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Association of the IFNAR1-17470 and IL-10-592 cytokine variants with susceptibility to chronic hepatitis B viral infections in a Chinese population

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ABSTRACT. An association between the sequence variants of cytokine genes and various clinical outcomes in subjects infected with the hepatitis B virus (HBV) has been demonstrated. However, the results are inconsistent and inconclusive. Further studies in other populations and the evaluation of a greater number of individuals may contribute to a better understanding of the influence of the cytokine genetic variants on the evolution of HBV infections. This study was performed to explore the relationships between the sequence variants of *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 and the susceptibility to chronic hepatitis B (CHB) in a Chinese population. A total of 160 patients with CHB and 124 individuals who had spontaneously

recovered (SR) from hepatitis B were enrolled in the present study. The variants at *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 were determined by PCR-restriction fragment length polymorphism analysis and were confirmed by bidirectional DNA sequencing. Significant differences were found between the CHB and the SR groups in the frequency and distribution of the genotypes of both *IFNAR1*-17470 and *IL-10*-592 genes. In comparison with the CHB patients with the *IFNAR1*-17470 G/G variant, the odds ratio (OR) of the CHB patients with the *IFNAR1*-17470 C/C variant developing chronic hepatitis was 2.06 (95%CI = 1.03-4.14). In addition, the OR of the patients with CHB having the IL-10-592 C/C variant developing chronic hepatitis was 2.77 (95%CI = 1.13-4.57) when compared with that of the patients with the *IL-10*-592 A/A variant. In conclusion, sequence variants of both the *IFNAR1*-17470 and *IL-10*-592 genes were correlated with susceptibility to CHB.

Key words: Hepatitis B virus; Chronic hepatitis B; Sequence variants; IFNAR1-17470; IL-10-592

INTRODUCTION

Infections with the hepatitis B virus (HBV) are an important worldwide public health problem (Kao and Chen, 2002). Variable clinical conditions result from exposure to the HBV, such as a spontaneous recovery from acute hepatitis, asymptomatic carrier status, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. In addition to the pathogenicity of the virus, immunological and genetic factors of the host influence the diverse spectrum of disease after infection with the HBV (Guidotti and Chisari, 2001; Jung and Pape, 2002; Kao, 2002). Sequence variants of a variety of genes in the host have been implicated in the diversity of the clinical course of HBV infections (Kim et al., 2003; Deng et al., 2004; Thio et al., 2004; Wang et al., 2004).

Cytokines play an important role in the anti-viral defense system through direct inhibition of viral replication and indirectly by determining the predominant pattern of the host immune response. Sequence variations in the coding, promoter, and untranslated regions of cytokine genes may alter the expression and activity of their respective proteins (Hollegaard and Bidwell, 2006). Cross-sectional studies have demonstrated an association between the sequence variants of cytokine genes and various clinical outcomes in subjects infected with the HBV (Migita et al., 2005; Tseng et al., 2006; Cheong et al., 2006). However, the results are inconsistent and inconclusive.

Tumor necrosis factor-α (TNF-α) plays a pivotal role in viral clearance and the host immune response to the HBV, and the TNF-α production capacity in individuals is influenced primarily by their genetic background (Kim et al., 2003). The *TNF-A* and *TNF-B* genes are located between the human leukocyte antigens *hLA-B* and *hLA-DR* on 6p21.3. The base replacement of G to A at site -308 leads to sequence variants in its promoter region. Several studies have reported conflicting results regarding the effect of the *TNF-α*-308 sequence variants on chronic hepatitis B (CHB) viral infections (Höhler et al., 1998; Du et al., 2006; Basturk et al., 2008).

