March 5, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16587-review.doc).

Title: Linked polymorphisms of PNPLA3 confer susceptibility to nonalcoholic steatohepatitis and decreased viral load in chronic hepatitis B

Author: Qin Pan, Rui-Nan Zhang, Yu-Qin Wang, Rui-Dan Zheng, Yu-Qiang Mi, Wen-Bin Liu, Feng Shen, Guang-Yu Chen, Jia-Fa Lu, Chan-Yan Zhu, Shu-Yi Zhang, Yi-Ming Chen, Wan-Lu Sun, Jian-Gao Fan

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16587

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) 1st phrase of the Discussion …"underlying" instead of "basic" diseases.

Answer: We have made the revision as reviewer suggested.

(2) 1st paragraph …."There are similar findings" instead of "Similar evidences have been shown" for multiple PNPLA3 SNPs

Answer: We have made the revision as reviewer suggested.

(3) 1st paragraph ….modifier for the development of a full spectrum of NAFLD:

which includesing simple steatosis, steatohepatitis, and liver fibrosis.

Answer: We have made the revision as reviewer suggested.

(4) Please restate in a more comprehensible way “Despite the discrepancy in mechanisms, the effect of PNPLA3 polymorphism on NAFLD may, but not necessary, be attributed to the abnormalities in plasma ALT and AST levels, fasting triglyceride level and IR, etc”

Answer: We have made the revision as reviewer suggested.

(5) Please correct “When evaluated by the NAS score (≥ 3), CHB patients with rs738409 G allele, rs3747206 T allele, rs4823173 A allele, and rs2072906 G allele had much higher susceptibilityle to havesuspected NASH or NAFLDNASH than those with rs738409 C allele, rs3747206 C allele, rs4823173 G allele, and rs2072906 A allele. These findings are similar to those found provide us with the fact that the role of PNPLA3 polymorphisms in CHB patients was well consistent with that in normal populations. Thus, in contrast to the HCV-induced hepatocyte steatosis in CHC patients, host metabolism rather than viral infection is responsible for the development of fatty liver disease, especially NASH, in Chinese CHB patients.”

Answer: We have made the revision as reviewer suggested.

(6) Please restate in a more comprehensible way “Another noticeable result lies in the effect of PNPLA3 polymorphisms on liver fibrosis”

Answer: We have made the revision as reviewer suggested.

(7) Please correct “These data suggested that PNPLA3 polymorphism is a critical part…”

Answer: We have made the revision as reviewer suggested.

(8) Please correct “It seems thereforeIn result that, PNPLA3 polymorphisms seem to serve as the negative regulator of HBV replication. Nowadays, NAFLD and CHB

have been uncovered demonstrated to share….".

Answer: We have made the revision as reviewer suggested.

(9) Please restate in a more comprehensible way. "Contrastively, activation of TLR4, which is recognized to be the ligand of LPS, by high fat diet (HFD)-induced NAFLD stimulates the innate immune response in both hepatocytes and kupffer cells"

Answer: We have made the revision as reviewer suggested.

(10) Please correct "In agree with our deduction, tThe NAFLD-based down-regulation of viral replication was previously is confirmed shown in a clinical trial of chronic hepatitis C (CHC) patients [20] and in animal model of HBV transgenic mice"

Answer: We have made the revision as reviewer suggested.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

Jian-Gao Fan, MD, PhD

Department of Gastroenterology

Xinhua Hospital

Shanghai Jiaotong University School of Medicine

1665 Kongjiang Rd.

Shanghai

P.R.China

Fax: +86-21-25077340

E-mail:fanjiangao@gmail.com