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Association between *TRMT61B* gene polymorphism and Wilms tumor susceptibility in Chinese children

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Abstract

Background Wilms tumor is among the most common pediatric malignant tumors. Although m^{1}A modification influences the structure and function of RNA and participates in tumorigenesis, the relationship between m^{1}A methyltransferase *TRMT61B* gene polymorphisms and Wilms tumor susceptibility is unclear.

Methods We examined the relationship between *TRMT61B* gene rs4563180 G > C polymorphism (detected by TaqMan probe method) in 414 children with Wilms tumor and 1199 healthy controls. The relationship between the genotype of each sublayer and the risk of Wilms tumor was studied by stratified analysis. The GTEx database was used to analyze the influence of *TRMT61B* rs4563180 G > C polymorphism on mRNA expression.

Results The *TRMT61B* gene polymorphism significantly reduced the susceptibility to Wilms tumor (GC vs. GG: adjusted odds ratio [AOR] = 0.72, 95% confidence interval [CI] = 0.56–0.93, *P* = 0.012; GC/CC vs. GG: AOR = 0.76, 95% CI = 0.60–0.96, *P* = 0.021). GC/CC genotype had a protective effect in boys and children with stage III tumors compared with rs4563180 GG genotype. Additionally, the C allele was significantly associated with decreased mRNA expression of *TRMT61B* gene compared with rs4563180G allele in cultured fibroblasts (*P* = 3.3e − 80), EBV-transformed lymphocytes (*P* = 9.5e − 14), and whole blood (*P* = 6.0e − 12).

Conclusions Our results confirm that *TRMT61B* gene is associated with the development of Wilms tumors, but its underlying mechanism requires further exploration.

Keywords *TRMT61B*, Wilms tumor, Susceptibility, Polymorphism, m^{1}A

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Background

As a malignant renal tumor, Wilms tumor is among the most common solid tumors in children [1]. The incidence of Wilms tumor is approximately 3.3 per million, accounting for 8% of childhood tumors and >90% of pediatric renal malignancies [2]. Since the 1970s, the 5-year survival rate of children with Wilms tumor has reached 90% with the diversification of treatment methods and the application of comprehensive treatment [3]. However, the prognosis and quality of life for high-risk children remain poor, especially in those with bilateral disease, recurrence, and adverse histological and molecular characteristics [4]. Additionally, approximately 24% of Wilms tumor survivors are at significantly increased risk of other diseases, including primary and secondary tumors, kidney failure, pulmonary interstitial fibrosis, kyphosis, infertility, and heart disease [5].

In recent years, the issue of RNA modification has received considerable critical attention. Furthermore, its role in regulating cell differentiation, cell signaling pathways, and cell metabolism has been certified [6]. Thus far, research discovered more than 170 RNA modifications. Of these, RNA methylation, including N1-methyladenosine (m^1A), N3-methylcytosine (m^3C), N5-methylcytosine (m^5C), N6-methyladenosine (m^6A) and N7-methylguanosine (m^7G), is the most abundant modification in human cells. m^1A modification can block Watson-Crick base pairing by adding a methyl group and a positive charge to the N1 position of adenosine, consequently changing the secondary structure of RNA and protein-RNA interactions and hindering cDNA synthesis and translation [7, 8]. m^1A originates mainly from the 5' UTR, particularly near the start codon or first exon-exon junction [9], and can be found in tRNA, rRNA, mRNA, and mitochondrial RNA. m^1A modification is regulated by effector proteins, including methyltransferase (TRMT6, TRMT10C, TRMT61A, TRMT61B, BMT2, and RRP8), demethylase (FTO, ALKBH1, and ALKBH3), and RNA binding protein (YTHDC1 and YTHDF1-3), but a systematic understanding of these m^1A-modified regulators in tumorigenesis is still in its infancy [10]. Previous studies showed that m^1A modification can influence various cellular processes, including RNA structural stability, folding, RNA-protein interaction, cell viability, self-renewal, cell proliferation, and cell death [11]. Meng X et al. found that upregulated mRNA is usually accompanied by cumulative m^1A modification, proving that m^1A modification has a positive effect on gene expression. Furthermore, the alteration of m^1A modification can improve translation efficiency; specifically, m^1A hypermethylated transcript increases mRNA expression, while m^1A hypomethylated transcript does not upregulate mRNA level [12]. m^1A modification can affect ribosome biogenesis in rRNA; however, it can promote correct folding and structural stability in tRNA [13].

