



## Original Article

# miR-146a rs2910164 C>G Polymorphism and Wilms Tumor Susceptibility in Eastern Chinese Children



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## Abstract

**Background and objectives:** Wilms tumor is the most common renal malignancy in children. *miR-146a*, a highly conserved small noncoding RNA, plays a critical role in various human diseases. Increasing studies have suggested that rs2910164 C>G polymorphism in *miR-146a* is associated with susceptibility to cancers. However, *miR-146a* rs2910164 C>G polymorphism influence on Wilms tumor remains unknown. The aim of this study was to evaluate the relationship between *miR-146a* rs2910164 C>G polymorphism and Wilms tumor susceptibility in Chinese children.

**Methods:** In the six-center case-control study, we enrolled 1,352 subjects from East China (416 cases and 936 healthy controls). The TaqMan method was adopted to genotype the *miR-146a* rs2910164 C>G polymorphism. Logistic regression models were utilized to assess the correlation between this polymorphism and the risk of Wilms tumor.

**Results:** No significant association was observed between *miR-146a* rs2910164 C>G polymorphism and the susceptibility to Wilms tumor. Further stratification analysis also did not detect a significant relationship.

**Conclusions:** The present study showed no association of *miR-146a* rs2910164 C>G polymorphism with the risk of Wilms tumor in the Eastern Chinese population. Subsequent studies with a larger sample size will be required to validate these results.

**Keywords:** Wilms tumor; *miR-146a*; Polymorphism; Susceptibility; Eastern Chinese population; Children.

**Abbreviations:** miRNA, microRNA; UTR, untranslated region; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; CRC, colorectal cancer.

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## Introduction

Wilms tumor is the most common type of renal malignant tumor in young children, accounting for over 90% of all renal tumors.<sup>1,2</sup> Wilms tumor often occurs unilaterally, with 5–10% occurring bilaterally.<sup>3</sup> The incidence has been reported to vary geographically and ethnically. It is higher in black populations in the USA and white populations of North America and Europe, while relatively lower in Asian populations. In China, the annual incidence of Wilms tumor is estimated to be 3.3 cases per million children.<sup>4,5</sup> With recent integration of surgery, radiation therapy, and chemotherapy, the overall survival rate of Wilms tumor is above 90%.<sup>6</sup> Although most children with Wilms tumor have a favorable prognosis, about 20% relapse within 2 years of diagnosis, and the survival rate for recurrent Wilms tumor is only 50%.<sup>7–9</sup> In addition, nearly 25% of Wilms tumor survivors develop chronic health prob-

lems such as subsequent malignant neoplasms, intestinal obstruction, kidney/heart failure, and premature ovarian insufficiency.<sup>10</sup> Therefore, uncovering the biology and genetics of Wilms tumor to better understand the pathogenesis of the disease and develop more effective treatments is of great importance.

MicroRNAs (miRNAs) are a group of highly conserved small noncoding RNA molecules, approximately 18–24 nucleotides in length.<sup>11</sup> They act as post-transcriptional regulators by binding to the 3' untranslated region (UTR) of targeted mRNAs, resulting in the degradation or repression of mRNAs and inhibiting gene expression.<sup>12,13</sup> *miR-146a* is a hot topic in recent research on miRNAs. Located on chromosome 5,<sup>14</sup> it is known to be essential for regulating inflammatory and immune responses.<sup>15,16</sup> According to current studies, *miR-146a* also plays pivotal roles in some cancers, such as chronic myeloid leukemia,<sup>17</sup> glioblastoma,<sup>18</sup> ovarian cancer,<sup>19</sup> and breast cancer.<sup>20</sup>

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation. SNPs can modulate the expression of miRNAs, which in turn influences certain aspects of disease, like individual susceptibility.<sup>21</sup> A series of SNPs in *miR-146a* have been reported to be associated with disease risk. Qiao *et al.*<sup>22</sup> observed a strong correlation between the *miR-146a* rs2910164 C>G polymorphism and the incidence of acute coronary syndromes in the Chinese Han population. A meta-analysis showed that the C allele of *miR-146a* rs2910164 was related to a decreased risk of gynecological cancers.<sup>23</sup> Although there is increasing evidence linking *miR-146a* rs2910164 C>G polymorphism to tumors, the association between this polymorphism and Wilms tumor susceptibility has not yet been confirmed. Therefore, we conducted a case-control study to evaluate the role of *miR-146a* rs2910164 C>G polymorphism on Wilms tumor risk in an Eastern Chinese population.

