Interferon gamma gene polymorphisms and chronic hepatitis B infections in Iranian population

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ABSTRACT

Background/Aims: Chronic hepatitis B is an important health problem in all countries. Interferon gamma (IFN-γ) is a proinflammatory T-helper 1 cytokine, which can exert antiproliferative and antitumor activities. Some single nucleotide polymorphisms (SNPs) in IFN-γ and IFN-γ R1 genes may influence the susceptibility to hepatitis B virus (HBV). Here, we evaluated the impact of IFN-γ (+874 T/A) and its receptor (-611A/G, +189G/C, and +95C/T) polymorphisms and the risk of HBV in Iranian patients.

Materials and Methods: SNPs of IFN-γ and its receptor genotypes were determined in 221 infected patients with HBV and 200 people without HBV using amplification-refractory mutation system polymerase chain reaction (PCR) and PCR restriction fragment length polymorphism method.

Results: In this study, we showed an obvious relationship between IFN-γ SNPs and susceptibility to chronic HBV. Our findings suggest that IFN-γ-874A allele increases the risk of disease, and carriers of the T allele have reduced susceptibility to infection. In addition, there was no relationship between the -611A/G, +189G/C, and +95C/T regions of IFN-γ R1 and HBV.

Conclusion: Our observations demonstrate +874 T/A SNP as a predicting factor in patients who have the risk of HBV.

Keywords: Interferon gamma, receptor, gene, polymorphisms, hepatitis B virus

INTRODUCTION

Nowadays, it is recognized that hepatitis B virus (HBV) is related to imperfect liver function through acute/chronic situations. Many liver malignant lesions (cirrhosis and hepatocellular carcinoma) are caused by hepatitis (1). The mechanism of infection is not entirely understood, but some studies have shown that the genetic factors change the pathogenesis of infection and can be a sign of disease (2, 3).

Cytokines can initiate and maintain the immune response to chronic diseases (4, 5). Genetic changes can affect the immune responses by changing the functions or levels of the cytokines and their receptors. Single nucleotide polymorphisms (SNPs) are biological markers because they occur at every 300 nucleotides and can affect the susceptibility of the infectious disease (6, 7).

Interferon gamma (IFN-γ) is a proinflammatory cytokine. It is a T-helper 1 (Th1) cytokine that can activate the cellular immunity via lymphocytes, such as cytotoxic CD8+ T cells (8). In patients with acute hepatitis B, a large amount of this cytokine is produced by T-lymphocytes (9). IFN-γ reduces the hepatitis B viral replication (10). In addition, low levels of IFN-γ are secreted in an inactive carrier (11). The abovementioned facts indicate that IFN-γ has a vital role in HBV susceptibility and clearance of infection. The SNPs in the regulatory regions and introns of the *IFN-γ* gene can change the expression of this cytokine, which increases the risk of hepatitis development (12). In addition, it has been shown that the production of cytokines can reduce the HBV replication in transgenic mice. In these animals, any lethal changes of hepatocytes are not found (11, 13, 14). Our recent study revealed an association between IFN-γ SNPs and chronic periodontitis as a chronic inflammation (15). The IFN-γ receptor is a heterodimeric protein. It has two subunits: IFN-γ R1 and IFN-γ R2. These subunits mediate the binding of IFN-γ to the cell surface through Janus family kinases (Jak1 and Jak2) and regulate the signaling cascade (16). Previous researches have shown that there were significant relationships between SNPs of IFN-γ and its receptor R1 and the pathogenesis of HBV. Goidotti et.al. (17) reported that SNPs in the promoter region of *IFN-γ R* cause hepatic fibrosis in the

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chronic infection. In other words, IFN-γ R1 variations, such as *rs1327474* (*-611A/G*), *rs11914* (*+189G/C*), and *rs7749390* (*+95C/T*) can affect *IFN-γ R1* gene expression and sensitivity of the cells to the IFN-γ (10, 11, 16-19). The *rs2430561* is located in intron areas of the *IFN-γ* gene. The TT and AA genotypes of +874 SNP produce high and low levels of IFN-γ, respectively. Reduced amount of IFN-γ can increase the risk of HBV disease (12, 20, 21). Recent studies indicated the relationship between the *rs2430561* and some chronic diseases, such as pulmonary tuberculosis (22), asthma (23), and brucellosis (24). Nowadays, studies have focused on the *rs2430561* and HBV risk and HBV-related diseases (10, 25-29). However, there are contradictory results in the field of *IFN-γ* and *IFN-γ R1* polymorphisms with the risk of hepatitis B infection. Owing to the impact of cytokines on HBV, in this case-control study, we have indicated the relationship between chronic HBV infection and 4 SNPs of the *IFN-γ* and its receptor R1 in a sample of the Iranian population.

