No association between IRF3 polymorphism and susceptibility to hepatitis B virus infection in Chinese patients

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Abstract

AIM: To investigate the association between three tag single nucleotide polymorphisms (tagSNPs) in interferon regulatory factors (IRF3) and the genetic susceptibility to chronic hepatitis B virus (HBV) infection.

METHODS: We performed a case-control study of 985 Chinese cases of chronic HBV infection and 294 self-limiting HBV-infected individuals as controls. Three tagSNPs in IRF3 (rs10415576, rs2304204, rs2304206) were genotyped with the Multiplex SNaPshot technique. The genotype and allele frequencies were calculated and analyzed.

RESULTS: The three SNPs showed no significant genotype/allele associations with chronic HBV infection. Overall allele P values were: rs10415576, P = 0.0908, odds ratio (OR) [95% confidence interval (CI)] = 1.1798 (0.9740-1.4291); rs2304204, P = 0.5959, OR (95% CI) = 1.0597 (0.8552-1.3133); rs2304206, P = 0.8372, OR (95% CI) = 1.0250 (0.8097-1.2976). Overall genotype P values were: rs10415576, P = 0.2106; rs2304204, P = 0.8458; rs2304206, P = 0.8315. There were no statistically significant differences between patients with chronic HBV infection and controls. Haplotypes generated by these three SNPs were also not significantly different between the two groups.

CONCLUSION: The three tagSNPs of IRF3 are not associated with HBV infection in the Han Chinese population.

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Key words: Chronic hepatitis B virus infection; Interferon regulatory factors tag single nucleotide polymorphisms; Genetic susceptibility; Haplotype

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is considered a multifactorial and polygenic disorder with viral, environmental, genetic, and immune components. Host immunological and genetic factors may influence the course of the disease\cite{1,2,3,4,5,6}. Genetics of the host such as single nucleotide polymorphisms (SNPs) in a variety of genes have been implicated in the diversity of the clinical course of HBV\cite{7,8}.

Interferon regulatory factors (IRFs) are transcriptional mediators of virus- and interferon (IFN)-induced signaling pathways and have been shown to be involved in antiviral defense, immune response, and cell growth regulation\cite{9}. Among the nine identified members of the IRF family (IRF1-IRF9), three IRFs (IRF3, IRF5 and IRF7) were found to function as direct transducers of virus-mediated signaling and play a crucial role in the expression of type 1 IFN genes\cite{10}. Interferon regulatory factor 3 (IRF3) is a member of the IRF family which plays a major role in gene expression of IFN regulatory factors, and is closely related to the level of interferon gene expression in condition of virus infection\cite{11,12,13,14}. Patients with chronic HBV infection failed to activate IRF3 following virus contraction and thereby are unable to secrete enough IFN-β to eradicate the HBV virus, which may partly contribute to persistent infection of HBV\cite{15}.

IRF3 plays an important role in the response of the innate immune system to viral infection\cite{16}. Polymorphisms in IRF3 can affect induction of IFN-β1 expression\cite{17}, and IRF3 is differentially activated during type 1 IFN responses in human macrophages\cite{18}. The aim of this study was to clarify whether IRF3 polymorphisms can serve as candidates for predicting clinical outcomes of the disease caused by HBV infection.

MATERIALS AND METHODS

Participants

Samples were obtained from 1279 unrelated Chinese Han patients with HBV infection. Chronic HBV-infected patients (n = 985; 687 males and 298 females) were recruited from the Infectious Disease Department as cases, and 294 self-limiting HBV-infected individuals were recruited as controls (132 females and 162 males). The average age was 44.2 years for the HBV chronic carriers and 44.9 years for the controls. All the patients with chronic HBV infection fulfilled the diagnostic criteria of the Proposal of Prevention and Treatment of Viral Hepatitis, 2005, issued by the Chinese Society of Infectious Diseases and Parasitology and the Society of Hepatology of the Chinese Medical Association\cite{19}. Clinical criteria for self-limiting HBV infection were positive for HBsAb and HBeAb, negative for HBsAg, and no history of HBV vaccination. Controls were age- and gender-matched to the cases.

Genomic DNA extraction

Blood samples were obtained from all participants, and DNA was extracted from peripheral blood leukocytes using a DNA extraction kit (Yuan Ping-Hao Biotechnology Co. Ltd., Tianjin, China). DNA samples (100 ng/µL) were stored at -80 °C.

