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Original Article

Association between APOBEC3B deletion polymorphism and susceptibility to chronic hepatitis B infection and outcomes of hepatocellular carcinoma in Chinese Han population

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Abstract: Aim: To investigate the association of Apolipoprotein B MRNA Editing Enzyme, Catalytic Polypeptide-Like 3B (APOBEC3B, A3B) deletion with susceptibility to chronic Hepatitis B Virus (HBV) infection and occurrence, prognosis of HCC in Chinese population. Methods: In this retrospective case-control study, a total of 654 patients with chronic HBV infection and 249 healthy controls were recruited. All subjects were ethnic Han Chinese. The patients included 104 chronic hepatitis B (CHB), 263 liver cirrhosis (LC) and 287 hepatocellular carcinoma (HCC). The APOBEC3B (A3B) intact (I) and deletion (D) alleles were genotyped using polymerase chain reaction (PCR) method. Totally 243 HCC patients was followed-up and their clinicopathologic characteristics was collected. Results: Compared with the II genotype, the DD genotype was significantly related to a increased risk of HCC after adjusting for age, sex, smoking, and drinking (OR=1.95, 95% CI: 1.03-3.69). No significant association between A3B deletion and chronic HBV infection (*P*=0.121, after adjusted by age, sex, smoking and drinking). No significant differences were found in the frequencies of genotype and alleles of A3B deletion among HBV infection patients (patients with hepatitis B, patients with HBV-related cirrhosis, and HBV-related HCC). No significant differences were found between the overall survival of the A3B deletion genotype. Conclusion: Our study provides epidemiological evidence that the A3B deletion homozygosity mediate occurrence of HBV-related HCC *in vivo*.

Keywords: APOBEC3B, polymorphism, susceptibility, chronic hepatitis B infection, hepatocellular carcinoma

Introduction

The apolipoprotein B MRNA editing enzyme, catalytic polypeptide (APOBEC) family of proteins comprises a group of cytidine deaminases that are able to edit DNA and/or RNA sequences [1, 2]. The members of this family are distinguished by the presence of one or two zinc-dependent cytidine deaminase active sites, characterized by the conserved amino acid sequences H-X-E-X(23-28)-P-C-X(2-4)-C (X is any amino acid) [3, 4]. The deamination mediated by these enzymes involves the hydrolytic removal of the amino group at the C4 position of a cytidine (C) or deoxycytidine (dC), generating a uridine (U) or deoxyuridine (dU) [2, 3]. Uracils in DNA (including cccDNA) are recognized and excised by cellular uracil DNA glycosylases (UNG) leading to DNA digestion [5-8]. The family of genes encoding seven APOBEC3 proteins (APOBEC3A, B, C, D, E, F, G, and H) is positioned in a tandem array on human chromosome 22 [4]. APOBEC3B (A3B) is one member of the large family with diverse physiological functions in innate and adaptive immunity, lipid metabolism, and heart development [9, 10].

Among the APOBEC3 family, A3A and A3 are capable of nuclear localization and may be able to directly gain access to cccDNA and human genome [5]. Activities of A3A and A3B could be induced by interferon-α or LTβR-agonist and were essential to induce cccDNA degradation [5]. The molecular mechanisms underlying A3B-mediated HBV restriction (including cccDNA) are primarily dependent on the editing, but

non-editing activities also plays a role [11, 12]. A 29.5-kb deletion occurs between exon 5 in A3A and exon 8 in an A3B gene cluster leading to the complete removal of the A3B coding region [13, 14]. This deletion has been suggested to be associated with increased risk of diseases and conditions, including human immunodeficiency virus-1 (HIV-1) infection and its progression to acquired immune deficiency syndrome (AIDS) [15] and autism [16]. Recently, this deletion has been reported to be associated with falciparum malaria [17], susceptibility to breast cancer [18, 19] and ovarian cancer [20].

Since A3B is an important host factor that may confer an intrinsic block to Hepatitis B Virus (HBV) and play an important role in the tumorigenesis [21, 22]. However, the association of A3B with HBV-related diseases and course and outcome of hepatocellular carcinoma (HCC) is not clear. Thus, this study was conducted to verify the association of A3B deletion with susceptibility to chronic HBV infection and HBV-related chronic hepatitis B (CHB), liver cirrhosis (LC) and HCC in a Chinese population. We further investigated the influence of A3B deletion and occurrence on outcomes of HCC. We anticipate the results will contribute to the development in prevention of HCC.

