Original Article

MYC gene associated polymorphisms and Wilms tumor risk in Chinese children: a four-center case-control study

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Background: Wilms tumor (WT) is a common embryonal malignancy in the kidney, ranking fourth in childhood cancer worldwide. *MYC*, a critical proto-oncogene, plays an important role in tumorigenesis. Single nucleotide polymorphisms in the *MYC* gene may lead to the deregulation of *MYC* proto-oncogene protein and thereby promote the initiation and development of tumors.

Methods: Here, we assessed the association between *MYC* gene associated polymorphisms and WT susceptibility by performing a case-control study with 355 cases and 1070 controls. Two *MYC* gene associated polymorphisms (rs4645943 C > T, rs2070583 A > G) were genotyped by TaqMan technique. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for evaluating the association between these two polymorphisms and WT susceptibility.

Results: No significant association was detected between the selected polymorphisms and WT risk in the overall analysis as well as stratification analysis.

Conclusions: These results indicate that neither of two selected *MYC* gene associated polymorphisms might affect WT susceptibility in the Chinese population. Large well-designed studies with diverse ethnicities are warranted to verify these results.

Keywords: *MYC*; polymorphism; Wilms tumor (WT); susceptibility

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Introduction

Wilms tumor (WT), also known as nephroblastoma, is the most prevalent pediatric renal cancer. It accounts for 6–7% of all childhood malignancies occurring in children younger than 15 years (1). The incidence of WT varies from one ethnic group to another, with the highest rate found in black African and the lowest rate in Asians (1). In the United States, the morbidity of WT is about 1 in

8,000 children, accompanying with 400–650 new cases yearly (2), while 1 per 10,000 children is diagnosed in Western descent (3). In China, the incidence rate of WT is approximately 3.3 per million, lower than that in Western countries (4). The various incidences of WT among different ethnicities reflect the implication of genetic backgrounds in the pathogenesis of this disease. Now, WT is believed to derive from embryonal nephric mesenchymal pluripotent precursor cells (5). With unknown factors, these cells fail to differentiate to nephrons and form various lesions (nephrogenic rests) instead, leading to the development of WT eventually (6). Great progress has been made in the treatment of WT. The survival rate has reached over 90% in patients with regional WT (7), and over 75% in those with metastatic disease (8). Despite the encouraging clinical outcomes, about 25% of survivors suffer chronic disorders. They are often high-risk patients with poor histologic and molecular characteristics, bilateral disease and relapse (9).

WT is a genetically heterogeneous and intricate disorder. The majority cases are sporadic, and only 1–2% are familial (10,11). To data, many WT susceptibility genes and epigenetic alterations have been reported (12). *Wilms tumor gene 1* (*WT1*) at 11p13 was a tumor suppressor, the mutation in which was first identified in WT. It encodes a transcription factor important in multiple phases of normal kidney. And the somatic mutations of *WT1* are seen in 10% to 20% of sporadic WT (10). *WT1* mutation also frequently accompany with canonical Wnt activation, due to the activating mutation of β-catenin (*CTNNB1*) (13). *WTX* encodes a protein facilitating β-catenin degradation. Its inactivating mutations may occur in 15% to 20% WT patients (14). It was reported that the mutations of *WT1*, *CTNNB1* and *WTX* are implicated in nearly 1/3 WT cases (15). Other genetic loci implicated in WT infrequently are the familial predisposition loci *FWT1* at 17q12-q21 and *FWT2* at 19q13.4 (16). And the *TRIP13*, which encodes a highly conserved AAA + ATPase that contributes to homolog pairing, synapsis, and recombination during meiosis. The biallelic loss-of-function mutations of *TRIP13* are prone to chromosome segregation dysfunction and confer a high risk of WT (17). Besides, the Q177R mutation of the transcription factors *SIX1/2* shifts DNA binding specificity, which may induce subtle changes in the gene regulatory capacity of *SIX1/2*, and thereby change the expression profile of downstream target gene. The mutations in the microRNA processing genes *DROSHA/DGCR8* affect the miRNA processing and maturing, then alter miRNA expression patterns, such as all members of the *miR-200* family and *Let-7a*. All of these mutations were reported to be involved in the development and progression of WT (18,19). Recent research reported that germline mutations of *CHEK2* may reduce its kinase activity and affect RNA splicing, therefore involving in the progress of WT. The *MYCN* germline mutations that lead to aberrant activation, the deletions of *DIS3L2*, the *HACE1* germline mutations that lead to promoter methylation and the germline mutations of *CDKN2A* and *CDKN2B* that lead to their homozygous deletion will all play a role in the WT development (20). Furthermore, SNPs in several genes including *BARD1* (21), *LIN28* (22), *miR-423* (23) and *ERCC2* (24) have been found to predispose to WT.