MATERIALS AND METHODS

Study subjects

In this study, 221 patients with chronic hepatitis B and 200 healthy individuals were evaluated. The Institutional Ethics Committee of the ZAUMS approved the study (grant number 6809). Patients with $HBsAg^+$ who referred to the Blood Transfusion Center in Zahedan, Iran, between March and August 2017 were selected. The liver function of these patients was impaired. Their transaminases levels were twice as normal for at least 6 months. All the patients with HBV were positive for HBsAg with enzyme-linked immunosorbent assay and HBV-DNA by reverse transcription-polymerase chain reaction (RT-PCR). Clinicopathological data and demographic characteristics were collected from the medical records and pathologic data (Table 1). Patients with hepatitis C virus (HCV), hepatitis E virus, hepatitis A virus, human immunodeficiency virus (HIV), alcohol consumption, drug abuse, and liver diseases were excluded. The control group had normal values for alanine transaminase levels and no history of HBV, HCV, and HIV, or they were $anti\text{-}HBs^+$ and $anti\text{-}HBc^+$ or patients with resolved HBV. Participants were selected from the same geographical area. All the groups were matched in terms of age, gender, and ethnicity; therefore, there was no significant difference between the two groups (p>0.05). Informed consent was obtained from all the participants.

MAIN POINTS

- *IFN-γ can exert antiproliferative and antitumor activities.*
- *SNPs in IFN-γ and IFN-γ R1 genes may influence the susceptibility to HBV.*
- *IFN-γ-874A allele increases the risk of HBV, and carriers of the T allele have reduced susceptibility to infection.*
- *+874 T/A SNP may be a predicting factor in patients who have the risk of HBV.*

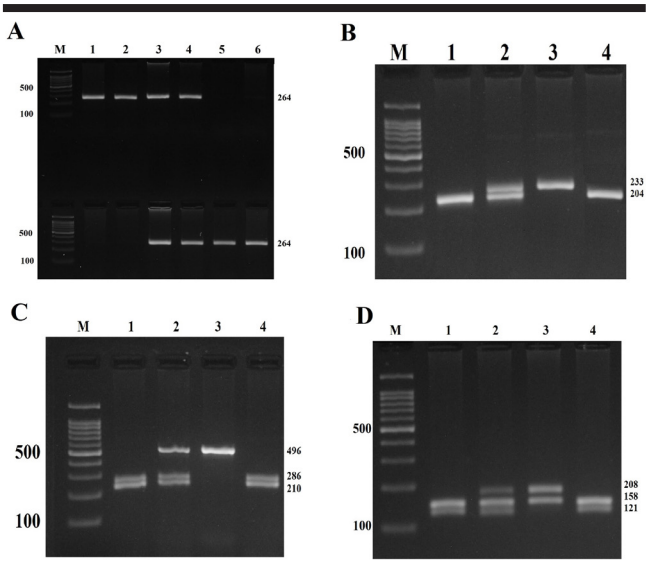

Figure 1. a-d. The electrophoresis pattern of IFN-γ (+874T/A), IFN-γR1 (-611A/G), (+189T/G), and (+95C/T) polymorphisms. (a) The electrophoresis pattern of ARMS-PCR on 2% agarose gel at +874 T/A SNP; M marker 100 bp, 1 and 2 genotype AA, 3 and 4 genotype AT, 5 and 6 genotype TT. (b) The digestion pattern of Hpy188I restriction enzyme on 3% agarose gel at -611 A/G SNP; M marker 100 bp, 1 and 4 genotype GG, 2 genotype AG, 3 genotype AA. (c) The digestion pattern of TaqI restriction enzyme on 2% agarose gel at +189T/G SNP, M marker 100 bp, 1 and 4 genotype GG, 2 genotype GT, 3 genotype TT. (d) The digestion pattern of BstC8I restriction enzyme on 3% agarose gel at +95 C/T SNP; M marker 100 bp, 1 and 4 genotype CC, 2 genotype CT, 3 genotype TT.

