RESEARCH ARTICLE

The correlation between *LIN28B* gene potentially functional variants and Wilms tumor susceptibility in Chinese children

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Background: Wilms tumor (WT) is the most common urologic cancer in children. However, genetic bases underlying WT remain largely unknown. Previous studies indicated that Lin28 homolog B (*LIN28B*) level is significantly elevated in some WT. Enforced expression of Lin28b during kidney development could induce WT. Genetic variations in the *LIN28B* gene may be related to WT susceptibility.

Method: In this study, we aimed to assess the association between *LIN28B* gene polymorphisms and WT susceptibility in Chinese children. Four potentially functional polymorphisms in the *LIN28B* gene (rs314276 C>A, rs221634 A>T, rs221635 T>C and rs9404590 T>G) were genotyped in 145 cases and 531 cancer-free controls, using Taqman method. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the associations.

Results: Our results showed that the rs314276 CA genotype was associated with a decreased WT risk (CA vs CC: adjusted OR=0.65, 95% CI=0.43-0.98, *P*=.042). Moreover, we found that carriers of the 1-3 risk genotypes had a significantly increased WT risk when compared to the non-carriers (adjusted OR=1.51, 95% CI=1.03-2.20, *P*=.035). The association with risk genotypes was more predominant in children 18 month old or younger and in females.

Conclusion: In summary, these results indicated that the *LIN28B* gene rs314276 C>A polymorphism alone and three combined polymorphisms may be able to modify WT susceptibility in Southern Chinese children. Our findings call for further validation in large studies with different ethnicities involved.

KEYWORDS

genetic susceptibility, *LIN28B*, polymorphism, Wilms tumor

1 | INTRODUCTION

Wilms tumor (WT), also known as nephroblastoma, is a malignant tumor that generally develops in children under 5 years of age, which resembles embryonic kidney morphologically.¹ It affects 1/10 000 children and accounts for 8% of childhood cancers in Western populations.² As to the Chinese subjects, the occurrence rate is approximately 3.3 cases per million.³ The tumor is identified as a prototype

of tumors arising from abnormal differentiation and development.² Though treatment outcome has improved and the overall survival rate (percentage of people still alive at the end time after diagnosis) has reached 90%, a considerable portion of the sufferers including those with diffuse anaplasia, recurrent and bilateral disease have survival rate less than 70%. These high-risk patients constitute 25% of WT cases.^{4,5} Furthermore, WT treatment comes at a cost, and up to 25% of survivors report severe chronic health problems 25-years after diagnosis.^{4,6,7} There remains strong clinical demands to improve treatments so as to minimize side effects later in life and find more

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effective therapies for high-risk histological subtypes and recrudescence patients.⁸

Mutations in the Wnt/ β -catenin pathway-related *Wilms tumor gene 1* (*WT1*), β -catenin, and *WTX* together have been detected in about one-third of WT cases. Extensive efforts have been made to seek causative genetic alteration for the rest of WT cases.² Several groups recently found that microRNA (miRNA) may play a pivotal role in WT development, and approximately 15% of WT patients harbor miRNA-processing gene mutations.^{2,5} *Lin28*, a direct target of miRNA let-7 and potent regulator of stem cell self-renewal and differentiation, is remarkably increased in some WTs. Enforced expression of *Lin28b* during kidney development could induce WT.^{1,2}

Understanding of the genetic events is a pivotal component of preventive oncology. The rapid advances in genotyping technologies and the knowledge on human genome have made genome-wide association studies (GWASs) possible for human diseases, including cancer.⁹ In the GWAS for WT which was carried out by Turnbull et al.,¹⁰ significant associations at 2p24 (rs3755132 G>T, rs807624 A>C) and 11q14 (rs790356 G>A), as well as candidate association signals at 5q14, 22q12, and Xp22 were identified.¹⁰ Recently, Yu et al.¹¹ found that there is a significant association between variant G allele of rs11788747 A>G polymorphism in *RECK* gene and WT risk in Chinese children. However, the underlying genetic basis of most cases of WT remains unknown.⁹

