Original Article

Nucleotide excision repair gene polymorphisms and hepatoblastoma susceptibility in Eastern Chinese children: A five-center case-control study

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Abstract

Objective: Nucleotide excision repair (NER) plays a vital role in maintaining genome stability, and the effect of NER gene polymorphisms on hepatoblastoma susceptibility is still under investigation. This study aimed to evaluate the relationship between NER gene polymorphisms and the risk of hepatoblastoma in Eastern Chinese Han children.

Methods: In this five-center case-control study, we enrolled 966 subjects from East China (193 hepatoblastoma patients and 773 healthy controls). The TaqMan method was used to genotype 19 single nucleotide polymorphisms (SNPs) in NER pathway genes, including *ERCC1*, *XPA*, *XPC*, *XPD*, *XPF*, and *XPG*. Then, multivariate logistic regression analysis was performed, and odds ratios (ORs) and 95% confidence intervals (95% CIs) were utilized to assess the strength of associations.

Results: Three SNPs were related to hepatoblastoma risk. *XPC* rs2229090 and *XPD* rs3810366 significantly contributed to hepatoblastoma risk according to the dominant model (adjusted OR=1.49, 95% CI=1.07−2.08, P=0.019; adjusted OR=1.66, 95% CI=1.12−2.45, P=0.012, respectively). However, *XPD* rs238406 conferred a significantly decreased risk of hepatoblastoma under the dominant model (adjusted OR=0.68, 95% CI=0.49−0.95; P=0.024). Stratified analysis demonstrated that these significant associations were more prominent in certain subgroups. Moreover, there was evidence of functional implications of these significant SNPs suggested by online expression quantitative trait loci (eQTLs) and splicing quantitative trait loci (sQTLs) analysis.

Conclusions: In summary, NER pathway gene polymorphisms (*XPC* rs2229090, *XPD* rs3810366, and *XPD* rs238406) are significantly associated with hepatoblastoma risk, and further research is required to verify these findings.

Keywords: Nucleotide excision repair; polymorphisms; hepatoblastoma; susceptibility

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Introduction

Hepatoblastoma, an embryonal solid tumor, is the most common primary pediatric liver malignancy and accounts for more than 60% of all malignant liver neoplasms (1). Hepatoblastoma mostly occurs prior to age 5 and is more common in males (2,3). Treatment for hepatoblastoma includes surgical resection, chemotherapy, and liver transplantation. Although advances in multimodal therapies have improved survival rates, patients with high-risk hepatoblastoma still have a dismal prognosis, and survivors may suffer from long-term treatment-related complications, including second malignancies and hearing loss (4,5). The etiology of hepatoblastoma has not yet been clarified. Although most cases of hepatoblastoma are sporadic, it is believed that premature birth or low birth weight and inherited syndromes such as Beckwith-Wiedemann syndrome can be risk factors for developing hepatoblastoma (6,7). Hence, a deeper grasp of tumor biology would enable us to make progress in the prevention, treatment, and prognosis of this disease.

Nucleotide excision repair (NER), one of the most important DNA repair mechanisms, can remove diverse bulky DNA lesions formed by radiation, environmental mutagens, or other chemical adducts, such as cyclobutene-pyrimidine dimers (CPDs), 6-4 pyrimidine-pyrimidone photoproducts (6-4PPs), and various aromatic amines (8,9). NER includes two subpathways: transcription-coupled NER (TC-NER) and global genome NER (GG-NER). The two pathways differ only in the step of recognizing DNA lesions (8,10). Increasing evidence has indicated that single nucleotide polymorphisms (SNPs) within NER pathway genes are associated with susceptibility to cancers, such as colorectal cancer (11), neuroblastoma (12), Wilms tumor (13), and ovarian cancer (14).

Our group previously conducted a seven-center case-control study, and to the best of our knowledge, we are the first to provide evidence that NER gene polymorphisms could predispose patients to hepatoblastoma risk in the Chinese pediatric population. However, only one study to date has investigated the role of NER pathway gene SNPs in hepatoblastoma risk, and the results need to be validated in another independent study. Therefore, we performed this five-center case-control study to assess this association in Eastern Chinese Han children.