Table 1. Demographic data of patients with chronic hepatitis B (HBV) and the control group.

Parameters	HBV, N (%)	Control, N (%)	p
Age (years)	29.81±8.05	31.11±7.54	0.091
Sex			
Male	122 (55.2)	109 (54.5)	0.885
Female	99 (44.8)	91 (45.5)	
Ethnicities			
Sistani	92 (41.6)	86 (43.0)	0.817
Baluch	59 (26.7)	48(24.0)	
Others	70 (31.7)	66 (33.0)	

HBV: hepatitis B virus; N: number.

Table 2. The PCR protocols for Genetic analysis of IFN-γ R1 (-611A/G), (+189T/G), and (+95C/T) and IFN+874 T/A gene polymorphisms using RFLP-PCR and ARMSPCR.

Polymorphism	Primers	PCR	PCR conditions	Restriction Enzyme	Allele Phenotype
-611A/G	F: AGAGCAGACCTCTTCATGAGAGGCTGTCT	RFLP-PCR	Denaturation: 95°C for 30 s	Hpy188I	G allele: 204 bp+29 bp
	R: ACATTTTTAGAAGAGAATGAGACTTCAAA		Annealing: 62°C for 30 s		A allele: 233 bp
			Extension: 72°C for 30 s		
			Final extension: 72°C for 5 min		
+189T/G	F: CTCTTTCTCCTACCCCTTGTCAT	RFLP-PCR	Denaturation: 95°C for 30 s	TaqI	G allele: 286 bp+210 bp
	R: CAGCGCATAATCGTATTTAAAAGTG		Annealing: 63.7°C for 30 s		T allele: 496 bp
			Extension: 72°C for 30 s		
			Final extension: 72°C for 5 min		
+95C/T	F: GCCATTTGGTGGTCCATTAC	RFLP-PCR	Denaturation: 95°C for 30 s	BstC8I	G allele:87 bp+121
	R: TCCAGACAGCTGGAATCAGT		Annealing: 62°C for 30 s		bp+158 bp
			Extension: 72°C for 30 s		T allele: 208 bp and
			Final extension: 72°C for 5 min		158 bp
+874 T/A	F (T allele): TTCTTACAACACAAAATCAAATCT	ARMSPCR	Denaturation: 95°C for 30 s	-	A allele: 264 bp
	F (A allele): TTCTTACAACACAAAATCAAATCA		Annealing: 57.1°C for 30 s		T allele: 264 bp
	R: TCAACAAAGCTGATACTCCA		Extension: 72°C for 30 s		
			Final extension: 72°C for 5 min		

RFLP-PCR, Restriction fragment length polymorphism; ARMSPCR, amplification refractory mutation system-based polymerase chain reaction.

DNA extraction and genotyping

Samples of 2 ml of whole blood were obtained from all the participants and stored in −80°C for subsequent DNA extraction. DNA was extracted from the buffy coat using the salting-out method. Furthermore, *+874 T/A* polymorphism was detected by the amplification-refractory mutation system PCR method; 2X Prime Taq Premix (Daejeon, Genet Bio, Korea) was used for PCR. The content of each reaction included: 1 µl of each primer, 100 ng/ml of DNA, 10 µl of Taq Premix, and 7 µl of water. PCR protocol was as follows: initial denaturation, 95°C for 5 min; 30 cycles of denaturation, 95°C for 30 s; annealing, 57.1°C for 30 s; extension, 72°C for 30 s; and final extension, 72°C for 5 min. The amplified products were separated in 2 sample products, 1 for each specific A or T allele of the *IFN-γ +874 A/T* variant (Figure 1a). *IFN-γ R1 rs1327474* (*-611A/G*), *rs11914* (*+189G/C*), and *rs7749390* (*+95C/T*) gene polymorphisms were analyzed by restriction fragment length polymorphism protocols. NCBI data bank (http:www.ncbi.nlm.nih.gov) was used to design the primers for SNPs (Table 2). Table 2 shows the PCR amplification conditions. The reaction products were identified by electrophoresis (Figures 1a-d). To confirm the results, 15% of the samples were regenotyped with DNA sequencing with 100% concordance of the quality.

