World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i44.9813

World J Gastroenterol 2016 November 28; 22(44): 9813-9821
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

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

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Author contributions: Xie DY and Wang SM contributed equally to this work; Xie DY, Wang SM and Yang JM conceived and designed the study; Lu DR designed and supervised the study; Wang SM analyzed the data and drafted the manuscript; Wang SM, Yang JM and Wang LH conducted the experiments and interpreted the data; Xie DY, Shang J, Mao Q, Lei CL and Luo GH collected the patients and offered material supports; Chen HY, Huai C and Qian J provided analytical oversight and revision suggestions; all authors have read and approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: June 24, 2016
Peer-review started: June 24, 2016
First decision: July 29, 2016
Revised: August 19, 2016
Accepted: September 8, 2016
Article in press: September 8, 2016
Published online: November 28, 2016

Abstract

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

hepatitis B (CHB) patients were enrolled in the study. All of these patients received IFNα treatment for a course of 48 wk, and were followed up for 24 wk after the treatment was end. Clinical information about virological response, hepatitis B e antigen (HBeAg) seroconversion rate and combined response at the end of the treatment, as well as the sustained response by the time of following up 24 wk after the treatment, was collected. Four tag-single nucleotide polymorphisms (SNPs) of *IFIT1* were selected and assessed for their association with these clinical outcomes.

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

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.

Xie DY, Wang SM, Yang JM, Wang LH, Chen HY, Huai C, Shang J, Mao Q, Lei CL, Luo GH, Qian J, Lu DR. *IFIT1* polymorphisms predict interferon-α treatment efficiency for hepatitis B virus infection. *World J Gastroenterol* 2016; 22(44): 9813-9821 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i44/9813.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i44.9813

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 Ⅰ 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 resultes 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 of 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 posttranscriptional procedure[28]. All the evidences indicate that IFIT1 is an important effector in both virus infection and IFNα 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) HBsAg-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) coinfection 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 Haploview 4.1 (available at http://www.broadinstitute.org/haploview). 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

Table 1 Patient charateristics

Patient characteristic	Total patient (*n*)
Total patient	225
Gender	225
Male	163 (72.4)
Female	62 (27.6)
Age	225
Median age (range)	26 (18-56)
Baseline ALT	225
Median (range)	150 (70-359)
Baseline AST	225
Median (range)	83 (30-294)
Baseline HBV DNA copies (log_{10}IU/L)	225
Median (range)	7.36 (3.52-8.90)
HBV genotype	197
Type A	8 (4.1)
Type B	94 (47.7)
Type C	15 (7.6)
Type B + C	80 (40.6)
Virological response[1]	225
Response	83 (36.9)
Non-response	142 (63.1)
HBeAg seroconversion[2]	225
Response	61 (27.1)
Non-response	164 (72.9)
Combined response[3]	225
Response	35 (15.6)
Non-response	190 (84.4)
Sustained response[4]	225
Response	59 (26.2)
Non-response	166 (73.8)

[1]Virological response was defined as serum HBV DNA level < 2000 IU/L at the end of the treatment; [2]HBeAg seroconversion was defined as the loss of HBeAg and the presence of anti-HBe at the end of the treatment; [3]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; [4]Sustained response was defined as the combined response at week 72 after the first dose of the treatment. ALT: Alanine aminotransferase; AST: Aspartate transaminase; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

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 χ^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 IFNα 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 IFNα 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 IFNα 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 IFNα treatment's virological response

All the SNPs were evaluated for their association with IFNα 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

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

HBV genotype	Total	Virological response[1]		HBeAg seroconversion[2]		Combined response[3]		Sustained response[4]	
		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; [2]HBeAg seroconversion was defined as the loss of HBeAg and the presence of anti-HBe at the end of the treatment; [3]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; [4]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			0.113			0.081			0.027[2]			0.204
Male	55	108		39	163		20	163		39	163	
Female	28	34		22	62		15	62		20	63	
Age			0.151			0.723			0.924			0.116
Baseline ALT			0.070			0.020[2]			0.391			0.181
Baseline AST			0.205			0.113			0.443			0.279
Baseline HBV DNA level			0.121			0.554			0.617			0.217
HBV genotype			0.012[2]			0.001[2]			0.038[2]			2.37×10^{-4}[2]
Type A	3	5		1	7		1	7		1	7	
Type B	42	52		38	56		19	75		37	57	
Type C	10	5		5	10		5	10		6	9	
Type B + C	22	58		11	69		7	73		10	70	

