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Original Article

Genetic variations in base excision repair pathway genes and risk of hepatoblastoma: a seven-center case-control study

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Abstract: Hepatoblastoma is a rare childhood liver cancer without known explicit etiology. Base excision repair (BER) pathway genes have been implicated in the pathophysiology of cancer, yet the role of BER pathway gene single nucleotide polymorphisms (SNPs) on hepatoblastoma risk still awaits to be explored. This study aims to determine whether hepatoblastoma risk be modulated by polymorphisms in the BER pathway genes based on genotyped data from 313 cases and 1446 controls. We applied TaqMan assay to genotype these included samples. We comprehensively genotyped 20 SNPs across six genes of BER, and estimated odds ratio (ORs), 95% confidence intervals (CIs), and *P*-values of the selected SNPs' contribution to the risk of hepatoblastoma using logistic regression models. Only SNP rs293795 in the *hOGG1* gene could significantly enhance hepatoblastoma risk under recessive model (adjusted OR=3.78, 95% CI=1.01-14.17, *P*=0.047). Stratified analysis revealed that rs159153 TC/CC genotype decreased hepatoblastoma risk in male subgroup. Moreover, rs293795 GG and 1-3 risk genotypes could increase hepatoblastoma risk in clinical stages I+II and male subgroups, respectively. False-positive report probability validated the reliability of the significant results. Our findings provide some clues of a potential risk effect of BER pathway gene *hOGG1* SNPs on hepatoblastoma. Further investigation is warranted to confirm these findings and to better elucidate the biological pathways involved.

Keywords: Hepatoblastoma, BER, polymorphism, susceptibility

Introduction

Hepatoblastoma is a rare malignant neoplasm that originated from undifferentiated liver cells during embryonic development [1, 2]. The incidence of hepatoblastoma is about 1/1.5*10^6~1/1.0*10^6, 90% of which occurs under the age of 5 years [3]. Though rare in incidence, hepatoblastoma takes up about 80% of primary liver malignancies in children [4]. Surgery with complete resection is the most effective cure option for hepatoblastoma. However, a large portion of hepatoblastoma children failed to accept this surgery [5, 6]. Preoperative chemotherapy for children with hepatoblastoma can greatly increase the 5-year overall survival rate to 70%~90% [7-9]. Therefore, early screening and timely treatment of hepatoblastoma are particularly important.

Unlike adult hepatocellular carcinoma, there is no significant correlation between hepatoblas-

Table 1. Frequency distribution of selected variables in hepatoblastoma patients and cancer-free controls

Variables	Cases (n=313)		Controls (n=1446)		*P*[a]
	No.	%	No.	%	
Age range, month	0.03-149.97		0.004-156.00		
Mean ± SD	23.75 ± 25.93		25.23 ± 19.38		0.251[b]
<17	168	53.67	642	44.40	
≥17	145	46.33	804	55.60	
Gender					0.983
Female	129	41.21	595	41.15	
Male	184	58.79	851	58.85	
Clinical stages					
I	97	30.99	/	/	
II	63	20.13	/	/	
III	64	20.45	/	/	
IV	27	8.63	/	/	
NA	62	19.81	/	/	

SD, standard deviation, NA, not available. [a]Two-sided χ^2 test for distributions between hepatoblastoma cases and cancer-free controls. [b]T-test for age distribution between hepatoblastoma patients and cancer-free controls.

toma development and hepatitis b virus, chronic hepatitis, or cirrhosis [10, 11]. According to relevant reports, the causes of hepatoblastoma include preterm birth, parental tobacco use, familial adenomatous polyposis, trisomy 18, *FGFR3* mutations, low birth weight, and Beckwith-Wiedemann syndrome [12-17]. However, so far, no clear exposures can lead to the occurrence of hepatoblastoma. In addition, even if parents are exposed to the same environmental factors, only a very small number of offspring eventually develop hepatoblastoma. Increasing evidence suggests that genetic predisposition may play an important role in the occurrence of hepatoblastoma. To date, only a handful of case-control studies have analyzed the effects of single nucleotide polymorphisms (SNPs) on the risk of hepatoblastoma, with sample sizes of less than 100 [18, 19]. Our research group also conducted several epidemiological investigations of hepatoblastoma [20-22]. There is no doubt that more characteristics of genetic variation in hepatoblastoma susceptibility will contribute to understanding the etiology of hepatoblastoma.

