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ORIGINAL ARTICLE

H19 gene polymorphisms and Wilms tumor risk in Chinese children: a four-center case-control study

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Abstract

Background: Wilms tumor is the most common pediatric renal cancer. However, genetic bases behind Wilms tumor remain largely unknown. *H19* is a critical maternally imprinted gene. Previous studies indicated that single nucleotide polymorphisms (SNPs) in the *H19* can modify the risk of several human malignancies. Epigenetic errors at the *H19* locus lead to biallelic silencing in Wilms tumors. Genetic variations in the *H19* may be related to Wilms tumor susceptibility.

Methods: We conducted a four-center study to investigate whether *H19* SNP was a predisposing factor to Wilms tumor. Three polymorphisms in the *H19* (rs2839698 G > A, rs3024270 C > G, rs217727 G > A) were genotyped in 355 cases and 1070 cancer-free controls, using Taqman method. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the associations.

Results: We found that all of these three polymorphisms were significantly associated with Wilms tumor risk alterations. The rs2839698 G > A polymorphism (AG vs. GG: adjusted OR = 0.74, 95% CI = 0.57–0.96, $p = 0.024$; AA vs. GG: adjusted OR = 1.52, 95% CI = 1.05–2.22, $p = 0.027$), the rs3024270 C > G polymorphism (CG vs. CC: adjusted OR = 0.61, 95% CI = 0.46–0.81, $p = 0.0007$; and the rs217727 polymorphism (AG vs. GG: adjusted OR = 0.76, 95% CI = 0.58–0.99, $p = 0.035$). The Carriers of 1, 2, and 1–2 risk genotypes were inclined to develop Wilms tumor compared with those without risk genotype (adjusted OR = 1.36, 95% CI = 1.02–1.80, $p = 0.037$; adjusted OR = 1.84, 95% CI = 1.27–2.67, $p = 0.001$; adjusted OR = 1.50, 95% CI = 1.17–1.92, $p = 0.002$, respectively). The stratified analysis further revealed that rs2839698 AA, rs217727 AA, and 1–2 risk genotypes could strongly increase Wilms tumor risk among children above 18 months of age, males, and with clinical stage I+II disease.

Abbreviations: CI, confidence interval; DMR, differentially methylated region; HWE, Hardy–Weinberg equilibrium; LD, linkage disequilibrium; lncRNA, long noncoding RNA; OR, odds ratio; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism..

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Conclusion: Our findings indicate that genetic variations in the *H19* may confer Wilms tumor risk.

KEYWORDS
H19, polymorphism, susceptibility, Wilms tumor

1 | INTRODUCTION

Wilms tumor, also known as nephroblastoma, is derived from the pluripotent embryonic kidney precursor. It is the most common renal malignancy in children, accounting for 85% of pediatric renal tumors (Birch & Breslow, 1995; Rivera & Haber, 2005; Vujanic & Sandstedt, 2010)Children are usually diagnosed ages 2–3 years and the male to female distribution is comparable. The incidence varying by race, a slight female predominance outside of Eastern Asia. (Cunningham et al., 2020) The prevalence of Wilms tumor is similar in black and white children (Breslow et al., 1994), but is around half in East Asian children, about three per million (Fukuzawa & Reeve, 2007). In China, the frequency of Wilms tumor is around 3.3 per million, ranking the fifth in the incidence of malignant tumors in children aged 0 to 4 years (Bao et al., 2013). Besides, about 1%–3% of Wilms tumor have a family history, probably due to rare germline mutations and incomplete expressiveness (Chu et al., 2010). Environmental factors and immigration factors seem not to play a prominent role in etiology (Birch & Breslow, 1995; Bunin & Meadows, 1993; Fukuzawa & Reeve, 2007). The survival rate of Wilms tumor is more than 90% after excluding some high-risk cases with anaplastic histology, bilateral lesions, and recurrent diseases (Dome et al., 2015). However, up to 25% of survivors reported severe chronic health problems (van Waas et al., 2012). Moreover, late diagnosis and high recurrence rates in patients are reported in underdeveloped regions (Phelps et al., 2018), based on the difficulty of stratification of increasingly refined tumor subtypes and the high cost of chemoradiotherapy for high-risk tumors (Dome et al., 2015). Therefore, to improve the outcomes, it is of great significance to enhance prevention and early diagnosis by developing accurate biomarkers to identify high-risk individuals.

