MYCN gene polymorphisms and Wilms tumor susceptibility in Chinese children

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Abstract

Background: Wilms tumor, derived from embryonic cells, accounts for a large proportion of pediatric renal tumors. MYCN encoded by MYCN proto-oncogene, a member of the MYC family, is a BHLH transcription factor. It plays a critical role in tumorigenesis and predicts poor clinical outcomes in various types of cancer. However, the role of MYCN remained unclarified in Wilms tumor. In this study, we investigated the association between MYCN gene polymorphisms and Wilms tumor susceptibility.

Methods: Four MYCN gene polymorphisms (rs57961569 G > A, rs9653226 T > C, rs13034994 A > G, and rs60226897 G > A) were genotyped in 183 cases and 603 controls. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated to evaluate the association between MYCN gene polymorphisms and Wilms tumor susceptibility.

Results: Overall, no significant association was found for any of the four MYCN gene polymorphisms. Interestingly, in the stratification analysis, the rs57961569 was found to be associated with decreased Wilms tumor susceptibility in the children older than 18 months (AOR = 0.65, 95% CI = 0.42-1.00, P = .050). Moreover, older children carrying 2-4 risk genotypes were at increased risk of Wilms tumor (OR = 1.55, 95% CI = 1.001-2.40, P = .0497). Haplotype GCAA was shown to significantly increased Wilms tumor risk (AOR = 2.40, 95% CI = 1.12-5.14, P = .024).

Conclusion: Our study demonstrated that these MYCN gene polymorphisms might be low penetrant variants in Wilms tumor.

Keywords
MYCN, polymorphism, susceptibility, Wilms tumor

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1 | INTRODUCTION

Wilms tumor is a classic embryonal tumor in the developing kidney, with a 90% cure rate.\textsuperscript{1-3} Despite the high cure rate in patients with low-risk Wilms tumor, patients with poor histologic and molecular characteristics, bilateral lesions, and recurrent disease have a much lower survival rate and deserve more attentions.\textsuperscript{4} Moreover, approximately 24% of Wilms tumor survivors are at a higher risk of other diseases, including second primary cancers, infertility, and cardiac disease.\textsuperscript{5,6} In the clinical, although Wilms tumor patients have a high cure rate, high-risk patients still have a very poor prognosis. Therefore, we must fully understand the polymorphisms in Wilms tumor patients to find more effective, cheaper, and safer treatment. At the same time, understanding the genetic inheritance of Wilms tumor is also an important premise to improve the prognosis of patients.

Some causal gene mutations have been reported in Wilms tumor. For instance, individuals with \textit{WT1} mutations have an enormous risk of Wilms tumor.\textsuperscript{7,8} A study by Ciceri et al suggested that constitutional anomalies of \textit{CHEK2} play an important role in the development of Wilms tumor.\textsuperscript{9} Moreover, a series of genetic alterations were identified associate with Wilms tumor susceptibility, including \textit{WTX},\textsuperscript{10} \textit{CITED1},\textsuperscript{11} \textit{SIX1},\textsuperscript{12} \textit{SIX2},\textsuperscript{13} \textit{TP53},\textsuperscript{14,15} \textit{HACE1},\textsuperscript{16} \textit{LIN28B},\textsuperscript{17} and \textit{KRAS}.\textsuperscript{18} Nevertheless, these genetic variations are

