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Original Article

A single nucleotide polymorphism of the interferon-γ gene and susceptibility to hepatitis B virus-related cirrhosis: a randomized controlled trial

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Abstract: Objective: This study aimed to explore the correlation between a single nucleotide polymorphism (SNP) of the interferon-γ (IFN-γ) gene and susceptibility to hepatitis B virus (HBV) -related cirrhosis in the Chinese population. Method: PCR-LDR was employed for the genotyping of two SNPs, rs1861494 and rs2069718, of the IFN-γ gene in 230 patients with HBV-related cirrhosis and 320 inactive HBsAg carriers without cirrhosis. It was then determined whether the Hardy-Weinberg (H-W) equilibrium was satisfied. The odds ratio (OR) and 95% confidence interval (CI) were analyzed using the chi-square test and univariate non-conditional logistic regression. Haplotypes were established using SHEsis and SNPStats online software and their interaction with non-genetic factors was analyzed. Results: Compared with the AA genotype of rs1861494 SNP, AG+GG genotypes increased the risk of HBV-related cirrhosis. There was a significant difference in the distribution of A and G alleles between the case group and the control group (P<0.05). There was also a significant difference in the distribution of AA, AG, GG, AA, and AG+GG genotypes and A/G alleles between the case group and the control group (P<0.05). This indicated that the G allele may be a risk factor for HBV-related cirrhosis. By analyzing the different distribution of haplotypes in the case group and the control group, we observed significant differences in the distribution of AA, AG and GA haplotypes between the case and control groups (P<0.05). Haplotypes of the IFN-γ gene did not interact with other relevant factors. Conclusion: The G allele of rs1861494 SNP as well as AG and GG genotypes and G allele of rs2069718 SNP may be risk factors of HBV-related cirrhosis. The AA haplotype may be a protective factor for HBV-related cirrhosis, while the AG haplotype is a risk factor for HBV-related cirrhosis.

Keywords: Interferon-γ (IFN-γ) gene, single nucleotide polymorphism, HBV-related cirrhosis

Introduction

Hepatitis B virus (HBV) infection is a worldwide public health concern. approximately 2 billion people have been infected with HBV, and the current number of people who suffer from HBV infection is about 350 million [1]. China has a high prevalence of HBV infection. The second national epidemiological survey on HBV infection has shown that the positive rate of HBsAg in the sampled population was 9.75%. It is estimated that there are about 120 million HBsAg carriers in China. HBV infection may lead to chronic severe hepatitis B, hepatocellular carcinoma and cirrhosis, among which cirrhosis causes the greatest harm [2, 3].

Despite the large number of people infected by HBV, only a small portion of them eventually develop HBV-related cirrhosis [4]. In addition to environmental and viral factors, different courses and outcomes of the disease are also associated with host susceptibility to HBV and the host's HBV immune status [5]. Recent molecular genetics have demonstrated a correlation between the polymorphism of some genes and the status of HBV infection, including interleukins (ILs), interferon-γ (IFN-γ) and estrogen receptor-α (ER1) [6-8]. Identifying susceptible genes associated with cirrhosis lays the basis for better treatment [9].

IFN-γ not only plays important regulatory and effector roles in innate and acquired immunity, it also serves as anti-fibrotic and pro-fibrinolytic factors [10]. IFN-γ is crucial for host resistance to HBV infection and the subsequent fibrosis

Table 1. Detailed information of two SNPs in the IFN-γ gene

SNP	W>M*	Mutation position	MAF	Location
rs1861494	A>G	Intron variant	0.33	12:68157629
rs2069718	A>G	Intron variant	0.17	12:68156382

*W means wild type gene, M means mutant gene.

[11, 12]. This study was a case-control study that performed genotyping to two SNPs of non-immune genes related to cirrhosis. The correlation between these two SNPs and genetic susceptibility of HBV-related cirrhosis was analyzed by logistic regression. The results shed new light on the screening of a population at high risk of cirrhosis among HBsAg carriers. Two SNPs of IFN-γ gene, rs1861494 and rs2069718, were genotyped in the Han population from Qingdao, China.

