Associations between the single nucleotide polymorphisms of *APOBEC3A*, *APOBEC3B* and *APOBEC3H*, and chronic hepatitis B progression and hepatocellular carcinoma in a Chinese population

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Abstract. The present study examined the relationships between the single nucleotide polymorphisms (SNPs) of three members of the apolipoprotein B mRNA-editing catalytic polypeptide-like 3 (*A3*) gene family, *A3A*, *A3B* and *A3H,* and hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC) in a Han Chinese population. A total of 654 patients were enrolled in the study between January 2012 and July 2016, including 104 patients with chronic HBV infection (CHB), 265 patients with HBV-related liver cirrhosis and 285 patients with HBV-related HCC. A total of two *A3A* SNPs (rs7286317 and rs7290153), three *A3B* SNPs (rs2267398, rs2267401 and rs2076109), and five *A3H* SNPs (rs56695217, rs139302, rs139297, rs139316 and rs139292) were genotyped using a MassArray system. Statistical analysis and haplotype estimation were conducted using Haploview and Unphased software. No significant associations were observed between the *A3A*, *A3B* and *A3H* SNPs and the development of CHB and HCC. Haplotype analysis revealed that the mutant haplotypes C-T-A, C-T-G, T-G-G and T-T-G from the *A3B* SNPs rs2267398-rs2267401-rs2076109 carried a lower risk of HCC than the reference haplotype. These findings suggested that there was no relationship between *A3A*, *A3B* and *A3H* SNPs and CHB progression or HCC development in the Han Chinese population.

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Abbreviations: APOBEC3, apolipoprotein B mRNA-editing catalytic polypeptide-like 3; SNPs, single nucleotide polymorphisms; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; LC, liver cirrhosis; HIV-1, human immunodeficiency virus 1; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; UTRs, untranslated regions; OR, odds ratio; CI, confidence intervals

Key words: CHB, HCC, Chinese population, SNPs, APOBEC3

Introduction

Hepatocellular carcinoma (HCC) is a common form of liver cancer associated with high mortality. It is estimated that ~600,000 new cases are diagnosed annually worldwide; HCC is relatively common in Asia-Pacific countries and sub-Saharan Africa (1). Hepatitis B virus (HBV) infection is believed to be the most common cause of HCC development, with the clinical course of HBV infection often progressing from chronic hepatitis B (CHB) to liver cirrhosis (LC) and then HCC (1). It is estimated that ~2-10% of CHB patients develop LC, some of which subsequently develop HCC; however, some HBV carriers can also spontaneously eliminate the virus (2). HBV infection is common in China due socio-economic factors. As a consequence, the incidence of HCC in China is relatively high, contributing to ~422,100 deaths annually (3).

The apolipoprotein B mRNA-editing catalytic polypeptide-like 3 (*APOBEC3*, *A3*) gene cluster is located in chromosome region 22q13.1 to q13.2 (4). This gene cluster encodes seven proteins, including A3A, A3B, A3C, A3DE, A3F, A3G and A3H (5) and is reported to perform important roles in various biological processes, including the innate immune response to viral infections (4,6). Among the seven protein family members, A3A and A3B are able to restrict the infection of a broad range of viruses, including parvovirus, HBV, hepatitis C virus, herpesvirus, human papillomavirus and human immunodeficiency virus 1 (HIV-1) (7-13). A3H is the most polymorphic member of the A3 subfamily, as it has various single nucleotide polymorphism (SNP) combinations that influence protein stability during resistance to HIV-1 infection (14). Besides their role in viral restriction, the dysregulation and hypermutation of A3 genes has recently been linked to carcinogenesis (15). In particular, a 29.5 kb germline deletion of *A3A/B* was associated with an increased risk of various cancer types, including breast and ovarian cancer. However, the effect has been inconsistent in different populations and for different types of cancer. For example, it has been suggested that the deletion of *A3A/B* was associated with an increased risk of breast cancer in European

women (16), Chinese women (17) and southeast Iranian women (18). However, this association was not observed in Swedish (19) or Moroccan (20) populations, or in the general European population (21). Few studies have investigated the association between *A3H* polymorphisms and cancer risk. Zhu *et al* (22) reported that the T allele of the rs139293 *A3H* SNP was associated with reduced lung cancer risk in a Chinese population; therefore, further studies are required to confirm the associations between *A3A*, *A3B* and *A3H* polymorphisms and HCC risk.

The present study evaluated the associations between the SNPs of *A3A*, *A3B* and *A3H,* and the development of chronic HBV and HBV-related HCC in a Han Chinese population.

