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Original Article

The association between polymorphisms of class II cytokine receptor genes and risk of HBV-related hepatocellular carcinoma

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Abstract: Chronic inflammation caused by hepatitis B virus (HBV) infections plays pivotal role in developing hepatocellular carcinoma (HCC). Class II cytokine receptors and their ligands are key antiviral and inflammatory modulators, however, the associations between genetic variations in the genes of class II cytokine receptors and HBV-related HCC risk are not determined yet. In the present study, we investigated the associations between single nucleotide polymorphisms (SNPs) in class II cytokine receptor genes and risk of HBV-related HCC. Five functional SNPs (rs2229207, rs1051393, rs2834167, rs2257167 and rs9808753) in code regions of 4 class II cytokine receptor genes (IFNAR1, IFNAR2, IFNGR2 and IL10RB) were genotyped using TaqMan genotyping assay in a hospital-based cohort with HBV infections patients, and their associations with HCC risk were evaluated by logistic regression model. Our data showed that SNP rs2257167 in IFNAR1 was significantly associated with risk of HBV-related HCC. In the stratified analysis, the association between rs2257167 and HCC risk remained significant in multiple subgroups under dominant genetic model. Furthermore, joint analysis suggested that there was significant interaction between rs2257167 genotypes and HBV-related HCC risk in female patients with P for interaction of 0.003. Conclusively, our study showed that IFNAR1, a gene of class II cytokine receptor cluster, may be a potential genetic biomarker for HBV-related HCC risk prediction after further validation.

Keywords: Hepatocellular carcinoma, HBV, class II cytokine receptor, single nucleotide polymorphism, cancer risk

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies and major cause of cancer-related deaths worldwide [1], especially in China [2]. The risk of developing HCC varies according to multifactor, chronic infection with hepatitis B virus (HBV) is the most frequent environmental factors, which is associated with varying degrees of chronic liver inflammation, and it often progresses to the development of cirrhosis and HCC [3]. Previous studies have indicated that most HCC patients in China have a history of HBV infection [4]. Chronic HBV infection seems to be the most important risk factor for HCC [5, 6]. Nevertheless, the molecular mechanism responsible for HCC in chronic HBV patients is not yet well known. Since only a fraction of HBV infected patients develop HCC during lifetime, genetic factors may play an important role in carcinogenesis of HCC [7, 8].

Chronic liver inflammation during persistent HBV infection plays a crucial role in HCC carcinogenesis [9]. Class II cytokine receptors and their ligands are crucial antiviral and inflammatory modulators during infection with viruses, including HBV infection [10, 11]. Class II cytokine receptor genes encode both subunits of the type I IFN receptor (IFNAR1 and IFNAR2) and subunits of both the IFN-γ receptor and IL-10 receptor (IFNGR2 and IL-10RB) [12]. Several researches have suggested that genetic polymorphisms in class II cytokine receptor genes were involved in chronic HBV infection, and was associated with clinical feature and outcomes of patients with persistent HBV infec-

tion [12-15]. Another research have shown that IFNAR1 was associated with hepatic carcinogenesis [16]. It has been reported that high levels of free IFNAR1/2 in the circulation was associated with various malignant disorders including HCC [17, 18]. Other investigations have demonstrated that IFNGR2 is linked to severe hepatic fibrosis in *Schistosoma mansoni* infection, and plays a critical role in the pathogenesis of T cell activation associated hepatitis [19]. Polymorphisms in the IFNGR2 gene appear to be associated with the variability of HBV viraemia [20]. Up-regulation of the expression of IFNGR2 enhances anti-proliferative effect of IFN-γ against HCC cells [21]. IL-10RB was related to chronic HBV infection, and may affect the outcome of HBV infection in China and Korean population [22, 23]. Accumulating evidences have suggested that class II cytokine receptor genes play a pivotal role in HBV infection and hepatic carcinogenesis. We hypothesize that polymorphism in class II cytokine receptor genes may influence the inflammatory process during HBV infection, which may be contribute to HCC progression.