As a critical maternally imprinted gene, the *H19* was discovered successively in different laboratories in the 1980 s. This gene located on chromosome 11p15.5 in humans is composed of five exons and four introns (Gabory et al., 2010). The expression of *H19* is highly increased in many embryos and decreased after birth (Lustig-Yariv et al., 1997). More and more evidence indicates that the *H19* is essential for human tumor growth from different biological processes (Si et al., 2019). Studies have shown that the *H19* was upregulated in lung cancer, gastric cancer, colon cancer, retinoblastoma, thyroid cancer, and breast cancer (Dai et al., 2019; Gan et al., 2019; Mahmoudian-Sani et al., 2019; Qi et al., 2019; Si et al., 2019; Zheng et al., 2019). However, the upregulated expression of the *H19* can inhibit pituitary tumor cell proliferation *in vitro* and *in vivo* (Wu et al., 2018). *H19* expression decreased in most hepatoblastomas (Ge et al., 2019). The epigenetic errors at the *H19* site in early embryonic development may result in the silencing of the double-alleles in Wilms tumor, thereby affecting the imprinting of parental alleles (Frevel et al., 1999). Matthew K Iyer et al. found many lncRNAs overlapping disease-associated single nucleotide polymorphisms (SNPs) (Iyer et al., 2015). Previous genomics

studies have demonstrated that SNPs in several genes are associated with the risk of Wilms tumor (Fu et al., 2018; Zhu, Fu, et al., 2018; Zhu, Jia, et al., 2018). It has been reported that *H19* rs2839698 G > A, rs3024270 C > G or rs217727 G > A polymorphism is not associated with neuroblastoma susceptibility in the whole study population, while in stratified analysis, girls with rs3024270 GG genotype had an increased risk of neuroblastoma (Hu et al., 2019). To date, no publication has been reported on the association between *H19* polymorphisms and Wilms tumor susceptibility. In this study, we scrutinized the association of several *H19* SNPs (rs2839698, rs3024270, and rs217727) and Wilms tumor risks based on a four-center study of Chinese children.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This study was approved by the ethics committee of each participating hospital.

2.2 | Study subjects

The cases were enrolled in this project according to previously reported criteria (Fu et al., 2019; Liu et al., 2019; Zhuo et al., 2019). In brief, 355 Wilms tumor cases and 1,070 healthy controls were included in this study (Table S1). The 355 cases were from four medical centers (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). All the control groups were healthy children selected from the same four regions whose age and gender were effectively matched to the patients as cases during the same period. Patients' age, gender, and clinical stages were collected by trained medical staff. We conducted this study following the approval of the Institutional Review Board of the participating hospitals. All the participants' parents provided signed informed consent before the examination.

2.3 | Polymorphism analysis

Each subject donated about 2 mL of peripheral blood for DNA extraction using a TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd.). We used the dbSNP database (https://www.ncbi.nlm.nih.gov/snp/), SNPinfo software (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html) and LDlink (https://ldlink.nci.nih.gov/) to select candidate SNPs. SNPs were limited to noncoding regions including 2000 base pairs of *H19* upstream and downstream [3' untranslated regions (UTRs), 5' UTRs and introns]; SNPs were predicted as potentially functional variations by the SNPinfo software; the minor allele frequencies (MAFs) of SNPs in the Chinese population should not be less than 5%; and the selected SNPs displayed (R^2<0.8) linkage disequilibrium (LD). Three SNPs (rs2839698 G > A, rs3024270 C > G, rs217727 G > A) in *H19* met the described criteria and chosen for genotyping by ABI Taqman probe (Applied Biosystems,) (Hu et al., 2019). The rs2839698 G > A and rs3024270 C > G are located in the transcription factor binding sites. We genotyped the gene polymorphisms using Taqman real-time PCR (He et al., 2012; He et al., 2016). The randomized and blinded process method was adopted while genotyping all samples. Approximately, 10% random selection samples were re-genotyped, and the genotype concordance rate was 100%.

