Research Article

AURKA rs8173 G>C Polymorphism Decreases Wilms Tumor Risk in Chinese Children

Tongyi Lu,1 Li Li,2 Jinhong Zhu,3 Jiabin Liu,1 Ao Lin,1 Wen Fu,1 Guochang Liu,1 Huimin Xia,1 Tiesong Zhang,2 and Jing He1

1Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children’s Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China
2Kunming Key Laboratory of Children Infection and Immunity, Yunnan Key Laboratory of Children’s Major Disease Research, Yunnan Institute of Pediatrics Research, Yunnan Medical Center for Pediatric Diseases, Kunming Children’s Hospital, Kunming 650228, Yunnan, China
3Department of Clinical Laboratory, Biobank, Harbin Medical University Cancer Hospital, Harbin 150040, Heilongjiang, China

Correspondence should be addressed to Tiesong Zhang; zts68420@sina.com and Jing He; hejing198374@gmail.com

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1. Introduction

Wilms tumor (WT), also known as nephroblastoma, is the most common renal malignancy in children [1, 2]. It accounts for 6% to 7% of malignant tumors in children under the age of 15 years, with an incidence rate of about 7–10 cases per million in Western countries [3]. The incidence rate of WT in Chinese is around 3.3 cases per million [4]. Over the past 20 years, because of the application of multimodality treatment, including surgery, radiotherapy, chemotherapy, and autologous stem cell transplantation, the overall survival rate of 5 years has increased from 30% to 90% [2, 5–7]. Despite the great achievements in the treatment of WT, the prognosis of nearly 25% of patients with high-risk diseases remains unsatisfying [8]. In addition, about 25% of survivors suffer from the high cost of treatment and the physical torment of some chronic conditions [9, 10].

Previous studies have found that genetic factors contribute to the risk of Wilms tumor and identified a number of genes associated with WT, including Wilms’ tumor protein 1 (WT1), β-catenin, tumor protein 53 (TP53), catenin beta 1 (CTNNB1), and AMER1 [11–13]. Although recent genome-wide studies on WT have revealed some previously unknown gene mutations implicated with WT, current known genetic variants are not adequate to fully elucidate the pathogenesis of WT [14]. Therefore, it is

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In this study, a total of 145 cases of WT were included.

2.1. Study Subjects.

2. Materials and Methods

2.2. SNP Selection and Genotyping.

2.3. Genotype and Gene Expression Correlation Analysis.

2.4. Statistical Analysis.

3. Results

3.1. Association between AURKA Gene Polymorphisms and Wilms Tumor Susceptibility.
formed fibroblast cells (\( \beta \) associated with altered C polymorphism was significantly as-
that the rs8173 G

### 3.2. Stratification Analysis

Subsequently, we explored the association between rs8173 G>C polymorphism and WT risk by stratified analysis. The results of the stratified analysis were based on the age, gender, and clinical stage (Table 2). We found that carriers of rs8173 GC/CC genotypes had a decreased WT risk when compared with GG genotype carriers, among children older than 18 months (AOR = 0.56, 95% CI = 0.34–0.93, \( P = 0.024 \)), male children (AOR = 0.54, 95% CI = 0.33–0.90, \( P = 0.017 \)), and those with the clinical stage III + IV diseases (AOR = 0.56, 95% CI = 0.35–0.90, \( P = 0.017 \)).

### 3.3. Haplotype Analysis

Based on a combined analysis of the three SNP polymorphisms in the AURKA gene, eight haplotypes were inferred (Table 3). Compared with the reference CAC haplotype, only CAG haplotype was associated with significant increased WT risk (AOR = 1.99, 95% CI = 1.05–3.77, \( P = 0.034 \)).

### 3.4. Genotype-Based mRNA Expression Analysis

We found that the rs8173 G>C polymorphism was significantly associated with altered AURKA gene expression in transformed fibroblast cells (\( P = 4.3 \times 10^{-12} \)) using data from GTEx portal (Figure 1).

### 4. Discussion

In this case-control study, we analyzed 143 WT patients and 531 controls to investigate the association between three AURKA SNPs (rs1047972, rs2273535, and rs8173) and WT risk of in Chinese children. To the best of our knowledge, this is the first study to investigate the association between AURKA gene polymorphisms and WT susceptibility.

