IFIT1 polymorphisms predict interferon-α treatment efficiency for hepatitis B virus infection

Dong-Ying Xie, Shi-Ming Wang, Jing-Min Yang, Liang-Hui Wang, Hong-Yan Chen, Cong Huai, Jia Shang, Qing Mao, Chun-Liang Lei, Guang-Han Luo, Ji Qian, Da-Ru Lu

AIM
To investigate the association between interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) polymorphisms and interferon-α (IFNα) treatment efficiency among Chinese hepatitis B virus (HBV) infection patients.

METHODS
Two hundred and twenty five newly diagnosed chronic HBV infection patients were included in our study. The polymorphism of IFIT1 gene was detected by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The treatment efficiency was defined as the change in HBV DNA copies in serum after treatment. The association between the IFIT1 polymorphism and treatment efficiency was assessed by logistic regression analysis. The results showed that the T allele of IFIT1 rs756944 polymorphism was associated with treatment inefficiency in HBV infection patients (OR = 2.87, 95% CI: 1.39-5.99, P = 0.004). The efficiency of IFNα treatment in patients with IFIT1 rs756944 polymorphism was significantly lower than those without it (OR = 2.58, 95% CI: 1.25-5.34, P = 0.009).

Abstract

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RESULTS
At the end of the treatment, HBeAg seroconversion was observed in 27.1% patients. Thirty-six point nine percent patients achieved virological response, and 15.6% patients exhibited combined response. Sustained response was obtained in 26.2% patients. The main HBV genotype of the study was genotype B. Patients who infected with HBV genotype B or C showed better treatment efficiency, no matter which clinical outcome was considered. Among the four SNPs assessed, rs303218 (A > G) was found to be significantly associated with the end point virological response when assuming additive model [OR = 0.64 (95%CI: 0.42-0.96), P = 0.032]. Patients who carried rs303218 GG genotype had a rather higher rate of achieving virological response (response rate: 52%, OR = 0.40, 95%CI: 0.18-0.91; P = 0.028) when compared to those had AA genotype (response rate: 27%). The most significant interaction was observed in patients who had relative lower baseline aspartate transaminase. No association between SNPs and HBeAg seroconversion, combined response or sustained response was observed.

CONCLUSION
IFIT1 involves in the regulation of IFNα treatment for CHB and its polymorphism rs303218 can predict the end point virological response. The finding requires further validation.

Key words: Virological response; Hepatitis B virus infection; IFIT1; Interferon-α therapy; Polymorphism

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Core tip: Interferon-α (IFNα) is the first line treatment for chronic hepatitis B virus (HBV) infection (CHB). However, its efficiency differs and biomarkers for predicting responses of IFNα are needed. The current study performed an epidemiologic study to investigate the association between Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) polymorphisms and clinical responses of IFNα treatment in newly diagnosed chronic HBV infection patients among Chinese population. We identified that IFIT1 polymorphism rs303218 could be a predictor for the end point virological response of IFNα therapy. The finding may provide insight to the potential role of IFIT1 in the individualized treatment of CHB in the future.

INTRODUCTION
Hepatitis B infection is a life-threatening disease caused by hepatitis B virus (HBV), which attacks liver. An estimated 350 million people are infected with hepatitis B chronically worldwide, which makes it a major global health problem[1]. According to WHO, more than 780000 people die of cirrhosis and hepatocellular carcinoma (HCC) caused by chronic hepatitis B (CHB). Currently, immune modulators such as interferon-α (IFNα) or pegylated interferon-α (PEG-IFNα) and antiviral agents such as nucleotide analogues (NAs) are two approved treatments for CHB patients[2]. Compared with NAs treatment, IFNα is less likely to develop drug resistance and its finite duration is an attractive treatment strategy for CHB patients. IFNα treatment showed high rates of off-therapy host immune control over HBV and increased rates of hepatitis B e antigen (HBeAg)/hepatitis B surface antigen (HBsAg) loss or seroconversion over time[3]. However, the fact that only 30%-40% patients benefit from the IFNα therapy is still an obstacle in CHB management[4]. Therefore, it is necessary to discover predictors for outcomes of IFNα treatment to improve the personalized therapy for CHB patients. Several host and virus factors such as gender, serum HBV DNA level and alanine aminotransferase (ALT) level are considered to have influence on IFNα efficiency, but they are weak at predicting responses at individual level[5]. More and more researches have shown that host genetic factors may play an important role in the response to IFNα treatment. Single nucleotide polymorphisms (SNPs) located on IL28B are reported to affect the response to IFNα based therapy for CHB patients[6-8]. Polymorphisms on HLA-DP and IRF5 are also associated with IFNα treatment efficiency[9,10]. It is also reported that genetic variants on STAT4 influenced the response of IFNα among CHB patients[11]. All the evidences indicate genetic variations on genes involved in immune response or IFNα signaling may lead to different clinical outcomes of IFNα therapy.

