

December 13, 2015

Dear editor and reviewer,

We thank you and the reviewer for all the very helpful recommendations on our manuscript ID WJG/23204 entitled "Genetic variation of occult hepatitis B virus infection". All the comments and recommendations were taken into consideration in the preparation of this revision. The paper went through language editing and typing errors was revised. We resubmit our manuscript in a revised form and hope that the revised paper now fits the standards of the journal.

Reviewer (code: 00013065)

The article is comprehensive, well and appropriate referenced (maybe somehow too much showing 166 references).

Comments:

- 1) The title implies a review of all HBV variations; however, this review is focused on OBI. Therefore my suggestion is to delete the "and" in the title to "genetic variation of occult hepatitis B virus infection"
- 2) There are some minor typing errors, e.g., first sentence of the Introduction, "... replicates via (not vie) reverse...." And 4th para 1st sentence of the preS/S-Mutation section "... substitutions of wild-type cysteines..." (not wide-type). Please check the document for more.
- 3) No Mutations section. There is a statement that "no (!) mutation" was found; however, because of the nature of HBV replication "no" mutation will never happen in HBV replication. I suggest specifying that no OBI-relevant mutations were detectable. This is also true for the title of this chapter and throughout the chapter.

Reply to the reviewer (code: 00013065):

The authors agree with the reviewer's suggestions and have made modifications accordingly.

1. The references have been reduced to 145.
2. Our response to comment 1: Page 1, line 5, the title of the paper was changed from "Genetic variation of hepatitis B virus and occult infection" to "Genetic variation of occult hepatitis B virus infection". Page 1, line 7, the running title was changed from "HBV variation and occult infection" to "HBV variation of occult infection" correspondingly.
3. Our response to comment 2: The paper went through language editing and typing errors was revised.
4. Our response to comment 3:
 - (1) The subtitle "No Mutations" in Page 20, line 7 was changed to "No OBI-relevant mutations" and "no mutation" in Page 20, lines 12-14 were changed to "no OBI-relevant mutation" according to the reviewer's suggestion.
 - (2) The authors agree that "no" mutation will never happen in HBV replication. Some researchers didn't find mutations in the " α " determinant in some OBI

patients, what's more, some studies didn't detect mutations in Pre-S/S gene in some OBIs. It is speculated that mutations outside the "α" determinant or Pre-S/S gene may be related to OBI. Besides, not each mutation of HBV genome could affect structure and/or function of HBV, and the relationship of mutation and OBI need to be explored by functional analysis.

- (3) "No mutation" in Page 20, lines 9 and 12 remain unchanged, while it doesn't deny the mutation-prone of HBV. "No mutation was detected in the 'α' determinant" in Page 20, line 9 indicated that mutations existed outside the "α" determinant instead of within it in some OBI patients and suggested that OBI may not be fully explained by mutations in the HBV "α" determinant. Similarly, "no mutation was detected in Pre-S/S gene" in Page 20, line 12 indicated that mutations weren't found in Pre-S/S gene but existed in other genes of HBV in some OBIs and suggested that OBI may not be fully explained by mutations in Pre-S/S gene.

Reviewer (code: 02528284):

Some minor criticisms and comments concerning the manuscript:

- 1) The title needs modification because the manuscript deals only with occult HBV.
- 2) I suggest to change subtitle Viral factors and Host factors
- 3) Please do a careful language editing and there are some minor typing errors

Reply to the reviewer (code: 02528284):

The authors agree with the reviewer's suggestions and have made modifications accordingly. Detailed responses to comments are provided below.

1. Our response to comment 1: Page 1, line 5, the title of the paper was changed from "Genetic variation of hepatitis B virus and occult infection" to "Genetic variation of occult hepatitis B virus infection" according to the reviewer's suggestion. Page 1, line 7, the running title was changed from "HBV variation and occult infection" to "HBV variation of occult infection" correspondingly.
2. Our response to comment 2: The subtitle "Viral factor" in Page 7, line 22 was changed to "Viral factors" and the subtitle "Host factor" in Page 8, line 19 was changed to "Host factors".
3. Our response to comment 3: The paper went through language editing and typing errors were revised.

Reviewer (code: 00073008):

In my opinion, the author should discuss a problem of HBV extrahepatic replication on the hidden infection more widely. This problem was primary investigated by prof. Michalak from Toronto in Woodchuck model. Especially interesting is the problem of minimal HBV replication in lymphatic tissue on the transmitting HBV infection. This problem was only mentioned in this article. I also do not have enough of the explanation of the role the cccDNA storage on the persistence of viral infection in humans hepatocytes. Maybe the author's intention was to focus on the role of HBV variants in

occult viral infection.

Reply to the reviewer (code: 00073008):

The authors agree with the reviewer's suggestions. This paper focused on the role of HBV variants in occult viral infection, and discussion about other parts is just mentioned but still need to supply. The relationship between extrahepatic replication of HBV especially in lymphatic tissue and OBI and the description of cccDNA storage on the persistence of viral infection were added in Page 8, line 23 to Page 9, line 2.

A list of major changes according to Guidelines and Requirements for Manuscript Revision-Review

1. Open-Access was added in Page 2, line 2-8.
2. Copyright was added in Page 3, line 15-16.
3. Citation was added in Page 4, line 1-2.
4. Acknowledgments were added in Page 22, line 20-22.

Thank you for taking the time to review the article and provide comments to help improve the quality and content of our review article, and I look forward to hearing of your editorial decision.

Sincerely,

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