Subjects and methods

Study subjects

A total of 654 patients with chronic HBV infection and 249 healthy controls were recruited from the First Hospital of Jilin University (Changchun, China). All the patients were ethnic Han Chinese. The patients were diagnosed as CHB (n=104), LC (n=263) and HCC (n=287) according to the guideline for the prevention and treatment of CHB (2010 version) and the diagnostic criteria (modified during the 10th National Conference on Viral Hepatitis and Hepatopathy 2000, China). The patients were frequency matched among each group patients on age and sex. Chronic hepatitis B infection was defined by persistent or intermittent elevation in alanine-transaminase (ALT) level (≥ 2xUTL) with elevated HBV-DNA (≥500 IU/ML) level for at least 6 months and were tested to be negative for markers of hepatitis C virus (HCV) and HIV. CHB/LC patients were characterized by active necroinflammatory liver disease without/with fibrosis on imaging examination. The diagnosis of HCC was all confirmed by histopathology. Exclusion criteria included the presence of autoimmune diseases and other liver diseases, such as other hepatitis virus infection (HAV/HEV), alcoholic liver disease, silt hemorrhagic liver disease, autoimmune liver disease, and intra-and extrahepatic bile duct stones. Healthy controls were liver disease-free individuals selected from physical examination center in our hospital, who were negative for HBsAg, HBeAg, anti-HBc, anti-HCV. Serum HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc and HCV antibody were measured by chemiluminescence method (Roche E411, Switzerland). This study was approved by the Review Board of the First Hospital of Jilin University and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants for the publication of this report.

Genotype analysis

The A3B intact (I) and deletion (D) alleles were genotyped using a previously reported polymerase chain reaction (PCR) method [23] with slight modifications. The Deletion and Insertion specific primers were designed as follows: Deletion_F: TAGGTGCCACCCCGAT; Deletion_R: TTGAGCATAATCTTACTCTTGTAC; Insertion1_F: TTGGTGCTGCCCCCTC; Insertion1_R: TAGAGACTGAGGCCCAT; and Insertion2_F: TGTCCCTTTTCAGAGTTTGAGTA; Insertion2_R: TGGAGCCAATTAATCACTTCAT. Deletion primers were specific to the deletion sequence configuration and generated a 700-bp PCR product upon amplification. Insertion1 and Insertion2 primers amplify only the insertion configuration and produce 490- and 705-bp products, respectively. Insertion and deletion PCR assays were performed separately. PCR was performed in 25 μl reactions composed of 1 μl of 10-μM dilution of the primers respectively, 12.5 μl of PCR SuperMix (Trans, Beijing), and 50-100 ng of DNA. The following cycling conditions were used: 2 min at 94°C, followed by 35 cycles at 94°C for 30 sec, 55°C for 30 sec, and 72°C for 1 min, followed by 5 min at 72°C. The products were pooled and visualized on a standard 1.0% agarose gel. Each individual was genotyped in replicate with the Deletion and Insertion1 primers to determine the genotype. In addition, each of the samples, which appeared to be

Table 1. Baseline characteristic of 956 study subjects

Groups	Healthy control	Chronic HBV patients					
	n=249	Non-HCC n=367	*P-value*[a]	HBV-related HCC n=287	*P-value*[b]	*P-value*[c]	*Total-P*
Gender (M/F)	208/41	292/75	0.216	246/41	0.484	0.652	0.108
Age (yrs)			0.246		0.531	0.690	0.147
<50	118 (47.4)	196 (53.4)		133 (46.3)			
≥50	131 (52.6)	171 (46.6)		154 (53.7)			
Smoking (%) (n)			0.551		*0.002*	0.219	*<0.001*
Ever	92 (36.9)	127 (34.6)		144 (50.2)			
Never	157 (63.1)	240 (65.4)		143 (19.8)			
Drinking (n) (%)			0.072		0.630	0.396	*0.040*
Ever	99 (39.8)	120 (32.7)		120 (41.8)			
Never	150 (60.2)	247 (67.3)		167 (41.8)			

P-value[a,b,c] represent the non-HCC, HCC, and chronic HBV patients compared with the healthy control group respectively. yrs, years; HBV, Hepatitis B Virus; HCC, hepatocellular carcinoma.