After virus infection, the expression of virus-responsive genes and antiviral cytokines such as type I interferon are induced to limit virus replication and modulate adaptive immune response. Interferon-stimulated genes (ISGs) are a subset of genes response to RNA- or DNA- virus infection or type 1 IFN treatment,
and they are mainly induced by IFN-α/β[12]. Under basal condition, ISGs are not expressed in most cell types. But they can be induced immediately to a high level after virus infection or IFN treatment[13]. Their products take on diverse roles such as enhancing innate immune capabilities, inhibiting virus infection and negatively regulating signaling through the JAK-STAT pathway[14]. Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) which is an effector molecule in antivirus pathways, locates in the cytoplasm. It is an important member of ISGs family which lacking enzymatic domains or activity. Tetratricopeptide repeats (TPR) motif mediates protein-protein interaction. Proteins containing TPR motifs regulate cell cycle, transcription, protein transport and protein folding, which enable IFIT1 to serve as an effector molecule on virus replication during responses to viral infections[15]. IFIT1 is induced within two hours of exogenous IFN-α treatment[16]. It is reported that IFIT1 acts as an important innate immune bottleneck which shows positive regulation on downstream genes[17]. High level of type I IFN is observed in IFIT1-expressing cells[18]. Researches have indicated that the antiviral activity of IFIT1 is modulated by 2'-O methylation of viral RNA. Abrogation of 2'-O methylation results in enhanced type I IFN and IFIT1 sensitivity[19-21]. IFIT1 can sense the methylation state of capped RNA and inhibit viruses by binding to their 5’ cap structure that lack 2'-O methylation[22,23]. It can also sense viral RNA by recognizing uncapped 5’-ppp and stop it from actively replicating[24]. Despite sensing 2'-O methylation viral RNA, IFIT1 also exerts its antivirus function through inhibiting steps in translation initiation. It is reported that IFIT1 reduces the translation efficiency by binding to the subunits eIF3 complex, which functions in several steps in translation initiation[25,26]. IFIT1 is also responsible for IFN-induced alteration of virus transcription and protein synthesis[27]. Silencing of IFIT1 leads to remarkable increased HBV replication, which indicates that IFIT1 plays an important role in the regulation of HBV transcription and postranscriptional procedure[28]. All the evidences indicate that IFIT1 is an important effector in both virus infection and IFN-α treatment. It has been reported that IFIT1 acts as a potential biomarker for Peg-IFNα treatment efficiency in hepatitis C virus (HCV) patients[29]. However, few researches mention about IFIT1’s role in HBV infected patients who treated with IFNα. To illuminate whether IFIT1 related to IFNα treatment efficiency for CHB, we conducted an association study that assessed the relationship between tag-SNPs on IFIT1 and clinical outcomes of IFNα treatment among 225 Chinese CHB patients.

MATERIALS AND METHODS

Patient recruitment

Patients enrolled in this study were newly diagnosed HBeAg-positive CHB patients who were recruited from nine Chinese hospital between August 2009 and May 2012, including the Third Affiliated Hospital of Sun Yat-Sen University, the Eighth People’s Hospital of Guangzhou, Nanfang Hospital, Shenzhen Third People’s Hospital, the First Affiliated Hospital of Guangxi Medical University, Henan Provincial People’s Hospital, the First Affiliated Hospital of Third Military Medical University, Xiangya Hospital Central South University, and Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology. The major criteria for clinical data collection and patient recruitment were: (1) written informed consent available and adherence to the treatment schedule; (2) age 18-60 years old; (3) HBeAg-positive and HBeAg-positive for more than six months; (4) serum level of HBV DNA > 20000 IU/mL; (5) serum ALT level > 40 IU/L; and (6) no diagnosed HCC or suspected to have HCC. The main exclusion criteria were: (1) previous IFN treatment, nucleos(t)ide analogues treatment or immunomodulatory therapy within six months; (2) coinfected with HCV, hepatitis D virus or human immunodeficiency virus (HIV); (3) autoimmune hepatitis, steatohepatitis or other active hepatopathy; and (4) evidence of decompensated liver disease. All patients received antivirus therapy with 6 MU IFNα-2b (rHuIFNα-2b, Amoytop) every other day for 48 wk. Evaluation of therapeutic efficiency was performed at the end of the treatment course and by the time of following up to 24 wk. Efficiency of the treatment was assessed by end point response including HBeAg seroconversion, virologic response and combined response at 48 wk, and by sustained response which was assessed at 72 wk. HBeAg seroconversion was defined as the loss of HBeAg and the presence of anti-HBe. Virological response was defined as serum HBV DNA level < 2000 IU/L. Combined response was defined as the combination of HBeAg seroconversion and virological response, as well as the normalization of serum ALT. Sustained response was defined as the combined response at week 72 after the first dose of the treatment.

