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Editor of World Journal of Gastroenterology
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Dear Editor,

Please find our revised manuscript named "**28007-Revised manuscript.docx**" enclosed in word format. We wish to re-submit the revised manuscript to *World Journal of Gastroenterology*. We hope it is acceptable for publication in your journal.

The information of the previously submitted article is
ESPS Manuscript NO: 28007
Title: Polymorphisms of IFIT1 predict efficiency of interferon-α therapy for hepatitis B virus (HBV) infection in Chinese population

We thank all the reviewers and editor for their kindly comments and suggestions. We have carefully revised the manuscript and all the changes in the revised manuscript were colored by red. Point-by-point responses to the comments are listed below.

Looking forward to hearing from you soon!

Sincerely,
Daru Lu

Reply to the editor

Thank you for your comments. We have revised the manuscript to satisfy the format of the journal.

1. We have revised the title to make it no more than 12 words.
2. We have changed all the inappropriate format according to your comments, such as the format of reference.
3. We have add the section of "Comment" in the revised manuscript.

Thank you very much.

Response to Reviewer #1(Reviewer's code: 03479057)

COMMENTS TO AUTHORS

The article represents an accepted population survey in an under- analysed population and contributes to the literature important information for genetic, global association studies. Its impact is significant and thus is appropriate for this journal. However, it requires major revision and should not be accepted in its present from. The IFN induced proteins with tetratricopeptide repeats 1 is related gene which can be strongly induced by IFN type 1. it suppress cellular translation and was shown to block viral replication thus the importance to focus on such SNPs . However, the author didn't mention: -The major genotype of HBV? -The effect of such gene variant SNPs on IFIT1 expression? Why it's important these polymorphisms that author did choose? As it was shown that IL28B are a major and important predictors for treatment response in both HCV and HBV infection, and as a very important factor, the author must take in consideration if the favourable SNP of IL28B can influence the result shown on this paper? As any treatment IFN-2b could engender a side effect during treatment course, so I'm asking the author if the 225 patient included in this study did not show any severe adverse reaction? and thus if all the patients get the same dose of treatment during the hole study? if it's not the case and some patient did show adverse effect, which oblige doctors to reduce treatment dose to 50% or more, can we suppose that treatment dose could be a new factor for modulation of treatment response? and thus treatment dose must be taken in consideration as a potential factors of treatment modulation?? In the discussion section,the author needs to discuss more his own results and compared with other done in other countries and this section requires major revision. The article is well written, but there were few errors need correction. I would recommend that the article be accepted with major revisions if these are satisfactorily done.

Response:

Thank you for your kindly comments.

The major genotype of HBV in this study was genotype B (47.7%), and patients infected with both B and C accounted for 40.7% of the cohort. Genotype A and genotype C were also observed (4.1% and 7.6%, respectively). Patients who infected with B or C showed better response to IFNα therapy, no matter which clinical outcome was considered. We have added the information of HBV genotype and its impact on clinical outcomes in the 'Patient characteristics and clinical outcomes' section in the revised manuscript, which was shown in red color. Table 1 was updated with the information of HBV genotype. We also added a new table in the article to exhibit the impact of HBV genotype on IFNα treatment responses. HBV genotype was significantly associated with virological response, which meant it was the only covariant for virological response. So we performed the unconditional logistic regression again, which was adjusted by HBV genotype. The results showed that rs303218 was still significantly associated with the end point virological response after adjusted for HBV genotype, which indicated that rs303218 may be a potential biomarker for IFNα treatment efficiency. We have updated the results in Table 3, Table 5 and Table 6. In the revised manuscript, we have altered the results statement in the 'IFIT1 polymorphisms and IFNα treatment's virological response' section. All the revisions in the revised manuscript were shown in red.

As described in the manuscript, we used tag-SNPs in the study to investigate the association between IFIT1 and IFNα treatment efficiency. The SNPs were selected by software Haploview 4.1 (available at http://www.broadinstitute.org/haploview) using the genotype data of Han Chinese in Beijing (CHB) population from the phase II HapMap SNP database. All the four SNPs selected in the study were located in the intron region of IFIT1. Intron SNPs may not have impact on the expression of IFIT1, and the mechanism about how the significant SNP rs303218 influenced the virological response of IFNα therapy remained unknown. Our finding suggested that IFIT1 may involve in the regulation of IFNα treatment, but the mechanism required further investigation. This was the goal of our future research.

It was a pity that we could not get the data of IL28B of the cohort, so we've no idea whether the favorable SNP of IL28B have influence on the results. And this was one of the disadvantages of our study. As described in the manuscript, although we have found that polymorphism rs303218 on IFIT1 can predict the end point virological response, the finding still required further validation.

As we described in the manuscript, all patients received antivirus therapy with 6 MU IFNα-2b (rHuIFNα-2b, Amoytop) every other day for 48 weeks. So we did not take treatment dose in consideration as a potential treatment modulation factor.

With key words of "IFIT1, polymorphisms, hepatitis B" or "IFIT1, polymorphisms, HBV" or "IFIT1, polymorphisms, IFNα", we did not found any researches focused on IFIT1 SNPs and Hepatitis B infection or IFNα treatment in Pubmed. So to the best of our knowledge, it might be the first study provides evidence for IFIT1 polymorphisms' role in predicting IFNα treatment responses. So we could not compared our findings with other done in other countries. As we discussed in the manuscript, our finding required further validation. It is very important to assess IFIT1's role in different ethnicities.

Response to Reviewer #2(Reviewer's code: 02943351)

COMMENTS TO AUTHORS

The impact of HBV genotype on the therapeutic response to IFN therapy has been recognized in several studies. In HBeAg-positive patients treated with standard IFN, the SVR is significantly better in genotype A and B patients than in genotype C and D patients. In China the most prevalent genotypes are the B and C, but in this study were not considered. It is highly recommended to determine the viral genotype.

Response:

Thank you for your positive comments.

We have added the information of HBV genotype and its impact on treatment efficiency in the revised manuscript. HBV genotype B was the major genotype of the study (47.7%). Patients infected with both B and C accounted for 40.7% of the cohort. Genotype A and genotype C were also observed (4.1% and 7.6%, respectively). Patients who infected with B or C showed better response to IFNα therapy, no matter which clinical outcome was considered. We have added the information of HBV genotype and its impact on clinical outcomes in the 'Patient characteristics and clinical outcomes' section in the revised manuscript. The information of HBV genotype was also added in Table 1. A new table, Table 2, were added in the article to exhibit the impact of HBV genotype on IFNα treatment responses. HBV genotype was significantly associated with virological response, which meant it was the only covariant for virological response. So we performed the unconditional logistic regression again, which was adjusted by HBV genotype. The results showed that rs303218 was still significantly associated with the end point virological response after adjusted for HBV genotype, which indicated that rs303218 may be a potential biomarker for IFNα treatment efficiency. We have updated the results in Table 3, Table 5 and Table 6. In the revised manuscript, we have alter the results statement in the 'IFIT1 polymorphisms and IFNα treatment's virological response' section. All the revisions in the revised manuscript were shown in red color.