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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 45308

Title: Characterization of hepatitis B virus X gene quasispecies complexity in mono-infection and hepatitis delta virus superinfection

Reviewer's code: 00722122

Reviewer's country: Pakistan

Science editor: Jia-Ping Yan

Date sent for review: 2019-01-08

Date reviewed: 2019-01-09

Review time: 1 Hour, 1 Day

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript "Characterization of Hepatitis B Virus X Gene Quasispecies Complexity in Monoinfection and Hepatitis Delta Virus Superinfection" is nicely presenting a good scientific work. However it requires some minor corrections or queries to be answered as

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follows 1. The authors have divided their patients into three groups as HBeAg-negative chronic HBV infection (CI, previously termed inactive carriers), HBeAg-negative chronic hepatitis B (CHB) and with chronic hepatitis delta. The first two groups are essentially the same as with chronic HBV infection as both are HBeAg negative. Based on "previously termed inactive carriers" is insufficient to put them in a separate group. Authors need to elaborate on it. 2. In genotype section of Data treatment heading "The nt haplotypes aligned at 0.25% ……..1 to 8 obtained from GenBank" is a very long sentence. It should be broken down into smaller fragments for easy comprehensibility. 3. In statistical analysis section, write "2-sample test" as 2-sample t test. 4. In the result section, authors have mentioned that 6 patients of total had liver cirrhosis or HCC. This may have an impact on the results. The authors need to analyze/discuss these variable bias. 5. In discussion, write full form of "ADAR-1" and why in particular this enzyme mutation should be investigated. Any reference? 6. HBsAg is not reported as log IU/mL. Therefore it is incorrectly written in table 1. Please revise or provide reference.

INITIAL REVIEW OF THE MANUSCRIPT

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[Y] No

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 45308

Title: Characterization of hepatitis B virus X gene quasispecies complexity in mono-infection and hepatitis delta virus superinfection

Reviewer's code: 03020625

Reviewer's country: China

Science editor: Jia-Ping Yan

Date sent for review: 2019-01-08

Date reviewed: 2019-01-15

Review time: 16 Hours, 6 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The aim of this study was to analyze the 5' end of the hepatitis B X gene (HBX) coding region and its upstream non-coding region (nt 1255-1611) by next-generation sequencing (NGS) to evaluate HBV quasispecies complexity between chronic hepatitis delta

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(CHD)-infected patients and chronic HBV-monoinfected patients (CHB and CI). The HBV quasispecies showed a trend to higher complexity in groups with lower viral replication (CHD and CI) than in the higher-replicating CHB patients. The authors proposed two possible mechanisms to explain how HDV can change the HBV quasispecies. There are few questions: 1. The authors performed liver histology examination, the results showed that 2/9 patients with CHD and 3/8 with CHB had liver cirrhosis, and 1/9 patients with CHD had HCC. It would be better to analyze whether the liver histology results could affect the complexity of HBV; 2. There was no subgenotype C1 reference sequences in Supplementary Figure 1; 3.It would be better to marke the significant difference of nt changes in Fig 3.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 45308

Title: Characterization of hepatitis B virus X gene quasispecies complexity in mono-infection and hepatitis delta virus superinfection

Reviewer's code: 00722050

Reviewer's country: Canada

Science editor: Jia-Ping Yan

Date sent for review: 2019-01-08

Date reviewed: 2019-01-16

Review time: 3 Hours, 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Hepatitis B is a chronic infection which affects 257 million people worldwide with 15 to 20 million affected with hepatitis delta virus. The hepatitis delta virus strongly suppresses hepatitis B virus replication. The mechanism of their interaction is unknown.

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These viruses show a dynamic distribution of mutants that results in viral quasispecies. This study included 24 patients of which 7/24 (29.2%) with HBeAg-negative chronic HBV infection (CI, previously termed inactive carriers), 8/24 (33.3%) with HBeAg-negative chronic hepatitis B (CHB) and 9/24 (37.5%) with chronic hepatitis delta (CHD). The aim of this study was to compare the HBV quasispecies complexity in the HBX 5' region between chronic hepatitis delta and chronic HBV monoinfected patients. The researchers also evaluated the pattern of nucleotide changes to investigate which nucleotides could be the cause of the quasispecies complexity. The researchers used a variety of serological and virological tests, in addition to amplification of hepatitis B and hepatitis D viruses regions of interest by next generation sequencing. The complexity of quasispecies and nucleotides were also analyzed. Novelty /Originality This article is sufficiently novel and interesting to warrant publication. No previous studies were found for the characterization of hepatitis B virus X gene quasispecies complexity in monoinfection and hepatitis delta virus superinfection. This article can contribute to the advancement of science and the delivery of healthcare as it has the potential to improve the management of hepatitis B infections. Presentation This article was clearly laid out with all the key elements present. The title clearly described the content of the article, while the abstract provided a good summary of the content of the manuscript. In the introduction the authors clearly stated their objectives and the aim of their investigation. The methodology used and results obtained were described by the authors. The study design was suitable for the aim of the study with adequate statistical analysis conducted on the results obtained. Appropriate graphs and pictures which were both clear and informative were included in the manuscript. In the discussion, the authors summarized their findings with these findings being relevant to previous studies. The results obtained supported the claims of the researchers with the speculations and extrapolations being reasonable. The article used language that was scientific. While the

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article provided a lot of information, the authors could have presented the information in a more organised and reader friendly manner. Importance The study demonstrated that the lower replication chronic hepatitis D and hepatitis B virus infection groups show a trend to higher quasispecies complexity than the higher replication chronic hepatitis B group. The findings of this study have the potential to improve the understanding of the mechanism of quasispecies in hepatitis B. References The references used in this manuscript were sufficient, appropriate and recent. Scientific Merit The researchers were able to come up with two possible hypothesis in an attempt to possibly explain the mechanism by which hepatitis delta virus enhances the hepatitis B virus quasispecies. The first hypothesis suggests that the activation of the host innate immune response under the effect of hepatitis delta virus. While the second hypothesis postulates a possible interaction between HDAg and RNA pol II, which could affect the replicative capacity and functionality of the enzyme. This study provided data on the influence of hepatitis delta virus on hepatitis B virus genetic diversity in the HBX gene. Results showed that in the hepatitis B stages with lower replication (CHD and CI), the hepatitis B virus quasispecies in the 5'end of HBX exhibited a trend toward higher complexity than in chronic hepatitis B. This study was warranted and the findings of this study can provide a better understanding of the mechanism of interaction between hepatitis B virus and hepatitis delta virus with regards to the complexity of hepatitis B virus quasispecies. Given the prevalence of Hepatitis B infections, a larger study population could have been used, which would have further validated the results obtained by the researchers. The total study population consisted of 24 patients. While the study population used to compare the HBV quasispecies complexity indices between HBeAg-negative and HBeAg-positive chronic hepatitis D patients consisted of ONLY 4 patients in each group. Recommendations such as the need for further research were addressed by the researchers. The section of limitations with comparison with other

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studies should be expanded. Ethical Issues There was neither plagiarism nor fraud in this manuscript.

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