The human genome was continuously exposed to exogenous (ionizing radiation chemicals, ultraviolet light) and endogenous (metabolic byproducts, intracellular hydrolysis) DNA damages [23, 24]. If not repaired accurately, DNA damages may cause genomic instability and eventually impact tumor susceptibility [25]. DNA repair systems inherently exist in preserving the integrity of genome [26]. Base excision repair (BER) pathway, a primary DNA repair system, is responsible for repairing base lesions and AP sites [27, 28]. BER pathway generally consists of human 8-oxoguanine DNA glycosylase (hOGG1), poly(ADP) ribose polymerase 1 (PARP1), apurinic/apyrimidinic endonuclease (APE1/APEX1), flap endonuclease 1 (FEN1), DNA ligase III (LIG3), and x-ray repair cross-complementing group 1 (XRCC1). In repairing DNA damage, the BER process may be generally divided into four steps: recognize and excise the damaged base, incise the DNA backbone, fill the nucleotide gap, and seal the remaining gap. Considerable evidence suggests the implication of abnormal expression of BER pathway proteins in multiple diseases including cancers [29]. Many BER pathway gene polymorphisms have been reported to contribute to risk of cancer [30]. Further molecular mechanism analysis showed that SNPs in the BER pathway genes may change protein dynamics, thereby limiting DNA repair ability and ultimately promoting the occurrence and development of cancer [31, 32].

While BER pathway genes work as probably carcinogenic to humans and several epidemiological studies reported associations between these gene polymorphisms and cancers, no available reports were found on the hepatoblastoma. To elucidate these relationships, we perform a multi-center case-control study among children of Chinese ancestry.

Material and methods

Study subjects

The selection of subjects has been described previously [33-35]. Cases with hepatoblastoma were recruited from seven regional hospitals in China. Controls were randomly selected from the hospital visitors and frequency-matched to the cases by age and sex (**Table 1**). Controls were free of hepatoblastoma history and residing in the same region as the cases. All sub-

jects signed their informed consent for agreeing the collection and use of blood samples in clinical research. The study was conducted after obtaining ethical approvals of hospital institutional review board.

Genotyping

We first used dbSNP database for SNPs identification and then used SNPinfo software to further extract those with potential function. A total of 20 SNPs in six BER pathway genes were screened out for analysis [36]. Genomic DNA was extracted from peripheral blood samples following the protocol of QIAamp DNA Blood mini kit (QIAGEN Inc., Valencia, CA). The genotyping was running on a TaqMan platform (Applied Biosystems, Foster City, CA, USA), with details in a previous study [37]. For quality control, we took several measures in genotyping, including: 1) case and control samples were blindly genotyped by technicians, 2) both positive and negative control (water) samples were included in each 384-well plate, and 3) re-genotyping 10% randomly selected samples (100% concordant rate).

Statistical analysis

Clinical variables were analyzed using a Chi-square test (gender) or *t* test (age), as appropriate. To determine the associations between SNPs and hepatoblastoma risk, unconditional logistic regression models were used with adjustment for age and gender. Odds ratios (ORs) and 95% confidence intervals (CIs) generated from the models were applied to quantify the associations. False-positive report probability (FPRP) analysis was performed to assess noteworthy associations. All statistical analyses were carried out with SAS v10.0 (SAS Institute Inc., Cary, NC). All tests for statistical significance used a two-sided alpha of 0.05.