Statistical Analysis

Statistical analysis was performed using the Statistical Packages for the Social Sciences (SPSS) program version 20 statistical software package (IBM Corp.; Armonk, NY, USA). To compare the relationship between genotypes and HBV, logistic regression (OR and 95% CI) was used. Data are expressed as mean±SD. P values less than 0.05 were considered as statistically significant.

RESULTS

Demographic data of the participants

Demographic data of the study participants are shown in Table 1. The mean age of patients and controls was 29.81±8.05 (age range of 12-67) years and 31.11±7.54 (age range of 17-67) years, respectively. There was no significant

difference between the 2 groups regarding age, gender, and ethnicities (p>0.05).

Genotyping of SNPs

Table 3 shows the genotype and allele frequency distributions of the IFN-γ and its receptor R1 SNPs. The distributions of alleles from all SNPs were in accordance with Hardy–Weinberg principle. The frequencies of *rs62559044* TT, TA, and AA genotypes in patients were 15.8%, 48.9%, and 35.3%, respectively, and in controls were 24%, 54.5%, and 21.5%, respectively. Significantly, AA genotype had a different frequency in the patients compared with the controls (OR=0.402, 95% CI=0.227–0.713). Moreover, the frequency of allele A in the patient group (59.7%) was higher than that in the control group (48.8%) (OR=1.559, 95% CI=1.187–2.049). Genotype and allele frequencies of *611A/G*, *+189T/G*, and *+95C/T* were not different between the 2 groups (p=0.953, p=0.251, and p=0.527, respectively). Table 4 reports the haplotype analysis. In this study, 12 haplotypes were derived. We did not find any significant differences with regard to the haplotype analysis between patients and healthy controls (p=0.172, X2=15.244).

Table 3. The frequency of genotypes and alleles of IFN-γ (+874T/A), IFN-γ R1 (-611A/G), (+189T/G), and (+95C/T) polymorphisms.

IFN-γ and IFN-γR1 polymorphisms	Control, No. (%)	HBV, No. (%)	OR (95% CI)	p
IFN-γ (+874T/A)				
AA	43 (21.5)	78 (35.3)	0.402 (CI=0.227–0.713)	0.002
TT	48 (24.0)	35 (15.8)	Ref=1	-
TA	109 (54.5)	108 (48.9)	0.736 (CI=0.442–1.226)	0.239
AA+TA	152 (76.0)	186 (84.2)	0.596 (CI=0.367–0.968)	0.037
Allele				
A	195 (48.8)	364 (59.7)	1.559 (CI=1.187–2.049)	0.001
T	205 (51.2)	178 (40.3)	Ref=1	-
IFN-γ R1 (-611A/G)				
AA	60 (30.0)	64 (29.0)	1.094 (CI=0.620–1.929)	0.757
GA	104 (52.0)	115 (52.0)	1.055 (CI=0.628–1.771)	0.839
GG	36 (18.0)	42 (19.0)	Ref=1	-
AA+GA	164 (82.0)	179 (81.0)	1.069 (CI=0.653–1.750)	0.791
Allele				
A	224 (56.0)	243 (55.0)	0.959 (CI=0.731–1.260)	0.766
G	176 (44.0)	199 (45.0)	Ref=1	-
IFN-γ R1(+189T/G)				
GG	23 (11.5)	31 (14.0)	0.883 (CI=0.488–1.597)	0.680
GT	61 (30.5)	52 (23.5)	1.396 (CI=0.895–2.177)	0.142
TT	116 (58.0)	138 (62.4)	Ref=1	-
GG+GT	84 (42.0)	83 (37.6)	1.204 (CI=0.814–1.780)	0.352
G	107 (26.8)	114 (25.8)	0.952 (CI=0.700–1.294)	0.752
T	293 (73.2)	328 (74.2)	Ref=1	-
IFN-γ R1(+95C/T)				
CC	45 (22.5)	47 (21.3)	Ref=1	-
TC	117 (58.5)	122 (55.2)	1.002 (CI=0.619–1.620)	0.995
TT	38 (19.0)	52 (23.5)	0.763 (CI=0.425–1.370)	0.365
TC+TT	155 (77.5)	174 (78.7)	0.930 (CI=0.586–1.478)	0.760
C	207 (51.8)	216 ()48.9	Ref=1	-
T	193 (48.2)	226 (51.1)	1.122 (CI=0.856–1.471)	0.404

IFN-γ: Interferon gamma; IFN-γR1: Interferon gamma receptor; HBV: hepatitis B virus; No: number; p: p-value; CI: confidence interval.