[1]*P* value was calculated by χ^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	0.005[3]	1 (Reference)	
	G	87/198	0.44		0.57	0.39-0.85
rs303215	T	93/227	0.41	0.045[3]	1 (Reference)	
	C	69/217	0.32		1.49	1.01-2.20
rs11203109	T	109/341	0.32	0.020[3]	1 (Reference)	
	C	37/81	0.46		0.56	0.34-0.92
rs303212	C	93/284	0.33	0.022[3]	1 (Reference)	
	T	65/148	0.44		0.62	0.41-0.94

[1]Number indicated the patients who responsed in the same group; [2]*P* value was calculated by univariable logistic regression analysis; [3]$P < 0.05$. SNP: Single nucleotide polymorphism.

by genotype. χ^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, showed that rs303218 presented a protective role in IFNα virological response when assuming additive model (OR = 0.64; 95%CI: 0.42-0.96; $P = 0.032$) (Table 5). Then stratified analysis was performed to investigate the SNP rs303218's effect in different subgroups. Continuous variables such as age, baseline ALT, baseline AST and baseline HBV DNA level, were dichotomized by median. According to Table 6, the most significant association between rs303218 and virological response was observed among patients who had baseline AST ≤ 83 (OR = 0.31; 95%CI: 0.16-0.61; $P = 0.001$). And rs303218 could also be a better virological response predictor for male patients (OR = 0.53; 95%CI: 0.33-0.88; $P = 0.013$), patients who had baseline ALT ≤ 150 (OR = 0.38; 95%CI: 0.20-0.74; $P = 0.003$)

Table 5 The association between rs303218 and virological response

SNP ID	Genotype	Genetic model[1]	No./total[2]	%	χ^2 test	Logistic regression analysis		
					P value[3]	OR	95%CI	*P* value[3,4]
rs303218	A A		19/70	0.27	0.022[3]	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[3]
		Add				0.64	0.42-0.96	0.032[3]

[1]The best fitting model was shown; [2]Number indicated the patients who responsed in the same group; [3]$P < 0.05$; [4]*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	No./total[1]	rs303218		
		OR	95%CI	*P* value[2]
Age (yr)				
≤ 26	39/117	0.79	0.42-1.48	0.453
> 26	44/108	0.59	0.33-1.04	0.070
Gender				
Male	55/163	0.53	0.32-0.88	0.013[3]
Female	28/62	1.03	0.46-2.31	0.947
Baseline ALT				
≤ 150	38/113	0.38	0.20-0.74	0.003[3]
> 150	45/112	0.91	0.52-1.60	0.734
Baseline AST				
≤ 83	34/114	0.31	0.16-0.61	0.001[3]
> 83	49/111	1.10	0.62-1.96	0.752
Baseline HBV DNA copies (log_{10} IU/mL)				
≤ 7.36	47/113	0.86	0.49-1.52	0.611
> 7.36	36/112	0.47	0.25-0.88	0.018[3]
HBV genotype				
Type B	42/94	0.74	0.42-1.31	0.304
Type C	10/15	2.19	0.36-13.51	0.397
Type B + C	22/80	0.41	0.19-0.86	0.018[3]

[1]Number indicated the patients who responsed in the same group; [2]*P* value was calculated by logistic regression analysis with adjustment of patient characteristics with $P < 0.05$ in univariate analysis in additive model (the adjusting covariate for virological response was HBV genotype); [3]$P < 0.05$. 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 eIF3, 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* intronic 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.

ACKNOWLEDGMENTS

The authors thank Jie Peng, Boping Zhou, Zhen Zhen, Guozhen Liu, Qin Ning, Qing Xie, Mobin Wan, Jianhe Gan, Yueqi Li, Chengwei Chen, Minde Zeng and Yimin Mao for their contributions in collection of patients. We also thank Xiamen Amoytop Biotech Co., Ltd for the help in data acquisition. We are grateful to all the subjects who participated in this study.

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

important information for genetic, global association studies. Its impact is significant.

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P- Reviewer: Sghaier I, Venegas M **S- Editor**: Yu J **L- Editor**: A
E- Editor: Zhang FF

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ISSN 1007-9327