ANSWERING REVIEWERS

August 27, 2012

Dear Editor,

Please find enclosed herewith the edited manuscript in Word format (file name APOE_IBD.Text Revised.docx).

Title: Genetic association of Apolipoprotein E polymorphisms with inflammatory bowel disease

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Name of Journal: *World Journal of Gastroenterology*

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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 reviewers:

Reviewer 1 (*00043819)*

In this article the Authors studied the association between APOE polymorphism and IBD in a Saudi Arabia population. The paper is well-written, and I think interesting for the Readers of WJG.

Answer

The authors thank the reviewer for his encouraging comments.

Reviewer 2 (*00044333)*

The authors presented genetic association of APOE polymorphisms with UC and CD. Although the case number is small, they described the results well and showed some new findings like association with CD. If the authors could add some additional results, like association with clinical phenotype, severity and prognosis, it would be helpful to improve the quality of manuscript.

Answer : The authors thank the reviewer for the valuable suggestions. Besides studying the association between alleles and genotypes of APOE polymorphism and IBD

susceptibility, an attempt has been made to study the association of this polymorphism with the gender of host, age of onset and clinical type of IBD (CD or UC) as well as form of IBD (familial or sporadic). The results have been discussed thoroughly. The further study has been planned to study the role of APOE polymorphism in prognosis and treatment of IBD.

Reviewer 3 (*00045410)*

A nice study documenting an association between APOE polymorphisms and IBD from Saudi Arabia. It confirms preliminary data from China that APOE polymorphisms constitute a greater risk for IBD albeit a small one. The authors should suggest the overall relative risk of development of IBD with one or more polymorphism(s) of APOE genes. Their data suggests similar association between APOE polymorphisms and ulcerative colitis as well as Crohn's disease except for frequency of genotpe ε3/ε4 was significantly higher in UC patients but not in CD patients. How do the authors explain this observation? Do the authors have data on other autoimmune diseases in their IBD patients? The APOE polymorphisms have been documented with a host of illnesses including autoimmune diseases and such varied illnesses as Alzheimer's disease and psychiatric illnesses. The authors could elaborate a bit more on the possible role of APOE polymorphisms in IBD. The authors mention that Crohn's disease was classified as per Montreal classification but they did not describe their results as per phenotypes of this classification. Similarly a comment on association of APOE polymorphisms with disease severity and treatment response could be given. I think there are far too many references which could be shortened. There are a few mistakes in some references e.g. ref 40. Some of the tables could be better represented as bar diagrams.

Answer: The authors thank the reviewer for valuable comments/suggestions.

1. The relative risk of development of IBD with the allele ε4 of APOE gene has been mentioned in the results section and also shown in Tables 1, 2 & 4 as suggested by the reviewer.
2. Our results indicated similar association between APOE polymorphisms with UC and CD except for the frequency of ε3/ε4 genotype which was significantly higher in UC (P= 0.03) but not in CD (P=0.66). However, the relative risk values calculated for

ε3/ε4 genotype in UC and CD being >1.0 (RR=2.34 and RR=1.28 respectively as shown in Table 4) indicated similar positive association for both.

3. The reviewer very rightly mentioned that the APOE polymorphisms have been documented with a host of illnesses including autoimmune diseases, Alzheimer's disease and psychiatric disorders. We have also reported association APOE polymorphism with schizophrenia, glaucoma and psoriasis in Saudi population. Keeping in mind these facts, the IBD patients having any autoimmune or psychiatric disorders were excluded from this study.
4. The possible role of APOE polymorphisms in IBD susceptibility has been discussed in detail in discussion section.
5. We also assessed CD patients based on Montreal classification but we could not find any significant variation to relate with the polymorphism results, may be because of small number of each phenotype.
6. Regarding treatment response, further study has been planned to study the role of APOE polymorphism in prognosis and treatment of UC and CD.
7. For the association of APOE polymorphisms with disease severity, the patients included in the study have severe disease at some time during disease period.
8. Some of the references has been deleted as suggested by the reviewer and all references has been checked for correctness.
9. A bar diagram (Figure 1) has been included as suggested.

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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