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Polymorphisms in ADAR1 gene affect response to interferon alpha based therapy for chronic hepatitis B in Han Chinese

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ABSTRACT

Host genetic polymorphisms in interferon pathway genes are reported to be associated with response to interferon therapy. Five hundred and forty-eight α interferon treatment-naïve chronic hepatitis B patients were enrolled in the retrospective nested case-control study. All patients received α interferon based treatment and were examined for therapy efficacy. We genotyped 115 polymorphisms from 16 interferon pathway genes using the MassArray system. We identified rs4845384 in ADAR1 gene is strongly associated with the outcome of interferon therapy allele dose-depended ($P = 0.0005$), with decreased odds ratios of 0.69 and 0.27 for GA and AA genotypes, respectively (95% confidence interval, 0.47–0.99 for GA; 0.11–0.64 for AA). Our study suggested that rs4845384 in ADAR1 associates with treatment-induced clearance of chronic hepatitis B.

1. Introduction

Hepatitis B virus (HBV) infection is a serious public health problem results in 0.5–1.2 million deaths per year, which is mainly caused by its clinical consequences such as chronic hepatitis B (CHB), cirrhosis, and hepatocellular carcinoma (Ganem and Prince, 2004). Interferon alpha (IFNα) has been used widely as an antiviral agent for CHB due to its antiviral and immunomodulatory activities (Saracco and Rizzetto, 1997). However, even after the most effective combination therapy of pegylated-IFN-alfa plus nucleoside analoges (NA), successful response to IFNα based therapy occurs in only 40% of CHB patients (Perrillo, 2009; Terrault, 2009). Specifically, various side effects such as a flu-like syndrome or hematologic abnormalities often result in dose reduction or premature withdrawal from IFNα based therapy (Papatheodoridis and Hadziyannis, 2004). Considering the length, side effects, and costs of IFNα treatment, accurate pre-treatment prediction of response to therapy is very important.

The mechanisms of modulating the responsive to IFNα therapy in CHB patients have been studied. Both viral and host factors have been implicated. Viral factors, such as HBV genotype, serum HBV-DNA level and alanine aminotransferase (ALT) levels have been reported to be associated with the outcome of IFNα therapy (Hoofnagle and di Bisceglie, 1997). On the other hand, it has been reported that genetic polymorphisms of cytokines, human leukocyte antigen (HLA) genes, and IFN-stimulated genes are associated with the difference in response to IFNα therapy (King et al., 2002; Wu et al., 2009; Zhu et al., 2011).

Since IFNα elicits the antiviral activity by activation of signaling molecules downstream of interferon receptors, genetic polymorphisms in interferon signaling pathway genes may potentially alter the responsiveness to IFNα therapy. The IFNα signaling pathway genes include the Janus-activated kinase (JAK)-signal transducer and activator of transcription (STAT) pathway genes and interferon-stimulating genes (ISGs) such as myxovirus resistance 1 (MxA), eukaryotic translation initiation factor 2-alpha kinase 2 (PKR), 2′,5′-oligoadenylate synthetase (OAS), adenosine deaminases acting on RNA (ADAR1)(Kalvakolanu, 2003; Samuel, 2001). In this retrospective nested case-control study, we examined whether single nucleotide polymorphisms (SNPs) in above IFNα signaling

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pathway genes are associated with IFNα therapy effect, using the tag-SNP approach.

2. Materials and methods

2.1. Subjects

The subjects enrolled in the present study were 548 Han Chinese IFNα treatment-naïve CHB patients recruited from the Beijing Youan Hospital between November 2005 and May 2008. The patients were included if the following evidences 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-IFNα-2a (Pegasys) based antiviral therapy, with the dose of 180ug for body weight ⩾70 kg or 135 μg for body weight <70 kg, subcutaneously once a week for 12 months. Three hundred and seven patients received PEG-IFNα-2a monotherapy, and 241 patients received combined therapy with IFN/nucleoside analoges (NA), namely, PEG-IFNα-2a plus Lamivudine 100 mg orally per day, or PEG-IFNα-2a plus Adefovir 10 mg orally per day, or PEG-IFNα-2a plus Entecavir 0.5 mg orally per day.