## Materials and methods

### Study subjects

In this study, 416 children with Wilms tumor and 936 healthy controls were recruited from six hospitals located in six different provinces of East China (Jiangsu, Anhui, Zhejiang, Fujian, Shandong, and Jiangxi). Recruitment details of the subjects were as previously described.<sup>24,25</sup> Information on age, gender, and clinical stage of patients was collected. This study received was performed in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of the Children's Hospital of Nanjing Medical University gave its approval to the study protocol (Approval No.: 202210185-1). All participants signed a written informed consent form for our research with the signature of their parent or legal guardian.

### Genotyping

Total genomic DNA was extracted from paraffin-embedded tissues and peripheral blood samples using QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA) and TIANGEN Blood DNA Extraction Kit (TianGen Biotech, Beijing) according to the manufacturer's protocol respectively. The samples were genotyped using TaqMan real-time PCR. To ensure the accuracy of the results, 10% of the samples were randomly selected for repeated testing and negative controls (water) were also included as reported previously.<sup>26–28</sup>

### Statistical analysis

Clinical variables between Wilms tumor patients and control samples were analyzed by *t*-test or two-sided  $\chi^2$  test as appropriate.

The goodness-of-fit  $\chi^2$  test was used to assess whether the selected SNPs in the controls were consistent with Hardy-Weinberg equilibrium (HWE). Using unconditional logistic regression adjusted for age and gender, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to investigate Wilms tumor risk. Further stratified analysis was performed according to age, gender, and clinical stages. A two-sided  $P < 0.05$  was considered as statistically significant. SAS v9.4 (SAS Institute, Cary, NC, USA) was used to perform all the analyses.

## Results

### Population characters

The frequency distribution of selected variables of all the participants is shown in Table S1. No significant difference in age and gender between Wilms tumor patients and controls was observed ( $P = 0.898$  for age and  $P = 0.742$  for gender). The mean age of cases and controls were  $34.09 \pm 26.35$  and  $33.87 \pm 30.88$  months old, respectively. Among all 416 cases, 29.81% were classified as clinical stage I, 34.86% were stage II, 18.51% were stage III, 9.13% were stage IV, and 7.69% as not available.

### *miR-146a* rs2910164 C>G polymorphism and Wilms tumor susceptibility

In this study, 416 cases and 936 controls were successfully genotyped. As shown in Table 1, *miR-146a* rs2910164 C>G obeyed the HWE in controls (HWE = 0.965). Genotype frequencies of CC, CG, and GG genotypes among cases were 36.78%, 47.12%, and 16.11%, while the controls were 35.26%, 48.18%, and 16.56% respectively. No significant differences were observed between cases and controls (CG vs. CC: adjusted OR = 0.94, 95% CI = 0.73–1.21,  $P = 0.619$ ; GG vs. CC: adjusted OR = 0.93, 95% CI = 0.66–1.32,  $P = 0.693$ ; CG/GG vs. CC: adjusted OR = 0.94, 95% CI = 0.74–1.19,  $P = 0.591$ ; GG vs. CC/CG: adjusted OR = 0.97, 95% CI = 0.71–1.32,  $P = 0.839$ ; and G vs. C: adjusted OR = 0.96, 95% CI = 0.81–1.13,  $P = 0.632$ ), even adjusted for age and gender. No significant association was ascertained between *miR-146a* rs2910164 C>G polymorphism and Wilms tumor susceptibility.

