

# World Journal of *Gastroenterology*

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**MINIREVIEWS**

- 161 Drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma: Current state of the art  
*Facciorusso A*

**ORIGINAL ARTICLE****Basic Study**

- 170 Antifibrogenic effects of vitamin D derivatives on mouse pancreatic stellate cells  
*Wallbaum P, Rohde S, Ehlers L, Lange F, Hohn A, Bergner C, Schwarzenböck SM, Krause BJ, Jaster R*
- 179 Metabolic and hepatic effects of liraglutide, obeticholic acid and elafibranor in diet-induced obese mouse models of biopsy-confirmed nonalcoholic steatohepatitis  
*Tølbøl KS, Kristiansen MNB, Hansen HH, Veidal SS, Rigbolt KT, Gillum MP, Jelsing J, Vrang N, Feigh M*
- 195 INT-767 improves histopathological features in a diet-induced *ob/ob* mouse model of biopsy-confirmed non-alcoholic steatohepatitis  
*Roth JD, Feigh M, Veidal SS, Fensholdt LK, Rigbolt KT, Hansen HH, Chen LC, Petitjean M, Friley W, Vrang N, Jelsing J, Young M*
- 211 Novel concept of endoscopic device delivery station system for rapid and tight attachment of polyglycolic acid sheet  
*Mori H, Kobara H, Nishiyama N, Masaki T*
- 216  $\beta$ -arrestin 2 attenuates lipopolysaccharide-induced liver injury *via* inhibition of TLR4/NF- $\kappa$ B signaling pathway-mediated inflammation in mice  
*Jiang MP, Xu C, Guo YW, Luo QJ, Li L, Liu HL, Jiang J, Chen HX, Wei XQ*
- 226 Hepatitis C virus core protein-induced miR-93-5p up-regulation inhibits interferon signaling pathway by targeting IFNAR1  
*He CL, Liu M, Tan ZX, Hu YJ, Zhang QY, Kuang XM, Kong WL, Mao Q*
- 237 Transplantation of bone marrow-derived endothelial progenitor cells and hepatocyte stem cells from liver fibrosis rats ameliorates liver fibrosis  
*Lan L, Liu R, Qin LY, Cheng P, Liu BW, Zhang BY, Ding SZ, Li XL*
- Case Control Study**
- 248 Genetic variants of interferon regulatory factor 5 associated with chronic hepatitis B infection  
*Sy BT, Hoan NX, Tong HV, Meyer CG, Toan NL, Song LH, Bock CT, Velavan TP*

**Retrospective Study**

- 257 Timing of surgery after neoadjuvant chemotherapy for gastric cancer: Impact on outcomes  
*Liu Y, Zhang KC, Huang XH, Xi HQ, Gao YH, Liang WQ, Wang XX, Chen L*
- 266 Predictive and prognostic value of serum AFP level and its dynamic changes in advanced gastric cancer patients with elevated serum AFP  
*Wang YK, Zhang XT, Jiao X, Shen L*

**SYSTEMATIC REVIEWS**

- 274 Neoadjuvant chemotherapy for gastric cancer. Is it a must or a fake?  
*Reddavid R, Sofia S, Chiaro P, Colli F, Trapani R, Esposito L, Solej M, Degiuli M*

**CASE REPORT**

- 290 Clinically diagnosed late-onset fulminant Wilson's disease without cirrhosis: A case report  
*Amano T, Matsubara T, Nishida T, Shimakoshi H, Shimoda A, Sugimoto A, Takahashi K, Mukai K, Yamamoto M, Hayashi S, Nakajima S, Fukui K, Inada M*
- 297 Mass forming chronic pancreatitis mimicking pancreatic cystic neoplasm: A case report  
*Jee KN*
- 303 Successful treatment of a giant ossified benign mesenteric schwannoma  
*Wu YS, Xu SY, Jin J, Sun K, Hu ZH, Wang WL*

**LETTER TO THE EDITOR**

- 310 *Candida* accommodates non-culturable *Helicobacter pylori* in its vacuole - Koch's postulates aren't applicable  
*Siavoshi F, Saniee P*

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## Case Control Study

# Genetic variants of interferon regulatory factor 5 associated with chronic hepatitis B infection

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## Abstract

### AIM

To investigate possible effects of IRF5 polymorphisms in the 3' UTR region of the *IFR5* locus on susceptibility

to hepatitis B virus (HBV) infection and progression of liver diseases among clinically classified Vietnamese patients.

### METHODS

Four *IRF5* SNPs (rs13242262A/T, rs77416878C/T, rs10488630A/G, and rs2280714T/C) were genotyped in clinically classified HBV patients [chronic hepatitis B (CHB),  $n = 99$ ; liver cirrhosis (LC),  $n = 131$ ; hepatocellular carcinoma (HCC),  $n = 149$ ] and in 242 healthy controls by direct sequencing and TaqMan real-time PCR assays.

