Association of Genetic Variation of Sodium Taurocholate Cotransporting Polypeptide with Chronic Hepatitis B Virus Infection

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Background: Sodium taurocholate cotransporting polypeptide (NTCP) plays an important role in the enterohepatic circulation of bile acids and hepatocyte function and was recently proposed to be a functional receptor for hepatitis B virus (HBV). **Objective:** This study investigated the association of the functional polymorphism c.800C>T (p.S267F) (rs2296651) of the *NTCP* gene with HBV infection. **Methods:** The study included 244 patients with chronic HBV infection, 76 HBV infection resolvers, and 113 healthy controls. The polymorphism was genotyped using the polymerase chain reaction–restriction fragment length polymorphism method. **Results:** The distribution of the genotype and allele frequency of rs2296651 polymorphism was significantly different among the HBV patients, HBV infection resolvers, and healthy controls ($p=0.034$ and $p=0.039$, respectively). The frequency of genotype CT in HBV patients was significantly higher than that in healthy controls (11.9% vs. 4.4%, $p=0.026$, odds ratios [OR]=2.913, 95% confidence intervals [95% CI]=1.097–7.738). The frequency of allele T in HBV patients was also significantly higher than that in healthy controls (5.9% vs. 2.2%, $p=0.029$, OR=2.793, 95% CI=1.067–7.312). The frequency of genotype CT and allele T in HBV patients was higher than that in HBV infection resolvers although the difference was not significant. The genotype and allele frequency between infection resolvers and healthy controls and between HBV patients with different clinical diseases had no significant difference. **Conclusion:** These findings suggest that the rs2296651 polymorphism may predispose the susceptibility to and chronicity of HBV infection.

Introduction

INFECTION WITH HEPATITIS B VIRUS (HBV) is associated with acute and chronic hepatitis, liver failure, liver cirrhosis, and hepatocellular carcinoma (HCC). The significant heterogeneity in infection outcome and the great variation in disease severity with HBV infection are determined by interplay between the virus and host factors (Ganem and Prince, 2004; Bertolotti and Gehring, 2006). HBV viral replication in hepatocytes may interfere with the functions of the liver, and the recognition of HBV-infected hepatocytes by viral-specific CD8 cells is supposed to be the key mechanism causing both hepatocellular damage and viral elimination (Maini *et al.*, 2000; Iannacone *et al.*, 2007). However, HBV entry into and replication in hepatocytes of the host are the prerequisites of HBV pathogenesis, and virus entry into host cells is mediated by the cellular receptor of the virus.

Sodium taurocholate cotransporting polypeptide (NTCP, also known as solute carrier family 10 member 1, SLC10A1),

a protein primarily found in the basolateral membranes of hepatocytes and encoded by the *NTCP* (*SLC10A1*) gene in humans (Hagenbuch and Meier, 1994), plays an important role in the enterohepatic circulation of bile acids and hepatocyte functions (Hagenbuch *et al.*, 1991; Ho *et al.*, 2004; Stieger, 2011). It is noteworthy that NTCP was recently proposed to be a functional cell surface receptor necessary for the entry of HBV to hepatocytes (Yan *et al.*, 2012).

Genetic variations may influence the expression levels and the function of proteins and single-nucleotide polymorphisms (SNPs) have been identified in the *NTCP* gene (Saito *et al.*, 2002; Ho *et al.*, 2004; Choi *et al.*, 2011; Pan *et al.*, 2011). However, whether the genetic variation in *NTCP* may influence the susceptibility and the outcome and disease course of HBV infection through affecting the roles of the NTCP molecule in the bile acid circulation, the hepatocyte functions, and the HBV viral entry into hepatocytes is unknown.

This study, therefore, investigated the association of *NTCP* functional polymorphism c.800C>T (p.S267F) (rs2296651)

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with chronic HBV infection in Chinese Han patients with various clinical diseases. Individuals spontaneously recovered from HBV infection and healthy individuals without HBV infection were included as controls. The results indicate that the rs2296651 polymorphism may be associated with the susceptibility to and chronicity of HBV infection.

