Abstract. The present study examined the relationships between the single nucleotide polymorphisms (SNPs) of three members of the apolipoprotein B messenger RNA-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.

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 messenger RNA-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 populations.
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 (HBsAg), 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 under- went 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 χ2 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 | rs7263517  | F: 5'-ACGTTGGATGGATGGCATCAGGAGATCGAGACCAC-3' | 45.1                      |
|          | rs7290153  | R: 5'-ACGTTGGATGCCGCTGCTATTATTTTGG-3'   | 45.5                      |
| APOBEC3B | Rs2267398  | F: 5'-ACGTTGGATGTTCCTCTCTTTGGGTGTCG-3'  | 46.1                      |
|          | rs2267401  | R: 5'-ACGTTGGATGATGCGCTCCCTCTCTTCAAAC-3' | 52.4                      |
|          | rs2076109  | F: 5'-ACGTTGGATGAGAGGAAGGACATTTCGCG-3'  | 49.6                      |
| APOBEC3H | Rs56695217 | F: 5'-ACGTTGGATGCTGTGAAATTTGCCGACTCTC-3' | 47.0                      |
|          | Rs139292   | R: 5'-ACGTTGGATGAAACAAAGCCGAGAATGCG-3'  | 58.2                      |
|          | Rs139297   | F: 5'-ACGTTGGATGATGTACAGCTACTACTGAC-3'  | 48.9                      |
|          | Rs139302   | R: 5'-ACGTTGGATGCTCTCAACCTAAGTAC-3'     | 49.1                      |
|          | Rs139316   | F: 5'-ACGTTGGATGCCAGGGAAGTCCATCTTTGAG-3' | 46.7                      |
|          |            | R: 5'-ACGTTGGATGAGAGGATTTTGAGCTTGGAC-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<sup>a</sup> | LC n=265 | P-value<sup>b</sup> | HCC n=287 | P-value<sup>c</sup> | Reference ranges |
|--------------------------------------|-----------|----------------------|-----------|----------------------|-----------|----------------------|------------------|
| Sex (M/F)                            | 84/20     | 0.823                | 210/55    | 0.063                | 246/41    | 0.286                | -                |
| Age<sup>e</sup>                      | 47 (43.53)| 0.368                | 49 (41.56)| 0.901                | 50 (46.56)| 0.006                | -                |
| Smoking<sup>e</sup>                  | 0.862     | <0.001               |           | 144 (50.2)           | 143 (49.8)| 0.013                | -                |
| Have ever smoked                     | 37 (35.6)| <0.001               |           | 91 (34.3)            |           |                      | -                |
| Have never smoked                    | 67 (64.4)| <0.001               |           | 174 (65.7)           |           |                      | -                |
| Alcohol consumption<sup>e</sup>      | 0.142     | <0.001               |           | 120 (41.8)           |           |                      | -                |
| Have ever consumed alcohol           | 28 (26.9)| <0.001               |           | 76 (73.1)            |           |                      | -                |
| Have never consumed alcohol          | 67 (64.4)| <0.001               |           | 172 (64.9)           |           |                      | -                |
| Serum HBV-DNA<sup>e</sup>            | 0.002     | 0.004                |           | 0.107                |           |                      | -                |
| Positive                             | 98 (94.2)| <0.001               | 211 (79.6)| 254 (88.5)           |           |                      | 13.0-35.0        |
| Negative                             | 6 (5.8)  | <0.001               | 55 (20.4) | 33 (11.5)            |           |                      | 7.0-40.0         |
| HBV load, log10 (IU/ml)<sup>d</sup>  | 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<sup>e</sup>                    | 0.814     | 0.359                | 100 (42.2)| 0.295                |           |                      | -                |
| Positive                             | 43 (48.9)| <0.001               |           | 99 (46.7)            |           |                      | 13.0-35.0        |
| Negative                             | 45 (51.1)| <0.001               |           | 113 (53.3)           |           |                      | 7.0-40.0         |
| ALT (U/l)<sup>d</sup>                | 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)<sup>d</sup>                | 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)<sup>d</sup>                | 87 (67,122.8)| 0.724              | 89 (68,125.5)| <0.001               | 129.5 (86.0,195.0)| <0.001   | 50.0-135.0        |
| GGT (U/l)<sup>d</sup>                | 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)<sup>d</sup>         | 0.16 (0.13, 0.20)| <0.001            | 0.12 (0.09, 0.16)| 0.192                | 0.13 (0.08,17)| <0.001        | 0.18-0.39        |
| Albumin (g/l)<sup>d</sup>            | 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)<sup>d</sup> | 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)<sup>d</sup>     | 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<sup>7</sup>l)<sup>d</sup> | 145 (117, 188)| <0.001            | 77 (53,121)  | <0.001               | 118.5 (78.8,172.0)| <0.001   | 100-300          |

