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JAK1 Gene Polymorphisms Are Associated with the Outcomes of Hepatitis B Virus Infection, but Not with α Interferon Therapy Response in a Han Chinese Population

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Aims: Janus kinase 1 (JAK1) is a key member in the interferon (IFN) signaling pathway. Recent studies suggested single-nucleotide polymorphisms (SNPs) in IFN pathway genes are associated with outcomes of hepatitis B virus (HBV) infection and response to IFNα therapy. The aim of the study is to investigate whether SNPs in *JAK1* were associated with outcomes of HBV infection and response to IFNα therapy. *Methods:* We enrolled 395 chronic hepatitis B (CHB) patients and 251 subjects with the inactive carrier state, and 256 CHB patients who received IFNα treatment, with therapy efficacy evaluated. Twelve SNPs: rs310227, rs7531799, rs7546545, rs17127174, rs3790541, rs10493373, rs2780898, rs310247, rs310196, rs2780895, rs4244165, and rs17127024 in JAK1, which could represent all SNPs with minor allele frequency >0.2 recorded in the HapMap database were genotyped using a polymerase chain reaction–restriction fragment length polymorphism protocol and the TaqMan method. *Results:* SNP rs17127024 was associated with outcomes of HBV infection in an allele frequency ($p=0.014$) and genotype distributions ($p=0.031$), while SNP rs4244165 was associated with outcomes of HBV infection only in genotype distributions ($p=0.008$). There were no significant differences in allele frequencies and genotype distributions of these SNPs between the response group and the nonresponse group to IFNα therapy. *Conclusions:* SNPs rs4244165 and rs17127024 in *JAK1* were associated with outcomes of HBV infection, but not with response to IFNα therapy.

Introduction

Hepatitis B virus (HBV) infection is a serious public health problem all over the world. HBV infection results in 0.5 to 1.2 million deaths per year, which is mainly caused by chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Rehermann and Nascimbeni, 2005). Generally, clinical consequences of HBV infection vary in different persons. About 90%–95% of infected adults can eliminate the virus spontaneously and only 5%–10% of them become chronic HBV carriers, among whom 20%-30% develop into chronic hepatitis B (CHB) and about 5% go on to liver cirrhosis and hepatocellular carcinoma after a long disease course (Ganem and Prince, 2004). Several factors are known to be involved in the procession of HBV infection, such as age, viral factors, host immunity, and genetic components (Wang, 2003; Schaefer, 2005). Genetic studies provide robust evidence that polymorphisms in the human genome contribute greatly to the susceptibility to HBV infection (Thio *et al.*, 2000).

Janus kinase 1 (JAK1), first identified in 1991, is a member of a new class of protein-tyrosine kinases, and there are four JAKs in mammals, JAK1, JAK2, JAK3, and Tyk2, which are crucial for cytokine receptor signaling and regulate blood formation and the immune response (Wilks *et al.*, 1991; Yamaoka *et al.*, 2004; Vainchenker *et al.*, 2008). The *JAK1* gene, with 25 exons and encoding a protein of 1154 amino acids, is located on chromosome 1p31.3. Recent studies have reported that polymorphisms in the *JAK1* gene may be functional and contribute to human cancer development and autoimmune diseases (Staerk *et al.*, 2005; Jeong *et al.*, 2008). Also, JAK1 is a

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key member in both the α/β interferon (IFNα/β) and IFNγ signaling pathways (which included 13 genes) (Kalvakolanu, 2003), so it should be playing an important role in IFN therapy and antivirus mechanism as in HBV infection. However, up to the present, there are no association studies concerning the *JAK1* gene and hepatitis B.

Here, we hypothesized that single-nucleotide polymorphisms (SNPs) in *JAK1* gene may be associated with outcomes of HBV infection and the efficiency of IFNα therapy. We performed a genetic association study on 12 SNPs (rs310227, rs7531799, rs7546545, rs17127174, rs3790541, rs10493373, rs2780898, rs310247, rs310196, rs2780895, rs4244165, and rs17127024), which showed moderate variations in JAK1 among Han Chinese subjects to elucidate host genetic factors that can affect the outcome of HBV infection and response to IFNα therapy.