2.4 | Statistical analysis

Departures from Hardy–Weinberg equilibrium (HWE) for the selected SNPs in controls were evaluated using a goodness-of-fit χ^2 test. Allele frequencies and demographic variables between the two groups were assessed by the χ^2 test. Risk associations between genotypes and Wilms tumor were determined from a logistic regression analysis. The ORs, 95% CIs, and the corresponding *P* value for each SNP was calculated with adjustment for age and gender. All statistical calculations were implemented with the utilization of SAS software version 9.4 (SAS Institute). Two-sided statistical tests were employed in this study. The significance threshold was defined as $p < 0.05$.

3 | RESULTS

3.1 | Associations between *H19* gene polymorphisms and Wilms tumor susceptibility

The detailed characteristics of all the subjects were shown in Table S1. A total of 355 patients and 1068 healthy controls were successfully genotyped. The genotype frequencies of the three selected *H19* polymorphisms and their associations with Wilms tumor susceptibility were presented in Table 1. We observed the genotype frequency distributions of the selected *H19* polymorphisms were no significant deviation with the HWE ($p = 0.245$ for rs2839698 G > A, $p = 0.138$ for rs3024270 C > G, $p = 0.992$ for rs217727 G > A polymorphism) in controls. In single-locus analysis, we observed that all three polymorphisms were significantly associated with Wilms tumor risk individually. The SNPs selected decreased

TABLE 1 Associations between *H19* polymorphisms and Wilms tumor risk.

Genotype	Cases (N = 355)	Controls (N = 1,068)	p^a	Crude OR (95% CI)	p	Adjusted OR (95% CI) [b]	p^b
rs2839698 (HWE = 0.245)							
GG	174 (49.01)	488 (45.69)		1.00		1.00	
AG	127 (35.77)	480 (44.94)		**0.74 (0.57–0.96)**	**0.025**	**0.74 (0.57–0.96)**	**0.024**
AA	54 (15.21)	100 (9.36)		**1.52 (1.04–2.20)**	**0.029**	**1.52 (1.05–2.22)**	**0.027**
Additive			0.0008	1.06 (0.89–1.27)	0.537	1.06 (0.89–1.27)	0.530
Dominant	181 (50.99)	580 (54.31)	0.277	0.88 (0.69–1.11)	0.277	0.88 (0.69–1.11)	0.275
Recessive	301 (84.79)	968 (90.64)	0.002	**1.74 (1.22–2.48)**	**0.002**	**1.75 (1.23–2.50)**	**0.002**
G	475 (66.90)	1,456 (68.16)		1.00		1.00	
A	235 (33.10)	680 (31.84)	0.532	1.06 (0.89–1.27)	0.532	1.06 (0.89–1.27)	0.526
rs3024270 (HWE = 0.138)							
CC	120 (33.80)	290 (27.15)		1.00		1.00	
CG	141 (39.72)	556 (52.06)		**0.61 (0.46–0.81)**	**0.0007**	**0.61 (0.46–0.81)**	**0.0007**
GG	94 (26.48)	222 (20.79)		1.02 (0.74–1.41)	0.888	1.03 (0.75–1.42)	0.861
Additive			0.0003	0.98 (0.83–1.16)	0.826	0.98 (0.83–1.17)	0.852
Dominant	235 (66.20)	778 (72.85)	0.017	**0.73 (0.56–0.95)**	**0.017**	**0.73 (0.57–0.95)**	**0.018**
Recessive	261 (73.52)	846 (79.21)	0.025	**1.37 (1.04–1.81)**	**0.026**	**1.38 (1.05–1.82)**	**0.023**
C	381 (53.66)	1,136 (53.18)	1.00		1.00		
G	329 (46.34)	1,000 (46.82)	0.825	0.98 (0.83–1.16)	0.825	0.98 (0.83–1.17)	0.850
rs217727 (HWE = 0.992)							
GG	177 (49.86)	486 (45.51)		1.00		1.00	
AG	130 (36.62)	469 (43.91)		**0.76 (0.59–0.99)**	**0.039**	**0.76 (0.58–0.99)**	**0.035**
AA	48 (13.52)	113 (10.58)		1.17 (0.80–1.70)	0.426	1.17 (0.80–1.71)	0.421
Additive			0.039	0.97 (0.81–1.16)	0.733	0.97 (0.81–1.16)	0.719
Dominat	178 (50.14)	582 (54.49)	0.154	0.84 (0.66–1.07)	0.155	0.84 (0.66–1.06)	0.144
Recessive	307 (86.48)	955 (89.42)	0.130	1.32 (0.92–1.90)	0.131	1.33 (0.93–1.91)	0.124
G	484 (68.17)	1,441 (67.46)		1.00		1.00	
A	226 (31.83)	695 (32.54)	0.728	0.97 (0.81–1.16)	0.728	0.97 (0.81–1.16)	0.714
Combined effect of risk genotypes[c]							
0	211 (59.44)	732 (68.54)		1.00		1.00	
1	92 (25.92)	237 (22.19)		**1.35 (1.01–1.79)**	**0.041**	**1.36 (1.02–1.80)**	**0.037**
2	52 (14.65)	99 (9.27)		**1.82 (1.26–2.64)**	**0.001**	**1.84 (1.27–2.67)**	**0.001**