The endogenous production of interferon serves as an initial defense mechanism against viral infection, and in clinical practice, interferon-α (IFN-α) treatment remains the mainstay of treatment for active hepatitis B. It has been demonstrated that cell surface IFNAR1 expression levels directly affect the efficiency of IFN-α-induced activity (Dondi et al., 2001). The corresponding *IFNAR1* gene is situated on chromosome 21q22.11. Several sequence variants in the *IFNAR1* promoter region have been reported (Aucan et al., 2003; Yoshida et al., 2005), and some variants were associated with IFNAR1 expression levels (Zhou et al., 2009a,b).

Interleukin 10 (IL-10) is another important cytokine that displays anti-inflammatory and anti-fibrotic functions (Lu et al., 2010). The *IL-10* gene is located on chromosome 1. Sequence variations in the *IL-10* promoter region can affect IL-10 production and increase susceptibility to inflammatory diseases. The proximal promoter contains 3 common sequence variants at positions -1082, -819, and -592 relative to the transcription start site (Yan et al., 2009).

In summary, sequence variations in the promoter regions of the *TNF-α*, *IFNAR1*, and *IL-10* genes contribute to the variable clinical outcomes of an HBV infection. Further studies in different populations and the evaluation of a greater number of individuals could contribute to a better understanding of the influence of the cytokine sequence variants on the evolution of HBV infections. Thus, the present study was initiated to genotype the *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 sequence variants in a southwestern Chinese population and to validate the association between genetic variations of these genes and the clinical presentation of HBV infections.

MATERIAL AND METHODS

Study subjects and sample collection

The study participants were composed of 160 patients with CHB and 124 individuals who had spontaneously recovered (SR) from hepatitis B. Written informed consent was obtained from all patients. Blood samples were collected from the CHB patients at the First Affiliated Hospital of Chongqing Medical University. As a control group, 124 spontaneously recovered individuals who had cleared a previous HBV infection, for example, subjects who were HBsAg$^-$ and anti-HBc IgG$^+$, were enrolled in the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in an *a priori* approval by the human research committee of the First Affiliated Hospital of Chongqing Medical University. The status of HBsAg, HBeAg, and HBcAb in the serum of all of the individuals was quantitatively determined with a chemiluminescence assay (Abbott Architect). The detailed demographic and serological profiles of the CHB patients and the SR control subjects are shown in Table 1.

Table 1. Demographic and serological profiles of the chronic hepatitis B (CHB) patients and the spontaneously recovered (SR) control subjects.

Groups	No.	Male/female	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc
CHB	60	31/29	+	-	+	-	+
	100	39/61	+	-	-	+	+
SR	124	64/60	-	-	-	-	+

Genotyping of sequence variants

Genomic DNA was isolated from whole blood by using a commercial DNA purification

kit (Qiagen, Hilden, Germany). The sequence variants of *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 were determined for all subjects by performing a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. The results were confirmed with bi-directional DNA sequencing. The primer sequences and PCR conditions used are listed in Table 2. The PCR amplicons were digested with restriction enzymes and the products were run on a 3% agarose gel.

Table 2. Primer sequences and amplification conditions of the genes.

Genes (variants)	Primer sequence (5'-3')	Initial denaturation	Denaturation	Annealing	Extension	Cycling No.
TNF-A-308	F: AGGCAATAGGTTTTGAGGGCCAT	94°C	94°C	58°C	72°C	35
(G-A)	R: TCCTCCCTGCTCCGATTCCG	5 min	1 min	1 min	1 min	
IL-10-592	F: CCTAGGTCACAGTGACGTGG	94°C	94°C	60°C	72°C	35
(A-C)	R: GGTGAGCACTACCTGACTAGC	2 min	30s	45s	1 min	
IFNAR1-17470	F: CTTTCCCTGTAGTAGTGGTTCT	95°C	95°C	60°C	72°C	35
(G-C)	R: CTGTAGTGAGCCGTGATTGT	5 min	30s	30s	30s	

Statistical analyses

All genotype and allele frequencies were determined by counting their frequency and verifying that they were consistent with the Hardy-Weinberg law. Comparisons were made with a chi-squared (χ^2) test and an independent samples *t*-test. Odds ratios (ORs) were determined with binary logistic regressions (SPSS, version 13.0) for each haplotype, allele, and genotype. The OR was used to reflect the likelihood of carrying a specific genetic sequence variant if a subject was persistently infected with the HBV. A genetic marker with an OR value lower or higher than 1 signified that the marker conferred resistance or susceptibility, respectively, to chronic HBV infection. A P value <0.05 was considered to be statistically significant.

