

Supplementary Table 1. Primers and probes for the genotyping of *HLA* class II genes genetic polymorphisms and PCR program

Genetic polymorphism	Primers and probes	Sequence (5' to 3')	PCR program
rs3135338 (T>C)	Forward Primer	TCCAGTCTATCGTATTTGCTTATCG	Step 1 95°C for 1 min Step 2 45 cycles of 95°C for 10 sec and 60°C for 30 sec Step 3 40°C for 10 sec.
	Reverse Primer	ATTACAAACATCACCACCAACACC	
	Probe 1	FAM-ACGTCGTAATAAACC-MGB	
	Probe 2	HEX-ACGTCGTAACAAACC-MGB	
rs477515 (C>T)	Forward Primer	CAAGCTAATTAATATATCTATCACC	
	Reverse Primer	AGGAAGACATTAGTCAAAGAGTA	
	Probe 1	FAM-TTCCTCCTGTCTGTCT-MGB	
	Probe 2	HEX-TTCCTTCTGTCTGTCTG-MGB	
rs2856718 (A>G)	Forward Primer	TTATGGTGCAGAATTTCTACCTGTG	
	Reverse Primer	GAGCTCCCTCTGGCAGGTTA	
	Probe 1	FAM-CATGGGATTAGACAGC-MGB	
	Probe 2	HEX-ATGGGATTAAACAGCTC-MGB	
rs9275319 (A>G)	Forward Primer	CACCCTTCATTTTTCTCCCTT	
	Reverse Primer	TGACAGTGCAGCCTTCAGTCT	
	Probe 1	FAM-CTCTGAGACCTTC-MGB	
	Probe 2	HEX-TCTGGGACCTTC-MGB	
rs3077 (C>T)	Forward Primer	TCAGCTTTTCTTCTCACTTCATGTG	
	Reverse Primer	TTGAGGTAATGGATAAGGACAGAGC	
	Probe 1	FAM-AAACTACCCAGTGGC-MGB	
	Probe 2	HEX-AAACTACTCCAGTG GCT-MGB	
rs9277535 (G>A)	Forward Primer	CAATGGTGAGCAGACTGCAAATC	
	Reverse Primer	AATGATAAAACATGCTCTCAGTAAGGTATATG	
	Probe 1	FAM-CCTGATAGGACCCGATTCCCACAGC-TAMRA	
	Probe 2	HEX-CCTGATAGGACCCATATTCCCACAGCA-TAMRA	

FAM, 6-carboxyfluorescein; HEX, 6-hexachloro-fluorescein; TAMRA, 6-carboxytetramethylrhodamine; MGB, minor groove binder; HLA, human leukocyte antigen.

Supplementary Table 2. Associations of *HLA* class II genes haplotypes with the risk of HCC compared to health control and HBV clearance subjects, respectively