SNP selection and genotyping

IFIT1 is about 13.9 kb long and locates on chromosome 10q23.31. To investigate the association between IFIT1 and IFNα treatment efficiency, 4 tag-SNPs located in IFIT1 gene region were selected according to the genotype data of Han Chinese in Beijing (CHB) population from the phase II HapMap SNP database, by software Haplovieview 4.1 (available at http://www.broadinstitute.org/haplovieview). The thresholds for tag-SNP selection were defined as 0.8 for correlation coefficient and a cutoff of 0.2 for MAF. Blood sample were collected at the time of recruitment. Genome DNA was extracted by salt-out method. All the selected SNPs were genotyped using DNA sequencing on illumine Miseq high throughout sequencing platform. Random duplicate sample were performed and all the
samples were concordant with the genotyping results. All SNPs were in Hardy-Weinberg equilibrium ($P > 0.001$). More details about these four tag-SNPs were shown in Supplementary Table 1.

**Statistical analysis**
Patient characteristics and clinical variables were test by $\chi^2$ tests or Student’s $t$ test against treatment responses. Factors that had $P$ value $< 0.05$ were regarded as covariates (Table 2). Univariable logistic regression analysis was performed to assess allele frequency distribution of $IFIT1$ SNPs in different patient groups. Chi-square test and unconditional logistic regression adjusted for covariates were used to assess whether $IFIT1$ SNPs’ genotypes had statistically significant difference in the distribution of clinical outcomes, and to estimate the association between efficiencies and SNPs by OR and in additive, dominant, recessive or co-dominant model. Stratified analysis was performed to investigate significant SNPs’ effects in different subgroups. All $P$ values reported in this study were two-sided, and $P < 0.05$ was considered statistically significant. All the statistical analyses were performed by SPSS (version 15.0; SPSS Inc., Chicago, Ill).

**RESULTS**

**Patient characteristics and clinical outcomes**
225 CHB patients who met the recruitment criterion were included in the study to investigate the association between $IFIT1$ polymorphisms and IFN-$\alpha$ treatment responses. Table 1 summarized patient characteristics and clinical outcomes. Male patients accounted for 72.4% of this cohort and the median age was 26 years old. The median baseline ALT and aspartate transaminase (AST) were 150 IU/L and 83 IU/L, respectively. Baseline HBV DNA level’s median is 7.36 log10 IU/mL. The main HBV genotype of this cohort was genotype B, which took over 47.7% of all the patients. Forty point six percent patients infected with both genotype B and C HBV at the same time. After 48 wk IFN-$\alpha$ treatment, 27.1% patients achieved HBeAg seroconversion. 36.9% patients’ serum HBV DNA level decreased below 2000 IU/L which meant virological response were attained in these patients. Combined response was observed in 15.6% patients. Twenty-four weeks off treatment follow-up showed that 26.2% patients obtained sustained response. According to Table 2, HBV genotype had impact on IFN-$\alpha$ therapy responses. Patients who infected with HBV genotype B or C showed better treatment efficiency than those infected with genotype A or those infected with both genotype B and C, no matter which clinical outcome was considered. As shown in Table 3, the level of baseline ALT was associated with HBeAg seroconversion ($P = 0.020$), and the distribution of combined response was significantly different between male and female patients ($P = 0.027$). HBV genotype exhibited significant association with all the clinical outcomes including virological response ($P = 0.012$), HBeAg seroconversion ($P = 0.001$), combined response ($P = 0.038$) and sustained response ($P = 2.37 \times 10^{-4}$). Other clinical characteristics including age, baseline AST and baseline HBV DNA level, showed association with none of the clinical outcomes.

