

## HMGB1 gene polymorphisms in patients with chronic hepatitis B virus infection

Chun-Qing Deng, Guo-Hong Deng, Yu-Ming Wang

Chun-Qing Deng, Guo-Hong Deng, Yu-Ming Wang, Institute of Infectious Diseases, Southwest Hospital, Third Military Medical University, Chongqing 400038, China

Chun-Qing Deng, Department of Infectious Diseases, the First Affiliated Hospital of Shanxi Medical University, Taiyuan 030001, Shanxi Province, China

**Author contributions:** Deng CQ and Wang YM designed the research; Deng CQ and Deng GH performed the research and analyzed the data; Deng CQ wrote the paper; Deng GH and Wang YM reviewed and revised the paper; all authors contributed to the study design and interpretation of the data.

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**Correspondence to:** Yu-Ming Wang, Professor, Institute of Infectious Diseases, Southwest Hospital, Third Military Medical University, No. 35 Gaotanyanzheng Street, Shapingba District, Chongqing 400038, China. [wym417@163.com](mailto:wym417@163.com)

Telephone: +86-23-68754858 Fax: +86-23-65334998

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### Abstract

**AIM:** To characterize high mobility group box chromosomal protein 1 (*HMGB1*) polymorphisms in patients infected with hepatitis B virus (HBV) and determine the different patterns in patient subgroups.

**METHODS:** A total of 1495 unrelated Han Chinese HBV carriers were recruited in this hospital-based case-control study. The *HMGB1* 1176 G/C polymorphism was genotyped by polymerase chain reaction-restriction fragment length polymorphism assay.

**RESULTS:** A significant association was observed between *HMGB1* 1176 G/C polymorphism and outcome of HBV infection. The subjects bearing 1176G/G genotype had an increased risk of susceptibility to

chronic hepatitis B, liver cirrhosis and severe hepatitis B when compared with those bearing at least one 1176C allele.

**CONCLUSION:** Patients with 1176G/G genotype of *HMGB1* gene are more likely to have a progressive status in HBV infection.

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**Key words:** High mobility group box chromosomal protein 1; Hepatitis B virus; Polymorphism; Intron

**Core tip:** We analyzed the relationship between the high mobility group box chromosomal protein 1 (*HMGB1*) 1176 G/C polymorphism and the susceptibility and outcome to hepatitis B virus (HBV) infection in a large hospital-based case-control study. Our results indicated that patients with 1176G/G genotype of *HMGB1* gene are more likely to have a progressive status in HBV infection. Our study emphasizes the importance of *HMGB1* in the pathophysiology of HBV-related diseases on the population level and will provide researchers new clue for the further basic research in pathogenesis of chronic HBV infection.

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### INTRODUCTION

Hepatitis B virus (HBV) infection is associated with a variety of diseases, including asymptomatic carrier (AsC), fulminant hepatitis, chronic hepatitis (CHB), liver cirrhosis (LC), and hepatocellular carcinoma (HCC). Persistent

HBV infection has been considered as a multifactorial and polygenic disorder with viral, environmental and genetic components. HBV genomic variability and a number of conventional risk factors, including age, gender, concurrent infection with hepatitis C virus, hepatitis D virus and human immune deficiency virus, are clearly the important factors contributing to the incidence of persistent HBV infection<sup>[1-4]</sup>. However, segregation analysis and twin studies strongly support the role of host genetic components in determining the chronicity of HBV infection<sup>[5,6]</sup>. A known and unknown number of identified or unidentified genes are likely to modify the susceptibility to persistent HBV infection<sup>[7-10]</sup>. Single nucleotide polymorphism (SNP) is currently believed to be a powerful tool for identifying genetic susceptibilities to common complex diseases<sup>[11,12]</sup>.

