

PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 40964

Title: Genetic associations of inflammatory bowel disease in a South Asian Population

Reviewer's code: 03662987

Reviewer's country: Malaysia

Science editor: Jin-Lei Wang

Date sent for review: 2018-08-27

Date reviewed: 2018-09-04

Review time: 8 Days

| SCIENTIFIC QUALITY | LANGUAGE QUALITY | CONCLUSION | PEER-REVIEWER STATEMENTS |
|---|---|---|---|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept | Peer-Review: |
| <input type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language | (High priority) | <input checked="" type="checkbox"/> Anonymous |
| <input type="checkbox"/> Grade C: Good | polishing | <input type="checkbox"/> Accept | <input type="checkbox"/> Onymous |
| <input checked="" type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade C: A great deal of | (General priority) | Peer-reviewer's expertise on the |
| <input type="checkbox"/> Grade E: Do not | language polishing | <input type="checkbox"/> Minor revision | topic of the manuscript: |
| publish | <input type="checkbox"/> Grade D: Rejection | <input type="checkbox"/> Major revision | <input type="checkbox"/> Advanced |
| | | <input checked="" type="checkbox"/> Rejection | <input checked="" type="checkbox"/> General |
| | | | <input type="checkbox"/> No expertise |
| | | | Conflicts-of-Interest: |
| | | | <input type="checkbox"/> Yes |
| | | | <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

The authors attempt to reveal the association of 16 risk SNPs, previously reported in Caucasian populations, with IBD patient in Sri Lanka. A good amount of subjects (200 CD; 214 UC; 465 controls) were recruited for the study from five localities across three major regions. The justification of research intend is valid and could yield meaningful

insights onto the predisposing genetic factors of IBD in Sri Lanka. The experimental design and typing method are suitable for a genetic association study.

Despite that, parts of the study are inadequately explained and analyzed, especially for data analysis of the genetic association, which may result in bias interpretation. I also found a number of inconsistencies that requires further formatting throughout the manuscript. I believe that the data in this manuscript is valuable and could fill the gap of knowledge for the mutation prevalence in IBD patients of South Asia, provided that a more comprehensive analysis is to be carried out on the data.

Below are some major comments to the authors:

1. Genetic association study should examine both allelic and genotypic distribution for each marker. Authors only analyzed the genotypic frequencies with a p value (2×3 contingency table on 2 df) as in Table 2. 2×2 contingency table with different genetic models (ie, dominant, recessive, additive) should be performed for chi-square test/Fisher's exact test with odds ratios and 95% confidence interval for a more meaning analysis.
2. It is unclear that which allele/genotype is risk/protective to the disease.
3. Are the patients diagnosed according to a set established criteria, such as Vienna classification? If yes, it should be stated in the manuscript and these characteristics should be summarized in Table 1.
4. Are the patients and controls comprised of different ethnicity (Sinhalese, Tamil, Muslim)? If yes, stratification analysis should be performed as genetic heterogeneity is readily known to cause bias in genetic association study.
5. Methods [study population]: Authors mentioned that an equal number of unrelated controls were recruited. But, there are 414 patients vs 465 controls, which is not equal. If it is not 1:1 matching, what is the actual ratio? It would be helpful to include the basic demographic data (eg, age, gender, ethnicity) of the controls in Table 1.

6. Authors could elaborate on the typing methods as it is too brief. The same for result section.
7. Table 1: why a significant test is needed (*p* value) since CD and UC are two known subtypes of IBD.
8. Table 2: CD and UC are two known distinct types of IBD, they should be analyzed separately, instead of together.
9. Table 2: The total number of cases is 415 here, as opposed to 414 mentioned in the text. Please check.
10. Authors should check the data and numbers in tables carefully. Table 1: the percentage is not tally with the number (eg, family history - $7/200 = 3.5\%$, instead of 4.65); Duration of disease should be in (mean, SD) instead of (number, %).

Minor comments:

1. Abstract [methods]: Subject information should be mentioned here.
2. All gene names should be standardized and in italic.
3. Check for consistency throughout the manuscript, eg IL12B/IL12-B;
south-asian/south Asian; case-control/case control; p/P/*p*; 100,000/100000; Bonferroni instead of Bon Ferroni.
4. Some keywords may be too lengthy, eg *LAMB1* gene mutation, *IL-12B* gene mutation, genetics of inflammatory bowel disease.
5. There is consistent appearance of unwanted hypen (-) at the end of the rows.
6. Methods [statistical analysis]: "The statistical methods in this study..." this sentence could be moved to acknowledgement, perhaps.
7. Table 3: Instead of expressing CD and UC as phenotype, I suggest 'subtype', as phenotype is better fit for clinical characteristics in this case control study.
8. Table 3: rs9822268 is located at intron-17 of *APEH* gene, not other gene.



**Baishideng
Publishing
Group**

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https:// www.wjgnet.com

9. Table 3: it is unclear that odds ratio in this table refers to which allele/genotype of the marker.

10. Table 4: some characteristics analyzed here are not included in table 1 nor mentioned in the text, eg GIT location of inflammation.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☒ No

BPG Search:

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- ☐ Duplicate publication
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- ☒ No

PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 40964

Title: Genetic associations of inflammatory bowel disease in a South Asian Population

Reviewer's code: 01467363

Reviewer's country: Slovenia

Science editor: Jin-Lei Wang

Date sent for review: 2018-08-27

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| | | | <input type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

Title: accurately reflects the topic and contents of the paper. **Short title:** appropriate.

Abstract: 201 words, is appropriate, structured. **Key words:** 6 key words, define the content of the paper. **Core tip:** 93 words, is appropriate. **Introduction:** 474 words, is informative, the reader is acquainted with the known facts about IBD patients and

research objectives: genome-wide association studies, GWAS, and candidate gene association studies have in the past identified more than 160 genes associated with IBD in Caucasians. The genetic contribution to IBD varies between regions and ethnicities. The authors highlight the fact that the study was conducted in a population that had not been studied before - among Sri Lankans! Material and methods: 621 words, the research methodology is properly explained (study design, data collection, genotyping, statistical analysis - Bonferroni correction is a conservative test that protects from Type 1 Error). Results: 141 words, results are mainly presented in 4 tables (Table 1. Characteristics of the patient population; table 2. Results of the cases control analysis for the association of SNPs with IBD; table 3. Associations of variants with Cohn's disease and Ulcerative Colitis; table 4. The association of SNPs with clinical characteristics of UC and CD). Discussion: 707 words, the authors comment on the results obtained and compare them with those in international literature (Caucasian population/Asian of Chinese origin). They also draw attention to the fact that the majority of SNPs investigated in this case - control study were not associated with IBD, other factors such as gene-gene interactions or gene-environment interaction may be the explanation. Conclusion: short, last paragraph, 45 words, the authors conclude that according to the results obtained, the study confirms heterogeneity of allelic mutations in South Asians compared to Caucasians. References: 28, from the period 2003 - 2017, references are appropriate, relevant, included are influential journals in this field (Gut, Gastroenterology, Nature, Nature genetics, Lancet, Inflammatory bowel diseases). Conflict of interest: the authors declared no conflict of interest; the study was funded by National Research Council of Sri Lanka (Grant number: NRC 13-108). Ethics of the study: the study was approved by the Ethical Review Committee (ERC) of the Faculty of Medicine, University of Kelaniya and Hospital ERCs where relevant. Opinion of the reviewer The manuscript is interesting, I suggest to accept the

contribution with minor corrections.

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- ☐ No

BPG Search:

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