Materials and methods

Study population. Between January 2012 and July 2016, a total of 654 patients from the First Hospital of Jilin University were enrolled in the present study, including 104 patients with CHB, 265 patients with HBV-related LC and 285 patients with HBV-related HCC. The criteria used to diagnose CHB, HBV-related LC and HBV-related HCC have been defined previously (23). Hepatitis A-, C-, D- or E-positive patients and those with HIV were excluded. In addition, patients who had suffered another organ malignancy in the past 5 years, had combined autoimmune diseases, or had other liver diseases, such as intra- and extra-hepatic bile duct stones, alcoholic liver diseases and hemorrhagic liver diseases, were also excluded. General characteristics, including gender, age, smoking history, drinking history, HBV infection history and treatment history, were gathered using a standardized questionnaire. Whole blood (5 ml) was collected from veins of each patient within 48 h of hospital admission and their hepatitis B profile was compiled, including hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), anti-hepatitis B core antigen (HBc), anti-HBe, hepatitis C, HBV DNA quantification, liver function, renal function, α-fetoprotein, blood lipids, blood glucose, blood routine, coagulation routine and abdominal color Doppler ultrasound (or liver computed tomography or magnetic resonance imaging). Patients were also assessed using the Child-Pugh score (24,25) and those with HCC underwent Barcelona clinic liver cancer staging (26). The present study was approved by the First Hospital Ethical Committee of Jilin University and written informed consent was obtained from all participants.

SNP selection and genotyping. *A3A*, *A3B* and *A3H* SNPs were selected from the functional regions of the exon, promoter and untranslated regions (UTRs) by GeneView (27) based on Hapmap (https://www.genome.gov/10001688/international-hapmap-project) and the 1,000 Genomes database (http://www.internationalgenome.org/), with a minor allele frequency of >10%. The SNPs rs7286317 and rs7290153 were selected for *A3A* since they are located in the microRNA-binding site of the 3′UTR. The SNPs rs2267398 and rs2267401, located in the transcription factor-binding site of the promoter region, were selected for *A3B* due to their potential roles in gene transcription, while the SNP rs2076109 was selected as it is a missense mutation that may regulate gene function by altering the protein structure. The SNPs rs56695217, rs139302, rs139297, rs139316 and rs139292 were selected for *A3H* because rs56695217 is located in the transcription factor-binding site, and the others are missense mutations. Haplotype analysis was performed using Haploview version 4.2 (http://www.broad.mit.edu/mpg/haploview) with rs2076109 (*A3B*), rs139297 (*A3H*), rs139302 (*A3H*) and rs139316 (*A3H*) tag-SNPs. The locations of the *A3A*, *A3B* and *A3H* genes and the selected SNPs are shown in Fig. 1.

Genomic DNA was isolated from whole blood using a blood genomic DNA kit (Sigma-Aldrich; Merck KGaA), according to the manufacturer's instructions. SNP genotyping was performed using a MassArray system (Sequenom), according to the manufacturer's protocol. All SNP primers were designed using Assay Designer (http://assay.archerdx.com/, version 3.2; Table I).

Statistical analysis. All data were analyzed using SPSS version 21.0 (IBM Corp.). Continuous variables are expressed as the mean ± standard deviation or as the median and the interquartile range (25 and 75%). Categorical variables are expressed as a percentage (%). Differences among multiple groups were compared using analysis of variance and the least significant difference multiple comparisons test. Haplotype analysis was performed using Unphased version 3.1.4 (28). The two-sided χ^2 test or Fisher's exact test was used to compare allele distributions. Multivariate logistic regression analysis was performed to calculate odds ratios and 95% confidence intervals after adjusting the factors of smoking, drinking and gender differences. $P<0.05$ was considered to indicate a statistically significant difference.

Results

General characteristics of the study population. The main general and clinical characteristics of the study population are summarized in Table II. No statistical differences were observed between the sex, age, or the percentage of smokers and alcohol consumers in the CHB and LC patient groups ($P<0.05$). In comparison, the median age and percentages of smokers and alcohol consumers were significantly higher for HCC patients than for CHB patients ($P=0.006$, 0.013 and 0.008, respectively); however, no significant difference was observed in their sex distributions. Furthermore, no significant differences were observed in the sex, age and percentage of alcohol consumers between the LC and HCC patients ($P<0.05$), but the percentage of smokers differed significantly ($P<0.001$).

No significant differences were observed between the HBeAg positive rate or alkaline phosphatase (ALP) level of the CHB and LC patients. However, the serum HBV-DNA positive rate, HBV load, and alanine transaminase (ALT), aspartate transaminase (AST) and glutamyl transpeptidase (GGT) levels of the CHB patients were significantly higher compared with those of the LC patients ($P<0.05$), suggesting that hepatocellular damage was more severe in CHB patients. Furthermore, the prealbumin, albumin and cholinesterase levels, and the platelet count were all significantly higher in CHB patients compared with LC patients ($P<0.05$), while the total bilirubin level was significantly lower in CHB patients compared with LC patients ($P<0.05$). The HBeAg positive rate, HBV load, ALT level, prealbumin level and total

Table I. Primer sequences for SNP genotyping.

