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Evaluation of susceptibility locus for response to interferon-α based therapy in chronic hepatitis B patients in Chinese

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ABSTRACT

In 2009, three independent genome-wide association studies reported that genetic variation in the interleukin 28B gene to be associated with the response to interferon-α/ribavirin therapy in hepatitis C virus genotype 1 infected patients. We carried out the present study to assess whether such polymorphisms also affect the therapy effect of another interferon-α responsive illness as chronic hepatitis B. Five hundred and twelve interferon-α treatment-naïve HBeAg seropositive chronic hepatitis B patients were enrolled in the present retrospective nested case-control study. All patients received PEG-IFN-α-2a based treatment and were examined for the therapy efficacy. SNP rs8099917 was genotyped using the MassArray system (Sequenom). Interestingly, the frequency of G allele of rs8099917 was significantly higher in response group than in non response group (8.3% vs. 3.9%, $p = 0.003$, OR = 0.44, 95%CI = 0.25–0.79). The genotype distributions of this SNP also differed significantly between two groups ($p = 0.003$). Our study suggested that the G allele of rs8099917 was associated with higher rate of response in HBeAg seropositive chronic hepatitis B patients treated with interferon α.

1. Introduction

Viral hepatitis is a global health problem that affects a significant proportion of the world's population. Chronic hepatitis B (CHB) or chronic hepatitis C (CHC) is the most common viral hepatitis, and interferon-α (IFN-α) based therapy is the common approved treatment for both hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. However, the standard IFN-α therapy does not produce virologic response in all treated patients. Successful response to IFN-α therapy occurs in only 25–50% of CHB patients treated with IFN-α for 4–6 months (Gish, 2005), and large-scale studies on 48-week-long IFN-α/ribavirin treatment showed that only one half of patients with HCV genotype 1 achieved sustained a virologic response (Fried et al., 2002). Specifically, various side effects such as a flu-like syndrome or hematologic abnormalities often result in dose reduction, or about one tenth of patients cannot tolerate the side effects and require premature withdrawal from IFN-α based therapy (Fried, 2002; Papatheodoridis and Hadziyannis, 2004). Considering the length, side effects, and costs of IFN-α treatment, accurate pre-treatment prediction of response to therapy is very important.

Till date, with the advances in pharmacogenetics, there is increasing information indicating that single nucleotide polymorphisms (SNPs) in drug-metabolism genes are closely associated with the metabolism and efficacy of drugs (Ahmadi et al., 2005). In 2009, three independent genome-wide association studies (GWAS) reported that genetic variation in the interleukin 28B (IL28B) gene to be associated with the response to IFN-α/ribavirin therapy in HCV genotype 1-infected patients (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009). These GWAS findings raise the inspiring prospect of a more personalized approach to treat viral hepatitis by tailoring treatment to patients who are most likely to benefit.

Unfortunately, the host genetic factors that was associated with response to IFN-α-based therapy in CHB patients are still unclear. Although some studies have reported several polymorphisms or haplotypes that are related to therapy response, these results have not been replicated in other populations (Chan et al., 2006; Chu et al., 2005; Gong et al., 2009; King et al., 2002; Kong et al., 2007; Wu et al., 2009).

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The IL28B gene encodes interferon-λ3, a growth factor with similarities to the interferon-α preparations used as treatment. Interferon-λ3 may contribute to virus clearance either spontaneously or during drug treatment (Sheppard et al., 2003). Although the mechanism of CHB and CHC is not identical, they share some common characteristics in the antiviral therapy, for IFN-α has been a first-line drug for CHB and CHC many years. Some studies have reported that polymorphisms in certain IFN pathway genes are associated with IFN-α therapy effect in both CHB and CHC patients (Knapp et al., 2003; Kong et al., 2007). So, we speculated that SNP associated with IFN-α therapy effect in CHC patients would be also associated with that in CHB patients. We carried out the present association study in Han Chinese population to confirm this hypothesis.

