

August 13, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: n°19121-Review.doc).

Title: Genetics of inflammatory bowel disease from multifactorial to monogenic forms

Author: Anna Monica Bianco, Martina Girardelli, Alberto Tommasini

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 19121

The manuscript has been improved according to the suggestions of reviewers:

Reviewer 00013033

Comment: Title is misleading, authors should consider an alternative subtitle.

Response: We change the title as suggested by the reviewer. The alternative subtitle is : “VEO-IBD is it multifactorial or monogenic disease?”

Comment: Introduction and “conventional” IBD genetic parts need revision and authors should explain why they concentrate on VEO-IBD and what they would like to highlight. At the moment, these part read as separate paragraphs, the link and the story behind it should be better explained.

Response: We concentrated on VEO-IBD since this is the field in which a greater benefit from genetic is expectable. Indeed, although monogenic causes of IBD are very rare, their frequency is tough to be higher in cases with VEO. Furthermore, whilst genetic knowledge has little practical impact on adult IBD, the identification of monogenic IBD can dramatically change the therapeutic options in VEO-IBD. In addition, monogenic IBD, mainly found among VEO-IBD, can represent simplified models to study the pathogenesis of intestinal inflammation.

Comment: It is now more than 163 loci shown to be associated with IBD, authors have to revise this (they can contact the international IBD genetic consortium, if needed).

Response: We add the correct number of IBD loci associated with the respective reference (number 7)

Comment: Moreover it is questionable if it is still IBD if a monogenic disease is diagnosed, or symptoms only resemble IBD? This part of the discussion is completely missing from the manuscript.

Response: We add this part in the discussion of the manuscript

Comment: In the conclusion part authors should give clear practical guidance and highlight that VEO- inflammatory bowel disease “like” symptoms warrant genetic investigations and through this the etiology can be defined in a proportion of the cases.

Response: We gave the guidance in the conclusion.

Editor Comment

Step 1. Please revise your manuscript according to the reviewers' comments.

Response: We revised our manuscript according to the reviewers' and editors comments.

Comment: A copy of signed statement should be provided to the BPG in PDF format, which are necessary for final acceptance, Thank you!

Response: We scanned a copy of signed statement as request.

Comment: Please provide the fax number.

Response: We provide the fax number

Comment: Please check all genes' names and change them to [italic](#)

Response: We check all genes in the manuscript and corrected in the italic form.

Comment: Audio core tip: In order to attract readers to read your full-text article, we request that the author make an audio file describing your final core tip, it is necessary for final acceptance. Please refer to Instruction to authors on our website or attached Format for detailed information.

Response: We recorded the Audio core tip and we attached the mp3 file as request.

Comment: Please reformat all the reference numbers like this. Please check throughout. Thank you!

Response: All the reference number were controlled and formatted as request.

Comment: Please check this number!

Response: The reference number is correct

Comment: Please simplify your table, maybe you can make several tables and note them clearly respectively. Thanks for your consideration.

Response: the table summarized all the genes mentioned in the manuscript so we cannot subdivide it. But we modified the following things:

- we deleted the OMIM number referred to the gene and kept the OMIM number referred to the disease.
- we simplified the clinical features

- we inserted the reference number instead of the PMID number

Step 2. Please update the manuscript according to the Guidelines and Requirements for Manuscript Revision-Review.

Response: We revised the manuscript according to the guidelines.

Step 3. Please provide an Audio Core Tip.

Response: The core tip was provided as an audio mp³ file.

Step 4. Please subject the manuscript to *CrossCheck* analysis and the final title to Google Scholar search, and store screenshot images of the results.

Response: Our Institute provides an internal software named Viper which has the same function of CrossCheck. Viper gave “No Plagiarised Text Found” result. Also the Google Scholar search didn’t provide a similar title (see the figure attached below).

The screenshot shows a Google Scholar search interface. The search bar contains the text "Genetics of inflammatory bowel disease from multifactorial to monogenic". Below the search bar, it indicates "Circa 2.410 risultati (0,12 sec)". The results are listed under the heading "Articoli". The first result is "Current status of genetics research in inflammatory bowel disease" by S Vermeire, P Rutgeerts, published in Genes and immunity, 2005. The second result is "Monogenic diseases associated with intestinal inflammation: implications for the understanding of inflammatory bowel disease" by HH Uhlig, published in Gut, 2013. The third result is "Revisiting Mendelian disorders through exome sequencing" by CS Ku, N Naidoo, Y Pawitan, published in Human genetics, 2011. The fourth result is "Age at onset and causes of disease" by B Childs, CR Scriver, published in Perspectives in Biology and Medicine, 1986. On the left side of the results, there are filters for "In qualsiasi momento" (Dal 2015, Dal 2014, Dal 2011, Intervallo specifico...), "Ordina per pertinenza", "Ordina per data", "Cerca nel Web", and "Cerca in Italiano". There are also checkboxes for "Includi brevetti" and "Includi citazioni".

Step 5. Please provide the files related to academic rules and norms.

Response: According to the academic rules and norms, the corresponding author signed and provided the PDF file named “Copyright Assignment”

Step 6. Please revise the language of your manuscript.

Response: The revised manuscript was carefully checked and corrected by a native English speaker.

Step 7. Please sign the Copyright Assignment form.

Response: The copyright assignment form was signed by all the authors and attached as PDF file.