

Dear Editor,

I really appreciate your constructive and valuable comments on our manuscript entitled "**Hepatitis B virus pre-S/S variants in liver diseases**" by Bing-Fang Chen. I have responded your comments and incorporated them into my revision (underlined) as shown in the next page. We hope this revision can meet the requirements of yours and the reviewers'. If you have any questions or need any further information, please feel free to contact me.

Sincerely yours,

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The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated.
2. References were checked.
3. Revision has been made according to the suggestions of the reviewers and editor, and highlighted in the updated version of the manuscript (underlined).

**Reviewer 02447091's comments:**

Bing-Fang Chen reviews the roles of hepatitis B virus pre-S/S variants in liver diseases and finds that most of them cause the intracellular retention of HBV envelope proteins and induction of ER stress, resulting in liver diseases. There is only one linguistic problem in this manuscript which is listed in minor comments listed below and this work is worth enough for possible publication in WJG.

Major comments None.

Minor comments 1. Page 8, line 12, page 15, line 7. Page 17, line 15. Others should be other.

**Responses:** As suggested by the Reviewer, these mistakes are corrected.

**Reviewer 01221188's comments:**

I think that this article will contribute to the clarification of the pathogenesis of HBV infection. Minor revision In the abstract, preS/S variants are classified into five types. In the discussion, however, preS/S variants are classified into six types. Leaders will be confused. Which classification is appropriate?

**Responses:** As suggested by the Reviewer, additional description is added. In the abstract: According to the mutation type, five pre-S/S variants have been identified: pre-S deletion, pre-S point mutation, pre-S1 splice variant, C-terminus S point mutation, and pre-S/S nonsense mutation. In the discussion: Based on the region mutated, at least six pre-S/S variants occurred.

**Reviewer 00012513's Comments:**

The review presented by Bing-Fang Chen, is very well developed and widely documented in a topic of great interest such as the variants of the preS and S regions of HBV. This review can be of great help to researchers about HBV infection. Only one comment should be added about the study by Shirvani-Dastgerdi E et al. J Hepatol. 2017; 67 (2): 246-254, which describes a very early codon stop variant in the surface region and the possible consequences of a

surface protein in which a large part of the S region is de-selected

**Responses:** As suggested by the Reviewer, this reference is added.

**Reviewer 02441021's comments:**

Excellent review, but for clinicians like myself, we need to know whether hepatitis B virus pre-S/S variants have any influence in response to treatment Interferons or with different nucleoside/nucleotide analogues?

**Responses:** As suggested by the Reviewer, we will review the role of pre-S/S variants in response to interferon treatment and nucleoside/nucleotide therapy in the future.