**$IFIT1$ polymorphisms and IFN-$\alpha$ treatment’s virological response**
All the SNPs were evaluated for their association with IFN-$\alpha$ treatment efficiency, including the end point responses and sustained response. It was considerable that none of the $IFIT1$ SNPs’ allele frequency showed distribution differences in HBeAg seroconversion, combined response or sustained response (data not shown), but all of them had significantly different allele frequency distribution among patients who achieved virological response (Table 4). So we further assessed these SNPs’ association with virological response
by genotype. $\chi^2$ test showed that the distribution of rs303218 (A > G) genotype was significant different ($P = 0.022$), which is the most significant SNP from the allele frequency distribution assessment. Patients who carried rs303218 GG genotype had a rather high rate of virological response (response rate: 52%) when compared to patients who had AA genotype (response rate: 27%), with OR of 0.40 (95%CI: 0.18-0.91) and $P$ value of 0.028. Unconditional logistic regression adjusted by covariate, which was HBV genotype for virological response, as well as the normalization of serum ALT at the end of the treatment; virological response was defined as the combined response at week 72 after the first dose of the treatment. HBV: Hepatitis B virus; R: Response; HBeAg: Hepatitis B e antigen.

Table 2  Hepatitis B virus genotype and interferon-α treatment responses

| HBV genotype | Total | Virological response | HBeAg seroconversion | Combined response | Sustained response |
|--------------|-------|----------------------|----------------------|------------------|-------------------|
|              |       | R | % | R | % | R | % | R | % |
| Type A       | 8     | 3 | 37.5 | 1 | 12.5 | 1 | 12.5 | 1 | 12.5 |
| Type B       | 94    | 42 | 44.7 | 38 | 40.4 | 19 | 20.2 | 37 | 39.4 |
| Type C       | 15    | 10 | 66.7 | 5 | 33.3 | 5 | 33.3 | 6 | 40.0 |
| Type B + C   | 80    | 22 | 27.5 | 11 | 13.8 | 7 | 8.8 | 10 | 12.5 |

$^1$Virological response was defined as serum HBV DNA level < 2000 IU/L at the end of the treatment; $^1$HBeAg seroconversion was defined as the loss of HBeAg and the presence of anti-HBe at the end of the treatment; $^1$Combined response was defined as the combination of HBeAg seroconversion and virological response, as well as the normalization of serum ALT at the end of the treatment; $^1$Sustained response was defined as the combined response at week 72 after the first dose of the treatment. HBV: Hepatitis B virus; R: Response; HBeAg: Hepatitis B e antigen.

Table 3  Association between clinical factors and responses

| Patient characteristics | Virological response | HBeAg seroconversion | Combined response | Sustained response |
|-------------------------|----------------------|----------------------|------------------|-------------------|
|                         | R | NR | P value$^1$ | R | NR | P value$^1$ | R | NR | P value$^1$ | R | NR | P value$^1$ |
| Gender                  |   |    |            |   |    |            |   |    |            |   |    |            |
| Male                    | 55 | 108 | 0.113 | 39 | 163 | 0.081 | 20 | 163 | 0.027$^2$ | 39 | 163 | 0.204 |
| Female                  | 28 | 34  | 0.151 | 22 | 62  | 0.070 | 15 | 62  | 0.002$^2$ | 20 | 63  | 0.116 |
| Age                     |   |    | 0.057$^2$ |   |    | 0.020$^2$ |   |    | 0.039$^2$ |   |    | 0.181 |
| Baseline ALT            |   |    | 0.057$^2$ |   |    | 0.020$^2$ |   |    | 0.039$^2$ |   |    | 0.181 |
| Baseline AST            |   |    | 0.113 | 0.113 | 0.020$^2$ | 0.443 | 0.279 |
| Baseline HBV DNA level  |   |    | 0.121 | 0.554 | 0.067 | 0.217 |
| HBV genotype            |   |    | 0.012$^2$ |   |    | 0.001$^2$ |   |    | 0.038$^2$ |   |    | 2.37 × 10^{-4}$^2$ |
| Type A                  | 3  | 5  | 0.113 | 1  | 7   | 0.081 | 1  | 7   | 0.027$^2$ | 1  | 7   | 0.204 |
| Type B                  | 42 | 52  | 0.151 | 38 | 56  | 0.070 | 19 | 75  | 0.002$^2$ | 36 | 57  | 0.116 |
| Type C                  | 10 | 5  | 0.121 | 5  | 10  | 0.554 | 5  | 10  | 0.067 | 6  | 9    | 0.217 |
| Type B + C              | 22 | 58  | 0.012$^2$ | 1  | 7   | 0.001$^2$ | 1  | 7   | 0.038$^2$ | 1  | 7   | 2.37 × 10^{-4}$^2$ |

