Research Article

The association of miR34b/c and TP53 gene polymorphisms with Wilms tumor risk in Chinese children

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Wilms tumor is the most common pediatric malignancy in the kidney. The miR34b/c is a downstream target gene of the transcription factor p53. The important role of TP53 mutations, the methylation of miR34b/c, and the interaction between these two molecules in tumorigenesis have been well documented. Due to the biological connection between p53 and miR34b/c, in the present study, we investigated the association between polymorphisms in these two molecules and Wilms tumor susceptibility through genotyping two important functional polymorphisms (miR34b/c rs4938723 T>C and TP53 rs1042522 C>G) in 183 cases and 603 controls. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) derived from the logistic regression analysis were used to assess the correlation of miR34b/c and TP53 polymorphisms with Wilms tumor risk. Our results indicated that the association of miR34b/c and TP53 polymorphisms with Wilms tumor susceptibility was not statistically significant. Stratified analysis by age, gender, and clinical stage, as well as combined effect analysis were also performed, yet, no significant association was found. In conclusion, our study indicated a lack of association between the two selected polymorphisms and Wilms tumor susceptibility. Our findings need to be verified in studies with larger sample size in the future.

Introduction

Wilms tumor, a malignant kidney tumor in children, currently has achieved a high survival rate in different geographical regions [1,2]. It is reported that approximately 98% of Wilms tumor are sporadic [3]; and approximately 80 percent of Wilms tumor patients are diagnosed before 5 years old [4]. Molecular genetics studies showed that Wilms tumor had a complex etiology involving genetic lesions in the multiple sites [5,6]; and various gene polymorphisms play pivotal roles in the occurrence of Wilms tumor. However, there remain numerous functional single nucleotide polymorphisms (SNPs) in oncogenes and tumor suppressor genes, whose roles in Wilms tumor susceptibility need to be clarified.

As we know, gene mutation is a crucial factor in the tumorigenesis of Wilms tumor. For example, mutations in the coding sequence of the p53 gene were found in Wilms tumor patients by several research groups [7,8]. Apart from that, Slade et al. [9] showed that translocation t(5;6)(q21;q21), leading to the inactivation of the HACE1 gene, predisposed Wilms tumor. Moreover, over the past decade, many genes have been found to be involved in the development of Wilms tumor, including MYCN [10], CTNNB1 [11], WTX [12], CHEK2 [6], BARD1 [13], hOGG1 and FEN1 gene [14] and KRAS [15].

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MicroRNAs are recognized as endogenous non-coding RNAs that can play different biological roles by targeting related genes [16]. In addition, microRNAs are considered promising biomarkers for their stability and ease of detection [17]. miR34b/c, a recognized tumor-suppressor gene, was found to be methylated in a variety of tumors [18]. Among the mir-34 family, miR34b/c has a stronger ability to inhibit tumor growth, which not only enhanced the attachment of tumor cells, but also inhibited the growth and invasion of cells [19]. On one hand, miR34b/c is a mediator of the P53 signaling network and on the other hand, TP53 can regulate the transcription of miR34b/c [20]. The rs4938723 T>C polymorphism, situated in the miR34b/c promoter region, influenced the expression of miR34b/c by affecting the binding efficiency of GATA-X transcription factor [21].

TP53 is a tumor suppressor, which inhibits tumorigenesis mainly by regulating gene transcription [22]. Mutations in TP53 are common in the most cancer types and have been the focus of various research groups. The TP53 can facilitate DNA repair by stalling the cell cycle in the G1 phase when DNA damage occurs [23]. Moreover, Franken et al. [24] reported that the expression of p53 protein was positively correlated with tumor invasion. TP53 rs1042522 C>G polymorphism, the polymorphic variant in TP53 codon 72, has been shown to be associated with susceptibility to a variety of tumors. miR34b/c cooperates with TP53 to control tumorigenesis. In the TP53-deficient cells, miR34b/c can overexpress to compensate the functions of p53, such as the regulation of senescence and apoptosis [25]. However, the combined effects of miR34b/c and TP53 rs1042522 C>G on Wilms tumor susceptibility remained unclarified. Thus, we conducted the present study to explore the association of miR34b/c and TP53 rs1042522 C>G polymorphisms with Wilms tumor risk.

Materials and methods

Study subjects

In the present study, we recruited 183 Wilms tumor patients and 603 cancer-free volunteers from Yuying Children’s Hospital of Wenzhou Medical University and Guangzhou Women and Children’s Medical Center [26,27]. The age, gender, and clinical stage of all participants are detailed in Supplementary Table S1. At the time of recruitment, all participants or their patients signed informed consent forms. In addition, this investigation was performed with the permission of the Institutional Review Boards of the Yuying Children’s Hospital of Wenzhou Medical University and Guangzhou Women and Children’s Medical Center.