MYC is located at chromosome 8 (8q24.21). It encodes a nuclear phosphoprotein transcription factor that plays key roles in the regulation of cellular proliferation, growth, apoptosis, metabolic transformation and oncogenesis (25). *MYC* family of proto-oncogenes is one of the most studied oncogenes (26). *MYC* is activated in approximately 70% of all human cancers and regulates about 10% of human genes involved in cellular malignant properties, such as promoting of cell proliferation and blocking cellular differentiation (27). Deregulation of *MYC* has been discovered in a great variety of human cancer, such as prostate cancer (28), and breast cancer (29). Single-nucleotide polymorphisms (SNPs) in the *MYC* are likely to lead to alterations in the structure and function of the protein (30), as well as the expression levels of *MYC*, thus contribute to cancer susceptibility (31). Several studies have reported numerous SNPs on chromosome 8q24 which contribute to cancer susceptibility of colorectal (32), prostate (33), breast cancer (34). However, as far as we know, there no reports about the associations between SNPs of *MYC* and WT susceptibility. Given this, we aimed to explore the association of two potentially functional SNPs (rs4645943 C > T, rs2070583 A > G) of *MYC* with WT risk in Chinese population through a four-center case-control study.

Methods

Study subjects

In this present study, a total of 355 cases with WT and 1,070 healthy controls were included (35,36). The 355 cases were collected from four hospitals (Guangzhou Women and Children's Medical Center, The First Affiliated Hospital of

Zhengzhou University, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, and Second Affiliated Hospital of Xi'an Jiao Tong University), and the 1,070 control subjects were enrolled randomly from the same areas at the same time (35,36). The demographic characteristics of all participants are displayed in *Table S1*. Written informed consent was obtained for each participant from their parents or guardians. This study got approved by each institutional review board of all participating hospitals. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Polymorphism selection and genotyping

From the dbSNP database (http://www.ncbi.nlm.nih.gov/) and SNPinfo (http://snpinfo.niehs.nih.gov/), two potentially functional polymorphisms (rs4645943 C > T, and rs2070583 A > G) of *MYC* gene were chosen base on the following selection criteria: (I) position located at exons, splice sites, 5' near gene, 5' untranslated regions (UTR), 3' near gene, 3' UTR; (II) the minor allele frequency (MAF) should be ≥5% in Chinese Han population; (III) potentially functional SNPs are identified by SNPinfo software (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm); (IV) selected SNPs were in low linkage disequilibrium (LD) with one another using an R^2 threshold lower than 0.8; (V) not explored in the published genome-wide association studies (GWASs) of WT (37). The rs4645943 C > T is a variant located in transcription start site upstream 2 Kb of *MYC* gene and the rs2070583 A > G, a SNP located in the *MYC* gene 3' UTR region, which may associate with the expression level of the *MYC* gene. For genotyping, the genomic DNA was extracted from peripheral blood leukocytes of all participants by the TIANamp Blood DNA Kit (TianGen Biotech, Beijing, China). The DNA samples were added to 96-well plates and diluted to 5 ng/μL. Genotyping for the SNPs was carried out in the 384-well format by the Taqman method. And ten percent of the samples were chosen randomly and re-genotyped. The concordance of the two sets of genotyping results was 100%.

