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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 23930

Title: Effects of interactions between environmental factors and KIF1B genetic variants on the risk of hepatocellular carcinoma in a Chinese cohort

Reviewer's code: 00005855

Reviewer's country: Japan

Science editor: Ze-Mao Gong

Date sent for review: 2015-12-28 10:08

Date reviewed: 2015-12-28 21:28

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The authors conducted a case-control study with hepatocellular carcinoma (HCC) patients and hospital-based controls to clarify the effect of rs17401966 in KIF1B on HCC and further examined the potential interaction between variants in KIF1B and environmental factors on the risk of HCC in a high-risk region. They found the gene-environment interaction between the KIF1B rs17401966 variant and alcohol consumption in the development of HCC in Chinese individuals. Their findings add valuable knowledge in the field of hepatology. There are a few issues to be addressed. Major 1. As the authors mentioned, the hospital-based samples as control may lead to selection bias of participants. It may be useful to present the clinical characteristics in detail such as the reasons (or diseases) to visit hospital. 2. In Table 1 showing the characteristics of study subjects, more than 25% of HCC patients were without HBV infection. It is recommended to present the etiology or detailed background of patients with HCC (case) such as HCV, alcohol consumption, nonalcoholic steatohepatitis, and so on. 3. There must be correlation among status of HBV, family history of HBV infection, and family history of HCC as variables in Table 1. Minor 1. In the "Genetic variant



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genotyping" section, was the genomic DNA extracted from leukocytes but not lymphocytes?



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 23930

Title: Effects of interactions between environmental factors and KIF1B genetic variants on the risk of hepatocellular carcinoma in a Chinese cohort

Reviewer's code: 00058381

Reviewer's country: Austria

Science editor: Ze-Mao Gong

Date sent for review: 2015-12-28 10:08

Date reviewed: 2015-12-29 01:47

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Major Comment: Drawbacks of this study are a relatively small sample size and a potential selection bias, further studies would be required, but this is duly mentioned by the authors at the end of the discussion. However, more information on the control group should be provided. **Minor Comments:** The references are not consistent with the style described in the Instructions for Authors. Table 1 (footnote): "ORs and 95% CIs was calculated by logistic regression models adjusted age." - Please correct this sentence. Page 11, first paragraph: "prolyhydroxylase" -> "prolyl hydroxylase"?



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 23930

Title: Effects of interactions between environmental factors and KIF1B genetic variants on the risk of hepatocellular carcinoma in a Chinese cohort

Reviewer's code: 02538806

Reviewer's country: Pakistan

Science editor: Ze-Mao Gong

Date sent for review: 2015-12-28 10:08

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	<input checked="" type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The current study was initiated to look for variants of KIF1B (rs17401966 and rs3748578) with HCC. The authors did not find a significant association between rs17401966 and HCC while a significant additive interaction was observed between rs17401966 and alcohol intake. This result is not consistent with the result reported by Zhang et al. thus it is a negative finding. The study samples were made up of individuals with different genetic architectures. Additionally, according to evolutionary theory, individual common variants often exert modest effects on common diseases. The meta-analysis of rs17401966 and HCC of 7,596 HCC cases and 9,614 controls supported Zhang et al., indicating a significant association between rs17401966 and HCC. If there is no indication of association the authors must show some correlations with other loci to make a presentable work. Perhaps, they have to show some mechanism(s) how alcohol intake (metabolism) may influence the outcome of HCC



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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 23930

Title: Effects of interactions between environmental factors and KIF1B genetic variants on the risk of hepatocellular carcinoma in a Chinese cohort

Reviewer's code: 00722050

Reviewer's country: Canada

Science editor: Ze-Mao Gong

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The manuscript regarding "Interactions between environmental factors and KIF1B genetic variants on the risk of hepatocellular carcinoma in a Chinese cohort" is very interesting and the results are very stimulating for further research in this area.

The manuscript is well written, but some parts need to be expanded.

The suggested significant association between rs17401966 genotypes and expression of KIF1B in liver tissues, with carriers of the G allele having greater KIF1B level than individuals with no G allele (AA carriers) is a quite controversial finding. This part should be discussed more.

It has been hypothesized that KIF1B can act as a tumor suppressor. Can you have pleiotropic effects of a tumor suppressor gene?

The gene-environment interaction between the KIF1B rs17401966 variant and alcohol consumption may contribute to the development of HCC in Chinese individuals, but it may be interesting to have a figure showing the alcohol consume in China and HCC rates as well.

The mechanism of carcinogenesis should be expanded to other hypotheses and probably a drawing



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showing the different actions and steps.

In genetics and genetic nomenclature, genes and proteins have different writing (e.g. Italic). There is no uniformity in the manuscript and this should be rectified.