

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77387

Title: Structure of the myenteric plexus in normal and diseased human ileum analyzed by X-ray virtual histology slices

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06170821

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Cambodia

Manuscript submission date: 2022-04-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-03 07:08

Reviewer performed review: 2022-05-08 15:49

Review time: 5 Days and 8 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Re: Manuscript NO: 77387 This is an experimental study dealing with the morphology of the myenteric plexus under normal and pathological conditions examined with a new methodological approach. The authors have a great expertise in this field, with several publications on this specific topic. Some changes are suggested to improve the paper. 1 Title. Does the title reflect the main subject/hypothesis of the manuscript? Yes. 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes. 3 Key words. Do the key words reflect the focus of the manuscript? Yes. 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? Yes. 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Yes. 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? The results fulfil the proposal of the study and provide new data on the morphology of the human myenteric plexus under normal and pathological conditions. 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Yes. 8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? Yes. 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? Not applicable.



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Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

10 Units. Does the manuscript meet the requirements of use of SI units? Yes. 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? The authors have a large experience in this topic and are appropriately self-cited. 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? Minor style and language corrections are suggested. 13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? Yes. 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? Yes. Specific comments I congratulate the authors on this new morphological approach. In the discussion section I suggest a deeper comment about the comparison of classic histology with the new method. Replace “resistent” with “resistant”. Style and language improvement is suggested.

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Reviewer's code: 04185382

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: Cambodia

Manuscript submission date: 2022-04-28

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-01 08:51

Reviewer performed review: 2022-05-08 17:46

Review time: 7 Days and 8 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The authors set out to visualize the ENS in full thickness biopsies of the human ileum using “x-ray phase-contrast nanotomography.” They examine tissue from six patients with GI dysmotility and three controls, and compare their findings to standard H&E staining. They identify several pathologic changes not seen by light microscopy and suggest that this method offers potential advantages for ENS analysis and histologic diagnosis of enteric neuropathies.

1. The image clarity and detail of the myenteric plexus provided by phase-contrast nanotomography and virtual sectioning is excellent and perhaps, as the others suggest, could help with histopathologic diagnosis of neuroenteric diseases. The study includes only a small number of patients, all with CIPO, but the clinical phenotype is not fully described. Did these patients have a known CIPO-associated mutation (e.g. ACTG2)? Was the onset in infancy or later in life? Did the histologic findings correlate in any way with their symptoms or with results of their GI workup?
2. Many other studies have included histopathology findings of CIPO and have identified vacuolar changes, desmosis, nuclear palisading, disordered smooth muscle, intracellular inclusion bodies, and cytoplasmic aggregates. Some references include Lehtonen et al, *Gastroenterology*, 143:14892, 2012; Hahn et al, *J Neurogastroenterol Motil*, 28:104, 2022; Moreno et al, *Am J Med Genet A*, 170:2965, 2016. How do the findings of the current study relate to the results of those published studies?
3. The first sentence of the abstract is not correct since there is no submucosal plexus in the esophagus or stomach.
4. The legend in Fig. 2B states “cellular nuclei of two telocytes are seen (two dark dots).” Arrows need to be added to point out these nuclei; but more importantly, how do the authors know these are telocyte nuclei?
5. In the last paragraph

of the Methods section, the authors state that telocytes, ICC, and fibroblasts cannot be differentiated without immunohistochemistry. If that's the case, why do the Results repeatedly refer to telocytes and telopodes? Could those cells instead represent ICCs or fibroblasts? Validation of the nanotomography findings with immunohistochemistry would strengthen the study. 6. The Results section refers to Fig. 5 before Fig. 4. The order of these figures may need to be changed. 7. How widely available is x-ray phase-contrast nanotomography? Is this a technique that hospitals can easily employ?

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: Cambodia

Manuscript submission date: 2022-04-28

Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2022-06-14 18:17

Reviewer performed review: 2022-06-15 11:35

Review time: 17 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
<https://www.wjgnet.com>

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors have responded satisfactorily to this Reviewer's comments and the manuscript is improved. I have no further questions or suggestions.