2. Materials and methods

2.1. Subjects

The subjects enrolled in the present study were 512 Han Chinese IFN-α treatment-naïve CHB patients recruited from the Beijing Youan Hospital between November 2005 and May 2008. The patients were included if the following characteristics were present: their serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were continuously > 40 IU/L; they were HBsAg-seropositive and HBeAg-seropositive for 6 months; their serum HBV DNA >2000 copies/mL. Patients were excluded if: (1) there was evidence of past or current infection with other hepatitis viruses or hepatitis not caused by HBV; (2) they had cirrhosis or hepatocellular carcinoma; or (3) they were not of Han ethnicity.

All the enrolled patients received PEG-IFN-α-2a (Pegasys) based antiviral therapy, with the dose of 180 μg for body weight ⩾70 kg or 135 μg for body weight <70 kg, subcutaneously once a week for 12 months. Two hundreds and eighty-two patients received PEG-IFN-α-2a monotherapy, and 230 patients received combined therapy with IFN/nucleoside analogues (NA), namely, PEG-IFN-α-2a plus lamivudine 100 mg orally per day, or PEG-IFN-α-2a plus adefovir 10 mg orally per day, or PEG-IFN-α-2a plus entecavir 0.5 mg orally per day.

Patients were then followed up for 6 months to evaluate the therapeutic effects. Sustained virologic response (SVR) was confirmed if the following characteristics were present: 6 months after the end of therapy, the patients had normal ALT and AST levels (<40 IU/L), their serum HBV DNA levels <500 copies/mL, and achieved HBeAg seroconversion. Patients who did not satisfy all of the abovementioned criteria were categorized as non-responsive (NR) patients. The characteristics of participating patients are described in Table 1.

2.2. Serological testing

Enzyme-linked immunosorbent assay was performed for the detection of serum HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc (IMX; Abbott Diagnostics, North Chicago, IL). The ALT and AST levels were measured by a continuous monitoring assay. Serum HBV DNA levels were measured by real-time PCR using Applied Biosystems 5700. HBV genotypes were detected by type-specific primers and polymerase chain reaction.

2.3. SNP selection and genotyping

Genomic DNA was extracted from peripheral blood by using a salting-out protocol. The SNP rs8099917 in IL28B was genotyped by the MassArray system (Sequenom), with forward PCR primer 5′-ACTGTATACAGCATGGTTCC-3′, reverse PCR primer 5′-CAATTTGT CACTGTTCCTCC-3′, and extension primer 5′-ctttcTTCCTTTCT GTGAGCAAT-3′. Twenty samples were randomly selected and directly sequenced, and we obtained 100% identical results.

2.4. Statistical analysis

By using the χ^2 test, we tested whether the genotype distributions for the studied SNP were in the Hardy–Weinberg equilibrium (HWE). We used 2×2 or 2×3 contingency tables for comparing allele and genotype frequencies between the response group and the non-response group. $P < 0.05$ was the criterion for statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 12.0.

3. Results

After IFN-α-based therapy, we evaluated the efficacy of IFN-α in the 512 patients on the basis of the criteria for combined assessment. There were no significant differences in response rates between the subgroups of the combined therapy group, i.e. Peg IFN-α-2a plus lamivudine, Peg IFN-α-2a plus adefovir, and Peg IFN-α-2a plus entecavir (data not shown). There were no significant differences in the distribution of age, gender, and HBV genotypes among the two groups, but the IFN monotherapy group had lower SVR rate compared with combined therapy group.

Table 1
Characteristics of chronic hepatitis B patients treated with IFN-α.