Gene	SNPs	Primer sequence	Annealing temperature (˚C)
APOBEC3A	rs7286317	F: 5'-ACGTTGGATGGTCAGGAGATCGAGACCATC-3'	45.1
		R: 5'-ACGTTGGATGCACGCCTGGCTAATTTTTTG-3'	
	rs7290153	F: 5'-ACGTTGGATGGGAAGATTCTTAATTTTGTG-3'	45.5
		R: 5'-ACGTTGGATGGATTATGCTCAATATTCTCAG-3'	
APOBEC3B	Rs2267398	F: 5'-ACGTTGGATGTTCTCCCTTCCTTGGTGTCG-3'	46.1
		R: 5'-ACGTTGGATGATGCGTCCCCTCTTCCAAC-3'	
	rs2267401	F: 5'-ACGTTGGATGTCTCTCAGCTGGGTCTGGA-3'	52.4
		R: 5'-ACGTTGGATGGGACCCAACGGAATTGCAAA-3'	
	rs2076109	F: 5'-ACGTTGGATGAGAGGAAGCACATTTCTGCG-3'	49.6
		R: 5'-ACGTTGGATGTGCTCCCCCTCTCAGAGCAT-3'	
APOBEC3H	Rs56695217	F: 5'-ACGTTGGATGCCTTGTAATTTGCCCACCTC-3'	47.0
		R: 5'-ACGTTGGATGAAGAACAAAGGCCAGATGCG-3'	
	Rs139292	F: 5'-ACGTTGGATGTCAGCTGGTAACACAAGAGG-3'	58.2
		R: 5'-ACGTTGGATGAGCCGAAACATTCCGCTTAC-3'	
	Rs139297	F: 5'-ACGTTGGATGTTGCACCAGTGGTAGTACAG-3'	48.9
		R: 5'-ACGTTGGATGGCTGGTTGACTTCATCAAGG-3'	
	Rs139302	F: 5'-ACGTTGGATGCAGGACAGTGCCTCACCTT-3'	49.1
		R: 5'-ACGTTGGATGCCTTCAACCCCTATAAGATG-3'	
	Rs139316	F: 5'-ACGTTGGATGCCAGGGAAAGTCATCTTGAG-3'	46.7
		R: 5'-ACGTTGGATGAAGAAGTTTGCAGCTTGGAC-3'	

SNP, single nucleotide polymorphism; F, forward; R, reverse; APOBEC3, apolipoprotein B mRNA-editing catalytic polypeptide-like 3.

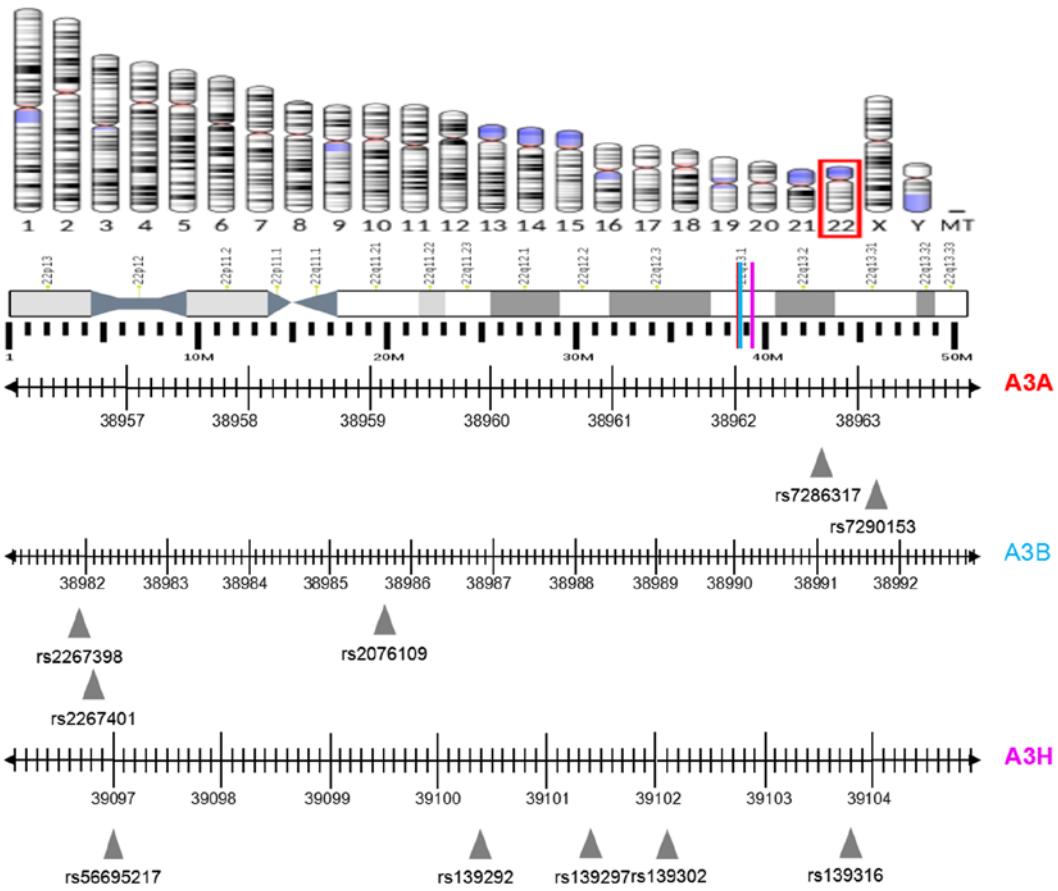

Figure 1. Location of the A3A, A3B and A3H gene and single nucleotide polymorphisms. A3, apolipoprotein B mRNA-editing catalytic polypeptide-like 3 gene family.