The intranuclear architectural protein termed high mobility group box chromosomal protein 1 (HMGB1) has recently been identified as a potent proinflammatory mediator when passively released to extracellular by necrotic cells, as opposed to apoptotic cells that will induce inflammation<sup>[13,14]</sup>. Furthermore, HMGB1 can also be actively secreted by stimulated macrophages or monocytes<sup>[15-17]</sup>. Active secretion from living inflammatory cells and passive release from necrotic cells implicate that HMGB1 may play a central role in proinflammatory reactions. It is well known that HBV infection is closely related with cytokines. Polymorphisms of cytokine gene, such as human leukocyte antigen, estrogen receptor alpha (*ESR1*), have been reported to be associated with HBV infection<sup>[18-21]</sup>. However, so far there has been no report on the association between *HMGB1* gene and HBV infection. We conducted a hospital-based case-control study including more than one thousand subjects with HBV infection to characterize the relationship between *HMGB1* gene polymorphism and HBV infection.

## MATERIALS AND METHODS

### Patients

Patients with HBV infection were randomly selected from the outpatient and inpatient referral center affiliated to the Institute for Infectious Diseases of Southwest Hospital treated between February 2002 and February 2012. Informed consent was obtained from all the patients to participate in the study. Participants finally included in the current study were from a subset of unrelated individuals from the referral center. The diagnostic criteria for chronic HBV infection were as follows: persistent presence of hepatitis B surface antigen (HBsAg), absence of anti-hepatitis B surface antibodies (anti-HBs), presence of anti-core IgG antibodies (anti-HBc), and presence of hepatitis B early antigen (HBeAg) or anti-hepatitis B e antibodies (anti-HBe) for 6 mo or longer despite of virus replication. Asymptomatic carriers had no fluctuation of serum alanine aminotransferase (ALT) levels and no obvious clinical symptoms. Chronic hepatitis B had a serum ALT fluctuation,  $1 \times$  the upper limit of normal (ULN)

$< \text{ALT} < 5 \times \text{ULN}$ , with or without other abnormal hepatic functions. Severe hepatitis B (SHB), which is currently equal to acute-on-chronic liver failure, presents the following symptoms: (1) fatigue with striking gastrointestinal tract symptoms; (2) rapidly worsening jaundice, with serum total bilirubin (TBIL) 10 times higher than ULN, or with a daily increase  $\geq 17.1 \mu\text{mol/L}$ ; (3) hemorrhagic tendency with international normalised ratio  $\geq 1.5$  or prothrombin activity  $\leq 40\%$  where other causes have been excluded; (4) progressive reduction in liver size; and (5) occurrence of hepatic encephalopathy. Liver cirrhosis and HCC were confirmed by liver biopsy, ultrasound, and/or computerized tomography scan. Healthy control individuals were recruited from Red Cross blood donor centers with or without anti-HBs, but HBsAg, anti-HBc, HBeAg, and anti-HBe were negative.

### DNA extraction

The leukocytes genomic DNA from 5 mL whole blood was isolated using Miller's method<sup>[22]</sup>. DNA samples were diluted to  $8 \text{ ng}/\mu\text{L}$  and distributed into 96-well plates (DNA panels), with 94 samples and 2 controls (DNA-free water) in each plate.

