

Dear Editors and reviewers,

We appreciate your valuable comments on our manuscript "Ethnic Differences in Genetic Polymorphism Associated with Irritable Bowel Syndrome" (NO. 54450)". The manuscript has been carefully revised in response to each of the peer reviewers' comments and suggestions as below. Changes are highlighted in the revised manuscript.

REVIEWER #1 (Code: 03887097)

Q1-4: 1. A lot of the content in this paper builds on that of an earlier review published in 2014. The earlier paper should be properly referenced (citation: ncbi.nlm.nih.gov/pmc/articles/PMC4273120). 2. Please change "IBS is one of functional gastrointestinal (GI) disorders" to "IBS is a functional gastrointestinal (GI) disorder". 3. "The development ... immunological activation, etc." This requires at least a citation. Suggest authors to cite a recent review on the role of inflammation in IBS (citation: ncbi.nlm.nih.gov/pmc/articles/PMC6159811). This is relevant to the discussion on the potential etiopathogenesis of IBS. 4. Please change "for readers to picture... genetic studies" to "for readers to get an overview of the potential ethnic differences in genetic polymorphism associated with IBS".

Response: Thanks for your thoughtful suggestions. We have referenced those articles (Page 5, Line118; Page5, Line124-126) and polished sentences (Page 4, Line 92; Page5, Line123-124) as you recommended.

Q5: "which certainly requires more concerns" - although the authors repeatedly assert that genetic polymorphisms associated with IBS deserve further concern, this remains unsubstantiated with clear evidence. What is lacking is a fundamental understanding of the mechanisms on how genetics may determine the clinical manifestations and therapeutic responses to subset of IBS patients.

Response: Thanks for this comment. We aimed to emphasize the consideration of ethnicity in studies related to IBS genetic polymorphisms.

The word “certainly” has been removed to avoid absolutization (Page 20, line 549). As you mentioned, it is crucial to understand the mechanisms. We agree that findings reached to the underlying mechanism such as “cis-regulatory variant revoked by c.*76 G>A affects miRNA-related expression in the regulation of serotonin receptor gene” (Page 8, line 206-209) are profound. But yet few studies succeed in uncovering the whole mechanism of connections between genetic polymorphisms and the clinical phenotype. Thus, this point of view has been included into our discussion about “Limitations and Challenges” (Page 21-22, line 583-587) -- “the specific mechanism in terms of how those genetic polymorphisms influence clinical manifestations and therapeutic responses in IBS patients has not been fully illuminated nowadays. It might interfere the subsequent investigation into the essence of ethnic impacts on IBS-related genetic polymorphisms”.

REVIEWER #2 (Code: 00643598)

Q1: *“In the text all acronyms should be explained”, See for example at the beginning of Introduction "IBS".*

Response: Thanks for your reminder. We have revised and rechecked abbreviations in the manuscript (Page 4, line 92 and 97).

Q2: *This is a narrative review, however should specify a general methodology of literature research (for example Medline from...to...; key words...)*

Response: Thanks for your advice. We have specified the general methodology of our search strategy in the manuscript as you suggested (Page 23, Line 621-630).

Q3: *When the authors discussed "GENETIC POLYMORPHISMS IN MUCOSAL IMMUNE/ INFLAMMATORY ACTIVATION2 a focus on microbiota and polymorphisms should be done. Please see and report 1) Altered profiles of fecal metabolites correlate with visceral hypersensitivity and may contribute to symptom*

severity of diarrhea-predominant irritable bowel syndrome. by Zhang WX et al. 2) Irritable bowel syndrome: the clinical approach. by Adriani A et al. In case of lacking data this should be highlighted. Hence, could a particular polymorphism influence microbiota composition and IBS?

Response: Thanks for your recommendations. We have retrieved latest articles and considered carefully about the role of microbiota in IBS-related genetic polymorphism. A paragraph has been added to address this issue in the revised version (Page 18-19, line 494-506) -- “The microbial composition is linked to mucosal lymphocyte phenotypes in post-infectious IBS; intestinal antibacterial gene expression relates to bacterial profiles and immune activity in IBS patients; both the altered profile of the intestinal microbiota and faecal microbial metabolites were evinced to be correlated with the symptom severity of IBS. As to the microbiota-related genetic polymorphism, mutations in the mitochondrial genome lead to divergent gut microbial compositions in mice. But since there is no evidence of a particular genetic polymorphism closely related to gut microbial communities in IBS patients yet, the potential ethnic impact of gut microbiota will not be discussed in detail here and it could be explored in the future”.

REVIEWER #3 (Code: 02941507)

Q: *An excellent review regarding Ethnic Differences in Genetic Polymorphism Associated with Irritable Bowel Syndrome. Every part of the review including the graphics and the table is perfect. A minor suggestion: A list with the abbreviations used in the paper might be useful for the readers.*

Response: Thanks for your precious comments. You could find the newly attached “List of Abbreviations” in our manuscript (Page 22-23, line 610-619).

Sincerely,

Prof. Xiucan Fang, MD, on behalf of all the authors.

Department of Gastroenterology

Peking Union Medical College Hospital, Chinese Academy of Medical
Sciences and Peking Union Medical College, Beijing 100730, China.

Tel: +86-10-69156892; Fax: +86-10-69161963

E-mail: fangxiucai2@aliyun.com