Currently, an increasing number of single-nucleotide polymorphisms (SNPs) are related to Wilms tumor susceptibility. For instance, Zhuo Z et al. found that *METTL14* gene SNPs were risk markers in pediatric Wilms tumor [14]. Zhu J et al. found that *hOGG1* rs1052133, *FEN1* rs174538, and rs4246215 polymorphisms might have potential protective effects against Wilms tumor [15]. Yu Y et al. found that mutant G of rs11788747 in *RECK* is associated with Wilms tumor risk [16]. In previous studies, we detected 10 SNPs of *RAN*, *RANBP2*, *NMYC*, *TP53*, and *miR34b/c* genes in 183 Wilms tumor patients and 603 healthy controls and found that rs7132224 A>G polymorphism of *RAN* gene significantly increased the risk of Wilms tumor, while rs57961569 G>A polymorphism of *NMYC* gene significantly reduced the risk [17–19]. Moreover, m^6A demethylase *ALKBH5* gene rs1378602 AG/AA genotype was associated with a significantly reduced risk of Wilms tumor in children with stage I disease, and carriers of protective genotypes had a lower risk of Wilms tumor in subgroups aged>18 months [20]. Since m^1A modifications have a stronger effect on RNA structure and function than m^6A, we have a reason to consider that m^1A-related regulatory genes are associated with Wilms tumor susceptibility. Studies have shown that *TRM61B* plays an important role in highly aggressive glioblastoma, gastric cancer and other tumors [21, 22]. Accordingly, we examined the genotype of *TRMT61B* gene in 406 children with Wilms tumor and 1198 healthy controls among the recruited 414 children with Wilms tumor and 1199 healthy controls, attempting to investigate the relationship between rs4563180 polymorphism and the risk of Wilms tumor. The results demonstrated that *TRMT61B* rs4563180 G>C could significantly reduce the risk of Wilms tumor and was correlated with its mRNA and protein expression levels. Our results highlight the importance of this m^1A regulatory gene in tumorigenesis.

Methods

Study subjects

In this hospital-based epidemiological study, we recruited 414 patients and 1199 controls from Guangzhou Women and Children's Medical Center. The case group (414 subjects) comprised newly diagnosed patients with Wilms tumor confirmed by histopathology or cytology, no history of other malignancy, and no prior chemoradiotherapy. The control group (1199 subjects) consisted of healthy controls who had no tumors or hereditary diseases and received health examinations. None of the subjects were related by blood. Demographic characteristics such as gender, age, ethnicity, and residence were strictly matched between the groups (Table S1). This

study was approved by the Ethics Committee of the Guangzhou Women and Children's Medical Center, and informed consent was obtained from subjects' parents or guardians.

SNP selection

We confirmed that rs4563180 G > C polymorphism is a potential functional SNP in *TRMT61B* gene based on standard criteria. Then, predicting SNP function through the online tool SNPinfo (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html), the result showed that rs4563180 G > C polymorphism is located in transcription factor binding sites, meaning that the SNP might participate in the regulation of *TRMT61B* transcription [23, 24]. Linkage unbalance analysis (LDlink software, https://ldlink.nih.gov/) was performed for the selected SNPs with $R^2 > 0.8$. All SNPs in Chinese had MAF ≥ 0.05.