Patients and Methods

Study subjects

Two hundred forty-four patients with chronic HBV infection, 76 HBV infection resolvers, and 113 healthy controls were included in this study. All the participants were of Chinese Han nationality and genetically unrelated. Of the 244 patients with chronic HBV infection, 120 patients were diagnosed with chronic hepatitis, 65 patients were diagnosed with liver cirrhosis, and 59 patients were diagnosed with HCC as had been described previously (Bruix and Sherman, 2005; Sorrell *et al.*, 2009; Duan *et al.*, 2011). The 76 subjects were classified as HBV infection resolvers based on the spontaneous recovery from HBV infection with serum negativity for HBsAg, HBeAg, and anti-HBe and positivity for anti-HBs and anti-HBc IgG. The 113 healthy controls were defined based on the serum negativity for HBsAg, HBeAg, anti-HBe, and anti-HBc without a history of hepatitis with or without positive anti-HBs in line with the history of hepatitis B vaccination. Infection of other hepatitis viruses, including hepatitis A virus, hepatitis C virus, and hepatitis E virus, human immunodeficiency virus infection, autoimmune disorders, and other non-HBV diseases, were excluded. The characteristics such as age and gender for all the study subjects are summarized in Table 1. Informed consent was provided by all the participants. The study protocol was approved by the Ethics Committee of First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University and conformed to the Declaration of Helsinki.

Genotyping of NTCP gene polymorphisms

Genomic DNA was extracted from whole blood using the TIANamp Genomic DNA Kit [Tiagen Biotech (Beijing) Co., Ltd.] according to the instructions of the manufacturer. The c.800C>T (p.S267F) (rs2296651) polymorphism in *NTCP* was genotyped using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method.

A 204-bp PCR fragment, including the c.800C>T (p.S267F) (rs2296651) polymorphism in *NTCP*, was amplified using the following primers: 5'-ATATGGCAATGAGGAGAAGC-3' (upstream) and 5'-TTCCCTCTGAGTGTATGTGG-3' (downstream). The PCR was performed in a volume of 25 μ L reaction containing 12.5 μ L 2 $\times$ Taq PCR Mix (Xi'an Runde Biotechnology Ltd.), 2 μ L genomic DNA (0.05 μ g/ μ L), 1.0 μ L

(10 μ M) of each primer, and 8.5 μ L sterile double distilled water. The amplification was performed with the following program. The mixture was first heated at 94°C for 3 min and then amplified for 35 cycles by denaturation at 94°C for 30 s, annealing at 58°C for 30 s, extension at 72°C for 30 s, and a final extension at 72°C for 10 min. The restriction fragments of *NTCP* c.800C>T polymorphism were obtained using *HphI* (New England Biolabs (Beijing) Ltd.) according to the instructions of the manufacturer. Digested fragments were analyzed by electrophoresis on 3% agarose gels stained with ethidium bromide and revealed under UV light using a UV-transilluminator (UVP Model White/2 UV; UVP, Inc.). The genotypes of the polymorphism in the individuals were determined according to the digestion pattern: genotype CC with a fragment of 204 bp, genotype CT with three fragments of 204, 120, and 84 bp, and genotype TT with two fragments of 120 and 84 bp.

Statistical analysis

Statistical analysis was performed using a SPSS13.0 software (SPSS, Inc.). The chi-square test or Student's *t*-test was used to compare parameters between groups. The chi-square test was used to estimate the Hardy–Weinberg equilibrium (HWE) and to compare the genotype and allele frequencies between the groups and to calculate odds ratios (OR) with 95% confidence interval (CI). A *p*-value less than 0.05 was considered significant.

Results

Characteristics of the study subjects and HWE of the polymorphism

The sex and age had no statistical differences between HBV patients, spontaneous resolvers, and healthy controls (Table 1, *p*>0.05). The distributions of the *NTCP* S267F polymorphism genotypes in the study populations, including HBV patients, HBV infection resolvers, and healthy controls, were in the HWE (Table 1).