DISCUSSION

Cytokines are immune mediators that change the nature of infections. Variations in the cytokine genes can affect inflammatory responses in different ethnic popu-

Table 4. Haplotype frequencies in chronic hepatitis B (case) and normal participants (control).

Haplotypes	Control group No. (%)	HBV group No. (%)
AATT	53 (26.5)	66 (29.9)
AGTG	8 (4.0)	11 (5.0)
AGCT	2 (1.0)	10 (4.5)
TACT	8 (4.0)	8 (3.6)
TGTT	13 (6.5)	13 (5.9)
AACT	15 (7.5)	9 (4.1)
AATG	57 (28.5)	45 (20.4)
AGTT	3 (1.5)	11 (5.0)
AACG	11 (5.5)	17 (7.7)
AGCG	3 (1.5)	4 (1.8)
TATT	22 (11)	21 (9.5)
TATG	5 (2.5)	6 (2.7)
TOTAL	200 (100.0)	221 (100.0)
$\chi 2=15.244$, p=0.172		

HBV: hepatitis B virus; No: number; P: p-value.

lations (30, 31). In this study, we examined the possible relationship between IFN-γ (*+874T/A*) and its receptor R1 (*-611A/G, +189G/C*, and *+95C/T*) SNPs and susceptibility to chronic HBV infection. In this study, we revealed an obvious association between *+874T/A* genotype and allele distributions and the risk of HBV. Our findings suggest that allele *A* increases the risk of disease, and the carriers of the T allele have reduced susceptibility to infection. In addition, there were no differences between the *-611A/G*, *+189G/C*, and *+95C/T* regions of IFN-γ R1 and HBV. Our findings are consistent with some studies (32, 33) and different with others (34-36).

IFN-γ (*+874T/A*) gene polymorphisms can change this cytokine production. According to previous studies; TT, AA, and TA genotypes are related to high, low, and intermediate secretion of IFN-γ, respectively. This SNP is located in the transcription factor binding site of nuclear factor kappa-light-chain-enhancer of activated B cells. Studies have revealed that the sequences containing *+874T* allele can bind to this factor (12). Therefore, individuals with *A* allele have a weak immune response against HBV infection because they have low plasma levels of IFN-γ, but people with the *T* allele have higher levels of this cytokine. This pattern was confirmed by the significantly increased prevalence of the AA genotype in patients with chronic HBV compared with the controls. Our findings indicated that TT and TA genotypes could reduce the risk of chronic HBV infection compared with AA genotype. Moreover, there was an obvious relationship between *+874A* allele and severity of the HBV infection compared with T allele. In other words, T allele may be a protective factor against HBV infection. Our results were inconsistent with those by Sharhan et al. (32) who reported *+874A* allele as a risk factor for chronic hepatitis B infection. Similar results in our study and the study by Sharhan et al. (32) could be because of the same geographical area (Asia), but the large sample size increases the power of this study. In agreement with our study, Sun et al. (33) revealed that *+874T/A* SNP increases the risk of HBV-related diseases. They reported that, especially in Asians, AA genotype is related to a 1.350-fold higher risk of hepatic lesions caused by HBV (33).

