BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 20196
Title: Overview of hepatitis B virus mutations and their implications in the management of infection
Reviewer's code: 03412690
Reviewer's country: Taiwan
Science editor: Jing Yu
Date sent for review: 2015-06-03 16:38
Date reviewed: 2015-06-17 07:12

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	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This article is a comprehensive review that makes a summary of the main mutations of HBV genome and present the most recent available data about HBV genetic variability and its significance in order to relate these aspects with liver disease evolution and should be accepted for publication in the World Journal of Gastroenterology. There are some comments below: 1. There are some important studies that discuss the significance of pre-S deletion mutation or its combination with other mutations. The author could address this issue in the article. Chen et al (Gastroenterology. 2006 Apr;130(4):1153-68) found that patients with progressive liver diseases have a higher frequency of pre-S deletion and all the deletion regions encompassed T- and B-cell epitopes, and most of them lost 1 or more functional sites. Chen et al. (Gastroenterology. 2007 Nov;133(5):1466-74) found that HBV with a complex mutation pattern (pre-S deletion, T1762/A1764, and T1766 and/or A1768 mutants) rather than a single mutation was associated with the development of liver cirrhosis. Pre-S mutant also plays pathogeneic role in the development of HCC. The pre-S mutant large surface antigens can activate endoplasmic reticulum (ER) stress to induce oxidative DNA damage and genomic instability

(Wang et al., 2006). The pre-S mutant also can upregulate cyclooxygenase-2 and cyclin A to induce cell-cycle progression and proliferation of hepatocytes (Wang et al., 2006). A recent study found that vascular endothelial growth factor-A (VEGF-A) is upregulated by pre-S mutants and that pre-S mutant-expressed Huh-7 cells exhibited activation of Akt/mTOR (mammalian target of rapamycin) signaling and increased growth advantage, which could be inhibited by VEGF-A neutralization (Yang et al., 2009). 2. Seroclearance of HBsAg during lamivudine therapy may not indicate viral clearance and mutation in S gene may play a role. A recent study by Hsu et al. (Gastroenterology. 2007 Feb;132(2):543-50) found that a mutation hot spot, P120A in the S gene, was associated with detection failure of HBsAg. 3. There are several studies that investigates the significance of HBV basal core promoter mutations (A1762T/G1764A) and the occurrence of HCC and its association with different HBV genotypes. The author could cite more studies in this issue. In several cross-sectional (Baptista et al., 1999; Kao et al., 2003) and longitudinal studies (Chou et al., 2008; Fang et al., 2008; Wu et al., 2008; Yuan et al., 2009), HBV basal core promoter mutations (A1762T/G1764A) are found to be associated with the occurrence of HCC. The REVEAL-HBV study from Taiwan found that the multivariable-adjusted hazard ratio of developing HCC was 1.73 for basal core promoter mutations and that the risk was highest among participants infected with genotype C HBV and who harbored the precore 1896 variant and mutations for the basal core promoter (Yang et al., 2008).