Dear Dr. Ma,

We thank you for your encouragement and advice. We would like to resubmit the manuscript entitled "**Uridine diphosphate glucuronosyltransferase 1A1 prevents the progression of liver injury**" (Manuscript ID: 88556) for further consideration for publication as an original research article in the *World Journal of Gastroenterology*. We also thank the reviewers for their constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are indicated with yellow highlights in the revised manuscript. In addition, our point-by-point responses to the reviewers' comments are provided below this letter. We have carefully checked every sentence in the revised manuscript to eliminate/reduce any potential syntax errors. This revised version of our manuscript has been proofread by two native English biologists from *Medjaden*, a professional publication-service company.

If I can be of any assistance regarding the processing of this manuscript, please contact me. I look forward to hearing from you soon.

Sincerely,

Yi-Huai He, MD

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Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This article has a good innovation. From the analysis of clinical samples, it is concluded that liver injury is closely related to UGT1A1 gene. Patients with severe liver disease exhibited relatively reduced levels of UGT1A1 protein in the liver. In mice with lipopolysaccharide (LPS) intervention and liver steatosis-mediated liver injury progression, the protein levels of UGT1A1 were decreased in the liver, which is similar to the observations in patients with severe liver disease. UGT1A1 knockout exacerbated CCl4- and ConA-induced liver injury in mice, intensified hepatocyte endoplasmic reticulum stress and oxidative stress, and disrupted lipid metabolism. UGT1A1 is involved in the progression of liver injury by regulating endoplasmic reticulum stress, oxidative stress and lipid metabolism homeostasis. However, minor modifications to the article are still needed.

1. Please supplement the references of LPS and CCl4-induced severe acute exacerbation of liver injury model

Response: We have supplemented the references requested.

Severe acute exacerbation (SAE) of liver disease is defined as the rapid deterioration of liver function in a short period of time, which can lead to liver failure or decompensated cirrhosis in the setting of pre-existing liver disease. SAE mainly consists of two parts: the underlying liver disease, which can be caused by various etiologies, and the acute exacerbation of the condition, which can be caused by multiple triggers. Mouse models of SAE of liver injury are usually established using long-term or chronic CCl_4 injections to induce chronic liver injury, followed by LPS or acetaminophen administration, or infection with *Klebsiella pneumoniae* to induce acute exacerbation of liver injury.

2. List acronyms

Response: We have included a List of Abbreviations in the revised manuscript (pages 52–54).

3. Significant differences are suggested to be indicated by *

Response: According to the journal guidelines, we have used letters (a or b) to indicate significant differences in the tables and figures in the revised manuscript.

4. All the HE and TUNEL experimental pictures in the experimental results were added with a ruler

Response: We had included a scale when taking all the HE and TUNEL experimental images, but the scale was too thin to be clearly seen in the images obtained. We therefore thickened the scale to make it more visible.

5. Remove the background line from all bar charts

Response: We appreciate your advice. We have removed the background lines from all the bar charts.

6. When it is proved that the ccl4 liver injury model increases the level of UGT1A1, it is inconsistent with clinical results. Why not just use LPS to model liver injury, that in the following experiments, ccl4 was still used first.

Response: From the experimental results of CCl_4 and ConA, it is known that UGT1A1 expression is induced in hepatocytes during liver injury, and disturbance of this induction process will aggravate liver injury. In patients with *UGT1A1* gene mutation and severe liver disease, the expression of UGT1A1 is disturbed. LPS can simulate only the disturbance in UGT1A1 expression, not the process of induction of its expression. The compensatory induction of UGT1A1 is a very important change

in liver injury. In addition, LPS alone does not cause significant liver injury (PMID: 34635364). LPS is often used as a trigger to induce exacerbation of liver injury. Therefore, we did not conduct follow-up experiments with LPS.

7. Brief the discussion

Response: We appreciate your advice. We have condensed the Discussion section.

8. Please indicate your fund number

Response: The grant numbers are provided on pages 2 and 3 of the revised manuscript.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Nice article that addresses the degreee in f liver injury related to genetic mutation

Response: We appreciate your kind comments.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Response: We have carefully checked every sentence in the revised manuscript to eliminate/reduce any potential syntax errors. In addition, this manuscript has been proofread by two native English biologists from *Medjaden*, a publication service company. We think that the revised manuscript can now be easily understood in terms of both its scientific context and language quality. Please see the language certificate provided by the company.

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

(1) Title: Abbreviations are not permitted. Please spell out any abbreviation in the title.

(2) Running title: Abbreviations are permitted. Also, please shorten the running title to no more than 6 words.

(3) Abstract: Abbreviations must be defined upon first appearance in the Abstract. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*).

(4) Key Words: Abbreviations must be defined upon first appearance in the Key Words.

(5) Core Tip: Abbreviations must be defined upon first appearance in the Core Tip. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

(6) Main Text: Abbreviations must be defined upon first appearance in the Main Text. Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (*H. pylori*)

(7) **Article Highlights:** Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).
Example 2: *Helicobacter pylori* (*H. pylori*)

(8) Figures: Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text. Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.

(9) Tables: Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

1. Conflict of interest statement: Academic Editor has no conflict of interest.

2. Academic misconduct: No academic misconduct was found.

3. Scientific quality: The authors submitted a basic study of low UGT1A1 level mediates liver injury progression. The manuscript is overall qualified.

(1) Advantages and disadvantages: The reviewers have given positive peer-review reports for the manuscript. Classification: Grade B and Grade B; Language Quality: Grade B and Grade B. Nice article that addresses the degree in liver injury related to genetic mutation. From the analysis of clinical samples, it is concluded that liver injury is closely related to UGT1A1 gene. Need to add references, adjust figures, and modify the discussion section.

(2) Main manuscript content: The author clearly stated the purpose of the study and the research structure is complete. However, the manuscript is still required a further revision according to the detailed comments listed below.

(3) Table(s) and figure(s): There are 9 Figures and 3 Tables should be improved. Detailed suggestions for each are listed in the specific comments section.

(4) References: A total of 87 references are cited, including 28 published in the last 3 years.

4. Language evaluation: The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240

Response: We appreciate your advice. We have carefully checked every sentence in the revised manuscript to eliminate/reduce any potential syntax errors. In addition, this manuscript has been proofread by two native English biologists from *Medjaden*, a publication service company. We have provided the language certificate from this company.

5. Specific comments:

(1) Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A,B, arrows, etc. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: .

Response: We appreciate your advice. We have provided editable figures in PPT format, and all the images in the manuscript are original. We have also modified the format of all the figure legends as requested, and provided a generic title and explanation for each figure.

(2) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published, and correctly indicate the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s)

as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

(3) Please don't include any *, #, †, §, ‡, ¥, @….in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as $^aP < 0.05$, $^bP < 0.01$ ($P > 0.05$ usually does not need to be denoted). If there are other series of P values, $^cP < 0.05$ and $^dP < 0.01$ are used, and a third series of P values is expressed as $^eP < 0.05$ and $^fP < 0.01$.

(4) Please provide all fund documents.

(5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text (and directly before the References).

6. Recommendation: Conditional acceptance.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the 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. When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the RCA, of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our

RCA database for more information at: https://www.referencecitationanalysis.com/, or visit PubMed at: https://pubmed.ncbi.nlm.nih.gov/.

Response: We have further refined the contents of the manuscript as suggested, and supplemented the highlights of the latest cutting-edge research articles.