

To: Editor in Chief,

World Journal of Gastroenterology

We want to thank the Chief editorial board and the reviewers for their instructive review and comments. We found them very useful and applied all the suggestions that were made by the two honorable reviewers. All changes have been saved in a Track Change Version for easier finding of the revised changes made. The other file refers to the “accepted all those changes” and is the copy of the “Revised 5 21 14...” version for the journal. This file has been also attached to the e-mail.

Thank you,

The Naser's team

University of Central Florida

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**Reviewer ID# 2528832**

In this study authors make a revision of present knowledge about the relation of gastrointestinal immune alterations and autism. The purpose is ambitious, because the knowledge is fragmentary and many data are inconclusive/contradictory. In the first 5 pages authors properly define some concepts and revise the knowledge about genetic factors. Then the authors go on with the analysis of acquired factors, exposing firstly the epidemiological relation between gastrointestinal disorders and autism.

- This part –especially from lines 152 to 172 could be considerably shortened. True information really begins at line 173: **Response:** We have significantly shortened this part. Please see page 7, 8, and 9 for deletions that were made in the track changes revised version.
- I also suggest to shorten the review of the well known absorptive mechanisms of the intestinal mucosa, especially information contained between lines 205-256: **Response:** We have significantly shortened this part as well. Please see page 10, and the first paragraph of page 11 in the track changes revised version.

- Similarly, although some observations contained between lines 257-282 are interesting, overall this part could be also shortened underscoring those aspects more directly (possibly) involved/related to autism pathophysiology: **Response:** We have significantly shortened this part as well. Please see page 12, from line 256 down and those of page 13 until line 280 in the track changes revised version.
- I also feel that the text between lines 333-345 and the paragraph dealing with microbiota should be shortened: **Response:** We have significantly shortened this part. Please see page 17, under the Microbiota and ASD, on page 18, 3 paragraphs have been deleted in the track changes revised version.
- Information about neurotrophic factors and neurotransmitters does not belong to the conclusions of the work (lines 413-477): **Response:** This was a very helpful suggestion. We brought this section into the main part of the manuscript and named it: Vasoactive Intestinal Peptide and other neuropeptides in ASD, please see the green lines in page 19-21, lines: 405-486, before the conclusion. Nothing was removed from the neuropeptides part that was written in the conclusion part since it was not suggested to be removed, but the location was odd. This section is very important due to controversies about the use of neurotrophic factors and we would respectfully suggest this part to stay in the manuscript as it was suggested to only be moved from the conclusion part. The moved part from conclusion can be seen from page 23-26 of the in the track changes revised version.
- Moreover, the first two paragraphs of the conclusion section lack any content: **Response:** We removed the first two paragraphs of the conclusion and added a few sentences on the material that was discussed in the main part of the manuscript to make a brief conclusion of the manuscript. Please see page 22 and 23 for the deleted and a few added sentences (line 472-500) in the track changes revised version.

#### **Reviewer ID# 980173**

This review article by Samsam et al summarizes the data published about the role of various factors in the pathogenesis of Autism Spectrum Disorders (ASD). The authors discuss the role of abnormalities associated with gastrointestinal (GI) and immune system in the development of

ASD. Based on the available information in the peer-reviewed literature, this review is of great significance and the information as presented is of broad interest to biologists and clinicians.

Minor points:

1. The authors need to re-format their reference list. Many references are not formatted properly and contain superscripted numbers. **Response:** The superscripted numbers have been removed from the references.

2. Authors may consider adding relevant references under sub-head "Non-genetic Factors Implicated in ASD" on page 7: **Response:** page 7, line 156, references [8, 28] have been added in the track changes revised version.