Statistical analysis

χ^2 test was applied to assess the differences in demographic characteristics and the frequency distributions of genotypes between WT cases and healthy controls. And the deviation from Hardy-Weinberg equilibrium (HWE) was evaluated by the goodness-of-fit χ^2 test in the control subjects. The assessment of relevance between *MYC* gene associated polymorphisms and WT susceptibility was performed by calculating odds ratios (ORs) and 95% confidence intervals (CIs). Furthermore, by unconditional multivariate logistic regression analysis, adjusted ORs and corresponding 95% CIs which adjusted for age and gender were calculated. Stratified analyses were conducted based on the age, gender and clinical stages. All statistical tests were two-sided and analyzed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). And when the P values <0.05 were considered as statistically significant.

Results

Relevance between MYC gene associated polymorphisms and WT risk

In this current case-control study, 355 cases and 1,070 controls were successfully genotyped. The genotype frequencies of two MYC gene associated polymorphisms are shown in *Table 1*, which were in accordance with HWE amongst the control subjects (P=0.990 for rs4645943 C > T; and P=0.482 for rs2070583 A > G). In single genotype analysis, no significant association was found between the two selected polymorphisms and the WT risk. And the same result was found in the combined analysis.

Stratification analysis of MYC gene associated polymorphisms with WT susceptibility

To explore whether the selected *MYC* gene associated polymorphisms affect WT susceptibility among different subgroups, stratified analyses were performed according to the age, gender and clinical stages (*Table 2*). However, no significant association was identified between the studied polymorphisms and the WT susceptibility in any subgroup.

Discussion

We conducted the present hospital-based study comprising 355 WT cases and 1,070 control subjects to investigate the relationship between two *MYC* SNPs and the WT risk. However, neither of the two selected SNPs was associated with WT risk. To the best of our knowledge, this is the first research exploring the association between polymorphisms in the *MYC* gene and WT risk.

Table 1 Logistic regression analysis of associations between *MYC* gene associated polymorphisms and Wilms tumor risk

Genotype	Cases (N=355) (%)	Controls (N=1,070) (%)	P[a]	Crude OR (95% CI)	P	Adjusted OR (95% CI)[b]	P[b]
rs4645943 C > T (HWE =0.990)							
CC	182 (51.27)	549 (51.31)	–	1.00		1.00	
CT	144 (40.56)	435 (40.65)	–	1.00 (0.78–1.29)	0.991	1.00 (0.77–1.28)	0.975
TT	29 (8.17)	86 (8.04)	–	1.02 (0.65–1.60)	0.941	1.01 (0.64–1.59)	0.972
Additive	–	–	0.997	1.00 (0.83–1.21)	0.965	1.00 (0.83–1.21)	0.995
Dominant	173 (48.73)	521 (48.69)	0.989	1.00 (0.79–1.27)	0.989	1.00 (0.79–1.27)	0.987
Recessive	326 (91.83)	984 (91.96)	0.937	1.02 (0.66–1.58)	0.937	1.01 (0.65–1.57)	0.964
rs2070583 A > G (HWE =0.482)							
AA	258 (72.68)	732 (68.41)	–	1.00		1.00	
AG	88 (24.79)	302 (28.22)	–	0.83 (0.63–1.09)	0.178	0.83 (0.63–1.09)	0.184
GG	9 (2.54)	36 (3.36)	–	0.71 (0.34–1.49)	0.366	0.70 (0.33–1.47)	0.347
Additive	–	–	0.297	0.83 (0.65–1.05)	0.121	0.83 (0.66–1.05)	0.119
Dominant	97 (27.32)	338 (31.59)	0.131	0.81 (0.62–1.06)	0.131	0.82 (0.62–1.06)	0.133
Recessive	346 (97.46)	1,034 (96.64)	0.439	0.75 (0.36–1.57)	0.441	0.74 (0.35–1.55)	0.418
Combined effect of protective genotypes[c]							
0	179 (50.42)	534 (49.91)	–	1.00		1.00	
1	82 (23.10)	213 (19.91)	–	1.15 (0.85–1.56)	0.375	1.14 (0.84–1.55)	0.393
2	94 (26.48)	323 (30.19)	–	0.87 (0.65–1.16)	0.332	0.87 (0.65–1.15)	0.327
Trend			0.276	0.95 (0.82–1.09)	0.426	0.94 (0.82–1.09)	0.418
0–1	261 (73.52)	747 (69.81)	–	1.00		1.00	
2	94 (26.48)	323 (30.19)	0.183	0.83 (0.64–1.09)	0.184	0.83 (0.64–1.09)	0.184