### TABLE 1 Association between MYCN gene polymorphisms and Wilms tumor susceptibility

| Genotype                  | Cases (N = 183) | Controls (N = 603) | P\textsuperscript{a} | Crude OR (95% CI) | P | Adjusted OR (95% CI)\textsuperscript{b} | P | Adjusted OR (95% CI)\textsuperscript{b} |
|--------------------------|-----------------|--------------------|----------------------|-------------------|---|--------------------------------------|---|---------------------|
| rs57961569 G > A (HWE = 0.582) |                 |                    |                      |                   |   |                                      |   |                     |
| GG                       | 90 (49.18)      | 259 (42.95)        | 1.00                 |                   |   |                                      |   |                     |
| GA                       | 74 (40.44)      | 277 (45.94)        | 0.77 (0.54-1.09)     | .142              | .077 (0.54-1.09) | .140 |
| AA                       | 19 (10.38)      | 67 (11.11)         | 0.82 (0.47-1.43)     | .479              | .082 (0.47-1.44) | .481 |
| Additive                 | .325            | 0.85 (0.66-1.10)   | .215                | .085 (0.66-1.10)  | .215 |
| Dominant                 | 93 (50.82)      | 344 (57.05)        | .78                 | .078 (0.56-1.08)  | .138 |
| Recessive                | 164 (89.62)     | 536 (88.89)        | .782                | .078 (0.56-1.08)  | .137 |
| rs9653226 T > C (HWE = 0.719) |                 |                    |                      |                   |   |                                      |   |                     |
| TT                       | 59 (32.24)      | 201 (33.33)        | 1.00                 |                   |   |                                      |   |                     |
| TC                       | 89 (48.63)      | 298 (49.42)        | 1.02 (0.70-1.48)     | .928              | 1.01 (0.70-1.48) | .944 |
| CC                       | 35 (19.13)      | 104 (17.25)        | 1.15 (0.71-1.85)     | .577              | 1.15 (0.71-1.85) | .580 |
| Additive                 | .840            | 1.06 (0.84-1.35)   | .613                | .106 (0.84-1.35)  | .618 |
| Dominant                 | 124 (67.76)     | 402 (66.67)        | .783                | 1.05 (0.74-1.50)  | .783 |
| Recessive                | 148 (80.87)     | 499 (82.75)        | .782                | 1.14 (0.74-1.74)  | .560 |
| rs13034994 A > G (HWE = 0.581) |                 |                    |                      |                   |   |                                      |   |                     |
| AA                       | 104 (56.83)     | 350 (58.04)        | 1.00                 |                   |   |                                      |   |                     |
| AG                       | 67 (36.61)      | 222 (36.82)        | 1.02 (0.72-1.44)     | .931              | 1.02 (0.72-1.45) | .916 |
| GG                       | 12 (6.56)       | 31 (5.14)          | 1.30 (0.65-2.63)     | .460              | 1.30 (0.65-2.63) | .458 |
| Additive                 | .759            | 1.08 (0.82-1.41)   | .603                | 1.08 (0.82-1.42)  | .592 |
| Dominant                 | 79 (43.17)      | 253 (41.96)        | .771                | 1.05 (0.75-1.47)  | .771 |
| Recessive                | 171 (93.44)     | 572 (94.86)        | .461                | 1.30 (0.65-2.58)  | .462 |
| rs60226897 G > A (HWE = 0.377) |                 |                    |                      |                   |   |                                      |   |                     |
| GG                       | 92 (50.27)      | 293 (48.59)        | 1.00                 |                   |   |                                      |   |                     |
| GA                       | 69 (37.70)      | 248 (41.13)        | 0.89 (0.62-1.26)     | .504              | 0.89 (0.62-1.27) | .508 |
| AA                       | 22 (12.02)      | 62 (10.28)         | 1.13 (0.66-1.94)     | .657              | 1.14 (0.66-1.95) | .647 |
| Additive                 | .642            | 1.00 (0.78-1.28)   | .922                | 1.00 (0.78-1.28)  | .981 |
| Dominant                 | 91 (49.73)      | 310 (51.41)        | .690                | 0.94 (0.67-1.30)  | .690 |
| Recessive                | 161 (87.98)     | 541 (89.72)        | .505                | 1.19 (0.71-2.00)  | .505 |
| Combined effect of risk genotypes |       |                    |                      |                   |   |                                      |   |                     |
| 0-1                      | 85 (46.45)      | 328 (54.39)        | 1.00                 |                   |   |                                      |   |                     |
| 2-4                      | 98 (53.55)      | 275 (45.61)        | .059                | 1.38 (0.99-1.92)  | .058 |

\textsuperscript{a}χ\textsuperscript{2} test for genotype distributions between Wilms tumor patients and controls.

\textsuperscript{b}Adjusted for age and gender.

