

Format for ANSWERING REVIEWERS

November 05, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13165 -review.doc).

Title: Association of IL-17 polymorphisms may be related with gastric cancer risk in Asian Populations

Author: Zi-Wen Long, Hong-Mei Yu, Ya-Nong Wang, Dan Liu, Yan-Zhi Chen, Yu-Xia Zhao, Lu Bai

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13165

The manuscript has been improved according to the suggestions of reviewers:

To Reviewer 00181101:

This is an interesting collection and meta-analysis of data on the risk of gastric cancer associated with IL17 genes polymorphisms. Gathered data and statistical analyses seem to be comprehensive and detailed, However authors should discuss more on the 'functional' effect of investigated polymorphisms, as in part it is addressed in the discussion section (page 9, last sentence). If the scientific hypothesis is that certain IL17 genetic variants predispose to enhanced inflammation and hence to increased risk of inflammation-related cancer (such as Hp-related gastric cancer), then authors should search for evidence of increased expression and function of IL17 axis and IL17-driven inflammatory response associated with rs2275913A and rs763780C alleles (in presence and absence of Hp infection). If these data are not available they should at least discuss on the need for future experimental models investigating functional effects of IL17 gene polymorphisms and how these studies should be designed in preclinical and clinical settings.

Response: Thank you for your advice and we are very sorry for our incomprehensive consideration that disturbed you, and we have added some contents in the discussion section (page 9, last sentence) regarding functional effect of investigated polymorphisms with "To be more specific, IL-17A and IL-17F have been suggested to share the similar functions with regard to their ability to stimulate various chemokines, cytokines and adhesion molecules in recruiting and activating neutrophils [21]. With regard to this, both of the two cytokines, coordinately or independently, may have an influence in promoting the development of gastric inflammation and further inducing the development of gastric malignancy. Moreover, IL-17F (7488T/C) was indicated to be related to H. pylori-infection to increase the activity of inflammation, and thereby revealing an association with the risk of intestinal-type gastric cancer [42]." And considering the present data are not available for deeper investigation, we added in the limitation part with "Finally, we failed to find out adequate evidence of increased expression and function of IL-17 axis and IL-17-driven inflammatory response associated with rs2275913A and rs763780C alleles(in presence and absence of H. pylori-infection), which largely restricted the comprehensive explanation of IL-17 polymorphisms and gastric cancer risk, and future experimental models concerning the enrollment of H. pylori-infection might be credible and authentic."

To Reviewer 00069023:

The article 'Association of IL -17 polymorphisms may be related with gastric cancer risk' by D. Liu et al. is an original article to elucidate the relationship between the IL-17 gene and gastric cancer risk, especially those carried with rs2275913 G>A and rs763780 T>C polymorphisms. The authors systematically reviewed published studies on IL-17 polymorphisms with gastric cancer risk in the current literatures and seven case-control studies met the inclusion criteria. The IL-17 gene polymorphisms might be important in determining an individual's susceptibility

to gastric cancer after a meta-analysis method. The results of this manuscript are important to readers that gastric cancer is related to gene molecular variation. But there are some points that the authors need to clarify:

Major point:

a. These participated subjects of seven case-control studies are confined to Asian people (4 Chinese populations, 2 Japanese populations and 1 Iranian population) rather than those in the world. The reviewer hopes the authors describe this point in title and abstract.

b. The authors need to review the accurate populations involved this study, because it will affect the final results. The accurate populations are 4 Chinese populations (ref. 7, 24, 31 and 32), 2 Japanese populations (ref. 21 and 30) and 1 Iranian population (ref. 8) rather than 5 Chinese, 1 Japanese and 1 Iranian population listed in Page 7, Line 13-14.

c. Minor point: 1. Please correct the accurate reference behind the author listed in Table 1.

Response: Thank you for your comments, we have revised the title into "Association of IL-17 polymorphisms may be related with gastric cancer risk in Asian Populations", added the population information in the abstract section with "exploring the association between IL-17 rs2275913 G>A and rs763780 T>C polymorphisms and susceptibility to gastric cancer in Asian populations" in the first sentence, and in the last sentence of the abstract with "There may be a relationship between the IL-17 gene and gastric cancer risk in Asian populations", and we re-checked carefully with regard to the accurate populations involved this study with "All articles were case-control studies that evaluated the correlation of IL-17 genetic polymorphisms and susceptibility to gastric cancer in Chinese populations (4 studies), Japanese population (2 study), and Iranian population (1 study)". We have corrected the accurate reference behind the author listed in Table 1.

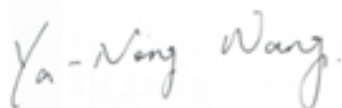
To Reviewer 02543990:

Although environmental factors play roles in the etiology of gastric cancer (adenocarcinoma), only a fraction of the exposed develop the disease, suggesting a genetic susceptibility in the general population. It is likely that single nucleotide polymorphisms (SNPs) located in gene promoter may cause differential gene expression, resulting in deregulated gene expression. In this manuscript, Liu D et al., extracted the published data to do meta-analysis of the relationship between the IL-17 gene polymorphisms and gastric cancer risk. They conclude that IL-17 rs2275913 and rs763780 polymorphisms are associated with increased susceptibility to gastric cancer. Overall, this is a very interesting study, the experiments are well designed and conducted, and the data are properly analyzed and presented, and the limitations of this study are also discussed. Thus, the result from this study may provide useful information in the field of IL-17 in gastric cancer. No significant flaws are noticed. It is suggested to revise the manuscript to get it more concise.

Response: I have paid attention to this question, we have revised this manuscript to get it more concise in a revised form.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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