Genotyping

We applied the TaqMan probe method to genotyping using Applied Biosystems 7900 real-time PCR system [25, 26]. A 5-μL reaction system was prepared with upstream and downstream primers + 2 MGB probes, and the 5' end of the probes was labeled FAM/VIC for wild-type/mutant base identification. We set up 8 negative controls for each well plate to ensure the accuracy of gene sequencing. Additionally, we randomly selected about 10% of the samples for repeated detection to ensure the reliability of the results.

Statistical analysis

Hardy-Weinberg balance test, T-test, χ^2 test, Logistic regression, and other statistical methods were used to analyze mRNA expression differences between different genotypes, as well as differences in demographic characteristics, tumor pathological classification, clinical stage, and genotype between the groups, and compare the frequency distribution of different genotypes in children with Wilms tumor and healthy controls. We used univariate analysis and multivariate logistic regression analysis to obtain the odds ratio (OR) and 95% confidence interval (CI) of each genotype. Moreover, the relationship between the genotype of each sublayer and the risk of Wilms tumor was studied by stratified analysis. GTEx database (https://www.gtexportal.org/home/) was used to analyze the influence of selected *TRMT61B* polymorphisms on mRNA expression. A $P < 0.05$ indicated a significant statistical difference.

Result

Association study

As shown in Table 1, rs4563180 G > C polymorphism significantly reduced the risk of Wilms tumor (GC vs. GG: adjusted OR = 0.72, 95% CI = 0.56–0.93, $P = 0.012$; GC/CC vs. GG: AOR = 0.76, 95% CI = 0.60–0.96, $P = 0.021$).

Stratified analysis

As shown in Table 2, the protective effect of GC/CC genotypes was more predominant in boys (adjusted OR = 0.71, 95% CI = 0.51–0.98, $P = 0.039$) and children with stage III disease (adjusted OR = 0.43, 95% CI = 0.26–0.72, $P = 0.001$) compared to the rs4563180 GG genotype.

Expression quantitative trait locus analyses

The rs4563180 genotypes had significant differences in gene expression (Fig. 1). Compared with the rs4563180 G allele, the C allele was significantly associated with decreased *TRMT61B* gene mRNA expression in cultured fibroblasts ($P = 3.3e-80$), EBV-transformed lymphocytes ($P = 9.5e-14$), and whole blood ($P = 6.0e-12$).

Discussion

Wilms tumor is among the most common pediatric malignant tumors, still carrying poor prognosis in high-risk children. This study aimed to investigate the association between *TRMT61B* gene polymorphism and Wilms tumor genetic susceptibility. We found that rs4563180G > C could significantly reduce the risk of

Table 1 Association between TRMT61B rs4563180 G > C polymorphism and Wilms tumor susceptibility

Genotype	Cases (*N* = 406)	Controls (*N* = 1198)	*P*[a]	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)[b]	*P*[b]
rs4563180 (HWE = 0.788)							
GG	273 (67.24)	729 (60.85)		1.00		1.00	
GC	111 (27.34)	409 (34.14)		**0.73 (0.56–0.93)**	**0.012**	**0.72 (0.56–0.93)**	**0.012**
CC	22 (5.42)	60 (5.01)		0.98 (0.59–1.63)	0.935	0.97 (0.59–1.62)	0.915
Additive			0.077	0.84 (0.69–1.02)	0.078	0.84 (0.69–1.02)	0.074
Dominant	133 (32.76)	469 (39.15)	0.022	**0.76 (0.60–0.96)**	**0.022**	**0.76 (0.60–0.96)**	**0.021**
GG/GC	384 (94.58)	1138 (94.99)		1.00		1.00	
CC	22 (5.42)	60 (5.01)	0.746	1.09 (0.66–1.80)	0.746	1.08 (0.65–1.79)	0.763

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

[a] χ^2 test for genotype distributions between Wilms tumor patients and cancer-free controls

[b] Adjusted for age and sex

Table 2 Stratify analysis of TRMT61B rs4563180 G > C polymorphism with Wilms tumor susceptibility

