

ANSWERING REVIEWERS



November 27, 2013

Dear Editor:

Thank you very much for considering our manuscript entitled "Molecular identification of hepatitis B virus genotypes/subgenotypes: revised classification hurdles and updated resolution" for publication in the *World Journal of Gastroenterology*. We greatly appreciate the insightful comments given by the referees that notably helped us to improve the manuscript. In the revised version, we addressed all issues raised by the reviewers. We hope you now find our manuscript suitable for publication in the *World Journal of Gastroenterology*. Please find attached a revised version of the review article with changes underlined and our point-to-point responses to the referees' comments below.

Please find enclosed the edited manuscript in Word format (file name: 6423-review revised.doc) with changes underlined.

Title: Molecular identification of hepatitis B virus genotypes/subgenotypes: revised classification hurdles and updated resolution

Authors: Mahmoud Reza Pourkarim, Samad Amini-Bavil-Olyaei, Fuat Kurbanov, Marc Van Ranst, and Frank Tacke

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6423

Point-to-point responses to the reviewers

Thank you very much for the thorough and fair review of our manuscript.

Reviewer #1:

Dr. Pourkarim and coworkers have presented an highly interesting review article on the identification and characterization of HBV geno-/subtypes and their possible misclassification. Overall the review article is well performed and structured, easy to read and concise in its content. However, there are some minor comments which should be addressed. Comments:

- 1) Neither in the abstract nor in the text it is stated that this article is a "review" article (dealing mainly with misclassification of HBV sub- and genotypes). This leaves the reader at the end alone what kind of article that is. As a suggestion one sentence in the Abstract section could start with "In this review article...."*

Response: Thank you for this excellent suggestion. We have added the following statement to the abstract: "In this review article, we aimed at highlighting potential pitfalls in genetic and phylogenetic analyses of HBV and suggest novel terms for HBV classification."

- 2) There are some typing errors, mainly the headings jump between upper and lower case, e.g., page 12, chapter 3.2. ff.*

Response: We apologize for these mistakes and fixed all typos errors.

3) *Concerning the suggestion of the authors to apply two new termini “recombino and immigro” in HBV classification, I have little doubts that this really will help to harmonize the field as there are two more new possibilities to generate confusion.*

Response: Thanks for your insightful comment. We fully agree that new terms carry the risk of creating even more confusion in the field. However, in this review, we not only wanted to discuss current problems and misclassification, but also propose creative solutions. From many discussions with leading experts (the authors are from four different HBV research centers from three continents!), it became apparent that the current term “subgenotype” is not accurate by itself to solve the existing confusions. We hope that the two terms (immigro-/recombino) will remind scientists to be more careful and cautious before introducing novel (sub)genotype strains. Furthermore, these terms will not only introduce the subgenotype number, but also add extra information about the isolates (recombination or exotic isolate through immigration). Nevertheless, in order to comply with the reviewer’s valid concern, we rephrased the abstract and the main text to a more cautious introduction of the terms (“suggest”, “propose”, “might help to”).

4) *The reference list is much too long (with 174 references). The authors may reduce the list and focus on “key” literature.*

Response: In this review article we have tried to gather all evidence, which supports the role of HBV (sub)genotypes on clinical outcome, evolution, epidemiological profiles, diagnosis and prophylaxis. In the attempt to highlight misclassifications, we also included studies reporting a “novel” subgenotype followed by studies disproving it. We agree with the referee that this too far increased the reference numbers. In the revised version, we remarkably reduced the number of references. However, we would like to point out that the WJG invitation letter stated that this series of invited-reviews does not have limitations for word counts, figures, tables or references.

Reviewer #2:

Authors of this review manuscript summarize the HBV classifications and suggested the revised classifications of subgenotypes. Also impacts and importance of genotypes on disease progression and so forth. I would be great to summarize more detailed, updated characteristics of genotypes and subtypes. Also, including serotypes in the table.

Response: Thanks for your comment. We agree with the reviewer that serotypes are important measures for HBV classification and added a paragraph in the revised manuscript on serotypes (section 1.2). However, as these serotypes are not defined by up-to-date molecular methods (such as sequencing), we prefer not to include the serotypes in the table, as this might cause major confusion (due to systematic differences between the molecular genotyping/subgenotyping and serotyping classification system and no direct comparability).

The authors suggested the new revised classifications but in the manuscript they follow the old classifications. It would be good to mention new version of revised classifications in the brackets.

Response: We thank the reviewer for this helpful comment. We have added old/new classifications in brackets in the text, wherever appropriate, and added the revised table 1, which now directly displays corresponding old/incorrect and the new/correct classification. We hope that this will be easiest for the readers to appreciate the differences between old and new versions of revised classifications. Also, the holistic phylogenetic trees constructed

for this review clearly show the phylogenetic status of different genotypes and subgenotypes before and after new classification. In the text, we have referred to Table 1 and two phylogenetic trees before and after correction of classification.

Minor points Better wording is strongly urged for section 1 title '1. Eradication of hepatitis B', since HBV has not been eradicated and not even close.

Response: Thanks for this excellent comment. The section title was changed to: "Possible eradication of hepatitis B virus: multi-factorial complications"

Also the better wording for 'Table 1.' Title, too

Response: Once again, thank you for your insightful comments. The title of Table 1 was replaced by "The misclassifications detected in HBV subgenotyping: causes and resolutions."

Sincerely yours

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