Association of genotype and allele frequencies of the polymorphism with chronic HBV infection

The distribution of genotype frequency of the *NTCP* c.800C>T (S267F) (rs2296651) polymorphism was significantly different among the HBV patients, HBV infection resolvers, and healthy controls (*p*=0.034, Table 2). Pairwise comparison showed that the frequency of genotype CT in HBV patients was higher than that in HBV infection resolvers (11.9% vs. 5.3%, *p*=0.097, OR=2.428, 95% CI=0.825–7.142) and significantly higher than that in healthy controls (11.9% vs. 4.4, *p*=0.026, OR=2.913, 95% CI=1.097–7.738, Table 2). The allele frequency of the rs2296651 polymorphism

TABLE 1. DEMOGRAPHICS AND HARDY–WEINBERG EQUILIBRIUM OF *NTCP* c.800C>T (S267F) (rs2296651) GENOTYPES IN HEPATITIS B VIRUS PATIENTS, HEPATITIS B VIRUS INFECTION RESOLVERS, AND HEALTHY CONTROLS

	Patients (n=244)	Resolvers (n=76)	Controls (n=113)	p
Gender (M/F)	147/97	45/31	72/41	0.775
Age [years, mean $\pm$ SD (range)]	41.68 $\pm$ 13.32 (18–76)	42.36 $\pm$ 13.23 (18–78)	40.98 $\pm$ 11.74 (21–68)	0.768
S267F HWE (observed vs. expected, <i>p</i>)	0.324	0.814	0.810	

HWE, Hardy–Weinberg equilibrium; NTCP, sodium taurocholate cotransporting polypeptide.

TABLE 2. GENOTYPE AND ALLELE FREQUENCIES OF *NTCP* c.800C>T (S267F) (rs2296651) POLYMORPHISM IN HEPATITIS B VIRUS PATIENTS, HEPATITIS B VIRUS INFECTION RESOLVERS, AND HEALTHY CONTROLS

<i>rs2296651</i>	Patients (n = 244)	Resolvers (n = 76)	Controls (n = 113)	Patients vs. resolvers		Patients vs. controls		Resolvers vs. controls	
				p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)
Genotype									
CC	215 (88.1)	72 (94.7)	108 (95.6)	Reference 0.034	2.428 (0.825–7.142)	0.097	2.913 (1.097–7.738)	0.791	1.200 (0.312–4.620)
CT	29 (11.9)	4 (5.3)	5 (4.4)						
TT	0 (0)	0 (0)	0 (0)						
Allele									
C	459 (94.1)	148 (97.4)	221 (97.8)	Reference 0.039	2.338 (0.809–6.759)	0.107	2.793 (1.067–7.312)	0.793	1.195 (0.316–4.522)
T	29 (5.9)	4 (2.6)	5 (2.2)						

Data are presented as *n* (%).
OR, odds ratio; 95% CI, 95% confidence intervals.

TABLE 3. GENOTYPE AND ALLELE FREQUENCIES OF *NTCP* c.800C>T (S267F) (rs2296651) IN PATIENTS WITH CHRONIC HEPATITIS, LIVER CIRRHOSIS, AND HEPATOCELLULAR CARCINOMA

<i>rs2296651</i>	CH (n = 120)	LC (n = 65)	HCC (n = 59)	CH vs. LC		CH vs. HCC		LC vs. HCC	
				p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)
Genotype									
CC	107 (89.2)	56 (86.2)	52 (88.1)	Reference 0.833	0.756 (0.305–1.877)	0.546	0.903 (0.340–2.397)	0.742	1.194 (0.415–3.437)
CT	13 (10.8)	9 (13.8)	7 (11.9)						
TT	0 (0)	0 (0)	0 (0)						
Allele									
C	227 (94.6)	121 (93.1)	111 (94.1)	Reference 0.843	0.770 (0.320–1.853)	0.559	0.908 (0.352–2.340)	0.751	1.179 (0.425–3.273)
T	13 (5.4)	9 (6.9)	7 (5.9)						