Materials and methods

Study subjects

A total of 193 patients with hepatoblastoma and 773 healthy controls (*Supplementary Table S1*) were recruited from five hospitals in Jiangsu, Anhui, Fujian, Shandong, and Jiangxi provinces. The recruitment details of the subjects were described in our previous study (15). Written informed consent was obtained from the subjects' parents or legal guardians before this study started. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the Children's Hospital of Nanjing Medical University (No: 202402008-1).

SNP selection and genotyping

Based on the standard criteria described previously, the potentially functional SNPs were selected using the dbSNP database (https://www.ncbi.nlm.nih.gov/snp) and SNPinfo (https://snpinfo.niehs.nih.gov/snpinfo/snpfunc.html) (12,16-18). The minor allele frequencies should be greater than 5% in the Chinese Han population, and no significant linkage disequilibrium (LD) existed among these selected SNPs (R^2<0.8). Total genomic DNA was extracted from paraffin-embedded tissues and peripheral blood samples using a QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA) and a TIANGEN Blood DNA Extraction Kit (TianGen Biotech, Beijing), respectively, according to the manufacturers' protocols. Then, the qualified DNA samples were diluted into 96-well plates. Genotyping was performed by the TaqMan method, as we described previously (19). Four positive controls and four negative controls were included in each 384-well plate. In addition, 10% of the DNA samples were randomly chosen for repeated genotyping, and the results were 100% consistent.

Statistical analysis

Differences in clinical variables between patients and controls were analyzed by two-sided χ^2 tests. The goodness-of-fit χ^2 test was adopted to estimate the Hardy-Weinberg equilibrium (HWE) in the controls. To explore the association between NER gene polymorphisms and hepatoblastoma risk, we used multivariate logistic regression analysis to calculate odds ratios (ORs) and 95%

confidence intervals (95% CIs). Further stratified analysis was conducted by age, sex, and clinical stage. Moreover, we conducted expression quantitative trait locus (eQTL) and splicing quantitative trait locus (sQTL) analyses using the Genotype-Tissue Expression (GTEx) database (https://gtexportal.org/home/) to assess the potential biological effects of the significant SNPs. A two-sided P<0.05 was considered to indicate statistical significance. All the statistical analyses were carried out using SAS software (Version 10.0; SAS Institute Inc., Cary, NC, USA).

Results

Participants' characteristics

The frequency distributions of selected variables of all participants are shown in *Supplementary Table S1*. No significant differences in age (P=0.097) or sex (P=0.730) were observed between the hepatoblastoma patients and controls. Among the patients, 25.39% were classified as clinical stage I, 31.61% as stage II, 20.21% as stage III, 11.40% as stage IV, and 11.40% could not be classified.

NER pathway gene SNPs and hepatoblastoma susceptibility

A total of 193 patients and 773 controls were successfully genotyped. Detailed information on the relationship between polymorphisms in NER pathway genes and hepatoblastoma risk is listed in *Table 1*. Only three SNPs associated with hepatoblastoma risk were detected. *XPC* rs2229090 and *XPD* rs3810366 were significantly related to increased hepatoblastoma risk according to the dominant model (adjusted OR=1.49, 95% CI=1.07–2.08, P=0.019; adjusted OR=1.66, 95% CI=1.12–2.45, P=0.012, respectively), whereas *XPD* rs238406 was significantly related to decreased hepatoblastoma risk (dominant model: adjusted OR=0.68, 95% CI=0.49–0.95, P=0.024).