### RESULTS

Comparing patients and controls, no significant association was observed for the four *IRF5* variants. However, the alleles rs13242262T and rs10488630G contributed to an increased risk of liver cirrhosis (LC *vs* CHB: OR = 1.5, 95%CI: 1.1-2.3, adjusted  $P = 0.04$ ; LC *vs* CHB: OR = 1.7, 95%CI: 1.1-2.6, adjusted  $P = 0.019$ ). Haplotype *IRF5*\*TCGT constructed from 4 SNPs was observed frequently in LC compared to CHB patients (OR = 2.1, 95%CI: 1.2-3.3, adjusted  $P = 0.008$ ). Haplotype *IRF5*\*TCAT occurred rather among CHB patients than in the other HBV patient groups (LC *vs* CHB: OR = 0.4, 95%CI: 0.2-0.8, adjusted  $P = 0.03$ ; HCC *vs* CHB: OR = 0.3, 95%CI: 0.15-0.7, adjusted  $P = 0.003$ ). The *IRF5*\*TCAT haplotype was also associated with increased levels of ALT, AST and bilirubin.

### CONCLUSION

Our study shows that *IRF5* variants may contribute as a host factor in determining the pathogenesis in chronic HBV infections.

**Key words:** Hepatitis B virus infection; Liver diseases; IRF5; *IRF5* polymorphisms; *IRF5* haplotypes

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**Core tip:** *IRF5* is expressed in immune cells and mediates Toll-like receptor signal transduction, playing a vital role in the induction of antiviral and inflammatory response. So far, multiple *IRF5* single nucleotide polymorphisms have been shown to be associated with autoimmune diseases. This study investigated the effects of four *IRF5* variants on susceptibility to hepatitis B virus (HBV) infection and liver disease outcomes in HBV infected patients. Two *IRF5* variants (rs13242262, rs10488630) and constructed haplotypes (TCGT, TCAT) were associated with clinical outcomes suggesting that *IRF5* variants may contribute to determine the pathogenesis of HBV infection.

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## INTRODUCTION

Hepatitis B virus (HBV) infection is a major health concern affecting approximately two billion individuals worldwide. 350 million people are chronically infected, putting them at risk to develop liver cirrhosis (LC) and hepatocellular carcinoma (HCC)<sup>[1]</sup>. The clinical outcome of HBV infection is heterogeneous and a consequence of the complex interaction between viral and host factors. The host's genetic background is crucial for the outcome of the disease. Evidence for a host genetic effects are based on a twin study<sup>[2]</sup> and genome wide association studies (GWASs)<sup>[3-5]</sup>. GWASs examine possible associations of large number of genetic variants across the entire human genome, taking into account distinct disease phenotypes of HBV infection<sup>[6]</sup>. Many important candidate genes have been shown to be significantly associated with susceptibility to HBV infection and the progression of HBV-related liver diseases<sup>[6-8]</sup>.

HBV is a noncytopathic virus as observed in a number of asymptomatic HBV carriers who have minimal hepatocellular injury and liver necroinflammation despite high levels of HBV replication<sup>[9]</sup>. Thus, hepatocellular injury is strongly dependent on the host immune responses<sup>[10]</sup>. Induction of type I interferons (IFNs) by viruses is crucial for innate immunity, which is primarily controlled by several transcriptional factors, in particular by interferon regulatory factors (IRFs)<sup>[11]</sup>. The IRF family comprises of nine members (IRF1 to IRF9), which are characterized by two major domains, a highly conserved amino (N)-terminal DNA binding domain and a C-terminal IFR association domain (IAD)<sup>[12]</sup>. These regions are important in mediating the interaction with transcription co-activators<sup>[13]</sup>. IRF5, a member of the IRF family, is expressed in B cells and innate immune cells and mediates Toll-like receptor signal transduction, leading to production of several inflammatory cytokines such as interleukin 12 and IFN- $\alpha$ <sup>[14-16]</sup>. Therefore, IRF5 plays a vital role in the induction of antiviral and inflammatory response<sup>[17,18]</sup>.

So far, multiple *IRF5* single nucleotide polymorphisms (SNPs) have been shown to be associated with autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis<sup>[19,20]</sup>. However, there are so far no data available on associations of *IRF5* variants with susceptibility to HBV infection and the clinical course of HBV-related liver diseases. This study aims to investigate possible effects of *IRF5* polymorphisms on susceptibility to HBV infection and progression of liver diseases among HBV patients in a Vietnamese population.

## MATERIALS AND METHODS

### Study subjects

379 unrelated Vietnamese HBV-infected patients were randomly recruited in a case-control design at the 108 Military Central Hospital and the 103 Military Hospital of the Vietnam Military Medical University, Hanoi, Vietnam.

