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

Wenya Li
Zhengzhou University First Affiliated Hospital https://orcid.org/0000-0001-6638-8675
Rui-Xi Hua
Sun Yat-sen University First Affiliated Hospital
Mi Wang
Guangzhou Women and Children's Medical Center
Da Zhang
Zhengzhou University First Affiliated Hospital
Jinhong Zhu
Guangzhou Women and Children's Medical Center
Songyang Zhang
Zhengzhou University First Affiliated Hospital
Yang Yang
Zhengzhou University First Affiliated Hospital
Jiwen Cheng
Xi'an Jiaotong University Second Affiliated Hospital
Haixia Zhou
Wenzhou Medical University Second Affiliated Hospital and Yuying Children's hospital
Jiao Zhang (fcczhangj7@zzu.edu.cn)
https://orcid.org/0000-0002-4977-263X
Jing He
Guangzhou Women and Children's Medical Center

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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 nucleotide polymorphisms (SNPs) in the *H19* can modify the risk of several human malignancies. Epigenetic errors at the *H19* locus lead to biallele 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* SNPs 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. 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 male patients above 18 months of age.

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

Background

Wilms tumor, also known as nephroblastoma, is derived from the pluripotent embryonic kidney precursor. Wilms tumor is the most common renal malignancy in children, accounting for 85% of pediatric renal tumors [1-3]. It is characterized by early diagnosis and male predominance worldwide, with incidence varying by race [4]. The prevalence of Wilms tumor is similar in black and white children [5], but is around half in East Asian children, about three per million [4]. 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 [6]. Besides, about 1-3% of Wilms tumor have a family history, probably due to rare germline mutations and incomplete expressiveness [7]. Environmental factors and immigration factors seem not to play a prominent role in etiology [1, 4, 8]. The survival rate of Wilms tumor is more than 90% after excluding some high-risk cases with anaplastic histology, bilateral lesions and recurrent diseases [9]. However, up to 25% of survivors reported severe chronic health problems [10]. Moreover, late diagnosis and high recurrence rates in patients are reported in underdeveloped regions [11], based on the difficulty of stratification of increasingly refined tumor subtypes and the high cost of chemoradiotherapy for high-risk tumors [9]. 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 1980s. This gene located on chromosome 11p15.5 in humans is composed of five exons and four introns [12]. The expression of *HI9* is highly increased in many embryos and decreased after birth [13]. *HI9* gene encodes a long non-coding RNA, which may have tumor-inhibiting functions [14]. More and more evidence indicates that the *H19* gene is essential for human tumor growth from different biological processes [15]. Studies have shown that the *H19* gene was upregulated in lung cancer, gastric cancer, colon cancer, retinoblastoma, thyroid cancer and breast cancer [15-20]. However, the up-regulated expression of the *H19* gene can inhibit pituitary tumor cell proliferation *in vitro* and *in vivo* [21]. Consistently, *H19* gene expression decreased in most hepatoblastomas [22]. Studies have shown that epigenetic errors at the *H19* gene site in early embryonic development may result in the silencing of the double-alleles in Wilms tumor, thereby affecting the imprinting of parental alleles [23]. Matthew K Iyer et al. found many lncRNAs overlapping disease-associated SNPs [24]. Previous genomics studies have demonstrated that SNPs in several genes are associated with the risk of Wilms tumor [25-27]. 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 [28]. To date, no publication has been reported on the association between *H19* gene polymorphisms and Wilms tumor susceptibility. In this study, we scrutinized the association of several *H19* gene SNPs (rs2839698, rs3024270, and rs217727) and Wilms tumor risks based on a four-center study of Chinese children.

Methods

Study subjects

The cases were enrolled in this project according to previously reported criteria [29-31]. In brief, 355 Wilms tumor cases and 1,070 healthy controls were included in this study (**Supplemental Table 1**). 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 selected from the same region as cases during the same period. Patients' age, sex, 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.

Polymorphism analysis

Each subject donated about 2 mL of peripheral blood for DNA extraction using a TIANamp Blood DNA Kit (TianGen Biotech Co. Ltd., Beijing, China). Three *H19* gene polymorphisms (rs2839698 G>A, rs3024270 C>G, rs217727 G>A) were chosen for genotyping by ABI Taqman probe (Applied Biosystems, Foster City, CA) [28]. We genotyped the gene polymorphisms using Taqman real-time PCR [32, 33]. 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%.

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 were calculated with adjustment for age and gender. All statistical calculations were implemented with the utilization of SAS software version 9.4 (SAS Institute, Cary, NC). Two-sided statistical tests were employed in this study. The significance threshold was defined as $P<0.05$.

Results

Associations between *H19* gene polymorphisms and Wilms tumor susceptibility

The detailed characteristics of all the subjects were shown in **Supplementary Table 1**. A total of 355 patients and 1068 healthy controls were successfully genotyped. The genotype frequencies of the three selected *H19* gene polymorphisms and their associations with Wilms tumor susceptibility were presented in **Table 1**.We observed the genotype frequency distributions of the selected *H19* gene polymorphisms were no significant deviation with the Hardy-Weinberg equilibrium (*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. 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).