Patients were then followed up for 6 months to evaluate the therapeutic effects. Sustained virological response (SVR) was confirmed if the following evidences 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-response (NR) patients. The characteristics of participating patients are described in Table 1.

The study was carried out in accordance with the guidelines of the Helsinki Declaration after obtaining written informed consent from all the subjects and was approved by the ethics committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences.

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. We selected 131 tag-SNPs for a total set of 16 candidate genes related to the IFN pathway, using the HapMap database (HapMap Data Rel 24/phase II Nov 08, on NCBI B36 assembly, dbSNP b126) and pairwise tagging method. With the selection criteria of r2 greater than 0.8 and minor allele frequency (MAF) of greater than 0.05 for the Han Chinese Beijing population, tag-SNPs were selected from the entire gene region from approximately 2000 bp upstream of the transcription start site to 2000 bp downstream of the 3′untranslated region (3′UTR) in each gene(Tsukada et al., 2009). The total number of tag-SNPs was 131. SNPs were genotyped by the MassArray system (Sequenom; Bioyong Technology Co. Ltd., Beijing, China). The detailed genotyping information is shown in Supplementary Table 1. For genotyping quality control, 5% of samples were randomly genotyped twice for duplication accuracy, which was calculated to be 100%.

Table 1
Characteristics of subjects in the present study.

	SVRs	NRs	*p*
Patients, *n*	190	358	
Age, *y*	33(11, 66)	31(10, 65)	0.39[a]
Median (minimum, maximun)			
Baseline ALT level, IU/L	103(42, 779)	95(42, 838)	0.005[a]
Median (minimum, maximun)			
Baseline AST level, IU/L	83(43, 739)	74.5(42, 571)	0.02[a]
Median (minimum, maximun)			
Sex			0.56[b]
Male	139	270	
Female	51	88	
Therapy Style			<0.001[b]
IFN monotherapy	86	221	
Combined therapy with IFN/NA	104	137	
HBV genotype			0.64[c]
B	49	97	
C	104	227	
No data	37	34	

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

2.4. Statistical analysis

We used 2 × 2 or 2 × 3 contingency tables for comparing allele and genotype frequencies. Tests for association of quantitative traits were performed using the Mann–Whitney *U* test for traits with abnormal distributions, or ANOVA for normally distributed traits. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 13.0 (SPSS Inc., Chicago, Illinois). We obtained estimates of linkage disequilibrium values (r2, D′) and the haplotype estimation using the SHEsis online software (Shi and He, 2005).

3. Results

We first searched for the association between tag-SNPs and the outcome of IFNα therapy. There were no significant differences in response rates between the subgroups of the combined therapy group, i.e. Peg IFNα2a plus Lamivudine, Peg IFNα2a plus Adefovir, and Peg IFNα2a plus Entecavir (data not shown), so all the subgroups were referred as combined therapy group. Of the 131 tag-SNPs, seven were failed in designing proper primers, and nine were failed in genotyping, so we had a final dataset of genotypes consisting of 115 SNPs in 548 patients, with an average call rate of 98.4%. There were nine SNPs deviated slightly from the HWE in SVR and/or NR groups ($0.01 < P < 0.05$), and one SNP rs10173099 deviated significantly from the HWE ($P = 0.005$) in SVR group (Supplementary Table 2). Single locus analysis indicated that four SNPs were associated with the outcome of IFNα therapy both in allele frequencies and genotype distributions, among which rs4845384 was the most significant. As shown in Table 2, the frequency of A allele was significantly lower in SVR group than in NR group (25.3% vs. 35.3%, $P = 0.0007$). The Cochran–Armitage trend test (assuming an additive model for A allele) revealed an allele dose-dependent association of rs4845384 with the outcome of IFN therapy ($P = 0.0005$), with decreased odds ratios of 0.69 and 0.27 for GA and AA genotypes, respectively (95% CI, 0.47–0.99 for GA; 0.11–0.64 for AA). When considering unadjusted additive model for each genotype, the OR is 0.60, with 95% CI 0.45–0.80 ($P = 0.0006$).

Table 2
Genotype distributions and allelic frequencies of associated SNPs in ADAR1 gene in HbeAg seropositive chronic hepatitis B patients treated with IFNα.

