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Research Paper

miR-423 rs6505162 C>A polymorphism contributes to decreased Wilms tumor risk

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Abstract

Wilms tumor (WT) is the most prevalent urologic malignancy in childhood. Nonetheless, the genetic factors underlying WT remain largely unknown. The *miR-423* rs6505162 C>A polymorphism is associated with the susceptibility to numerous cancers; however, no investigations have been conducted on its association with WT. To evaluate the correlation between the *miR-423* rs6505162 C>A polymorphism and WT risk in Chinese children, we genotyped this polymorphism using the Taqman method in 145 cases and 531 cancer-free controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of the association. The results showed that the rs6505162 CA genotype was associated with decreased susceptibility to WT (CA versus CC: adjusted OR=0.65, 95% CI=0.42-0.99, *P*=0.047). In the stratified analysis, we found that CA/AA genotypes conferred a significantly decreased overall risk of WT in children younger than 18 months (adjusted OR=0.30, 95% CI=0.14-0.63, *P*=0.002) and those with clinical stage I+II WT (adjusted OR=0.42, 95% CI=0.20-0.85, *P*=0.017) when compared with CC genotype. In summary, the *miR-423* rs6505162 C>A polymorphism may negatively modify WT susceptibility in Chinese children. Our findings should be validated in larger studies involving other ethnicities.

Key words: Wilms tumor; *miR-423*; polymorphism; genetic susceptibility

Introduction

Wilms tumor (WT), also called nephroblastoma, morphologically resembles embryonic kidney cells. WT is a pediatric cancer that develops in young children, generally those younger than 5 years old [1]. It accounts for 8% of childhood malignancies and affects 1/10,000 children. The tumor is considered a prototype of tumors resulting from abnormal differentiation and development of tissues [2]. Over the past decades, the treatment outcome has greatly improved, and the overall survival rate has reached 90%; however, a considerable portion of the suffers, including those with unfavourable histologic features, bilateral tumors and recurrent cases have survival rates less than 70%. These higher risk groups compose 25% of WT patients [3, 4]. Furthermore, treatment of WT comes at a cost, with up to 25% of the survivors reporting severe chronic health problems 25 years after diagnosis [3, 5, 6]. There remain intense clinical demands to find more effective therapies for high-risk subtypes and to minimize side effects later in life [7].

It has been demonstrated that mutations of the Wnt/β-catenin pathway-related *Wilms tumor gene 1*, *β-catenin*, and *WTX* account for approximately 1/3 of WT cases. Extreme efforts are being made to find the genetic factors involved in the other 2/3 of WT cases [2]. Some reports have noted that microRNA (miRNA) may play a key role in WT development, and 15% of WT cases habor mutations in the miRNA-processing genes [2, 4].

The abnormal expression of miR-423 (both mature forms of miR-423, which are called miR-423-3p and miR-423-5p) has been discovered in multiple cancers. The rs6505162 C>A polymorphism (nucleotide alteration from C to A), mapping to 17q11.2, is located in *pre-miR-423* [8-11]. An increasing number of studies have been conducted to estimate the association between the *miR-423* rs6505162 C>A polymorphism and the risk of developing different cancers [12-19]. It has been found that the A allele of rs6505162 increases the risk of breast cancer [14, 15], but it decreases the risk of lung cancer and bladder cancer [17, 18]. In a recent meta-analysis that included 17 eligible case-control studies, a significant association between *miR-423* rs6505162 C>A and cancer susceptibility was observed in recessive models. Stratified analysis also revealed that those with the A allele had a significantly decreased risk of lung cancer [20].

Nucleotide polymorphism is highly likely to play different roles in different types of cancer depending on the inherent cancer-specific heterogeneity [21, 22]. Although it has been illustrated that rs6505162 is relevant to human cancers, the association between the *miR-423* rs6505162 C>A polymorphism and WT susceptibility has not been demonstrated. Because of its implication in cancer, we hypothesized that this polymorphism might be able to modify WT susceptibility. Therefore, we performed a hospital-based case-control study with the purpose of determining whether this polymorphism is associated with WT risk in Chinese children.