Patients were assigned to subgroups of disease based on clinical manifestations and liver function tests. Subgroups included chronic hepatitis (CHB,  $n = 99$ ), liver cirrhosis (LC,  $n = 131$ ) and hepatocellular carcinoma (HCC,  $n = 149$ ). The diagnostic criteria have previously been described<sup>[21]</sup>. Based on clinical manifestations and laboratory parameters, patients were assigned to the different clinical subgroups as previously described. Briefly, the CHB patients were characterized based upon clinical syndromes such as fatigue, anorexia, jaundice, hepatomegaly, hard density of the liver, splenomegaly, hyperbilirubinemia, elevated levels of AST and ALT, HBsAg positive for longer than 6 mo. The HBV-related LC patients were characterized as patients infected with HBV (HBsAg positive) showing the clinical manifestations such as anorexia, nausea, vomiting, malaise, weight loss, abdominal distress, jaundice, edema, cutaneous arterial "Spider" angiomas, palma erythema, ascites, shrunken liver, splenomegaly, hyperbilirubinemia, elevated levels of AST and ALT, prolonged serum prothrombin time, and decreased serum albumin. The HBV-related hepatocellular carcinoma patients were characterized as patients infected with chronically HBV (HBsAg positive), abdominal pain, an abdominal mass in the right upper quadrant, blood-tinged ascites, weight loss, anorexia, fatigue, jaundice, prolonged serum prothrombin time, hyperbilirubinemia, elevated levels of AST, ALT and serum  $\alpha$ -fetoprotein (AFP), ultrasound showed tumor, liver biopsy and histopathology showing tumor cells. None of the patients were under any antivirals during sampling. None of the patients had a history of alcohol or drug abuse. All participants were confirmed to be negative for anti-HCV and anti-HIV antibodies by ELISA assays. Liver function tests including the assessment of alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin and direct bilirubin, albumin and prothrombin levels were performed using an autoanalyser (AU640 Chemistry Analyzer, Beckman Coulter, CA, United States). 242 blood samples from healthy individuals (HC) were collected from blood banks as the control group. All 242 control individuals were negative for HBsAg, anti-HCV and anti-HIV antibodies. All specimens were frozen at  $-20^{\circ}\text{C}$  until use.

### IRF5 SNP selection

The four *IRF5* SNPs rs13242262A/T, rs77416878C/T, rs10488630A/G, and rs2280714G/A located closely at the 3' downstream regions of the *IRF5* locus were selected for this study. Two SNPs (rs13242262, and rs2280714) have been shown to be associated with *IRF5* mRNA expression and activation of the interferon  $\alpha$  pathway in different world populations<sup>[22]</sup>.

### IRF5 variant genotyping

Genomic DNA was isolated from 200  $\mu\text{L}$  of whole blood using a DNA purification kit (Qiagen, Hilden, Germany).

The fragments containing the SNPs rs13242262A/T and rs77416878C/T were amplified by PCR using the primer pairs IRF5-F1: 5'-AGG CCT GTG CAG TTC TAC TCC C-3' and IRF5-R1: 5'-CCT CAC ACT GGC CTG CCT TTA C-3'. PCR amplifications were carried out in 25  $\mu\text{L}$  reaction volumes containing: 1  $\times$  PCR buffer, 0.2 mmol/L dNTPs, 1 mmol/L  $\text{MgCl}_2$ , 0.15 mmol/L of each primer, 1 unit of Taq polymerase and 50 ng of genomic DNA. Cycling conditions: denaturation at  $95^{\circ}\text{C}$  for 5 min, followed by 35 cycles of three-step cycling with denaturation at  $94^{\circ}\text{C}$  for 40 s, annealing at  $61^{\circ}\text{C}$  for 40 s, and extension at  $72^{\circ}\text{C}$  for 45 s and a final extension at  $72^{\circ}\text{C}$  for 7 min.

PCR products were purified using the Exo-SAP-IT PCR Product Cleanup Reagent (Affymetrix Santa Clara, mmol/L) 5  $\mu\text{L}$  of purified PCR products were used as templates. Sequencing was performed using the BigDye terminator v.1.1 cycle sequencing kit (Applied Biosystems, Foster City, CA, United States) on an ABI 3130XL DNA sequencer according to the manufacturer's instructions. The polymorphisms were identified by assembling DNA sequences with the reference sequence of the *IRF5* gene obtained from the NCBI database (GenBank accession number: NC-00007). In addition, the two SNPs rs10488630A/G, and rs2280714G/A were genotyped using TaqMan<sup>®</sup> SNP genotyping assays according to the instruction of the manufacturer.

### Statistical analysis

The data were analyzed using R version 3.1.2 (<http://www.r-project.org>). Permutation tests were used to compare groups for quantitative variables permuted for 1000 iterations. Genotype and haplotype frequencies were analyzed by gene counting and expectation-maximum (EM) algorithms and the significance of deviation from Hardy-Weinberg equilibrium was tested using the random-permutation procedure as implemented in the Arlequin v. 3.5.1.2 software (<http://lgb.unige.ch/arlequin>). We used a binary logistic regression model adjusted for age and gender to analyze associations of *IRF5* variants and haplotypes with HBV-related liver diseases. The false discovery rate correction method was used for multiple comparisons<sup>[23]</sup> and adjusted  $P$  values are given. The level of significance was set at a value of  $P < 0.05$  and all reported  $P$  values are two-sided.