$^1$P value was calculated by $\chi^2$ test or Student’s t-test depending on which variables were analyzed; $^2$P < 0.05. ALT: Alanine aminotransferase; AST: Aspartate transaminase; HBV: Hepatitis B virus; R: Response; NR: Non-response; HBeAg: Hepatitis B e antigen.

Table 4  The association between single nucleotide polymorphisms and virological response by allele frequencies

| SNP ID   | Genotype | No./total$^1$ | % | $P^2$ | OR   | 95%CI |
|----------|----------|---------------|---|-------|------|-------|
| rs303218 | A        | 75/242        | 0.31 | 0.003$^1$ | 1 (Reference) |
|          | G        | 87/198        | 0.44 | 0.57 | 0.39-0.85 |
| rs303218 | T        | 93/227        | 0.41 | 0.045$^1$ | 1 (Reference) |
|          | C        | 69/217        | 0.32 | 1.49 | 1.01-2.20 |
| rs11203109 | T    | 109/341      | 0.32 | 0.020$^1$ | 1 (Reference) |
|          | C        | 37/81         | 0.46 | 0.56 | 0.34-0.92 |
| rs303212 | T        | 93/284        | 0.33 | 0.022$^1$ | 1 (Reference) |
|          | C        | 65/148        | 0.44 | 0.62 | 0.41-0.94 |

$^1$Number indicated the patients who responded in the same group; $^2$P value was calculated by univariable logistic regression analysis; $^3$P < 0.05. SNP: Single nucleotide polymorphism.
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### Table 5 The association between rs303218 and virological response

| SNP ID | Genotype | Genotype model | No./total | % | \( z^2 \) test | Logistic regression analysis |
|--------|----------|----------------|-----------|---|-----------------|-----------------------------|
| rs303218 | A A | 19/70 | 0.27 | 0.022<sup>1</sup> | 1 (Reference) |
|        | G A | 37/102 | 0.36 | 0.77 | 0.38-1.55 | 0.467 |
|        | G G | 25/48 | 0.52 | 0.40 | 0.18-0.91 | 0.028<sup>2</sup> |
|        | Add |  |  | 0.64 | 0.42-0.96 | 0.032<sup>2</sup> |

<sup>1</sup>The best fitting model was shown; <sup>2</sup>Number indicated the patients who responded in the same group; \( P < 0.05 \); \( P \) value was calculated by logistic regression analysis with adjustment of patient characteristics with \( P < 0.05 \) in univariate analysis (the adjusting covariate for virological response was HBV genotype). HBV: Hepatitis B virus.

### Table 6 Stratified analyses of rs303218 and virological response

| Variables                      | OR         | 95%CI       | \( P \) value<sup>2</sup> |
|--------------------------------|------------|-------------|--------------------------|
| Age (yr)                       |            |             |                          |
| \( \leq 26 \)                  | 0.79       | 0.42-1.48   | 0.453                    |
| \( > 26 \)                     | 0.59       | 0.33-1.04   | 0.070                    |
| Gender                         |            |             |                          |
| Male                           | 0.53       | 0.32-0.88   | 0.013<sup>3</sup>        |
| Female                         | 1.03       | 0.46-2.31   | 0.947                    |
| Baseline ALT                   |            |             |                          |
| \( \leq 150 \)                 | 0.38       | 0.20-0.74   | 0.003<sup>5</sup>        |
| \( > 150 \)                    | 0.91       | 0.52-1.60   | 0.734                    |
| Baseline AST                   |            |             |                          |
| \( \leq 83 \)                  | 0.31       | 0.16-0.61   | 0.001<sup>3</sup>        |
| \( > 83 \)                     | 1.10       | 0.62-1.96   | 0.752                    |
| Baseline HBV DNA copies (log10 IU/mL) |          |             |                          |
| \( \leq 7.36 \)                | 0.86       | 0.49-1.52   | 0.611                    |
| \( > 7.36 \)                   | 0.47       | 0.25-0.88   | 0.018<sup>6</sup>        |
| HBV genotype                   |            |             |                          |
| Type B                         | 0.74       | 0.42-1.31   | 0.304                    |
| Type C                         | 1.19       | 0.56-2.35   | 0.397                    |
| Type B + C                     | 0.41       | 0.19-0.86   | 0.018<sup>6</sup>        |