<sup>a</sup>CHB vs. LC; <sup>b</sup>LC vs. HCC; <sup>c</sup>CHB vs. HCC, calculated by analysis of variance and the least significant difference multiple comparisons test. <sup>d</sup>Data are expressed as the median (25, 75%). <sup>e</sup>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

| SNP     | CHB patients (n=104) | LC patients (n=265) | HCC patients (n=287) |
|---------|----------------------|---------------------|----------------------|
|         | N (%) | OR (95%CI) | P-value<sup>a</sup> | N (%) | OR (95%CI) | P-value<sup>b</sup> | N (%) | OR (95%CI) | P-value<sup>c</sup> |
| Number detected | n=102 |          |                      | n=265 |          |                      | n=285 |          |                      |
| AA      | 75 (73.5) | 1 | 0.95 (0.56,1.60) | 0.85 | 197 (74.3) | 1 | 200 (70.2) | 1 |
| AG      | 27 (26.5) | 68 (25.7) | 1.30 (0.89,1.91) | 0.18 | 68 (25.7) | 1.30 (0.89,1.91) | 0.18 | 85 (29.8) | 1.24 (0.74,2.08) | 0.42 |
| A allele | 177 (86.8) | 462 (87.2) | 0.84 (0.60,1.18) | 0.32 | 462 (87.2) | 0.84 (0.60,1.18) | 0.32 | 485 (85.1) | 0.87 (0.55,1.39) | 0.56 |
| G allele | 27 (13.2) | 68 (12.8) | 0.96 (0.60,1.56) | 0.88 | 68 (12.8) | 0.96 (0.60,1.56) | 0.88 | 85 (14.9) | 0.87 (0.55,1.39) | 0.56 |

### B, Rs7290153 genotype and allele

| SNP     | CHB patients (n=104) | LC patients (n=265) | HCC patients (n=287) |
|---------|----------------------|---------------------|----------------------|
|         | N (%) | OR (95%CI) | P-value<sup>a</sup> | N (%) | OR (95%CI) | P-value<sup>b</sup> | N (%) | OR (95%CI) | P-value<sup>c</sup> |
| Number detected | n=97 |          |                      | n=246 |          |                      | n=267 |          |                      |
| CC      | 78 (80.4) | 1 | 0.88 (0.44,1.75) | 0.72 | 198 (80.5) | 1 | 217 (81.3) | 1 |
| CT      | 14 (14.4) | 31 (12.6) | 0.83 (0.48,1.47) | 0.52 | 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) | 17 (6.9) | 1.02 (0.51,2.04) | 0.95 | 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 | 48 | 0.90 (0.57,1.41) | 0.65 | 48 | 0.90 (0.57,1.41) | 0.65 | 50 | 0.95 (0.52,1.73) | 0.86 |
| C allele | 170 (87.6) | 427 (86.8) | 1 | 1 | 427 (86.8) | 1 | 464 (86.9) | 1 |
| T allele | 24 (12.4) | 65 (13.2) | 1.01 (0.70,1.45) | 0.96 | 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 $\chi^2$ test or Fisher's exact test was used in the comparison of allele distributions. *CHB vs. LC; *LC vs. HCC; *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

| SNP     | CHB patients (n=104)      | LC patients (n=265)      | HCC patients (n=287)      |
|---------|---------------------------|--------------------------|----------------------------|
|         | N (%) OR (95%CI)          | N (%) OR (95%CI)         | N (%) OR (95%CI)           |
| 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) | 125 (48.8) 1.11 (0.75,1.63) | 135 (49.6) 0.85 (0.50,1.47) |
| TT      | 18 (18.8) 0.71 (0.35,1.44) | 41 (16.0) 1.15 (0.68,1.94) | 44 (16.2) 0.77 (0.38,1.56) |
| CT+TT   | 68 (70.8) 0.74 (0.44,1.24) | 166 (62.1) 1.12 (0.77,1.61) | 179 (62.2) 0.83 (0.50,1.39) |
| 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) | 207 (40.4) 0.98 (0.76,1.25) | 223 (41.0) 1.17 (0.84,1.63) |

B. Rs2267401 genotype and allele

| SNP     | CHB patients (n=104)      | LC patients (n=265)      | HCC patients (n=287)      |
|---------|---------------------------|--------------------------|----------------------------|
|         | N (%) OR (95%CI)          | N (%) OR (95%CI)         | N (%) OR (95%CI)           |
| 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) | 65 (24.5) 0.89 (0.53,1.46) | 61 (21.5) 0.88 (0.47,1.69) |
| TT      | 48 (47.1) 1.25 (0.70,2.22) | 142 (53.6) 1.00 (0.65,1.54) | 160 (56.3) 1.29 (0.72,2.29) |
| GT+TT   | 77 (75.1) 1.13 (0.66,1.93) | 207 (78.0) 0.97 (0.64,1.46) | 221 (78.2) 1.13 (0.66,1.93) |
| G Allele| 79 (38.7) 1               | 181 (38.2) 1             | 187 (37.9) 1               |
| T Allele| 125 (61.3) 1.22 (0.87,1.70) | 349 (63.8) 0.95 (0.74,1.22) | 381 (64.1) 1.00 (0.71,1.42) |
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, rs139302, 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 compared with 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