(Continues)

TABLE 1 (Continued)

Genotype	Cases (N = 355)	Controls (N = 1,068)	p^a	Crude OR (95% CI)	p	Adjusted OR (95% CI) [b]	p^b
Trend			0.002	**1.35 (1.14–1.60)**	**0.0005**	**1.36 (1.15–1.61)**	**0.0004**
0	211 (59.44)	732 (68.54)		1.00		1.00	
1–2	144 (40.56)	336 (31.46)	0.002	**1.49 (1.16–1.91)**	**0.002**	**1.50 (1.17–1.92)**	**0.002**

Significance of bold values are the p values less than 0.05 or the 95% CIs excluded 1.

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

[b] Adjusted for age and gender.

[c] Risk genotypes were carriers with rs2839698 AA, rs3024270 GG and rs217727 AA genotypes.

the risk of Wilms tumor in the heterozygous state while increased the risk in the homozygous state. Specifically, the risk estimates for the these SNPs were as follows: the rs2839698 G > A polymorphism (AG vs. GG: adjusted OR = 0.74, 95% CI = 0.57–0.96, $p = 0.024$; AA vs. GG: adjusted OR = 1.52, 95% CI = 1.05–2.22, $p = 0.027$; AA vs. GG/AG: adjusted OR = 1.75, 95% CI = 1.23–2.50, $p = 0.002$), the rs3024270 C > G polymorphism (CG vs. CC: adjusted OR = 0.61, 95% CI = 0.46–0.81, $p = 0.0007$; CG/GG vs. CC: adjusted OR = 0.73, 95% CI = 0.57–0.95, $p = 0.018$; GG vs. CC/CG: adjusted OR = 1.38, 95% CI = 1.05–1.82, $p = 0.023$), and the rs217727 polymorphism (AG vs. GG: adjusted OR = 0.76, 95% CI = 0.58–0.99, $p = 0.035$).

While analyzing the combined effect of risk genotypes, we found that subjects carrying 1 or 2 risk genotypes had a significantly increased Wilms tumor risk when compared with those without risk genotypes (adjusted OR = 1.36, 95% CI = 1.02–1.80, $p = 0.041$; and adjusted OR = 1.84, 95% CI = 1.27–2.67, $p = 0.001$). Moreover, we found that subjects with 1–2 risk genotypes were significantly more likely to develop Wilms tumor than subjects carrying no risk genotypes (adjusted OR = 1.50, 95% CI = 1.17–1.92, $p = 0.002$).