Result

Association between BER pathway gene SNPs and hepatoblastoma risk

Detailed clinical characteristics information of hepatoblastoma cases (n=313) and cancer-free controls (n=1446) was presented in our previous published studies [35, 38]. A successful genotype rate of more than 95% was achieved. Relationships between polymorphisms in BER pathway genes and hepatoblastoma susceptibility are shown in **Table 2**. Specifically, there were 3, 3, 2, 3, 3, and 6 SNPs genotyped in the *PARP1*, *hOGG1*, *FEN1*, *APEX1*, *LIG3*, and *XRCC1* genes, respectively. In the single locus analysis, only one BER gene SNP, *hOGG1* gene rs293795, significantly impacts hepatoblastoma risk under recessive model (adjusted OR=3.78, 95% CI=1.01-14.17, *P*=0.047). No significant effect on risk of hepatoblastoma was observed for the rest of SNPs under dominant and recessive models (**Figures 1**, **2**).

Stratification analysis

We next carried out stratification analysis in the strata of age, gender, and clinical stage (**Table 3**). Regarding SNP rs159153, TC/CC genotype was significantly associated with decreased hepatoblastoma risk in male (adjusted OR=0.60, 95% CI=0.39-0.93, *P*=0.022). Compared with the AA/AG genotype, the rs293795 GG genotype increased hepatoblastoma risk in children with clinical stages I+II tumor (adjusted OR=5.67, 95% CI=1.34-24.05, *P*=0.019). We further set rs1052133 GG, rs159153 CC, and rs293795 AG/GG genotypes as risk genotypes. After combining the risk genotypes, we observed that patients with 1-3 risk genotypes were more likely to develop hepatoblastoma in male (adjusted OR=1.39, 95% CI=1.01-1.92, *P*=0.045).

False-positive report probability (FPRP) analysis

FPRP analysis was conducted to confirm the significant findings (**Table 4**). The threshold for FPRP was preset as 0.2. At the prior probability level of 0.25, findings for male in rs159153 TC/CC vs. TT and male in risk genotypes 1-3 vs. 0 remained noteworthy.

Discussion

The current knowledge of genetic predisposition to hepatoblastoma is incomplete. Challenge remains to fully unearth the full spectrum of hepatoblastoma susceptibility variations. In this study, we set as a pioneer to comprehensively genotype 20 SNPs of the critical genes in BER pathway. We here obtained a significant hepatoblastoma risk-associated SNP rs293795 of the *hOGG1* gene. The findings of

Table 2. Relationship between polymorphisms in base excision repair pathway genes and hepatoblastoma susceptibility in Chinese children

Gene	Polymorphism	Allele		Cases			Controls			AOR (95% CI)[a]	P^a	AOR (95% CI)[b]	P^b
		W	M	WW	WM	MM	WW	WM	MM				
PARP1	rs1136410	A	G	101	157	49	501	665	279	1.08 (0.83-1.40)	0.561	0.79 (0.56-1.10)	0.157
PARP1	rs2666428	T	C	185	111	11	911	492	42	1.12 (0.87-1.45)	0.365	1.22 (0.62-2.41)	0.560
PARP1	rs8679	A	G	272	33	2	1279	162	4	0.99 (0.67-1.46)	0.971	2.38 (0.43-13.07)	0.318
hOGG1	rs1052133	G	C	103	153	55	449	749	247	0.91 (0.70-1.18)	0.484	1.05 (0.76-1.44)	0.789
hOGG1	rs159153	T	C	254	52	5	1139	292	14	0.84 (0.61-1.14)	0.263	1.68 (0.60-4.71)	0.323
hOGG1	rs293795	A	G	273	34	4	1289	151	5	1.14 (0.78-1.67)	0.492	3.78 (1.01-14.17)	0.049
FEN1	rs174538	A	G	95	142	76	491	635	319	1.18 (0.90-1.53)	0.230	1.13 (0.85-1.51)	0.402
FEN1	rs4246215	T	G	94	142	77	490	641	314	1.19 (0.91-1.55)	0.198	1.17 (0.88-1.56)	0.271
APEX1	rs1130409	T	G	111	147	54	481	704	260	0.90 (0.70-1.16)	0.416	0.96 (0.69-1.32)	0.784
APEX1	rs1760944	T	G	110	156	46	487	687	271	0.93 (0.72-1.20)	0.582	0.75 (0.53-1.05)	0.097
APEX1	rs3136817	T	C	251	57	4	1176	253	16	1.06 (0.78-1.45)	0.701	1.18 (0.39-3.55)	0.773
LIG3	rs1052536	C	T	147	127	36	680	634	132	0.98 (0.77-1.26)	0.897	1.31 (0.88-1.93)	0.182
LIG3	rs3744356	C	T	301	7	2	1398	48	0	0.88 (0.43-1.81)	0.729	/	/
LIG3	rs4796030	A	C	92	142	76	426	720	300	0.99 (0.75-1.29)	0.922	1.25 (0.93-1.66)	0.137
XRCC1	rs1799782	G	A	143	140	27	710	611	125	1.13 (0.88-1.44)	0.347	1.00 (0.65-1.55)	0.997
XRCC1	rs25487	C	T	169	116	25	803	529	114	1.04 (0.82-1.34)	0.732	1.02 (0.65-1.60)	0.939
XRCC1	rs25489	C	T	253	51	6	1169	250	27	0.95 (0.69-1.30)	0.753	1.07 (0.44-2.62)	0.886
XRCC1	rs2682585	G	A	234	69	7	1126	292	28	1.15 (0.87-1.54)	0.328	1.19 (0.52-2.76)	0.681
XRCC1	rs3810378	G	C	165	122	23	777	541	128	1.02 (0.80-1.30)	0.878	0.82 (0.51-1.30)	0.387
XRCC1	rs915927	T	C	236	72	2	1125	297	24	1.11 (0.83-1.49)	0.470	0.39 (0.09-1.65)	0.200