Table II. General and clinical characteristics of study subjects.

Characteristics	CHB n=104	P-value[a]	LC n=265	P-value[b]	HCC n=287	P-value[c]	Reference ranges
Sex (M/F)	84/20	0.823	210/55	0.063	246/41	0.286	-
Age[d]	47 (43,53)	0.368	49 (41.5,56)	0.901	50 (46,56)	0.006	-
Smoking[e]		0.862		<0.001		0.013	-
Have ever smoked	37 (35.6)		91 (34.3)		144 (50.2)		
Have never smoked	67 (64.4)		174 (65.7)		143 (49.8)		
Alcohol consumption[e]		0.142		0.123		0.008	-
Have ever consumed alcohol	28 (26.9)		93 (35.1)		120 (41.8)		
Have never consumed alcohol	76 (73.1)		172 (64.9)		167 (58.2)		
Serum HBV-DNA[e]		0.002		0.004		0.107	-
Positive	98 (94.2)		211 (79.6)		254 (88.5)		
Negative	6 (5.8)		55 (20.4)		33 (11.5)		
HBV load, log10 (IU/ml)[d]	6.1 (4.2, 7.3)	<0.001	4.6 (2.1, 6.3)	0.565	4.6 (3.1, 6.0)	<0.001	1.3-8.2
HBeAg[e]		0.814		0.359		0.295	-
Positive	43 (48.9)		99 (46.7)		100 (42.2)		
Negative	45 (51.1)		113 (53.3)		137 (57.8)		
ALT (U/l)[d]	172 (53, 496.5)	<0.001	42 (24, 86)	0.715	43.5 (27.8, 69.3)	<0.001	13.0-35.0
AST (U/l)[d]	99 (39.5, 249.5)	<0.001	47 (31, 90)	<0.001	62.0 (38.0,110.0)	0.005	7.0-40.0
ALP (U/l)[d]	87 (67,122.8)	0.724	89(68,125.5)	<0.001	129.5 (86.0,190.5)	<0.001	50.0-135.0
GGT (U/l)[d]	93 (38.3, 161.8)	<0.001	49.5 (27, 100.8)	<0.001	112.5 (51.3, 254.3)	0.018	7.0-45.0
Prealbumin (g/l)[d]	0.16 (0.13, 0.20)	<0.001	0.12 (0.09, 0.16)	0.192	0.13 (0.08, 0.17)	<0.001	0.18-0.39
Albumin (g/l)[d]	37.5 (32.0, 41.2)	<0.001	30.5 (25.3, 36.0)	<0.001	33.1 (28.3, 37.3)	<0.001	40.0-55.0
Total bilirubin (μmol/l)[d]	19.6 (13.3, 48.0)	0.035	27.6 (16.2, 61.4)	0.314	25.9 (16.5, 44.2)	0.101	0.0-8.6
Cholinesterase (U/l)[d]	6,019 (4,343, 8,281)	<0.001	3,289 (2,356, 4,744)	0.012	3,918.0 (2,488.3, 5,762.0)	<0.001	4,300-12,000
Platelet count (x10^9/l)[d]	145 (117, 188)	<0.001	77 (53, 121)	<0.001	118.5 (78.8, 172.0)	<0.001	100-300

[a]CHB vs. LC; [b]LC vs. HCC; [c]CHB vs. HCC, calculated by analysis of variance and the least significant difference multiple comparisons test. [d]Data are expressed as the median (25, 75%). [e]Data are expressed as N (%). HBV, hepatitis B virus; CHB, chronic hepatitis B; LC, liver cirrhosis; HCC, hepatocellular carcinoma; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; M, male; F, female; HBeAg, hepatitis B e antigen.

Table III. Genotype and allele frequencies of two SNPs of APOBEC3A.

A, Rs7286317 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=102			n=265			n=285		
AA	75 (73.5)	1		197 (74.3)	1		200 (70.2)	1	
AG	27 (26.5)	0.95 (0.56,1.60)	0.85	68 (25.7)	1.30 (0.89,191)	0.18	85 (29.8)	1.24 (0.74,2.08)	0.42
A Allele	177 (86.8)	1		462 (87.2)			485 (85.1)	1	
G Allele	27 (13.2)	0.96 (0.60,1.56)	0.88	68 (12.8)	0.84 (0.60,1.18)	0.32	85 (14.9)	0.87 (0.55,1.39)	0.56

B, Rs7290153 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=97			n=246			n=267		
CC	78 (80.4)	1		198 (80.5)	1		217 (81.3)	1	
CT	14 (14.4)	0.88 (0.44,1.75)	0.72	31 (12.6)	0.83 (0.48,1.47)	0.52	30 (11.2)	0.78 (0.39,1.57)	0.48
TT	5 (5.2)	1.30 (0.46,3.70)	0.62	17 (6.9)	1.02 (0.51,2.04)	0.95	20 (7.5)	1.41 (0.51,3.92)	0.51
CT+TT	19	0.99 (0.55,1.80)	0.97	48	0.90 (0.57,1.41)	0.65	50	0.95 (0.52,1.73)	0.86
C Allele	170 (87.6)	1		427 (86.8)	1		464 (86.9)	1	
T Allele	24 (12.4)	1.0 (0.65,1.78)	0.77	65 (13.2)	1.01 (0.70,1.45)	0.96	70 (13.1)	0.94 (0.57,1.54)	0.79