Stratification analysis

We then conducted stratified analyses for the three significant polymorphisms (*XPC* rs2229090, *XPD*

Table 1 Association between polymorphisms in NER pathway genes and hepatoblastoma risk in Eastern Chinese children

Gene	Polymorphism	n								AOR (95% CI)[a]	P[a]	AOR (95% CI)[b]	P[b]	HWE
		Allele		Cases (N=193)			Controls (N=773)							
		W	M	WW	WM	MM	WW	WM	MM					
ERCC1	rs2298881	C	A	79	73	41	284	342	146	0.85 (0.62–1.18)	0.339	1.15 (0.78–1.69)	0.491	0.019
ERCC1	rs3212986	C	A	88	89	16	368	323	81	1.09 (0.80–1.50)	0.581	0.76 (0.43–1.33)	0.329	0.420
ERCC1	rs11615	G	A	102	78	13	441	291	40	1.20 (0.87–1.65)	0.260	1.29 (0.67–2.47)	0.443	0.367
XPA	rs1800975	T	C	39	107	47	199	383	191	1.39 (0.94–2.05)	0.096	0.99 (0.68–1.43)	0.945	0.803
XPA	rs3176752	G	T	156	35	2	602	160	11	0.82 (0.55–1.23)	0.340	0.70 (0.15–3.18)	0.643	0.921
XPC	rs2228001	A	C	79	92	22	300	369	104	0.91 (0.66–1.26)	0.580	0.82 (0.50–1.34)	0.425	0.572
XPC	rs2228000	C	T	81	93	19	364	319	90	1.24 (0.90–1.71)	0.190	0.84 (0.50–1.41)	0.504	0.119
XPC	rs2607775	C	G	175	17	2	715	56	2	1.28 (0.74–2.23)	0.381	1.84 (0.17–20.39)	0.621	0.420
XPC	rs1870134	G	C	108	72	13	418	307	48	0.92 (0.67–1.27)	0.628	1.06 (0.56–2.01)	0.857	0.398
XPC	rs2229090	G	C	64	103	26	328	331	114	1.49 (1.07–2.08)	0.019	0.90 (0.57–1.43)	0.655	0.044
XPD	rs3810366	G	C	37	116	40	214	370	188	1.66 (1.12–2.45)	0.012	0.81 (0.55–1.20)	0.292	0.262
XPD	rs238406	G	T	72	83	38	224	370	178	0.68 (0.49–0.95)	0.024	0.80 (0.54–1.19)	0.266	0.291
XPD	rs13181	T	G	162	29	2	646	119	7	0.98 (0.64–1.51)	0.937	1.13 (0.23–5.50)	0.883	0.561
XPF	rs2276466	C	G	114	71	8	496	245	31	1.24 (0.90–1.72)	0.188	1.01 (0.45–2.23)	0.988	0.914
XPG	rs2094258	C	T	68	91	31	308	339	126	1.20 (0.86–1.67)	0.275	1.01 (0.66–1.56)	0.958	0.047
XPG	rs751402	C	T	92	74	24	328	371	74	0.78 (0.57–1.08)	0.132	1.34 (0.82–2.20)	0.241	0.034
XPG	rs2296147	T	C	125	56	9	484	261	28	0.86 (0.61–1.20)	0.368	1.31 (0.61–2.83)	0.492	0.321
XPG	rs1047768	T	C	107	69	14	393	325	55	0.80 (0.58–1.10)	0.169	1.02 (0.55–1.87)	0.958	0.270
XPG	rs873601	G	A	63	94	33	218	374	181	0.78 (0.55–1.09)	0.145	0.68 (0.45–1.02)	0.064	0.402

NER, nucleotide excision repair; AOR, adjusted odds ratio; 95% CI, 95% confidence interval; HWE, Hardy-Weinberg equilibrium. [a], adjusted for age and sex for dominant model; [b], adjusted for age and sex for recessive model.