Materials and Methods

Subjects

The subjects enrolled in the present study were 395 CHB patients (322 men/73 women, mean age = 32.63 ± 10.64 years) and 251 subjects with inactive carrier state as controls (173 men/78 women, mean age = 30.70 ± 10.84 years). All subjects were recruited from Beijing Youan Hospital from November 2001 to October 2003 and were all Northern Chinese Han from Beijing. Subjects with inactive carrier state were identified with the following diagnostic criteria: HBsAg seropositive for more than 1 year, with normal liver functional indexes and without any signs and symptoms of hepatitis. CHB was diagnosed if: serum level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were continuously abnormal, HBsAg and/or HBeAg seropositive, anti-HBs seronegative after the sixth month from acute infection. Exclusion criteria: (1) evidence of past or current infection by other hepatitis viruses or hepatitis not caused by HBV; (2) cirrhosis or hepatocellular carcinoma; or (3) not of Han ethnicity. Out of the 395 CHB patients, 256 treatment-naïve CHB patients were treated by IFNα-1b (Sanyuan Genetic Company, Beijing, China) alone, first 3–5 million units per day (MU/d) for 2 weeks, and then followed by 3–5 MU every other day for 6 months. Patients were then followed up for 6 months to evaluate the therapeutic effects: complete response (CR) is confirmed by the following evidences: ALT and AST normal, HBV-DNA negative, HBeAg converts to negative, or with anti-HBe seropositive. Partial response (PR) is confirmed by: only ALT and AST becomes normal; or HBeAg converts to negative, but HBV-DNA remains positive. Nonresponse (NR) is defined if any criteria mentioned above are not satisfied. The study was carried out in accordance with the guidelines of the Helsinki Declaration, performed after obtaining informed consent from all subjects, and approved by the ethics committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences.

Serological testing

Enzyme-linked immunosorbent assay (ELISA) was used for detection of serum HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc (IMX; Abbott Diagnostics, North Chicago, IL).

SNP selection and genotyping

Genomic DNA was extracted from the peripheral blood by using a salting-out protocol (Miller *et al.*, 1988). We selected Tag-SNPs in the present study using the Tagger Pairwise Tagging protocol with an r^2 cutoff value of 0.8, and minor allele frequency (MAF) >0.2 according to HapMap Data Phase II, Sept 08, on NCBI B36 assembly, dbSNP b126 of Han Chinese Beijing. The 12 SNPs (rs310227, rs7531799, rs7546545, rs17127174, rs3790541, rs10493373, rs2780898, rs310247, rs310196, rs2780895, rs4244165, and rs17127024) genotyped in the present study could represent all SNPs with MAF >0.2 recorded in the HapMap database of the *JAK1* gene. The SNP ID numbers and detailed sequence information are available at www.ncbi.nlm.nih.gov/SNP/. The 12 SNPs were genotyped using a polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) protocol and the TaqMan method (Applied Biosystems, Foster City, CA), according to the manufacture's protocols. The details of the PCR-RFLP genotyping experiments are summarized in Table 1. All the samples were successfully genotyped. For genotyping quality control, 5% of samples were randomly selected and directly sequenced, and we obtained 100% identical results.