Variables	rs4563180 (case/control)		Crude OR	*P*	Adjusted OR [a]	*P*[a]
	GG	GC/CC	(95% CI)		(95% CI)	
Age, month						
≤ 18	92/277	48/188	0.77 (0.52–1.14)	0.192	0.78 (0.53–1.15)	0.209
> 18	181/452	85/281	0.76 (0.56–1.02)	0.065	0.77 (0.57–1.03)	0.080
Sex						
Females	126/322	64/199	0.82 (0.58–1.17)	0.271	0.82 (0.58–1.17)	0.273
Males	147/407	69/270	**0.71 (0.51–0.98)**	**0.037**	**0.71 (0.51–0.98)**	**0.039**
Clinical stages						
I	91/729	46/469	0.79 (0.54–1.14)	0.205	0.77 (0.53–1.12)	0.178
II	70/729	45/469	1.00 (0.68–1.48)	0.997	0.99 (0.67–1.47)	0.975
III	73/729	20/469	**0.43 (0.26–0.71)**	**0.001**	**0.43 (0.26–0.72)**	**0.001**
IV	27/729	18/469	1.04 (0.57–1.90)	0.908	1.05 (0.57–1.93)	0.880

OR, odds ratio; CI, confidence interval

[a] Adjusted for age and sex, omitting the corresponding variable

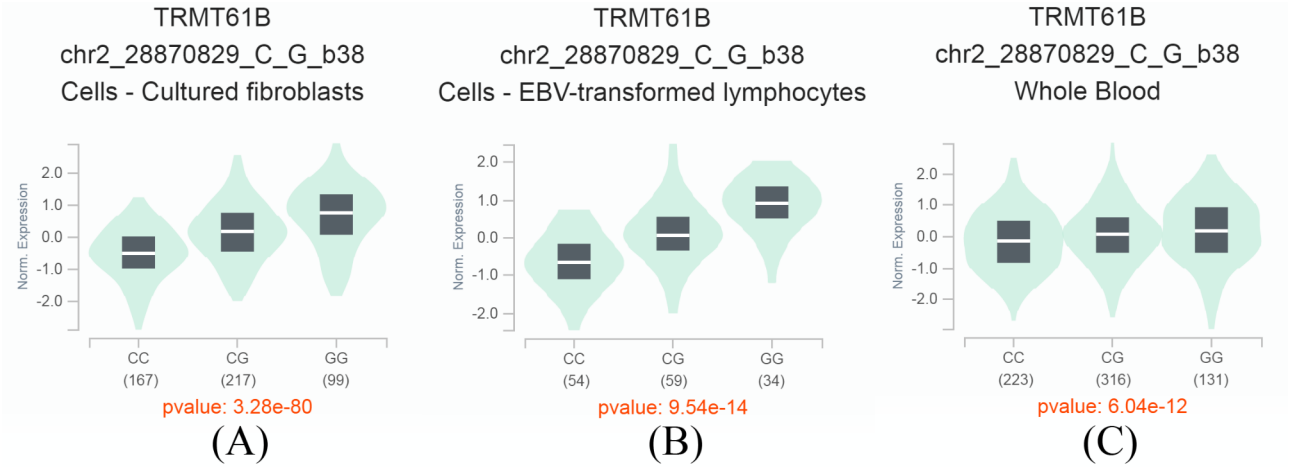

Fig. 1 eQTL analysis showed the influence of *TRMT61B* gene rs4563180 G > C on surrounding gene expression. In cultured fibroblasts (**A**), EBV-transformed lymphocytes (**B**), and whole blood (**C**), the C allele was significantly associated with decreased mRNA expression of *TRMT61B* gene compared with the rs4563180G allele

Wilms tumor. The result might provide us with new ideas for improving the diagnosis, treatment, and prognosis of Wilms tumor.