<sup>1</sup>Number indicated the patients who responded in the same group; \( P < 0.05 \); \( P \) value was calculated by logistic regression analysis with adjustment of patient characteristics with \( P < 0.05 \) in univariate analysis ( HBV genotype); \( P < 0.05 \). ALT: Alanine aminotransferase; AST: Aspartate transaminase; HBV: Hepatitis B virus.

and patients whose baseline HBV DNA level were higher than 7.36 log10 IU/mL (OR = 0.47; 95%CI: 0.25-0.88; \( P = 0.018 \)), as well as patients who infected with both HBV genotype B and C (OR = 0.41; 95%CI: 0.19-0.86; \( P = 0.018 \)).

### DISCUSSION

IFNα or PEG-IFNα is the first-line treatment for Chronic HBV infection. It can maintain high rates of off-therapy host immune control over HBV. However, IFNα therapy gives benefits to only 30%-40% CHB patients, which suggests the necessity for discovering efficiency predictors for IFN treatment to improve the personalized therapy for CHB patients. It is reported that female patients, higher ALT level and lower serum HBV DNA level may indicate a better IFNα response[30]. But all of these host or virus factors are not ideal predictors at individual level. Researchers expect that biomarkers that rely on the basis of patients’ genetic background can highlight the road to personalized medicine. As one of the key components of IFNα induced pathways, IFIT1 is indispensable for IFNα to eliminate HBV. However, few researches focused on its role in HBV management, especially its pharmacogenetic effects. In this study, we investigated whether IFIT1 gene polymorphisms could predict IFNα treatment efficiency among Chinese CHB patients. The results showed that rs303218 was associated with end point virological response after 48 wk IFNα therapy. Patients who carried GG genotype of rs303218 achieved higher rate of virological response when compared to GA/AA genotype.

IFNα is an important innate immune response cytokine which acts as the first line defense of HBV infection[31]. Patients who have CHB may have reduced ability of producing IFNα, but they show response to exogenous IFNα and then induce ISGs expression to activate related signaling to inhibit HBV replication[32,33]. The function of ISGs includes enhancing innate immune capabilities and inhibiting virus infection. IFIT1 is one of the most immediately induced ISGs after exogenous IFNα treatment. The most well-known function of IFIT1 is that it can sense and recognize the 2'-O unmethylated RNA and block the translation of viral RNA lacking 2'-O methylation[22,34]. It can also recognize the uncapped 5'—ppp and stop it from actively replicating[35]. But viruses that using cellular RNA polymerase II to synthesize their mRNA may escape the IFIT1-mediated restriction[36]. However, there are other ways that IFIT1 exerts its anti-virus function. For example, IFIT1 acts as an important modulator in virus transcription and replication. It can inhibit cap-dependent protein synthesis by binding to the subunits of translation initiation complex eIF3[25,37]. Researches has demonstrated that IFIT1 can restrict HCV growth by inhibiting HCV replication, and the expression level of IFIT1 can be potential biomarker of response to IFNα in patients with HCV[29,38]. IFIT1 restricts the translation and replication of many other viruses such as HPV, HIV and alphavirus, and promotes the induction of IFNα to enhance immune response[18,39,40]. All these evidences demonstrate...
the importance of IFIT1 in immune system and virus inhibition. STAT/JAK pathway has been reported to be a vital role in pharmacogenomics of IFNα treatment. As an essential member of STAT/JAK pathway, IFIT1 may participate in affecting IFNα therapy responses by modulating downstream STAT/JAK signaling. Recently, it is reported that IFIT1 involves in the control of HBV by limiting replication and slowing down the spread of HBV, which further illustrates that IFIT1 takes part in HBV restriction and may influence IFNα treatment efficiency\(^{[28]}\). Our findings indicated that rs303218 was associated with virological response, which also suggested IFIT1's indispensable role in controlling HBV replication.