SNP, allele (1/2)	Allele, *n* (%)			Genotype, *n* (%)			Cochran Armitagetrend test	*p*/OR (95% CI)	
	1	2	*p*/OR (95% CI)	11	12	22	*p*	11 vs. 12	11 vs. 22
rs4845384 (G/A)									
NRs (*n* = 357)	462(64.7)	252(35.3)	0.0007	147(41.2)	168(47.1)	42(11.8)	0.0005	0.04	0.0008
SVRs (*n* = 190)	284(74.7)	96(25.3)	0.62(0.46–0.83)	102(53.7)	80(42.1)	8(4.2)		0.69(0.47–0.99)	0.27(0.11–0.64)
rs4636449 (C/G)									
NRs (*n* = 357)	592(0.829)	122(0.171)	0.001	246(0.689)	100(0.280)	11(0.031)	0.001	0.002	0.19
SVRs (*n* = 190)	343(0.903)	37(0.097)	0.52(0.35–0.79)	156(0.821)	31(0.163)	3(0.016)		0.49(0.30–0.78)	0.43(0.09–1.69)
rs7531982 (T/A)									
NRs (*n* = 357)	337(0.472)	377(0.528)	0.004	76(0.213)	185(0.518)	96(0.269)	0.004	0.02	0.004
SVRs (*n* = 190)	214(0.563)	166(0.437)	0.69(0.54–0.90)	61(0.321)	92(0.484)	37(0.195)		0.62(0.40–0.96)	0.48(0.28–0.82)
rs1127313 (T/C)									
NRs (*n* = 357)	350(0.490)	364(0.510)	0.008	82(0.230)	186(0.521)	89(0.249)	0.008	0.02	0.01
SVRs (*n* = 189)	217(0.574)	161(0.426)	0.71(0.55–0.92)	64(0.339)	89(0.471)	36(0.190)		0.61(0.40–0.95)	0.52(0.30–0.89)

Note: P values were calculated from case-control analysis by the χ^2 test and unadjusted for multiple testing.

Stratification analysis was then conducted. The results remained significant except in HBV genotype B patients (Supplementary Table 3). The three other associated SNPs were rs7531982, rs4636449 and rs1127313 (Table 2). To adjust the P values for multiple testing, we applied Bonferroni correction (totally 115 SNPs). In this conservative adjustment, only rs4845384 reached the borderline significance ($P = 0.08$).

The four associated SNPs were all in the ADAR1 gene. Linkage disequilibrium analysis showed that the four SNPs were in LD though not absolutely ($D' \geqslant 0.911$, $0.172 \leqslant r2 \leqslant 0.896$). As there were 10 tag-SNP studied in ADAR1 gene, we conducted haplotype analysis of the 4 and 10 SNPs in ADAR1 gene, respectively. As shown in Supplementary Table 4, when analyzing haplotypes of 10 SNPs (rs7531982, rs4636449, rs4845384, rs3738030, rs3738031, rs3766924, rs9427097, rs11264224, rs1127313, rs9616), haplotype A-G-A-T-C-G-T-A-C-T was associated the most significantly with the outcome of IFNα therapy (16.6% in NR group, 8.9% in SVR group, $P = 0.0005$). When analyzing haplotypes of four SNPs (rs7531982, rs4636449, rs4845384, rs1127313), haplotype A-G-A-C was the most significantly (17.0% in NR group, 9.7% in SVR group, $P = 0.001$). Notably, in these two associated haplotypes, the alleles from the four associated SNPs rs7531982, rs4636449, rs4845384, rs1127313 were the same, and these haplotype *P* values were comparable with that for single marker analysis. Therefore, we deduced that the single marker rs4845384 was responsible for the association.

We next used binary logistic regression to eliminate the influence of confounding factors (HBV genotype, therapy style, age, gender). The result showed that rs4845384 was still association with the different effect of IFNα therapy ($P = 0.002$, OR = 0.60, 95%CI = 0.43–0.83).