Previous studies have found that AURKA was over-expressed in several common human malignancies, which in turn promoted cell proliferation and tumor progression and metastasis [33–35]. The abnormal expression of AURKA could lead to abnormal chromosome segregation, decreased chromosome stability, and finally increase the susceptibility to malignant transformation [36]. Studies in recent years have shown that AURKA SNPs were closely related to cancer risk. An early study by Lee et al. indicated that the AURKA gene rs2273535 was associated with oral cancer risk [28]. A research by Guo et al. [37] illustrated that the rs2273535 polymorphism was closely related to the increased risk of breast cancer, especially in Asian populations. Interestingly, studies have also found that the Ph allele variation in AURKA rs2273535 appears to prevent breast cancer in Malaysian Chinese [38]. In addition, Dai et al. [26] reported that the AURKA rs1047972 polymorphism was associated with reduced incidence of breast cancer in Caucasians. These findings suggest that the effects of AURKA SNPs might be tissue dependent and ethnicity dependent.

We previously did not find a significant association between AURKA SNPs and neuroblastoma susceptibility [31]. Interestingly, in this study, our results showed that AURKA rs8173 G>C significantly reduced the WT risk, although no significant association was found for AURKA rs1047972 C>T and rs2273535 T>A. In addition, stratified analysis revealed that individuals carrying AURKA rs8173 GC/CC genotypes had significantly decreased susceptibility to WT in several subgroups, including older than 18 months, male, and clinical stages III + IV.
A previous study showed that the AURKA rs2273535 polymorphism had a strong LD with the rs1047972 genotype. Patients with AURKA haplotype variants exhibited high kinase activity and tended to develop advanced gastric cancer more readily [39]. In this study, we found that the WT risk in individuals with rs1047972/rs2273535/rs8173 CAG haplotype almost doubled, when compared with individuals with CAC haplotype. However, there were no significant association between the other six haplotypes and the risk of WT.

AURKA has been extensively investigated in neuroblastoma. ShRNA-mediated AURKA gene silencing assays have demonstrated that reducing AURKA expression would inhibit cell proliferation in neuroblastoma [40–42]. It is worth mentioning that studies also have found that overexpression or expansion of AURKA is associated with poor prognosis in a variety of cancer patients and inhibition of AURKA expression can trigger tumor cell death [21–23]. Previous studies have shown that the LIN28B-RAN-AURKA axis was involved in the development of neuroblastoma, and AURKA, as a confluence of LIN28B-RAN signaling, could further promote cell cycle progression by phosphorylating many cell cycle regulators and stabilizing N-myc protein (encoded by MYCN gene) [41, 42]. The LIN28B-RAN-AURKA-MYCN signaling cascade in the development of neuroblastoma provides a new insight into the molecular mechanism by which AURKA rs8173 reduced the risk of WT. The role of AURKA in the development of Wilms tumor is currently lacking. However, based on literature search, we found that AURKA is involved in a variety of tumors. Because of the universal contributions of AURKA in tumors, we hypothesized that AURKA might be also implicated in WT and therefore performed the current study. Based on previous reports, we speculated that the AURKA rs8173 might reduce the risk of

Table 2: Stratification analysis of AURKA rs8173 genotypes with Wilms tumor susceptibility.

| Variables          | rs8173 (cases/controls) | OR (95% CI) | P    | AOR (95% CI) | P     |
|--------------------|-------------------------|-------------|------|--------------|-------|
| Age (months)       |                         |             |      |              |       |
| <18                | 34/97                   | 0.65 (0.37–1.13) | 0.127| 0.65 (0.38–1.13) | 0.128 |
| >18                | 37/99                   | 0.55 (0.33–0.91) | 0.021| 0.56 (0.34–0.93) | 0.024 |
| Gender             |                         |             |      |              |       |
| Female             | 31/92                   | 0.70 (0.40–1.21) | 0.199| 0.70 (0.40–1.22) | 0.203 |
| Male               | 40/104                  | 0.52 (0.32–0.86) | 0.011| 0.54 (0.33–0.90) | 0.017 |
| Clinical stages    |                         |             |      |              |       |
| I + II             | 25/196                  | 0.66 (0.37–1.16) | 0.144| 0.71 (0.40–1.26) | 0.245 |
| III + IV           | 41/196                  | 0.57 (0.36–0.91) | 0.019| 0.56 (0.35–0.90) | 0.017 |

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio. *Adjusted for age and gender, without the corresponding stratification factor.