As we know that, the polymorphism of rs303218 locates in the intron region of IFIT1. Other than causing missense mutation which results in protein dysfunction, intronic polymorphisms may locate in the regulatory element sites, such as splice donor, acceptor, or cis-regulatory element region, which means they might regulate cell metabolism through modulating mRNA splicing and gene expression patterns\(^{[41-43]}\). NCBI database shows that IFIT1 has three isoforms. They are different from each other by their different alternate initiation translation site. A reasonable conjecture is that different IFIT1 isoform may have different affinity to IFIT family members or to the translation initiation complex such as elf3, or they may display different capability of recognizing 2'-O unmethylated RNA or uncapped 5’-ppp. However, no evidence was found to support that variants on IFIT1 facilitated gene splicing or gene expression. A recent research showed that a variant known as rs304478, which located within 2 kb upstream of IFIT1, was an independent predictive factor for pegylated-IFN therapy in HCV patients\(^{[44]}\). Although rs304478 was not included in the present study due to its relative lower MAF in Chinese population, it highlighted a fact that IFIT1 could be potential biomarker for IFNα treatment efficiency. Another assumption is that the real reason affecting IFIT1 mRNA stability or protein synthesis, is the effective SNPs which are in linkage disequilibrium with rs303218. Nevertheless, all these are just hypothesis that need more researches to discover the real facts of how IFIT1 intrinsic SNPs influence IFNα treatment efficiency, and it is necessary to find the actual genetic variations that affect responses of IFNα.

In conclusion, the study investigated the association between IFIT1 polymorphisms and clinical outcomes of IFNα treatment for CHB patients among Chinese population. The results provided evidences for IFIT1’s part in IFNα treatment efficiency. Our study highlights the potential role of IFIT1 in predicting IFNα treatment's end point virological response, although the exact mechanism needs to further investigate. The findings needs to be validated in an independent cohort to further illuminate the effects of IFIT1’s variants for IFNα therapy. And it is meaningful to assess IFIT1’s predicting potential in different ethnicities.

Function studies are needed to explore the mechanism between IFIT1 and IFNα therapy.

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**COMMENTS**

**Background**

Hepatitis B infection is a major global health problem. As a life-threatening disease, many people die of chronic hepatitis B (CHB) related cirrhosis and hepatocellular carcinoma. Interferon-α (IFNα) treatment showed high rates of achieving off-therapy responses and low rate of developing drug resistance, which makes it the first-line treatment for CHB patients. However, the obstacle that only 30%-40% CHB patients benefit from IFNα treatment still limit the CHB management. Although several host and viral factors are considered to influence IFNα therapy efficiency, but they are not ideal at individual level. Researches have shown that host genetic characteristics such as genetic variations may provide new approaches to predict responses of IFNα based therapy, especially those genes involved in immune response or IFNα signaling. Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) is one of the immediately induced genes by IFNα, which plays an important role in antivirus pathways. Deregulation of IFIT1 may have great influence on hepatitis B virus (HBV) transcription which indicated that IFIT1 could be potential biomarkers for predicting IFNα treatment efficiency. In this study, we perform an association study that investigated the relationship between polymorphisms on IFIT1 and clinical outcomes of IFNα therapy among Chinese CHB patients.

**Research frontiers**

IFIT1 is an important effector molecule in antivirus pathways. It is responsible for IFN-induced alteration of virus transcription and protein synthesis. However, few prior researches focus on IFIT1's role in CHB patients who treated with IFNα. The results of the study contribute to illustrating IFIT1's role in IFNα treatment, and provide evidences for IFIT1's potential in predicting efficiency of IFNα therapy.

**Innovations and breakthroughs**

The study clarifies the role of IFIT1 in the regulation of IFNα treatment for CHB by an epidemiologic study among Chinese patients. It highlights IFIT1's potential in predicting IFNα therapy's end point virological response.

**Applications**

The study identifies that polymorphism rs303218 on IFIT1 could be a predictor for the end point virological response of IFNα therapy, which may provide insight to the individualized treatment of CHB in the future.

**Terminology**

IFIT1: Interferon-induced protein with tetratricopeptide repeats 1. Virological response: Defined as serum HBV DNA level < 2000 IU/L at the end of the treatment.

**Peer-review**

The IFN induced proteins with tetratricopeptide repeats 1 is related gene which can be strongly induced by IFN type 1. It suppress cellular translation and was shown to block viral replication thus the importance to focus on such single nucleotide polymorphisms. The article represents an accepted population survey in an under-analysed population and contributes to the literature.
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