Statistical analysis

By using the χ^2 test, we tested whether the allele frequencies and genotype distributions for the studied SNPs were in Hardy–Weinberg equilibrium (HWE). We used 2×2 or 2×3 contingency tables for comparing allele and genotype frequencies between subjects with inactive carrier state and CHB patients. $p < 0.05$ was the criterion for statistical significance. All statistical analyses were performed using the Statistical Package for the

Table 1. Outline of *JAK1* Single-Nucleotide Polymorphisms Genotyping

Loci	*Primer sequences (5′-3′)*	*Tm (°C)*	*PCR product (bp)*	*Restriction enzyme*	*Genotype (bp)*
rs2780895	F: CACAGGTAGATTTGGAGGAG R: AAGACGCTGATTGAGGTGAG	60	676	*Nde*I	CC: 676 CT: 676 + 314 + 362 TT: 314 + 362
rs4244165	F: GTGACTGCATAGTGGAGGTG R: CTTTAGAAGCCCCTATTGCC	60	415	*Hae*III	TT: 415 GT: 415 + 160 + 255 GG: 160 + 255
rs17127024	F: GTGAGCAGGTGGAGAGAATC R: TACTGGCACAAAGCAGGACC	64	395	*Hae*III	TT: 395 GT: 395 + 227 + 168 GG: 227 + 168

Tm, annealing temperature; *JAK1*, Janus kinase 1; PCR, polymerase chain reaction.

Social Sciences (SPSS), version 12.0. We estimated linkage disequilibrium (LD) values (D'), r^2 values, and haplotypes by using the SHEsis online software (Shi and He, 2005).

Results

We first conducted genotyping experiments for the 12 *JAK1* polymorphisms. Genotype distributions of rs310247, rs4244165, and rs17127024 were deviated from the HWE in subjects with inactive carrier state. The genotype distributions and allelic frequencies of *JAK1* polymorphisms in the CHB patients and subjects with inactive carrier state are presented in Table 2. The SNP rs17127024 was associated with outcomes of HBV infection. The frequency of the G allele was 70.3% in CHB patients vs. 76.5% in subjects with inactive carrier state ($p = 0.014$, odds ratio = 0.726, 95% confidence interval = 0.561–0.938). The frequencies of the rs17127024 genotypes also differed significantly between the two groups ($p = 0.031$). The SNP rs4244165 had similar allelic frequencies, but different genotype distributions ($p = 0.008$) between CHB patients and subjects with inactive carrier state. The genotype distributions and allelic frequencies of other SNP genotyped did not significantly differ between the CHB patients and subjects with inactive carrier state.

The degree of LD for these 12 SNPs was analyzed, and there was no apparent LD except for that between rs7531799 and rs10493373 ($D' = 0.99$, $r^2 = 0.95$). We constructed haplotypes using these 12 SNPs and found no apparent associated haplotype.

Out of the 395 CHB patients, 256 patients received IFNα treatment, and the therapy efficacy was evaluated. The total response rate was 69.1% (177/256), with 16.0% of CR (41/256) and 53.1% of PR (136/256), and NR rate was 30.9% (79/256). There was no significant difference in the distribution of age and gender among three groups. Since the CR rate was fairly low, the CR group and the PR group were combined into the response group to be analyzed. There were no significant differences in allele frequencies and genotype distributions of all the studied SNPs between the two groups (Table 3). We also compared allele frequencies and genotype distributions of these SNPs in the CR and NR groups, or in the CR and PR + NR groups, and the results were still negative (data not shown). We then conducted haplotype analyses and found no

Table 2. Genotype Distributions and Allelic Frequencies of Single-Nucleotide Polymorphisms in the *JAK1* Gene in Chronic Hepatitis B Patients and Subjects with Inactive Carrier State