Single nucleotide polymorphism (SNP) is the most common type of genetic variation, which can be used as a biomarker of genetic background to predict the risk, therapeutic response and prognosis of malignancies. Considering the important role of class II cytokine receptor genes in HBV infection, it is worthy to investigate SNPs effects in these genes on drug sensitivity, clinicopathological characteristics and prognosis of HBV-associated liver disease, especially in development of HBV related HCC. It was reported that polymorphisms in IFNAR1 gene were associated with HBV and HCV infections [13, 24], and with the susceptibility of HCC and other cancers [25, 26]. Additionally, SNP in IFNGR2 gene was significantly associated with multiple sclerosis susceptibility [27], SNPs in IL10RB gene were associated with chronic HBV status, HBV natural clearance, systemic sclerosis and the presence of HCC [28, 29]. However, to date, the association of SNPs in class II cytokine receptor genes with the susceptibility of HCC in a Chinese population remains to be determined. To further explore the role of genetic variants in the class II cytokine receptor genes in HCC development, we genotyped a set of potentially functional SNPs in the IFNAR1, IFNAR2, IFNGR2 and IL10RB genes in a hospital-based Chinese population with HBV infection and evaluated their association with HCC susceptibility.

Materials and methods

Study population and data collection

The subjects in this study were identified from an existing and ongoing clinic-based patient cohort. Patients are consecutively enrolled when they visited the Department of Infection Disease, Henan University Affiliated Huaihe Hospital for the treatment of liver diseases such as HBV infection, HCV infection, cirrhosis, and HCC. Patient enrollment started in 2013 and is still ongoing. Since more than 90% of the patients in this cohort were of Chinese ancestry and had HBV infection, to minimize the potential confounding effects from ethnicity and disease etiology, we restricted the study subjects in the current analysis to Chinese HBV infected patients only. This study was approved by the Institutional Review Board of Henan University. A written informed consent was obtained from each patient.

Demographic and clinical data were obtained from each patient through medical chart review and/or consulting with the treating physicians. Demographic variables collected in this study included age, gender, ethnicity, smoking status, drinking status, cirrhosis status and family history of cancer, cirrhosis or HBV infection. Liver cirrhosis and HCC were diagnosed by the combined use of clinical tests and imaging studies.

DNA isolation and genotyping

Five milliliter of venous blood sample was collected from each patient, and genomic DNA was isolated from whole blood using the E.Z.N.A. Blood DNA Midi Kit (Omega Bio-Tek, Norcross, GA) according to the manufacturer's guidelines as described previously [30]. Five SNPs rs2229207 (F8S; exon2; T>C), rs1051393 (F10V; exon2; G>T), rs2834167 (K47E; exon2; G>A), rs2257167 (L168V; exon4; G>C) and rs9808753 (R64Q; exon2; G>A) in four gene (IFNAR1, IFNAR2, IFNGR2 and IL10RB) were selected in this study. These four genes are located on human chromosome 21q22 in a class II cytokine receptor gene cluster. The genotyping of genetic polymorphisms was performed via the TaqMan method according to

Table 1. Distribution of selected host characteristics by case-control status

Variables	Cases (n=202)	Controls (n=406)	*P* value*
Age, mean ± SD	54.69 ± 9.26	53.36 ± 9.51	0.102
Gender			
Male	171 (84.7%)	319 (78.6%)	
Female	31 (15.3%)	87 (21.4%)	0.074
Smoking status			
Never	94 (46.53%)	256 (63.05%)	
Ever	108 (53.47%)	150 (36.95%)	1.228×10^{-4}
Drinking status			
Never	91 (45.05%)	237 (58.37%)	
Ever	111 (54.95%)	169 (41.63%)	0.002
Cirrhosis			
No	57 (28.22%)	252 (62.07%)	
Yes	145 (71.78%)	154 (37.93%)	3.363×10^{-16}
Family HBV			
No	120 (59.41%)	223 (54.93%)	
Yes	82 (40.59%)	183 (45.07%)	0.294
Family cirrhosis			
No	170 (84.16%)	335 (82.51%)	
Yes	32 (15.84%)	71 (17.49%)	0.610
Family cancer			
No	118 (58.42%)	283 (69.70%)	
Yes	84 (41.58%)	123 (30.30%)	0.006

*P values were derived from the X^2 test for categorical variables, and t test for continuous variables.

the protocol of TaqMan SNP Genotyping Assays (Applied Biosystems, CA, USA). Laboratory personnels conducting genotyping were blinded to patients' information.