AOR, adjusted odds ratio; CI, confidence interval, HWE, Hardy-Weinberg equilibrium. [a]Adjusted for age and sex for dominant model (MM/WM vs. WW). [b]Adjusted for age and sex for recessive model (MM vs. WW/WM).

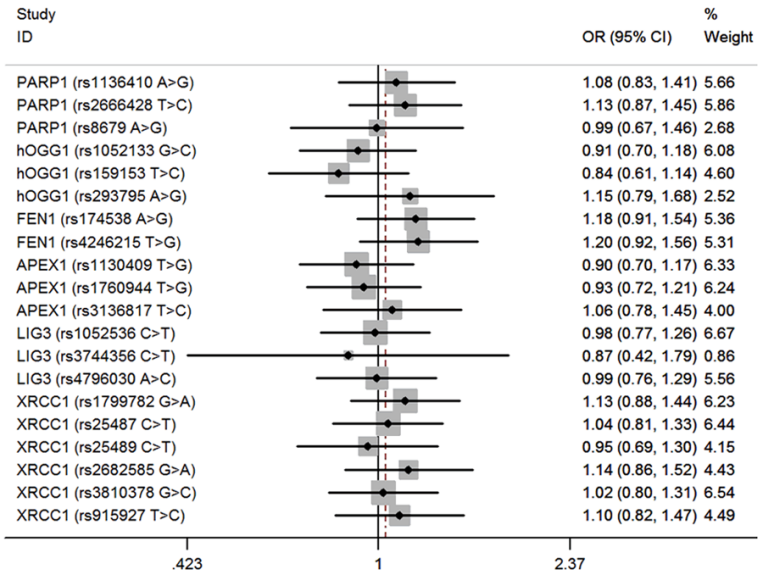

Figure 1. Forest plot for the association between BER gene SNPs and hepatoblastoma susceptibility under the recessive model (MM vs. WW/WM). For each SNP, the estimates of OR and its 95% CI are plotted with a box and a horizontal line.

our research may contribute to the identification of individuals susceptible to hepatoblastoma for tailored early detection or other preventive interventions.