Table 2. Baseline characteristic of chronic HBV infection subgroups

	CHB (n=104)	*P-value*[a]	LC (n=263)	*P-value*[b]	HCC (n=287)	*P-value*[c]	*Total-P*
	n (%)		n (%)		n (%)		
Gender (M/F)	84/20		209/54		246/41		0.115
Age (yrs)							0.167
<50	62 (59.6)		134 (51.0)		133 (46.3)		
≥50	42 (40.4)		129 (49.0)		154 (53.7)		
Smoking (%) (n)		0.806		*0.000*		*0.011*	*0.000*
Ever	35.6 (37)		34.2 (90)		50.2 (144)		
Never	64.4 (67)		65.8 (173)		49.8 (143)		
Drinking (n) (%)		0.138		0.100		*0.007*	*0.020*
Ever	26.9 (28)		35.0 (92)		41.8 (120)		
Never	73.1 (76)		65.0 (171)		58.2 (167)		

CHB, chronic hepatitis B; LC, liver cirrhosis; HCC, hepatocellular carcinoma. *P-value*[a,b,c] represent the CHB *vs.* LC, LC *vs.* HCC, and CHB *vs.* HCC respectively.

homozygous for the deletion, was genotyped using a second set of oligonucleotides for the insertion (Insertion2) in order to prevent false negatives.

Assessment of treatment outcome

Further investigations were performed to evaluate the association between A3B deletion and the clinicopathologic characteristics of HCC patients. Among the 287 HCC patients, follow-up information of 243 people was received. The average follow-up time was 26.99±15.59 (month). Demographic and clinical characteristics of the included patients were obtained from the medical records. Overall survival (OS) was calculated between the first day of diagnosis and death or last known follow-up.

Statistical methods

The independent segregation of alleles was tested for the Hardy-Weinberg equilibrium (HWE). Statistical analysis was performed by SPSS software version 17.0 (SPSS, Chicago). The rank-sum test or χ^2 text was used to evaluate the differences in demographic and clinical data among the groups. For the association between genotype and allele with the disease, χ^2 test and logistic regression analysis was used to calculate the *p*-value, odds ratios (OR), and 95% confidence interval (CI) after adjusting for age, gender and environmental factors. For

Table 3. Genotype and allele frequencies of A3B deletion in each group

Genotype	Healthy control (n=249)	Hepatitis B patients															Total-*P*
		Non-HCC (n=367)						HBV-related HCC (n=287)									
	N (%)	N (%)	OR (95% CI)[a]	*P*-value[a]	*OR (95% CI)[a]	*P*-value[a]		N (%)	OR (95% CI)[b]	*P*-value[b]	*OR (95% CI)[b]	*P*-value[b]		OR (95% CI)[c]	*P*-value[c]	*OR (95% CI)[c]	*P*-value[c]	
II	113 (45.4)	158 (43.1)	1					122 (42.5)	1									
ID	119 (47.8)	178 (48.5)	1.3 (0.69-2.47)	0.693	1.04 (0.74-1.46)	0.845		130 (45.3)	1.01 (0.71-1.45)	0.948	1.04 (0.72-1.49)	0.837		1.05 (0.77-1.42)	0.779	1.04 (0.77-1.41)	0.802	0.909
DD	17 (6.8)	31 (8.4)	1.00 (0.58-1.71)	0.414	1.30 (0.68-2.48)	0.435		35 (12.2)	1.91 (1.01-3.59)	*0.044*	1.95 (1.03-3.69)	*0.041*		1.57 (0.88-2.79)	0.124	1.58 (0.89-2.83)	0.121	0.109
ID+DD	136	209	0.98 (0.58-1.65)	0.568	1.08 (0.78-1.20)	0.649		165	1.12 (0.80-1.58)	0.504	1.17 (0.82-1.65)	0.385		1.11 (0.83-1.49)	0.487	1.12 (0.83-1.50)	0.457	0.778
I Allele	345 (29.1)	494 (28.8)	1					374 (29.4)	1									
D Allele	153 (70.9)	240 (71.2)	1.10 (0.86-1.40)	0.466				200 (29.1)	1.21 (0.93-1.59)	0.152				1.14 (0.92-1.43)	0.238			
χ^{2*}	3.749	3.818						0.002										
P	0.0528	0.0507						0.9675										