4. Discussion

Till date, with the advances in pharmacogenetics, there is accumulating information indicating that SNPs in drug-metabolism genes are closely associated with the metabolism and efficacy of drugs (Ahmadi et al., 2005). Unfortunately, the host genetic factors that associated with response to IFNα therapy in CHB patients are still unclear. Although studies have reported several polymorphisms related to IFNα therapy effect, these results have not been replicated in other populations (King et al., 2002). However, there are more studies in chronic hepatitis C patients. In 2009, three independent genome wide association studies (GWAS) reported genetic variation in IL28B gene to be associated with the response to IFNα/ribavirin therapy in hepatitis C virus (HCV) patients(Ge et al., 2009; Suppiah et al., 2009; Tanaka et al., 2009). These findings raise the bright prospect of studies in CHB patients to find personalized approach for treating CHB by tailoring treatment to patients who are most likely to benefit.

The ADAR1 is a downstream antiviral protein stimulated by interferon through JAK-STAT pathway. The human ADAR1 gene maps to 1q21.1-21.2. The ADAR1 spans ~40 kb and includes 17 exons (Wang et al., 1995; Weier et al., 1995). ADAR1 transcription initiates from three different promoters, one interferon inducible (P_IA) and the two others constitutively active (P_CB, P_CC), which encode an IFN-inducible (p150) and a constitutively expressed (p110) form (Patterson and Samuel, 1995). The exons related to three promoters are designated and aligned linearly as exon 1B, 1A and 1C (George and Samuel, 1999). ADAR1 catalyzes adenosine to inosine editing of RNA, which is of broad physiologic significance that can lead to either a proviral or an antiviral consequence, dependent upon the virus–host combination (Samuel, 2011). The exact role ADAR1 plays in HBV infection is not clear. Although HBV is a DNA virus, in the central dogma of DNA–RNA–protein, ADAR1 may play an important role on the RNA intermediate so as to interfere HBV replication.

The tag-SNP rs4845384 located between exon 1B and 1A, so it is an intron SNP when p110 form is expressed, and when p150 form is expressed, rs4845384 is a 5′upstream SNP. According to HapMap data, rs4845384 is a tag-SNP capturing 14 SNPs, among which, rs1127326, rs1127317 and rs1127314 are 3′-UTR SNPs, and rs2229857 is a nonsynonymous SNP. The above evidences indicate that rs4845384 may be functional itself, or be a genetic marker in LD with other functional SNPs.

A recently GWAS study in multiple sclerosis patients received IFNβ therapy reports rs2229857 in ADAR1 is one of the seven most associated SNPs. Notably, IFNα and IFNβ are both type I interferon which share the same interferon pathway. The rs2229857 is one of the SNPs captured by rs4845384 according to HapMap data (r2 = 0.855), and the minor alleles of the two SNPs are both nonresponse susceptible alleles (Comabella et al., 2009). Another study genotyped 56 polymorphisms in IFN pathway genes, and found rs1127309 in ADAR1 was associated with outcome of IFNα therapy in chronic hepatitis C patients (Welzel et al., 2009). Although this SNP is not included in the present study, as we use a Tag SNP strategy which is based on the HapMap database; unfortunately

rs1127309 is not recorded in the HapMap database. Nevertheless, it is informative that SNP in ADAR1 gene can predict therapy effect in chronic hepatitis C patients.

To the best of our knowledge, the present work is the most systematic pharmacogenetic study with the largest sample set regarding antiviral treatment of HBV infection. Nevertheless, there are some improvements for future studies. We select tag-SNPs in the present study, but some rare variants may be not recorded in the HapMap database yet. The coding region of ADAR1 should be sequenced to identify whether there is any new SNP that results in mRNA substitution.

5. Conclusions

In conclusion, we identified in the present study that a tag-SNP rs4845384 located in the ADAR1 gene is associated with the outcome of IFNα therapy in CHB patients, and this association is still significant after stratification analysis and logistic regression. 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.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.antiviral.2012.03.004.

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Glossary

ADAR1: adenosine deaminases acting on RNA
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CHB: chronic hepatitis B
GWAS: genome-wide association studies
HBV: hepatitis B virus
HCV: hepatitis C virus
HWE: Hardy–Weinberg equilibrium
IFN: interferon
JAK: janus-activated kinase
NA: nucleoside analogues
NR: non-response
PR: partial response
R: response
SC: individuals who spontaneously cleared HBV
SNP: single nucleotide polymorphism
STAT: signal transducer and activator of transcription
SVR: sustained virological response