SNP ID	*Groups*	*Genotypes* (n %)			p-*Value*	*Allele frequencies* (n %)		p-*Value*	*OR (95% CI)*
rs310227		GG	GA	AA		G	A		
	CHB	26 (0.066)	158 (0.401)	210 (0.533)	0.683	210 (0.266)	578 (0.734)	0.471	1.096 (0.854–1.408)
	Controls	21 (0.084)	101 (0.402)	129 (0.514)		143 (0.285)	359 (0.715)		
rs7531799		TT	TC	CC		T	C		
	CHB	69 (0.188)	184 (0.501)	114 (0.311)	0.639	322 (0.439)	412 (0.561)	0.869	1.056 (0.841–1.327)
	Controls	49 (0.195)	129 (0.514)	73 (0.291)		227 (0.452)	275 (0.548)		
rs7546545		TT	TC	CC		T	C		
	CHB	62 (0.158)	198 (0.505)	132 (0.337)	0.397	322 (0.411)	462 (0.589)	0.362	0.899 (0.714–1.131)
	Controls	39 (0.157)	113 (0.456)	96 (0.387)		191 (0.385)	305 (0.615)		
rs17127174		CC	CT	TT		C	T		
	CHB	229 (0.584)	139 (0.355)	24 (0.061)	0.323	597 (0.761)	187 (0.239)	0.729	1.047 (0.807–1.360)
	Controls	138 (0.550)	102 (0.406)	11 (0.044)		378 (0.753)	124 (0.247)		
rs3790541		GG	GA	AA		G	A		
	CHB	192 (0.489)	172 (0.438)	29 (0.074)	0.887	556 (0.707)	230 (0.293)	0.872	0.980 (0.767–1.253)
	Controls	123 (0.490)	107 (0.426)	21 (0.084)		353 (0.703)	149 (0.297)		
rs10493373		TT	TG	GG		T	G		
	CHB	109 (0.298)	183 (0.500)	74 (0.202)	0.985	401 (0.548)	331 (0.452)	0.895	0.985 (0.784–1.237)
	Controls	74 (0.296)	124 (0.496)	52 (0.208)		272 (0.544)	228 (0.456)		
rs2780898		TT	TC	CC		T	C		
	CHB	83 (0.217)	201 (0.525)	99 (0.258)	0.414	367 (0.479)	399 (0.521)	0.225	1.150 (0.918–1.441)
	Controls	65 (0.261)	126 (0.506)	58 (0.233)		256 (0.514)	242 (0.486)		
rs310247		CC	CT	TT		C	T		
	CHB	73 (0.194)	167 (0.444)	136 (0.362)	0.308	313 (0.416)	439 (0.584)	0.139	1.191 (0.945–1.501)
	Controls	43 (0.171)	102 (0.406)	106 (0.422)		188 (0.375)	314 (0.625)		
rs310196		TT	TG	GG		T	G		
	CHB	215 (0.548)	151 (0.385)	26 (0.066)	0.788	581 (0.741)	203 (0.259)	0.551	0.926 (0.719–1.193)
	Controls	133 (0.532)	97 (0.388)	20 (0.080)		363 (0.726)	137 (0.274)		
rs2780895		CC	CT	TT		C	T		
	CHB	210 (0.532)	165 (0.418)	20 (0.051)	0.309	585 (0.741)	205 (0.259)	0.247	1.159 (0.903–1.488)
	Controls	126 (0.502)	105 (0.418)	20 (0.080)		357 (0.711)	145 (0.289)		
rs4244165		GG	GT	TT		G	T		
	CHB	166 (0.420)	185 (0.468)	44 (0.111)	0.008	517 (0.654)	273 (0.346)	0.102	1.213 (0.962–1.529)
	Controls	104 (0.414)	98 (0.390)	49 (0.195)		306 (0.610)	196 (0.390)		
rs17127024		GG	GT	TT		G	T		
	CHB	199 (0.504)	157 (0.397)	39 (0.099)	0.031	555 (0.703)	235 (0.297)	0.014	0.726 (0.561–0.938)
	Controls	153 (0.610)	78 (0.311)	20 (0.080)		384 (0.765)	118 (0.235)		

CHB, chronic hepatitis B patients; Controls, subjects with inactive carrier state; OR, odds ratio; CI, confidence interval; SNP, single-nucleotide polymorphism.