## RESULTS

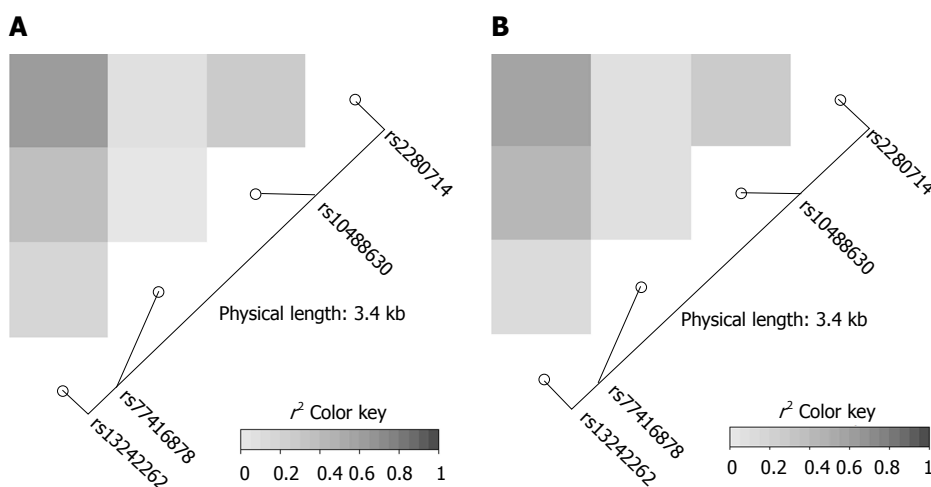
### Baseline characteristics of study participants

The baseline characteristics of the 379 HBV-infected patients from the different subgroups with well-characterized clinical profiles and from the 242 healthy controls are described in Table 1. Most patients and controls were male (81% and 64%). The median age of patients increased according to progression of liver disease; healthy controls were younger than the patients. The levels of ALT, AST and bilirubin were

**Table 1 Clinical profiles of 242 healthy individuals and 379 hepatitis B virus-infected patients**

Characteristics	HC (n = 242)	CHB (n = 99)	LC (n = 131)	HCC (n = 149)	P values
Age (yr)	39 (18-79)	41 (19-78)	52 (17-78)	53 (18-79)	< 0.0001
Gender (Male/Female)	156/86	82/17	105/26	119/30	< 0.0001
AST (IU/L)	NR	219 (17-3732)	74 (12-720)	59 (16-513)	< 0.0001
ALT (IU/L)	NR	158 (12-4593)	59 (9-1354)	47 (13-471)	< 0.0001
Total bilirubin (μmol/L)	NR	46.6 (1.8-795)	31 (1.2-722)	17 (2-290)	< 0.0001
Direct bilirubin (μmol/L)	NR	29.9 (1-512)	17 (1-450)	7.1 (1.2-189)	< 0.0001
Albumin (g/L)	NR	42 (23-48)	30 (20-47)	39 (27-49)	< 0.0001
Prothrombin (% of standard)	NR	85 (50-120)	47.5 (15-101)	80 (31-115)	< 0.0001
HBV-DNA (copies/mL)	NA	$1.8 \times 10^5$ ( $4 \times 10^2$ - $8.1 \times 10^6$ )	$8.3 \times 10^4$ ( $2 \times 10^2$ - $4.1 \times 10^6$ )	$9.4 \times 10^4$ ( $2.9 \times 10^2$ - $1.0 \times 10^5$ )	NS
Alfa Feto Protein (IU/L)	NR	4.3 (1.5-300)	8.6 (1.2-400)	196 (1.1- 438)	< 0.0001

CHB: Chronic hepatitis B; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma; PLT: Platelets; AST and ALT: Aspartate and alanine amino transferase; IU: International unit; NS: Not significant; NA: Not applicable; NR: Normal range.



**Figure 1** IRF5 linkage disequilibrium maps. Pairwise  $r^2$  between 4 polymorphisms in the IRF5 locus in the 3' UTR region in Vietnamese hepatitis B virus infected patients (A) and in healthy controls (B) are presented. The color scale from white to dark indicates  $r^2$  values from 0 to 1. The blocks of grey and dark grey represent SNPs that are all in high linkage disequilibrium with each other.

significantly higher in patients with CHB compared to the other subgroups ( $P < 0.0001$ ). As expected, the albumin and prothrombin levels as well as platelet counts were significantly lower in patients with LC compared to patients without LC ( $P < 0.001$ ). Alpha-fetoprotein (AFP) levels were higher in HCC patients with or without LC compared to CHB and LC groups ( $P < 0.0001$ ). Viral loads did not differ significantly between HBV virus subgroups ( $P > 0.05$ ).

#### Association IRF5 variants with HBV-related liver diseases

The genotype frequencies of the four IRF5 variants rs13242262A/T, rs10488630A/G, rs77416878C/T, rs2280714T/C in HBV patients and in HCs were in Hardy-Weinberg equilibrium ( $P > 0.05$ ). Linkage disequilibrium analysis revealed strong allelic combinations between rs13242262 and rs2280714; rs13242262 and rs10488630; rs10488630 and rs2280714 for both HBV infected patients and HCs (Figure 1). Genotype and allele frequencies of the IRF5 SNPs in patients and HCs as well as the comparisons between different subgroups are given in Tables 2 and 3.