Tag SNP selection

We selected SNPs on the basis of the following principal criteria: tag SNPs (tagSNP) were identified using genotype data from the panel (Han Chinese in Beijing) of the phase II HapMap Project. The criteria for tagSNPs were $r^2 > 0.8$, minor allele frequency MAF > 0.1, functional relevance and importance, and SNPs significantly associated with diseases in previous studies. A total of three tagSNPs in IRF3 gene (rs10415576, rs2304204 and rs2304206) were selected, which captured 100% of common SNPs (minor allele frequency > 0.1) in the HapMap Chinese database at $r^2 > 0.8$.

Genotyping

The three SNPs in IRF3 were genotyped using the Multiplex SNPshot technique. The primers and probes were designed by primer3.0 software and were rs10415576 (5’ to 3’): forward primer: CAGAGTGAACAGGGACGTGAT; reverse primer: ATTGCTCCAAAGGATGCCTAGTG, and extension primer: GCTGGTTGGCATTCAGTGC; both rs2304204 and rs2304206, forward primer: TCCCATCGGCTTTTGGGTCT, reverse primer: CCTTCCGCTCTCCGTCTC, and extension primer: TTTTTGCTGTTTATTTATATCAGGATGTGC. The polymerase chain reaction (PCR) amplification conditions were: a 15-µL final volume containing 10 × 1.5 µL buffer, 0.3 µL dNTPs (10 mmol/L), 0.9 µL MgCl2 (25 mmol/L), 0.1 µL Taq DNA polymerase (TAKARA Biotechnology Co. Ltd., Dalian, China), 0.5 µL each primer (10 pmol/L), and 1 µL DNA template (20 mg/L). Conditions for the multiplex PCR reaction using Touch-down PCR response procedures included initial denaturation at 95 °C for 15 min, denaturation at 94 °C for 40 s, annealing at 63 °C for 1 min, and recursive-descent 0.5 °C, followed by extension at 72 °C for 1.5 min, for a total of 15 cycles. This was followed by 25 cycles of denaturation at 94 °C for 40 s, annealing at 56 °C for 40 s, and extension at 72 °C for 1.5 min, with a final extension at 72 °C for 8 min. Amplified samples were stored at 4 °C. After amplification, 1.5 µL PCR product was examined on an agarose gel to test for successful amplification.

SNPshot reaction: take the purified PCR product, each concentration of 0.2 µmol/L SNPshot primer mixture, SNPshot fluorescent mixtures (containing Taq DNA polymerase and different fluorescently labeled ddNTP, TAKARA Biotechnology Co. Ltd., Dalian, China) consisting of an PCR reaction system. SNPshot response procedures: initial denaturation at 96 °C for 10 s; denaturation at 96 °C for 10 s, annealing at 53 °C for 5 s, extension at 60 °C for 30s, for a total of 25 cycles, and finally extension at 60 °C for 30s. Amplified samples were stored at 4 °C. SNPshot PCR products using SAP purification, in 10 µL SNPshot PCR product with 1 U SAP or...
Table 1  Genotype and allele distributions of interferon regulatory factors tag single nucleotide polymorphisms in patients with chronic hepatitis B virus infection and with self-limiting hepatitis B virus infection \(n\) (%)

| IRF3 | Chronic HBV infection | Acute HBV infection | \(P\) value | OR (95% CI) |
|------|-----------------------|---------------------|-------------|-------------|
| rs10415576 | \(n = 985\) | \(n = 294\) | | |
| AA   | 347 (35.23) | 119 (40.48) | 1.0 | |
| GG   | 135 (13.71) | 33 (11.22) | 0.125 | 1.4029 (0.9091-2.1650) |
| AG   | 503 (51.07) | 142 (48.30) | 0.172 | 1.2148 (0.9187-1.6063) |
| A    | 1197 (60.76) | 380 (64.63) | 0.091 | 1.1798 (0.9740-1.4291) |
| G    | 773 (39.24) | 208 (35.37) | | |
| rs2304204 | \(n = 985\) | \(n = 294\) | | |
| AA   | 542 (55.03) | 166 (56.46) | | |
| GG   | 54 (5.48) | 14 (4.76) | 0.594 | 1.1813 (0.6400-2.1807) |
| AG   | 389 (39.49) | 114 (38.78) | 0.75 | 1.0451 (0.7965-1.3713) |
| A    | 1473 (74.77) | 446 (75.85) | 0.596 | 1.0579 (0.8552-1.3133) |
| G    | 497 (25.23) | 142 (24.15) | | |
| rs2304206 | \(n = 985\) | \(n = 294\) | | |
| CC   | 639 (64.87) | 191 (64.97) | 1.0 | |
| TT   | 30 (3.05) | 7 (2.38) | 0.562 | 1.2810 (0.5539-2.9627) |
| CT   | 316 (32.08) | 96 (32.65) | 0.909 | 0.9839 (0.7437-1.3016) |
| C    | 1594 (80.91) | 478 (81.29) | 0.837 | 1.0250 (0.8097-1.2976) |
| T    | 576 (19.09) | 110 (18.71) | | |