SNP Selection and genotyping

In this research, we selected two most frequently investigated SNPs in miR34b/c and TP53 (miR34b/c rs4938723 and TP53 rs1042522 polymorphisms) to investigate their associations with Wilms tumor susceptibility. TaqMan method was used for genotyping [28–30]. In addition, negative controls were included in genotyping. In order to ensure the accuracy of genotyping, we blindly took 10% samples for repeated testing, and the results were 100% consistent.

Statistical analysis

The Hardy–Weinberg equilibrium (HWE) of control subjects was estimated by a goodness-of-fit χ2 test. The logistic regression analysis was performed. Adjusted odds ratios (ORs) as well as 95% confidence intervals (CIs) were used to assess the correlation of miR34b/c rs4938723 and TP53 rs1042522 polymorphisms with Wilms tumor risk. We considered the difference to be statistically significant only when P < 0.05.

Results

Correlation of miR34b/c rs4938723 and TP53 rs1042522 polymorphisms with Wilms tumor susceptibility

The detailed results are summarized in the Table 1. Both the polymorphisms were in agreement with the HWE (P = 0.459 for the miR34b/c rs4938723 T>C polymorphism, P = 0.533 for the TP53 rs1042522 C>G polymorphism). In our result, for miR34b/c rs4938723, the carriers with TC (adjusted OR = 0.73, 95% CI = 0.51–1.06, P = 0.097) or CC (adjusted OR = 1.42, 95% CI = 0.83–2.43, P = 0.202) genotypes showed no significant association with Wilms tumor risk compared with carriers of the TT genotype. Besides, no significant association was found between rs4938723 and Wilms tumor risk under the additive (adjusted OR = 1.02, 95% CI = 0.79–1.32, P = 0.880), dominant (adjusted OR = 1.85, 95% CI = 0.60–5.89, P = 0.345) or recessive models (adjusted OR = 1.63, 95% CI = 0.98–2.73, P = 0.061). For TP53 rs1042522, the carriers with CG (adjusted OR = 1.51, 95% CI = 1.00–2.39, P = 0.051) or GG (adjusted OR = 1.11, 95% CI = 0.66–1.85, P = 0.700) genotypes showed no significant association with Wilms tumor risk compared with carriers of the CC genotype. Besides, no significant association was found between rs1042522 and Wilms tumor
Table 1 Association between miR34b/c rs4938723 T>C and TP53 rs1042522 C>G polymorphisms with Wilms tumor susceptibility

| Genotype  | Cases (n=170) | Controls (n=600) | P¹ | Crude OR (95% CI) | P | Adjusted OR (95% CI)² | P² |
|-----------|---------------|-----------------|----|------------------|---|----------------------|---|
| miR34b/c rs4938723 T>C (HWE = 0.459) |               |                 |    |                  |   |                      |   |
| TT        | 86 (50.59)    | 279 (46.50)     | 1.00 |                  |   | 1.00                 |   |
| TC        | 60 (35.29)    | 266 (44.33)     | 0.73 (0.51–1.06) | 0.098 | 0.73 (0.51–1.06) | 0.097 |
| CC        | 24 (14.12)    | 55 (9.17)       | 1.42 (0.83–2.42) | 0.205 | 1.42 (0.83–2.43) | 0.202 |
| Additive  |               |                 | 0.881 | 1.02 (0.79–1.32) | 0.881 | 1.02 (0.79–1.32) | 0.880 |
| Dominant  | 84 (44.91)    | 321 (53.50)     | 0.346 | 0.85 (0.60–1.19) | 0.346 | 0.85 (0.60–1.19) | 0.345 |
| Recessive | 146 (85.88)   | 545 (90.83)     | 0.060 | 1.63 (0.98–2.72) | 0.062 | 1.63 (0.98–2.73) | 0.061 |

TP53 rs1042522 C>G (HWE = 0.533)

| Genotype | Cases (n=170) | Controls (n=600) | P¹ | Crude OR (95% CI) | P | Adjusted OR (95% CI)² | P² |
|----------|---------------|-----------------|----|------------------|---|----------------------|---|
| CC       | 39 (22.94)    | 175 (29.17)     | 1.00 |                  |   | 1.00                 |   |
| CG       | 98 (57.65)    | 291 (48.50)     | 1.51 (1.00–2.29) | 0.052 | 1.51 (1.00–2.29) | 0.051 |
| GG       | 33 (19.41)    | 134 (22.33)     | 1.11 (0.66–1.85) | 0.704 | 1.11 (0.66–1.85) | 0.700 |
| Additive |               |                 | 0.102 | 1.07 (0.84–1.36) | 0.587 | 1.07 (0.84–1.37) | 0.584 |
| Dominant | 131 (77.06)   | 425 (70.83)     | 0.110 | 1.38 (0.93–2.06) | 0.111 | 1.39 (0.93–2.06) | 0.109 |
| Recessive| 137 (80.59)   | 466 (77.67)     | 0.415 | 0.84 (0.55–1.28) | 0.415 | 0.84 (0.55–1.28) | 0.416 |