### Stratification analysis

To further explore whether *miR-146a* rs2910164 C>G polymorphism was related to Wilms tumor risk under certain conditions, we stratified participants by age, gender, and clinical stage. Similarly, no significant correlation was observed (Table 2).

## Discussion

In this six-center case-control study, we genotyped 416 cases and 936 controls from East China to elucidate the role of *miR-146a* rs2910164 C>G polymorphism on Wilms tumor risk. To our knowledge, this is the first case-control study on the association of *miR-146a* rs2910164 C>G polymorphism with Wilms tumor risk. However, we found that this polymorphism was not relevant to the risk of Wilms tumor in children from East China.

*miR-146a* is a highly conserved small noncoding RNA, which is located on chromosome 5q33.3.<sup>14</sup> And the rs2910164 C>G polymorphism is located within the mature *miR-146a* seed regions.<sup>29</sup> As noted previously, SNPs in miRNAs can affect the expression of mature miRNAs which, in turn, affect the progression of various diseases.<sup>30–32</sup> The role of *miR-146a* rs2910164 C>G polymorphism in cancer risk has attracted great attention recently. A

**Table 1. Association between *miR-146a* rs2910164 C>G polymorphism and Wilms tumor susceptibility**

Genotype	Cases (N = 416)	Controls (N = 936)	<i>P</i> <sup>a</sup>	Crude OR (95% CI)	<i>P</i>	Adjusted OR (95% CI) <sup>b</sup>	<i>P</i> <sup>b</sup>
<b>rs2910164 (HWE = 0.965)</b>							
CC	153 (36.78)	330 (35.26)		1.00		1.00	
CG	196 (47.12)	451 (48.18)		0.94 (0.73–1.21)	0.619	0.94 (0.73–1.21)	0.619
GG	67 (16.11)	155 (16.56)		0.93 (0.66–1.32)	0.690	0.93 (0.66–1.32)	0.693
Additive			0.630	0.96 (0.81–1.13)	0.630	0.96 (0.81–1.13)	0.632
Dominant	263 (63.22)	606 (64.74)	0.590	0.94 (0.74–1.19)	0.590	0.94 (0.74–1.19)	0.591
CC/CG	349 (83.89)	781 (83.44)		1.00		1.00	
GG	67 (16.11)	155 (16.56)	0.835	0.97 (0.71–1.32)	0.836	0.97 (0.71–1.32)	0.839
C	502 (60.34)	1,111 (59.35)		1.00		1.00	
G	330 (39.66)	761 (40.65)	0.629	0.96 (0.81–1.13)	0.629	0.96 (0.81–1.13)	0.632

<sup>a</sup> $\chi^2$  test for genotype distributions between Wilms tumor patients and controls. <sup>b</sup>Adjusted for age and gender. CI, confidence interval; OR, odds ratio.

meta-analysis including 6506 cases and 6,576 controls showed that *miR-146a* rs2910164 C>G polymorphism significantly correlates to the susceptibility of lung cancer, and this polymorphism may be a risk factor of lung cancer.<sup>33</sup> By genotyping 295 patients with breast cancer and 295 healthy subjects, Rahim *et al.*<sup>34</sup> observed that *miR-146a* rs2910164 C>G was associated with an increased risk of breast cancer in Pakistani female population. Additionally, Hashemi *et al.*<sup>35</sup> found that the *miR-146a* rs2910164 polymorphism had no significant impact on conferring to risk of prostate cancer in an Iranian population. A study in Mexican patients failed to detect any significant contribution of the *miR-146a* rs2910164 C>G polymorphism to colorectal cancer (CRC) risk,<sup>36</sup> whereas another analysis suggested that rs2910164 may decrease the risk of CRC among Europeans, but not among Asians.<sup>37</sup> The above conclusions collectively indicate that *miR-146a* rs2910164 polymorphism may play different roles in different cancers, possibly due to differences in sample sizes, population sources, and living conditions. Therefore, it is necessary to validate the exact role of *miR-146a* rs2910164 C>G polymorphism in particular cancer type under specific population.