### Gene polymorphism

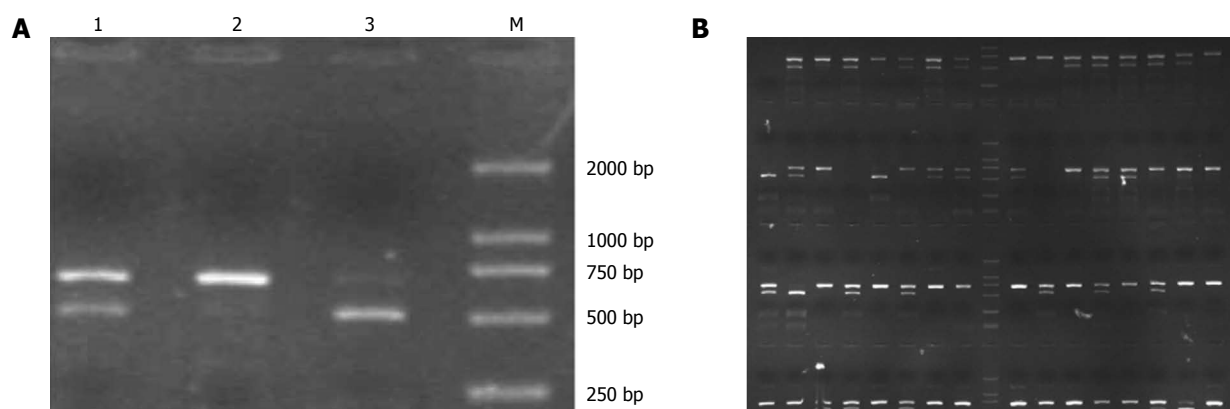
We used the current recommendations of human genome SNP described at <http://www.ncbi.nlm.gov/SNP> under accession number NT024524. The higher allele variation frequency selected in position 1176 G/C, the intron 4 of *HMGB1* gene, was studied to determine whether any association identified was specific to HBV infection. The SNP was named in a same way to *HMGB1* (1176G/C).

### Genotype

The genotyping was analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. Appropriate primer pairs (sense 5'-3' GTCTCCTTTGCCAGTGTATCTC and anti-sense 5'-3'GTACACAGCCTTTGTCTGAGTCTG) were designed by Primer Premier 5.0 software (Premier Biosoft International, Palo Alto, CA, United States). PCR condition was as follows: one cycle of predenature 3 min at  $95^\circ\text{C}$ , 30 cycles of denature 30 s at  $94^\circ\text{C}$ , hybridization for 30 s at  $54^\circ\text{C}$ , an extension cycle of 50 s at  $72^\circ\text{C}$ , and a last cycle of delay 5 min at  $72^\circ\text{C}$ . Restriction enzyme BclI (recognition site T/GATCA) was obtained from NEB; the fragments were separated by electrophoresis on 3% agarose gel and stained with ethidium bromide for visualization under ultraviolet light. The observed genotypes were also identified by direct sequencing before large-scale test was started.

### Statistical analysis

An allele frequency was directly calculated by its genotype. The observed genotype frequencies and allele frequency were compared using  $\chi^2$  test between the variables to determine if they were in Hardy-Weinberg equilibrium.



**Figure 1** High mobility group box chromosomal protein 1 (1176G/C) restriction fragment length polymorphism genotyping. A: The typical pattern of three genotypes; B: Panel genotyping. 1: GC genotype; 2: GG genotype; 3: CC genotype; M: Marker DL2000.

**Table 1** High mobility group box chromosomal protein 1 polymorphism (1176G/C) between various clinical subgroups infected with hepatitis B virus

	Sex	Age (yr)	Genotype			Allele frequency	
	(M/F)	(mean $\pm$ SD)	GG	CC	GC	G	C
AsC ( <i>n</i> = 199)	116/83	34.762 $\pm$ 11.282	107	9	83	0.7462	0.2538
AHB ( <i>n</i> = 15)	11/4	30.201 $\pm$ 10.221	9	1	5		
CHB ( <i>n</i> = 929)	730/199	34.312 $\pm$ 11.549	572	33	324	0.6530	0.3470
SHB ( <i>n</i> = 157)	129/28	39.989 $\pm$ 11.792	91	6	60	0.7707	0.2293
LC ( <i>n</i> = 175)	142/33	41.950 $\pm$ 11.437	104	13	58	0.7600	0.2300
HCC ( <i>n</i> = 20)	14/6	49.256 $\pm$ 12.232	10	1	9		
LC + CHB ( <i>n</i> = 1104)	872/232	35.461 $\pm$ 11.642	676	46	382	0.7853	0.2147
LC + CHB + SHB ( <i>n</i> = 1261)	1001/260	36.001 $\pm$ 11.852	767	52	442	0.7835	0.2165

There was age difference in any two subgroups except between AsC and CHB,  $P < 0.05$ ; There was sex difference between AsC and any other subgroups,  $P < 0.05$ ; AsC: Asymptomatic carrier; AHB: Acute hepatitis B; CHB: Chronic hepatitis B; SHB: Severe hepatitis B; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma.