Table 3. Genotype Distributions and Allelic Frequencies of Single-Nucleotide Polymorphisms in the *JAK1* Gene in Chronic Hepatitis B Patients Treated with Interferon α

SNP ID	*Groups*	*Genotypes* (n %)			p-*Value*	*Allele frequencies* (n %)		p-*Value*	*OR (95% CI)*
rs310227		GG	GA	AA		G	A		
	NR	5 (0.064)	29 (0.372)	44 (0.564)	0.897	39 (0.250)	117 (0.750)	0.664	0.909 (0.590–1.399)
	CR + PR	14 (0.079)	67 (0.379)	96 (0.542)		95 (0.268)	259 (0.732)		
rs7531799		TT	TC	CC		T	C		
	NR	13 (0.181)	37 (0.514)	22 (0.306)	0.639	63 (0.438)	81 (0.562)	0.389	1.192 (0.799–1.777)
	CR + PR	25 (0.159)	74 (0.471)	58 (0.369)		124 (0.395)	190 (0.605)		
rs7546545		TT	TC	CC		T	C		
	NR	14 (0.179)	38 (0.487)	26 (0.333)	0.871	66 (0.423)	90 (0.577)	0.717	0.932 (0.637–1.364)
	CR + PR	32 (0.182)	91 (0.517)	53 (0.301)		155 (0.440)	197 (0.560)		
rs17127174		CC	CT	TT		C	T		
	NR	49 (0.628)	23 (0.295)	6 (0.077)	0.634	121 (0.776)	35 (0.224)	0.512	0.861 (0.551–1.346)
	CR + PR	101 (0.571)	63 (0.356)	13 (0.073)		265 (0.749)	89 (0.251)		
rs3790541		GG	GA	AA		G	A		
	NR	34 (0.430)	42 (0.532)	3 (0.038)	0.265	110 (0.696)	48 (0.304)	0.513	0.872 (0.577–1.316)
	CR + PR	90 (0.511)	75 (0.426)	11 (0.062)		255 (0.724)	97 (0.276)		
rs10493373		TT	TG	GG		T	G		
	NR	22 (0.306)	36 (0.500)	14 (0.194)	0.823	80 (0.556)	64 (0.444)	0.541	0.883 (0.593–1.315)
	CR + PR	53 (0.338)	78 (0.497)	26 (0.166)		184 (0.586)	130 (0.414)		
rs2780898		TT	TC	CC		T	C		
	NR	18 (0.234)	41 (0.532)	18 (0.234)	0.265	77 (0.500)	77 (0.500)	0.113	0.999 (0.675–1.479)
	CR + PR	28 (0.165)	88 (0.518)	54 (0.318)		144 (0.424)	196 (0.576)		
rs310247		CC	CT	TT		C	T		
	NR	15 (0.203)	32 (0.432)	27 (0.365)	0.914	62 (0.419)	86 (0.581)	0.996	0.999 (0.675–1.479)
	CR + PR	36 (0.217)	67 (0.404)	63 (0.380)		139 (0.419)	193 (0.581)		
rs310196		TT	TG	GG		T	G		
	NR	44 (0.564)	29 (0.372)	5 (0.064)	0.913	117 (0.750)	39 (0.250)	0.814	1.053 (0.683–1.625)
	CR + PR	99 (0.559)	64 (0.362)	14 (0.079)		262 (0.740)	92 (0.260)		
rs2780895		CC	CT	TT		C	T		
	NR	43 (0.544)	33 (0.418)	3 (0.038)	0.804	119 (0.753)	39 (0.247)	0.859	0.961 (0.623–1.483)
	CR + PR	97 (0.548)	70 (0.395)	10 (0.056)		264 (0.746)	90 (0.254)		
rs4244165		GG	GT	TT		G	T		
	NR	34 (0.430)	34 (0.430)	11 (0.139)	0.178	102 (0.646)	56 (0.354)	0.298	1.234 (0.830–1.834)
	CR + PR	80 (0.452)	85 (0.480)	12 (0.068)		245 (0.692)	109 (0.308)		
rs17127024		GG	GT	TT		G	T		
	NR	43 (0.544)	28 (0.354)	8 (0.101)	0.312	114 (0.722)	44 (0.278)	0.267	0.792 (0.524–1.196)
	CR + PR	79 (0.446)	80 (0.452)	18 (0.102)		238 (0.672)	116 (0.328)		

NR, nonresponse; CR, complete response; PR, partial response.

haplotype that was associated with a response to IFN treatment (data not shown).