\textsuperscript{c}Risk genotype was with rs57961569 GG, rs9653226 TC/CC, rs13034994 AG/GG, and rs60226897 AA.
not sufficient to explain the whole genetic pathogenesis involved in Wilms tumor.

MYCN encoded by the MYCN proto-oncogene is a MYC gene family member. This protein plays an indispensable role in the processes of cell growth, proliferation, differentiation, and apoptosis. In recent years, several groups reported amplified MYCN gene in different human cancers, such as human neuroblastoma, small cell lung carcinomas, astrocytoma, and retinoblastoma. In addition, MYCN copy number increased in 17.5% of basal cell carcinoma patients. Despite all these achievements, the implication of MYCN gene in Wilms tumor remains not fully clarified, especially the effects of potentially functional single nucleotide polymorphisms (SNPs). Thus, we conducted this study to identify the association between MYCN SNPs and Wilms tumor susceptibility.

2 | MATERIALS AND METHODS

2.1 | Study subjects

In this hospital-based epidemiological study, we recruited 183 patients and 603 controls from Yuying Children's Hospital of Wenzhou Medical University and Guangzhou Women and Children's Medical Center. Age, gender, and clinical stage distributions of all participants are summarized in Table S1. All the guardians of participants were voluntary to donate blood samples and signed informed consent forms. All individuals were independently recruited. This study was permitted by the Institutional Review Board of both the centers.

2.2 | SNP selection and genotyping

Four polymorphisms (rs57961569 G > A, rs9653226 T > C, rs13034994 A > G, and rs60226897 G > A) in the MYCN gene were selected in this study as we described previously. Specific criteria of SNPs selection and genotyping methods have been described in our previous study. All the above four polymorphisms are located at the binding sites of transcription factors, which have potential effects on the binding ability of transcription factors. In addition, they all have a minor allele frequency greater than 5% in the Chinese population.

2.3 | Statistical analysis

Hardy-Weinberg equilibrium (HWE) among controls was calculated using goodness-of-fit chi-squared test. And the differences in demographic variables and SNPs frequencies between cases and controls were tested using two-sided chi-squared test. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were adopted to appraise the association of MYCN gene SNPs with Wilms tumor risk. Difference between groups was deemed to be effective significant when \( P < .05 \). All of the statistical analyses were processed with the version 9.4 SAS (SAS Institute, Cary, NC).

| Variables | Age, month | Genotypes (case/controls) | Risk genotypes (case/controls) | OR (95% CI) | AOR (95% CI) | \( P \) | \( \alpha \) |
|-----------|------------|--------------------------|--------------------------------|-------------|-------------|------|-----|
|            | \( \leq 18 \) | GG/GA/AA | 35/124 | 1.01/0.81/1.00 | 0.64/0.41/0.99 | 0.94 | \( .01 \) |
| Gender     | Male       | 55/135 | 49/130 | 0.73/0.45/1.23 | 0.42/0.25/0.71 | \( .15 \) | \( .18 \) |
|            | Female     | 40/119 | 41/148 | 0.74/0.50/1.23 | 0.51/0.32/0.80 | \( .15 \) | \( .18 \) |
|            |            | 50/140 | 52/200 | 0.74/0.50/1.23 | 0.42/0.25/0.71 | \( .15 \) | \( .18 \) |
| Clinical stages | I + II | 34/259 | 33/344 | 0.73/0.44/1.21 | 0.42/0.25/0.71 | \( .15 \) | \( .18 \) |
|            | III + IV   | 34/259 | 33/344 | 0.73/0.44/1.21 | 0.42/0.25/0.71 | \( .15 \) | \( .18 \) |

\( \alpha \) Adjusted for age and gender, without the corresponding stratify factor. Bold values indicate the 95% CI excluded 1 or \( P < .05 \).
3 | RESULTS

3.1 | Characteristics of study population

The characteristics of subjects from Wenzhou and Guangzhou are summarized in Table S1. All the participants were under the age of 15 years, and the mean age was 29.64 months (±25.71, range = 1-144 months) for cases and 29.00 months (±24.00, range = 0.07-156 months) for controls, respectively. The discrepancy in age and gender between the cases and controls was not statistically significant (P = .997 for age and P = .997 for gender). In the case group, 6.56% of the patients were in clinical stage I, 30.05% were in II, 31.69% were in III, 21.86% were in IV, and 9.84% were not available (NA).