*: HWE. I, intact; D, deletion. *P-value*[a,b,c] represent the non-HCC, HCC, and chronic HBV patients compared with the healthy control group respectively. The two-sided χ^2 test was used when compared with the control group.*Adjusted for age, smoking, and drinking when compared with the healthy controls by logistic regression analysis.

Table 4. Genotype and allele frequencies of A3B deletion in chronic HBV infection subgroups

Genotype	CHB (n=104)					LC (n=263)					HCC (n=287)					Total-*p*
	n (%)	OR (95% CI)[a]	*P*-value[a]	*OR (95% CI)[a]	*P*-value[a]	n (%)	OR (95% CI)[b]	*P*-value[b]	*OR (95% CI)[b]	*P*-value[b]	N (%)	OR (95% CI)[c]	*P*-value[c]	*OR (95% CI)[c]	*P*-value[c]	
II	46 (44.2)	1				112 (42.6)	1				122 (42.5)					
ID	50 (48.1)	1.05 (0.66-1.69)	0.836	1.03 (0.64-1.67)	0.898	128 (48.7)	0.93 (0.65-1.33)	0.698	0.95 (0.66-1.36)	0.762	130 (45.3)	0.98 (0.61-1.57)	0.934	0.98 (0.61-1.57)	0.916	0.926
DD	8 (7.7)	1.18 (0.49-2.83)	*0.709*	1.07 (0.43-2.63)	0.889	23 (8.7)	1.40 (0.78-2.51)	*0.262*	1.46 (0.81-2.65)	0.209	35 (12.2)	1.57 (0.88-2.79)	0.124	1.65 (0.71-3.82)	0.239	0.359
ID+DD	58	1.07 (0.68-1.69)	0.774	1.05 (0.66-1.66)	0.842	151	1.00 (0.72-1.41)	0.985	1.02 (0.72-1.44)	0.900	165	1.07 (0.68-1.69)	0.761	1.08 (0.68-1.71)	0.741	0.950
I Allele	142 (68.3)	1				352 (66.9)	1				374 (65.2)	1				
D Allele	66 (31.7)	1.06 (0.75-1.50)	0.726			174 (33.1)	0.92 (0.72-1.19)	0.537			200 (34.8)	0.87 (0.62-1.22)	0.417			0.675
χ^{2d}	1.251					2.592					0.002					
P	0.2633					0.1074					0.9675					

[d]: HWE. *P-value*[a,b,c] represent the CHB vs LC, LC vs HCC, and CHB vs HCC respectively. The two-sided χ^2 test was used when compared with the control group.*Adjusted for age, smoking, and drinking when compared with the healthy controls by logistic regression analysis.