rs3810366, and *XPD* rs238406) by age, sex, and clinical stage (*Table 2*). We found that *XPC* rs2229090 GC/CC had enhanced effects on hepatoblastoma risk in children aged ≥17 months (adjusted OR=1.95, 95% CI=1.18–3.22, P=0.010), females (adjusted OR=1.84, 95% CI=1.07–3.17, P=0.027), and patients with clinical stage I+II (adjusted OR=1.65, 95% CI=1.07–2.54, P=0.022) subgroups. Similarly, *XPD* rs3810366 GC/CC was significantly related to increased hepatoblastoma risk in participants aged <17 months (adjusted OR=1.77, 95% CI=1.04–2.99, P=0.034), males (adjusted OR=2.17, 95% CI=1.26–3.75, P=0.005), and patients with clinical stage I+II disease (adjusted OR=1.78, 95% CI=1.07–2.98, P=0.027). Moreover, *XPD* rs238406 GT/TT was strongly associated with a reduced risk of hepatoblastoma in children at clinical I+II stages (adjusted OR=0.61, 95% CI=0.40–0.92; P=0.020).

Genotype-based mRNA expression analysis

We further explored the biological effects of the three significant SNPs using eQTL and sQTL analyses. The eQTL results showed that the rs2229090 C allele was significantly associated with increased *XPC* mRNA expression in cultured fibroblasts (*Figure 1*). Furthermore, the sQTL results showed that the rs2229090 C allele significantly reduced alternative splicing of *XPC* mRNA in whole blood (*Figure 2A*) and cultured fibroblasts (*Figure 2B*). We also found that the rs3810366 C allele was significantly associated with an increase in *PPP1R13L* mRNA expression in cultured fibroblasts (*Figure 3A*) and a decrease in *ERCC2* mRNA expression in the pancreas (*Figure 3B*), and the rs238406 T allele was significantly associated with a decrease in *PPP1R13L* mRNA expression in cultured fibroblasts (*Figure 3C*) and an increase in *ERCC2* mRNA expression in the pancreas (*Figure 3D*).

Discussion

The NER pathway is an essential mechanism for removing DNA damage induced by both exogenous and endogenous factors (8). Many efforts have previously been made to investigate the role of NER pathway gene polymorphisms in the development of cancer. Here, we found that *XPC* rs2229090, *XPD* rs3810366, and *XPD* rs238406 were significantly related to hepatoblastoma risk by conducting a five-center case-control study, and the association remained significant in stratified analyses.

As a key initiator of the GG-NER pathway, XPC plays an essential role in the recognition of damaged DNA by binding to HR23B to form the XPC-HR23B complex (20,21). *XPC* gene polymorphisms are involved in different types of cancer. A previous study revealed that the *XPC* intron 11 C>A polymorphism could contribute to an increased risk of prostate cancer in a Japanese population

Table 2 Stratification analysis for association of *XPC* and *XPD* genotypes with hepatoblastoma susceptibility in Eastern Chinese children

Variables	*XPC* rs2229090 (case/control) (n)		AOR (95% CI)[a]	P[a]	*XPD* rs3810366 (case/control) (n)		AOR (95% CI)[a]	P[a]	*XPD* rs238406 (case/control) (n)		AOR (95% CI)[a]	P[a]
	GG	GC/CC			GG	GC/CC			GG	GT/TT		
Age (month)												
<17	39/152	66/217	1.19 (0.76–1.86)	0.455	21/113	84/256	1.77 (1.04–2.99)	0.034	38/106	67/263	0.71 (0.45–1.12)	0.143
≥17	25/176	63/228	1.95 (1.18–3.22)	0.010	16/101	72/302	1.49 (0.83–2.69)	0.180	34/118	54/285	0.66 (0.41–1.06)	0.085
Sex												
Female	22/136	56/187	1.84 (1.07–3.17)	0.027	19/88	59/234	1.19 (0.67–2.10)	0.562	29/96	49/226	0.71 (0.42–1.20)	0.199
Male	42/192	73/258	1.30 (0.85–1.99)	0.222	18/126	97/324	2.17 (1.26–3.75)	0.005	43/128	72/322	0.67 (0.43–1.02)	0.063
Clinical stages												
I+II	34/328	76/445	1.65 (1.07–2.54)	0.022	20/214	90/558	1.78 (1.07–2.98)	0.027	44/224	66/548	0.61 (0.40–0.92)	0.020
III+IV	18/328	43/445	1.76 (1.00–3.10)	0.052	13/214	48/558	1.41 (0.75–2.66)	0.289	20/224	41/548	0.84 (0.48–1.47)	0.538

AOR, adjusted odds ratio; 95% CI, 95% confidence interval. [a], adjusted for age and sex, omitting the corresponding stratify factor.

