Author's response to reviews

Title: Effects of prevalent point mutations and mutation combinations at BCP and precore regions of HBV during liver disease progression

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Author's response to reviews: see over
Dear Dr. Graham:

Thank you very much for your editing on our manuscript “High prevalent multi-mutations of BCP and precore in patients with HBV-related advanced liver diseases” submitted to BMC Infectious Diseases. We are also grateful for reviewers valuable comments and suggestions. Accordingly a revised version is now finished for re-submission.

From reviewers’ reports, as well as during our revision process, we fully realized that our previous version was poorly composed in both organization and language. Therefore, in this version, in addition to revise the paragraphs according to reviewers’ comments, we also extensively revised the sections of Abstract, Results, Discussion, and Conclusions. To make you and reviewers read the new manuscript easily, we uploaded both versions of the “tracked changes” and the clear copy.

Meanwhile, we would like to have a new title for this manuscript as the “Effects of prevalent point mutations and mutation combinations at BCP and precore regions of HBV during liver disease progression”. We believe this title fits the contents more accurately.

Enclosed please also find our point by point responses to the referees. We hope this improved manuscript will be acceptable to publish on BMC Infectious Diseases.

We heartedly appreciate your further reading and editing on this manuscript. I am looking forward to hearing from you.

Best regards

Sincerely yours,

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Response to referee 1:

We thank for reviewers’ comments and suggestions. We have revised the manuscript accordingly:

1) “The paper however is difficult to follow and the many figures and tables are poorly connected with the study results and are not sufficiently discussed.

   We actually felt the same as the reviewer so in this version, we basically rewrote the Results and Discussion to improve the frame of this manuscript. All figures and tables were carefully linked to the text.

2) The message should be more clearly stated and the original relevant findings clearly differentiated from a bulk of less significant data.”

   Indeed in previous version some result descriptions were too trivial or lacking of focusing. We paid a lot of attention on this aspect during the revision. Also, we removed certain non-important data such as A1727G mutation in the results and mutation accumulation part in the discussion.

3) “The English needs attention. Some abbreviations, for example “ALD” are not introduced in the text nor explicited properly.”

   Most sentences were revised in this version. Also, abbreviations and other grammar details were carefully checked.

Response to referee 2:

We thank for reviewer’s comments and suggestions. We have revised the manuscript accordingly:

Abstract

1) “The overall presentation of the abstract is not satisfactory.”

   We rewrote the abstract.

2) “The sample size of abstract contradicts with the methods as well as with the results.”

   We apologize for this contradiction. The number was checked and corrected.

3) “Acronyms in the abstract needs to be defined like ALD.”

   Thank you for the advice, abbreviations and other grammar details were carefully checked in new version.

4) “How do they explain the absence of any correlation of T1653 mutation with the disease severity?”

   We did not analyze T1653 mutation mainly because it locates near one terminus of our amplicons, where sequencing signals were sometime not satisfied for analysis.
5) “you do not communicate the rates of viral load of your patients in the results with reference to the wild and mutant viruses which establishes that they are the patients who have raised rates of DNA.”

Indeed it would be very helpful in understanding the possible role of mutation in viral loads. However, in our previous studies we found that HBV titers changed often during the infection, and the fluctuation of viral loads could be due to multi reasons in addition to mutations in viral genome. Also, we had only DNA titers of one time point. Therefore, we were unable to correlate the viral loads to mutations in this cross-sectional study. However, we would like to compare our mutation patterns with viral titers at different time points in future studies.

Discussion

6) “It seems to be of purely local as opposed to international interest.”

In our analysis, we compared the mutation combinations of our sequences with those retrieved from global NCBI database. We found no significant difference in mutations and their combination patterns, indicating what we observed are not uncommon or not only limited in China. If we over-emphasized northern China, we have revised this expression.

7) “Discussion part is not up to the mark and does not contain a comprehensive data from the present pool of information on HBV mutations.”

We basically rewrote discussion accordingly.