The etiology of Wilms tumor is not precisely known, and the onset and progression of Wilms tumor is closely connected to various genetic alterations. *WT1*, a tumor suppressor gene, was the

first gene implicated in Wilms tumor tumorigenesis.<sup>38</sup> With the rapid development of biotechnology, an increasing number of genetic markers associated with Wilms tumor have been identified, including mutations in *CTNNB1* and *WTX*, as well as the loss of *IGF2/H19* imprinting.<sup>39,40</sup> In addition, multiple genetic variants have been identified as Wilms tumor risk loci.<sup>41</sup> In previous case-control studies, we also revealed some Wilms tumor susceptibility genes including *hOGGI*,<sup>42</sup> *FEN1*,<sup>42</sup> *XPD*,<sup>43</sup> *TRMT6*,<sup>44</sup> and *MET-TL14*.<sup>45</sup> However, these are not sufficient to explain the tumorigenesis of Wilms tumor. It is necessary to validate more genetic variants to better understand the pathogenesis of Wilms tumor to identify the underlying biomarkers as well as therapeutic targets. To date, the role of *miR-146a* rs2910164 C>G polymorphism with Wilms tumor susceptibility remains largely unknown. To elucidate the exact role of this polymorphism on Wilms tumor risk, we undertook a case-control study focused on the Chinese population. Unexpectedly, we did not observe any association of rs2910164 with susceptibility to Wilms tumor.

Several possible limitations should be addressed in this study. First, the relatively small sample size may be insufficient to establish a solid connection between genetic variations and Wilms tumor risk. Increased sample size may lead to better statistical power and more reliable results. Furthermore, all participants were

**Table 2. Stratification analysis for the association of *miR-146a* rs2910164 C>G polymorphism with Wilms tumor susceptibility**

Variables	rs2910164 (cases/controls)		Crude OR (95% CI)	<i>P</i>	Adjusted OR <sup>a</sup> (95% CI)	<i>P</i> <sup>a</sup>
	CC	CG/GG				
Age, month						
≤18	48/149	94/255	1.14 (0.77–1.71)	0.511	1.16 (0.77–1.73)	0.483
>18	105/181	169/351	0.83 (0.61–1.12)	0.227	0.83 (0.61–1.12)	0.229
Gender						
Female	67/146	117/259	0.98 (0.69–1.41)	0.932	0.99 (0.69–1.42)	0.957
Male	86/184	146/347	0.90 (0.65–1.24)	0.521	0.90 (0.66–1.25)	0.537
Clinical stage						
I+II	104/330	165/606	0.86 (0.65–1.14)	0.305	0.87 (0.66–1.15)	0.319
III+IV	40/330	75/606	1.02 (0.68–1.53)	0.920	1.01 (0.67–1.52)	0.975

<sup>a</sup>Adjusted for age and gender, omitting the corresponding stratify factor. CI, confidence interval; OR, odds ratio.

enrolled from the Chinese Han population. Therefore, the conclusions reached in this study may not be applicable to other ethnic groups. Lastly, we only evaluated one SNP in this research. Many other potential *miR-146a* polymorphisms should be investigated in the future.

## Conclusions

This six-center case control study illustrated that *miR-146a* rs2910164 C>G polymorphism was not relevant to Wilms tumor susceptibility in Chinese children. Further studies should be conducted with larger sample sizes, considering genetic factors and environmental factors.

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## Conflict of interest

None.

## Author contributions

CZ and RH designed this study. HY, CZ and RH wrote the paper. JC and HY performed the experiments. SZ, HZ, YW, HL, SH and CZ collected the clinical information and samples. CD and RH provided the data analyses and prepared the tables. All authors approved this version to be published.

## Ethical statement

This study received was performed in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of the Children's Hospital of Nanjing Medical University gave its approval to the study protocol (Approval No.: 202210185-1). All participants signed a written informed consent form for our research with the signature of their parent or legal guardian.

## Data sharing statement

All the data are available upon request from the correspondence authors.

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