Statistical analysis

Statistical analysis was conducted by using the SPSS version 19.0 software package (IBM, Armonk, NY, USA). The continuous variable and categorical variables in this study were analyzed by t-test and chi-squared test analyses, respectively. The Hardy-Weinberg (HWE) of each SNP in control subjects was tested by a goodness-of-fit χ^2 test. Three genetic models were conducted for SNPs analysis, and the odds ratios (OR) and 95% confidence intervals (CIs) of the association between SNPs and HCC risk were calculated by logistic regression model, which adjusted by age, gender, smoking status, drinking status, cirrhosis, family history of HBV, family history of cirrhosis, and family history of cancer. All P values in this study were two-sided, and $P < 0.05$ was considered to be significant.

Results

Demographic characteristics of the study population

In this study, we included 202 HBV-related HCC patients and 406 cancer-free HBV infected control patients that were frequency-matched to cases based on age and gender. As shown in **Table 1**, the age (Mean ± SD) for HCC and control group was 54.69 ± 9.26 and 53.36 ± 9.51 years, respectively. Majority of the patients had a smoking (108/202) or drinking (111/202) history in HCC cases, and minority patients had a smoking (150/406) or drinking (169/406) history in controls. Major patients with cirrhosis in HCC cases, but minor patients with cirrhosis in controls ($P=3.363\times10^{-16}$). There were no statistically significant difference in distributions of age, gender, family HBV and family cirrhosis history status between cases and controls.

Association between SNPs and risk of HBV related HCC

We investigated the association between selected SNPs (rs2229207, rs1051393, rs2834167, rs2257167 and rs9808753) in class II cytokine receptor genes and the risk of HBV related HCC by logistic regression model using multivariate analysis under dominant, recessive, and additive genetic models. Our data showed that SNP rs2257167 in IFNAR1 gene had significantly associated with increased HCC risk under dominant (OR=1.57, 95% CI 1.05-2.35, P=0.027), recessive (OR=2.01, 95% CI 1.07-3.78, P=0.031), and additive genetic models (OR=1.48, 95% CI 1.10-1.98, P=0.009), with adjusting for age, gender, smoking status, drinking status, cirrhosis, family history of HBV, family history of cirrhosis, and family history of cancer (**Table 2**).

To exclude the potential effects of confounding factors, we further performed the stratified analysis on the effects of SNP rs2257167 under dominant model by age, gender, smoking status, drinking status, cirrhosis, family history of HBV, family history of cirrhosis, and family history of cancer. The significant increased HCC risk associated with variant-containing genotypes of rs2257167 was remained in the sub-

Table 2. The association between SNPs and HCC risk

Gene and SNP	Genotype	Case (n=202)	Control (n=406)	OR (95% CI)*	*P* value
IFNAR2	TT	131	260	Reference	
rs2229207	TC	55	110	1.19 (0.77-1.84)	0.443
(F8S; exon2; T>C)	CC	12	20	1.15 (0.50-2.64)	0.736
HWE P 0.069	Dom			1.18 (0.78-1.78)	0.427
	Rec			1.10 (0.48-2.48)	0.826
	Add			1.13 (0.81-1.56)	0.476
IFNAR2	GG	66	139	Reference	
rs1051393	GT	93	167	1.05 (0.68-1.63)	0.824
(F10V; exon2; G>T)	TT	40	88	0.89 (0.52-1.53)	0.680
HWE P 0.006	Dom			1.00 (0.66-1.50)	0.988
	Rec			0.87 (0.54-1.39)	0.560
	Add			0.96 (0.74-1.24)	0.737
IL10RB	GG	62	125	Reference	
rs2834167	GA	92	193	0.91 (0.58-1.43)	0.687
(K47E; exon2; G>A)	AA	44	74	1.20 (0.70-2.06)	0.516
HWE P 0.974	Dom			0.99 (0.65-1.51)	0.972
	Rec			1.26 (0.79-2.03)	0.331
	Add			1.08 (0.82-1.41)	0.597
IFNAR1	GG	102	217	Reference	
rs2257167	GC	68	132	1.40 (0.91-2.16)	0.130
(L168V; exon4; G>C)	CC	25	31	2.28 (1.18-4.41)	0.014
HWE P 0.092	Dom			1.57 (1.05-2.35)	0.027
	Rec			2.01 (1.07-3.78)	0.031
	Add			1.48 (1.10-1.98)	0.009
IFNGR2	GG	57	113	Reference	
rs9808753	GA	93	180	0.88 (0.56-1.39)	0.582
(R64Q; exon2; G>A)	AA	48	102	0.86 (0.51-1.47)	0.589
HWE P 0.081	Dom			0.87 (0.57-1.34)	0.535
	Rec			0.93 (0.59-1.47)	0.769
	Add			0.93 (0.71-1.21)	0.576