Table 5. Clinicopathologic characteristics of 243 followed-up HCC patients

	II (n=103)	ID (n=110)	DD (n=30)	*P*-value
Male (n) (%)	91 (88.3)	94 (85.5)	26 (80.0)	0.823
Age (yrs)	50.01±7.325	49.68±8.038	49.13±6.689	0.421
Tumor numbers (n) (%)				0.953
1-2	54 (52.4)	60 (54.5)	16 (53.3)	
≥3	49 (47.6)	50 (45.5)	14 (46.7)	
Tumor sizes (n) (%)				0.822
≤5 cm	43 (41.7)	50 (45.5)	14 (46.7)	
>5 cm	60 (58.3)	60 (54.5)	16 (53.3)	
With cirrhosis (n) (%)				0.226
Yes	96 (93.2)	105 (95.5)	26 (86.7)	
No	7 (6.8)	5 (4.5)	4 (13.3)	
Child-Pugh degree (n) (%)				0.065
A	35 (34.0)	46 (41.8)	19 (63.3)	
B	41 (39.8)	41 (37.3)	8 (26.7)	
C	27 (26.2)	23 (20.9)	3 (10.0)	
BCLC degree (n) (%)				0.474
0-A	17 (16.5)	25 (22.7)	7 (23.3)	
B-D	86 (83.5)	85 (77.3)	23 (76.7)	
With portal tumor thrombus (n) (%)				0.356
Yes	46 (44.7)	45 (40.9)	9 (30.0)	
No	57 (55.3)	65 (59.1)	21 (70.0)	
AFP level				0.685
<400	54 (52.4)	64 (58.2)	16 (53.3)	
≥400	49 (47.6)	46 (41.8)	14 (46.7)	
Smoking (n) (%)				0.633
Ever	51 (49.5)	54 (49.1)	12 (40.0)	
Never	52 (50.5)	56 (50.9)	18 (60.0)	
Drinking (n)(%)				0.964
Ever	44 (42.7)	46 (41.8)	12 (40.0)	
Never	59 (57.3)	64 (58.2)	18 (60.0)	

BCLC, Barcelona Clinic Liver Cancer; AFP, Alfa fetal protein.

multivariate analysis of qualitative data, χ^2 test was used and $P<0.05$ was used as the cutoff of significance. If there was significance, post-hoc pairwise comparisons were performed with Bonferroni's method for adjustment of the test level of α (0.05/3=0.017). Survival probabilities were estimated by using the Kaplan-Meier method. All the analyses were carried out by using SPSS software (SPSS, Chicago, USA).

Results

Characteristics of the patients

Tables 1, **2** provides a description of the relevant demographics of all groups. The statistical results showed no significant difference in gender and age among groups ($P> 0.05$). But there were significant differences in HCC *vs.* healthy control ($P=0.002$), CHB *vs.* HCC ($P=0.011$) and LC *vs.*HCC ($P=0.000$) in smoking, and in CHB *vs.* HCC in drinking ($P=0.007$).

The genotype frequencies of A3B deletion were categorized in groups, as shown in **Tables 3**, **4**. Furthermore, HWE test showed that the genotype distribution conformed to the HWE.

Association between A3B deletion and HBV infection

The genotype and allele frequencies of A3B gene deletion among the non-HCC group, CHB patients and the healthy control are shown in

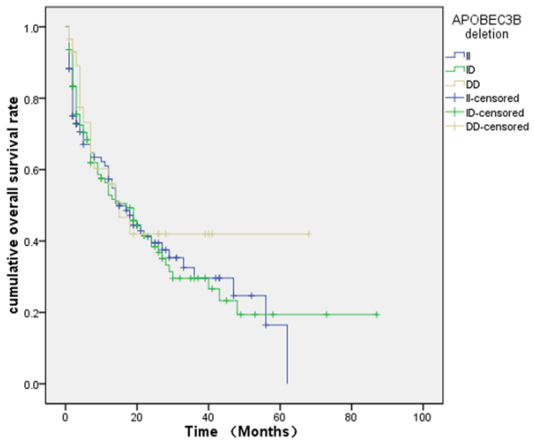

Figure 1. Kaplan-Meier analysis on the influence of APOBEC3B deletion polymorphism on overall survival of HCC.

Table 3. No significant differences were found (P>0.05).

Association between A3B deletion and HCC

The genotype and allele frequencies of A3B deletion among the HCC and the healthy controls are shown in **Table 3**. Compared with the II genotype, the DD genotype was significantly related to a increased risk of HCC after adjusting for age, sex, smoking, and drinking (OR=1.95, 95% CI: 1.03-3.69, P=0.041), indicating A3B deletion homozygote facilitated the occurrence of HCC. But no significant differences were found in the frequencies of alleles between the HCC patients and healthy controls.

Association between A3B deletion and HBV infection subgroups

The distribution of genotypes and alleles of A3B deletion showed no significant difference among HBV infection patients (patients with CHB, patients with HBV-related LC and HBV-related HCC) and healthy controls (**Table 4**).

