

Title: Multi-locus genetic risk score predicts risk for Crohn's disease in Slovenian population

ESPS Manuscript NO: 24304

Dear Editor,

Thank you for the carefully conducted review of our contribution and constructive guidance to improve the manuscript.

In the revised manuscript, the authors strictly followed the recommendations of the editorial board of your esteemed journal:

- we transformed the title page in a case - control study,
- expanded the number of keywords,
- the abstract is written according to recommendations , we took into account the limitations on the number of words,
- we corrected a few sentences in the manuscript, which are highlighted,
- the contribution was supplemented with commentary,
- attached are all required documents, whereas »Original documents – informed consent and Ethics committee decision« are in slovenian language,
- attached are two positive opinions of the Slovenian Ethics Commission obtained in 2007 and 2011, for additional analysis of the samples.
- we thank the editorial office of WJG for performing the cross-check of the manuscript and
- we thank the reviewers for the encouraging assessment of the contribution.

The authors hope that the article is now properly edited for publication.

Queries

Step 1. Reviewers had no additional comments. We corrected a few sentences in order to be more comprehensible and avoid possible misunderstandings. The corrections are minor. All sentences are listed below as well as highlighted in the manuscript. The same goes for some abbreviations which were previously overlooked.

Page 8: For individual SNPs, AUC ranged from 0.50 to 0.57 (median 0.53) for SNPs with the lowest effects sizes versus SNPs with the highest effect sizes, respectively, but the difference between these two most distant AUC values was not significant ($P=0.06$).

Page 8: Significantly better ($P<10^{-4}$) discriminatory ability than in an individual marker was achieved when 8 nominally significant SNPs ($P<0.05$) were included in a model with AUC of 0.69 (95% CI 0.64-0.74).

Page 10: The highest discriminatory ability of individual SNPs yielded only 0,57 at best, which support findings from study by Jacobsdottir *et al*, that “individual markers are poor classifiers even with replicated high effect sizes”

Page 11: This may be due to interference of different factors modifying genetic architecture (geographical placement, pollutants, adherence to particular diet, etc.)

Page 14: Population specific genetic models may offer more optimal risk stratification for selected population than ethnically and genetically diverse consortiums.

Step 2. We updated the manuscript according to the requirements for case-control study and added all missing segments (highlighted as well).

Step 3. The audio Core Tip is provided.

Step 4. We have provided a screenshot image for the plagiarism analysis in Google Scholar. The cross check image/results will be provided by the editorial office of WJG.

Step 5. We have provided the files related to academic rules and norms including **Institutional Review Board statement, informed consent statement, biostatistics statement, conflict-of-interest statement, and data sharing statement.**

Step 6. The study was not supported by any funding agency.

Step 7. The language verification certificate is provided.

Step 8. The Copyright Assignment form is provided.

Comments to the reviewers:

1. Reviewer 01557574

Date sent for review: 2016-01-18 16:30

Date reviewed: 2016-01-20 20:15

Dear Author, This article title with "Multi-locus genetic risk score predicts risk for Crohn's disease in Slovenian population " should be published at WJGO. It is well documented. It gives us important informations. Sincerely yours.

Authors: Thank you very much!

2. Reviewer 00050232

Date sent for review: 2016-01-18 16:30

Date reviewed: 2016-02-13 00:36

The present work has originality. The research study on genetic risk predictor for Crohn's disease using a reasonable number of SNPs has merits and the only shortcoming is sample size, which was very small. However, the sample population is homogeneous, thus attenuating the effects of the small sample size. The methodology used is adequate and the discussion is consistent. Therefore, the work deserves to be published.

Authors: Thank you very much!

Yours sincerely,

Katarina Zupančič, Kristijan Skok, Katja Repnik, Rinse K. Weersma, Uroš Potočnik, Pavel Skok.