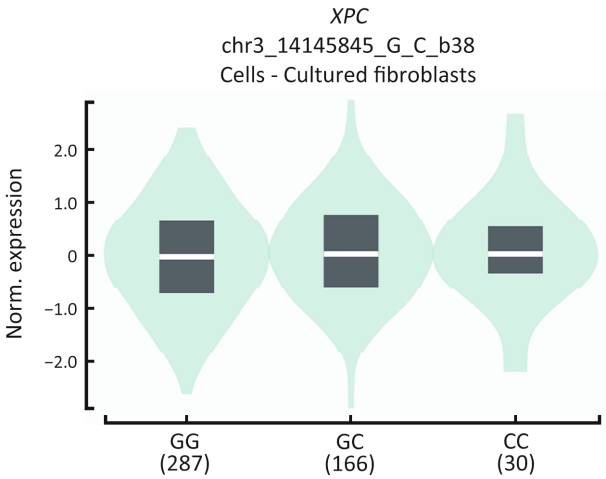

Figure 1 eQTL analysis for *XPC* rs2229090 G>C. The *XPC* rs2229090 C allele was significantly associated with increased *XPC* mRNA expression in cultured fibroblasts (P=1.64e−9). eQTL, expression quantitative trait locus.

(22). In addition, Zhang *et al.* (23) reported that the *XPC* rs2229090 GC/CC genotype could increase the risk of glioma in certain subgroups, while Zheng *et al.* (24) failed to detect any significant contribution of the rs2229090 polymorphism to neuroblastoma risk in Chinese children. *XPD*, also known as *ERCC2*, encodes a DNA helicase (25). XPD is a part of the transcription factor II H complex and participates in the unwinding of DNA, which is one of the main NER steps (26,27). *XPD* polymorphisms have been reported to be linked to the risk of cancer, such as lung cancer (28), cutaneous melanoma (29), and colorectal cancer (30). A recent meta-analysis showed that *XPD* rs238406 was closely linked to skin cancer risk (31). Our previous study revealed that the *XPD* rs3810366 and rs238406 polymorphisms were significantly associated with the risk of neuroblastoma (12) and Wilms tumor (13). However, Yin *et al.* (32) suggested that rs238406 was not associated with breast cancer susceptibility among nonsmoking Chinese individuals. The different roles of these SNPs in different cancer types may be attributed to differences in sample sizes, population sources, and environmental factors. Therefore, it is essential to validate the exact role of NER gene polymorphisms in particular cancer types in specific populations.

In our previous study, significant associations with hepatoblastoma susceptibility were shown for *XPC* rs2607775 and *XPC* rs1870134. Interestingly, the current analysis revealed that *XPC* rs2229090, *XPD* rs3810366, and *XPD* rs238406 were significantly related to hepatoblastoma risk. We speculated that this might be due to differences in geography and environment. However, *XPC* rs2229090 did not exactly obey HWE in controls (HWE=0.044), and replication studies are required to verify these findings. We further performed eQTL and sQTL analyses to explore the possible mechanism by which rs2229090, rs3810366, and rs238406 affect hepatoblastoma risk. The eQTL results showed that the rs2229090 C allele increased the expression of *XPC* mRNA in cultured fibroblasts, and the sQTL revealed that the rs2229090 C allele reduced alternative splicing of *XPC* mRNA in whole blood and cultured fibroblasts. As a DNA repair factor, *XPC* plays an important role in tumorigenesis. Rezvani *et al.* (33) revealed that *XPC* silencing could lead to the tumorigenic transformation of normal keratinocytes. Wang and coworkers also found that the expression of *XPC* was significantly lower in lung adenocarcinoma cancer tissues than in paracancerous tissues and could affect the