IRF3: Interferon regulatory factors 3. HBV: Hepatitis B virus; OR: Odds ratio; CI: Confidence interval.

1 U CIP, were mixed and insolated at 37 °C for 1 h, and 75 °C for 15 min to inactivate the enzyme. The samples can be stored at 4 °C for 24 h or -20 °C permanently.

DNA sequencing: the SNaPshot product was diluted 20-fold. In a total volume of 10 µL we mixed 8.6 µL HiDiFormamide (high-purity formamide), 0.9 µL GeneScan-120 LIZ Size Standard, and 0.5 µL SNaPshot purification product. Samples were incubated at 95 °C for 5 min, chilled quickly for 4 min, and then loaded on an ABI 3730XL Genetic Analyzer (Applied Biosystems, CA, United States) for capillary electrophoresis, running GeneMapper4.0 software analysis of experimental results.

Statistical analysis
Allele and genotype frequencies were obtained by direct counting, and the Chi-square test was used to compare allele and genotype distributions. The quality of the genotype data was assessed by Hardy-Weinberg equilibrium in the case and control samples using Fisher’s exact test (\(P > 0.05\)). Odds ratios (OR) and 95% confidence intervals [95% confidence interval (CI)] were calculated according to Woolf’s method.

RESULTS
We investigated the distribution of the three SNPs in 985 Chinese HBV-infected patients (cases) and 294 self-limiting HBV-infected patients (controls). All genotypes of the IRF-3 polymorphisms were in Hardy-Weinberg equilibrium in both the cases and controls. The genotype frequencies and allele distributions of IRF3 polymorphisms in each subgroup of HBV-infected patients are summarized in Table 1. The genotype frequencies for AA, GG, and AG of IRF3 rs10415576 were 55.23%, 13.71%, and 31.07% in case samples, and 40.48%, 11.22%, and 48.30% in control samples, respectively, without significant differences between cases and controls (\(P = 0.2105\)). The genotype frequencies for AA, GG, and AG of IRF3 rs2304204 were 55.03%, 5.48%, and 39.49% in case samples, and 56.46%, 4.76%, and 38.78% in control samples, respectively, without significant differences between cases and controls (\(P = 0.8372\)). The genotype frequencies for CC, TT, and CT of IRF3 rs10415576 were 64.87%, 3.05%, and 32.08% in case samples, and 64.97%, 2.38%, and 32.65% in control samples, and no significant differences were noted (\(P = 0.8315\)).

In addition, no statistically significant differences were found when the allele frequencies of SNPs rs10415576, rs2304204 and rs2304206 were compared between patients with chronic HBV infection and controls. Overall allele \(P\) values were: rs10415576, \(P = 0.0908\), OR (95% CI) = 1.1798 (0.9740-1.4291); rs2304204, \(P = 0.5959\), OR (95% CI) = 1.0579 (0.8552-1.3133); rs2304206, \(P = 0.8372\), OR (95% CI) = 1.0250 (0.8097-1.2976).

Haplotype analysis
We also estimated the IRF3 haplotype frequencies and evaluated the association among these variants and HBV infection. We observed four haplotype combinations, but no significant association was found in the distribution of the haplotype frequencies between cases and controls (\(P > 0.05\)). Haplotype frequencies lower than 0.03 were ignored in the analysis (Table 2).