	SVRs	NRs	*p*
Patients, *n*	162	350	
Age, y median (minimum, maximum)	33(11, 66)	31(10, 65)	0.26[a]
Baseline ALT level, IU/L median (minimum, maximum)	102(42, 779)	93(42, 708)	0.006[a]
Baseline AST level, IU/L median (minimum, maximum)	79(43, 739)	73(42, 571)	0.01[a]
Sex			0.74[b]
Male	119	262	
Female	43	88	
Therapy style			<0.001[b]
IFN monotherapy	59	223	
Combined therapy with IFN/NA	103	127	
HBV genotype			0.79[c]
B	38	97	
C	94	226	
No data	30	27	

[a] Mann–Whitney *U* test.
[b] Chi-square test.
[c] Chi-square test between HBV genotype B and C.

Table 2
Genotype distributions and allelic frequencies of rs8099917 in chronic hepatitis B patients treated with IFNα.

HBeAg seropositive CHB patients			Genotype/allele	SVRs	NRs	*p*	OR	95% CI
All patients, No. (%)			G/G	0(0)	1(0.3)			
			G/T	27(16.7)	25(7.1)	0.003		
			T/T	135(83.3)	324(92.6)			
			G	27(8.3)	27(3.9)	0.003	0.44	0.25–0.79
			T	297(91.7)	673(96.1)			
Stratification analysis	HBV genotype	genotype B, No. (%)	G/T	5(13.2)	11(11.3)			
			T/T	33(86.8)	86(88.7)			
			G	5(6.6)	11(5.7)		0.85	0.26–2.93
			T	71(93.4)	183(94.3)			
		genotype C, No. (%)	G/G	0(0)	1(0.4)			
			G/T	16(17.0)	13(5.8)			
			T/T	78(83.0)	212(93.8)			
			G	16(8.5)	15(3.3)		0.37	0.17–0.81
			T	172(91.5)	437(96.7)			
	Therapy style	Mono IFN therapy group, No. (%)	G/T	6(10.2)	15(6.7)			
			T/T	53(89.8)	208(93.3)			
			G	6(5.1)	15(3.4)		0.65	0.23–1.92
			T	112(94.9)	431(96.6)			
		Combined therapy group, No. (%)	G/G	0(0)	1(0.8)			
			G/T	21(20.4)	10(7.9)			
			T/T	82(79.6)	116(91.3)			
			G	21(10.2)	12(4.7)		0.44	0.20–0.96
			T	185(89.8)	242(95.3)			
	Sex	Men only, No. (%)	G/G	0(0)	1(0.4)			
			G/T	19(16.0)	17(6.5)			
			T/T	100(84.0)	244(93.1)			
			G	19(8.0)	19(3.6)		0.43	0.21–0.87
			T	219(92.0)	505(96.4)			
		Women only, No. (%)	G/T	8(18.6)	8(9.1)			
			T/T	35(81.4)	80(90.9)			
			G	8(9.3)	8(4.5)		0.46	0.15–1.42
			T	78(90.7)	168(95.5)			

Patients with higher baseline ALT and AST levels may have higher SVR rates (Table 1).

Genotype distributions of rs8099917 were in HWE. In the single locus analysis, the frequency of G allele was significantly higher in SVR group than in NR group (8.3% vs. 3.9%, $p = 0.003$, OR = 0.44, 95%CI = 0.25–0.79). The genotype distributions of this SNP also differed significantly between SVR and NR groups ($p = 0.003$). The Cochran-Armitage trend test (assuming an additive model for T allele) revealed an allele dose-dependent association of rs8099917 with the outcome of IFN therapy ($p = 0.0027$). Stratification analysis was then conducted. As shown in Table 2, the results remained significant in the HBV genotype C patients (OR = 0.37, 95%CI = 0.17–0.81), combined therapy group (OR = 0.44, 95%CI = 0.20–0.96), and male patients (OR = 0.43, 95%CI = 0.21–0.87). However, the association was not significant in the HBV genotype B patients, mono IFN therapy group, and female patients, which may be due to the relative small sample sets in the above three subgroups. On the other hand, the frequencies of G allele were all higher in the SVR groups.