Intensive investigations have been performed regarding the impact of BER pathway gene SNPs on susceptibility of cancer. Using the Spanish sample, Jonine D. Figueroa et al. [39] comprehensively determined the relationship between 43 candidate SNPs in 12 BER genes (*XRCC1*, *hOGG1*, *LIG1*, *MUTYH*, *PARP1*, *PARP3*, *PARP4*, *POLB*, *APEX1*, *POLD1*, *PCNA*, and *LIG3*) and the risk of bladder cancer. They detected that *POLB* rs3136717 and *PARP1* rs1136410 significantly predispose to bladder cancer, whereas *hOGG1* rs125701 protects from getting bladder cancer. Our research team also focuses on the role of BER gene polymorphisms on cancer

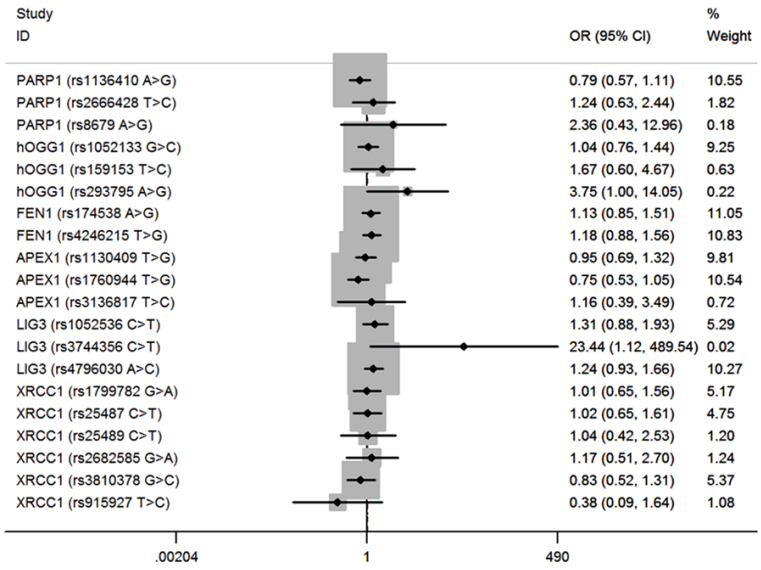

Figure 2. Forest plot for the association between BER gene SNPs and hepatoblastoma susceptibility under the dominant model (MM/WM vs. WW). For each SNP, the estimates of OR and its 95% CI are plotted with a box and a horizontal line.

risk. We have observed significant associations between *hOGG1* rs1052133, *FEN1* rs4246215, *FEN1* rs174538 polymorphisms and susceptibility of Wilms tumor in the Chinese population [30]. More recently, of the 20 SNPs in BER pathway genes genotyped, only *FEN1* gene rs174538 could impact the risk of neuroblastoma [36]. So far, the role of BER pathway gene SNPs in hepatoblastoma has not yet been illustrated. Given the specific role of BER pathway gene SNPs in specific cancer, it is necessary to carry out another study regarding the hepatoblastoma.

The current analysis revealed that among the 20 SNPs analyzed, only *hOGG1* gene rs293795 significantly predisposed to hepatoblastoma. Further stratification analysis did reveal some significant relationships among *hOGG1* gene SNPs with hepatoblastoma risk under some subgroups. FPRP analysis further validated the strength of the significant findings. The current negative results were plausible as most of the SNPs are only with small to moderate impact on the risk of cancer. hOGG1 is a multifunctional DNA glycosylase that plays a major role in the repair of DNA oxidative damage [40]. hOGG1 could specifically recognize the 8-OH-dG damage and then efficiently catalyze and excise the damage [41]. *hOGG1* gene is located on chromosome 3p25 and consists of eight exons. *hOGG1* is a polygenetic gene that has been reported to be greatly involved in multiple cancers [42, 43]. Moreover, SNPs in *hOGG1* gene are also reported in cancer etiology. Mohammed Alanazi et al. [44] found that *hOGG1* gene rs293795 did not show any association with breast cancer. Qin et al. [45] also failed to detect a relationship between *hOGG1* gene rs293795 and risk of non-small cell lung cancer. A similar negative result was also obtained in our previous study regarding neuroblastoma [46]. The conflicting role of the same rs293795 on different cancers indicating that the same SNP may exert a different role in different cancers.