[a], χ^2 test for genotype distributions between Wilms tumor patients and cancer-free controls; [b], adjusted for age and gender; [c], protective genotypes were carriers with rs4645943 CT/TT, and rs2070583 AG/GG genotypes. OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

As a proto-oncogene, *MYC* encodes a transcription factor that regulates the expression of approximately 15% of human genes directly or indirectly (38). It can interact with its partner protein *MAX* and bind to E-box DNA elements located in regulatory regions of target genes, then activate gene expression (39). Moreover, as *MYC* participates in the biogenesis of multiple components of the ribosome, it can regulate gene expression indirectly at the translational level (40). Importantly, *MYC* is a multifunctional protein, it acts as a master regulator that commands cellular proliferation, differentiation, metabolism, migration/invasion, apoptosis, microenvironment remodeling, angiogenesis, and immune responses by involving in multiple signaling pathways (41-43).

Deregulation of *MYC* has been repeatedly reported in a wide spectrum of human cancer, including breast cancer (44), and lung cancer (45). The deregulation of *MYC* leads to the aberrant expression of its downstream target genes, then causes the changes in the biological behaviors and functions, and promotes oncogenesis eventually. Although the major causes of oncogene deregulation are DNA amplification and gene mutation, SNPs may also cause an abnormality of gene structure and gene expression, then lead to functional change. There are plenty of studies reporting that SNPs in the *MYC* gene result in the dysregulation of *MYC*, and then modify the cancer susceptibility. For example, Wirtenberger *et al.* found that polymorphisms rs4645959 A > G within the N-terminal

Table 2 Stratification analysis for association between genotypes derived from *MYC* gene associated polymorphisms and Wilms tumor susceptibility

Variables	rs4645943 (case/control)				rs2070583 (case/control)				Combine genotypes (case/control)			
	CC	CT/TT	AOR (95% CI)[a]	P[a]	AA	AG/GG	AOR (95% CI)[a]	P[a]	0–1	2	AOR (95% CI)[a]	P[a]
Age, month												
≤18	58/224	67/201	1.30 (0.87–1.95)	0.196	89/295	36/130	0.92 (0.60–1.43)	0.721	90/302	35/123	0.97 (0.62–1.50)	0.874
>18	124/325	106/320	0.87 (0.64–1.18)	0.371	169/437	61/208	0.77 (0.55–1.07)	0.119	171/445	59/200	0.77 (0.55–1.09)	0.138
Gender												
Female	81/227	82/221	1.04 (0.73–1.49)	0.835	114/312	49/136	0.99 (0.67–1.46)	0.938	115/315	48/133	0.99 (0.67–1.46)	0.949
Male	101/322	91/300	0.97 (0.70–1.34)	0.848	144/420	48/202	0.70 (0.48–1.01)	0.055	146/432	46/190	0.72 (0.50–1.05)	0.089
Clinical stage												
I	57/549	62/521	1.14 (0.78–1.67)	0.492	79/732	40/338	1.09 (0.73–1.63)	0.677	80/747	39/323	1.12 (0.75–1.69)	0.573
II	48/549	44/521	0.96 (0.63–1.47)	0.844	70/732	22/338	0.68 (0.41–1.12)	0.126	70/747	22/323	0.72 (0.44–1.19)	0.203
III	43/549	36/521	0.88 (0.56–1.40)	0.595	61/732	18/338	0.65 (0.38–1.11)	0.114	62/747	17/323	0.64 (0.37–1.11)	0.108
IV	21/549	26/521	1.30 (0.72–2.34)	0.378	32/732	15/338	1.02 (0.54–1.90)	0.959	32/747	15/323	1.08 (0.58–2.03)	0.806
I + II	105/549	106/521	1.06 (0.78–1.42)	0.724	149/732	62/338	0.89 (0.65–1.23)	0.491	150/747	61/323	0.93 (0.67–1.29)	0.679
III + IV	64/549	62/521	1.02 (0.70–1.47)	0.930	93/732	33/338	0.77 (0.50–1.16)	0.211	94/747	32/323	0.78 (0.51–1.19)	0.248