The two-sided χ^2 test or Fisher's exact test was used in the comparison of allele distributions. [a]CHB vs. LC; [b]LC vs. HCC; [c]CHB vs. HCC, adjusted for age, gender, smoking and alcohol consumption by logistic regression analysis. APOBEC3, apolipoprotein B mRNA-editing catalytic polypeptide-like 3; SNPs, single nucleotide polymorphisms; CHB, chronic hepatitis B; LC, liver cirrhosis; HCC, hepatocellular carcinoma; OR, odds ratio; CI, confidence intervals.

Table IV. Genotype and allele frequencies of three SNPs of APOBEC3B.

A, Rs2267398 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=96			n=256			n=272		
CC	28 (29.2)	1		90 (35.2)	1		93 (34.2)	1	
CT	50 (52.1)	0.75 (0.44,1.29)	0.31	125 (48.8)	1.11 (0.75,1.63)	0.61	135 (49.6)	0.85 (0.50,1.47)	0.57
TT	18 (18.8)	0.71 (0.35,1.44)	0.34	41 (16.0)	1.15 (0.68,1.94)	0.61	44 (16.2)	0.77 (0.38,1.56)	0.47
CT+TT	68	0.74 (0.44,1.24)	0.26	166	1.12 (0.77,1.61)	0.56	179	0.83 (0.50,1.39)	0.49
C Allele	106 (55.2)	1		305 (59.6)	1		321 (59.0)	1	
T Allele	86 (44.8)	0.84 (0.60,1.17)	0.30	207 (40.4)	0.98 (0.76,1.25)	0.85	223 (41.0)	1.17 (0.84,1.63)	0.36

B, Rs2267401 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=102			n=265			n=284		
GG	25 (24.5)	1		58 (21.9)			63 (22.2)		
GT	29 (28.4)	0.93 (0.49,1.77)	0.82	65 (24.5)	0.89 (0.53,1.46)	0.62	61 (21.5)	0.88 (0.47,1.69)	0.69
TT	48 (47.1)	1.25 (0.70,2.22)	0.45	142 (53.6)	1.00 (0.65,1.54)	0.99	160 (56.3)	1.29 (0.72,2.29)	0.39
GT+TT	77	1.13 (0.66,1.93)	0.67	207	0.97 (0.64,1.46)	0.87	221	1.13 (0.66,1.93)	0.65
G Allele	79 (38.7)	1		181 (34.2)	1		187 (32.9)	1	
T Allele	125 (61.3)	1.22 (0.87,1.70)	0.25	349 (65.8)	0.95 (0.74,1.22)	0.67	381 (67.1)	1.00 (0.71,1.42)	0.98

Table IV. Continued.

C, Rs2076109 genotype and allele

SNP	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
	N (%)	OR (95%CI)	P-value[a]	N (%)	OR (95%CI)	P-value[b]	N (%)	OR (95%CI)	P-value[c]
Number detected	n=94			n=234			n=246		
AA	24 (25.5)	1		57 (24.4)	1		54 (22.0)	1	
AG	20 (21.3)	1.30 (0.65,2.61)	0.46	62 (26.5)	1.12 (0.67,1.89)	0.67	64 (26.0)	1.70 (0.83,3.50)	0.15
GG	50 (53.2)	0.95 (0.53,1.71)	0.87	115 (49.1)	0.13 (0.72,1.79)	0.59	128 (52.0)	1.21 (0.67,2.21)	0.53
AG+GG	70	1.05 (0.61,1.83)	0.86	177	1.13 (0.73,1.74)	0.58	192	1.03 (0.63,1.69)	0.89
A Allele	68 (36.2)	1		176 (37.6)	1		172 (35.0)	1	
G Allele	120 (63.8)	0.94 (0.66,1.37)	0.73	292 (62.4)	0.89 (0.69,1.16)	0.39	320 (65.0)	1.35 (0.76,2.39)	0.31

The two-sided χ^2 test or Fisher's exact test was used in the comparison of allele distributions. [a]CHB vs. LC; [b]LC vs. HCC; [c]CHB vs. HCC, adjusted for age, gender, smoking and alcohol consumption by logistic regression analysis. APOBEC3, apolipoprotein B mRNA-editing catalytic polypeptide-like 3; SNPs, single nucleotide polymorphisms; CHB, chronic hepatitis B; LC, liver cirrhosis; HCC, hepatocellular carcinoma; OR, odds ratio; CI, confidence intervals.

bilirubin level did not differ significantly between LC and HCC patients (P<0.05). Additionally, the levels of AST, ALP, GGT, albumin and cholinesterase, and the platelet count were all significantly lower in LC patients compared with HCC patients (P<0.05), suggesting that the LC patients had a lower level of hepatocellular damage than the HCC patients.