3.2 | Stratification analysis

We then performed a stratified analysis to explore how age, gender, and clinical stages influence the association between selected polymorphisms and Wilms tumor susceptibility (Table 2). Compared to the rs2839698 GG/AG genotype, the risk effects of AA genotype were more predominant in children above 18 months of age (adjusted OR = 1.73; 95% CI = 1.09–2.74, $p = 0.020$), and those with clinical stage I+II disease (adjusted OR = 1.83, 95% CI = 1.20–2.79, $p = 0.005$). There is no difference in risk with respect to patient gender, the female (adjusted OR = 1.94, 95% CI = 1.11–3.39, $p = 0.021$), male (adjusted OR = 1.63, 95% CI = 1.02–2.58, $p = 0.040$). Consistently, with the rs217727 GG/AG genotype as reference, AA genotype was associated with an increased risk of Wilms tumor for children above 18 months of age (adjusted OR = 1.65; 95% CI = 1.06–2.58, $p = 0.027$), male (adjusted OR = 1.60, 95% CI = 1.01–2.54, $p = 0.047$), clinical stage I + II cases (adjusted OR = 1.60, 95% CI = 1.05–2.44, $p = 0.029$). However, no association was observed between rs3024270 and Wilms tumor susceptibility in subgroups defined by age, gender, and clinical stages.

We also interrogated the cumulative effects of these SNPs on Wilms tumor risk in the stratified analysis. We found that the presence of 1–2 risk genotypes was significantly associated with the risk of Wilms tumor in children above 18 months of age (adjusted OR = 1.66; 95% CI = 1.21–2.27, $p = 0.002$), male (adjusted OR = 1.59, 95% CI = 1.14–2.21, $p = 0.006$),

TABLE 2 Stratification analysis for association between *H19* genotypes and Wilms tumor susceptibility.

Variables	rs2839698 (case/control)		Adjusted OR[a] (95% CI)	p[a]	rs3024270 (case/control)		Adjusted OR[a] (95% CI)	p[a]	rs217727 (case/control)		Adjusted OR[a] (95% CI)	p[a]	Risk genotypes (case/control)		Adjusted OR[a] (95% CI)	p[a]
	GG/AG	AA			CC/CG	GG			GG/AG	AA			0	1–2		
Age, month																
≤18	104/382	21/43	1.76 (0.99–3.10)	0.052	92/335	33/90	1.32 (0.84–2.10)	0.233	112/375	13/50	0.85 (0.45–1.63)	0.629	77/284	48/141	1.24 (0.82–1.87)	0.315
>18	197/586	33/57	**1.73 (1.09–2.74)**	**0.020**	169/511	61/132	1.41 (0.99–2.01)	0.054	195/580	35/63	**1.65 (1.06–2.58)**	**0.027**	134/448	96/195	**1.66 (1.21–2.27)**	**0.002**
Gender																
Female	140/412	23/35	**1.94 (1.11–3.39)**	**0.021**	121/361	42/86	1.46 (0.96–2.23)	0.080	146/400	17/47	0.99 (0.55–1.79)	0.982	103/314	60/133	1.38 (0.95–2.01)	0.096
Male	161/556	31/65	**1.63 (1.02–2.58)**	**0.040**	140/485	52/136	1.32 (0.91–1.91)	0.144	161/555	31/66	**1.60 (1.01–2.54)**	**0.047**	108/418	84/203	**1.59 (1.14–2.21)**	**0.006**
Clinical stage																
I+II	117/968	34/100	**1.83 (1.20–2.79)**	**0.005**	156/846	55/222	1.35 (0.95–1.89)	0.091	178/955	33/113	**1.60 (1.05–2.44)**	**0.029**	121/732	90/336	**1.64 (1.21–2.22)**	**0.002**
III+IV	108/968	18/100	1.66 (0.96–2.85)	0.069	93/846	33/222	1.36 (0.89–2.07)	0.161	115/955	11/113	0.81 (0.42–1.55)	0.523	82/732	44/336	1.17 (0.79–1.73)	0.42

Significance of bold values are the p values less than 0.05 or the 95% CIs excluded 1.

[a] Adjusted for age and gender, omitting the corresponding stratify factor.

and clinical stage I+II patients (adjusted OR = 1.64, 95% CI = 1.21–2.22, $p = 0.002$) when compared with those of 0 risk genotype.