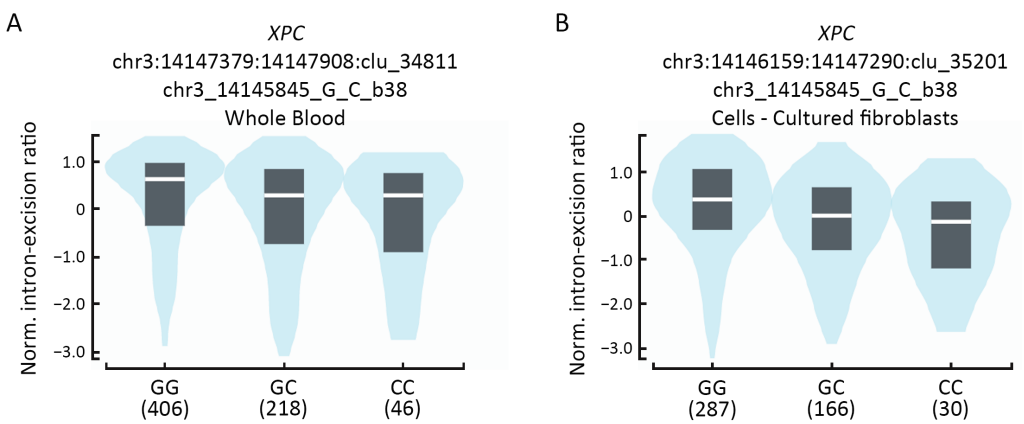

Figure 2 sQTL analysis for *XPC* rs2229090 G>C. The *XPC* rs2229090 C allele significantly reduced alternative splicing of *XPC* mRNA in whole blood (P=4.65e−7) (A) and cultured fibroblasts (P=7.82e−7) (B). sQTL, splicing quantitative trait locus.