Associations between genotype and allele frequency in A3A, A3B and A3H SNPs. The genotype and allele frequency of the *A3A* polymorphisms in CHB patients and healthy individuals are displayed in Table III. No significant associations were detected between the genotype and allele frequency of the two *A3A* SNPs (rs7286317 and rs7290153) and chronic hepatitis B progression or HCC occurrence (P<0.05). Furthermore, as shown in Tables IV and V, no significant associations were observed between the three *A3B* SNPs (rs2267398, rs2267401 and rs2076109) or the five *A3H* SNPs (rs56695217, rs139302, rs139297, rs139316 and rs139292) and chronic hepatitis B progression or HCC occurrence (P<0.05).

Haplotype analysis of A3A, A3B and A3H. Haplotype analysis was also performed on the two *A3A* SNPs, three *A3B* SNPs and five *A3H* SNPs using Unphased version 3.1.4. No haplotypes were found for the two *A3A* SNPs or five *A3H* SNPs (data not shown). The distribution of the *A3B* haplotype rs2267398-rs2267401-rs2076109 was significantly different between the LC and HCC groups (Table VI). The C-G-G haplotype was used as a reference, with the results showing that the mutant C-T-A, C-T-G, T-G-G and T-T-G haplotypes of rs2267398-rs2267401-rs2076109 were associated with a lower risk of HCC compared with the reference haplotype (Table VII).

Discussion

It is estimated that ~55% of HCC cases are associated with CHB (29,30). Members of the A3 protein family have been reported to edit the HBV genome and reduce HBV replication *in vivo* and *in vitro* (31,32). However, the effects of the SNPs of A3 genes have not yet been evaluated in a Chinese population. To the best of the authors' knowledge, the present study is the first to investigate the association between *A3A*, *A3B* and *A3H* SNPs and the development of CHB and HBV-related HCC in a Chinese population. There were two major findings of the present study: i) The rs7286317 and rs7290153 SNPs of *A3A,* and the rs56695217, rs139292, rs139297, rs139302 and rs139316 SNPs of *A3H,* had no relationship with CHB progression or HCC development; and ii) the rs2267398, rs2267401 and rs2076109 SNPs of *A3B* may not affect the likelihood of CHB progression or HCC development. However, the C-T-A, C-T-G, T-G-G and T-T-G haplotypes of rs2267398-rs2267401-rs2076109 were associated with a lower risk of HCC development than the reference haplotype C-G-G.

APOBEC cytosine deaminases are known to confer innate immunity against retroviruses by generating lethal hypermutations in viral genomes (33). Köck and Blum (31) assessed the ability of *A3G*, *A3C* and *A3H* to edit HBV genomes, finding that each gene could edit HBV DNA and that each protein was likely to contribute (to varying degrees) to genome modification in human liver cells. Previously, it was demonstrated that

Table V. Genotype and allele frequencies of five SNPs of APOBEC3H.

A, Rs56695217 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=89			n=235			n=241		
CC	11 (12.4)	1		29 (12.3)			26 (10.8)		
CG	76 (85.4)	1.03 (0.49,2.17)	0.94	203 (86.4)	1.26 (0.71,2.25)	0.43	214 (88.8)	1.17 (0.54,2.56)	0.69
GG	2 (2.2)	0.60 (0.09,4.13)	0.60	3 (1.3)	0.34 (0.03,3.64)	0.36	1 (0.4)	0.11 (0.01,1.37)	0.08
CG+GG	78	1.02 (0.48,2.15)	0.96	206	1.25 (0.70,2.22)	0.45	215	1.14 (0.53,2.47)	0.74
C Allele	98 (55.1)	1		261 (55.5)	1		266 (55.2)	1	
G Allele	80 (44.9)	0.98 (0.69,1.39)	0.91	209 (44.5)	0.99 (0.76,1.27)	0.92	216 (44.8)	1.00 (0.71,1.42)	0.98

B, Rs139292 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=95			n=247			n=250		
DEL	42 (44.2)	1		111 (44.9)	1		112 (44.8)	1	
CAA.DEL	53 (55.8)	0.97 (0.60,1.57)	0.90	134 (54.3)	1.04 (0.72,1.49)	0.84	137 (54.8)	1.03 (0.91,0.63)	0.91
CAA	0 (0.0)	0.73 (0.66,0.80)	1.00	2 (0.8)	0.50 (0.60,7.09)	0.68	1 (0.4)	0.73 (0.66,0.80)	1.00
DEL+CAA	53	0.99 (0.61,1.60)	0.95	136	1.03 (0.72,1.48)	0.86	138	1.03 (0.63,1.69)	0.89
DEL Allele	137 (72.1)	1		356 (72.1)	1		361 (72.2)	1	
CAA Allele	53 (27.9)	0.69 (1.00,1.46)	1.00	138 (27.9)	0.99 (0.75,1.31)	1.00	139 (27.8)	0.99 (0.69,1.45)	1.00

