

Jie Wang, Science Editor, Editorial Office

Thank you for the swift and positive evaluation of our manuscript entitled: A New Tight Junction Protein 2 Variant Causing Progressive Familial Intrahepatic Cholestasis Type 4 in Adults (**Manuscript NO.:** 51702).

We wish to thank the reviewers for their positive and constructive comments. We have made appropriate changes in accordance with their suggestions and think the manuscript has improved. Please below find a point-to-point reply to specific comments.

Attached a revised version of the manuscript with track changes and all other necessary files are uploaded in the system.

We hope the manuscript is now acceptable for publication in World Journal of Gastroenterology.

Yours sincerely

Chunshan Wei and Henning Grønbaek

Editorial comments and changes:

Answer:

We have corrected the manuscript number from 02998289 to 51702 (**line 2**) and updated the title to: A New Tight Junction Protein 2 Variant Causing Progressive Familial Intrahepatic Cholestasis Type 4 in Adults (**line 5-6, Line 111-112**).

We have completed the affiliations in detail of first author Chunshan Wei (**line 18-19**), to The Fourth Clinical Medical College of Guangzhou University of Chinese Medicine, Shenzhen 518033, China.

We have corrected the punctuation convention of **line 192**, replaced “a number” as “a few” in **line 345**, and deleted all redundant blanks in **table 1** and the “1/12” between “**table 2**”.

Comments to reviewers:

Reviewer #1: Regarding "Case Report of a New Tight Junction Protein 2 Variant Causing Progressive Familial Intrahepatic Cholestasis Type 4 in Adults", the authors declared that a novel TJP2 variant is associated with PFIC4 causing severe liver disease with cirrhosis and liver cancer in adolescents/adults. I found it of some interest but I have some issues: 1- There are many grammar and typos errors through the manuscript, I recommended grammar check again. 2- Tables are not clear and required more clarification 3- Some sections were numbered but other are not.

Answer:

1. Thank you for your comments! The manuscript has been edited by American Journal Editors and we have checked the grammar again and corrected a few errors highlighted in yellow.

2. We have edited the tables for clarity and also edited section numbers, changes marked in yellow.

3. The **line numbers** missing in the sections of **tables** have been added in the revised manuscript.

Reviewer #2: The manuscript by Wei et al. presented an interesting case report with a big family with progressive familial intrahepatic cholestasis type 4. The manuscript was well-written and the content was very informative.

Answer: Thank you for the positive comments!

Reviewer #3: The manuscript by Wei et al. provides a case report on a novel TJP2 variant in one individual from a consanguineous family, and association of that variant with late onset progressive familial intrahepatic cholestasis (PFIC). Analysis of multiple family members suggests a possible causal relationship between the variant and the disease. Previous reports of TJP2 variants are reviewed in some detail, and indicate that disease tended to manifest at an earlier age. They also describe variants in other genes screened, which may also be associated with modifying the specifics of the liver disease manifestation. While the data are largely presented in a series of clear tables, the accompanying text describing the individuals is a little hard to follow. Specifically, there seems to be a time line problem in the discussion of P2.6, and P2.9 does not include the year the data was collected (presumably 2018).

*Answer: Thank you very much for the positive comments! Regarding time-line issues we have clarified this in the revised version of the manuscript. Patient 2.6 was first seen in 2016 and lab values are provided in the table for this time point. Patient 2.9 was seen in 2018. We have added the time in **line 264**.*

Reviewer #4: Good paper.

Answer: Thank you very much for the positive comment!

Reviewer #5: Wei et al. reported a case who presented familial intrahepatic cholestasis with the variant form of the tight junction protein 2. Although the style of the paper is the case report, they investigated a whole family genetic analysis and revealed the relations. It is very interesting and very informative.

Answer: Thank you very much for the positive comments!

Yours sincerely

Henning Grønbaek