Although it is well-illustrated that *LIN28B* gene has an impact on metastasis and prognosis of human cancers, particularly on childhood cancers including WT and neuroblastoma,¹²⁻¹⁴ The association of *LIN28B* gene single nucleotide polymorphisms with WT susceptibility and clinical features has been clarified. Our research group has previously identified that the *LIN28B* gene rs221634 A>T polymorphism was associated with an increased neuroblastoma risk in Southern Chinese children.¹⁵ Regarding the biological importance of *LIN28B* gene and its implication in WT, we performed this hospital-based case-control study to determine whether polymorphisms in *LIN28B* gene were also associated with WT risk in Chinese children.

2 | MATERIALS AND METHODS

2.1 | Study subjects

A total of 145 newly diagnosed and histopathologically confirmed WT patients were enrolled in this investigation. All cases were unrelated ethnic Chinese Han individuals and recruited from the Guangzhou Women and Children's Medical Center between March 2001 and June 2016. We also included a total of 531 age-, gender-, race-matched cancer-free volunteers recruited from the same hospital.¹⁶⁻²⁰ Each individual donated 2 mL blood for genomic DNA extraction. The response rate (agree to involve in the current study) was approximately 90% and 95% for WT cases and cancer-free controls respectively. The research was performed with the approval of the Institutional Review Board of Guangzhou Women and Children's Medical Center. All of the participants provided written informed consent signed by their legal guardians.

2.2 | Polymorphisms selection and genotyping

We chose four potentially functional polymorphisms (rs314276 C>A, rs221634 A>T, rs221635 T>C and rs9404590 T>G) in the *LIN28B* gene based on the criteria as we described previously.¹⁵ We performed genotyping using Taqman real-time PCR system as reported elsewhere.²¹ Additionally, approximately 10% samples were selected randomly and genotyped with sequencing for quality control, and the reproducibility was 100%.

2.3 | Statistical analysis

Genotype frequencies of the polymorphisms and the demographic variables between WT cases and controls were compared using the chi-squared test. Deviation from Hardy-Weinberg equilibrium (HWE) in control subjects was examined by a goodness-of-fit chi-squared test for each polymorphism. The associations between the selected polymorphisms and WT risk were measured by calculating the odds ratios (ORs) and 95% confidence intervals (CIs), using unconditional univariate and multivariate logistic regression analyses. Stratified analysis was performed for subgroups by age, gender and clinical stages. All statistical tests were two-sided. $P < .05$ was considered as statistically significant. All statistical analyses were performed using SAS software (Version 9.1; SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Demographic characteristics

As shown in Table 1, we enrolled 145 patients with an average age of 26.17 ± 21.48 months and 531 cancer-free subjects with an

TABLE 1 Frequency distribution of selected variables for Wilms tumor cases and cancer-free controls

Variables	Cases (N=145)		Controls (N=531)		P^a
	No.	%	No.	%	
Age range, month	1-132		0.07-156		.725
Mean $\pm$ SD	26.17 $\pm$ 21.48		29.73 $\pm$ 24.86		
≤ 18	66	45.52	233	43.88	
> 18	79	54.48	298	56.12	
Gender					.956
Female	64	44.14	233	43.88	
Male	81	55.86	298	56.12	
Clinical stages					
I	4	2.76			
II	49	33.79			
III	50	34.48			
IV	33	22.76			
NA	9	6.21			

SD, standard deviation; NA, not available.

^aTwo-sided χ^2 test for distributions between Wilms tumor cases and cancer-free controls.

average age of 29.73 ± 24.86 months. There were no significant differences in age ($P=.725$) and gender ($P=.956$) between the case and control groups. According to the NWTs-5 criteria,²² 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. Additionally, the stage of 9 (6.21%) cases was unable to be determined.