Data are presented as *n* (%).
CH, chronic hepatitis; LC, liver cirrhosis; HCC, hepatocellular carcinoma.

was also differently distributed among the patients, resolvers, and healthy controls ($p=0.039$, Table 2). The frequency of allele T in HBV patients was higher than that in resolvers (5.9% vs. 2.6%, $p=0.107$, OR=2.338, 95% CI=0.809–6.759) and significantly higher than that in healthy controls (5.9% vs. 2.2%, $p=0.029$, OR=2.793, 95% CI=1.067–7.312, Table 2). The genotype and allele frequency between HBV infection resolvers and healthy controls had no significant difference ($p=0.791$ and $p=0.793$, respectively, Table 2).

Association of genotype and allele frequencies of the polymorphism with clinical diseases of chronic HBV infection

The genotype and allele frequencies of the rs2296651 polymorphism between patients with chronic HBV infection diagnosed as chronic hepatitis, liver cirrhosis, and HCC had no significant differences (all $p>0.05$, Table 3).

Discussion

NTCP is a member of the solute carrier family of transporters and plays a critical role in the maintenance of enterohepatic recirculation of bile acids and hepatocyte function. NTCP was shown to also transport additional substrates such as hormones and xenobiotics, including drugs and toxins (Stieger, 2011; Claro da Silva *et al.*, 2013). Notably, NTCP was recently identified as a functional cellular receptor for HBV (Yan *et al.*, 2012). Functionally relevant polymorphisms in NTCP would be expected to impact the bile acid homeostasis, liver function, and the entry of HBV into hepatocytes. The presence of multiple SNPs in NTCP has been demonstrated in different ethnic populations with significantly various frequency distributions (Saito *et al.*, 2002; Ho *et al.*, 2004; Choi *et al.*, 2011; Pan *et al.*, 2011). Some of the SNPs were revealed to be functionally relevant to the expression of the NTCP molecule and the efficiency of transporting xenobiotics such as statins (Ho *et al.*, 2004, 2006; Choi *et al.*, 2011). Most of these SNPs are absent or less frequent in Chinese (Ho *et al.*, 2004; Pan *et al.*, 2011), but one SNP, the c.800C>T (p.S267F) (rs2296651) polymorphism in exon 4 of NTCP has been identified in Asians, including Chinese (Ho *et al.*, 2004; Pan *et al.*, 2011). This SNP is related to a nonsynonymous substitution and the position was suggested to be critical and specific for bile acid substrate binding/recognition and was predicted to be located to the third putative extracellular loop of the NTCP molecule (Ho *et al.*, 2004). Together with the function of NTCP as a receptor for HBV, this SNP was hypothesized to also possibly affect the interaction between the receptor and the HBV in addition to the function for bile acid uptake. Therefore, it was selected and investigated for the association with chronic HBV infection in Chinese populations in this study.

The frequency of the c.800C>T (S267F) variant in the control population of this study (4.4%) is higher than the previously reported frequencies in Koreans (3.1%) and lower than in Chinese–Americans (7.5%) (Ho *et al.*, 2004) and Vietnamese (9.2%) populations (Pan *et al.*, 2011). The frequency is also lower than that previously documented in Chinese (7.4%) (Pan *et al.*, 2011). These may reflect the differences of the ethnic and geographic distributions of this SNP. Consistent with the results of the previous study (Ho *et al.*, 2004), we did not find individuals homozygous for allele T of this polymorphism.