*Adjusted for age, gender, smoking status, drinking status, cirrhosis, family history of HBV, family history of cirrhosis and family history of cancer.

group patients of females (P=0.001), never smokers (P=0.023), never drinkers (P=0.018), no family history of HBV (P=0.026), no family history of cirrhosis (P=0.011), and no family history of cancer (P=0.026), using multivariate analysis with adjusting for appropriate variables (**Table 3**).

Joint analysis of rs2257167 and selected host characteristics

To reveal the interaction between rs2257167 and selected host characteristics, we conducted joint analyses of rs2257167 and selected host characteristics on HCC risk. As data shown in **Table 4**, female patients with variant-containing genotypes exhibited significant increased risk with OR of 2.58 (95% CI 1.14-5.82, P=0.022), comparing to male patients with wild genotype using multivariate analysis. The results showed a statistically significant interaction between the genotypes of rs2257167 and gender on HBV-related HCC risk (P=0.003).

Haplotype of class II cytokine receptor genes and HCC risk

Since five selected SNPs were close together in a cluster of class II cytokine receptor genes, which located on human chromosome 21q22. Therefore, we further conducted the haplotype analysis of five SNPs to determine whether any particular haplotype may be associated with HBV-related HCC risk. At least 11 haplotypes were derived from these 5 SNPs in HCC and control groups. As shown in **Table 5**, we found haplotype H9 (0_1_0_0_1, 0: wild type allele; 1: variant allele) statistically significant reduced the cancer risk by 0.33 fold (95% CI 0.12-0.90, P=0.030).

Discussion

In the current study, we investigated the effects of five functional SNPs from four genes (IFNAR1, IFNAR2, IFNGR2 and IL10RB) of class II cytokine receptor gene cluster on the risk of HBV-related HCC. We found that SNP rs2257167 in IFNAR1 was significantly associated with HCC risk. Furthermore, joint analysis suggested that there were significant interaction between rs2257167 genotypes and gender on HBV-related HCC risk. To the best of our knowl-

Table 3. rs2257167 polymorphism and HCC cancer risk stratified by host characteristics