C, Rs139297 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=102			n=263			n=280		
CC	41 (40.2)	1		115 (43.7)	1		118 (42.1)	1	
CG	16 (15.7)	0.84 (0.42,1.68)	0.63	38 (14.4)	0.95 (056,1.62)	0.85	36 (12.9)	0.85 (0.42,1.72)	0.65
GG	45 (44.1)	0.87 (0.52,1.44)	0.58	110 (41.8)	1.78 (0.81,1.70)	0.39	126 (45.0)	1.07 (0.64,1.79)	0.79
CG+GG	61	0.86 (0.54,1.38)	0.53	143	1.12 (0.79,1.58)	0.53	174	1.01 (0.63,1.63)	0.97
C Allele	98 (49.4)	1		268 (49.8)			272 (77.0)	1	
G Allele	106 (50.6)	0.89 (0.64,1.23)	0.48	258 (50.2)	1.15 (0.89,1.48)	0.28	288 (23.0)	0.98 (0.71,1.35)	0.90

Table V. Continued.

D, Rs139302 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=89			n=229			n=255		
CC	34 (38.2)	1		86 (37.6)	1		81 (31.8)	1	
CG	20 (22.5)	1.1 (0.57,2.11)	0.79	56 (24.5)	1.38 (0.86,2.20)	0.18	74 (29.0)	1.53 (0.80,2.94)	0.20
GG	35 (39.3)	0.98 (0.55,1.72)	0.93	87 (30.8)	1.25 (0.82,1.91)	0.30	100 (39.2)	1.31 (0.73,2.33)	0.37
CG+GG	55	1.02 (0.61,1.70)	0.94	143	1.30 (0.89,1.90)	0.18	174	1.39 (0.83,2.24)	0.21
C Allele	88 (49.4)	1		228 (49.8)	1		236 (46.3)	1	
G Allele	90 (50.6)	0.99 (0.70,1.40)	0.94	230 (50.2)	0.87 (0.68,1.12)	0.28	274 (53.7)	0.88 (0.63,1.24)	0.47

E, Rs139316 genotype and allele

	CHB patients (n=104)			LC patients (n=265)			HCC patients (n=287)		
SNP	N (%)	OR (95%Cl)	P-value[a]	N (%)	OR (95%Cl)	P-value[b]	N (%)	OR (95%Cl)	P-value[c]
Number detected	n=103			n=263			n=281		
CC	17 (16.5)	1		43 (16.3)	1		37 (13.2)	1	
CT	46 (44.7)	1.02 (0.52,1.97)	0.96	117 (44.5)	0.26 (0.75,2.10)	0.39	133 (47.3)	1.36 (0.69,2.69)	0.38
TT	40 (38.8)	1.01 (0.51,2.00)	0.97	103 (39.2)	1.24 (0.73,2.10)	0.42	111 (39.5)	1.40 (0.69,2.77)	0.37
CT+TT	86	1.01 (0.54,1.89)	0.97	220	1.25 (0.77,2.03)	0.37	244	1.37 (0.72,2.60)	0.34
C Allele	80 (38.3)	1		203 (38.6)	1		207 (36.8)	1	
T Allele	126 (61.2)	1.01 (0.73,1.41)	0.95	323 (61.4)	0.93 (0.73,1.86)	0.55	355 (63.2)	1.09 (0.78,1.51)	0.61

The two-sided χ^2 test or Fisher's exact test was used in the comparison of allele distributions. [a]CHB vs. LC; [b]LC vs. HCC; [c]CHB vs. HCC, adjusted for age, gender, smoking and alcohol consumption by logistic regression analysis. APOBEC3, apolipoprotein B mRNA-editing catalytic polypeptide-like 3; SNPs, single nucleotide polymorphisms; CHB, chronic hepatitis B; LC, liver cirrhosis; HCC, hepatocellular carcinoma; OR, odds ratio; CI, confidence intervals.

Table VI. Distributions of SNPs of apolipoprotein B mRNA-editing catalytic polypeptide-like 3B in the different groups.

Groups	SNPs	χ^2	df	P-value
CHB vs. LC	rs2267398-rs2267401	3.87	3	0.276
	rs2267398-rs2076109	5.25	3	0.153
	rs2267401-rs2076109	2.51	3	0.472
	rs2267398-rs226740-rs2076109	7.33	6	0.291
CHB vs. HCC	rs2267398-rs2267401	1.01	3	0.798
	rs2267398-rs2076109	0.149	3	0.985
	rs2267401-rs2076109	0.405	3	0.939
	rs2267398-rs2267401-rs2076109	1.764	6	0.940
LC vs. HCC	rs2267398-rs2267401	8.210	3	0.042
	rs2267398-rs2076109	1.368	3	0.713
	rs2267401-rs2076109	3.278	3	0.351
	rs2267398-rs2267401-rs2076109	14.25	6	0.027

CHB, chronic hepatitis B; LC, liver cirrhosis; HCC, hepatocellular carcinoma; SNP, single nucleotide polymorphism.

Table VII. Analysis of the rs2267398-rs2267401-rs2076109 haplotypes of apolipoprotein B mRNA-editing catalytic polypeptide-like 3B in patients with LC and HCC.