Materials and methods

Subjects

From January 2015 to December 2016, 230 patients confirmed as having HBV-related cirrhosis at Qingdao Sixth People's Hospital were randomly selected. In the meantime, 320 inactive HBsAg carriers without symptoms of cirrhosis who received a physical examination at the hospital were also included. Patients in the case group were aged 32-71 years (50.00±8.04 years), and those in the control group were aged 29-72 years (50.48±7.39 years). The cases had a full medical history taken. After they were discharged, their medical records were reviewed to collect laboratory test data. All recruited cases signed the informed consent. The research protocol was approved by the ethics committee of Qingdao Sixth People's Hospital.

Sample collection

For the case group and control group, 2 ml of fasting peripheral venous blood was collected in the morning from each individual. EDTA was added to the blood samples as an anticoagulant, and the samples were subpackaged and stored at -80°C. Genomic DNA was extracted using the Axygene blood genomic DNA extraction kit and preserved at -20°C.

SNP selection and genotyping

Two SNPs were selected in the IFN-γ gene, and they satisfied any one of the following criteria: (1) having been reported to be associated with HBV-related cirrhosis; (2) being heterozygous and having minor allele frequency (MAF)>0.05; (3) having a mutation capable of causing functional changes. Tag SNPs of the IFN-γ gene were selected for the Chinese population on http://gvs.gs.washington.edu/GVS144/. It was also ensured that r^2>0.8 while MAF>0.05. Finally, two representative SNPs in the IFN-γ gene were chosen, namely, rs1861494 and rs2069718. For more details, see **Table 1**.

Genotyping of the two SNPs in the IFN-γ gene was performed using PCR-LDR. PCR amplified products containing the target DNA fragment were cleaved using restriction endonucleases. The presence of SNPs was determined according to the differences in length and number of cleaved fragments by gel electrophoresis. Primers were designed using NCBI and Primer Premier 5 software.

Statistical analysis

All statistical analyses were undertaken using IBM SPSS 21.0 software. We tested whether the Hardy-Weinberg (H-W) equilibrium was satisfied for all haplotypes. A chi-square test was used to analyze the distribution of genotypes and alleles among the groups. OR and 95% CI were analyzed using a chi-square test and a univariate non-conditional logistic regression. The relative risk of mutants and homozygous wild-types in SNPs in causing HBV-related cirrhosis was compared. Linkage disequilibrium analysis was performed using SHEsis on-line software (http://analysis.bio-x.cn/myAnalysis.php). Haplotypes were established and their interactions with other relevant factors were analyzed using SNPStats on-line software (http://bioinfo.iconcologia.net/snpstats/start.htm). A two-sided hypothesis test was adopted, with the significance level α set as 0.05.

Results

Intergroup comparison of baseline data

A total of 550 cases, including 230 patients with HBV-related cirrhosis and 320 inactive HBsAg carriers, were included. The baseline information of the case group and control group is shown in **Table 2**. There was no significant difference in terms of age, drinking status, and family history between the two groups (P>0.05). However, we observed significant difference in gender, ALT, HBV-DNA and smoking status (P<0.05). See **Table 2**.

Table 2. Distribution of baseline physicochemical indicators between the two groups

Items	Groups	Case group	Control group	t/χ^2	*P*
Age (year)		49.36±8.14	50.35±7.95	1.033	0.303
ALT (U/L)		153.99±24.89	119.98±24.49	11.524	<0.001
HBV-DNA (Log)		5.67±1.59	4.20±1.05	9.204	<0.001
Gender	Male	110	97	3.131	0.077
	Female	30	43		
Drinking	Yes	50	41	1.319	0.251
	No	90	99		
Smoking	Yes	64	42	7.348	0.007
	No	76	98		
Family history	Yes	24	13	4.590	0.052
	No	116	127		

Table 3. H-W equilibrium test of the two SNPs in the two groups

Group	SNP	WW	WM	MM	W	M	HWE χ^2	*P*
Case group	rs1861494	78	53	9	209	71	0.001	0.999
	rs2069718	79	52	9	210	70	0.013	0.910
Control group	rs1861494	94	41	5	229	51	0.041	0.840
	rs2069718	102	34	4	238	42	0.317	0.573

Table 4. Distribution of genotype and allele frequencies of CD44 SNP in the two groups