RESULTS

General clinical characteristics

The clinical details and the results of the biochemical analyses from the CHB and SR subjects at the time of the study are shown in Tables 1 and 3. While no significant differences were found in the age, gender, or alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels between the CHB and the SR subjects, there were significant differences between the 2 groups in the antibody statuses for HBsAg and HBcAb (Table 3).

Table 3. Clinical characteristics of the chronic hepatitis B (CHB) patients and spontaneously recovered (SR) controls.

	CHB group (N = 160)	SR control (N = 124)	P
Age	42.15 ± 15.15	42.95 ± 9.53	>0.05
Gender			
Male	70 (44%)	64 (52%)	>0.05
Female	90 (56%)	60 (48%)	
ALT (IU/L)	61.75 ± 232.35	38.15 ± 64.12	>0.05
AST (IU/L)	52.04 ± 143.92	39.15 ± 67.73	>0.05
HBsAg (IU/mL)	206.77 ± 270.24	0.01 ± 001	<0.05
HBcAb (S/CO)	13.20 ± 3.34	4.29 ± 2.83	<0.05

TNF-A-308, *IFNAR1*-17470, and *IL-10*-592 genotyping

The 107-bp PCR product of the *TNF-A* gene was incubated with *Nco*I at 37°C overnight. Homozygotes with the wild type A allele displayed a single band corresponding to the 107 base pair (bp) fragment. Homozygotes with the G allele displayed an 87-bp band, and the heterozygotes displayed both the 107- and 87-bp fragments (Figure 1A).

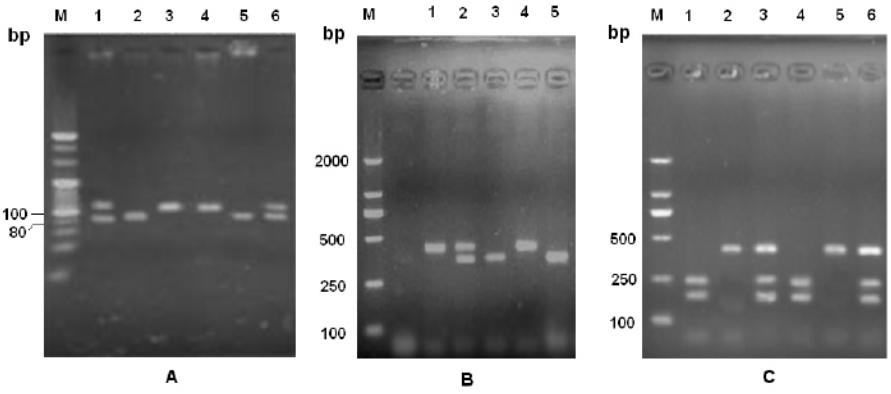

Figure 1. Identification of TNF-A-308, IFNA R1-17470, and IL-10-592 sequence variants by RFLP. PCR amplicons of TNF-A, IFNA R1, and IL-10 were digested with *Nco*I, *Rsa*I, and *Bsm*AI, respectively, and the representative individuals with variant genotypes were shown for each gene. **A.** TNF-A-308 variant: *Lane M* = marker; *lanes 1* and *6* = G/A genotype; *lanes 3* and *4* = A/A genotype; *lanes 2* and *5* = G/G genotype; **B.** IFNAR1-17470 variant: *lane M* = marker; *lanes 1* and *4* = C/C genotype; *lanes 3* and *5* = G/G genotype: *lane 2* = G/C genotype; **C.** IL-10-592 variant: *lane M* = marker; *lanes 1* and *4* = A/A genotype; *lanes 2* and *5* = C/C genotype; *lanes 3* and *6* = A/C genotype.

