Author's response to reviews

Title: Lack of association between the GRP78 polymorphisms in the promoter and 3' UTR and susceptibility to chronic HBV infection in a Chinese Han population

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**Title:** Lack of association between the *GRP78* polymorphisms in the promoter and 3' UTR and susceptibility to chronic HBV infection in a Chinese Han population.

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Dear Dr. Melissa Norton and Dr. Scott Edmunds,

Thank you for reviewing the above-referenced manuscript submitted earlier to your office.

We express our appreciation to you and colleagues.
In accord with the Reviewers’ comments and suggestions, the manuscript has been revised accordingly and extensively, and the changes have been highlighted in the revised manuscript. We feel that the revised manuscript has been strengthened substantially by the Reviewers’ comments and suggestions, and we are very appreciated of their time and efforts. A point-by-point response to the reviewers’ comments and suggestions has been prepared and follows this cover letter. In addition, we corrected some spelling errors.

The format for our manuscript has been properly prepared and corresponds with *BMC Medical Genetics* style.

Sincerely yours,

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Response to comments of Reviewers

Reviewer 1 (Fredrik O Vannberg)

Minor Essential Revision

1. The Reviewer’s comments are right that the title should be mended. Including the negative results described in this study, the title has been mended “Lack of association between the GRP78 polymorphisms in the promoter and 3’ UTR and susceptibility to chronic HBV infection in a Chinese Han population”. (See the Title).

2. Here, we thank for the reviewer’s comments on a previous paper studying -87bp (T>A) in GRP78 by our group several months ago. So, we remove the “first” as a priority claim and stress “This was one of the series of studies to investigate …” in the Discussion. (See the first paragraph of Discussion).

3. Thanks for the reviewer’s assessment about the difference of mean age of controls between the previous paper (-87bp and HBV) and the present paper. Here, we clarify that the first population come from several hospitals of Guangzhou Medical College, and the second population come from the above hospitals and the Department of Cancer, Zhongshan School of Medicine in Sun Yat-sen University in Guangzhou city of Southern China. They were different studies. (See the Methods Section, Page 6).

4. According to the reviewer’s comments, a gene diagram was added to the Figure 1. (See
5. The Reviewer is right that we should clarify as to the reasoning of the SNP selection.

As a part of series of studies about relationship of polymorphism(s) and stress-associated diseases, we hypothesized that polymorphisms in promoter and 3' untranslated region (UTR), which were known to be involved in regulation of gene expression, may be contributing factors or markers of a stress-associated disease, such as virus infection. (See the last Paragraph of Background).

Reviewer 2 (Natalia Soriano-Sarabia)

Major Compulsory Revision

1. The Reviewer’s comments are right that the title is not clear. According to the reviewers’ comments, the title had been changed. (See the Title).

2. The Reviewer’s comments are right about the Abstract (Methods), So a word “possible” was inserted for easily reading. (See the Methods of Abstract).

3. The reviewer’s comments are appropriate that we should state our recent reports in the same field in the present study. So we added lots of describes about our previous studies involving in HBV infection and liver cancer. (See the last Paragraph of Background).

4. a) The reviewer’s comments are appropriate that we should clearly state the aim for the
present study. The aim was added to the Abstract. (See the last sentence in the Background of Abstract).

b) According to the reviewer’s comments, for defining the “controls”, the word “controls” has been changed to “healthy subjects”. (See the last sentence of Background Section).

5. The Reviewer’s comments were appropriate that we should clearly state the time-points for patients to be considered chronic HBV-infected. The diagnosis of chronic HBV infection was based on the presence of HBsAg and HBeAg, or HBsAg and anti-HBe, together with the absence of anti-HBs, for at least 36 months (according to the corresponding inpatient and outpatient records) prior to enrolment. (See the first Paragraph of Subjects in the Methods section).

6. The Reviewer’s comments are right. And we have introduced our work published in 2009. So the discussion has been changed accordingly. (See the last paragraph in the Background section and the first sentence in the Discussion section).

7. In the second paragraph of the Discussion, we discussed the possible association between the haplotypes in GRP78 promoter region and bipolar disorder, because in this paragraph we focus on the possible function in the promoter region of GRP78. So, we think, this discussion is appropriate. (See the second paragraph of the Discussion).

8. The Reviewer’s comments were appropriate that we should clearly state the limitations
of the study. However, additional studies from larger populations among Han Chinese, and from diverse ethnic populations, are warranted before the importance of GRP78 polymorphisms in chronic HBV risk can be fully ascertained. (See the last sentence in the last paragraph of Discussion).

9. According to the Reviewer’s suggestion, written English has been reviewed and some errors had been revised.

Minor Revision
1. a) The diagnosis of chronic HBV infection was based on the presence of HBsAg and HBeAg, or HBsAg and anti-HBe, together with the absence of anti-HBs, for at least 36 months (according to the corresponding inpatient and outpatient records) prior to enrolment. (See the Methods section).

b) “8g one day” has been changed to “8g per day”. (See the Methods section).

c) “Patients who received antiviral therapy including interferon or nucleoside analogues within one year of enrollment were also excluded” means that the cases were not influenced by antiviral therapy.

d) ALT level was described. (See Table 1 and the last sentence of the first paragraph in the Results section).

2. The cases were defined as patients with chronic HBV infection. (See the first sentence of Subjects in the Methods).
3. $p$-trend means in all cases. (See Table 2, 3 and 4).

4. Thanks for the Reviewer’s comment that we did miss a word “infection”. (See the last sentence of the fourth paragraph in the Results section).

5. We are sorry for the written English. Indeed, “Our epidemiologic studies…” means the present work. So, it has been changed to “The present study”. (See the third paragraph in the Discussion).

6. According to the Reviewer’s comments, the fourth paragraph of the Discussion has been deeply checked. (See the fourth paragraph of the Discussion).

Discretionary Revisions

1. According to the reviewer’s comments, the number of patients has been added in Table 1. (See Table 1).