Stratified variables	Genotype	Cases	Controls	OR (95% CI)*	*P* value
Age					
Subjects < 54	GG	35	113	Reference	
	CG + CC	42	92	1.61 (0.88-2.93)	0.121
Subjects ≥ 54	GG	67	104	Reference	
	CG + CC	51	71	1.51 (0.84-2.70)	0.165
Gender					
Female	GG	11	56	Reference	
	CG + CC	19	25	9.35 (2.42-36.12)	0.001
Male	GG	91	161	Reference	
	CG + CC	74	138	1.24 (0.80-1.94)	0.332
Smoking status					
Never	GG	46	138	Reference	
	CG + CC	44	99	1.93 (1.09-3.41)	0.023
Ever	GG	56	79	Reference	
	CG + CC	49	64	1.20 (0.67-2.17)	0.539
Drinking status					
Never	GG	40	126	Reference	
	CG + CC	48	96	1.98 (1.12-3.50)	0.018
Ever	GG	62	91	Reference	
	CG + CC	45	67	1.16 (0.64-2.08)	0.625
Cirrhosis					
No	GG	23	126	Reference	
	CG + CC	32	110	1.88 (0.97-3.63)	0.061
Yes	GG	79	91	Reference	
	CG + CC	61	53	1.50 (0.90-2.51)	0.123
Family HBV					
No	GG	59	123	Reference	
	CG + CC	57	81	1.88 (1.08- 3.30)	0.026
Yes	GG	43	94	Reference	
	CG + CC	36	82	1.20 (0.66- 2.17)	0.556
Family cirrhosis					
No	GG	85	184	Reference	
	CG + CC	80	128	1.78 (1.14-2.78)	0.011
Yes	GG	17	33	Reference	
	CG + CC	13	35	0.87 (0.32-2.40)	0.794
Family cancer					
No	GG	55	144	Reference	
	CG + CC	58	116	1.86 (1.08-3.21)	0.026
Yes	GG	47	73	Reference	
	CG + CC	35	47	1.29 (0.69-2.40)	0.424

*Adjusted for age, gender, smoking status, drinking status, cirrhosis, family history of HBV, family history of cirrhosis and family history of cancer, where appropriate.

edge, this is the first study to comprehensively evaluate the associations between SNPs from class II cytokine receptor genes and risk of HBV-related HCC in Chinese population.

It was reported that IFNAR1, a member of class II cytokine receptors, plays a pivotal role in HBV persistent infection [12, 31]. IFNAR1 has been reported to play a crucial role in early-onset colorectal cancer carcinogenesis [32]. The expression of IFNAR1 and IFNAR2 independently are important for the anti-proliferative effect of IFNA in HCC cells [33, 34], and the expression level of IFNAR1 in the circulation was associated with various malignant disorders including HCC [17, 18]. Moreover, other studies suggested that genetic polymorphisms within IFNAR1 was involved in chronic HBV infection, and was associated with clinical feature and outcomes of HBV infection, as well as HCC development [13-15, 25, 35]. Consistently in our study, we identified that SNPs rs2257167 in IFNAR1was significantly associated with susceptibility of HCC in patients with HBV infection. SNP rs2257167 is located in exon 4 of IFNAR1, affects the first base of the Val codon (GTT), leading to a Val-to-Leu missense mutation, it is possible to influence the function of IFNAR1. The underlying mechanisms of rs2257167 involved in HCC development worthy to be further investigated.

Additionally, it has been reported that SNP rs9808753 in IFNGR2 gene is significantly associated with multiple sclerosis susceptibility [27]. SNP rs2834167 in IL10RB gene was associated with chronic HBV status, HBV natural clearance, systemic sclerosis and the presence of HCC [28, 29]. However, we did not iden-

Table 4. Joint analysis of rs2257167 and selected host characteristics

Variables*	Case/control	OR (95% CI)†	*P* value
Age			
GG and Age < 54	35/113	Reference	
GG and Age ≥ 54	67/104	1.87 (1.06-3.31)	0.031
GC + CC and Age < 54	42/92	1.79 (1.00-3.21)	0.05
GC + CC and Age ≥ 54	51/71	2.72 (1.48-4.98)	0.001
P for interaction			0.604
Gender			
GG and Male	91/161	Reference	
GG and Female	11/56	0.37 (0.15-0.91)	0.031
GC + CC and Male	74/138	1.21 (0.78-1.87)	0.39
GC + CC and Female	19/25	2.58 (1.14-5.82)	0.022
P for interaction			0.003
Smoking status			
GG and Never smoking	46/138	Reference	
GG and Ever smoking	56/79	2.45 (1.30-4.63)	0.006
GC + CC and Never smoking	44/99	1.88 (1.08-3.29)	0.026
GC + CC and Ever smoking	49/64	3.18 (1.65-6.12)	0.001
P for interaction			0.359
Drinking status			
GG and never drinking	40/126	Reference	
GG and ever drinking	62/91	1.40 (0.73-2.67)	0.306
GC + CC and never drinking	48/96	2.14 (1.21-3.78)	0.009
GC + CC and ever drinking	45/67	1.62 (0.81-3.23)	0.17
P for interaction			0.131
Cirrhosis			
GG and no cirrhosis	23/126	Reference	
GG and with cirrhosis	79/91	5.66 (3.12-10.27)	0.001
GC + CC and no cirrhosis	32/110	1.83 (0.96-3.50)	0.067
GC + CC and with cirrhosis	61/53	8.09 (4.27-15.33)	0.001
P for interaction			0.554

