ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

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

Title: RAGE Gene Three Polymorphisms with Crohn's Disease Susceptibility in Chinese Han Population

Author: Zhengting Wang, Jiajia Hu, Rong Fan, Jie Zhou, Jie Zhong

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4571

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

Reviewer #1:

(1) Please check the entire manuscript in order to avoid typing an punctuation errors (Conh's, hapotypes, did'nt among others sould be corrected).

Answer: We have carefully check the entire manuscript and corrected the punctuation errors.

(2) Please clarify if some relationship exist between Table 1 of your manuscript and the article which is linked to this Table (PLoS One. 2012; 7(6): e39814.) If all data are collected from a single population should be mentioned in your manuscript and cite the article about original project or any previously reported with the common studied population.

Answer: We confirmed the subjects enrolled in this study was not same to the Niu's study.

(3) The major suggestion from me on this manuscript is about improving approach the known functions suggested for RAGE and the probable implication of polymorphism with greater detail as is herein presented (you can include references such as (1) Sterenczak KA, Nolte I, Murua Escobar H.RAGE splicing variants in mammals. Methods Mol Biol. 2013;963:265-76, (2)Rouhiainen A, Kuja-Panula J, Tumova S, Rauvala H. RAGE-mediated cell signaling. Methods Mol Biol. 2013;963:239-63.). Also you can infer in better form the impact of your Gene-polymorphism detected if you infer about the traslational consequences of the presence of any of the three reported polymorphism. This can be made by a carefully analysis of posible consequences in protein sequence (inclusively by a quick analysis using computational tools from NCBI) and revision on the reported data.

Answer: We have revised the paper and added the references according to the reviewer's suggestion.

Reviewer #2:

(1) The authors declared that "312 CD patients and 479 healthy controls were age- and sex-matched", but the number of cases were 312, the number of controls were 479. So the cases were NOT age- and sex-matched with the controls. Actually, in Table 1, 42 patients were diagnosis under 17 years, but the controls were not pointed out how many people under 17 years.

Answer: In this study, 42 patients were diagnosed under 17 years old in the CD group with 63 patients in the contrast group, which showed no statistical difference.

We grouped 1:1.5 into CD and contrast group and get 312 cases in the CD group and 479 cases in the contrast group. Both age and gender are similar in two groups. Thus, we revised accordingly due to Reviewer's suggestion.

2) The statistical analysis reported in the manuscript was appropriate. Although, the study should give a reasonable power analysis to detect an association, and explain why the number of samples in the manuscript could (or not) support a conclusion. The reviewer believed the sample size in this study perhaps was not large enough for a case-control population study.

Answer: In response, we have performed a power calculation as suggested. At the 0.05 level of significance with the two-sided test，our study had 69% and 53% of power to detect a significant association of the rs1800624 and rs2070600 polymorphisms with the risk of CD under a dominant genetic model，respectively. Meanwhile, we have addressed the relative small samples is one of the limitations in this study in **Discussion.** However, In China, the incidence and prevalence rates of Crohn's Disease are lower than those in the US. So relatively speaking, a single centered case-control study will not get a large quantity of cases.

3) The recent publications in the same field are missing. Did the authors compare their results with recent GWAS, especially the studies using Chinese cohorts? They should write some comments in the discussion.

Answer: In response, we have searched the current literature databases as suggested on Sep 20, 2013, however, we failed to find any GWAS results using Chinese CD cohorts.

4) The reviewer has questions about the selections of the "three SNPs".

Answer: The "three SNPs" in RAGE gene located at the promoter region, exon3 and exon4, respectively. They were most common studied in several pathophysiological processes associated with inflammation, such as diabetes complications, arthritis, as well as asthma. Therefore, we selected the "three SNPs" as candidates.

5) The possible associations between the selected SNPs and RAGE expression (mRNA and proteins) and/or clinical symptoms were missing. This could enhance the conclusion.

Answer: We have addressed the association between SNPs and RAGE expression and

function in the **Discussion (Paragraph 2 and 3)**. Meanwhile, thanks a lot for the reviewer's advise and we would conducted a multicenter research to answer to association between SNPs and clinical symptoms in the near future based this single-center research,

3 References and typesetting were corrected

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

Sincerely yours,

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