Materials and methods

Study subjects

A total of 145 children who were diagnosed with histopathologically confirmed WT, according to the NWTS-5 criteria, were included in this study. The diagnosis of this disease was based on both imaging and pathological examination. Tumor tissues were obtained from all cases by surgery or needle biopsy for pathological examination. All Chinese Han patients were recruited from the Guangzhou Women and Children's Medical Center, mainly between March 2001 and June 2016 [23-27]. In addition, 531 unrelated, age-, gender-, race-matched cancer-free volunteers recruited from the same medical centre were also enrolled [28-30]. Each individual donated 2 ml of blood for genomic DNA extraction. The response rate was nearly 90% and 95% for WT cases and cancer-free controls respectively. The investigation was conducted with the approval of the Institutional Review Board of the Guangzhou Women and Children's Medical Center. All the participants had written informed consent provided by their guardians.

DNA extraction and genotyping

We isolated total genomic DNA from peripheral blood leukocytes using the TIANamp Blood DNA Kit (TianGen Biotech Co., Ltd., Beijing, China) [28]. The *miR-423* rs6505162 C>A polymorphism was genotyped using the TaqMan real-time PCR methodas described previously [31-33]. Genotyping was performed blind to the status of the case or control. Moreover, approximately10% of samples were randomly selected to perform repeated assays, and the reproducibility was 100%.

Statistical analysis

The frequency distribution of the polymorphism and the demographic variables between WT cases and controls were compared using the chi-squared test. Hardy-Weinberg equilibrium (HWE) in control subjects was tested by a goodness-of-fit chi-squared test. The association of the *miR-423* rs6505162 C>A polymorphism with WT risk was assessed by calculating the odds ratios (ORs) and 95% confidence intervals (CIs), using unconditional multivariate logistic regression analyses. Stratified analyses were performed for subgroups by age, gender and clinical stages. All statistical tests were two-sided. $P < 0.05$ was considered as statistically significant. All statistical analyses were performed using SAS software (Version 9.4; SAS Institute, Cary, NC, USA).

Results

Demographic characteristics

As shown in **Supplemental Table 1**, no striking differences in age or gender between the two groups [25, 26]. There were 4 (2.76%), 49 (33.79%), 50 (34.48%), and 33 (22.76%) individuals with clinical stage I, II, III, and IV Wilms tumor, respectively, according to the NWTS-5 criteria [34].

Association between miR-423 rs6505162 C>A polymorphism and WT susceptibility

The genotype distributions of the *miR-423* rs6505162 C>A polymorphism in WT cases and cancer-free controls are shown in **Table 1**. A total of 145 cases and 530 controls were successfully

genotyped. Genotype analysis for the *miR-423* rs6505162 C>A polymorphism suggested that there was no significant deviation from HWE in the control group (P=0.576). We observed that the rs6505162 CA genotype had decreased risk of WT at an adjusted OR of 0.65 (95% CI=0.42-0.99, P=0.047) when compared to the CC genotype. No significant associations were observed for other models (AA vs. CC: adjusted OR=0.91, 95% CI=0.33-2.50; AA/CA vs. CC: adjusted OR=0.67, 95% CI=0.45-1.01; AA vs. CC/CA: adjusted OR=1.02, 95% CI=0.37-2.81; and A vs. C: adjusted OR=0.75, 95% CI=0.52-1.06).

Stratified analysis

We further observed the association between the *miR-423* rs6505162 C>A polymorphism with WT risk in the stratified analysis by age, gender, and clinical stages (**Table 2**). We found that carriers of CA/AA genotypes had significantly decreased overall risk of WT in children younger than 18 months (adjusted OR=0.30, 95% CI=0.14-0.63, P=0.002) and clinical stage I+II WT (adjusted OR=0.42, 95% CI=0.20-0.85, P=0.017) compared with CC genotype carriers. We also found a borderline association between a decreased WT risk and the CA/AAgenotypes in females (adjusted OR = 0.57, 95% CI=0.31-1.07, P=0.081).