3.2 | Associations between *LIN28B* gene polymorphisms and WT susceptibility

The genotype frequencies of the four polymorphisms in WT cases and cancer-free controls were shown in Table 2. Of all the participants, 142 cases and 530 controls were successfully genotyped. The genotype frequencies of all the four selected polymorphisms in

TABLE 2 Genotype frequencies of *LIN28B* gene polymorphisms and Wilms tumor susceptibility

Genotype	Cases (N=142)	Controls (N=530)	P ^a	Crude OR (95% CI)	P	Adjusted OR (95% CI) ^b	P ^b
rs314276 (HWE=0.756)							
CC	77 (54.23)	254 (47.92)		1.00		1.00	
CA	45 (31.69)	228 (43.02)		0.65 (0.43-0.98)	.040	0.65 (0.43-0.98)	.042
AA	20 (14.08)	48 (9.06)		1.37 (0.77-2.46)	.283	1.36 (0.76-2.43)	.304
Additive			.027	0.97 (0.73-1.29)	.840	0.97 (0.73-1.28)	.824
Dominant	65 (45.77)	276 (52.08)	.182	0.78 (0.54-1.13)	.183	0.78 (0.54-1.13)	.185
Recessive	122 (85.92)	482 (90.94)	.089	1.65 (0.94-2.88)	.080	1.62 (0.93-2.84)	.090
rs221634 (HWE=0.228)							
AA	53 (37.32)	163 (30.75)		1.00		1.00	
AT	65 (45.77)	274 (51.70)		0.73 (0.48-1.10)	.133	0.73 (0.48-1.10)	.127
TT	24 (16.90)	93 (17.55)		0.79 (0.46-1.37)	.406	0.80 (0.46-1.39)	.429
Additive			.321	0.86 (0.65-1.13)	.268	0.86 (0.66-1.13)	.280
Dominant	89 (62.68)	367 (69.25)	.140	0.75 (0.51-1.10)	.137	0.74 (0.51-1.10)	.136
Recessive	118 (83.10)	437 (82.45)	.857	0.96 (0.58-1.57)	.858	0.97 (0.59-1.59)	.902
rs221635 (HWE=0.527)							
TT	91 (64.08)	345 (65.09)		1.00		1.00	
TC	44 (30.99)	168 (31.70)		0.99 (0.66-1.49)	.973	1.01 (0.67-1.52)	.964
CC	7 (4.93)	17 (3.21)		1.56 (0.63-3.88)	.337	1.55 (0.62-3.85)	.349
Additive			.640	1.09 (0.79-1.52)	.603	1.10 (0.79-1.53)	.570
Dominant	51 (35.92)	185 (34.91)	.823	1.05 (0.71-1.54)	.822	1.06 (0.72-1.56)	.771
Recessive	135 (95.07)	513 (96.79)	.345	1.57 (0.64-3.85)	.329	1.54 (0.63-3.80)	.347
rs9404590 (HWE=0.786)							
TT	81 (57.04)	286 (53.96)		1.00		1.00	
TG	50 (35.21)	205 (38.68)		0.86 (0.58-1.28)	.459	0.87 (0.58-1.29)	.475
GG	11 (7.75)	39 (7.36)		1.00 (0.49-2.03)	.991	0.99 (0.49-2.03)	.981
Additive			.750	0.93 (0.69-1.26)	.652	0.94 (0.70-1.26)	.657
Dominant	61 (42.96)	244 (46.04)	.471	0.88 (0.61-1.28)	.513	0.89 (0.61-1.29)	.525
Recessive	131 (92.25)	491 (92.64)	.876	1.06 (0.53-2.12)	.876	1.05 (0.52-2.11)	.891
Combined effect of risk genotypes							
0	82 (57.75)	357 (67.36)		1.00		1.00	
1	39 (27.46)	113 (21.32)		1.50 (0.97-2.32)	.067	1.50 (0.97-2.32)	.069
2	11 (7.75)	26 (4.91)		1.84 (0.88-3.88)	.108	1.84 (0.88-3.90)	.107
3	10 (7.04)	34 (6.42)		1.28 (0.61-2.70)	.515	1.27 (0.60-2.67)	.535
Trend			.173	1.19 (0.97-1.45)	.096	1.18 (0.97-1.45)	.102
0	82 (57.75)	357 (67.36)		1.00		1.00	
1-3	60 (42.25)	173 (43.64)	.034	1.51 (1.03-2.21)	.033	1.51 (1.03-2.20)	.035

OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

^a χ^2 test for genotype distributions between Wilms tumor patients and controls.