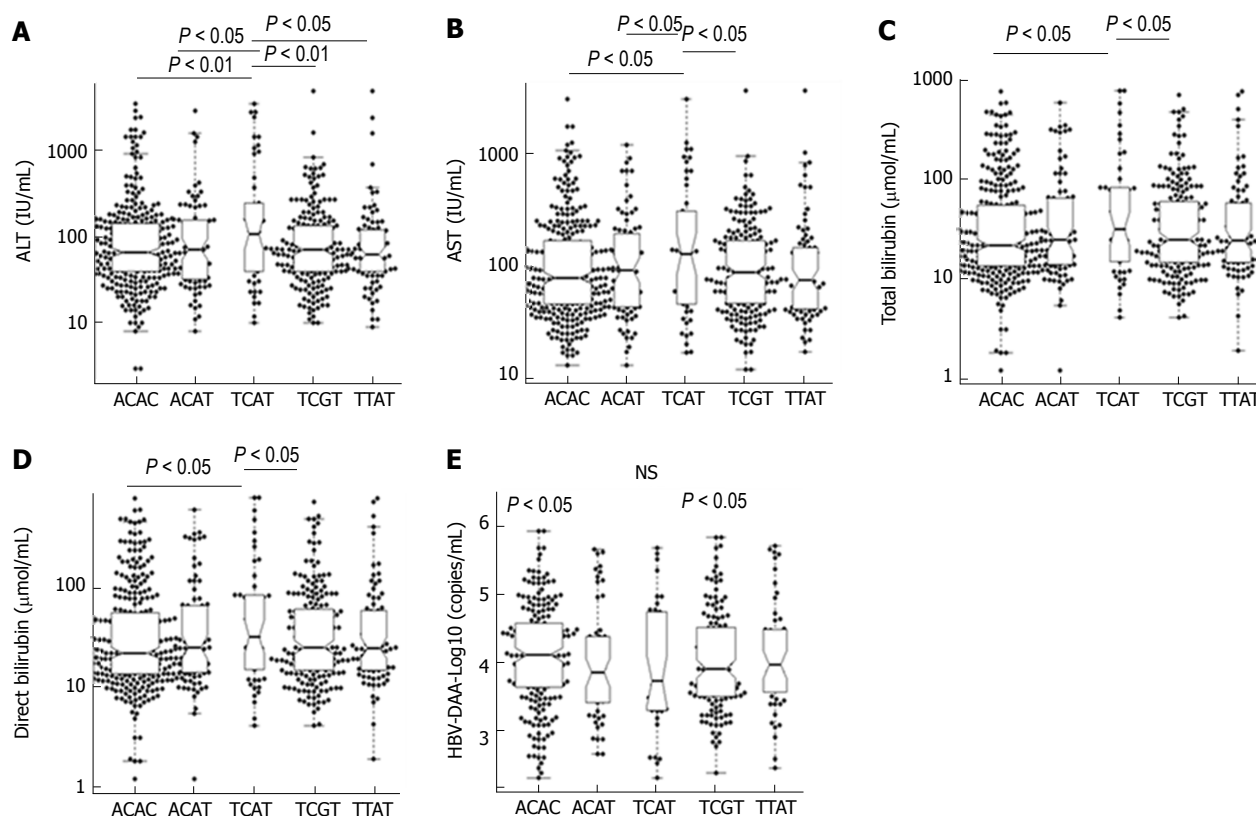
Genotype and allele frequencies of the four IRF5

SNPs did not differ between HBV patients or subgroups and controls, indicating that IRF5 SNPs are not associated with HBV infection *per se*. Among chronic HBV carriers, rs13242262TT and rs10488630GG genotype were significantly more frequent among LC patients compared to CHB patients (rs13242262TT: OR = 3.1, 95%CI: 1.2-7.8, adjusted  $P = 0.014$ ; rs10488630GG, OR = 3.0, 95%CI: 1.0-9.5, adjusted  $P = 0.045$ , Table 2). A similar trend was observed for rs13242262T (OR = 1.5, 95%CI: 1.1-2.3, adjusted  $P = 0.04$ ) and rs10488630G (OR = 1.7, 95%CI: 1.1-2.6, adjusted  $P = 0.019$ ; Table 2). For SNPs rs77416878C/T, and rs2280714T/C all comparisons between patient subgroups using binary logistic model adjusted for age and gender did not indicate any significant difference (Table 3). These results show that, of the four SNPs genotyped, the two variants rs13242262 and rs10488630 are associated with liver disease progression.

#### Association of IRF5 haplotypes with HBV-infected liver diseases

Haplotypes were constructed based on the four SNPs. Among nine IRF5 haplotypes detected, the five common





**Figure 2 Association of IRF5 haplotypes with clinical parameters in hepatitis B virus patients.** Box-plots illustrate median values with 25 and 75 percentiles with whiskers to 10 and 90 percentiles; the distribution of IRF5 haplotypes to liver enzymes, bilirubin and hepatitis B virus viral load was executed using pairwise permutation tests. Adjusted  $P$  values are presented under the false discovery rate correction method applied for multiple comparisons. NS: Not significant; AST and ALT: Aspartate and alanine amino transferase.

haplotypes rs13242262/rs77416878/rs10488630/rs2280714 ACAC, TCGT, TCAT, ACAT, and TTAT were observed in both HCs and HBV patients. Their frequencies are summarized in Table 4. We compared the haplotype frequencies between HCs and all HBV patients as well as the disease subgroups (HC vs all HBV; HC vs LC; HC vs CHB; HC vs HCC). The results did not indicate any significant difference (data not shown).

