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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 36089
Title: Study of factors that influence HBV-NTCP interactions in a Spanish population: HBV preS1 variability and prevalence of the rs2296651 polymorphism
Reviewer's code: 00052339
Reviewer's country: Japan
Science editor: Ze-Mao Gong
Date sent for review: 2017-09-28
Date reviewed: 2017-10-03
Review time: 4 Days

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
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[Y] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Study of factors that influence HBV-NTCP interactions in a Spanish population: HBV preS1 variability and prevalence of the rs2296651 polymorphism Casillas R et al. This manuscript showed the results of polymorphism of PreS1 region of HBV and human NTCP gene because of the possibility of interaction between PreS1 and NTCP gene product. The results shown here are not novel and definite. The following points should be addressed: #1 The PCR method should be reconstructed, for example, other primer settings or nested PCR. The rate of successful PCR were very low such as 18 out of 41. Hence, the results of these 18 cases may have much bias. #2 What role is Group B? Did the author try to amplify PreS1 region using the serum or liver tissue of Group B? If Group B just gave the white blood cells or lymphocytes to investigate rs2296651 SNP (S267F), it must be combined to Group C as a control. I think Group B may be divided

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into two subgroups depending on the titer of anti-HBc Ab. If the anti-HBcAb is high, the patient may be HBV carrier with loss of HBsAg. #3 The results of SNP of rs2296651 region were not novel

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 36089
Title: Study of factors that influence HBV-NTCP interactions in a Spanish population: HBV preS1 variability and prevalence of the rs2296651 polymorphism
Reviewer's code: 02607378
Reviewer's country: Australia
Science editor: Ze-Mao Gong
Date sent for review: 2017-09-28
Date reviewed: 2017-10-05
Review time: 7 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[ ] 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		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Manuscript has now been significantly strengthened with improved clarity.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 36089
Title: Study of factors that influence HBV-NTCP interactions in a Spanish population: HBV preS1 variability and prevalence of the rs2296651 polymorphism
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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		[Y] No	[ ] Major revision
		BPG Search:	
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Casillas in the largely revised manuscript describe their studies of variation/conservation of the receptor interacting domain in the large envelope protein of HBV as well as the prevalence of rs2296651 in NTCP, the HBV receptor, in a Spanish population. Although authors well addressed most previous concerns, there are still some critical issues that should be taken care of before this manuscript can be published. Specific comments. 1. The critical argument for the aim of the current study, which is described in the last paragraph of introduction, is that "The degree of sequences variability in a domain is an indication of the extent to which sequence conservation is important in the domain." First, this statement needs support of references with evidence. Second, the so-called domain in the entire manuscript means one on the protein while only genomic sequences were examined experimentally in the current

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study. Authors should discuss this and bear in mind that only sense mutation may result in amino acid sequence change. Third, change(s) of amino acid sequence even in the function/active protein domain may or may not impact the functional interaction. The current study did not perform relevant studies and thus authors should be causations when interpreting the results. 2. Current study actually examined the sequence conservation on viral genome and SNP in subject for viral-receptor interaction, but no any "factor" was examined and no study was performed to test the impact of sequence change on the interaction. Therefore, the title is not appropriate with "factor" that influences … . Instead, it should be something such as "Analyses of HBV preS1 variability and prevalence of the rs2296651 polymorphism in a Spanish population". This concept should be applied to the entire manuscript. 3. The rationale to study sequence variation/conservation in the HBV genome should be further illustrated. It should be clarified that whether one individual can be infected by multiple genotypes of HBV, whether infected viral genomes may have various mutations etc. and what is the impact of HBV subgenotype on this variation/conservation examined here. 4. Please clarify how PCR fragment sizes were determined based on the genomic position on page 9 since the sizes following the nt position are very confusion. In most cases, for example, 2844-56 means 2844 to 2856. Here, it appears that authors want to describe a region starting at position 2844, passing the end of the genome and reaching position 56. However, the genome size or the last nt should be provided considering varied sizes of different HBV genotypes. 5. English writing has been largely improved, but still some faults remain. Right terms should be used consistently through the manuscript. Authors should go through the manuscript carefully again and clearly tell readers what they want to describe using right English. Some, but not all, examples are listed below. 1) It sounds better to change the AIM of Abstract to "Determine variability/conservation of the receptor-interacting domain in the large envelope proteins (LHBs) of hepatitis B virus (HBV) and prevalence of rs2296651 (S267F) polymorphism in sodium-taurocholate cotransporter polypeptide (NTCP), the HBV receptor, in a Spanish population." 2) In Methods of Abstract, NTCP should not be explained again in which, "included and" can be deleted. Or HBV receptor-interacting domain should be used to maintain the consistency of wording. For your information, searching "NTCP-interacting domain" in Pubmed database or google did not yield any result showing this grouped term. In addition, viron vs. host should be clarified, such as "Variability …. Of HBV receptor-interacting domain (aa2-48 in viral genotype D)...". "…, both in the HBV preS1 region," should be deleted. "by next-generation sequencing" should be removed to after the "compared" and add "of viral genome in 18 CHB…". 3) In Results of Abstract, NTCP should be replaced by receptor to be consistent with text above. "HBV preS1 NTCP interacting domain" is an incorrect term and no result was produced from searching this

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grouped term from Pubmed. The conservation is among different viral genomes, but not between aa 9-21, meaning that "the conservation of aa 9-21 region/sequence is stable among examined viral genomes". It is not "referring to", but "in". 4) In the introduction, the 2nd paragraph on page 6, "… , encoded by" should be " … , encoded by the SLC10A1 gene and located on chromosome 14, as …".

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 36089
Title: Study of factors that influence HBV-NTCP interactions in a Spanish population: HBV preS1 variability and prevalence of the rs2296651 polymorphism
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Reviewer's country: Latvia
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Review time: 12 Days

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
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[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Interactions between hepatitis B virus (HBV) and sodium-taurocholate cotransporting polypeptide (NTCP) in hepatocytes could be influenced by the HBV preS1 region and/or the NTCP variability in HBV infected patients. Obviously, the analysis of such variations is important for the appropriate use of anti-HBV drugs which blocks HBV entry by coupling with NTCP or HBV preS1 proteins. The absence of rs2296651 polymorphism in the studied Spanish population is of local importance, as the particular mutation was reported predominantly at Asian population. Subsequently, the number of CHB patient samples with analyzed preS1 sequence is insufficient to drive rigorous conclusions about variability/conservation of that region. In general I do not see this research as basic study, but consider as excellent methodological approach. I highly recommend to improve the method of HBV DNA isolation from serum samples of

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patients with lower viral load by use of larger sample volumes and organic /inorganic extraction methods, instead of Qiagen kit with columns in this particular case.