Epidemiological evidence of association between A3B deletion and HCC overall survival

There was no significant difference in the clinicopathologic characteristics (**Table 5**, all P> 0.05) and the overall survival (**Figure 1**, P=0.661) among the three genotypes of A3B deletion.

Discussion

The APOBEC family of cytidine deaminases plays an important role within innate immunity by deteriorating the genetic information of HBV through hypermutation-dependent and -independent mechanisms [1]. Through G-to-A hypermutation, APOBECs also edit HBV DNA, and facilitate the mutation of HBV DNA, which might help the virus to evolve, and even to escape from the immune responses [24]. In the chronic infection patients, the mutation rate of HBV DNA caused by APOBECs was found to be significantly associated with the extent of fibrosis [25]. In our present study, we performed a large retrospective case-control study that determined the association between A3B gene mutation and the presence of chronic hepatitis B infection and HBV-related HCC in a Chinese population.

The association between A3B deletion and HBV infection has been investigated in several reports, though the findings are controversial. H. Abe *et al.* firstly reported that A3B deletion homozygosity was associated with mild liver fibrosis (P=0.0019), but no significant association between deletion and chronic HBV infection was found in 724 HBV carriers and 469 healthy control [26]. S. Ezzikouri *et al.* found the similar results that no significant difference in the frequency of deleted A3B alleles between patients with chronic hepatitis B and control subjects, however, subjects with Del/Del genotype displayed a trend for increased susceptibility to HBV infection compared to the wild type genotype (P=0.07) in 179 HBV chronic carriers and 216 healthy control from the Moroccan population [27]. Our data found no significant association between A3B deletion and chronic HBV infection (P=0.121, after adjusted by age, sex, smoking and drinking). There were also no significant difference of genotypes and alleles between three HBV-related diseases (CHB, LC and HCC) and healthy controls. The results indicated the deletion of A3B may not contribute to the disease progression after chronic hepatits B infection.

Recent analyses of the mutations have implicated APOBEC mutagenesis has been found to be widespread throughout cancer genome, suggesting this type of mutagenesis is functionally linked with cancer development [28-

30]. A3B is overexpressed in several lymphoma cells and many types of tumor tissues [29], including hepatocellular carcinoma [31]. It is speculated that AB catalyzed genomic uracil lesions are responsible for a large proportion of both dispersed and clustered mutations in multiple distinct cancers [29]. In the present study we identified that genotype DD significantly associated with increased development of HBV-related HCC. This result was consistent with the results of Zhang *et al*.'s research [12] which showed higher frequency of the A3B deletion allele in persistent HBV carriers (P=0.0015) and HCC patient (P=1.28 × 10^{-11}) compared to controls. Aberrant expression of A3B can evoke genomic instability by inducing base substitutions into human genome, which might lead to tumorigenesis in human cells *in vitro* [32].

We further investigated the association of A3B deletion and the clinicopathologic characteristics and survival of HCC patients, which to our knowledge, is the first report on the association. The results showed that there was no significant association between A3B and both clinicopatholgy and survival. All together, the A3B deletion significantly affects the occurrence of HCC but not affects its progress or outcomes.

In conclusion, our study provides epidemiological evidence that the A3B deletion homozygosity may mediate occurrence of HBV-related HCC *in vivo* however not affect the progression of disease after HBV infection and HCC. The role of inhibiting and editing of the HBV genome in such defense systems should be further investigated. Due to the inconsistency, further research into the function of APOBEC3 deletion and its potential biological mechanism may be necessary.

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Disclosure of conflict of interest

None.

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References

[1] Janahi EM and McGarvey MJ. The inhibition of hepatitis B virus by APOBEC cytidine deaminases. J Viral Hepat 2013; 20: 821-8.

[2] Vieira VC and Soares MA. The role of cytidine deaminases on innate immune responses against human viral infections. Biomed Res Int 2013; 2013: 683095.

[3] Wedekind JE, Dance GS, Sowden MP and Smith HC. Messenger RNA editing in mammals: new members of the APOBEC family seeking roles in the family business. Trends Genet 2003; 19: 207-16.

[4] Jarmuz A, Chester A, Bayliss J, Gisbourne J, Dunham I, Scott J and Navaratnam N. An anthropoid-specific locus of orphan C to U RNA-editing enzymes on chromosome 22. Genomics 2002; 79: 285-96.