Genotype	Haplotype	Health Controls (%)	HBV natural clearance subjects (%)	HBV-HCC (%)	HBV- HCC versus Health Controls		HBV- HCC versus HBV natural clearance subjects	
					AOR (95% CI)	<i>P</i> value	AOR (95% CI)	<i>P</i> value
Subtotal	TCAACG	18.35	22.34	27.60	1		1	
	CCAACG	3.98	2.72	3.02	0.55(0.35-0.86)	<0.01	1.34(0.51-3.56)	0.54
	CCGACG	3.04	5.73	3.44	0.69(0.44-1.09)	0.09	0.52(0.29-0.95)	0.04
	TCAACA	5.92	4.86	5.98	0.74(0.53-1.04)	0.07	1.19(0.62-2.26)	0.61
	TCAATA	7.54	7.04	6.93	0.65(0.47-0.88)	0.02	0.93(0.53-1.63)	0.84
	TCGACG	7.51	7.49	10.13	0.97(0.71-1.34)	0.83	1.55(0.86-2.81)	0.12
	TCGATA	7.42	6.20	6.21	0.57(0.42-0.78)	<0.01	0.86(0.51-1.43)	0.62
	TTAACG	4.82	6.18	4.03	0.72(0.49-1.05)	0.23	1.00(0.50-1.99)	0.45
Genotype B	TCAACG	18.35	22.34	33.14	1		1	
	CCAACG	3.98	2.72	5.45	0.77(0.34-1.78)	0.54	1.89(0.58-6.13)	0.30
	CCGACG	3.04	5.73	5.62	0.87(0.35-2.15)	0.77	0.52(0.17-1.58)	0.28
	TCAACA	5.92	4.86	1.85	0.33(0.11-0.94)	0.04	0.44(0.16-1.25)	0.16
	TCAATA	7.54	7.04	4.90	0.35(0.15-0.84)	0.02	0.36(0.13-1.02)	0.07
	TCGACG	7.51	7.49	9.94	1.01(0.54-1.89)	0.98	1.66(0.72-3.82)	0.32
	TCGATA	7.42	6.20	3.38	0.33(0.14-0.78)	0.01	0.42(0.14-1.20)	0.07
	TTAACG	4.82	6.18	0.86	0.18(0.04-0.79)	0.03	0.35(0.07-1.63)	0.22
Genotype C	TCAACG	18.35	22.34	27.86	1		1	
	CCAACG	3.98	2.72	3.45	0.59(0.35-0.98)	0.04	1.59(0.58-4.34)	0.37

CCGACG	3.04	5.73	3.01	0.63(0.37-1.08)	0.09	0.48(0.25-0.94)	0.03
TCAACA	5.92	4.86	5.20	0.67(0.43-1.03)	0.06	1.19(0.58-2.44)	0.64
TCAATA	7.54	7.04	7.18	0.68(0.47-0.99)	0.05	0.98(0.53-1.81)	0.95
TCGACG	7.51	7.49	10.02	0.95(0.66-1.36)	0.78	1.70(0.90-3.22)	0.10
TCGATA	7.42	6.20	5.88	0.49(0.33-0.73)	<0.01	0.69(0.38-1.26)	0.23
TTAACG	4.82	6.18	4.44	0.79(0.51-1.24)	0.49	0.79(0.42-1.51)	0.48

AOR, odds ratio adjusted for age and gender; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HLA, human leukocyte antigen.

Supplementary Table 3. Associations of *HLA* class II genes haplotypes with chronic HBV infection including HCC patients

Genotype	Haplotype	HBV natural clearance subjects (%)	HBV-infected subjects (%)	HBV-infected subjects versus HBV natural clearance subjects	
				AOR (95% CI)	<i>P</i> value
Subtotal	TCAACG	22.34	25.61	1	
	CCAACG	2.72	3.91	1.79(0.74-4.30)	0.20
	CCGACG	5.73	3.36	0.60(0.36-0.99)	0.04
	TCAACA	4.86	5.62	1.42(0.78-2.61)	0.24
	TCAATA	7.04	6.78	0.93(0.56-1.54)	0.77
	TCGACG	7.49	9.67	1.35(0.80-2.27)	0.27
	TCGATA	6.20	6.05	0.92(0.58-1.46)	0.70
	TTAACG	6.18	4.77	1.01(0.58-1.74)	0.92
Genotype B	TCAACG	22.34	27.47	1	
	CCAACG	2.72	7.22	2.77(0.98-7.10)	0.05
	CCGACG	5.73	3.21	0.50(0.22-1.12)	0.09
	TCAACA	4.86	6.30	1.45(0.73-2.91)	0.26
	TCAATA	7.04	4.71	0.65(0.31-1.36)	0.24
	TCGACG	7.49	10.05	1.49(0.75-2.97)	0.28
	TCGATA	6.20	6.79	0.83(0.43-1.60)	0.59
	TTAACG	6.18	4.21	0.95(0.45-2.00)	0.99
Genotype C	TCAACG	22.34	23.32	1	
	CCAACG	2.72	3.60	1.82(0.71-4.66)	0.21
	CCGACG	5.73	3.33	0.66(0.38-1.14)	0.14
	TCAACA	4.86	4.51	1.35(0.69-2.62)	0.38

TCAATA	7.04	7.28	1.06(0.62-1.83)	0.82
TCGACG	7.49	9.79	1.45(0.83-2.53)	0.19
TCGATA	6.20	5.75	0.87(0.53-1.45)	0.60
TTAACG	6.18	5.16	0.93(0.54-1.62)	0.81

AOR, odds ratio adjusted for age and gender; CI, confidence interval; HBV, hepatitis B virus; HLA, human leukocyte antigen.