When false-positive report probability analysis was performed, the noteworthy findings disappeared at the prior probability level of 0.1 and FPRP threshold of 0.2 (**Table 3**).

Discussion

In this hospital-based case-control study, we explored the correlation between the *miR-423* rs6505162 C>A polymorphism and WT susceptibility and subsequently analysed the effects of combinations of this polymorphism and clinical features. It has been identified that the *miR-423* rs6505162 C>A polymorphism is associated with WT risk in a Chinese population.

Table 1. Genotype distributions of *miR-423* rs6505162 C>A polymorphism and Wilms tumor susceptibility.

Genotype	Cases (N=145)	Controls (N=530)	P [a]	Crude OR (95% CI)	P	Adjusted OR (95% CI) [b]	P [b]
rs6505162 (HWE=0.576)							
CC	106 (73.10)	342 (64.53)		1.00		1.00	
CA	34 (23.45)	170 (32.08)		**0.65 (0.42-0.99)**	**0.045**	**0.65 (0.42-0.99)**	**0.047**
AA	5 (3.45)	18 (3.40)		0.90 (0.33-2.47)	0.832	0.91 (0.33-2.50)	0.847
Additive			0.131	0.74 (0.52-1.06)	0.099	0.74 (0.52-1.06)	0.104
Dominant	39 (26.90)	188 (35.47)	0.053	0.67 (0.45-1.01)	0.054	0.67 (0.45-1.01)	0.057
Recessive	140 (96.55)	512 (96.60)	0.976	1.02 (0.37-2.79)	0.976	1.02 (0.37-2.81)	0.963
C	246 (84.83)	854 (80.57)		1.00		1.00	
A	44 (15.17)	206 (19.43)	0.098	0.74 (0.52-1.06)	0.099	0.75 (0.52-1.06)	0.104

[a] χ^2 test for genotype distributions between Wilms tumor patients and controls.
[b] Adjusted for age and gender.

Table 2. Stratification analysis for the association between *miR-423* rs6505162 C>A polymorphism and Wilms tumor risk.

Variables	CC	CA/AA	Crude OR	P	Adjusted OR [a]	P [a]
	(Cases/Controls)		(95% CI)		(95% CI)	
Age, month						
≤18	57/152	9/81	**0.30 (0.14-0.63)**	**0.002**	**0.30 (0.14-0.63)**	**0.002**
>18	49/190	30/107	1.09 (0.65-1.82)	0.749	1.09 (0.65-1.81)	0.754
Gender						
Females	48/147	16/86	0.57 (0.31-1.07)	0.078	0.57 (0.31-1.07)	0.081
Males	58/195	23/102	0.76 (0.44-1.30)	0.314	0.76 (0.44-1.30)	0.316
Clinical stage						
I+II	43/342	10/188	**0.42 (0.21-0.86)**	**0.018**	**0.42 (0.20-0.85)**	**0.017**
III+IV	56/342	27/188	0.88 (0.54-1.44)	0.602	0.88 (0.54-1.44)	0.609

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age and gender.

Table 3. False-positive report probability analysis for the significant findings between *miR-423* rs6505162 C>A polymorphism and Wilms tumor risk.

Genotype	Crude OR (95% CI)	P [a]	Statistical power [b]	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
CA vs. CC	0.65 (0.42-0.99)	0.045	0.442	0.234	0.478	0.910	0.990	0.999
CA/AA vs. CC								
≤18	0.30 (0.14-0.63)	0.002	0.024	0.157	0.358	0.860	0.984	0.998
I+II	0.42 (0.21-0.86)	0.018	0.116	0.315	0.580	0.938	0.994	0.999

OR, odds ratio; CI, confidence interval.
[a] χ^2 test was adopted to calculate the genotype frequency distributions.
[b] Statistical power was calculated using the number of observations in the subgroup and the OR and P values in this table.