4 | DISCUSSION

In the current hospital-based case-control study, we demonstrated the association of three *H19* polymorphisms with Wilms tumor susceptibility. This article was the first report indicating that *H19* SNPs were related to Wilms tumor risk.

The genetic changes that underpin Wilms tumor are diverse, many studies have defined cancer genes that harbor likely driver mutations (Treger et al., 2019). *H19* is found in an imprinted region of chromosome 11, contains five exons and four small introns, and the three SNPs we studied rs2839698, rs217727, and rs3024270 located in exon 1, exon 5, and intron, respectively (Harati-Sadegh et al., 2020). DNA methylation influences gene expression and protein levels through epigenetic modification, thereby promoting the development of various diseases (Okamoto et al., 1997). Differentially methylated regions (DMRs) are generally considered CpG rich, usually are associated with the genetic or epigenetic modifications. The *H19* DMR located upstream of the transcription initiation site regulates its gene activity (Yang et al., 2020). It is well known that hypermethylation of *H19* DMR, lead to the expression of biallelic imprinted insulin-like growth factor 2 (IGF2), which is an important step in Wilms tumorigenesis (Gao et al., 2014). A recent literature showed that hypermethylation of the *H19* locus occurred in premalignant kidney cells, revealed the driving factors of Wilms tumor (Coorens et al., 2019). The genotype-specific methylation changes at the *H19* imprinting control region (ICR) in assisted reproductive technology derived placentas is associated with the polymorphism rs10732516 (Marjonen et al., 2018). This may suggest that the effect of *H19* risk SNPs on DNA methylation in Wilms tumor, and then, affect the development of the tumor.

Noncoding RNAs are known to play central roles in the dynamic control of transcriptional and gene expression (Scacalossi et al., 2019). LncRNAs contribute to the pathogenesis of various cancers by participating in the control of cell cycle, proliferation, differentiation, and apoptosis (Do & Kim, 2018; Fatica & Bozzoni, 2014). So far, 10 polymorphisms in *H19* have been identified as predisposing factors to various cancer types, among which the rs217727 has been most frequently studied, followed by rs2839698 (Hashemi et al., 2019). *H19* plays an essential role in the tumor progression of breast cancer (Si et al., 2019), bladder cancer (Luo et al., 2013), gastric cancer (Gan et al., 2019), and other tumors (Ren et al., 2018; Yoshimura et al., 2018; Zheng et al., 2019), other than that, mutations in the *H19* coding sequence are also closely related to tumors, despite unknown regulatory mechanisms (Gabory et al., 2010; Wang et al., 2015). The

following evidence suggests that SNPs may affect the expression and function of *H19*. The rs2839698 polymorphism may influence the folding structures of lncRNA *H19* and change the target microRNAs of lncRNA *H19*, thereby increasing the risk of colorectal cancer (Li et al., 2016), this is consistent with our conclusion that heterozygous genotypes may reduce the risk of Wilms tumor. And the rs2839698 SNP has been predicted to affect hepatocellular cancer risk and prognosis, the polymorphism could contribute more functions than the environmental factors in the ever-smoking subgroup. (Yang et al., 2018) Verhaegh et al. found that the folding structures of rs217727 and rs2839698 of lncRNA *H19* were different under TT and CC genotypes, and both the T and C genotype of them had a significantly decreased risk of bladder cancer (Verhaegh et al., 2008), our results complemented the effect of polymorphic genotypes on tumors. What is more, the rs217727 CT+TT genotype was associated with a lower risk of breast cancer in women who were pregnant more than twice (Xia et al., 2016), the heterozygote genotype also can reduce the risk of Wilms tumor according to our data. Patients with gastric adenocarcinoma treated by surgery alone who carried the rs2839698 GA genotype achieved significantly longer median disease-free survival time. Li et al. provided that invasive bladder cancer in carrying rs3024270 CC genotype maybe have a good prognosis. (Li & Niu, 2019; Wang et al., 2018) Inversely, there is also evidence that polymorphisms (rs217727 G > A, rs2839698 G > A, and rs3741219 A > G) in *H19* are not related to prognosis. (Biedermann, 2020).

