April 6, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2597-review.doc).

Title: Different regional distribution of *SLC25A13* mutations in Chinese patients with neonatal intrahepatic cholestasis

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 2597

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

1 Format has been updated according to the editor's request.

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

Reviewer 00053433

This is a retrospective study aimed at investigating the regional distribution of SLC25A13 mutations in Chinese patients with neonatal intrahepatic cholestasis. The topic is relevant, since biochemical diagnosis of citrin deficiency is not widely available and mutation analysis of the SLC25A13 gene is crucial to diagnosis. The study was well-conducted and the manuscript is reasonably well written (although English review is obviously needed), with good scientific value.

However, some issues should be addressed by the authors.

1) Authors are strongly suggested to ask a native English speaker to check the manuscript

for spelling and grammar. Text comprehension is compromised in many parts of the manuscript.

Answer: After editor's recommendation, we have already made improvements to the wording and grammar of the manuscript with the help of American Journal Experts. Even though, we asked a native speaker to proof the manuscript again to make sure the correction of grammar and spelling.

2) For the sake of clarity, the results of the inclusion process and mutation identification should be presented in a flowchart.

Answer: A flow-chart is added in the manuscript as fig 1.

3) Authors should clarify if a WRITTEN informed consent was obtained from all participants or their guardians.

Answer: the consent was obtained from all the patients or their parents, which is stated in page 6 line 22.

4) Table 1. Authors should indicate the reference number for each study

Answer: The reference number has been rewritten according to the reviewer's request.

Reviewer 02444760

The manuscript of 'Different regional distribution of SLC25A13 mutations in Chinese patients with neonatal intrahepatic cholestasis' focuses on the mutation spectra of SLC25A13 gene in different parts of China. As defined by the mutation point, c.851_854del, c.1638_1660dup23, c.615+5G>A and c.1750+72_1751-4dup17insNM_138459.3:2667 are the hotspots. Thirteen other mutation types have also been recorded. As compared to that of border and northern regions, mutant alleles seem to be more common in the southern region. These findings may shed light on the genetic characteristics of neonatal intrahepatic cholestasis in Chinese patients and, as a result, serve as potential tool for the clinical diagnosis.

Major comments

1) This research investigates the frequency of SLC25A13 mutations in 3 regions of China. In result, the mutation spectrum of SLC25A13 gene varies considerably among different regions of China. Four common mutations display higher frequency in the southern region than in border and northern regions. However, only 61 patients enrolled in the study are from northern China, which is much lower than that of border and southern regions. Subsequently, there are merely 4 mutant alleles found in this population. Then whether the bias of sampling should be responsible for the genetic difference between 3 regions of China? Additional data and, at least, detailed discussion are suggested.

Answer: Yes. The number of patients from the northern region is small. That is one limitation of this paper. However, up to now, no significant correlation between *SLC25A13* mutation types and severity of the disease is observed, so the smaller sample size would not lead to bias of sampling in this study. The detailed discussion is listed in page 13 last sentence.

2) Different frequency of common mutations has been reported in various areas of China. Is there any inconsistence among previous reports and the present study? Thorough comparison and rational explanation would be appreciated.

Answer: The mutation alleles of previous study were concentrating in the southern region of China and few mutation alleles were reported in the border and northern regions. The ratio of common mutation in this southern region is consistent with the previous study, which is added in the page 12 line 8-10.

Minor comments

1) Some expression, such as 'In north the mutation c.851_854del accounted for 50% (2/4) of the mutant alleles.' (P. 11), 'with different mutations having a higher proportion in the border and north regions than in the south regions' (P. 12), seem to be unsuitable and even mistake.

Answer: Thanks for your review. If you meant expressions such as" In north/north regions/ south region" were incorrectly used, we changed them to "northern region/border region/southern region" to describe regions of interest all through the article.

If your comment was about the unsuitable statistics of the mutation data, then we

explained limitation of this study and write it at the end of the manuscript.

We also corrected the sentence "with different mutations having a higher proportion in the border and north regions than in the south regions" to "with other mutations having a higher proportion in the border and north regions than in the south regions".

2) The manuscript illustrates the distribution of mutant alleles that have been enrolled in the study. Unfortunately, the reviewer can only find 2 parts, not 3 parts of China, as separated by the Yangtze River. The southern, border and northern areas would be better clearly distinguished, such as by different colors. What is worse, both *Liaoning* and *Henan* have been labeled in the wrong place.

Answer: Thanks for your comments. We changed Chinese map with different colors with different regions and clearly distinguished three regions. Provinces with wrong labels were corrected

Editor:

1) For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies .

If you believe that the language of your manuscript has reached or exceeded Grade A and would like to sign a guarantee. However, if we later find that the language of your manuscript has not reached GradeA, your paper will be rejected

Answer: The wording and grammar had been improved by the editor's recommended company last year, American Journal Experts, and the language certificate provide in the attachment. Even though, we asked a native speaker to proof the manuscript again to make sure the correction of grammar and spelling.

2) Please delete the extra space

Answer: The extra space is deleted in the whole manuscript.

3) Please write the COMMENTS section here. See the format in the attachment file-revision policies (Highlighted contents).

Answer: the comments section is added in the manuscript.

4) The number of references are no less than 30

Answer: The references are added to 32.

5) Fig 1:Please use a table represent the information

Answer: The fig 1 was edited according to the review, so the three regions were marked in

three colors. Would you think it is suitable for the manuscript?

6) Please revise the format of table as required.

Answer: Revision has been made according to the demand.

7) Pleae indicate citation number.

Answer: The reference number has been rewritten according to the reviewer's request.

3 References and typesetting were corrected

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

Sincerely yours,

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