

Dear Editors and Reviewers.

Thank you for your kind suggestions and comments on our manuscript entitled "Novel ABCB4 mutations in an infertile female patient with progressive familial intrahepatic cholestasis type 3: A case report" (Manuscript ID: 71163). We have carefully revised the manuscript and uploaded supplementary materials according to these comments. Our replies to these comments are provided below and are highlighted in blue.

Reviewer #2:

1) The title of the article refers to an infertile woman and progressive familial intrahepatic cholestasis type 3 diseases. Please mention in the introduction and discussion what is the connection between progressive familial intrahepatic cholestasis type 3 diseases and infertility and link these two issues. If there is no logical connection then this is not a rare report.

Response: Thank you for your valuable comments. The coexistence of PFIC3 and infertility has not been reported in the previously published literature. Although there is no evidence of a causal relationship between PFIC3 and infertility, the condition of our patient is rare and unique. These new manifestations add to the information on the clinical features of PFIC3.

2) In the present case, the authors indicate that the patient is infertile Has it been investigated what causes this infertility? Has it been investigated that this fertility problem is not related to the patient's spouse? Therefore, it is necessary to examine infertility cases for both couples and mention them in a table in the manuscript.

Response: Thank you for your valuable comments. The cause of the patient's infertility is not clear. According to the previous examination, it is considered to be related to partial oviduct stenosis and genetic factors cannot be completely excluded. The infertility examination of the patient's spouse was normal.

3) In the analysis of laboratory data, a series of data is mentioned In the discussion section, the relationship between these data and Coco's disease has not been investigated. It is also necessary to indicate the normal amount of this data in a table so that readers can understand the rate of increase and decrease of this data in this disease.

Response: Thank you for your valuable comments. We included a table with information on the changes in the patient's liver function indicators and added the latest data (Table 2) . In the discussion section, we analyze the changes in these data.

4) I suggest that clinical factors, histology, gene analysis, etc. be listed in a separate table to distinguish this type of progressive familial intrahepatic cholestasis type 3 diseases from types 1 and 2.

Response: Thank you for your valuable comments. We included a table with information on the differences between PFIC3 and PFIC1 and PFIC2, which are

shown in Table 1.

5) In the field of gene analysis, it is necessary to fully explain the gene analysis device, the method of examining gene mutations, and data analysis.

Response: Thank you for your valuable comments. We have expanded on the instruments and reagents for genetic analysis, as well as the methods for mutation detection and data analysis.

6) The explanations given in the histology section are not enough. Pathological findings should be shown on the images. Textured images should be displayed at a higher magnification.

Response: Thank you for your valuable comments. We adjusted the histological images, added images with higher magnification, and expanded on the pathological results shown in the images.

7) In the final diagnosis section, it is necessary to write the final result by mentioning a few sentences and sufficient reasons.

Response: Thank you for your valuable comments. In the final diagnosis section, we added the diagnostic basis.

8) The descriptions written in the MRI imaging are not enough. Understanding these images is very vague, so more explanations are necessary, and pathological findings should be identified on the images.

Response: Thank you for your valuable comments. We have fully explained the image obtained by MRI as being consistent with the histological manifestation.

9) The text of the manuscript needs to be edited in terms of writing and grammar.

Response: Thank you for your valuable comments. We edited the manuscript for grammar and phrasing. A new language editing certificate has been submitted.

Once again, thank you very much for your constructive comments and suggestions. These have helped us improve the quality of the paper in terms of both the English language and the depth of the topic.

Kind regards,

Tian-Fu Liu

E-mail: drliutf@126.com

Corresponding author: Ling-Yi Zhang

E-mail: zhanglymd@126.com