Previously published studies identified that RNA methylation has a close relationship with immune response, tumor cell metastasis, and proliferation; thus, RNA methylation–related proteins become potential tumor therapeutic targets [27]. Abnormal mutations in the genome of m^1A regulators can influence transcription and translation, leading to abnormal cell proliferation and tumor growth. Studies suggested that m^1A regulators, including *TRMT6*, *TRMT61A*, and *ALKBH3*, promote tumorigenesis in gastrointestinal cancer [28, 29], hepatocellular carcinoma [28], glioma [29], prostate cancer [30, 31], and colorectal cancer [32]. In ovarian and breast cancer, *ALKBH3* increases CSF-1 mRNA through m^1A modification, thereby enhancing translation and cancer cell aggressiveness [33]. *ALKBH3* can also facilitate the invasiveness of cancer cells by destroying tRNA [34]. In hepatocellular carcinoma, *TRMT6/TRMT61A* stimulates cholesterol synthesis by upregulating a subgroup of m1A-tRNA and promotes carcinogenesis [35].

m^1A methylation depends on the *TRMT6/TRMT61A* methyltransferase complex [36]. Moreover, *TRMT10C* and *TRMT61B* participate in m^1A methylation [37, 38]. Research showed that *TRM6/TRM61* mRNA expression is significantly upregulated in highly invasive glioblastoma [29]. In the prognostic model based on *TRMT61B* of holistic methylation, *TRMT61B* gene expression might indicate poor clinical prognosis in patients with gastric cancer [26]. However, we did not find data between m^1A-modified methyltransferase and Wilms tumor susceptibility. Compared with existing studies, our latest results indicated that changes in polymorphism in the potential functional SNP of *TRMT61B* gene could significantly reduce the risk of Wilms tumors (GC vs. GG: adjusted odds ratio [AOR] = 0.72, 95% confidence interval [CI] = 0.56–0.93, $P = 0.012$; GC/CC vs. GG: AOR = 0.76,

95% CI = 0.60–0.96, $P = 0.021$). GC/CC genotype had a protective effect in boys and children with stage III tumors compared with rs4563180 GG genotype. Furthermore, a stratified analysis demonstrated significant protective effects in boys and children with stage III stage disease. Similarly, Li L et al. demonstrated the protective role of *TRMT61B* gene in renal clear cell carcinoma [39]. Our findings highlight the importance of m^1A regulators in tumorigenesis. Therefore, *TRMT61B* is hitherto the m^1A methyltransferase gene associated with Wilms tumor.

However, there were some limitations in this study. First, the sample size was small, affecting the accuracy of statistical analysis. Second, experimental subjects were restricted to Chinese children, and the experimental results are not applicable to other regions. Finally, the specific mechanism by which *TRMT61B* gene reduces the risk of Wilms tumor remains unclear, necessitating further research.

Conclusions

In summary, we showed that *TRMT61B* gene rs4563180G > C significantly reduced the risk of Wilms tumor, bringing new directions in diagnosis and treatment of Wilms tumor.

Abbreviations

m^1A	N1-methyladenosine
m^3C	N3-methylcytosine
m^5C	N5-methylcytosine
m^6A	N6-methyladenosine
m^7G	N7-methylguanosine
SNP	Single-nucleotide polymorphism
OR	Odds ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13670-7.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

All authors contributed significantly to this work. X.H., X.W., H.Z., J.Z., J.C., S.L., J.H., and J.R. performed the research study and collected the samples and clinical data; X.H., C.D., and J.H. analyzed the data and prepared all the Tables and Figures; X.H., W.T and J.L. wrote the paper; J.H., and J.R. conceptualized and designed the research study and performed data management, review and editing.

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Data availability

All the data are available upon request from the correspondence authors (Jing He or Jichen Ruan).

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (ethical approval no: 202016601). This study was conducted according to the guidelines of the Declaration of Helsinki, and informed consent was acquired from the subjects' parents or guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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