An observed  $P > 0.01$  was considered in Hardy-Weinberg equilibrium, and  $P < 0.05$  was considered significantly different between the variables. All the analyses were performed with SPSS11.0 statistical software (SPSS Inc., Chicago, IL, United States).

## RESULTS

### *HMGB1* 1176G/C polymorphism genotyping

*HMGB1* 1176G/C polymorphism was genotyped by PCR-RFLP assay (Figure 1). A total of 1495 clearly diagnosed and genotyped patients were enrolled. The clinical characteristics, such as age and sex, are listed in Table 1. Apparently, age or sex difference existed in the studied subgroups. Hardy-Weinberg equilibrium by  $\chi^2$  test showed  $P = 0.494 > 0.01$  (Table 1), which confirmed that the studied group was in Hardy-Weinberg equilibrium.

### Case-control association study

Because age or sex difference existed in the studied subgroups, it is essential to detect the association between observed SNP and HBV infected subgroups, and age and sex factors were considered by logistic regression (Table 2). A statistically significant difference in the dis-

tribution of *HMGB1* polymorphism (1176G/C) was observed between subgroups of AsC and LC (OR = 1.571, 95%CI: 1.108-2.227,  $P = 0.011$ , codominant model); AsC and CHB (OR = 1.354, 95%CI: 1.085-1.689,  $P = 0.007$ , codominant model); AsC and CHB + SHB + LC (OR = 1.401, 95%CI: 1.010-1.944,  $P = 0.044$ , recessive model); OR = 1.329, 95%CI: 1.070-1.651,  $P = 0.010$ , codominant model, AsC and CHB + LC (OR = 1.406, 95%CI: 1.011-1.956,  $P = 0.043$ , recessive model; OR = 1.355, 95%CI: 1.088-1.687,  $P = 0.007$ , codominant model).

## DISCUSSION

*HMGB1* is a nuclear DNA-binding protein, which also functions as a pleiotropic cytokine, implicated in the pathology of several different immune-mediated diseases. The human *HMGB1* gene is located on chromosome 13. Kornblit *et al.*<sup>[23]</sup> firstly elaborated six polymorphisms and four mutations identified in the *HMGB1* gene, located in -1615A/G, 982C/T, 3814C/G, 1779T/G, -196C/A, 1808C/G, 4519\_4521delGAT, -1377delA, 1747delT, 1888insT, respectively. In other studies, several associations have been observed, revealing the importance of the genetic variation in the *HMGB1* gene. In their report, the -1377delA<sup>A/-</sup> genotype or the -1377delA<sup>-/-</sup> genotype

**Table 2** Association between high mobility group box chromosomal protein 1 (1176G/C) single nucleotide polymorphism and hepatitis B virus infected subgroups

Subgroup	Dominant model		Recessive model		Codominant model	
	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)
LC/CHB	0.075	0.533 (0.267-1.065)	0.945	0.988 (0.701-1.392)	0.120	0.844 (0.682-1.045)
LC/SHB	0.183	0.508 (0.188-1.376)	0.747	1.075 (0.693-1.669)	0.326	0.872 (0.664-1.146)
LC/AsC	0.168	2.320 (0.702-7.672)	0.108	1.572 (0.906-2.728)	0.011	1.571 (1.108-2.227)
AsC/SHB	0.473	1.616 (0.436-5.999)	0.489	1.204 (0.711-2.040)	0.206	1.254 (0.883-1.782)
AsC/CHB	0.238	1.660 (0.716-3.851)	0.052	1.389 (0.997-1.935)	0.007	1.354 (1.085-1.689)
SHB/CHB	0.916	1.050 (0.425-2.592)	0.474	1.137 (0.800-1.614)	0.462	1.090 (0.866-1.371)
SHB + LC/CHB + AsC	0.362	0.760 (0.421-1.371)	0.824	0.971 (0.747-1.262)	0.316	0.918 (0.777-1.085)
AsC/CHB + SHB + LC	0.330	1.505 (0.662-3.421)	0.044	1.401 (1.010-1.944)	0.010	1.329 (1.070-1.651)
AsC/CHB + LC	0.256	1.619 (0.704-3.721)	0.043	1.406 (1.011-1.956)	0.007	1.355 (1.088-1.687)