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

ɛnotype	Cases (N=355)	Controls (N=1068)	P^a	Crude OR (95% CI)	*P*	Adjusted OR (95% CI) [b]	P^b
2839698 (HWE=0.245)							
;G	174 (49.01)	488 (45.69)		1.00		1.00	
.G	127 (35.77)	480 (44.94)		**0.74 (0.57-0.96)**	**0.025**	**0.74 (0.57-0.96)**	**0.024**
.A	54 (15.21)	100 (9.36)		**1.52 (1.04-2.20)**	**0.029**	**1.52 (1.05-2.22)**	**0.027**
.dditive			0.0008	1.06 (0.89-1.27)	0.537	1.06 (0.89-1.27)	0.530
)ominant	181 (50.99)	580 (54.31)	0.277	0.88 (0.69-1.11)	0.277	0.88 (0.69-1.11)	0.275
ɛecessive	301 (84.79)	968 (90.64)	0.002	**1.74 (1.22-2.48)**	**0.002**	**1.75 (1.23-2.50)**	**0.002**
;	475 (66.90)	1456 (68.16)		1.00		1.00	
.	235 (33.10)	680 (31.84)	0.532	1.06 (0.89-1.27)	0.532	1.06 (0.89-1.27)	0.526
3024270 (HWE=0.138)							
:C	120 (33.80)	290 (27.15)		1.00		1.00	
:G	141 (39.72)	556 (52.06)		**0.61 (0.46-0.81)**	**0.0007**	**0.61 (0.46-0.81)**	**0.0007**
;G	94 (26.48)	222 (20.79)		1.02 (0.74-1.41)	0.888	1.03 (0.75-1.42)	0.861
.dditive			0.0003	0.98 (0.83-1.16)	0.826	0.98 (0.83-1.17)	0.852
)ominant	235 (66.20)	778 (72.85)	0.017	**0.73 (0.56-0.95)**	**0.017**	**0.73 (0.57-0.95)**	**0.018**
ɛecessive	261 (73.52)	846 (79.21)	0.025	**1.37 (1.04-1.81)**	**0.026**	**1.38 (1.05-1.82)**	**0.023**
	381 (53.66)	1136 (53.18)		1.00		1.00	
;	329 (46.34)	1000 (46.82)	0.825	0.98 (0.83-1.16)	0.825	0.98 (0.83-1.17)	0.850
217727 (HWE=0.992)							
;G	177 (49.86)	486 (45.51)		1.00		1.00	
.G	130 (36.62)	469 (43.91)		**0.76 (0.59-0.99)**	**0.039**	**0.76 (0.58-0.99)**	**0.035**
.A	48 (13.52)	113 (10.58)		1.17 (0.80-1.70)	0.426	1.17 (0.80-1.71)	0.421
.dditive			0.039	0.97 (0.81-1.16)	0.733	0.97 (0.81-1.16)	0.719
)ominant	178 (50.14)	582 (54.49)	0.154	0.84 (0.66-1.07)	0.155	0.84 (0.66-1.06)	0.144
ɛecessive	307 (86.48)	955 (89.42)	0.130	1.32 (0.92-1.90)	0.131	1.33 (0.93-1.91)	0.124
;	484 (68.17)	1441 (67.46)		1.00		1.00	
.	226 (31.83)	695 (32.54)	0.728	0.97 (0.81-1.16)	0.728	0.97 (0.81-1.16)	0.714
)mbined effect of risk genotypes [c]							
	211 (59.44)	732 (68.54)		1.00		1.00	
	92 (25.92)	237 (22.19)		**1.35 (1.01-1.79)**	**0.041**	**1.36 (1.02-1.80)**	**0.037**
	52 (14.65)	99 (9.27)		**1.82 (1.26-2.64)**	**0.001**	**1.84 (1.27-2.67)**	**0.001**
'rend			0.002	**1.35 (1.14-1.60)**	**0.0005**	**1.36 (1.15-1.61)**	**0.0004**
	211 (59.44)	732 (68.54)		1.00		1.00	
-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**

:^{2} test for genotype distributions between Wilms tumor patients and controls.
ıdjusted for age and gender.
Risk genotypes were carriers with rs2839698 AA, rs3024270 GG and rs217727 AA genotypes.

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).

Stratification analysis

We then performed a stratified analysis to explore how age, gender, and clinical stage 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 was more predominant in children above 18 months of age (adjusted OR=1.73; 95% CI=1.09-2.74, *P*=0.020), 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), and those with clinical stage I+II disease (adjusted OR=1.83, 95% CI=1.20-2.79, *P*=0.005). Consistently, with the rs217727 GG/AG genotype as references, AA genotype carriers 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, sex, 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), 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.