SNP site	Gene type	Case group	Control group	OR (95% CI)	*P*
rs1861494	AA	78 (55.7)	94 (67.1)	Reference	
	AG	53 (37.9)	41 (29.3)	1.558 (0.939-2.585)	0.086
	GG	9 (6.4)	5 (3.6)	2.169 (0.698-6.740)	0.181
	AA	78 (55.7)	94 (67.1)	Reference	
	AG+GG	62 (44.3)	46 (32.9)	1.624 (1.000-2.639)	0.050
	AA+AG	131 (93.6)	135 (96.4)	Reference	
	GG	9 (6.4)	5 (3.6)	1.855 (0.606-5.681)	0.279
	A	209 (74.6)	229 (81.8)	Reference	
	G	71 (25.4)	51 (18.2)	1.392 (1.012-1.916)	0.041
rs2069718	AA	79 (56.4)	102 (72.9)	Reference	
	AG	52 (37.1)	34 (24.3)	1.975 (1.171-3.330)	0.011
	GG	9 (6.4)	4 (2.9)	2.905 (0.863-9.780)	0.085
	AA	79 (56.4)	102 (72.9)	Reference	
	AG+GG	61 (43.6)	38 (27.1)	2.073 (1.257-3.418)	0.004
	AA+AG	131 (93.6)	136 (97.1)	Reference	
	GG	9 (6.4)	4 (2.9)	2.336 (0.702-7.771)	0.167
	A	210 (75.0)	238 (85.0)	Reference	
	G	70 (25.0)	42 (15.0)	1.667 (1.181-2.353)	0.003

H-W equilibrium test of genotypes of the two SNPs in the two groups

An H-W equilibrium test was performed for two SNPs in the IFN-γ gene. The results showed that at the H-W equilibrium was satisfied for the two SNPs (P>0.05). No natural selection and migration occurred in the study population, and the subjects were representative of the population (**Table 3**).

Distribution of genotype and allele frequencies of the two SNPs of the IFN-γ gene in the case group and control group

As indicated by univariate logistic regression, there was no significant difference in the genotype distribution of rs1861494 SNP between the two groups. Neither was there a significant difference in the frequencies of A and G alleles between the two groups (P=0.250>0.05). However, there was a significant difference in the frequencies of AA, AG, and GG genotypes as well as A and G alleles of the rs2069718 SNP between the two groups (P<0.05). This indicated that the AG and GG genotypes and the G allele may be risk factors of HBV-related cirrhosis. The results are shown in **Table 4**.

Correlation between IFN-γ gene haplotypes and HBV-related cirrhosis

By comparing the frequencies of haplotypes between the two groups, it was found that the AA haplotype is a protective factor of HBV-related cirrhosis (OR=0.666, 95% CI: 0.520~0.852, P=0.001). The AG haplotype (OR=1.674, 95% CI: 1.200~2.336, P=0.002) is a risk factor

Table 5. Correlation between IFN-γ gene haplotype and HBV-related cirrhosis

Haplotype*	Case group (n=280)	Control group (n=280)	χ^2	OR (95% CI)	*P*
AA[a]	158.98 (0.568)	199.58 (0.713)	12.785	0.529 [0.373~0.752]	<0.001
AG[a]	50.02 (0.179)	29.42 (0.105)	6.230	1.853 [1.136~3.023]	0.013
GA	51.02 (0.182)	38.42 (0.137)	2.115	1.401 [0.888~2.211]	0.146
GG	19.98 (0.071)	12.58 (0.045)	1.782	1.633 [0.790~3.373]	0.182

OR, odds ratio; CI, confidence interval. *Haplotypes of rs1861494 and rs2069718 SNPs are presented successively; [a]The haplotypes correlated significantly to HBV-related cirrhosis (P<0.05).