Incubation with *Bsm*AI at 55°C overnight cleaved the 420-bp PCR product of the *IFNAR1*-17470 G/G variant into 2 fragments of 359 and 61 bp. Homozygotes with the wild-type C allele were undigested at the polymorphic site and yielded only 1 band of 420 bp. The G/C heterozygotes displayed all 3 bands (Figure 1B).

In a similar manner, the amplicon of the *IL-10* gene was digested with *Rsa*I at 37°C overnight. The *IL-10*-592 A/A genotype generated 2 fragments of 236 and 176 bp. The C/C genotype yielded a single 412-bp band and the A/C genotype yielded 3 bands of 412, 236, and 176 bp (Figure 1C).

All of these variants were further confirmed genetically through bi-directional DNA sequencing (data not shown).

Frequency and distribution of the genotypes and alleles of the *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 genes in the patients with CHB and the SR control group

Chi-square tests demonstrated that all of the nine genotypes and allele frequencies were consistent with the Hardy-Weinberg law. Table 4 presents the different frequencies and distributions of the genotypes for *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 in the 2 study groups. While no significant differences were found in the distribution of the *TNF-A*-308 variants between the CHB patients and the SR controls, the frequencies of the *IFNAR1*-17470 C

and *IL-10*-592 C alleles were significantly higher in the CHB group than in the SR control group (χ^2 = 7.90 and 6.26, respectively, P < 0.05).

Table 4. Frequencies and distribution of the genotypes and allele of *TNF-A*-308, *IFNAR1*-17470, *IL-10*-592 in the chronic hepatitis B (CHB) and spontaneously recovered (SR) groups.

Genotypes	SR (N = 124)		CHB (N = 160)
TNF-A-308			
G/*G*	92 (0.74)		116 (0.72)
G/*A*	28 (0.22)		37 (0.23)
A/*A*	4 (0.04)		7 (0.05)
Alleles		χ^2 = 0.27, P > 0.05	
G	212 (0.85)		269 (0.84)
A	36 (0.15)		51 (0.16)
IFNAR1-17470			
G/*G*	38 (0.31)		46 (0.29)
G/*C*	68 (0.55)		69 (0.43)
C/*C*	18 (0.14)		45 (0.28)
Alleles		χ^2 = 7.90, P < 0.05	
G	144 (0.58)		161 (0.50)
C	104 (0.42)		159 (0.50)
IL-10-592			
C/*C*	16 (0.13)		34 (0.21)
A/*C*	48 (0.39)		70 (0.44)
A/*A*	60 (0.48)		56 (0.35)
Alleles		χ^2 = 6.26, P < 0.05	
C	80 (0.32)		138 (0.43)
A	168 (0.68)		182 (0.57)

IFNAR1-17470 C/C and *IL-10*-592 C/C variants were associated with susceptibility to chronic HBV infection

Table 5 presents the different risks of each variant of *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 in the 2 study groups. While no significant differences between the CHB patients and the SR controls were found for the ORs of the *TNF-A*-308 variants, both the *IFNAR1*-17470 C/C and the *IL-10*-592 C/C variants were associated with a higher susceptibility to chronic HBV infections. The OR of the CHB patients with the *IFNAR1*-17470 C/C variant developing chronic hepatitis was 2.06 (95%CI = 1.03-4.14) in comparison with patients with the G/G variant. Similarly, the OR of the CHB patients with the *IL-10*-592 C/C variant developing chronic hepatitis was 2.77 (95%CI = 1.13-4.57) when compared with that of the patients with the A/A variant.

Table 5. Risks of *TNF-A*-308, *IL-10*-592, *IFNAR1*-17470 polymorphisms for the development of chronic hepatitis B (CHB) among patients and controls.