^bAdjusted for age and gender.

Bold values indicate the 95% CI excluded 1 or P less than 0.05.

controls were consistent with HWE. We observed that carriers of the rs314276 CA genotype had decreased WT risk at an adjusted OR of 0.65 (95% CI=0.43-0.98, $P=.042$) when compared with carriers of the CC genotype. Moreover, no significant association or trend was observed for the rest three polymorphisms. While the risk genotypes were combined, we did not find the subjects with 1, 2, and 3 risk genotypes have a significantly increased WT risk. Thus, we found that subjects carrying 1-3 risk genotypes had an increased WT risk (adjusted OR=1.51, 95% CI=1.03-2.20, $P=.035$) when compared with the non-carriers.

3.3 | Stratified analysis

We next evaluate the association of the rs314276 C>A and combined risk genotypes with WT susceptibility in the stratified analysis, as shown in Table 3. No significant association with the rs314276 C>A polymorphism was observed in subgroups defined by age, gender, and clinical stages. We only found a borderline significantly increased risk associated with the rs314276 AA variant genotype in females (adjusted OR=2.06, 95% CI=0.91-4.70, $P=.085$). As to the risk genotypes, the association between the 1-3 risk genotypes and WT risk was statistically significant in children 18 months of age or younger (adjusted OR=1.81, 95% CI=1.03-3.18, $P=.041$) and females (adjusted OR=2.08, 95% CI=1.18-3.68, $P=.012$).

4 | DISCUSSION

In our current hospital-based case-control study, we explored the association between *LIN28B* gene polymorphisms and WT risk, and found the rs314276 C>A polymorphism was associated with WT susceptibility in a Southern Chinese population.

The *LIN28B* gene is located on chromosome 6q21, consisting of seven exons.²³ This gene was first identified by Guo et al.²⁴ in human hepatocellular carcinoma. They found the 3'UTR of the *LIN28B* gene contains complementary sites to let-7 microRNA and *LIN28B* gene may be negatively regulated by let-7.²⁴ *LIN28B* protein was found to be elevated in colon tumors, and its overexpression correlated with decreased patient survival and increased tumor recurrence.^{25,26} Further studies also found that the overexpression of *LIN28B* was associated with poor prognosis in head and neck cancer,²⁷ gastric cancer,²⁸ oral squamous cell carcinoma patients,^{29,30} breast cancer,³¹ ovarian cancer,³² and neuroblastoma.³³⁻³⁵ In cases of pediatric cancers, such as germ cell tumors, neuroblastoma and WT, *LIN28B* appears to prolong the embryonic patterns of tissue growth.¹² Urbach et al.¹² demonstrated that *LIN28B* overexpression occurred in up to 30% of human Wilms tumors, suggesting implication of the Lin28/Let-7 pathway in kidney development and tumorigenesis.¹²

Interestingly, later studies illustrated that the *LIN28B* gene rs314276 C>A polymorphism, included in our current study, is associated with timing of puberty,³⁶ BMI variation across the life course,³⁷ finger-length ratio,³⁸ growth in height from birth to adulthood,³⁹ central precocious puberty and early puberty in girls,⁴⁰ as well as childhood obesity and age at menarche.⁴¹ Furthermore, this polymorphism

TABLE 3 Stratification analysis of risk genotypes with Wilms tumor susceptibility