*GG, homozygous wild-type genotype; GC, heterozygous genotype; CC, homozygous variant genotype. †Adjusted for age, gender, smoking status, drinking status, cirrhosis, family history of HBV, family history of cirrhosis and family history of cancer, where appropriate.

tify significant associations between SNPs in IFNGR2 or IL10RB gene and HBV related HCC susceptibility. These data suggest that the effect on cancer risk conferred by SNPs in class II cytokine receptor genes might dependent on specific population.

As one of the subunits of the type I interferon receptor, IFNAR-1 can be activated by IFNA and IFNB [36]. Our results indicate that the IFNA/B pathway cannot only participate in the early-stage pathogenesis and persistently exhibits of HBV infection, but it also influences final outcomes, and HBV related HCC development. Further analysis indicated that rs2257167 still had statistically significant association with HBV related HCC susceptibility in the subgroup of females, never smokers, never drinkers, no family history of HBV, no family history of cirrhosis, and no family history of cancer. And joint analyses showed that female patients with variant-containing genotypes exhibited significant increased risk of HBV related HCC. We also observed that haplotype H9 (0_1_0_0_1, 0: wild type allele; 1: variant allele) statistically significant reduced the HBV related risk, compared with the common haplotype H1 (0_0_0_0_0, 0: wild type allele). The rare allele genotypes of rs1051393 and rs9808753 seems to be a protective genotype when compare common allele genotypes. This finding supports the importance of another SNP rs1051393 and rs9808753 associated with HBV related HCC progression. However, the present study was only exploratory, and the results need to be validated in other independent cohorts.

Conclusively, our study showed that variant genotype of SNP rs2257167 in IFNAR1, a member of class II cytokine receptor gene cluster, had significantly associated with increased HCC cancer risk in HBV-infected patients. Further functional studies are warranted to reveal the underlying mechanism of class II cytokine receptor genes in HCC development, and further observational studies are need to expend our findings to clinical utility.

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Table 5. Haplotype analysis of 5 selected SNPs in class II cytokine receptor gene cluster

Haplotype	Haplotype sequence*	Haplotype frequency (%)	Case/control	OR (95% CI)†	*P* value
H1	0_0_0_0_0	12.5	52/100	1 (reference)	
H2	0_1_1_0_0	12.3	46/103	1.12 (0.65-1.92)	0.686
H3	0_1_1_0_1	6.2	24/51	0.85 (0.43-1.68)	0.643
H4	0_0_0_1_1	5.4	26/40	1.37 (0.68-2.77)	0.378
H5	0_0_0_0_1	5.1	21/41	1.05 (0.50-2.19)	0.893
H6	1_0_0_0_0	4.7	18/39	1.05 (0.50-2.23)	0.895
H7	0_1_1_1_1	3.8	18/28	1.47 (0.67-3.20)	0.339
H8	1_0_0_1_1	3.7	13/32	0.95 (0.43-2.10)	0.896
H9	0_1_0_0_1	3.6	7/37	0.33 (0.12-0.90)	0.030
H10	0_0_1_0_1	2.8	10/24	0.74 (0.29-1.90)	0.526
H11	0_0_1_0_0	2.5	9/21	0.85 (0.32-2.25)	0.743

*0 indicates the common allele, 1 indicates the rare allele. And class II cytokine receptor gene cluster in the sequence of rs2229207-rs1051393-rs2834167-rs2257167-rs9808753. †Adjusted for age, gender, smoking status, drinking status, cirrhosis, family history of HBV, family history of cirrhosis and family history of cancer.

Disclosure of conflict of interest

None.

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