Discussion

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)	0.423

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

In the current hospital-based case-control study, we demonstrated the association of three *H19* gene 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 [34]. *H19* is found in an imprinted region of chromosome 11, contains five exons and four small introns, and the three SNPs rs2839698, rs3024270 and rs217727 located in exon 1, intron and exon 5, respectively [35]. DNA methylation influences gene expression and protein levels through epigenetic modification, thereby promoting the development of various diseases [36]. 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 [37]. It is well known that hypermethylation of *H19* DMR, lead to the expression of biallelic IGF2, which is an important step in Wilms tumorigenesis [38]. A recent literature showed that hypermethylation of the H19 locus occurred in premalignant kidney cells, revealed the driving factors of Wilms tumor [39]. The genotype-specific methylation changes at the *H19* ICR in assisted reproductive technology derived placentas is associated with the polymorphism rs10732516 [40]. It has also been reported hypomethylation status in promoter region of *H19* gene indicated a higher risk of preeclampsia, *H19* mRNA expression was higher in recessive model , but there was no association between mRNA expression and placental *H19* associated polymorphisms [35]. This may suggest that the effect of *H19* risk SNPs on DNA methylation in Wilms tumor.

Non-coding RNAs are known to play central roles in the dynamic control of transcriptional and gene expression [41]. LncRNAs contribute to the pathogenesis of various cancers by participating in the control of cell cycle, proliferation, differentiation, and apoptosis [42, 43]. *H19* gene is the only imprinted gene that can encode lncRNA and play a role in the mRNA level [44]. 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 [45]. *H19* plays an essential role in the tumor progression of breast cancer [15], bladder cancer [46], gastric cancer [17], and other tumors [20, 47, 48], other than that, mutations in the *H19* gene coding sequence are also closely related to tumors, despite unknown regulatory mechanisms [12, 49]. The following evidence suggests that SNPs may affect the expression and function of the *H19* gene. 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 [50]. Verhaegh et al. found that the folding structure of rs217727 and rs2839698 of lncRNA *H19* was different under TT and CC genotypes, and both the T and C genotype of them had a significantly decreased risk of bladder cancer [51]. What's more, the rs217727 CT+TT genotype was associated with a lower risk of breast cancer in women who were pregnant more than twice [52]. The above results indicated that the *H19* gene 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 [53], and the different genotypes of SNPs might facilitate an individualized diagnosis of cancer.

There are other explanations of the relationship between lncRNA *H19* and tumors. The miR675 signal axis plays a vital role in tumorigenesis, which is a microRNA, embedded in the *H19* gene's first exon [54]. Li et al. first demonstrated that miR675 promoted liver carcinogenesis through the cascade of miR675-HP1α-EGR1-*H19*-PKM2 signaling and clearly demonstrated that miR675 overexpression stimulated liver cancer cell growth, vice versa [55]. Wu et al. revealed that lncRNA *H19* promoted laryngeal squamous cell carcinoma (LSCC) progression via miR-148a-3p and DNMT1, indicating that *H19* plays the role of microRNA sponge in promoting tumor development [56]. Another study suggested that the effect of *H19* in GC is mediated by the direct upregulation of ISM1 and the indirect suppression of CALN1 expression via miR-675 [57]. Additionally, functional SNP rs217727 in *H19* is highly likely to be involved in breast cancer development in hormone-signaling pathways [58].

In stratified analysis, Wilms tumor risk of rs2839698 variant AA genotypes was more evident in subgroups of age above 18 months, female, male, and clinical stage I+II cases. The same genotype is also associated with an increased risk of gastrointestinal cancer [45]. Similar results were obtained in rs217727 AA except in gender considerations, only males. In addition, previous data showed that stratified analysis of rs217727 C>T showed both dominant and recessive effects associated with increased risk of oral squamous cell carcinoma (OSCC) and lung cancer [45]. 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 [59]. Studies demonstrated T variant of rs217727 was strongly associated with an increased risk of coronary artery disease (CAD) and gastric cancer (GC) [60, 61]. These facts may partially explain the apparent imbalance of the analyzed SNPs. We did not find any associations between the rs3024270 genotype and Wilms tumor in stratified analysis.

There are potential limitations of the current study: 1) the relatively small sample size and lacking participants from different ethnic groups, 2) the consideration of only three polymorphisms without potential function, and 3) unknown living environmental factors on.

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 tumors. Thus, the results of our study should be verified in studies with larger samples from different ethnicities.

Abbreviations

SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: confidence interval; HWE: Hardy-Weinberg equilibrium; PCR: Polymerase chain reaction; lncRNA: long non-coding RNA

Declarations

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.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WYL、RXH and MW designed and organized the manuscript. DZ, JHZ、SYZ、YY, JWC and HXZ collected and analysed 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.

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ORCID

Jing He, https://orcid.org/0000-0002-1954-2892

Wenya Li, https://orcid.org/0000-0001-6638-8675

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