Table 6. Analysis on interactions between IFN-γ gene haplotypes and other relevant factors

Haplotype	Frequency	OR (95% CI)		*P*
		Male	Female	
AA	0.6428	1.00	1.12 (0.48-2.63)	0.22
GA	0.1572	1.57 (0.84-2.94)	1.65 (0.58-4.67)	
AG	0.1394	2.00 (1.00-4.00)	1.95 (0.60-6.30)	
GG	0.0606	3.01 (1.00-9.10)	0.32 (0.03-3.86)	
		Non-smoking	Smoking	0.39
AA	0.641	1.00	1.56 (0.68-3.60)	
GA	0.159	1.22 (0.60-2.50)	3.24 (1.41-7.44)	
AG	0.1412	1.63 (0.72-3.70)	3.18 (1.30-7.75)	
GG	0.0588	3.42 (0.96-12.19)	1.19 (0.24-5.99)	
		No family history	Family history	0.21
AA	0.6412	1.00	1.91 (0.48-7.71)	
GA	0.1588	1.45 (0.79-2.67)	3.51 (0.90-13.68)	
AG	0.141	1.71 (0.87-3.34)	6.41 (1.17-35.19)	
GG	0.059	3.82 (1.05-13.84)	0.72 (0.10-4.97)	
		Non-drinking	Drinking	0.30
AA	0.6415	1.00	1.99 (0.90-4.38)	
GA	0.1585	2.07 (1.02-4.19)	1.87 (0.73-4.79)	
AG	0.1407	2.39 (1.07-5.35)	2.97 (1.10-7.99)	
GG	0.0593	2.42 (0.78-7.48)	1.59 (0.27-9.38)	
		≤50 year	>50 year	0.84
AA	0.6421	1.00	0.62 (0.29-1.30)	
GA	0.1579	1.69 (0.79-3.65)	0.90 (0.41-1.96)	
AG	0.14	1.85 (0.90-3.83)	1.21 (0.43-3.44)	
GG	0.06	1.25 (0.35-4.40)	1.65 (0.39-6.89)	

of HBV-related cirrhosis. The frequency of the AA haplotype in patients with HBV-related cirrhosis was significantly lower compared with the control group; however, the frequency of the AG haplotype in patients with HBV-related cirrhosis was significantly higher compared to the control group. The results are shown in **Table 5**.

IFN-γ gene haplotypes and their interactions with other relevant factors

IFN-γ gene haplotypes and their interactions with other relevant factors were analyzed. Interactions of the four haplotypes of the two SNPs in the IFN-γ gene with age, gender, smoking status, drinking status and family history were analyzed. By taking the AA haplotype as reference, the haplotype did not interact with any of these factors generally (P>0.05). But as judged by OR for some factors compared with the AA haplotype, the AG and GA haplotypes in smokers were associated with a higher risk of HBV-related cirrhosis compared to the AA haplotype among the non-smokers. AG and GA haplotypes in those with a family history and a drinking history were associated with a higher risk of HBV-related cirrhosis compared to the AA genotype among those without a family history or a drinking history. This indicated local interaction between genetic factors, smoking and drinking status, and family history. The results are shown in **Table 6**.

Discussion

Chronic hepatitis B is a highly prevalent infectious disease in China, which is characterized by a high transmission rate, a long course, a lack of special treatment options, and high costs [13]. HBV-related cirrhosis is the end-stage liver disease evolving from chronic hepatitis B. The long course and poor prognosis of chronic liver disease bring great harm to the physical and psychological health of patients [14].

We observed significant differences in baseline ALT and HBV-DNA, gender distribution, and smoking status between the case group and control group. The levels of ALT and HBV-DNA were significantly higher in the case group com-

pared to the control group. Serum ALT is a good serological marker of the severity and prognosis of liver disease. The serum HBV-DNA level is the most direct and reliable indicator of viral activity and also the initiating factor of HBV-related cirrhosis. We noted a significant improvement of serum ALT and HBV-DNA levels in patients with HBV-related cirrhosis compared to the control group, showing that the two indicators were measures of HBV-related diseases. Moreover, there were more smokers in the case group than in the control group, which suggested that smoking may be a risk factor of HBV-related cirrhosis. It has been reported that the incidence of HBV-related cirrhosis is much higher in males than in females [15], which is consistent with our study. This is probably because males are under greater stress than females and they are more likely to adopt some unhealthy life styles, such as smoking and drinking.

