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Association between *TP53* gene Arg72Pro polymorphism and Wilms' tumor risk in a Chinese population

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Abstract: Wilms' tumor is one of the most prevalent pediatric malignancies, ranking fourth in childhood cancer worldwide. *TP53* is a critical tumor suppressor gene, which encodes a 53 kDa protein, p53. The p53 functions to protect against cancer by regulating cell cycle and apoptosis and maintaining DNA integrity. *TP53* gene is highly polymorphic. Several *TP53* gene polymorphisms have been considered to be associated with cancer risk. Of them, a nonsynonymous polymorphism, Arg72Pro (rs1042522 C>G), has been most extensively studied for the association with cancer risk; however, few studies have investigated its effect on Wilms' tumor. Because of the central role of p53 in cell cycle control, the *TP53* gene Arg72Pro polymorphism is also a good potential candidate predisposition locus for this pediatric cancer. We genotyped this polymorphism in 145 patients and 531 cancer-free controls recruited from Chinese children by Taqman methodology. Overall, our result suggested a lack of association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor. In the stratified analysis, we found that carriers of CG/GG genotypes had a significantly increased Wilms' tumor risk in children not older than 18 months (adjusted odds ratio =2.04, 95% confidence interval =1.003–4.13, P=0.049) compared with CC genotype carriers. Our study indicated that the *TP53* gene Arg72Pro polymorphism may have a weak, age-related effect on Wilms' tumor risk in Chinese children. These findings need further validations in other populations with larger sample size.

Keywords: *TP53*, polymorphism, Wilms' tumor, susceptibility

Introduction

Wilms' tumor, also known as nephroblastoma, is the fourth most frequently diagnosed childhood cancer worldwide. It constitutes ~6% of all cancers detected among children younger than 15 years. The incidence rate of Wilms' tumor varies geographically. The occurrence rate of Wilms' tumor is ~1/8,000 children, with 400–650 new cases annually, in the USA[1,2] and ~1/10,000 children in Western populations.[3] Wilms' tumor is also one of the most common renal tumors in children in China but less prevalent than that in Western countries, with an incidence rate of ~3.3 per million.[4] Up to 2% of Wilms' tumor cases are familial, with a known causal genetic lesion.[5] No more than 5% of cases can be attributed to known causes, and the genetic basis underlying most Wilms' tumors remains largely unknown.[6,7]

The human *TP53* gene, encoding a 53 kDa protein (p53), is located on chromosome 17p13.1. *TP53* gene is one of the most commonly mutated genes in human cancers.[8] The *TP53* gene is a tumor suppressor gene, playing an important role in the maintenance of DNA integrity, cell cycle control, and apoptosis.[9–11] According to dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP), at least 1,462 single-nucleotide

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polymorphisms (SNPs) have been identified in the *TP53* gene so far, supporting its highly polymorphic nature. Among them, the most commonly reported SNP is a non-synonymous Arg72Pro (rs1042522 C>G) polymorphism. This polymorphism is located in the exon 4 of the *TP53* gene and can lead to the replacement of arginine (Arg) with proline (Pro) at codon 72. This polymorphism is able to alter the primary structures as well as biochemical functions of the p53 protein.[12–14] It has been reported that the Arg72 form of p53 is more effective in inducing apoptosis and protecting cells from malignant transformation than the Pro72 variant.[12,15] Numerous studies have been carried out to investigate the association between this polymorphism and cancer susceptibility.[16–20] However, very few studies have investigated its association with Wilms' tumor susceptibility and clinical outcomes until now.[21,22] In light of the important tumor-suppressing role of *TP53* gene, we investigated the association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor susceptibility in the current hospital-based case–control study with 145 cases and 531 cancer-free controls.

Subjects and methods

Subjects

This study consisted of 145 newly diagnosed and histopathologically confirmed Wilms' tumor patients from the Department of Pediatric Urology, Guangzhou Women and Children's Medical Center.[23] Patients were enrolled between March 2001 and June 2016. Controls were chosen from children who visited for routine physical examination, as we described previously.[24–29] A total of 531 ethnicity-, age-, and gender-matched cancer-free controls were included in the study. Written informed consent was obtained from all subjects or their legal guardians in accordance with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Guangzhou Women and Children's Medical Center.