1χ² test for genotype distributions between Wilms tumor patients and controls.
2Adjusted for age and gender.

Table 2 Stratification analysis of risk genotypes with tumor susceptibility

| Variables | rs4938723 (cases/controls) | OR (95% CI) | P | AOR (95% CI)¹ | P¹ | rs1042522 (cases/controls) | OR (95% CI) | P | AOR (95% CI)¹ | P¹ |
|-----------|----------------------------|-------------|---|---------------|---|---------------------------|-------------|---|---------------|---|
| Age, months |                            |             |   |               |   |                           |             |   |               |   |
| ≤18       | 64/247                     | 9/21        | 1.65 (0.72–3.79) | 0.234 | 1.64 (0.71–3.75) | 0.244 | 11/90/59/188 | 1.79 (0.95–3.40) | 0.234 | 1.77 (0.94–3.36) | 0.234 |
| >18       | 82/208                     | 15/34       | 1.60 (0.83–3.09) | 0.157 | 1.63 (0.85–3.15) | 0.143 | 25/95/72/237 | 1.15 (0.69–1.93) | 0.157 | 1.16 (0.69–1.93) | 0.157 |
| Gender    |                            |             |   |               |   |                           |             |   |               |   |
| Female    | 67/244                     | 9/21        | 1.56 (0.69–3.57) | 0.291 | 1.56 (0.68–3.57) | 0.291 | 21/79/55/186 | 1.11 (0.63–1.96) | 0.291 | 1.11 (0.63–1.96) | 0.291 |
| Male      | 79/301                     | 15/34       | 1.68 (0.87–3.24) | 0.121 | 1.68 (0.87–3.24) | 0.121 | 19/96/70/239 | 1.70 (0.96–2.99) | 0.121 | 1.70 (0.96–2.99) | 0.121 |
| Clinical stages |                      |             |   |               |   |                           |             |   |               |   |
| I+II     | 58/545                     | 7/55        | 1.20 (0.52–2.75) | 0.067 | 1.25 (0.54–2.88) | 0.060 | 15/175/50/425 | 1.37 (0.75–2.51) | 0.067 | 1.38 (0.75–2.52) | 0.067 |
| III+IV   | 75/545                     | 13/55       | 1.72 (0.90–3.29) | 0.013 | 1.73 (0.90–3.31) | 0.012 | 22/175/66/425 | 1.24 (0.74–2.07) | 0.013 | 1.23 (0.74–2.06) | 0.013 |

¹Adjusted for age and gender, without the corresponding stratifying factor.
AOR: adjusted odds ratio

risk under the additive (adjusted OR = 1.07, 95% CI = 0.84–1.37, P=0.584), dominant (adjusted OR = 1.39, 95% CI = 0.93–2.06, P=0.109) or recessive models (adjusted OR = 0.84, 95% CI = 0.55–1.28, P=0.416). In summary, neither of the two selected polymorphisms showed significant association with Wilms tumor risk.

Stratification analysis
We then analyzed the correlation of miR34b/c rs4938723 and TP53 rs1042522 polymorphisms with Wilms tumor susceptibility in subgroups stratified by age, gender and clinical stage (Table 2). However, no significant association was observed.

Combined effect analysis
As shown in the Table 3, no statistically significant association was detected in the combined effect analysis. However, the individuals with both miR34b/c rs4938723 TC genotype and TP53 rs1042522 CC genotype might have a borderline significantly decreased risk of Wilms tumor (adjusted OR = 0.51, 95% CI = 0.25–1.01, P=0.053).
Table 3 The association of combined genotypes of miR34b/c rs4938723 T>C and TP53 rs1042522 C>G polymorphisms with Wilms tumor risk