We further compared haplotype frequencies between the HBV subgroups. Haplotype TCGT was found more frequently among LC compared to CHB patients (LC vs CHB: OR = 2.1, 95%CI: 1.2-3.3, adjusted  $P = 0.008$ ), indicating that this haplotype may contribute significantly to an increased risk of LC in HBV carriers. However, a contradictory finding was observed for the haplotype TCAT, which was observed significantly more frequent in CHB compared to LC and HCC patients (LC vs CHB: OR = 0.4, 95%CI: 0.2-0.8, adjusted  $P = 0.037$  and HCC vs CHB: OR = 0.3, 95%CI: 0.15-0.7, adjusted  $P = 0.003$ ). This haplotype appears to partly protect from the risk of the advanced clinical manifestations LC and HCC in chronic HBV carriers. There were no differences in comparisons of the TCGT and TCAT haplotype frequencies between LC and HCC patients. Also, no significant difference was observed when frequencies of other haplotypes were compared (Table 4).

### Association of IRF5 polymorphisms and haplotypes with clinical parameters

To explore the possible impact of the four SNPs on disease outcomes, the SNP frequencies were correlated with several liver function tests, a cancer marker, and viral loads. No significant associations of IRF5 genotypes with the parameters ALT, AST, total and direct bilirubin, prothrombin, AFP and HBV-DNA loads were observed (adjusted  $P > 0.05$ ).

We further examined the association of five common IRF5 haplotypes with clinical outcomes of HBV infection. Patients with haplotype TCAT had higher levels of AST, ALT, total bilirubin and direct bilirubin compared to the other haplotypes (Figure 2). No significant differences of viral loads, prothrombin and AFP levels among five common haplotypes were observed.

## DISCUSSION

IRF5 is a particularly interesting member of the IRF family, which are crucial in the innate immune response with a variety of activities like activation of type I IFN genes, inflammatory cytokines and tumor suppressors<sup>[24,25]</sup>. Therefore, IRF5 is involved in many conditions, including autoimmune diseases, viral infections and cancers<sup>[11,19,20]</sup>. In this study, we studied the role of IRF5 polymorphisms in HBV

**Table 2 Association of IRF5 rs13242262A/T and rs10488630A/G with hepatitis B virus-related liver cirrhosis *n* (%)**

IRF5 variants	HC, <i>n</i> = 242	CHB, <i>n</i> = 99	LC, <i>n</i> = 131	HCC, <i>n</i> = 149	LC <i>vs</i> CHB	
					OR (95%CI)	<i>P</i> value
rs13242262 A/T						
AA	67 (27.7)	27 (27.3)	32 (24.4)	45 (30.2)	Reference	NS 0.014
AT	119 (49.2)	59 (59.6)	65 (49.6)	77 (51.7)	1.0 (0.5-2.0)	
TT	56 (23.1)	13 (13.1)	34 (26.0)	27 (18.1)	3.1 (1.2-7.8)	
Allele						
A	253 (52.3)	113 (57)	129 (49.2)	165 (55.3)	Reference	0.040
T	231 (47.7)	85 (43)	133 (50.8)	133 (44.7)	1.5 (1.1-2.3)	
Dominant						
AA	67 (27.7)	27 (27.3)	32(24.4)	45 (30.2)	Reference	NS
AT + TT	175 (72.3)	72 (72.7)	99 (75.6)	104 (69.8)	1.3 (0.7-2.6)	
Recessive						
AA + AT	186 (76.9)	86 (87)	97 (74.0)	122 (81.9)	Reference	0.0057
TT	56 (23.1)	13 (13)	34 (26.0)	27 (18.1)	2.8 (1.3-5.9)	
rs10488630 A/G						
AA	115 (47.5)	58 (58.6)	59 (45.1)	73 (49.0)	Reference	0.100 0.045
AG	104 (43.0)	36 (36.4)	56 (42.7)	63 (42.3)	1.6 (0.9-2.9)	
GG	23 (9.5)	5 (5.0)	16 (12.2)	13 (8.7)	3.0 (1.0-9.5)	
Allele						
A	334 (69)	152 (76.8)	174 (66.4)	209 (72.3)	Reference	0.019
G	150 (31)	46 (23.2)	88 (33.6)	89 (27.7)	1.7 (1.1-2.6)	
Dominant						
AA	115 (47.5)	58 (58.6)	59 (45.0)	73 (49)	Reference	0.035
AG + GG	127 (52.5)	41 (41.4)	72 (55.0)	76 (51)	1.8 (1.0-3.2)	
Recessive						
AA + AG	219 (90.5)	94 (94.9)	115 (87.8)	136 (91.3)	Reference	0.100
GG	23 (9.5)	5 (5.1)	16 (12.2)	13 (7.8)	2.4 (0.8-7.2)	

HC: Healthy controls; CHB: Chronic hepatitis B; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma.