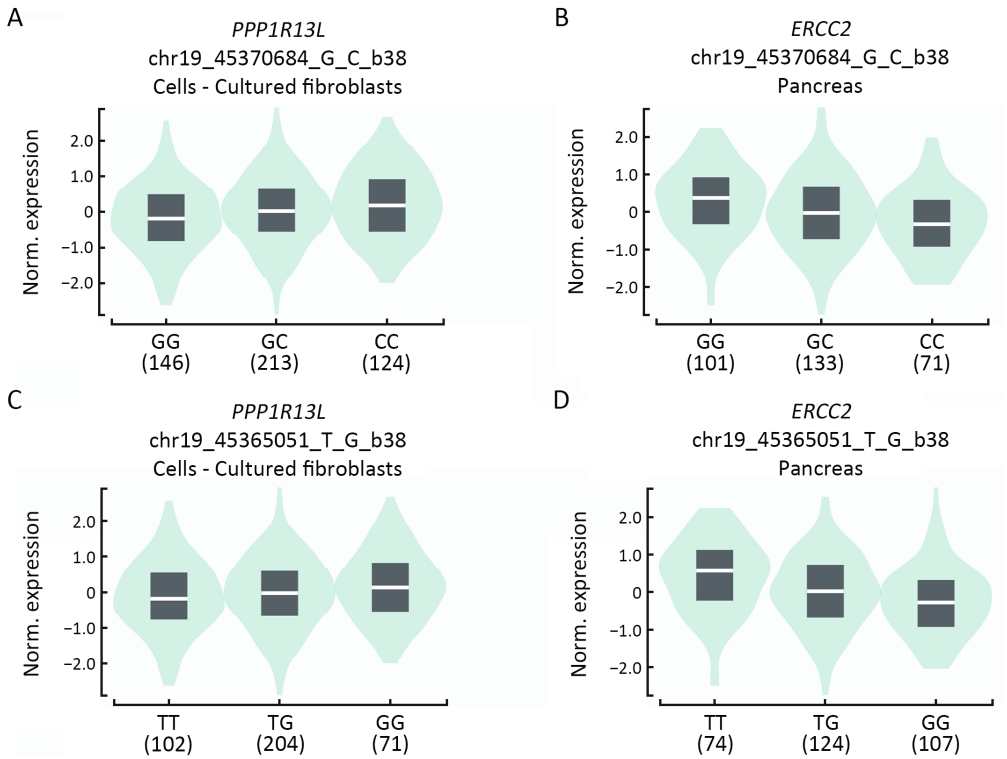

Figure 3 eQTL analysis for *XPD* rs3810366 G>C and *XPD* rs238406 G>T. The *XPD* rs3810366 C allele was significantly associated with increased *PPP1R13L* mRNA expression in cultured fibroblasts (P=2.28e−10) (A) and decreased *ERCC2* mRNA expression in the pancreas (P=1.84e−9) (B). The *XPD* rs238406 T allele was significantly associated with decreased *PPP1R13L* mRNA expression in cultured fibroblasts (P=2.3e−8) (C) and increased *ERCC2* mRNA expression in the pancreas (P=3.65e−13) (D). eQTL, expression quantitative trait locus.

proliferation and migration of lung cancer cells (34). Alternative splicing is a crucial posttranscriptional regulatory mechanism, and splicing repair events have been observed in the onset and progression of cancers, including neuroblastoma (35,36). In addition, Jin *et al.* (37) reported that the rs156697 variant could impact the risk of non-small cell lung cancer by altering *GSTO2* splicing. However, more studies are needed to determine the important role of the *XPC* gene in hepatoblastoma. We also found that the rs3810366 C allele and rs238406 T allele were significantly associated with *PPP1R13L* gene expression levels. PPP1R13L expression is generally believed to be elevated in multiple cancers (38,39). Laska *et al.* (40) provided evidence that increased levels of PPP1R13L could increase tumorigenesis and progression, suggesting that PPP1R13L could function as an oncoprotein. Xue *et al*. (41) also reported that a high expression level of *PPP1R13L* was associated with poor clinical prognosis in lung cancer patients, indicating its potential oncogenic role in lung cancer. These findings suggest that the functional effects of rs2229090, rs3810366, and rs238406 on local or distant genes may influence the risk of hepatoblastoma. However, further experiments are needed to verify our results.

Several limitations should be mentioned in this study. First, the participants involved in this study were all Han Chinese, and the findings may not be applicable to people of other ethnicities. Furthermore, given insufficient sample information, environmental factors were not included. Additionally, false-positive results may occur without rigorous correction, and a larger sample size is needed to validate our results. Finally, the specific mechanism of NER gene polymorphisms in hepatoblastoma susceptibility is unclear, and further biological experiments should be performed to elucidate this mechanism.

Conclusions

We found a significant association between NER pathway gene polymorphisms (*XPC* rs2229090, *XPD* rs3810366, and *XPD* rs238406) and hepatoblastoma susceptibility in Eastern Chinese children. Further replication studies and biological experiments are required to verify these findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Frequency distribution of selected variables in hepatoblastoma patients and cancer-free controls from East China

Variables	n (%)		P[a]
	Cases (N=193)	Controls (N=773)	
Age (month)			0.097
Range	0.03–156.00	0.001–156.00	
$\bar{x}\pm s$	23.95±23.22	27.54±24.10	
<17	105 (54.40)	369 (47.74)	
≥17	88 (45.60)	404 (52.26)	
Sex			0.730
Female	78 (40.41)	323 (41.79)	
Male	115 (59.59)	450 (58.21)	
Clinical stages			–
I	49 (25.39)	–	
II	61 (31.61)	–	
III	39 (20.21)	–	
IV	22 (11.40)	–	
NA	22 (11.40)	–	

NA, not available. [a], two-sided χ^2 test for distributions between hepatoblastoma cases and cancer-free controls.