

ANSWERING REVIEWERS

August 25, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Genetic polymorphisms of CTLA-4 and MDR1 increase the risk for ulcerative colitis

Author: Jia-Jun Zhao, Hong-Yu Li, Di Wang, Hui Yao, Da-Wei Sun

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16250

Reviewer 1:

The manuscript evaluates multiple polymorphic studies of CLTA4, MDR1 in ulcerative colitis. The manuscript is very well written and carried out. However, minor details should be addressed and corrected.

1、 Title should contain the word: meta-analysis or multiple studies.

Response: We're appreciated for your kind advice. The title now has been revised "*Genetic polymorphisms of CTLA-4 and MDR1 increase the risk for ulcerative colitis: a meta-analysis*".

2、 (page numbers are missing)

Response: Thanks a lot. Page numbers have been added into our manuscript now in order.

3、 In the discussion: the results should be compared with GWAS results. If there is any, it should be said.

Response: Thank your for your comments. We have added "*Recent genome-wide association studies (GWAS) have discovered multiple genes and loci for UC risk factors, for example, GWAS meta-analyses have established more than 30 loci in CD, and several of these loci have also been found to be correlated to UC. The GWAS that evaluated the correlation between UC and the variants of the CTLA-4 gene and MDR1 genes have produced contradictory or inconclusive results, we found that the associations have been found in some, but not all populations*" into the discussion section.

4、 In the discussion: The definition of the diseases should be discussed. It may be one limitation factors that in some article the patients have mild or severe disease. Are all the disease definitions the same in all selected articles?

Response: We're grateful to you for your helpful comments. We have added "*UC is a non-specific chronic inflammatory disorder which, together with CD, is known as IBD, and it is characterized by diffuse mucosal inflammation confined to the colon. Evidence has revealed that genetic factors and immune dysregulation may be two main important components in the etiology and pathogenesis of UC*" into the discussion section.

Reviewer 2:

1、 The authors address with their meta-analysis the risk of ulcerative colitis in the presence of genetic polymorphisms of CTLA and MDR1. The title should inform that this is a meta-analysis. Since page numbering has not been provided the pages were numbered by the reviewer beginning at title page for reviewing purposes.

Response: Thank you for your comments. The title now has been changed into “**Genetic polymorphisms of CTLA-4 and MDR1 increase the risk for ulcerative colitis: a meta-analysis**”. Additionally, page numbers have been added into our manuscript now in order beginning at title page.

2、 Introduction: This section is too long. The explanations regarding CTLA-4 (here the display should be unified either CTLA-4 or CTLA4) and MDR1 are not focus of this manuscript and the reader should be familiar with this. Therefore, the first paragraph on page #3 should be significantly shortened or deleted.

Response: We’re grateful to you for your helpful advice. First, the word “CTLA4” appeared in this manuscript has all been unified as “CTLA-4”. Since CTLA-4 and MDR1 are not focus of this manuscript and the reader should be familiar with this, we have significantly shortened or deleted some redundant information on the explanations regarding CTLA-4 and MDR1, and the manuscript is more concise now.

3、 Materials and Methods: The authors list the sources for their CASP criteria. This is sufficient and every reader may comprehend. Additional information is therefore redundant (page #5, line #7 ff). A sensible additional criterion in this context would be the clarification if the analyzed did have valid power calculations; from the CASP criteria this is in general not obvious but does have relevance for the quality assessment of the studies.

Response: We would like to express our thankfulness for your helpful comments on this paper. As you said, there was no need to list all the items of CASP criteria and reader can comprehend it if we just list the sources for CASP criteria. Therefore, we deleted “**The CASP criteria for case-control studies include Section A (CASP01~CASP07); Section B (CASP08~CASP09) and Section C (CASP10~CASP11). In detail, the 11 questions were described as following: the study address a clearly focused issue (CASP01); the research problem is appropriate and the research design answers the research problem (CASP02); the cases recruited in an acceptable way (CASP03); the controls selected in an acceptable way (CASP04); the measurement for exposure factors is accurate to minimize bias (CASP05); the study controls other important confounding factors (CASP06); the research result is complete (CASP07); the research result is precise (CASP08); the research result is reliable (CASP09); the research result is applicable to the local population (CASP10); the research result fit with other available evidence (CASP11)**” in the part of Data extraction and quality assessment.

4、 Results: The tables with their columns are pretty tight and therefore chosen unclear. Comma digits requiring 2 lines are not the best presentation. Furthermore, a relevant amount of information is redundant between tables and figures, as an example table 2 and figure 3. These double presentations should be shortened. Discussion: Within the discussion the authors try to correlate their results quite often with single studies, see page #8, line 17-20 (ref #35) etc. It is not very sensible to compare the results of a meta-analysis with those of single studies. Once the authors decided on criteria for the selection of the studies then the results of the meta-analysis are as they are. Taken together the here presented manuscript is a solid work, which should be published after minor revisions.

Response: Thank you for your helpful comments. We have made some adjustments on the tables, and they can be clearly distinguished now by readers. We have deleted some redundant information on the legends, and try to make it in one line as much as possible. In addition, since some tables and figures appeared several times in our manuscript, we marked A to F to avoid duplicate narration. In the discussion section, the cite of single study was for proof or evidence, and additionally, the study we cited were not included in our meta-analysis. Further, we have also added “**Recent genome-wide association studies (GWAS) have discovered multiple genes and loci for UC risk factors, for example, GWAS meta-analyses have established more than 30 loci in CD, and several of these loci have also been found to be correlated to UC. The GWAS that evaluated the correlation between UC and the variants of the CTLA-4 gene and MDR1 genes have produced contradictory or inconclusive results, we found that the associations have been found in some, but not all populations**” into the discussion section for compare the our results with GWAS results.

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Peter LAKATOS', with a long horizontal stroke extending to the right.

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