**Table 3 Allele and genotype frequencies of IRF5 rs77416878C/T and rs2280714T/C in Vietnamese patients with hepatitis B virus-related liver diseases *n* (%)**

IRF5 variants	HC, <i>n</i> = 242	CHB, <i>n</i> = 99	LC, <i>n</i> = 131	HCC, <i>n</i> = 149
rs77416878				
CC	192 (79.4)	79 (79.8)	98 (74.8)	115 (77.2)
CT	48 (19.8)	19 (19.2)	32 (24.4)	31 (20.8)
TT	2 (0.8)	1 (1)	1 (0.8)	3 (2)
Allele				
C	432 (89.3)	177 (89.4)	228 (87)	261 (87.6)
T	52 (10.7)	21 (10.6)	34 (13)	37 (12.4)
Dominant				
CC	192 (79.4)	79 (79.8)	98 (74.8)	115 (77.2)
CT + TT	50 (20.6)	20 (20.2)	33 (24.4)	34 (22.8)
Recessive				
CC + CT	240 (99.2)	98 (99)	130 (99.2)	146 (98)
TT	2 (0.8)	1 (1)	1 (0.8)	3 (2)
rs2280714				
TT	84 (34.7)	31 (31.3)	47 (35.9)	39 (26.2)
TC	114 (47.1)	52 (52.5)	69 (52.7)	87 (58.4)
CC	44 (18.2)	16 (16.2)	15 (11.4)	23 (15.4)
Allele				
T	282 (58.3)	114 (57.6)	163 (62.2)	165 (55.4)
C	202 (41.7)	84 (42.4)	99 (37.8)	133 (44.6)
Dominant				
TT	84 (34.7)	31 (31.3)	47 (35.9)	39 (26.2)
TC + TT	158 (65.3)	78 (68.7)	84 (64.1)	110 (73.8)
Recessive				
TT + TC	198 (81.8)	83 (83.8)	116 (88.6)	126 (84.6)
CC	44 (18.2)	16 (16.2)	15 (11.4)	23 (15.4)

HC: Healthy controls; CHB: Chronic hepatitis B; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma. All comparisons between groups using binary logistic model adjusted for age and gen did not indicate a significant difference (adjusted *P* > 0.05, data not shown in this table).

infected patients. *IRF5* variants are associated with LC progression in patients with CHB while the constructed haplotypes are associated with LC and HCC progression in CHB patients. In addition, *IRF5* variants and their constructed haplotypes are associated with clinical outcomes of HBV infection. For the first time we provide evidence of the functional role of *IRF5* in immune response to the clinical outcome of HBV infection.

Host immune factors are crucial to the pathogenesis of HBV infection through genetic and epigenetic modifications and *via* the effects of cytokines<sup>[26]</sup>. Interferons are produced by the host in response to certain viral infections in order to inhibit viral replication. Induction of *IFN* is required for the defense against hepatitis viruses and further progression of related liver disease<sup>[27]</sup>. *IRF5* is a transcriptional factor that can induce type I interferons and, therefore, appears to play an important role in the clinical course of HBV infection. To the best of our knowledge, this study is the first exploratory investigation of *IRF5* polymorphisms addressing the clinical outcome of HBV-related liver diseases. Among four SNPs studied here, rs13242262A/T and rs10488630A/G appeared were with liver cirrhosis. In addition, the *IRF5* haplotypes *TCGT* and *TCAT* are associated with liver cirrhosis in patients with chronic hepatitis B. SNP rs10488631 located in the same region was identified to be associated with primary biliary cirrhosis in populations of European descent<sup>[28]</sup>. However, this SNP was homogeneous in Asian populations and therefore excluded from analyses in this study. In addition, SNPs rs3807306

**Table 4** Haplotype distribution among chronic hepatitis B virus carriers and the association of IRF5 haplotypes with hepatitis B virus-infected liver diseases *n* (%)

Haplotypes	HC, <i>n</i> = 484	CHB, <i>n</i> = 198	LC, <i>n</i> = 298	HCC, <i>n</i> = 262	LC <i>vs</i> CHB		HCC <i>vs</i> CHB		HCC <i>vs</i> LC	
					OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
ACAC	196 (40.6)	83 (41.9)	98 (37.4)	132 (44.3)	Reference		Reference		Reference	
TCGT	141 (29.0)	37 (18.7)	86 (32.7)	81 (27.2)	2.1 (1.2-3.3)	0.008		NS	0.7 (0.4-1.1)	0.08
TCAT	33 (6.8)	27 (13.6)	12 (4.6)	13 (4.4)	0.4 (0.2-0.8)	0.037	0.3 (0.15-0.7)	0.003		NS
ACAT	54 (11.2)	24 (12)	30 (11.5)	31 (10.4)		NS		NS		NS
TTAT	49 (10.2)	18 (9.1)	34 (13)	33 (11.1)		NS		NS		NS
ACGC	2 (0.4)	1 (0.5)	0 (0)	1 (0.3)		NS		NS		NS
ACGT	5 (1)	5 (2.5)	1 (0.4)	3 (1)		NS		NS		NS
TTCG	2 (0.4)	0 (0)	1 (0.4)	0 (0)		NS		NS		NS
TTGT	2 (0.4)	3 (1.5)	0 (0)	4 (1.3)		NS		NS		NS

HCC: Hepatocellular carcinoma. Comparison between HC *vs* HBV patient group did not indicate any significant difference (data not shown in this table). OR and *P* values were calculated by using binary logistic model adjusted for age and gender, CHB: Chronic hepatitis B; LC: Liver cirrhosis.

and rs4728142 in the *IRF5* gene have been implicated as susceptibility loci for primary biliary cirrhosis<sup>[29]</sup>.

