

## Format for ANSWERING REVIEWERS

December 21, 2013

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 6887-TOPIC HIGHLIGHT-revised.doc).

**Title:** Role of gene polymorphisms in gastric cancer and its precursor lesions: current knowledge and perspectives in Latin American countries

**Author:** Miguel A. Chiurillo

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6887

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

### 1 Format has been updated

### 2 Revision has been made according to the suggestions of the reviewer

#### (1) Reviewed by 00003649

Comments: Minor points 1. The last sentence in page 6 (In total were evaluated....) is unclear to understand. Please have a check and make clearer. 2. Some of the abbreviations (for examples, SSCP and SSOP) were described just one time. I would suggest not presenting these abbreviations. 3. Typo: Latin America countries -> Latin American countries (page 3, 4, 5 etc).

**R: all points were considered and the suggestions and corrections were assumed.**

#### (2) Reviewed by 00340828

Comments: However, there are a number of very recent studies published by the groups of P.R. Taylor in NIH and P. Rosenstiel in Germany both using diverse ethnic populations to summarize findings on a number of new genes and variants associated with the risk of GC development with new methodologies and approaches. Their major findings are necessary to be integrated into the beginning and more importantly in the perspectives of the review, since the author realizes the Latin American population is highly admixed in nature, and sample source and size are pivotal to the success of the study. In addition, a few minor but important items should also be modified: 1. All gene symbols should be in italic throughout the article; 2. The reference is missing for the last paragraph of page 4; 3. The reference numbers are missing after "58 articles" at the beginning of page 7; 4. Reference #93 is not cited anywhere; 5. A few misspelled, misphrased or missing words: a. Change "leaded" to "led" in the second paragraph of page 3; b. Remove "gene" after "TP53" in the second paragraph of page 9, for "TP53 Arg72Pro"; c. Add a "to" for "In regard to the analysis.....", or could be "Regarding the analysis....." without "In", in the third paragraph of page 14; d. Change "for" to "to" for "in order to....." in the last paragraph of page 14.

**R: all points were considered and suggestions and corrections were assumed.**

Some studies of the group of Dr. Taylor were already mentioned in the original version of the manuscript. However, taking into account the suggestion of the reviewer, I considered other publications of this important research group and added a paragraph in the conclusion and perspectives.

Please take into account the reference numbers at the end of the second paragraph on page 7. These studies are used to make Figure 1. In many cases they are not used in the rest of the article.

### **(3) Reviewed by 02537458**

Comments:

Comments Scope The article does fit the scope of the journal. The concept of the paper is not new; there are plenty of review articles devoted to this issue in recent literature. Format and structure The author made an attempt to make a comprehensive literature review of 64 inherited variations in 40 genes, that's very pretentious task. Furthermore, besides gastric cancer itself, Dr. Chiurillo considers premalignant lesions as well. To be honest, this are the reasons why the paper's body is so inarticulate and vague.

**R: the aim of the review is to emphasize the importance of gastric cancer in Latin America, taking into account some particular characteristics of this region of the world, and emphasizing the importance or the role of host genetic polymorphisms in this multifactorial disease.**

I attempted to do a review of most studies (case-control) of the association between gene polymorphisms and gastric cancer published with samples from Latin Americans countries. Not only to discuss the contribution in this regard that has been done so far, but to establish some of its limitations. Several of these works, since they have not been written in English, have not been taken into account in some meta-analyses. Studies analyzing premalignant lesions of the stomach were also included, because I believe in the importance of this research for better management of gastric cancer.

**I tried to improve the writing of most of the manuscript.**

For example, when considering the SNPs within the IL-10 gene, the authors showed the results of 2 case-control studies and after that mentioned the meta-analysis based on 12 studies. What for? If there are, say, 40 studies and 2 meta-analyses devoted to an SNP, obviously there is no need to waste words discussing separate studies, isn't it? In case if there are no meta-analyses, it is compulsory to mention all the studies in your article then.

**R: I do not completely agree with the reviewer in this regard. I think that meta-analyses not invalidate the results of previous or future works, especially in a regional context. Regarding *IL-10* polymorphisms, the studies that were considered more relevant were discussed, and I brought up the meta-analysis of Zhu *et al.* (2011) in order to emphasize the controversies and inconsistencies observed in studies worldwide and the alleged role of the ethnic factor.**

The choice of genes for the review is also not good. It is well-known that *H.pylori* plays a major role in gastric cancer, and Dr. Chiurillo mentioned this in his work repeatedly. It would be logical to discuss studies devoted to Toll-like receptors` SNPs and how they affect gastric cancer risk specifically in Hispanic population.

Nevertheless, the author included only one such study and therefore couldn't do a proper analysis of this interesting question. Brief search in pubmed revealed the following studies which could have been analyzed in this article: PMID: 22468087 (Brazil), 18755634 (Mexico). A review article must have clear purpose.

**R: The choice of genes and polymorphisms discussed was made based on the number of published papers, study design, the proportion of studies that reported positive associations and those including "less common" or recently considered candidate genes for gastric cancer in GWAS.**

**I agree with the comment about the importance of Toll-like receptors in infection with *H. pylori* and its possible influence on the risk of gastric cancer. Therefore, out of the four studies found about TLR2 and TLR4 polymorphisms, two Brazilian reports already were briefly discussed in the original version of the manuscript. However, understanding the importance of Toll-like receptors in the context of this work, it was included a paragraph in the revised version where the four studies are discussed.**

In the introductory paragraph, the author claims that significant variations in the incidence of gastric cancer have been observed between different ethnic groups like African-Americans, Hispanics and Native Americans, and this may be due to, besides other factors, genetic variation. According to this thesis, Dr. Chiurillo should have, presumably, critically analyzed the difference between the results from Hispanic populations altogether and other populations altogether to reveal some, let's say, ethnicity-specific associations. Otherwise, focusing on Hispanic population specifically (not comparing it to others) doesn't make sense at all (unless facilitating the task). Of course, the reason that Latin America countries display some of the highest mortality rates worldwide is acceptable for writing a review article as well, but frankly, that's not very convincing.

**R: As is generally considered in population studies, it is necessary to take into account the possible effect of mixed origin and the possibility of substructures in some Latin American populations. Although, in studies reviewed there are differences in results that can be attributable to genetic background of populations, I can't establish that there are ethnicity-specific associations.**

In conclusion section, Dr. Chiurillo gives very common and vague generalizations which are well-known and boring. Suggest rewrite this section.

**R: I tried to improve the section Conclusions and Perspectives.**

Minor reservations. Table 1 should include (1) model of inheritance, (2) odd ratios, and (3) confidence intervals. Genes should be italicized when mentioned in the text.

**R: Table 1 now includes information about model of inheritance, OR and CI when they were available.**

**Genes were italicized.**

**3 References and typesetting were corrected. Please take into account the reference numbers at the end of the second paragraph on page 7. These studies are used to make Figure 1. In many cases they are not used in the rest of the article.**

**4 It was included three studies that they had not been considered in the original version of the article. Because of this, a paragraph on the analysis of polymorphisms of *IL-8* was also added.**

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

Sincerely yours,

A handwritten signature in dark ink, appearing to read 'Miguel Angel Chiurillo', with a stylized flourish at the end.

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