Dear Editor,

Thank you very much for the comments from the reviewers. We have revised our manuscript based on the reviewers' suggestions, and tracked changes in the text for the reviewers' convenience. The comments are addressed below in a point-by-point manner. We hope the changes are satisfactory, and that you will now find the manuscript acceptable for publication. This manuscript has been edited and proofread by *Medjaden* Bioscience Limited, to ensure the use of grammatically correct and idiomatic English.

Reply to the Reviewer 1

Comment 1: HBV genotype and viral load were reported to be associated with CHB and HCC. Unfortunately these information was not well study in this study.

Reply 1.1： We appreciate the suggestion. All the participants were native Han people in Northeast China. According to a report in the literature, most common HBV genotype was C (93.63%), with subgenotype group C2 (83.73%) predominating in northeast China (1). We thought the genotypes of HBV had less effect on the disease progression in our study population. Therefore, HBV genotypes were not extensively studied.

The viral loads in each group are shown in the Supplemental Table 1. The HBV viral load in non-HCC tended to be higher than in HCC group, but there was no statistically significant difference. A recent meta-analysis on the contribution of serum hepatitis B virus load in the carcinogenesis of HCC showed a non-linear dose-response association between HBV DNA level and HCC risk (2). Therefore, we elected not to focus on HBV viral load and HCC disease progression in our study population.

References

(1)Wang HY, Li D, Liu W et al. Hepatitis B virus subgenotype C2 is the most prevalent subgenotype in northeast China. Clin. Microbiol.Infect. 2010; 16: 477–81.

(2) Chen X, Wu F, Liu Y et al. The contribution of serum hepatitis B virus load in the carcinogenesis and prognosis of hepatocellular carcinoma: evidence from two meta-analyses.Oncotarget. 2016; 30 Jun.

Comment 2: The Table 2 is complicated. Please use a simple table to demonstrate rs8177832 and rs2011861 polymorphism are more significant to others.

Reply 1.2: We appreciate the suggestion. As recommended, we have created a simplified new Table 2.

Comment 3: A multivariate analysis may be needed to support the role of rs8177832 and rs2011861 in persistent HBV infection or HCC development.

Reply 1.3. We apologize for the confusion. We did use the multivariate analysis on the distribution of genotype and allele among each group. Logistic regression analysis was used to calculate the P-value, OR and 95% Cl after adjusting for age, gender and environmental factors. This has now been clarified in the revised manuscript on **Page 7, Line 17-19.**

Reviewer: 2

Comment 1: Please tell me the etiology which HBV patient go to HCC, from the point of APOBEC 3G.

Reply 2.1. We appreciate the question. APOBEC3G can lead to hypermutation of host DNA or HBV DNA which may cause DNA breaks and carcinogenic protein mutants through activation of damage responses. This is now stated in the discussion from **Page 11, Line 20 to Page 12, Line 5**.

Comment 2: Please comment novel therapeutic therapy by use of APOBEC3G rs8177832 for HCC with HBV.

Reply 2.2. We appreciate the suggestion. It may be possible to transfect the protective mutation gene into somatic cells, such as liver cells, and make it

express the gene product. Alternatively, the gene product itself could be introduced resulting in therapeutic properties such as anti-viral or anti-HCC effects. Statements have now been added to the discussion section on **Page 14, Line 12-15**.

Reviewer: 3

Comment 1: Hepatitis e antigen (HBeAg) seroconversion is an important event in the natural history of HBV infection. Does the HBeAg seroconversion correlate with the A3G rs8177832 polymorphism?

Reply 3.1. We appreciate the question. Yes, the AG genotype and AG plus GG genotype of rs8177832 was shown to have high HBeAg seroconversion rate in non-HCC group, and tended to have high HBeAg seroconversion rate in CHB group. There was no difference between the ratio of HBeAg(+)HBeAb(-)/ HBeAg(-)HBeAb(+) in the rs2011861 polymorphisms. These results are shown in Supplemental Table 3, and a statement to that effect has now been added to the results section on **Page 11, Line 1-11**.

Comment 2: Authors indicated the rs2011861 polymorphism is associated with an increased risk of HCC. Are the also associated with the rs2011861 polymorphism?

Reply 3.2. We appreciate the question, and apologize for the confusion. We have now simplified the table to show the results more clearly. There was no distribution difference in rs2011861 polymorphisms between healthy individuals and other groups (non-HCC and CHB).

Rs20118 61	Healthy control	Non-HCC	HCC	HCC(N=287) control (N=299)	VS	Healthy	Non-HCC(N=370) Healthy control (N=299)	VS	CHB(N=657) control (N=299)	VS	Healthy

	N=299(%)	N=370(%)	N=287(%)	OR(95%Cl)	*P-value*[a]	OR(95%Cl)	*P-value*[b]	*OR(95%Cl)*	*P-value*[c]
CC	53 (18.7)	55(15.1)	33(11.8)	1		1		1	
CT	127(44.7)	170(46.7)	135(48.4)	1.69(1.02-2.80)	*0.042*	1.25(0.80-1.95)	0.328	1.42(0.95-2.13)	0.085
TT	104(36.6)	139(38.2)	111(39.8)	1.82(1.08-3.06)	*0.024*	1.27(0.81-2.02)	0.301	1.48(0.98-2.24)	0.063
CT+TT	231	309	246	1.75(1.08-2.82)	*0.022*	1.26(0.83-1.91)	0.277	1.45(0.99-2.11)	0.053
C Allele	233(41.0)	280(38.5)	201(36.0)	1		1		1	
T Allele	335(59.0)	448(61.5)	357(64.0)	1.24(0.97-1.57)	0.085	1.11(0.89-1.39)	0.350	1.16(0.95-1.42)	0.140

Comment 3: The sentence "The current report is the first to describe the relationship between rs8177832 and rs2011861 and the risk of HBV infection and occurrence of HCC." in page 12 (discussion section), is difficult to read. English writing should be improved by a native English speaker.

Reply 3.3. We apologize for the confusion. We have now clarified this statement on **Page 13, Line 13-15** in the revised manuscript.

This revised manuscript has been edited and proofread by Medjaden Bioscience Limited.