Manuscript Reference and Title:

Manuscript No and Journal: 47176 World Journal of Hepatology

Title: The Expanding Etiology of Progressive Familial Intrahepatic Cholestasis

We thank the reviewers for taking the time to evaluate our manuscript and provide feedback enabling the most accurate publication possible. To address the points raised, we made additions and subtractions to the text as suggested. By addressing the reviewers' comments, we have improved the content and presentation of the manuscript, as discussed below in the point-by-point response. We have *highlighted in red* all the changes in the manuscript to facilitate re-review of the manuscript.

Overall Changes Suggested by Editor:

1. The name of the journal, manuscript no., and manuscript type have been added.
2. A Running Title has been added
3. The reference citations have been changed per formatting guidelines.
4. Core tip section has been added
5. Regarding the statistical analysis, no statistics were used in the crafting of this manuscript. A certifying letter is included in the uploaded documents.
6. Article Highlights Sections have been added
7. The images are in JPEG format.
8. A new copyright agreement for the World Journal of Hepatology has been uploaded with signatures

Response to Reviewer 1:

Reviewer 1:

This article is an interesting review of the etiology of progressive familial intrahepatic cholestasis, which is classified "historical PFIC" and "Expanded PFIC"."

Response: We thank the reviewer for their comments.

"There are still some benefits for physicians or pediatricians, but there are still some problems. (1) The article has not been written strictly according to the requirements of PRISM. This is not a systematic analysis or meta-analysis, but a general review."

Response: We thank the reviewer for their comments. As an invited manuscript submission, we sought to provide 'systemic review' by summarizing the current literature regarding PFIC and PFIC-related disorders. The literature for PFIC is still quite small, and while the original focus for PRISMA was for randomized trials (there have been none in PFIC), we wanted to utilize where applicable to optimize our report. We recognize that not all sections are applicable.

(2) The time span of literature retrieval is limited to February to March 2019, which is obviously not enough.

Response: The literature retrieval timeline refers to the timeframe which authors spent search for and retrieving articles from the PubMed database. The timeframe reflects the time from which the invitation was accepted (February 2019) thru the time of the initial manuscript drafting and completion (March 2019). It is not a reflection of the timeframe for the published articles, which ranges from 1969 thru 2019.

Reviewer 2:

"This is a meticulous meta analysis on the etiology of PFIC. The genetic etiology of the disease is expanding and this study is worth to be published since clearly summarizes the genetic factors."

Response: We thank the reviewer for their comments.

"The surgical treatment methods can be explained in more detailed. Transplantation, the last treatment option can be mentioned."

Response: We appreciated the reviewers' comments. Regarding transplantation, we sought to highlight the role of transplant in the various 'Historical PFIC' disorders for which it has been reported including:

ATP8B1: "Liver transplant is indicated in those with a refractory course and in those who develop end stage disease." We additionally unscored the complications particularly related to increasing diarrhea and steatosis in the allograft after transplant.

ABCB11: "Liver transplant has been successfully used to treat severe BSEP disease and in those who develop tumor." We additionally unscored the complications particularly related to BSEP recurrence secondary to allo-reactive BSEP Ab formation after transplant.

ABCB4: "Temporizing surgical interventions as described above are rarely successful due to the severity of disease when diagnosed and liver transplant remains the only definitive therapy."

For the 'Expanded PFIC' we looked to reference transplant where reported recognizing that most series were small, and in several, transplant was pursued prior to establishment of the diagnosis.

TJP2: "Due to the severity of presentation, 9 of the initial 12 patients described underwent liver transplant; 2 have survived with portal hypertension, and one passed away of their disease."

NR1H4: "Three patients underwent liver transplant with 2 of 3 showing steatosis in the graft organ on follow up."

MYO5B: "…liver transplant has been undertaken if pruritis is refractory, though it does not address extrahepatic symptoms."

"Various surgical methods have been performed to treat PFIC: partial external biliary diversion (PEBD), ileal exclusion (IE) and liver transplantation (LTx).partial internal biliary diversion (PIBD) is probably the treatment of choice so far using a jejunal conduit. Different segments of intestines were offered as conduit and different operation techniques are defined as cholecystojejunocolonic, cholecystoileocolonic and cholecystileocolonic anastomoses. Ramachandran offered a jejunal conduit for internal biliary diversion which Gun et al had six patients with this method.(Gün F, Erginel B, Durmaz O, Sökücü S, Salman T, Celik A. An outstanding non-transplant surgical intervention in progressive familial intrahepatic cholestasis: partial internal biliary diversion.) Therefore Fig 2 describing the surgical methods are not enough, limited may be revised and these articles can be referred for surgical aspect."

Response: The appreciate the reviewer's comments. We have looked address the concern by expanding on the descriptions regarding the surgical approach to treating PFIC. We have added text to the FIC1 section. Fig 2 is meant to showcase examples of the different surgical approaches to management of PFIC and not an exhaustive representation of all reported procedures. The figure legend has been amended to reflect this and the text has been

expanded to better explain various options. References have been added as well per the reviewer’s suggestions.