There was no significant difference in genotype and allele frequencies of the rs1861494 SNP in the IFN-γ gene between the case group and control group. Previous studies on SNPs of the IFN-γ gene have indicated that the GG genotype of the rs1861494 SNP was associated with a lower risk of HBV-related cirrhosis [16]. Another study showed that the AA genotype of the rs1861494 SNP was associated with a higher susceptibility to HBV-related cirrhosis [17]. However, we did not observe the protective effect of genotype GG on cirrhosis or that the AA genotype was a risk factor of HBV-related cirrhosis. There was evidence indicating that SNP in the IFN-γ gene did not correlate to susceptibility to hepatocellular carcinoma in the US population [18]. The reason may be that HBV-related cirrhosis is jointly influenced by genetic and environmental factors. Trait expression is not only related to genes, but also to lifestyle, nutritional status, geographical factors and economic levels. Differences in sample size and the introduction of confounding factors and sampling errors may all interfere with the results.

We observed significant difference in allele frequencies of the rs2069718 SNP between the case group and control group. However, the rs2069718 SNP has been rarely reported. It is believed that the rs2069718 SNP correlated to the susceptibility of many diseases. In one report [19], rs2069718 SNP of the IFN-γ gene correlated to retinal scarring and AG and GG genotypes were risk factors for retinal scarring. Moreover, rs2069718 SNP has also been found to be related to a susceptibility to systemic lupus erythematosus, pneumonia-induced septicemia, and osteoporosis [20, 21]. We found significant differences in the frequencies of AA, AG and GG genotypes as well as the A and G alleles of the rs2069718 SNP ($P<0.05$). Thus, the AG and GG genotypes and the G allele of the rs2069718 SNP were risk factors for HBV-related cirrhosis. However, few existing studies have focused on the rs2069718 SNP, and this finding needs to be further verified.

The occurrence and development of diseases are not the result of a single allele, but of the interactions between several SNPs, which are passed down to the next generation in the form of a haplotype [22]. Some phenotypes are also influenced by non-genetic factors. Establishing haplotypes and analyzing their interactions with non-genetic factors will contribute to revealing the pathogenesis of the disease. We compared the frequencies of haplotypes between the case group and control group, and it was found that the AA haplotype was a protective factor of HBV-related cirrhosis (OR=0.666, 95% CI: 0.520~0.852, P=0.001). The AG haplotype (OR=1.674, 95% CI: 1.200~2.336, P=0.002) is a risk factor for HBV-related cirrhosis, and its frequency was significantly higher in the case group than in the control group. By analyzing the interactions between the haplotypes and other factors, we also found that the haplotypes of the two SNPs in the IFN-γ gene did not correlate to any of the above factors ($P>0.05$). The reported risk factors of HBV-related cirrhosis include smoking, drinking, and age. Haplotypes did not interact with any of these factors generally ($P>0.05$). But as judged by OR for some factors compared to the AA haplotype, the AG and GA haplotypes in smokers were associated with a higher risk of HBV-related cirrhosis compared to the AA haplotype among non-smokers. The AG and GA haplotypes in those with a family history and a drinking history were associated with a higher risk of HBV-related cirrhosis compared to the AA genotype among those without a family history or a drinking history. This suggests a local interaction among genetic factors, smoking and drinking status, and family history, and this finding needs to be further verified.

SNPs are considered to be relevant to host susceptibility and a tolerance to diseases and toxins, diversity of clinical manifestations and response to medication therapy [23]. Infection by the same HBV subtype via the same pathway may lead to a different prognosis of subjects of the same ethnic group, gender and age, including acute hepatitis, chronic hepatitis, cirrhosis, or hepatic cancer. A study on the correlation between SNP and disease susceptibility will help screen the subjects carrying the susceptible genotypes, so as to develop preventive measures against the occurrence and development of the diseases. Identifying susceptible or protective genotypes or alleles in patients with HBV-related cirrhosis using the molecular genetics technique is crucial for predicting the high risk for HBV-related cirrhosis among HBsAg carriers. HBV-related cirrhosis can be effectively inhibited by preventive intervention, which offers significant social and academic benefits.

To conclude, by comparing haplotype frequencies between the case group and control group, we identified the haplotypes susceptible to or protective for HBV-related cirrhosis among HbsAg carriers. An interaction analysis was performed between the haplotypes, age, and gender, and a profound study was conducted on the interaction between genetic factors and non-genetic factors that contributed to the susceptibility to HBV-related cirrhosis. Given the few studies on the correlation between two SNPs in the IFN-γ gene and HBV-related cirrhosis, our findings will shed new light on the clinical treatment and research of HBV-related cirrhosis. More studies are needed to confirm our results.

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Disclosure of conflict of interest

None.

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