Haplotype	LC (%)	HCC (%)	OR (95%CI)	P-value
C-G-G	8 (1.1)	9 (5.6)	1	
C-T-A	254 (33.8)	56 (34.6)	0.19 (0.07, 0.53)	<0.001
C-T-G	191 (25.4)	35 (21.6)	0.16 (0.06, 0.45)	<0.001
T-G-A	2 (0.3)	0 (0.0)	0.47 (0.28,0.78)	0.474
T-G-G	246 (32.7)	50 (30.9)	0.18 (0.07, 0.49)	<0.001
T-T-A	25 (3.3)	10 (6.2)	0.36 (0.11,1.18)	0.087
T-T-G	26 (3.5)	2 (1.2)	0.07 (0.01, 0.38)	0.001

CHB, hepatitis B virus; LC, liver cirrhosis; HCC, hepatocellular carcinoma; OR, odds ratio; CI, confidence intervals.

the *A3G* rs8177832 SNP was associated with a decreased risk of CHB infection and HCC, while the rs2011861 SNP was associated with an increased risk of HCC (23). Furthermore, it has been shown that *A3A* is an efficient HBV DNA editor, while *A3A* and *A3B* serve crucial roles in inducing the degradation of HBV covalently closed circular DNA (34). Therefore, it was speculated that these three genes may be associated with disease progression following HBV infection.

The present study analyzed the association between *A3A*, *A3B* and *A3H* SNPs and the progression of HBV infection. A total of 654 patients were included in the study, consisting of 104 patients with CHB, 265 patients with HBV-related LC and 285 patients with HBV-related HCC. However, the results demonstrated that the SNPs of these three genes were not associated with disease progression following HBV infection. Haplotype analysis suggested that the C-T-A, C-T-G, T-G-G and T-T-G haplotypes of rs2267398-rs2267401-rs2076109 were associated with a lower risk of HCC compared with the reference haplotype C-G-G. It was hypothesized that this may be due to the linkage between different functional genes. Previous studies have shown that APOBEC-specific mutations are common in tumor genomes (35,36) and that the expression level of APOBEC mRNA is positively correlated with the APOBEC-specific mutation rate (37). *In vitro*, *A3B* has been shown to promote the proliferation of the hepatoma cell line HepG2 by upregulating the expression of heat shock protein 1 (38). Therefore, *A3B* may be the predominant APOBEC-specific mutation-inducing gene in the development of primary liver cancer. Notably, clinical data have demonstrated that the deletion of ~29.5 kb between *A3A* exon 5 and *A3B* exon 8 causes the loss of the entire *A3B* coding region and increases the risk of HCC (39,40). Furthermore, genome sequencing has revealed that *A3B* deletion can increase the APOBEC-specific mutation rate in the tumor genome (38). Consequently, it has been hypothesized that *A3B* gene deletion may cause the expression of A3AΔA3B (A3A after A3B deletion) to be more stable and efficient (41,42) and that A3AΔA3B may be the predominant mutagenic factor. Therefore, haplotype changes may affect HCC occurrence by altering the gene expression and editing the functions of A3A and A3B. However, the exact mechanisms by which this occurs requires further investigation.

The present study had a number of limitations. First, healthy controls were not enrolled in this study to evaluate the effect of the *A3A*, *A3B* and *A3H* SNPs on susceptibility to HBV infection. Second, some disease factors were not considered in the present study, such as the age at which HBV infection occurred, which is closely associated with the outcome of HBV infection (43). However, exact HBV infection age data are not available from most places in China due to socioeconomic factors. According to previous studies, ~90% of infants infected perinatally become chronic carriers, unless vaccinated at birth. The risk of CHB decreases to 30% in children infected between ages 1 and 4 years, and to <5% in persons infected as adults (44-46). Therefore, most patients with CHB infection are likely to have been infected in infancy. Since it was not possible to acquire the exact infection age, the present study assumed the age of patients as the length of infection. Therefore, age-matched patients with CHB, HBV-related LC and HBV-related HCC were recruited. Third, the associations were analyzed solely by statistical analysis and were not validated experimentally. Therefore, further studies using larger sample sizes from different populations alongside experimental validation should be conducted to verify the results of the present study.

In conclusion, the present study demonstrated that there was no association between the rs7286317 and rs7290153 SNPs of *A3A*, the rs2267398, rs2267401 and rs2076109 SNPs of *A3B,* and the rs56695217, rs139292, rs139297, rs139302 and rs139316 SNPs of *A3H* and CHB progression or HCC development. However, the C-T-A, C-T-G, T-G-G and T-T-G haplotypes of rs2267398-rs2267401-rs2076109 were associated with a lower risk of HCC than the reference haplotype C-G-G.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XH, JN and PG conceived and designed the study. XH, HX and XW acquired the data. HX and JN analyzed and interpreted the data. JW performed the statistical analysis. XH drafted the manuscript. JN and PG revised the manuscript for important intellectual content. All authors given final approval of the version to be published.

Ethics approval and consent to participate

The present study was approved by the First Hospital Ethical Committee of Jilin University. Written informed consent was obtained from all participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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