DNA extraction and genotyping of *TP53* gene Arg72Pro polymorphism

Total genomic DNA was mainly isolated from the peripheral blood leukocytes using the TIANamp Blood DNA Kit (TianGen Biotech Co., Ltd., Beijing, China) as described previously.[26] The *TP53* gene Arg72Pro polymorphism was genotyped using the TaqMan real-time PCR method.[26,30] Genotyping was performed blindly to the status of the case or control. Moreover, 10% of the samples were randomly selected to perform repeated assays, and the results were 100% concordant.

Statistical analysis

χ^2 test was adopted to compare demographic characteristics and the frequency distributions of genotypes between cases and controls. Deviation from Hardy–Weinberg equilibrium (HWE) was tested using the χ^2 goodness-of-fit test for the control subjects. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor susceptibility. Adjusted ORs and corresponding 95% CIs adjusting for age and gender were calculated by unconditional multiple logistic regression model. Stratified analyses were performed by age, gender, and clinical stages. All the statistical tests were two sided, and *P*-values <0.05 were considered as statistically significant. Statistical analysis was performed using the SAS software (Version 9.4; SAS Institute, Cary, NC, USA).

Results

Subject characteristics

Epidemiological characteristics of Wilms' tumor patients and cancer-free controls are listed in Table S1. The mean age was 26.17 months (±21.48, range =1–132 months) for Wilms' tumor patients and 29.73 months (±24.86, range =0.07–156 months) for controls. No significant differences were observed between the patients and controls in the distribution of age (*P*=0.725) and gender (*P*=0.956). According to the classification of childhood renal tumors defined by NWTS-5 criteria,[31] 4 (2.76%), 49 (33.79%), 50 (34.48%), and 33 (22.76%) patients had clinical stages I, II, III, and IV Wilms' tumor, respectively. Unfortunately, tumor specimens were not available for nine (6.21%) patients.

Association between *TP53* gene Arg72Pro polymorphism and Wilms' tumor risk

The genotype frequencies of the *TP53* gene Arg72Pro polymorphism in the Wilms' tumor patients and controls are listed in Table 1. Genotype analysis for the *TP53* gene Arg72Pro polymorphism revealed that there was no significant deviation from the HWE in the control group (*P*=0.440). We did not observe any significant association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor susceptibility (CG vs CC: adjusted OR =1.48, 95% CI =0.95–2.32, *P*=0.086; GG vs CC: adjusted OR =1.02, 95% CI =0.58–1.78, *P*=0.948; CG/GG vs CC: adjusted OR =1.33, 95% CI =0.87–2.04, *P*=0.191; and GG vs CC/CG: adjusted OR =0.78, 95% CI =0.49–1.25, *P*=0.307).

We further explored the association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor susceptibility

Table 1 Genotype distributions of *TP53* gene rs1042522 C>G polymorphism and Wilms' tumor risk

Genotype	Cases (N=144), n (%)	Controls (N=530), n (%)	*P*-value[a]	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)[b]	*P*-value[b]
rs1042522 (HWE =0.440)							
CC	34 (23.61)	155 (29.25)		1.00		1.00	
CG	83 (57.64)	255 (48.11)		1.48 (0.95–2.32)	0.083	1.48 (0.95–2.32)	0.086
GG	27 (18.75)	120 (22.64)		1.03 (0.59–1.79)	0.929	1.02 (0.58–1.78)	0.948
Additive			0.127	1.04 (0.80–1.35)	0.792	1.03 (0.79–1.34)	0.814
Dominant	110 (76.39)	375 (70.75)	0.176	1.34 (0.87–2.05)	0.183	1.33 (0.87–2.04)	0.191
Recessive	117 (81.25)	410 (77.36)	0.310	0.79 (0.50–1.26)	0.317	0.78 (0.49–1.25)	0.307