Supplementary Table 4. The HBV mutations significantly associated with the risk of HBV-HCC compared with HCC-free HBV infected subjects.

HBV mutations	Genotype C HBV-infected subjects		Genotype B HBV-infected subjects	
	AOR (95%CI)	<i>P</i>	AOR (95%CI)	<i>P</i>
core promoter region				
APOBEC-signature mutations in the core promoter region (<2 vs ≥2)	2.61(2.04-3.33)	4.22×10 ⁻¹⁴	NS	NS
C1653T	2.28(1.63-3.21)	1.83×10 ⁻⁶	NS	NS
T1674C	1.67(1.17-2.38)	4.88×10 ⁻³	NS	NS
T1753C	2.68(1.89-3.84)	5.03×10 ⁻⁸	NS	NS
A1762T	4.20(3.07-5.80)	8.46×10 ⁻¹⁹	2.16(1.25-3.76)	5.66×10 ⁻³
G1764A	3.92(2.84-5.46)	2.93×10 ⁻¹⁶	1.99(1.16-3.45)	1.31×10 ⁻²
A1762T/G1764A	3.99(2.92-5.47)	5.18×10 ⁻¹⁸	2.30(1.33-4.01)	2.98×10 ⁻³
A1846T	1.36(1.00-1.86)	4.91×10 ⁻²	NS	NS
preS region				
APOBEC-signature mutations in the preS region (<3 vs ≥3)	1.87(1.33-2.64)	3.54×10 ⁻⁴	NS	NS
C6A	2.15(1.38-3.44)	9.82×10 ⁻⁴	NS	NS
C9A	6.98(3.44-16.17)	6.03×10 ⁻⁷	2.72(1.13-6.34)	3.12×10 ⁻²
A30T	16.61(6.55-56.17)	1.47×10 ⁻⁷	2.51(1.40-4.31)	1.60×10 ⁻³

T48A	6.05(2.97-14.05)	4.25×10^{-6}	33.96(5.00-704.87)	2.33×10^{-3}
A51T	13.48(5.29-45.68)	1.21×10^{-6}	NS	NS
T53C	2.15(1.19-3.91)	1.14×10^{-2}	8.69(2.39-36.19)	1.54×10^{-3}
C75A	8.22(2.71-35.68)	9.20×10^{-4}	2.60(1.31-5.40)	7.57×10^{-3}
G104C	3.91(2.82-5.42)	6.14×10^{-17}	18.51(5.82-70.43)	3.42×10^{-6}
C108T	16.48(6.79-46.92)	8.30×10^{-9}	28.94(5.79-526.85)	1.20×10^{-3}
A134C	21.45(7.78-88.85)	3.19×10^{-7}	2.92(1.70-5.11)	1.22×10^{-4}
G146C	3.61(2.60-4.90)	3.13×10^{-15}	3.41(1.51-7.70)	2.83×10^{-3}
A3215C	17.01(6.86-56.76)	6.76×10^{-8}	2.71(1.61-4.80)	4.71×10^{-14}
PreS1 deletion	2.08(1.33-3.29)	1.56×10^{-3}	NS	NS
PreS2 deletion	1.42(0.96-2.11)	8.45×10^{-2}	NS	NS
PreS deletion	2.35(1.71-3.26)	4.27×10^{-4}	NS	NS

AOR, odds ratio adjusted for age and gender; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma. NS, not statistically significant.

