We apreciated the comments and the oportunity to imporve the quality of the manuscript ID 59404 - A molecular overview of Progressive Familial Intrahepatic Cholestasis - and we hope that after this, the manuscript will reach the high bar for the World Journal of Gastroenterology readers. The comments for all the reviewer's questions and the changes in the main text were provided in **blue**.

Reviewer #1: In this manuscript entitled "A molecular overview of Progressive Familial Intrahepatic Cholestasis", Sriram Amirneni et al introduced and summarized the recent progress in the molecular characteristics of the five types of Progressive Familial Intrahepatic Cholestasis (PFIC1, PFIC2, PFIC3, PFIC4, and PFIC5). I have two relatively minor concerns:

(1) A table is wanted to summarize the clinical features, clinical outcomes, gene mutation information, diagnosis of different types of PFIC.

(2) A molecular mechanism figure is also wanted to illustrate the molecular characteristic of PFIC.

We apreciate the comments! A table sumarizing the molecular and clinical findinds in PFIC was included. Also, new figures were made which represent the mechanism of each protein/pathway involved in the development of PFIC.

Reviewer #2: The manuscript "A molecular overview of progressive familial intrahepatic cholestasis" reviewed ATP8B1、ABCB11、MDR3 genes causing progressive familial intrahepatic cholestasis (PFIC) type 1, type 2 and type 3, which are autosomal recessive disease. The authors also discussed the alterations in the NR1H4, TJP2, and MYO5B genes which have been reported linked with new phenotypes of PFIC type 4, type 5. It provided a brief overview of the molecular mechanism and clinical features associated with each type of PFIC. PFIC is a genetic disease affecting the bile secretion process of the hepatocytes due to alteration protein metabolism. It is necessary to understand

the molecular alterations in this disease to elucidate new targets and pathways that could be focus of the new management in the future. This article reviewed the genes and their variations associated with PFIC. As well, while describing the clinical conditions, it reviewed the development of cholestasis condition and its pathways and mechanisms of the related genes. It will help readers updates the knowledge of molecular and mechanism of the disease and maybe help in the development of new models which could be potentially be used in the treatment method in the future. Suggestions for improvement:

(1) As a review, it is suggested to demonstrate which sources and the duration of years of literatures was researched.

Our review is based on 65 published papers starting from 1993, but we also included papers published this year. We included this information in the main manuscript.

(2) In the section of HOW TO STUDY PFIC, the authors mentioned pluripotent stem cell as a potential method in the treatment of PFIC. We only see a few sentences describing the possibility. Reviewer would like to suggest collect more studies involved in the cholestasis management, in animal models or human being. If there are more studies in this field, reviewer suggest describe as a separate section of pluripotent stem cell as a potential method in the treatment of PFIC.

We appreciate this comment! In this review, our main goal in the section 'HOW TO STUDY PFIC?' is to show the readers the different models available to study this disease, for example, using induced pluripotent stem cells (iPS cells). We belive that iPS cells derived from patients with rare diseases may be used as a model to test potential treatments since very few patients are available to enroll in clinical trials.

(3) Figure 1 placed in the wrong place.

The figure 1 was removed.

(4) Figure 1 and 2 seems too simple to demonstrate the PFIC diseases and their related genes, or the mechanism of bile acid production.

A new figure was made that shows the mechanism of each protein and pathway that contributes to the development of PFIC.

(5) Grammar improvement: capital spellings in the main text might need to correct pending on the journal requirements, such as: "Progressive Familial Intrahepatic Cholestasis……" in abstract, core tip, last paragraph in page 5, second paragraph in page 8, conclusion.

We carefully checked the text again and improved the grammar.

Science editor: 1 Scientific quality: The manuscript describes a minireview of the progressive familial intrahepatic cholestasis. The topic is within the scope of the WJG. (1) Classification: Grade C and Grade C; (2) Summary of the Peer-Review Report: This article reviewed the genes and their variations associated with PFIC. As well, while describing the clinical conditions, it reviewed the development of cholestasis condition and its pathways and mechanisms of the related genes. It will help readers updates the knowledge of molecular and mechanism of the disease and maybe help in the development of new models which could be potentially be used in the treatment method in the future. A table is wanted to summarize the clinical features, clinical outcomes. gene mutation information, diagnosis of different types of PFIC. A molecular mechanism figure is also wanted to illustrate the molecular characteristic of PFIC. The questions raised by the reviewers should be answered; and (3) Format: There are 2 figures. A total of 66 references are cited, including 19 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B and Grade B. 3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an

invited manuscript. The study was performed with 6 financial supports. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. 5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

We appreciate the comments and the opportunity to edit the manuscript. A table summaring the clinical features, clinical outcomes, gene mutation information, and diagnosis of the different types of PFIC was placed in the manuscript.

All the documents necessary for the ressubimission were uploaded to the system and the PMID for the refereces were added. The DOI for the references were already in the manuscript.

Editorial office director: I have checked the comments written by the science editor.

Thank you for the opportunity to improve our manuscript.

Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the

author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

We revised the whole manuscript based on the Peer-Review Report, the Editorial Office's comments, and the Criteria for Manuscript Revision by Authors. We hope that after these changes, the manuscript has reached the qualifications to be published in the World Journal of Gastroenterology.