s               | 131/629       | 31/183                    | 0.82          | 0.367        | (0.54–1.26)| 0.90  | 0.520 | (0.64–1.26) | 77/314 | 85/498 | 0.71 | 0.047 | (0.50–0.996) | 75/312 | 87/500 | 0.74 | 0.079 | (0.52–1.04) |
| III + IV                  | 158/629       | 53/183                    | 1.14          | 0.466        | (0.80–1.62)| 1.09  | 0.573 | (0.80–1.48) | 77/314 | 134/498 | 1.07 | 0.660 | (0.78–1.47) | 77/312 | 134/500 | 1.06 | 0.699 | (0.78–1.46) |

Abbreviation: AOR, adjusted OR.

¹Adjusted for age and gender, omitting the corresponding stratify factor.
present study. The negative results might be attributed to the limited sample size. The relatively small sample size might not be large enough to detect an association.

Several limitations in our study should be mentioned. First, the sample size in the present study might not be large enough to draw accurate conclusions. Increasing the sample size would increase the power to detect risk variants and increase the credibility of any observed associations. Analyses with large sample sizes are essential to verify our results. Second, the etiology of neuroblastoma is complex and multifactorial. Several important factors such as dietary intake and living environment contribute to neuroblastoma pathogenesis. The results should be explained with caution, because these confounding factors were not included in the current study. Third, only three AURKA SNPs were investigated in our study. Other polymorphisms in the AURKA gene should be investigated in future study. Fourth, the genotype distribution in this hospital-based study may not reflect that in the general population, which would inevitably result in selection bias.

In summary, our study confirmed that none of the AURKA polymorphisms (rs1047972 C>T, rs2273535 T>A, and rs8173 G>C) were associated with neuroblastoma susceptibility in two distinct Chinese populations. Future studies with larger sample sizes and different ethnicities are required to further clarify the effect of AURKA SNPs on the risk of neuroblastoma.

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**Competing interests**
The authors declare that there are no competing interests associated with the manuscript.

**Author contribution**
All authors contributed significantly to this work: J.T., J. Zhang, F.-H.W., J.-H.Z., J.-H.L., H.W., and J.H. performed the research study and collected the data. J.H. and Y.Q. analyzed the data; H.X., J.H., and W.L. designed the research study. J.T. and J. Zhu wrote the paper. J.H. prepared all the tables. All authors reviewed the manuscript. In addition, all the authors read and approved the manuscript.

**Abbreviations**
GWAS, genome-wide association study; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.

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