The association was analyzed by logistic regression analysis with adjustment for covariates, including age, sex, and alcohol consumption. Dominant model: GG + GC/CC, recessive model: GG/GC + CC, codominant model: GG/GC/CC; *P* and OR values were calculated by logistic regression. AsC: Asymptomatic carrier; AHB: Acute hepatitis B; CHB: Chronic hepatitis B; SHB: Severe hepatitis B; LC: Liver cirrhosis; OR: Odds ratio.

showed a significant association with delayed mortality, independent of age and number of the systemic inflammatory response syndrome (SIRS) criteria<sup>[24]</sup>. Subsequent estimation revealed that several polymorphisms have a potential regulatory impact on HMGB1 transcription. Genetically determined risk factors associated with early and late mortality and death due to infection have been identified, explaining some of the inherited risks in this heterogeneous patient population. Associations between genetic variation and disease severity parameters are also established. Studies of association between HMGB1 polymorphisms and disease have been also reported with allogeneic hematopoietic cell transplantation (HCT)<sup>[25]</sup>. Patient homozygosity or heterozygosity for the-1377delA minor allele is associated with increased risk of relapse and increased relapse-related mortality. Furthermore, patient homozygosity for the 3814C/G minor allele is associated with increased overall survival and progression-free survival. Patient carriage of the 2351insT minor allele can reduce the risk from grade II to IV acute graft-versus-host disease whereas donor homozygosity is associated with chronic acute graft-versus-host disease. These findings suggest that the inherited variation in HMGB1 is associated with outcome after allogeneic HCT following myeloablative conditioning regimens. Zeng *et al*<sup>[26]</sup> found that three SNPs act as tag SNPs for the entire HMGB1 gene in multiple organ dysfunction syndromes. The rs2249825 and the haplotype TCG can be used as relevant risk estimate for the development of sepsis in patients with major trauma.

As is well known, the susceptibility of HBV infection is closely related to the variation of some important genes. Deng *et al*<sup>[27]</sup> have demonstrated that polymorphisms at the *ESR1* gene locus are associated with persistent HBV infection. Subsequently, Yan *et al*<sup>[18]</sup> have also demonstrated an association between cis-acting regulatory variation of the *ESR1* gene and hepatitis B virus-related liver cirrhosis. Some important variations of cytokine gene also influenced the susceptibility to HBV infection. Deng *et al*<sup>[28]</sup> have found that the novel regulatory polymorphism G-201A in the promoter of inter-

feron gamma-inducible protein of 10 kilodaltons (*IP-10*, *CXCL10*) gene might be a part of the genetic variation underlying the susceptibility of individuals to disease progression of chronic HBV infection. In another study, Yan *et al*<sup>[29]</sup> demonstrated that the -592C allele and the -1082A-819C-592C haplotype in the *IL-10* gene promoter were associated with an increased susceptibility to acute liver failure in HBV carriers.