MiRNAs are a category of single-stranded, non-coding, endogenous RNAs approximately 22 nucleotides in length. They guide RNA-induced silencing complexes to the miRNA recognition elements of the targeted protein-coding transcripts or other competitive endogenous RNAs, and thus play a role in post transcriptional control [35, 36]. There are approximated to be at least 300 miRNAs (and there might be as many as 1000) in the human genome, which makes miRNAs one of the largest categories of gene regulator [37]. It has been reported that over 1/2 of miRNAs are located in cancer-associated genomic regions or fragile sites and are involved in tumorigenesis as suppressors or oncogenes [38]. The aberrant expression of different miRNAs in cancer development has been observed [37]. It is reasonable to suppose that miRNA expression and maturation might be altered by single nucleotide polymorphisms in miRNAs. These polymorphisms could influence the effects of miRNAs on their target genes, potentially leading to aberrant metabolism and modified cancer susceptibility [38-40].

As reported before, rs6505162 is located in the first intron of the *nuclear speckle splicing regulatory protein* (*NSRP1*) gene [15], which produces two mature transcripts called miR-423-3p and miR-423-5p [41]. The abnormal expression of miR-423 has been discovered in multiple cancers, but the potential role of miR-423 in cancer is complicated and varies in different cancer types. Different expression patterns of miR-423 have been found; for example, miR-423 is under-expressed in oral cancer [42] but over-expressed in head and neck cancer [43]. MiR-423 acts as a tumor suppressor in some tumors [42], but as an oncogene in the other ones [44]. In addition, it has been reported that the rs6505162 C>A polymorphism promotes mature miR-423 expression in cell lines from breast cancer and endometrial carcinoma [45, 46]. It is still ambiguous whether modulations of mature levels of miR-423 arerelated to the involvement of this polymorphism in many other cancers [38]. All these inconsistent results remind us of the significant heterogeneity among cancer types [38].

Considering the importance of the *miR-423* rs6505162 C>A polymorphism in carcinogenesis, we assessed the association of the *miR-423* rs6505162 C>A polymorphism with WT risk. To the best of our knowledge, this is the first study to verify the association between the *miR-423* rs6505162 C>A polymorphism and pediatric tumor susceptibility. Also, there is no other study investigated the association between other polymorphisms within pre-miRNAs and WT risk. We found that the rs6505162 CA genotype was associated with a decreased susceptibility for WT. The rs6505162 polymorphism lies within an intron of the *NSRP1*gene, and it is predicted by SNPinfo (http://snpinfo.niehs.nih.gov/) software to be a transcription factor binding site. The C>A alteration may cause alteration in binding ability and downstream gene expression, and sequentially modify WT susceptibility. In the subgroup analysis, the CA/AA genotype was more common among children younger than 18 months and with clinical stage I+II tumors, which may be ascribed to genetic susceptibility as well as limited sample size. In summary, these results indicated that the *miR-423* rs6505162 C>A polymorphism may modify WT susceptibility in Southern Chinese children. Further functional studies are needed to investigate the specific mechanisms by which this polymorphism modifies cancer risk.

Although this is the first study to assess the correlation between the *miR-423* rs6505162 C>A polymorphism and WT risk, several limitations should be addressed. First, it may have limited statistical power because of the relatively small sample size. Only 145 cases and 531 controls were included in this study due to the low occurrence rate of WT. Thus, statistic power of this study was compromised and the noteworthy findings might be chance observations (FPRP values larger than 0.2 at the prior probability level of 0.1). Second, selection and information bias might be unavoidable because of the nature of a retrospective study design, which limited our ability to correlate gene-environmental interactions with WT susceptibility. Finally, we conducted a case-control designed study to evaluate the association of the *miR-423* rs6505162 C>A polymorphism with WT risk, and we have not explored the potential mechanisms of this polymorphism in cell lines, which should be studied in the future.

In conclusion, in this study, we found that the *miR-423* rs6505162 C>A polymorphism may be associated with a decreased WT susceptibility in a Chinese population. However, well-designed prospective studies with larger sample sizes, different ethnicities, and more polymorphisms, as well as further functional studies are needed to confirm our findings.

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Abbreviations

WT: Wilms tumor; miRNA: microRNA; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval.

Supplementary Material

Supplementary table.
http://www.jcancer.org/v09p2460s1.pdf

Competing Interests

The authors have declared that no competing interest exists.

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