The above results indicated that *H19* encoding the SNP altering the biological characteristics of lncRNA *H19* and the occurrence and development of tumors. The lncRNA *H19* could be a potential diagnostic and prognostic marker in the development of tumors (Qi & Du, 2013), and the different genotypes of SNPs might facilitate an individualized diagnosis of cancer.

Although *H19* is the first imprinted noncoding transcript to be recognized and is one of the most abundant and conserved transcripts in mammalian development, its physiological function is still unclear. Previous investigations have revealed its expression is tightly linked with fetal tumor tissue differentiation. (Ariel et al., 1997) Up to now, this oncogenic fetal lncRNA has been verified to be involved in the pathogenesis of different human cancers. Increasing evidence implicated that lncRNAs can be directly regulated by miRNAs, there is a pan-cancer analysis shows that *H19* and its intragenic miRNA miR-675 tend to positively correlated in multiple cancers. (Tan et al., 2019).Tsang *et al*. demonstrated that *H19*-derived miR-675, exerted their functions by directly targeting on retinoblastoma protein, and then, regulated colorectal cancer (Tsang et al., 2010). Keniry et al., (2012) discovered that the mechanisms of processing and function of miR-675 in embryonic and extraembryonic cell lines are likely to be relevant to fetal growth and cancer syndromes, it is possible that the genotype at this SNP site influences the transcription of miR-675, which in turn affects some of its target genes. Considering that one of the three SNPs, rs2839698, is located 800 bp upstream of miR-675, we, therefore, speculate the influence of rs2839689 may change the structure of *H19* at the miRNA binding sites and affect the stability, ultimately influence their interaction function. Further studies are needed to explore the specific mechanism. In contrast, no such genotype-phenotype correlation was observed for the other SNPs. Although the rs217727 C > T polymorphism and the rs3024270 C > G polymorphism did not affect H19 mRNA expression levels, mutation may alter the translational efficiency, which may ultimately influence the function of *H19*. Based on previous evidence, *H19* DMR imprinting center mutations leading to Wilms tumorigenesis (Scott et al., 2008).

In stratified analysis, Wilms tumor risk of rs2839698 variant AA genotype was more evident in subgroups of age above 18 months and clinical stage I+II cases. The same genotype is also associated with an increased risk of gastrointestinal cancer (Hashemi et al., 2019). Similar results were obtained in rs217727 AA except in gender consideration, only males. In addition, previous stratified analysis of rs217727 C > T showed both dominant and recessive effects associated with increased risk of oral squamous cell carcinoma and lung cancer (Hashemi et al., 2019). Our results further revealed the critical influence of G and A genotype in *H19* rs217727. In line with our observations, the study has revealed that the carriers of rs217727 AA genotype had a significantly increased risk of bladder cancer in young male patients (Hua et al., 2016). Studies demonstrated T variant of rs217727 was strongly associated with an increased risk of coronary artery disease and gastric cancer (Gao et al., 2015; Yang et al., 2015). These facts may partially explain the apparent imbalance of the analyzed SNPs. We did not find any association between the rs3024270 genotype and Wilms tumor in stratified analysis.

There are potential limitations of the current study: (a) the relatively small sample size and lacking participants from different ethnic groups, (b) the consideration of only three polymorphisms without potential function, and (c) unknown living environmental factors on.

5 | CONCLUSION

We verified that the rs2839698 G > A, rs3024270 C > G, rs217727 G > A polymorphisms were significantly associated with the risk of Wilms tumor. Further stratified data showed that older children, early clinical stage and gender were risk factors. These results reveal the intricacy of *H19* functions and the dual role of *H19* polymorphisms in the development of Wilms tumor. Thus, the results of our study should be verified in studies with larger samples from different ethnicities.

6 | ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of the participating hospitals. All the participants' parents provided signed informed consent before the examination.

CONSENT FOR PUBLICATION

Not applicable.

7 | ACKNOWLEDGMENTS

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

WYL, RXH, and MW designed and organized the manuscript. DZ, JHZ, SYZ, YY, JWC, and HXZ collected and analyzed the data. JZ and JH reviewed the papers and revised the manuscript. All the authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data sets during and/or analyzed during the current study available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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