| SNP     | CHB patients (n=104)                  | LC patients (n=265)                  | HCC patients (n=287)                  |
|---------|---------------------------------------|-------------------------------------|---------------------------------------|
|         | N (%) or (95%CI) | P-value<sup>a</sup> | N (%) or (95%CI) | P-value<sup>b</sup> | N (%) or (95%CI) | P-value<sup>c</sup> |
| Number detected | n=89 |                       | n=235 |                       | n=241 |                       |
| CC      | 11 (12.4) |                       | 29 (12.3) |                       | 26 (10.8) |                       |
| CG      | 76 (85.4) | 1.03 (0.49,2.17) | 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) | 0.34 (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) | 1.25 (0.70,2.22) | 0.45 | 215 | 1.14 (0.53,2.47) | 0.74 |
| C Allele | 98 (55.1) |                       | 261 (55.5) |                       | 266 (55.2) |                       |
| G Allele | 80 (44.9) | 0.98 (0.69,1.39) | 0.99 (0.76,1.27) | 0.92 | 216 (44.8) | 1.00 (0.71,1.42) | 0.98 |

B, Rs139292 genotype and allele

| SNP     | CHB patients (n=104)                  | LC patients (n=265)                  | HCC patients (n=287)                  |
|---------|---------------------------------------|-------------------------------------|---------------------------------------|
|         | N (%) or (95%CI) | P-value<sup>a</sup> | N (%) or (95%CI) | P-value<sup>b</sup> | N (%) or (95%CI) | P-value<sup>c</sup> |
| Number detected | n=95 |                       | n=247 |                       | n=250 |                       |
| DEL     | 42 (44.2) |                       | 111 (44.9) |                       | 112 (44.8) |                       |
| CAA,DEL | 53 (55.8) | 0.97 (0.60,1.57) | 1.04 (0.72,1.49) | 0.84 | 137 (54.8) | 1.03 (0.91,1.63) | 0.91 |
| CAA     | 0 (0.0) | 0.73 (0.66,0.80) | 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) | 1.03 (0.72,1.48) | 0.86 | 138 | 1.03 (0.63,1.69) | 0.89 |
| DEL Allele | 137 (72.1) |                       | 136 |                       | 138 |                       |
| CAAAllele | 53 (27.9) | 0.69 (1.00,1.46) | 0.99 (0.75,1.31) | 1.00 | 139 (27.8) | 0.99 (0.69,1.45) | 1.00 |

C, Rs139297 genotype and allele

| SNP     | CHB patients (n=104)                  | LC patients (n=265)                  | HCC patients (n=287)                  |
|---------|---------------------------------------|-------------------------------------|---------------------------------------|
|         | N (%) or (95%CI) | P-value<sup>a</sup> | N (%) or (95%CI) | P-value<sup>b</sup> | N (%) or (95%CI) | P-value<sup>c</sup> |
| Number detected | n=102 |                       | n=263 |                       | n=280 |                       |
| CC      | 41 (40.2) |                       | 115 (43.7) |                       | 118 (42.1) |                       |
| CG      | 16 (15.7) | 0.84 (0.42,1.68) | 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) | 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) | 1.12 (0.79,1.58) | 0.53 | 174 | 1.01 (0.63,1.63) | 0.97 |
| C Allele | 98 (49.4) |                       | 268 (49.8) |                       | 272 (77.0) |                       |
| G Allele | 106 (50.6) | 0.89 (0.64,1.23) | 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

| SNP     | CHB patients (n=104) | LC patients (n=265) | HCC patients (n=287) |
|---------|----------------------|---------------------|----------------------|
|         | N (%) | OR (95%CI) | P-valuea | N (%) | OR (95%CI) | P-valueb | N (%) | OR (95%CI) | P-valuec |
| 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

| SNP     | CHB patients (n=104) | LC patients (n=265) | HCC patients (n=287) |
|---------|----------------------|---------------------|----------------------|
|         | N (%) | OR (95%CI) | P-valuea | N (%) | OR (95%CI) | P-valueb | N (%) | OR (95%CI) | P-valuec |
| 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 χ² test or Fisher’s exact test was used in the comparison of allele distributions. *CHB vs. LC; †LC vs. HCC; ‡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.
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.

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

| Groups          | SNPs                                      | $\chi^2$ | 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          | <0.001  |
| 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 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, rs39292, rs39297, rs39302 and rs39316 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 JN 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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