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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37880

Title: Gender disparity in viral load, inflammation and liver damage on transgenic mice models carrying hepatitis B virus full genome with preS1 W4P mutation

Reviewer's code: 01805500

Reviewer's country: Italy

Science editor: Xue-Jiao Wang

Date sent for review: 2018-01-13

Date reviewed: 2018-01-13

Review time: 4 Hours

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

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COMMENTS TO AUTHORS

- Authors correctly state that.....In this study, we sought to construct the W4P TG mice model system constructively expressing HBV full genomes, which can help us to study the gender disparity of liver disease progression, including chronic hepatitis, steatohepatitis, cirrhosis and HCC in HBV chronic infection....
- 1) **but do not offer readers a complete view of the role of IL-6, key cytokine also in NAFLD/NASH that is the leading cause of HCC, due to obesity pandemic, see.....Could metabolic syndrome lead to hepatocarcinoma via non-alcoholic fatty liver disease?**
- **2) World J Gastroenterol. 2014 Jul 28;20(28):9217-28.**

REPLY

1) According to reviewer's comment, we added the following sentences in the Discussion section and recommended references. "Furthermore, increased hepatic IL-6 production also likely plays a pivotal role in the development of non-alcoholic fatty liver disease, non-alcoholic steatohepatitis (NASH), and insulin resistance, which are the leading causes of HCC[35-40]. Thus, our W4P TG model showing increased hepatic IL-6 production could provide a novel insight into the relationships between IL-6 production due to an infection caused by an HBV variant on the one hand, and development of NASH, type 2 diabetes, or HCC on the other hand." **(line 271 to 276)**

2) Added references

- 35 **Haukeland JW**, Damas JK, Konopski Z, Loberg EM, Haaland T, Goverud I, Torjesen PA, Birkeland K, Bjoro K, Aukrust P. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J*

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Hepatol 2006; **44**: 1167-1174 [PMID: WOS:000237984400020 DOI: 10.1016/j.jhep.2006.02.011]

- 36 **Abiru S**, Migita K, Maeda Y, Daikoku M, Ito M, Ohata K, Nagaoka S, Matsumoto T, Takil Y, Kusumoto K, Nakamura M, Komori A, Yano K, Yatsuhashi H, Eguchi K, Ishibashi H. Serum cytokine and soluble cytokine receptor levels in patients with non-alcoholic steatohepatitis. *Liver International* 2006; **26**: 39-45 [PMID: WOS:000235135700005 DOI: 10.1111/j.1478-3231.2005.01191.x]
- 37 **Abdelmalek MF**, Diehl AM. Nonalcoholic fatty liver disease as a complication of insulin resistance. *Med Clin N Am* 2007; **91**: 1125-+ [PMID: WOS:000251224600009 DOI: 10.1016/j.mcna.2007.06.001]
- 38 **Grivennikov SI**, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann Rheum Dis* 2011; **70**: I104-I108 [PMID: WOS:000287516800016 DOI: 10.1136/ard.2010.140145]
- 39 **Michelotti GA**, Machado MV, Diehl AM. NAFLD, NASH and liver cancer. *Nat Rev Gastro Hepat* 2013; **10**: 656-665 [PMID: WOS:000326632100007 DOI: 10.1038/nrgastro.2013.183]
- 40 **Scalera A**, Tarantino G. Could metabolic syndrome lead to hepatocarcinoma via non-alcoholic fatty liver disease? *World J Gastroentero*

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2014; **20**: 9217-9228 [PMID: WOS:000339389800001 DOI: 10.3748/wjg.v20.i28.9217]

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37880

Title: Gender disparity in viral load, inflammation and liver damage on transgenic mice models carrying hepatitis B virus full genome with preS1 W4P mutation

Reviewer's code: 00068723

Reviewer's country: Japan

Science editor: Xue-Jiao Wang

Date sent for review: 2018-01-13

Date reviewed: 2018-01-14

Review time: 1 Day

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[Y] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[ ] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

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COMMENTS TO AUTHORS

- The authors investigated the role of preS1 W4P mutation in liver carcinogenesis male preference. Male showed higher liver weight and increased fat accumulation and liver enzymes as compared with female.
- 3) **More information on preS1 W4P would be necessary. For example, comparison of sequence between wild type and the mutant.**
- 4) **Findings of the liver of the transgenic mice were fat accumulation, increased liver weight, and elevated liver enzymes. How did the author speculate about the findings? Fat accumulation indicated fatty liver. In some liver congenital conditions, liver weight increases.**
- **5) Were there any relations between preS1 W4P mutation and fat accumulation? Was increased liver weight related with fat accumulation? It was not clear that preS1 W4P would cause hepatocellular carcinoma via fat accumulation, increased liver weight and liver enzymes.**

REPLY

3) According to reviewer's comment, we added the supplementary figure showing comparison of LHB region sequence between wild type and mutants