DISCUSSION
The human IRF3 gene is located on chromosome 19q13.3-q13.4, and encodes a 50-KDa protein. The ubiquitously expressed IRF3 is activated in infected cells upon recognition of double-stranded RNA, which is considered the common signature of virus-infected cells. Lau et al indicated that hepatitis C virus (HCV) can transiently trigger IRF3 activation during virus spread and that in chronic HCV, IRF3 activation within infected hepatocytes occurs but is limited.

Several studies have described the importance of IRF3 polymorphisms. The effect of the A to T substitution on the splicing efficiency of intron 5 of mouse IRF3 sequences for AA, GG, and AG of IRF3 rs10415576 were 55.23%, 13.71%, and 31.07% in case samples, and 40.48%, 11.22%, and 48.30% in control samples, respectively, without significant differences between cases and controls (\(P = 0.2105\)). The genotype frequencies for AA, GG, and AG of IRF3 rs2304204 were 55.03%, 5.48%, and 39.49% in case samples, and 56.46%, 4.76%, and 38.78% in control samples, respectively, without significant differences between cases and controls (\(P = 0.8372\)). The genotype frequencies for CC, TT, and CT of IRF3 rs10415576 were 64.87%, 3.05%, and 32.08% in case samples, and 64.97%, 2.38%, and 32.65% in control samples, and no significant differences were noted (\(P = 0.8315\)).

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was confirmed using an in vitro splicing assay. The A to T polymorphism in intron 5 of IRF3 affects induction of IFN-β1 expression16. Zhang et al19 showed that SNPs in codon 427 of human IRF3 may be related to the susceptibility to esophageal cancer. The risk of esophageal cancer in participants with the C allele is 2.38 folds higher that in those with the G allele. However, Sánchez et al23 suggest that the IRF3 polymorphisms (rs2304204, rs7251 and rs2304207) do not appear to play a major role in the susceptibility or severity of systemic lupus erythematosus in a Spanish population. We selected three SNPs in IRF3 (rs10415576, rs2304204, and rs2304206) using genotype data from the panel (Han Chinese in Beijing) of the phase II HapMap Project. The three tagSNPs captured 100% of common SNPs (minor allele frequency > 0.1) in the HapMap Chinese database at r² > 0.8. We analyzed the associations of the three SNP alleles with HBV-infected patients compared with spontaneously cleared HBV controls. The results indicated that there were no significant differences between cases and controls in the genotype or haplotype frequencies of any of the three SNPs we analyzed, suggesting that tagSNPs of IRF3 do not predict the outcome of HBV infection.

In conclusion, although IRF3 is a functional gene with a relevant role in HBV pathogenesis, our study demonstrates that the tagSNPs of IRF3 do not correlate with genetic susceptibility to chronic HBV infection in Chinese patients. Further genetic studies are needed to examine the polymorphisms in other IRF3 SNPs and the possible association with disease progress in chronic HBV infection.

**COMMENTS**

**Background**

Persistent hepatitis B virus (HBV) infection is considered a multifactorial and polygenic disorder with viral, environmental, and genetic components, as well as contributions from HBV genomic variability, host age, gender, concurrent infection with the hepatitis C virus, hepatitis D virus, and human immune deficiency virus. Interferon regulatory factors (IRF3) play an important role in the response of the innate immune system to viral infection. IRF3 polymorphisms affect induction of interferon (IFN)-β1 expression.

**Research frontiers**

This study is the first to investigate the association between three tag single nucleotide polymorphisms (tagSNPs) (rs10415576, rs2304204 and rs2304206) of IRF3 and the genetic susceptibility to chronic HBV infection in Chinese patients using the Multiplex SNaPshot technique.

**Innovations and breakthroughs**

The three tagSNPs of IRF3 were not related to genetic susceptibility to HBV infection.

**Applications**

Based on the results of this study, further genetic studies are needed to examine the roles of other IRF3 SNPs and their association with disease progress in chronic HBV infection.

**Terminology**

IRF3 is located on chromosome 19q3.3-q3.4, and encodes a 50-KDa protein.

**Peer review**

The manuscript analyzed the association between polymorphisms of IRF3 and clinical outcomes of HBV infection. Three SNPs of IRF3 were genotyped using Multiplex SNaPshot technique and compared between chronic HBV infection and self-limiting HBV infection patients. The overall data are negative and showed that SNPs of IRF3 did not affect the outcome of HBV infection. The data may have a significant clinical implication.

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