Supplementary Table 5. The HBV mutations significantly associated with the risk of LC, compared with ASCs and CHB

HBV mutations	Genotype C HBV-infected subjects		Genotype B HBV-infected subjects	
	AOR (95%CI)	<i>P</i>	AOR (95%CI)	<i>P</i>
core promoter region				
APOBECs signature mutants in core promoter region (<2 vs ≥2)	2.04(1.31-3.16)	1.48×10 ⁻³	7.51(1.67-53.23)	1.66×10 ⁻²
C1653T	1.70(1.01-2.85)	4.35×10 ⁻²	NS	NS
A1726C	2.63(1.53-4.51)	4.20×10 ⁻⁴	NS	NS
T1674C/G	0.49(0.30-0.80)	5.01×10 ⁻³	NS	NS
T1753C	1.80(1.08-3.00)	2.37×10 ⁻²	6.90(1.64-35.45)	1.09×10 ⁻²
A1762T	4.70(3.06-7.33)	3.44×10 ⁻¹²	2.46(1.14-5.33)	2.14×10 ⁻²
G1764A	14.19(8.14-26.4)	6.00×10 ⁻¹⁹	6.23(2.78-14.77)	1.58×10 ⁻⁵
C1766T	4.44(2.08-9.80)	1.44×10 ⁻⁴	7.51(1.67-53.23)	1.66×10 ⁻²
A1762T/G1764A	4.84(3.14-7.56)	1.83×10 ⁻¹²	2.45(1.13-5.33)	2.30×10 ⁻²
T1768A	19.79(6.46-86.58)	3.12×10 ⁻⁶	29.18(4.62-575.67)	2.55×10 ⁻³
G1809A	10.77(1.33-221.85)	4.26×10 ⁻²	NS	NS
preS region				
APOBECs signature mutants in preS region (<3 vs ≥3)	5.02(2.90-8.77)	1.03×10 ⁻⁸	7.06(2.89-18.81)	3.60×10 ⁻⁵

C6A	13.93(4.99-58.11)	1.33×10^{-5}	18.10(5.89-64.44)	1.48×10^{-6}
C9A	19.72(5.93-122.37)	4.75×10^{-5}	NS	NS
T48A	39.23(8.36-700.52)	3.16×10^{-4}	NS	NS
A51C/T	18.31(5.50-113.70)	7.37×10^{-5}	NS	NS
C75A	0.50(0.26-0.90)	2.74×10^{-2}	NS	NS
T2857C	3.95(1.69-9.94)	2.15×10^{-3}	NS	NS
A3215C	22.23(6.70-137.87)	2.30×10^{-5}	24.89(4.66-464.31)	2.50×10^{-3}
PreS1 deletion	2.12(1.19-3.75)	9.87×10^{-3}	4.29(1.05-18.83)	4.17×10^{-2}
PreS2 deletion	2.07(1.10-3.81)	2.19×10^{-2}	NS	NS

AOR, odds ratio adjusted for age and gender; CI, confidence interval; ASCs, asymptomatic hepatitis B surface antigen carriers; CHB, chronic hepatitis B; LC, liver cirrhosis. NS, not statistically significant.

Supplementary Table 6. Significant associations of *HLA* class II genes haplotypes with the frequencies of LC-associated HBV mutations

Haplotype	LC-associated HBV mutation	AOR (95% CI)	<i>P</i> value
TCAACG		1.00	
CCGACG	T1674C/G	2.43(1.14-5.19)	0.02
TCGACG	C6A	2.33(1.20-4.54)	0.01
	C75A	0.16(0.05-0.49)	<0.01
	C1653T	2.25(1.17-4.31)	0.02
	C1766T	2.28(1.03-5.08)	0.04
TCGATA	T1674C/G	2.25(1.22-4.12)	0.01
TTAACG	T1674C/G	2.18(1.08-4.40)	0.03
	T48A	2.40(1.01-5.84)	0.04

AOR, odds ratio adjusted for age and gender; CI, confidence interval; HBV, hepatitis B virus; LC, liver cirrhosis; HLA, human leukocyte antigen.