Discussion

We carried out an association study and confirmed that the SNPs rs4244165 and rs17127024 in the *JAK1* gene are associated with outcomes of HBV infection in Han Chinese subjects. However, the distribution of SNPs may differ greatly with ethnicity and region. Also, the sample size involved in the present study is not large enough, and it is possible that these findings may be incidental. Further studies in other ethnic groups and the confirmation of the present finding in a larger sample set in the Han Chinese population are therefore required to clarify the role of these polymorphisms.

In the present study, the genotype distribution of rs310237, rs4244165, and rs17127024 deviated from HWE in subjects with inactive carrier state. The reason to apply HWE is to eliminate the possibility of genotyping errors in molecular genetics studies. For genotyping quality control, 20% of samples were randomly genotyped again by another person, and we obtained 100% identical results. On the other hand, HWE should be applied in normal control subjects. In the present study, however, we chose subjects with the inactive carrier state as controls, to ensure that both cases and controls were exposed in the same virus background.

JAK1 is a key factor in the IFN signaling pathway (Kalvakolanu, 2003). IFNα has been one of the first line drugs for hepatitis B due to its antiviral and immunomodulatory activities (Saracco and Rizzetto, 1997). Endogenous IFNs (α, β, and γ) should also be important in modulating the antiviral activity of the body. So, we concluded that JAK1 was important in HBV infection. Up to now, however, there are few association studies concerning *JAK1* gene polymorphisms and hepatitis B. However, some studies reported that polymorphisms in the IFN signaling pathway genes and IFN genes were associated with outcomes of HBV infection (Liu *et al*., 2006; Song le *et al*., 2006; Abbott *et al*., 2007; Zhou *et al*., 2007; Wu *et al*., 2009). Zhou *et al.* (2007) reported that a T-408C polymorphism in the promoter region of the *IFNAR1* gene changed promoter activity and were associated with outcomes of HBV infection in Hong Kong Chinese. Ligand binding (IFNα) to IFNAR1 causes an aggregation of the receptor IFNAR1, leading to a juxtapositioning of JAK. This permits the tyrosine phosphorylation of JAK and the receptor polypeptide (Kalvakolanu, 2003). We reported in the

present study that polymorphisms in the *JAK1* gene were also associated with outcomes of HBV infection. As these SNPs are intron polymorphisms, it is probable that they are genetic markers in LD with other functional polymorphisms, which should be confirmed in future studies. Our present work indicated that genes in the IFN signaling pathway could be candidates for hepatitis B.

King *et al.* (2002) studied 22 genetic polymorphisms in the IFN pathway, and identified an intron polymorphism (rs3759756) in the *eIF-2α* gene that may influence the IFN response in hepatitis B patients. We reasoned that the *JAK1* gene polymorphisms may influence the host response to IFN treatment in HBV infection. However, in the present study, we failed to discover any significant association of allele frequency or genotype distribution of the 12 SNPs in the *JAK1* gene between response groups and NR groups to IFNα treatment. Nowadays, pegylated interferon (PEG-IFN) therapy has been licensed for hepatitis B and is becoming the standard therapy. However, in the present study, the IFN treatment of patients was all with standard IFNα-1b, which may lead to some limitations. After all, PEG-IFN is essentially similar as standard IFN for they are only different style preparations of IFN, so we speculated that the mechanism of nonresponse to standard IFN might be similar to those with PEG-IFN. Up to now, association studies concerning the IFN response in hepatitis B patients are limited, and the results are in controversy. Further studies choosing more systematized SNPs, together with a larger sample set are required to clarify the association between IFN pathway genes and the IFN response in hepatitis B patients.

In summary, in the present study, we found for the first time that polymorphisms in the JAK1 gene were associated with outcomes of HBV infection, but not with the response to IFNα therapy.

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Author Disclosure Statement

The authors declare that they have no competing interests.

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