Genotypes	Risk for CHB OR (95%CI)
TNF-A-308	
G/G	1.00
A/A	1.39 (0.39-4.89)
A/G	1.05 (0.60-1.84)
IFNA R1-17470	
G/G	1.00
C/C	2.06 (1.03-4.14)[&]
G/C	0.84 (0.49-1.44)
IL-10-592	
A/A	1.00
C/C	2.77 (1.13-4.57)[&]
A/C	1.56 (0.93-2.62)

[&]P < 0.05.

DISCUSSION

Sequence variants of a variety of cytokine genes have been implicated in the diversity of the clinical course of HBV infections. In the present study, no significant differences were found between the CHB and the SR groups in the distribution or ORs of the *TNF-A*-308 variants. However, the frequencies of the *IFNAR1*-17470 C and *IL-10*-592 C alleles were significantly higher in the patients with CHB than in the SR control group. Both the *IFNAR1*-17470 C/C and *IL-10*-592 C/C variants were associated with a higher susceptibility to chronic HBV infections in the Chinese population studied.

Although Basturk et al. (2008) found that the frequency of the *TNF-A*-308 G/G variant in a Turkish population was significantly higher in individuals infected with the HBV than in the healthy controls, this study found no significant differences between the CHB and the SR groups in the distribution or the ORs of the *TNF-A*-308 variants. This discrepancy may be due to the different control groups used in the studies. While Basturk et al. (2008) recruited healthy individuals to use for their control group, our group recruited individuals who had spontaneously recovered from hepatitis B as controls.

The variants in the *IFNAR1* promoter region at -568/-77 and the sequence variants in the *IFNAR1* coding region at 19158C/G have previously been shown to be associated with a susceptibility to chronic HBV infections (Zhou et al., 2009b). Further exploration at the functional level demonstrated that a C/G variant at 19,158 resulted in a non-synonymous substitution in the extracellular region of IFNAR1, leading to a decreased stability of the IFNAR1 protein. Moreover, a later study demonstrated that 2 linked sequence variants at -408 and -3 of the *IFNAR1* promoter were associated with a susceptibility to chronic HBV infections (Zhou et al., 2009a). Further investigation of the functional mechanisms involved revealed that an infection with the HBV decreased the transcriptional levels of the *IFNAR1*-3T variant. Our data correlating the *IFNAR1*-17470 C/C variant with the onset of chronic HBV infections are consistent with a recent study that also found that the C/C variant of *IFNAR1*-17470 was present more frequently in the patients infected with HBV than in the SR controls (Song et al., 2008).

The seroconversion of HBeAg generally indicates a diminished active viral replication rate and a decrease in disease activity (Fattovich et al., 1986). A recent prospective cohort study (Wu et al., 2010) demonstrated that the *IL-10*-1082 G/G variant is associated with higher serum levels of IL-10 and an early, spontaneous HBeAg seroconversion. Yan et al. (2009) have demonstrated that the CHB *IL-10*-592 C susceptibility allele also displayed greater transcription activity than did the *IL-10*-592 A allele. We predict that the *IL-10*-592 C/C variant may also be associated with higher serum levels of IL-10, and thus, with early and spontaneous HBeAg seroconversion in patients with CHB.

In conclusion, the present study explored the relationships between the *TNF-A*-308, *IFNAR1*-17470, and *IL-10*-592 sequence variants and susceptibility to CHB in a southwestern Chinese population. Both the *IFNAR1*-17470 C/C and *IL-10*-592 C/C variants were associated with higher susceptibilities to chronic HBV infections. However, whether and how the *IFNAR1*-17470 and *IL-10*-592 C/C variants influence IFNAR1 and IL-10 protein expression and the response to treatment by patients with CHB infections remain to be elucidated. We are presently performing mutagenesis and luciferase assays to explore the functional significance of the *IFNAR1*-17470 and *IL-10*-592 variants.

Conflicts of interest

The authors declare no conflict of interest.

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