September 19, 2014

Dear Editor,

Thank you very much for your decision letter and advice on our manuscript.

Please find enclosed the edited manuscript in Word format (file name: 13228-review.docx).

Title: *PNPLA3* I148M variant in nonalcoholic fatty liver disease: demographic and ethnic characteristics and the role of the variant in nonalcoholic fatty liver fibrosis

Author: Li-Zhen Chen, Yong-Ning Xin, Ning Geng, Man Jiang, Ding-Ding Zhang, Shi-Ying Xuan

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13228

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

1 Format of the review has been updated.

2 Revision has been made according to the suggestions of the reviewers.

(1) Replies to Reviewer 742517:

Major comments: 1. This manuscript clearly summarizes a well-known *PNPLA3* variant, I148M, that underlies NAFLD. Regretfully, association of *PNPLA3* I148M and the spectrum of NAFLD (simple steatosis, nonalcoholic liver disease, nonalcoholic steatohepatitis), and also its histopathological mechanisms, have already been reviewed previously. Thus there may be limited origination in this manuscript. 2. According to the manuscript, 'we explore the role of the *PNPLA3* I148M in the development of nonalcoholic fatty liver fibrosis and hypothesize the underlying mechanisms by speculating a pro-fibrogenic network' (page 2), and 'we speculate a pro-fibrogenic network that the *PNPLA3* I148M variant may promote the development of fibrogenesis by activating the Hh signaling pathway' (page 3). However, reviewer does not be able to find the composition of pro-fibrogenic network. Exact definition of this network is then suggested. Minor comments: The effect of *PNPLA3* I148M on NAFLD, and NAFLD-related liver fibrosis, has been uncovered in patients with different age, gender, and ethics. Taken into account of the multiple clinical trials, table rather than text seems to be a best solution to display these findings.

Response: Thanks for your insightful suggestions. This manuscript summarized the association between the *PNPLA3* I148M variant and NAFLD, and especially its role in nonalcoholic fatty liver fibrosis. We have taken into account of age, gender, ethnicity and metabolic syndrome, and clearly reviewed the demographic and ethnic characteristics of the association, which may translate it into more individualized decision-making and personalized medicine in the future. The pro-fibrogenic network was stated in the penultimate paragraph (page 10, line 20-28). We speculated that cross-talk between the Hh signaling pathway and activated HSCs, as well as hepatic progenitor cells and cholangiocytes, forms a pro-fibrogenic network together and leads to excessive generation and deposition of ECM and eventually fibrogenesis. Table 1 (page 9, line 1) has been

added in the manuscript which was stated in page 9, line 1. It displayed the included studies evaluating the association between the *PNPLA3* I148M variant and NAFLD, which may help to understand the issue.

(2) Replies to Reviewer 69262 and Reviewer 69814:

Reviewer 69262: It is a good review on the subject. Usually when it is a paper review the tables and figures help to understand the issue. I suggest making two or three tables bringing together information on the subject, and add one or two more figures.

Reviewer 69814: Interesting review. Some more tables and figures will make it easier for the reader to follow.language revision is needed.

Response: Thanks for your helpful comment. Table 1 (page 9, line 1) and Figure 1 (page10, line 31) have been added in the manuscript, which may make it easier to understand the issue. Table 1 displayed the included studies evaluating the association between the *PNPLA3* I148M variant and NAFLD. Figure 1 showed the hypothetical molecular mechanism by which the *PNPLA3* I148M variant participates in the development and progression of nonalcoholic fatty liver fibrosis.

(3) Replies to Reviewer 2890067:

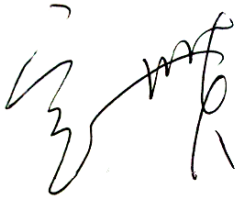
Reviewer 2890067: This is an interesting paper which may improve our knowledge in the fiels. The subject matter is suitable for the intended audience and it fits the journal scope. Article is mostly clearly written, but Title is suggestive of the article's content. Article is appropriately organized and the headings are indicative of content. I suggest to accept this paper in the present form.

Response: Thanks for your acception.

3 References and typesetting were also corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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