[a], adjusted for age and gender, omitting the corresponding stratify factor. AOR, adjusted odds ratio; CI, confidence interval.

domain of *MYC* led to an amino acid transition from Asn to Ser; and the heterozygous carriers of the Asn11Ser had increased breast cancer risk (46). SNPs in cis regulators of transcription of *MYC* gene may change its germline expression levels and contribute to cancer susceptibility. The rs13281615 located in the non-coding region near the *MYC* has been reported to associate with the risk of colorectal cancer (47), prostate cancer (48), breast cancer (49). The rs6983267 affects the binding of *MYC* with transcription factor 7-like 2 (TCF7L2) and TCF4 (50), and it is proved to up-regulate the transcription of *MYC* by Takatsuno *et al.* (51). And the rs6983267 has been reported to modify the cancer susceptibility, such as gastric cancer (52). Guo *et al.* demonstrated that rs4645948 located in 5' UTR of the *MYC* gene increased the transcriptional activity of *MYC*, and thus increased risk of developing nasopharyngeal carcinoma (53). These studies mention above all indicated that SNPs in the *MYC* gene may affect its expression and function, then contribute to the cancer susceptibility.

The rs4645943 C > T and rs2070583 A > G polymorphisms are located in 5' UTR and 3' UTR region of the *MYC* gene, respectively, two crucial regions for regulating its expression. The polymorphism rs4645943 C > T has been reported to be associated with prostate cancer risk (28). However, no study has reported the association between this polymorphism and the WT risk. Moreover, there is no association study regarding rs2070583 A > G and cancer susceptibility. In this current case-control study, we attempt to investigate the association between the selected SNPs in the regulatory region of *MYC* gene and WT susceptibility in a Chinese population. However, no association between two selected polymorphisms and WT risk was found. The two selected polymorphisms might not affect the *MYC* gene expression and function, and therefore would not modify the susceptibility to WT.

Several limitations should be mentioned in this study. First, the sample size is moderate. A larger sample size would increase the statistical power and the credibility of the conclusions. Second, only two polymorphisms of the *MYC* gene were evaluated, other potentially functional *MYC* SNPs should be investigated. Third, selection bias is inevitable, resulting from this hospital-based study design. Therefore, the study population may not fully represent the general population.

In summary, our results showed that both two *MYC* gene associated polymorphisms (rs4645943 C > T, and rs2070583 A > G) were not associated with WT risk in Chinese population. Future studies with larger sample size comprising different ethnicities should be performed to confirm our conclusion.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Our study design received approval from the each institutional review board of all participating hospitals. Written informed consent was obtained from all patients. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Frequency distribution of selected variables in Wilms tumor patients and controls

Variables	Cases (n=355)		Controls (n=1,070)		P[a]
	No.	%	No.	%	
Age range, month	1–148.63		0.03–156		0.131
Mean ± SD	30.67±23.96		32.27±26.89		
≤18	125	35.21	425	39.72	
>18	230	64.79	645	60.28	
Gender					0.182
Female	163	45.92	448	41.87	
Male	192	54.08	622	58.13	
Clinical stages					
I	119	33.52			
II	92	25.92			
III	79	22.25			
IV	47	13.24			
NA	18	5.07			

[a] Two-sided χ^2 test for distributions between Wilms tumor patients and cancer-free controls. SD, standard deviation.