Notes: [a]χ^2 test for genotype distributions between Wilms' tumor patients and controls. [b]Adjusted for age and gender.
Abbreviations: CI, confidence interval; OR, odds ratio; HWE, Hardy–Weinberg equilibrium.

in the stratified analysis by age, gender, and clinical stages (Table 2). Significant association was observed in children aged 18 months or younger (OR =2.06, 95% CI =1.02–4.18, *P*=0.045, and adjusted OR =2.04, 95% CI =1.003–4.13, *P*=0.049). It was suggested that younger children (≤18 months old) with CG/GG genotypes were at significantly higher risk of Wilms' tumor than those with CC genotypes. However, no significant associations were observed in other stratified analyses.

Discussion

In the current hospital-based case–control study with 145 cases and 531 unrelated cancer-free controls, we did not observe any significant association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor susceptibility among Southern Chinese children. Interestingly, we found that the carriers of CG/GG genotypes, if 18 months old or younger, had a significantly increased Wilms' tumor risk compared with counterparts carrying wild-type CC genotypes.

The *TP53* gene (gene ID: 7157) is also known as *P53* gene. It encodes a p53 tumor suppressor protein that contains DNA binding, transcriptional activation, and oligomerization domains.[32,33] The p53 protein can regulate the expression of target genes in response to diverse cellular stresses, thereby inducing DNA repair, cell cycle arrest, metabolism changes, apoptosis, and cellular senescence accordingly.[9–11,34] The p53 protein has been recognized as the guardian of human cells against cancer.[9,35] However, this gene is highly mutated, and mutations in the *TP53* gene have been implicated in the various types of cancer in human beings.[36] Apart from the predisposition to mutations, *TP53* is also highly polymorphic. A great number of SNPs has been identified in the *TP53* gene. Several *TP53* gene SNPs have been shown to confer cancer susceptibility, such as the rs78378222 A>C polymorphism discovered by whole-genome sequencing in 2011. We recently performed a meta-analysis to investigate the association between *TP53* gene rs78378222 A>C and overall cancer risk.[37] Evidence from 34 studies including 36,599 cases and 91,272 controls confirmed that this polymorphism was significantly associated with an increased overall cancer risk.[37] The *TP53* gene Arg72Pro polymorphism is the most extensively investigated variant among the known *TP53* gene susceptibility loci, which was first reported by Matlashewski et al.[38] Intriguingly, the two alleles of this nonsynonymous polymorphism differ in the capacity of inducing target gene

Table 2 Stratification analysis for the association between *TP53* gene rs1042522 C>G polymorphism and Wilms' tumor risk

Variables	rs1042522 (cases/controls)		Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value[a]
	CC	CG/GG				
Age, months						
≤18	11/68	55/165	**2.06 (1.02–4.18)**	**0.045**	**2.04 (1.003–4.13)**	**0.049**
>18	23/87	55/210	0.99 (0.57–1.71)	0.973	1.00 (0.58–1.73)	0.993
Gender						
Females	18/71	46/161	1.13 (0.61–2.08)	0.702	1.12 (0.61–2.07)	0.711
Males	16/84	64/214	1.57 (0.86–2.87)	0.143	1.56 (0.85–2.86)	0.150
Clinical stage						
I + II	10/155	42/375	1.74 (0.85–3.55)	0.130	1.77 (0.86–3.65)	0.119
III + IV	22/155	61/375	1.15 (0.68–1.93)	0.609	1.14 (0.68–1.92)	0.627

Notes: [a]Adjusted for age and gender. The results are presented in bold if the 95% CI excluded 1 or $P<0.05$.
Abbreviations: CI, confidence interval; OR, odds ratio.

transcription, consequentially modifying cancer susceptibility differentially.[13,39,40]