[5] Lucifora J, Xia Y, Reisinger F, Zhang K, Stadler D, Cheng X, Sprinzl MF, Koppensteiner H, Makowska Z, Volz T, Remouchamps C, Chou WM, Thasler WE, Hüser N, Durantel D, Liang TJ, Münk C, Heim MH, Browning JL, Dejardin E, Dandri M, Schindler M, Heikenwalder M, Protzer U. Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA. Science 2014; 343: 1221-8.

[6] Mangeat B, Turelli P, Caron G, Friedli M, Perrin L, Trono D. Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts. Nature 2003; 424: 99-103.

[7] Harris RS, Bishop KN, Sheehy AM, Craig HM, Petersen-Mahrt SK, Watt IN, Neuberger MS, Malim MH. DNA deamination mediates innate immunity to retroviral infection. Cell 2003; 113: 803-9.

[8] Schröfelbauer B, Yu Q, Zeitlin SG, Landau NR. Human immunodeficiency virus type 1 Vpr induces the degradation of the UNG and SMUG uracil-DNA glycosylases. J Virol 2005; 79: 10978-87.

[9] Conticello SG. Creative deaminases, self-inflicted damage, and genome evolution. Ann N Y Acad Sci 2012; 1267: 79-85.

[10] Refsland EW and Harris RS. The APOBEC3 family of retroelement restriction factors. Curr Top Microbiol Immunol 2013; 371: 1-27.

[11] Bonvin M and Greeve J. Effects of point mutations in the cytidine deaminase domains of APOBEC3B on replication and hypermutation of hepatitis B virus in vitro. J Gen Virol 2007; 88: 3270-4.