The process of liver cirrhosis in HBV infection is a results of the interplay between viral factors and host immune responses through activation of inflammatory cytokines<sup>[30]</sup>. A recent study has shown that among several *IRF5* SNPs, the variants rs13242262, rs2280714 and rs10488630 in the 3'UTR region are associated with increased *IRF5* mRNA expression<sup>[22]</sup>. Studies have indicated that a variety of cytokines are dependent on *IRF5*<sup>[24,31]</sup>. Several *IRF5*-modulated genes (*e.g.*, *ISGs* and *STATs*) involved in the type I IFN signaling pathway are significantly over-expressed in response to viral infection<sup>[18]</sup>. This supports the findings of our study, namely that these SNPs may contribute to progression of HBV-related liver diseases through regulating *IRF5* expression and subsequent activation of genes in the type I IFN signaling pathway like *ISG15* as seen in our study<sup>[7]</sup>. Furthermore, although all four studied SNPs were not associated with HCC, the haplotype *TCAT* contributes to a decreased risk of HCC development in patients with chronic hepatitis B. Data concerning the association between *IRF5* and HCC are scarce. Nevertheless, methylation of *IRF5* has been suggested to be associated with HCC in a Korean study<sup>[32]</sup>. The role of *IRF5* in the development of HBV-related HCC needs to be explored further.

Although SNPs rs77416878C/T and rs2280714T/C are not associated with HBV-related liver disease and no significant association of all four SNPs studied with clinical parameters, constructed haplotypes are associated with clinical outcomes. Notably, the haplotype *TCAT* was observed significantly more frequent in CHB compared to LC and HCC patients, suggesting that this haplotype appears to partly protect from the risk of the advanced clinical manifestations LC and HCC in chronic HBV carriers. However, patients with the haplotype *TCAT* had higher levels of AST, ALT, total bilirubin and direct bilirubin compared to the other haplotypes. In fact, the clinical outcome or clinical progression of liver diseases in HBV infected patients are affected by several factors and are considered as

a result of viral-host interaction. Therefore, we believe that haplotype *TCAT* is an important host factor in HBV infection but this haplotype only may not be a host factor in determining the overall clinical outcome of disease.

Until now, most studies have identified distinct *IRF5* haplotypes to be associated with high serum IFN- $\alpha$  activity and with systemic lupus erythematosus<sup>[33-36]</sup>. In addition, the *IRF5* risk haplotype *TCC*, which contains the risk alleles rs13242262, rs10488631 and rs2280714 are associated with increased *IRF5*, IFN- $\alpha$ , and IFN-inducible chemokine expression in healthy individuals<sup>[22]</sup>. However, our study did not assess the relationship of the *IRF5* risk haplotypes *ACAC*, *TCAT*, *TCGT* with *IRF5* expression, IFN- $\alpha$  activity and other related *IFN- $\alpha$*  gene. This is one of the study's limitations; in fact the function of *IRF5* in HBV infection needs further investigations. Nevertheless, we assume that the *IRF5* risk haplotypes may affect the expression of multiple downstream genes in the IFN- $\alpha$  signaling pathway and certain inflammatory cytokines in HBV infection.

In conclusion, *IRF5* variants rs13242262A/T and rs10488630A/G are associated with LC progression in patients with CHB. *IRF5* haplotypes appear to influence the outcome of HBV infection. Further studies in this direction will provide insights into a role of *IRF5* variants as prognostic markers of HBV-related liver diseases.

## ARTICLE HIGHLIGHTS

### Research background

Hepatitis B virus (HBV) infection is a major health concern in Vietnam. Investigations were carried out to determine *IRF5* polymorphisms in the 3' UTR region of the *IRF5* locus on susceptibility to HBV infection and progression of liver diseases among clinically classified Vietnamese patients.

### Research motivation

*IRF5* is a particularly interesting member of the *IRF* family, which are crucial in the innate immune response with a variety of activities like activation of type I *IFN* genes, inflammatory cytokines and tumor suppressors. There are so far no data available on associations of *IRF5* variants with susceptibility to HBV

infection and the clinical course of HBV-related liver diseases.

## Research objectives

This study aims to investigate possible effects of IRF5 polymorphisms on susceptibility to HBV infection and progression of liver diseases among clinically classified Vietnamese patients.

## Research methods

The four *IRF5* SNPs rs13242262A/T, rs77416878C/T, rs10488630A/G, and rs2280714G/A located closely at the 3' downstream regions of the *IRF5* locus were selected for this study. *IRF5* variant genotyping was performed by direct sanger sequencing and by application of TaqMan® SNP genotyping assays.

## Research results

Three hundred seventy-nine unrelated Vietnamese HBV-infected patients were randomly recruited in a case-control design. *IRF5* variants are associated with LC progression in patients with CHB while the constructed haplotypes are associated with LC and HCC progression in CHB patients. In addition, *IRF5* variants and their constructed haplotypes are associated with clinical outcomes of HBV infection.

## Research conclusions

Host immune factors are crucial to the pathogenesis of HBV infection. For the first time the authors provide evidence of the functional role of human *IRF5* in immune response to the clinical outcome of HBV infection. *IRF5* variants rs13242262A/T and rs10488630A/G are associated with LC progression in patients with CHB. *IRF5* haplotypes appear to influence the outcome of HBV infection.

## Research perspectives

Further studies in this direction will provide insights into a role of *IRF5* variants as prognostic markers of HBV-related liver diseases.

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