In addition, Conde et al. (34), Sun et al. (35), and Karatayli et al. (36) indicated the lack of a significant relationship between *+874T/A* SNP and HBV infection. The *+874T/A* SNP was more common in the study population by Conde et al. (34), which presented a lack of relationship between *+874T/A* SNP and chronic hepatitis B infection. In contrast, this study reported that *+874AA* genotype and *A* allele could increase the susceptibility to infection. Sun et al. (35) did not found a significant relationship between *+874 T/A* SNP and HBV-related liver cirrhosis, but they revealed that AA genotype has a higher frequency in the Chinese patients than the Tunisian patients. Moreover, they found that A/A haplotype (+874 and +2109 locus of IFN-γ) could increase the risk of HBV-related liver cirrhosis, whereas T/G haplotype could decrease the risk of HBV-related liver cirrhosis. It means that T/G haplotype is a protective factor, and A/A haplotype can increase the risk of chronic HBV as a risk factor. Despite different results, findings by Sun et al. (35) confirm our results with regard to the relationship between *+874A* allele and HBV infection. Karatayli et al. (36) studied the +874 position of the *IFN-γ* gene in patients with chronic hepatitis delta (CHD), chronic hepatitis B (CHB), and resolved HBV. They reported that frequency of the AA genotype was 14%, 31%, and 20% of CHD, CHB, and resolved HBV individuals, respectively. They did not find a significant difference with regard to the genotypes and the alleles A and T between the groups. Instead, in this study, although the frequency of the alleles was not significantly different between the groups, it was found that the amount of allele A in patients with CHB was slightly more than the other groups.

Also, IFN-γ has a multifunctional role in the host defense against infections. It is possible that genetic variations, such as other SNPs of the *IFN-γ* gene (*-746G*), may have

an effect on pathogenesis of the disease (37). Moreover, IFN-γ by binding to its receptors can activate the JAK-STAT intracellular signaling pathway, and SNPs of receptors may have functional effects on natural history of the disease (38). These conflicting results may be because of the small sample size and genetic variations among different populations. Therefore, the real effect of the *+874T/A* polymorphism remains unknown.

It seems that IFN-γ R1 polymorphisms are associated with chronic diseases (39). In this regard, Kardom et al. (19) revealed that *IFN-γ R1-56 T/C* SNP is related to tuberculosis.. Furthermore, Zhou et al. (20) reported that the T allele of *-56 T/C* SNP was associated with risk of HBV infection in Chinese patients. Similar to our results, they could not find a significant relationship between IFN-γ receptor *R1-611A/G* SNP and chronic hepatitis B. Isomi et al. (40) assessed the relationship between the *-56 T/C* polymorphism and malaria and did not find any significant difference between *-56T/C* SNP and malaria. It seems that *-56T/C* SNP has been related to HBV more than other SNPs within the *IFN-γ R1* gene (41). In addition, different ethnicities influence the variations of the *IFN-γ R1*gene polymorphisms. For example, there is a deletion/insertion SNP at position -470 in Africans but not in Europeans and Asians (20). It is revealed that IFN-γ receptors R1 and R2 play a key role in the immune response against hepatitis B infection. Deficiencies in the transcription and function of these receptors can change the nature of infectious diseases, such as chronic HBV infection. However, according to our results, it seems that *IFN-γ R1* (*-611A/G, +189G/C*, and *+95C/T*) SNPs may not affect the risk of chronic hepatitis B.

Haplotypes are used for the identification of predisposing genes of complex diseases. We performed haplotype analysis for all SNPs. It is revealed that people with haplotype AG (*+874A* allele and *+2109G* allele) have an increased susceptibility to hepatitis B (27). In our study, haplotype analysis among patients and the control group did not show any significant differences.

In summary, as we revealed in this study, *IFN-γ +874T/A*, not *IFN-γ R1* (*-611A/G, +189G/C*, and *+95C/T*) polymorphism can influence the risk of chronic hepatitis B. Frequencies of genotypes are different in various ethnicities, for example, amount of allele A of the *+874T/A* is much more in the Asian population than the Caucasian population. In addition, some parameters (genotyping methods, inclusion criteria, and sample sizes) can give contradictory results. In conclusion, it seems that allele A of the *+874T/A* SNP can be considered as a risk factor for susceptibility to chronic hepatitis B. Finally, owing to the complexity of HBV infection, a study of the polymorphisms of other important cytokines and their receptors in patients with HBV is recommended.

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of the Zahedan University of Medical Sciences (IR.ZAUMS.REC.1393.6809, 2018, grant number 6809).

Informed Consent: Informed consent was written and signed by all individual participants included in the study.

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Conflict of Interest: The authors have no conflict of interests to declare.

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