4. Discussion

In the present study, we found that the G allele of rs8099917 is associated with good response to IFN-α therapy in 512 CHB patients. To the best of our knowledge, this is the largest cohort addressing HBV pharmacogenetic study. Nevertheless, the sample size involved in the present study is not large enough, and it is possible that these findings may be incidental. Therefore, it is necessary to perform further studies in other ethnic groups and to confirm the present findings in a larger sample set. Only HBeAg-seropositive CHB patients were enrolled in the present study, so future studies concerning HBeAg-seronegative CHB patients should be conducted.

The three GWAS studies mainly reported two SNPs near IL28B gene to be strongly associated with SVR in CHC patients (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009), namely, rs12979860, rs8099917. The three studies were carried out within an American, Australian, and Japanese population, respectively. The most significant polymorphism in each study were as follows: rs12979860 in American, rs8099917 in Australian and Japanese. Notably, rs8099917 is the third most significant polymorphisms in American study, but rs12979860 was not reported in the Australian and Japanese studies. On the other hand, rs12979860 and rs8099917 were in linkage disequilibrium in American and Japanese population (Abe et al., 2011; Ge et al., 2009). Taken these factors together, we concluded rs8099917 may be the most typical SNP in the Asian population, so we chose this SNP as the candidate SNP.

Interestingly, the frequency of the minor allele (G) of rs8099917 was reported to be a risk factor for nonresponse to IFN-α therapy in CHC patients (Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009). But in the present study, the frequency of the G allele was significantly higher in the response group of CHB patients. To some extent, this result seemed puzzling, but the following points should be noted.

First and most importantly, CHB and CHC are two different diseases, although they share some common in antiviral therapy. A certain gene may play an important role in both diseases. Studies reported rs12979860 in IL28B was associated with spontaneous clearance of HCV (Thomas et al., 2009), but this same SNP did not determine the outcome of the HBV infection (Martin et al., 2010). Second, we confirmed that the genotyping result was cor-

rect, and the criteria of SVR and NR were in accordance with the standard way. The stratification analysis showed that in all the subgroups, the frequencies of the G allele were higher in the SVR group. So we concluded that the present result should not be adventitious. Last, there is possibility that rs8099917 is just a genetic marker, for the SNP is located 8.9 kb from the end of transcription of IL28B. The three GWAS reported the associations all in HCV genotype 1 patients, but in genotype 2 and 3 infected patients, there is controversy about the role of this SNP (Kawaoka et al., 2011; Sarrazin et al., 2011). Whether rs8099917 influenced mRNA transcription was also controversial. Tanaka et al. (2009) reported lower IL28B expression levels in individuals carrying the G alleles in peripheral blood mononuclear cells. But Abe et al. (2011) reported that expression of IL28 was significantly higher in liver samples in patients with the G alleles, whereas in peripheral blood mononuclear cells IL28B expression levels did not differ significantly among different genotypes. On the other hand, the minor allele frequency of rs8099917 differs greatly across races (e.g. 0.183 in European Caucasian, 0.089 in Japanese, 0.033 in Han Chinese, from HapMap data). Clinical trials reported East Asians have higher SVR rates than patients of European ancestry when infected with HCV genotype 1 (Liu et al., 2008), whereas Asian patients were less likely to experience SVR compared to Caucasians when infected with HBV (Perrillo et al., 2002). So, we speculated there is possibility that rs8099917 may be a genetic marker representing the ethnicity differences, and this may partially explain why a certain allele is associated with lower SVR rate in HCV but higher SVR rate in HBV.

In summary, we have shown that the G allele of rs8099917 was associated with higher rate of SVR in HBeAg seropositive CHB patients treated with IFN-α. Additional studies are needed to understand the mechanisms underlying the beneficial effect of this SNP in both HBV and HCV.

Conflict of interest

The authors declare that they have no competing interests.

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