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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 74364

Title: The mechanism and therapeutic strategy of hepatic TM6SF2-deficient non-alcoholic fatty liver diseases (NAFLD) via in-vivo and in-vitro experiments

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02941525
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: Italy
Author's Country/Territory: China

Manuscript submission date: 2021-12-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-10 15:41

Reviewer performed review: 2022-01-14 15:48

Review time: 4 Days

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In the present original article Li et al investigated the role of TM6SF2 in the pathogenesis of non alcoholic fatty liver disease (NAFLD), both in humans, cell cultures and in a murine model of NALFD (high fat diet and TM6SF2-KO). My most relevant comment is that Authors found that in liver tissue of NAFLD patients, TM6SF2 is overexpressed, while downregulation of the same gene leads to steatosis in mice and cell lines. These two results seem contradictory, and Authors did not comment on, nor tried to explain the result. Minor comments: 1) Abstract: please explain the meaning of ACC. 2) Some linguistic corrections are necessary (see for example page 4: "the enhanced the processes"). 3) Page 4: the statements in the last 7 lines of the Introduction should be supported by references. 4) Figure 1B: please explain the meaning of GSE abbreviations.

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Reviewer's code: 00160386
Position: Peer Reviewer
Academic degree: MAMS, PhD
Professional title: Director, Senior Scientist
Reviewer's Country/Territory: India
Author's Country/Territory: China

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Review time: 11 Days

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
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SPECIFIC COMMENTS TO AUTHORS

The study by Zuyin Li et al., where the mechanism and therapeutic strategy of hepatic TM6SF2-deficient NAFLD was demonstrated through in-vivo and in-vitro experiments is interesting. There are major concerns regarding the analysis of transcriptome data and the in vitro experiments. The other major concern is the gene expression of TM6SF2. The comments are given below: Major Comments 1. While the authors suggest that "Hepatic TM6SF2 levels are elevated in both NAFLD patients and mouse NAFLD models" in the first line of Results, they claim "In vivo and in vitro experiments confirmed that TM6SF2 knockdown increases intracellular lipid deposition". There seems to be confusion with these opposing statements and needs clarification. 2. The primer sequence listed for Human TM6SF2 in the Supplementary table are F: 5′-GCATTGATGAGCGCCCTAATC-3′ and R: 5′-AGTGGGTCATAGGAGACCTCG-3′. Both these primers are designed in Exon 2 of the gene. Usually it is a norm to design the primers for qRT-PCR in the intron-exon boundaries or two different exons with an intervening large intron to avoid amplification from residual DNA in the converted cDNA. How would the authors justify the expression? 3. In Figure 1A, the authors depict the hepatic mRNA levels of TM6SF2 in liver specimens of Healthy subjects and subjects with simple steatosis or nonalcoholic steatohepatitis. They suggest that the expression of TM6SF2 was normalized to ACTB mRNA levels. It is a norm to represent the relative gene expression as fold change. It is confusing that they have represented as relative mRNA levels. How did they quantify the mRNA? They have to either change the representation in the figure or write the method clearly in the Figure legend.

Minor Comments In Abstract – Background third line add "in", the sentence should

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read "resulting in no therapeutic strategy …" In Abstract – Method – The method of evaluation of TM6SF2 expression in liver samples collected from both NAFLD mouse models and human subjects must be mentioned. In Abstract – Results – The number of liver samples collected from NAFLD patients and mouse models should be mentioned.

The authors mention that the hepatic expression of TM6SF2 are elevated in both mouse models and human tissues. It is suggested to give the basis for this interpretation (Fold change, IHC result). In introduction, the authors have identified HSD17B13 gene as conferring susceptibility to NAFLD, while it is reported to protect against the phenotype.

Main Text Materials and Methods The method of samples collection (RNA Later, TRIZOL, Snap frozen, FFPE etc.,) of Liver specimens must be mentioned. Was the diagnosis of NAFLD in these specimens made by a single or multiple pathologists? This must be mentioned. Were the samples blinded for each of the pathologists if multiple pathologists have screened the sections. Real-time RT-PCR assay The product size of all the primers should be mentioned in the Supplementary table. Bioinformatic analyses The software used to analyze the data sets is not mentioned. In the microarray analysis the authors set the cut off to identify DEGs at a fold change of >1.2. Usually it is set at 2. How do the authors justify a more relaxed cut off?