4) Previously, we reported that W4P LHBs led to increased IL-6 production, which resultantly promote HCC. Furthermore, IL-6 has been reported to be positively related to obesity, T2D, and NAFLD or NASH. So, we expect that W4P TG mice has the potential to modify liver lipid metabolism in W4P TG MICE. To consider reviewer's concern, we added the following sentences explaining the relationship between IL-6, T2D, and NAFLD or NASH in the Discussion section and recommended references. "Furthermore, increased hepatic IL-6 production also likely plays a pivotal role in the development of non-alcoholic fatty liver disease,

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non-alcoholic steatohepatitis (NASH), and insulin resistance, which are the leading causes of HCC[35-40]. Thus, our W4P TG model showing increased hepatic IL-6 production could provide a novel insight into the relationships between IL-6 production due to an infection caused by an HBV variant on the one hand, and development of NASH, type 2 diabetes, or HCC on the other hand." (line 271 to 276)

.

5) We did not prove hepatocellular carcinoma via fat accumulation, increased liver weight and liver enzymes in this study. So, we describe above mentioned limitations in the discussion and need of the future study for the issued to be addressed in the discussion section. "Our study had some limitations. Unfortunately, we did not prove predominant carcinogenesis in males in our W4P transgenic mice. Therefore, further studies are necessary to demonstrate higher male susceptibility to liver carcinogenesis in our W4P TG mice model and clarify its mechanism in future. In addition, the relationships between increased hepatic production of IL-6 in mice expressing HBV genome with the W4P mutation and fat accumulation, increased liver weight, and HCC development also remain to be elucidated in future." (line 277 to 282)

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37880

Title: Gender disparity in viral load, inflammation and liver damage on transgenic mice models carrying hepatitis B virus full genome with preS1 W4P mutation

Reviewer's code: 00722239

Reviewer's country: Japan

Science editor: Xue-Jiao Wang

Date sent for review: 2018-01-13

Date reviewed: 2018-01-14

Review time: 1 Day

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

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COMMENTS TO AUTHORS

- The authors have successfully developed W4P-TG mouse model system and showed gender disparity in hepatomegaly, liver enzyme and steatosis in their model. This is the very interesting study. Although the authors referred to the male predominance in HBV-related HCC in their introduction, the results of this study did not prove the male predominant carcinogenesis of HBV-related HCC. Generally, risky lifestyle such as alcohol intake and smoking differ between male and female and these risky lifestyles may be involved in the reason of male predominant liver carcinogenesis. Even in countries in which hepatitis C is the main cause of liver carcinogenesis like Japan, the incidence of HCC is predominantly higher in male. I consider that this is a conclusive study regarding development of W4P-TG mouse model
- 6) **but further studies are necessary to clarify the mechanism of male predominant liver carcinogenesis. The authors should describe these limitations in the text.**

REPLY

6) **To consider reviewer's concern, we describe limitations of our study in the discussion and need of the future study for the issued to be addressed in the discussion section. "**Our study had some limitations. Unfortunately, we did not prove predominant carcinogenesis in males in our W4P transgenic mice. Therefore, further studies are necessary to demonstrate higher male susceptibility to liver carcinogenesis in our W4P TG mice model and clarify its mechanism in future. In addition, the relationships between increased hepatic production of IL-6 in mice expressing HBV genome with the W4P mutation and fat accumulation, increased liver weight, and HCC

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development also remain to be elucidated in future.**" (line 277 to 282)**

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37880

Title: Gender disparity in viral load, inflammation and liver damage on transgenic mice models carrying hepatitis B virus full genome with preS1 W4P mutation

Reviewer's code: 02451157

Reviewer's country: Taiwan

Science editor: Xue-Jiao Wang

Date sent for review: 2018-01-11

Date reviewed: 2018-01-15

Review time: 3 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

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COMMENTS TO AUTHORS

- This is an interesting paper that discover the mutation in LHBsAg in liver disease progress. The data fits the content.
- 7) **However, this paper needs minor language polishing**.

REPLY

7) According to reviewer's comment, we further edit our revised paper via English edit company (Editage).

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37880

Title: Gender disparity in viral load, inflammation and liver damage on transgenic mice models carrying hepatitis B virus full genome with preS1 W4P mutation

Reviewer's code: 00053888

Reviewer's country: United Kingdom

Science editor: Xue-Jiao Wang

Date sent for review: 2018-01-13

Date reviewed: 2018-01-15

Review time: 2 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

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COMMENTS TO AUTHORS

- The authors have produced an excellent manuscript and carried out an interesting molecular study. The preS1 W4P mutation in HBV seems to confer an advantage to the development of HCC in those with HBV but only male mice are affected. This has significant potential clinical applications. The study is well designed, well carried out and the manuscript is well written.
- 8) **There are only a small number of grammatical/typographical errors that need correcting but otherwise this manuscript should be published.**

REPLY

8) According to reviewer's comment, we further edit our revised paper via English edit company (Editage).

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