[12] Zhang T, Cai J, Chang J, Yu D, Wu C, Yan T, Zhai K, Bi X, Zhao H, Xu J, Tan W, Qu C, Lin D. Evidence of associations of APOBEC3B gene deletion with susceptibility to persistent HBV infection and hepatocellular carcinoma. Hum Mol Genet 2013; 22: 1262-9.
[13] McCarroll SA, Hadnott TN, Perry GH, Sabeti PC, Zody MC, Barrett JC, Dallaire S, Gabriel SB, Lee C, Daly MJ, Altshuler DM; International HapMap Consortium. Common deletion polymorphisms in the human genome. Nat Genet 2006; 38: 86-92.
[14] Tuzun E, Sharp AJ, Bailey JA, Kaul R, Morrison VA, Pertz LM, Haugen E, Hayden H, Albertson D, Pinkel D, Olson MV, Eichler EE. Fine-scale structural variation of the human genome. Nat Genet 2005; 37: 727-32.
[15] An P, Johnson R, Phair J, Kirk GD, Yu XF, Donfield S, Buchbinder S, Goedert JJ, Winkler CA. APOBEC3B deletion and risk of HIV-1 acquisition. J Infect Dis 2009; 200: 1054-8.
[16] Celestino-Soper PB, Shaw CA, Sanders SJ, Li J, Murtha MT, Ercan-Sencicek AG, Davis L, Thomson S, Gambin T, Chinault AC, Ou Z, German JR, Milosavljevic A, Sutcliffe JS, Cook EH Jr, Stankiewicz P, State MW, Beaudet AL. Use of array CGH to detect exonic copy number variants throughout the genome in autism families detects a novel deletion in TMLHE. Hum Mol Genet 2011; 20: 4360-70.
[17] Jha P, Sinha S, Kanchan K, Qidwai T, Narang A, Singh PK, Pati SS, Mohanty S, Mishra SK, Sharma SK, Awasthi S, Venkatesh V, Jain S, Basu A, Xu S; Indian Genome Variation Consortium, Mukerji M, Habib S. Indian Genome Variation, M Mukerji, S Habib. Deletion of the APOBEC3B gene strongly impacts susceptibility to falciparum malaria. Infect Genet Evol 2012; 12: 142-8.
[18] Xuan D, Li G, Cai Q, Deming-Halverson S, Shrubsole MJ, Shu XO, Kelley MC, Zheng W, Long J. APOBEC3 deletion polymorphism is associated with breast cancer risk among women of European ancestry. Carcinogenesis 2013; 34: 2240-3.
[19] Burns MB, Lackey L, Carpenter MA, Rathore A, Land AM, Leonard B, Refsland EW, Kotandeniya D, Tretyakova N, Nikas JB, Yee D, Temiz NA, Donohue DE, McDougle RM, Brown WL, Law EK, Harris RS. APOBEC3B is an enzymatic source of mutation in breast cancer. Nature 2013; 494: 366-70.
[20] Qi G, Xiong H and Zhou C. APOBEC3 deletion polymorphism is associated with epithelial ovarian cancer risk among Chinese women. Tumour Biol 2014; 35: 5723-6.
[21] Zhang T, Cai J, Chang J, Yu D, Wu C, Yan T, Zhai K, Bi X, Zhao H, Xu J, Tan W, Qu C, Lin D. Evidence of associations of APOBEC3B gene deletion with susceptibility to persistent HBV infection and hepatocellular carcinoma. Human Molecular Genetics 2013; 22: 1262-1269.
[22] Vartanian JP, Guétard D, Henry M, Wain-Hobson S. Evidence for Editing of Human Papillomavirus DNA by APOBEC3 in Benign and Precancerous Lesions. Science 2008; 320: 230-233.
[23] Kidd JM, Newman TL, Tuzun E, Kaul R, Eichler EE. Population stratification of a common APOBEC gene deletion polymorphism. PLoS Genet 2007; 3: e63.
[24] Vartanian JP, Henry M, Marchio A, Suspène R, Aynaud MM, Guétard D, Cervantes-Gonzalez M, Battiston C, Mazzaferro V, Pineau P, Dejean A, Wain-Hobson S. Massive APOBEC3 editing of hepatitis B viral DNA in cirrhosis. PLoS Pathog 2010; 6: e1000928.
[25] Beggel B, Münk C, Däumer M, Hauck K, Häussinger D, Lengauer T, Erhardt A. Full genome ultra-deep pyrosequencing associates G-to-A hypermutation of the hepatitis B virus genome with the natural progression of hepatitis B. J Viral Hepat 2013; 20: 882-9.
[26] Abe H, Ochi H, Maekawa T, Hatakeyama T, Tsuge M, Kitamura S, Kimura T, Miki D, Mitsui F, Hiraga N, Imamura M, Fujimoto Y, Takahashi S, Nakamura Y, Kumada H, Chayama K. Effects of structural variations of APOBEC3A and APOBEC3B genes in chronic hepatitis B virus infection. Hepatol Res 2009; 39: 1159-68.
[27] Ezzikouri S, Kitab B, Rebbani K, Marchio A, Wain-Hobson S, Dejean A, Vartanian JP, Pineau P, Benjelloun S. Polymorphic APOBEC3 modulates chronic hepatitis B in Moroccan population. J Viral Hepat 2013; 20: 678-86.
[28] Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, Gordenin DA. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. Nat Genet 2013; 45: 970-6.
[29] Burns MB, Temiz NA, Harris RS. Evidence for APOBEC3B mutagenesis in multiple human cancers. Nat Genet 2013; 45: 977-83.
[30] Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjörd JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jäger N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, López-Otín C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN,

Teague JW, Totoki Y, Tutt AN, Valdés-Mas R, van Buuren MM, van 't Veer L, Vincent-Salomon A, Waddell N, Yates LR; Australian Pancreatic CancerGenome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR. Signatures of mutational processes in human cancer. Nature 2013; 500: 415-21.

[31] Xu R, Zhang X, Zhang W, Fang Y, Zheng S, Yu XF. Association of human APOBEC3 cytidine deaminases with the generation of hepatitis virus B x antigen mutants and hepatocellular carcinoma. Hepatology 2007; 46: 1810-20.

[32] Bonvin M, Achermann F, Greeve I, Stroka D, Keogh A, Inderbitzin D, Candinas D, Sommer P, Wain-Hobson S, Vartanian JP, Greeve J. Interferon-inducible expression of APOBEC3 editing enzymes in human hepatocytes and inhibition of hepatitis B virus replication. Hepatology 2006; 43: 1364-74.