Table 3: Frequency of inferred haplotypes of the AURKA gene based on observed genotypes and their association with the risk of Wilms tumor.

| Haplotypes | Cases (n = 286) | Controls (n = 1062) | Crude OR (95% CI) | P    | AOR (95% CI) | P     |
|------------|----------------|--------------------|-------------------|------|--------------|-------|
| CAC        | 62 (21.68)    | 279 (26.27)        | 1.00              |      | 1.00         |       |
| CAG        | 17 (5.94)     | 36 (3.39)          | 2.00 (1.06–3.77)  | 0.033| 1.99 (1.05–3.77) | 0.034 |
| CTC        | 18 (6.29)     | 86 (8.10)          | 0.89 (0.50–1.57)  | 0.676| 0.91 (0.51–1.62) | 0.748 |
| CTG        | 153 (53.50)   | 533 (50.19)        | 1.21 (0.88–1.68)  | 0.240| 1.21 (0.88–1.67) | 0.249 |
| TAC        | 8 (2.80)      | 34 (3.20)          | 1.00 (0.44–2.25)  | 0.990| 0.99 (0.44–2.24) | 0.983 |
| TAG        | 2 (0.70)      | 11 (1.04)          | 0.77 (0.17–3.55)  | 0.736| 0.74 (0.16–3.40) | 0.694 |
| TTC        | 2 (0.70)      | 8 (0.75)           | 1.06 (0.22–5.09)  | 0.945| 1.09 (0.23–5.28) | 0.913 |
| TTG        | 24 (8.39)     | 75 (7.06)          | 1.35 (0.79–2.30)  | 0.266| 1.34 (0.79–2.29) | 0.279 |

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio. *The haplotype order was rs1047972, rs2273535, and rs8173; *obtained in logistic regression models with adjustment for age and gender.

A previous study showed that the AURKA rs2273535 polymorphism had a strong LD with the rs1047972 genotype. Patients with AURKA haplotype variants exhibited high kinase activity and tended to develop advanced gastric cancer more readily [39]. In this study, we found that the WT risk in individuals with rs1047972/rs2273535/rs8173 CAG haplotype almost doubled, when compared with individuals with CAC haplotype. However, there were no significant association between the other six haplotypes and the risk of WT.

![Figure 1: Genotype-based mRNA expression alteration in transformed fibroblasts cells for AURKA rs8173 G>C polymorphism based on data from the GTEx portal database (https://www.gtexportal.org/home/).](image)
WT by inhibiting the proliferation and migration of tumor cells through the LIN28B-RAN-AURKA-MYCN signaling pathway.

Some shortcomings should be mentioned in our research. First, the study included 145 patients and 531 controls. Because of the limited sample size, some important results may be accidental. Studies with large samples are indispensable to verify our results. Second, only three AURKA SNPs were investigated in the study. Other potentially functional AURKA gene polymorphisms should be studied in the future. Third, the genotype distribution in this hospital-based study might not represent genotype distribution across the general population, which may bias the case-control study to some extent. Finally, functional experiments should be conducted to strengthen the findings in the current study.

5. Conclusions
Overall, our study confirmed that the AURKA rs8173 G>C polymorphism is associated with reduced WT risk in Chinese children. In the future, multicenter collaboration is needed to further expand the sample size from different regions and different races to clarify the impact of AURKA SNPs on the risk of WT more accurately.

Abbreviations
WT: Wilms tumor
WT1: Wilms’ tumor protein 1
TP53: Tumor protein 53
CTNNB1: Catenin beta 1
AURKA: Aurora kinase A
SNP: Single nucleotide polymorphism
HWE: Hardy–Weinberg equilibrium
OR: Odds ratio
CI: Confidence interval.

Data Availability
All the data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest
The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions
Tongyi Lu, Li Li, and Jinhong Zhu contributed equally to this work. All authors contributed significantly to this work. TL, JL, AL, WF, and GL performed the research study and collected the samples and data. JH analyzed the data. HX, JH, and TZ designed the research study. TL, LL, and JZ wrote the paper. JH prepared all the tables and figures. In addition, all authors read, reviewed, and approved the final manuscript to be published.

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Supplementary Materials
Supplemental Table 1: frequency distribution of selected variables for Wilms tumor cases and cancer-free controls. Supplemental Table 2: polymorphisms captured by the three included AURKA polymorphisms as predicted by SNPInfo online software. Supplemental Figure 1: linkage disequilibrium (LD) analysis for the three included polymorphisms in Han Chinese population consisting of CHB (Han Chinese in Beijing, China) and CHS (Southern Han Chinese) subjects. Supplemental Figure 2: diagram showing all the genotyped samples for the three included polymorphisms. (Supplementary Materials)

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