As so far, numerous studies have been conducted to investigate the association between this polymorphism and cancer susceptibility.[16–20] Klug et al[16] carried out a meta-analysis by including a total of 49 studies with 7,946 cases and 7,888 controls. They found that the *TP53* gene Arg72Pro polymorphism was not associated with cervical cancer risk when the analyses were restricted to methodologically sound studies. Dahabreh et al[17] did not find any significant association between *TP53* gene Arg72Pro polymorphism and colorectal cancer with evidence from 23 studies including 6,514 cases and 9,334 controls. Xu et al[18] combined 15 publications and found that the *TP53* gene Arg72Pro polymorphism was associated with a significantly increased bladder cancer risk among Asians but not among Caucasians. Dahabreh et al[19] carried out a meta-analysis involving breast cancer (68 studies), lung cancer (42), colorectal cancer (26), ovarian cancer (16), and endometrial cancer (8). They found that the association with the *TP53* gene Arg72Pro polymorphism only existed among studies using tumor tissue as the source of genotyping material for cases (22 studies) but not among studies using other sources of genotyping material (eg, blood). However, it should be noted that the use of tumor tissue as the source of genotyping material for cases can lead to bias in the association studies. In the study by Tian et al[20] with 14 investigations, including 2,506 cases and 4,386 controls, no association was observed between the *TP53* gene Arg72Pro polymorphism and leukemia risk.

However, there is lack of evidence of the association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor risk to date. Only one case–control study has been performed to examine the association of this polymorphism with Wilms' tumor risk[22] using controls from other studies. In the study with 46 cases and 300 controls, Andrade et al[22] found that carriers of the rs1042522 C allele may associate with an increased Wilms' tumor risk. In our present study, we failed to find any significant association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor risk, which was similar to most previous investigations in other types of cancer.[16,17,20] Failure to find any significant association between the *TP53* gene Arg72Pro polymorphism and Wilms' tumor risk may be ascribed to the weak effect of low-penetrant SNPs, ethnicity difference, as well as the limited sample size in the current study. We found that the *TP53* gene Arg72Pro polymorphism may contribute to a weak effect for Wilms' tumor risk in Chinese children aged 18 months and younger, which may be ascribed to the fact that young children may be more genetic susceptible to Wilms' tumor risk; besides, it may be a chance finding for the sample size, which is relatively small.

Although this is the first investigation to assess the association between *TP53* gene Arg72Pro polymorphism and Wilms' tumor risk in Chinese children, our results should be interpreted with cautious for several limitations should be addressed. First, due to the low occurrence rate of Wilms' tumor, only 145 cases were included in this study, which may have limited statistical power. Second, because of the nature of retrospective study design, we were only able to collect age, gender, ethnicity, and geographical factors for cases and controls. Other factors, such as dietary intake and parental environment exposures, were not available. Third, we just performed a case–control designed study to investigate the association between *TP53* Arg72Pro polymorphism and Wilms' tumor risk and we did not explore the potential mechanisms in cell lines for this polymorphism, which need to be investigated in future. Finally, we included only the most frequently investigated Arg72Pro polymorphism, and other *TP53* gene polymorphisms (such as rs78378222 A>C) were not examined in this study.

Conclusion

This study indicated that the *TP53* gene Arg72Pro polymorphism may contribute to a weak effect for Wilms' tumor risk in Chinese children aged 18 months and younger. However, further prospective studies with larger sample size, different ethnicities, and more polymorphisms are required to confirm our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

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

Variables	Cases (n=145)		Controls (n=531)		*P*-value[a]
	N	%	N	%	
Age range, months (mean ± SD)	1–132 (26.17±21.48)		0.07–156 (29.73±24.86)		0.725
≤18	66	45.52	66	45.52	
>18	79	54.48	79	54.48	
Gender					0.956
Females	64	44.14	233	43.88	
Males	81	55.86	298	56.12	
Clinical stage					
I	4	2.76			
II	49	33.79			
III	50	34.48			
IV	33	22.76			
NA	9	6.21			

Note: [a]Two-sided χ^2 test for distributions between Wilms' tumor patients and controls.
Abbreviations: NA, not available; SD, standard deviation.