3.2 | Correlation of MYCN gene polymorphisms with Wilms tumor risk

The detailed results are presented in Table 1. None of the four selected polymorphisms showed obvious deviation from the HWE in the control groups (P = .582 for the rs57961569 G > A polymorphism, P = .719 for the rs9653226 T > C polymorphism, P = .581 for the rs13034994 A > G polymorphism, P = .377 for the rs60226897 G > A polymorphism). Overall, no significant association was found between MYCN gene polymorphisms and Wilms tumor risk. No significant results were observed for the combined effect of risk genotypes either.

3.3 | Stratification analysis

Stratification analysis was performed according to age, sex, and clinical stages (Table 2). The rs57961569 GA/AA genotypes significantly decreased Wilms tumor susceptibility in the children older than 18 months (adjusted OR = 0.65, 95% CI = 0.42-1.00, P = .050). In addition, children with 2-4 risk genotypes have a greater risk of developing Wilms tumor than those with 0-1 risk genotype (OR = 1.55, 95% CI = 1.001-2.40, P = .0497). However, the association was not statistically significant after adjusting for age and gender, which turns out that age and gender were confounding factors.

3.4 | Haplotype analysis

As shown in the Table 3, it is obvious that haplotype GCAA significantly increased Wilms tumor risk (adjusted OR = 2.40, 95% CI = 1.12-5.14, P = .024) compared to reference haplotype GTAG.

4 | DISCUSSION

We performed the current study to investigate the association of MYCN gene polymorphisms with Wilms tumor risk. We found no significant association between four included polymorphisms of MYCN and Wilms tumor risk in 183 cases and 603 controls. However, stratification and haplotype analyses revealed the potential contribution of MYCN polymorphisms to Wilms tumor risk.

Several groups have explored the influence of MYCN gene on Wilms tumor. It is proved that the expression level of MYCN increased in Wilms tumor,29-32 and MYCN gene can up-regulate the expression of CRABP-II in Wilms tumor patients to promote tumor progression.33 A study executed by Williams et al showed that MYCN gene contributed to the development of Wilms tumor through manifold mechanisms.34 In addition, the effect of MYCN gene polymorphisms...
on Wilms tumor may be related to RA signaling pathway. The contradiction of results may be caused by the small sample size and racial differences.

Moreover, a large number of studies have demonstrated that the MYCN gene is closely related to neuroblastoma. A study by Zaatiti et al indicated that neuroblastoma IMR-32 cell lines had significantly decreased proliferation ability after MYCN knockout. MYCN not only is related to the development of neuroblastoma, but also is one of the most powerful prognostic markers of neuroblastoma. We have delved the association between MYCN gene SNPs and neuroblastoma susceptibility before, and we found that SNP rs57961569 G > A was significantly associated with neuroblastoma risk. MYCN also regulated the regulatory circuits of genes involved in the progression of neuroblastoma through TBPAP4. Moreover, a study by Liu et al found that MYCN was involved in the malignant characteristics of erythroleukemia by inhibiting the activation of p21. What's more, amplified MYCN gene was observed in rhabdomyosarcoma, pediatric T-cell acute lymphoblastic leukemia, astrocytoma, and meningioma.

Our study is the first investigation to explore the relationship of MYCN gene SNPs with Wilms tumor susceptibility. There are several flaws in our research. First, only four genotypes were included in our research. The association between other MYCN polymorphisms and Wilms tumor susceptibility should be further explored. Secondly, the relatively small sample size, because of the low incidence of Wilms tumors, led to limited statistical power. Additionally, the environmental factors or environment-genes interaction were not considered in this study.

In conclusion, no significant association was found between MYCN gene polymorphisms and Wilms tumor risk in overall analysis, but stratification and haplotype analyses suggested that MYCN gene polymorphisms might be low penetrant variants in Wilms tumor susceptibility. Studies with larger sample size are need to verify our finding.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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