Dear Editor,

We submit the revised version of our manuscript re-titled **"Genetic variants of interferon regulatory factor 5 associated with chronic hepatitis B infection"** to be considered for publication in World Journal of Gastroenterology. We sincerely thank the editor and reviewer for considering our study and for providing valuable comments and suggestions. We have carefully considered all the comments and revised the manuscript accordingly. We believe that the manuscript has been improved. All changes in the text were highlighted and rebuttals to the queries are interleaved as below.

Thank you very much for your time and consideration.

With best regards

PD Dr. Thirumalaisamy P. Velavan

Reviewer 1:

COMMENTS TO AUTHORS

This is an interesting study in which the association of IRF5 haplotypes with clinical parameters and progression of HBV-associated liver diseases were studied. The authors found that IRF5 variants rs13242262A/T and rs10488630A/G display a strong association with the progression of B-virus liver cirrhosis. The connection of IRF5 haplotypes and anti-B-viral immune response is not fully clear, but using large search engines, no up to date data can be found in this topic. English language needs minor polishing. After minor revison I suggest to accept the manuscript for publication.

We thank the reviewer

Reviewer 2

"This study aims to investigate possible effects of IRF5 polymorphisms on susceptibility to HBV infection and progression of liver diseases among clinically classified Vietnamese patients" is confuse. Could the authors rewrite this sentence and define "clinically classified Vietnamese patients"?

We restructured the sentence as 'This study aims to investigate possible effects of *IRF5* polymorphisms on susceptibility to HBV infection and progression of liver diseases among HBV patients in a Vietnamese population.'

The description of the methodology is not written clearly. The authors must get a lot of attention to this part of the manuscript, because the quality of the methodology will be essential to reinforce the results of the study. Clarification should be provided for this matter. • How was made the diagnosis of hepatitis B? Could the authors revise the reference 21? • Did the patients receive antiviral therapy? •

We have provided this information in the text in detail and as below

Based on clinical manifestations and laboratory parameters, patients were assigned to the different clinical subgroups as previously described. Briefly, the CHB patients were characterized based upon clinical syndromes such as fatigue, anorexia, jaundice, hepatomegaly, hard density of the liver, splenomegaly, hyperbilirubinemia, elevated levels of AST and ALT, HBsAg positive for longer than 6 months. The HBV-related LC patients were

characterized as patients infected with HBV (HBsAg positive) showing the clinical manifestations such as anorexia, nausea, vomiting, malaise, weight loss, abdominal distress, jaundice, edema, cutaneous arterial ‘‘Spider’’ angiomas, palma erythema, ascites, shrunken liver, splenomegaly, hyperbilirubinemia, elevated levels of AST and ALT, prolonged serum prothrombin time, and decreased serum albumin. The HBV-related hepatocellular carcinoma patients were characterized as patients infected with chronically HBV (HBsAg positive), abdominal pain, an abdominal mass in the right upper quadrant, blood-tinged ascites, weight loss, anorexia, fatigue, jaundice, prolonged serum prothrombin time, hyperbilirubinemia, elevated levels of AST, ALT and serum a-fetoprotein (AFP), ultrasound showed tumor, liver biopsy and histopathology showing tumor cells.

None of the patients were under any antivirals during sampling

Clarification should be provided for the statistical strategies adopted regarding variance heterogeneity or non-normal distribution.

We have tested for normal distribution and have applied non parametric tests for data which were not normally distributed. The distribution of IRF5 haplotypes to liver enzymes, bilirubin and HBV viral load was executed using pairwise permutation tests. Adjusted P values were calculated by pairwise permutation tests. All additional data has been provided in the figure legend.

Results • 688 words. • The patients should be better characterized.

Yes they were characterized and appropriate definitions were provided in the revised text.

Discussion: • The authors should discuss in more details their findings • Reviewer conclusion: Accept but needs revision (minor).

Thanks for this comment, we have done as appropriate and have not extrapolated the findings.

Reviewer 3

In the manuscript entitled “Genetic variants of interferon regulatory factor 5 associated with chronic hepatitis B infection” the authors genotyped four IFR5 SNPs in HBV patients and healthy controls by direct sequencing and real time PCR. In Introduction add a paragraph about the situations of Hepatitis in Vietnam and government’s progress towards World Health Organization’s Global Health Sector Strategy on viral Hepatitis (2016-2021). In study and subject heading. 242 samples from healthy individuals were collected from blood banks as the control group. Please write if they were screened for the presence of Hepatitis B and C and were negative in screening. Table 1: If you have the data of different clinical parameters of Healthy individuals than instead of writing NR, you can write the median and range values for them. Minor English language improvement required. The manuscript is well written and well presented. The article is suited well for publication in WJG after minor revision.

Thank you for these suggestions, we have included necessary information as suggested.

All 242 control individuals were negative for HBsAg, anti-HCV and anti-HIV antibodies. We do not have data on these Control individuals, as they are from blood bank.