Variables	rs314276 (cases/controls)		OR		P ^a	Adjusted OR ^a		P	Adjusted OR ^a		P ^a
	CC/CA	AA	CC/CA	AA		(95% CI)	(95% CI)		(95% CI)	(95% CI)	
Age, month											
≤18	54/213	10/20	1.97 (0.87-4.46)		.103	1.97 (0.87-4.46)		.103	1.82 (1.03-3.19)		.041
>18	68/269	10/28	1.41 (0.66-3.05)		.379	1.42 (0.66-3.07)		.317	1.32 (0.79-2.21)		.294
Gender											
Females	54/213	10/19	2.07 (0.91-4.72)		.082	2.06 (0.91-4.70)		.085	2.08 (1.18-3.68)		.012
Males	68/269	10/29	1.36 (0.63-2.94)		.427	1.33 (0.62-2.87)		.532	1.16 (0.70-1.94)		.567
Clinical stages											
I+II	46/482	5/48	1.09 (0.41-2.88)		.860	1.03 (0.39-2.74)		.219	1.46 (0.81-2.65)		.211
III+IV	70/482	12/48	1.72 (0.87-3.40)		.118	1.72 (0.87-3.40)		.075	1.53 (0.95-2.46)		.079

OR, odds ratio; CI, confidence interval.

^aAdjusted for age and gender.

Bold values indicate the 95% CI excluded 1 or P less than 0.05.

was also shown to be associated with the risk and survival of cancer, such as colon cancer,^{25,42} epithelial ovarian cancer,^{43,44} non-small cell lung cancer,⁴⁵ oral cavity cancer,⁴⁶ and neuroblastoma.³³

Considering the importance of *LIN28B* gene in carcinogenesis, we chose four potentially functional polymorphisms in this gene to study their association with WT susceptibility. To the best of our knowledge, this is the first study to demonstrate the association between *LIN28B* gene polymorphism and WT risk in Chinese children, although several previous articles have reported on its association with other types of cancer. Of the four investigated polymorphisms, we found that only the rs314276 CA genotype was associated with a decreased WT risk. We also found that carriers of the 1-3 risk genotypes were at significantly increased WT risk when compared to the non-carriers. The rs314276 C>A polymorphism is located in the intron region of *LIN28B* gene, it is a transcription factor binding sites as predicted by SNPinfo (<http://snpinfio.niehs.nih.gov/>) software and may alter the gene expression then lead to the alteration of WT risk. In the subgroup analysis, the 1-3 risk genotype carriers were more prominent for the children with age no more than 18 months and females which may be ascribed to the genetic susceptibility as well as limited sample size. In summary, these results indicated that the *LIN28B* gene rs314276 C>A polymorphism may contribute to WT susceptibility in Southern Chinese children. Failure to find the association for the other three polymorphisms in this study may be ascribed to the limited sample size as well as the weak effects of these low-penetrant polymorphisms. Further functional studies are needed to investigate the specific mechanisms by which this polymorphism modifies cancer susceptibility.

Although this is the first study to investigate the association of *LIN28B* gene polymorphisms with WT risk, several limitations should be noted. First, only 145 cases and 531 controls were included in this study. The comparatively small sample size, especially for the cases, may reduce the power in statistical analysis. Second, selection bias may exist. All the subjects were enrolled only from our hospital and restricted to a Chinese Han population, thus these finding may not be directly generalized into other populations. Third, we only included four potentially functional polymorphisms in the study. In the future, all functional polymorphisms in *LIN28B* gene should be investigated in different ethnicities, which may yield a meaningful conclusion. Finally, selection and information bias might be unavoidable because of the nature of retrospective study design. Also, some important information was unavailable in our study, such as the paternal exposures, living environment, and dietary intake for the included children, which limited our ability to perform gene-environmental interactions analysis in WT susceptibility.

In conclusion, we found that the *LIN28B* gene rs314276 C>A polymorphism may associate with a decreased Wilms tumor susceptibility in Southern Chinese children. However, well-designed prospective studies with larger sample size involving different ethnicities, as well as further functional studies are needed to confirm our findings.

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