| Genotypes | Cases (n=170) | Controls (n=600) | OR (95% CI) | P | AOR (95% CI)1 | P1 |
|-----------|--------------|------------------|-------------|---|--------------|----|
| rs4938723 | rs1042522    |                  |             |   |              |    |
| TT CC     | 22 (12.94)   | 89 (14.83)       | 1.00        |   | 1.00         |    |
| TT CG     | 46 (27.06)   | 128 (21.33)      | 0.95 (0.57–1.58) | 0.828 | 0.95 (0.57–1.59) | 0.837 |
| TT GG     | 18 (10.59)   | 62 (10.33)       | 0.76 (0.40–1.47) | 0.417 | 0.77 (0.40–1.47) | 0.425 |
| TC CC     | 14 (8.24)    | 73 (12.17)       | 0.50 (0.25–1.01) | 0.052 | 0.51 (0.25–1.01) | 0.053 |
| TC CG     | 35 (20.59)   | 137 (22.83)      | 0.67 (0.39–1.15) | 0.147 | 0.67 (0.39–1.15) | 0.148 |
| TC GG     | 11 (6.47)    | 56 (9.33)        | 0.52 (0.24–1.10) | 0.086 | 0.52 (0.24–1.10) | 0.087 |
| CC CC     | 3 (1.76)     | 13 (2.17)        | 0.61 (0.16–2.26) | 0.456 | 0.61 (0.16–2.27) | 0.461 |
| CC CG     | 17 (10.00)   | 26 (4.33)        | 1.72 (0.83–3.55) | 0.143 | 1.73 (0.84–3.57) | 0.140 |
| CC GG     | 4 (2.35)     | 16 (2.67)        | 0.66 (0.21–2.10) | 0.479 | 0.66 (0.21–2.10) | 0.476 |

1 Obtained in logistic regression models with adjustment for age and gender.

Discussion

We conducted this case–control study to explore the correlation of miR34b/c rs4938723 and TP53 rs1042522 polymorphisms with Wilms tumor risk. No significant association was found in the single locus and stratified analyses. However, the combine effect analysis suggests that the combination of these two gene polymorphisms may have a potential influence on Wilms tumor susceptibility.

To our knowledge, the association between miR34b/c and Wilms tumor susceptibility has not been investigated. miR34b/c has been shown to be intimately connected to the development and prognosis of a variety of tumors, including gastric cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, hepatocellular carcinoma, neuroblastoma and many others [31–35]. In our previous study, we found that miR34b/c rs4938723 T>C polymorphism has a protective effect on neuroblastoma [36]. Sato et al. [37] reported that miR34b/c methylation in circulating DNA could be used to predict disease progression in malignant pleural mesothelioma patients. Moreover, in a meta-analysis, miR34b/c gene polymorphism was shown to increase the risk of gastric cancer and liver cancer while decreasing the risk of esophageal squamous cell carcinoma and colorectal cancer [38].

TP53 rs1402522 is one of the most investigated TP53 gene polymorphisms. However, we found no significant association between the TP53 rs1402522 polymorphism and Wilms tumor risk. A study by Liu et al. [39] revealed that the effect of TP53 rs1402522 polymorphism on Wilms tumor risk is very weak, which is consistent with our result. Another study conducted by Fu et al. [40] also showed no significant association between TP53 rs1402522 polymorphism and Wilms tumor risk, and they found that CG/GG genotypes carriers significantly increased Wilms tumor risk in children younger than 18 months of age, compared with CC genotype carriers. Moreover, it is reported that TP53 rs1042522 may not confer susceptibility to cancers, such as neuroblastoma [41], retinoblastoma [42]. miR34b/c is involved in the TP53 pathway, and their ‘double hit’ (methylation of miR34 and TP53 mutations) has been shown to affect survival in a variety of tumors [43]. The negative result in the current study might result from the small sample size.

Several limitations should be addressed. First, in the process of tumorigenesis, the interaction among various gene polymorphisms is very complex. Only selecting two gene polymorphisms might lead to false-negative results. Second, we did not recruit enough participants for the present study. The sample size might not be adequate to detect real association if it is weak. Third, all the recruiters were from Guangzhou and Wenzhou. As a result, selection bias might exist. Our results should be explained with caution.

In summary, our statistical results showed that the association of miR34b/c rs4938723 and TP53 rs1042522 polymorphisms with Wilms tumor susceptibility was not statistically significant. Our findings require validation in the studies with larger sample size.

Competing Interests

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

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Author Contribution
All authors contributed significantly to this work. J.W., S.L., Y.M., Z.W., X.H., X.T., J.S. and H.Z. performed the research study and collected the samples and data. J.H. analyzed the data. J.H. and J.R. designed the research study. J.W., J.Z., X.H., J.H., and J.R. wrote the paper. J.H. prepared all the tables. All authors reviewed the manuscript. In addition, all authors have read and approved the manuscript.

Abbreviations
CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; SNP, single nucleotide polymorphism.

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