The results of this study showed that the distribution of genotype and allele frequency of the NTCP c.800C>T (S267F) (rs2296651) polymorphism was significantly different among the HBV patients, HBV infection resolvers, and healthy controls. The frequency of genotype CT and allele T in HBV patients was significantly higher than that in healthy controls. Although the difference was not statistically significant, the frequency of genotype CT and allele T in HBV patients was also higher than that in HBV infection resolvers. The genotype and allele frequency between HBV infection resolvers and healthy controls and between HBV patients with different clinical diseases had no significant difference. Theoretically, the rs2296651 polymorphism may influence the HBV infection through at least three aspects, namely, the entry of the virus into hepatocytes, the bile acid circulation, and the hepatocyte function. The influence of bile acid circulation and the hepatocyte function may be involved in the disease course and the progression or the disease severity of HBV infection. However, our results did not indicate any association of this SNP with the outcome and disease severity of HBV infection. It is indicated that this polymorphism may have no considerable influence on the disease course and severity of HBV infection irrespective of the effect on the transport activity of bile acid (Ho *et al.*, 2004) and statins such as rosuvastatin (Ho *et al.*, 2006; Pan *et al.*, 2011). In fact, the potential association of this SNP with a clinical phenotype, to our knowledge, has not been documented so far. The results of this study showed that the patients with chronic HBV infection had higher genotype CT and allele T of the polymorphism as compared with healthy control individuals and HBV infection resolvers, although the difference was only statistically significant in comparison with healthy controls. It is suggested that this polymorphism is associated with the susceptibility to and chronicity of HBV infection possibly through affecting the interaction between the virus and the NTCP molecule, a receptor of the virus. Receptors confer the cell permissiveness to the virus and also serve as necessities for the virus transmission between cells, probably explaining the predisposing effect of the SNP in the receptor NTCP gene on both the susceptibility and chronicity in HBV infection, especially the susceptibility. It should be noted that the polymorphism genotyped in this study appears to be not located within the amino acids 157 to 165 of NTCP, which have been demonstrated to be critical for viral entry of HBV (Yan *et al.*, 2012, 2013). Whether it is conformationally and/or functionally important for influencing the viral entry awaits to be clarified.

NTCP was demonstrated to specifically interact with the receptor-binding region of HBV pre-S1 (Yan *et al.*, 2012). Recent studies showed that cyclosporin A and its derivatives, neutralizing antibody against HBV surface protein, and compounds known to inhibit the NTCP transporter activity could inhibit HBV entry using NTCP through interfering with the binding between NTCP and the pre-S1 domain of the HBV large envelope protein (Iwamoto *et al.*, 2014; Nkongolo *et al.*, 2013; Watashi *et al.*, 2013), thus, proposing a novel strategy to identify anti-HBV agents by targeting NTCP. Whether NTCP polymorphisms, including the rs2296651 polymorphism, are relevant to the action of anti-HBV agents targeting NTCP may be a focus of future investigation.

The SNP rs2296651 was a so-called Asian-specific SNP (Pan *et al.*, 2011) since it was reported in the Asian population (Saito *et al.*, 2002; Ho *et al.*, 2004; Pan *et al.*, 2011). Asia is among the highly endemic areas of HBV (Hwang and Cheung, 2011). It is

unclear whether the results of this study can be partly extrapolated to a link between the high endemicity of HBV infection and the high frequency of this SNP in Asian populations.

Clearly, our findings require confirmation in a large sample size population with different ethnic backgrounds. Studies are definitely warranted to elucidate the influence of this functional SNP of the NTCP, a HBV functional receptor, on the efficiency of HBV viral entry into cells and viral transmission between cells. The confirmation and clarification of these issues may consolidate the relevance of this SNP in monitoring the disease progression and in designing novel prevention and intervention strategies based on the genetic background of the HBV-affected individuals.

In conclusion, the findings of this study suggest a possible contribution of the SNP rs2296651 in the gene of NTCP, which was identified as a functional receptor for HBV, to the genetic susceptibility to HBV infection and chronicity in the Chinese Han population, possibly through affecting the role of the NTCP molecule in mediating HBV infection, instead of influencing the enterohepatic circulation of bile acids and/or hepatocyte function. The confirmation of these findings in replicative studies with large cohorts of HBV patients controlled with different ethnic populations and the elucidation of the possible functional effects on the HBV viral entry to and the viral transmission between hepatocytes may shed light on understanding the mechanisms of the susceptibility and persistence of HBV infection and designing novel preventive and therapeutic strategies for HBV infection.

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Author Disclosure Statement

No conflict of interest to declare.

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