Our study has weaknesses that should be considered. One limitation is the possibility of selection bias of subjects, as all the subjects were hospital based. Another limitation is the lack of incorporation of genetic-environmental interaction analysis, as hepatoblastoma is a complex disease not just caused by genetic aberrance. Moreover, cautions should be taken when interpreting the conclusion here to other ethnicities, since only Chinese population was analyzed. What's more, though as a multi-center study with moderate sample size, for subgroups the sample size is still limited. Statistical conclusion of these stratification analyses will be impaired to some extent at the present time. Of note, the exact functional role and molecule mechanisms of *hOGG1* gene in hepatoblastoma await to be explored.

Conclusion

In summary, the current study was the first case-control investigation reporting the role of BER pathway gene SNPs on risk of hepatoblastoma in Chinese ancestry children. Our findings provide suggestions of *hOGG1* genetic association for hepatoblastoma in Chinese ancestry children. Further genetic studies leveraging larger sample sizes are warranted to refine this association and reveal the underlying biology of hepatoblastoma.

Table 3. Stratification analysis for the association between *hOGG1* genotypes and hepatoblastoma susceptibility in Chinese children

Variables	rs159153 (case/control)		AOR (95% CI)[a]	*P*[a]	rs293795 (case/control)		AOR (95% CI)[a]	*P*[a]	Risk genotypes[b] (case/control)		AOR (95% CI)[a]	*P*[a]
	TT	TC/CC			AA/AG	GG			0	1-3		
Age, month												
<17	135/516	31/126	0.93 (0.60-1.44)	0.739	164/641	2/1	7.62 (0.69-84.76)	0.099	87/372	79/270	1.28 (0.91-1.81)	0.160
≥17	119/623	26/180	0.76 (0.48-1.19)	0.231	143/799	2/4	2.88 (0.52-15.89)	0.226	83/469	62/334	1.06 (0.74-1.51)	0.764
Sex												
Female	99/484	29/110	1.29 (0.81-2.05)	0.282	127/593	1/1	4.67 (0.29-75.10)	0.277	75/332	53/262	0.89 (0.60-1.32)	0.563
Male	155/655	28/196	0.60 (0.39-0.93)	0.022	180/847	3/4	3.57 (0.79-16.13)	0.098	95/509	88/342	1.39 (1.01-1.92)	0.045
Clinical stages												
I+II	134/1139	26/306	0.73 (0.47-1.13)	0.154	157/1440	3/5	5.67 (1.34-24.05)	0.019	92/841	68/604	1.02 (0.73-1.42)	0.902
III+IV	76/1139	14/306	0.68 (0.38-1.22)	0.197	90/1440	0/5	/	/	46/841	44/604	1.34 (0.87-2.05)	0.180

AOR, adjusted odds ratio; CI, confidence interval. [a]Adjusted for age and sex, omitting the corresponding stratify factor. [b]Risk genotypes were carriers with rs1052133 GG, rs159153 CC and rs293795 AG/GG genotypes.

Table 4. False-positive report probability analysis for significant findings

Genotype	OR (95% CI)	*P*[a]	Statistical power[b]	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
rs293795 A>G								
GG vs. AA/GA	3.752 (1.002-14.055)	0.0497	0.092	0.619	0.830	0.982	0.998	1.000
Stage I/II	5.503 (1.303-23.246)	0.0204	0.046	0.570	0.799	0.978	0.998	1.000
rs159153 TC/CC vs. TT								
Male	0.604 (0.392-0.931)	0.0223	0.330	0.169	0.378	0.870	0.985	0.999
Risk genotypes 1-3 vs. 0								
Male	1.379 (1.000-1.900)	0.0497	0.699	0.176	0.390	0.876	0.986	0.999

OR, odds ratio; CI, confidence interval. [a]Chi-square test was used to calculate the genotype frequency distributions. [b]Statistical power was calculated using the number of observations in each subgroup and the corresponding ORs and *P* values in this table.

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Disclosure of conflict of interest

None.

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