Nevertheless, there are few reports about the association between HMGB1 gene and HBV infection, especially reports about the association between HMGB1 polymorphisms and HBV infection. In this study, we used the current recommendations of human genome SNPs described at <http://www.ncbi.nlm.gov/SNP> under accession number NT024524. The higher allele variation frequency was selected in position 1176 G/C, the intron 4 of HMGB1 gene. There has been no report about this SNP up to date. We genotyped the polymorphisms of 1495 cases, including AsC, CHB, SHB, LC and HCC. The distribution of HMGB1 1176G/C genotypes in studied sample of unrelated men and women from the referral center were in Hardy-Weinberg equilibrium ( $P > 0.01$ ), so it is important to consider whether our studied sample could be representative. Yan *et al*<sup>[18]</sup> and Deng *et al*<sup>[28]</sup> had scanned the polymorphisms on the same cohort. Because differences in age or sex existed in the studied subgroups, we detected the association by logistic regression between observed SNP and HBV infected subgroups, and the age and sex factors were considered. As a result, there was statistically significant evidence of association. The fraction calculated by relative risk indicated that HMGB1 1176G/G genotype was more susceptible to CHB, LC and SHB than 1176C/C and 1176G/C genotype. In other words, the patients with 1176G/G genotype of HMGB1 gene are more likely to have a progressive status in HBV infection. The results suggest that allele 1176G is closely related to the ponderance of disease. These findings underscore a potentially important role of HMGB1 in influencing the development of HBV infection.

In another study, we had successfully cloned and analyzed 154 bp nucleotides in intron 4 near the fourth

exon-intron boundary, and found that the region contained sequences 1176 G/C polymorphism characteristic of an enhancer using PGL3 reporter gene systems. We demonstrated that the SNP 1176 G/C could affect the function. Furthermore, this activity was enhanced by the SNP: G→C change in position 1176, providing the basis for molecular investigations of the *HMGB1* gene in HBV infection. Subsequent reports would focus on this investigation.

In conclusion, our results showed that the *HMGB1* 1176G/G genotype was related to the outcomes of hepatitis B infection, and patients with 1176G/G genotype of *HMGB1* gene are more likely to have a progressive status in HBV infection. The subjects bearing 1176G/G genotype have an increased risk of susceptibility to CHB, LC and SHB compared with those bearing at least one 1176C allele. However, further work is needed to validate our results, and clarify more potential functions of human *HMGB1* gene.

## COMMENTS

### Background

Chronic hepatitis B virus (HBV) infection is a serious public health problem worldwide. Host genetic factors play a role in determining the outcome and progression of the infection. A large number of studies on the association between cytokine gene polymorphisms and the risk of chronic hepatitis B (CHB) have been conducted. High mobility group box 1 (*HMGB1*) functioned as a pleiotropic cytokine and implicated in the pathology of several different immune-mediated diseases. However, there has been no report about the association between *HMGB1* gene and HBV infection.

### Research frontiers

*HMGB1* has recently been identified as a potent proinflammatory mediator when passively released extracellularly by necrotic cells, as opposed to apoptotic cells that will induce inflammation. Furthermore, *HMGB1* can also be actively secreted by stimulated macrophages or monocytes. Active secretion from living inflammatory cells and passive release from necrotic cells implicate that *HMGB1* may play a central role in proinflammatory reactions.

### Innovations and breakthroughs

This study characterizes the relationship between *HMGB1* gene polymorphism and HBV infection, and concluded that the *HMGB1* 1176G/G genotype was related to the outcomes of hepatitis B infection, and patients with 1176G/G genotype of *HMGB1* gene are more likely to have a progressive status in HBV infection.

### Applications

The study results suggest that the subjects bearing *HMGB1* 1176G/G genotype have an increased risk of susceptibility to CHB, liver cirrhosis and severe hepatitis B compared with those bearing at least one 1176C allele, which will provide new clue for the further basic research in pathogenesis of chronic HBV infection.

### Peer review

The authors have done a good job and found an association between the 1176G/C polymorphism of *HMGB1*, a proinflammatory mediator, and hepatitis B virus infection. The results are interesting and suggest that *HMGB1* is a mediator of the immune response to HBV infection.

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