Dear Dr. Lian-Sheng Ma,

We are grateful to you and the reviewers for handling and reviewing our manuscript entitled “Autosomal recessive 333 base pair Interleukin 10 receptor alpha subunit deletion in very early-onset inflammatory bowel disease” (Manuscript NO.: 67926, Observational Study). We have revised the manuscript accordingly and addressed all the comments and suggestions below. We hope the revised manuscript is now suitable for publication. We thank you for you and look forward to hearing from you soon.

Yours sincerely,

Yuan Xiao, MD, PhD
Department of Pediatrics
Ruijin Hospital
Shanghai Jiao Tong University School of Medicine
Reviewer #1:

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** VEO-IBD has been linked to several monogenic variations. It's very difficult to diagnose and manage VEO-IBD compared to adult iBD. I would like to appreciate authors for focusing their resources on this complex clinical entity. All the four patients had elevated IL-10 activity which is an indirect indicator of IL10RA dysfunction. Even though whole exon sequencing was not conclusive, whole genome sequencing identified a novel 333bp deletion in IL10RA. I felt the only limitation of this study is cost effectiveness and feasibility of whole genome sequencing compared to whole exon sequencing which needs less resources compared to WGS.

(1) We appreciate the reviewer’s comment. In this study, because of the inconclusive results of TGPS and WES, the employment of WGS was to identify possible pathogenic mutations, including the IL10RA gene, and thus assist in diagnosis and treatment. Although WGS contributes substantially to disease burden, genome-wide read coverage allows reliable detection of CNVs compared to WES. Profiting from this advantage, we identified a novel 333bp deletion spanning two introns and one exon which was repeatedly missed by WES. Based on our findings, we have customized the MLPA probe which could detect such 333bp deletion and other exons deletion or duplication in the IL10RA gene. Thus, clinically diagnosed IL10RA dysfunction patients will receive WES+MLPA rather than WGS to identify such IL10RA mutations in the future.

(2) We have defined the abbreviations upon their first appearance in “Abstract” and have added ORCID number in page 1 according to the requirements. We have also added “ARTICLE HIGHLIGHTS” section as required.

Authors must revise the manuscript according to the Editorial Office’s comments and suggestions, which are listed below:
(1) **Science editor:** 1. Scientific quality: The invited manuscript describes "Autosomal recessive 333 bp IL10RA deletion mutation in patients with very early-onset inflammatory bowel disease". The topic is within the scope of the WJG. (1) Classification: Grade A; (2) Summary of the Peer-Review Report: (03764458): VEO-IBD has been linked to several monogenic variations. Its very difficult to diagnose and manage VEO-IBD compared to adult iBD. I would like to appreciate authors for focussing their resources on this complex clinical entity. All the four patients had elevated IL-10 activity which is an indirect indicator of IL10RA dysfunction. Even though whole exon sequencing was not conclusive, whole genome sequencing identified a novel 333bp deletion in IL10RA. I felt the only limitation of this study is cost effectiveness and feasibility of whole genome sequencing compared to whole exon sequencing which needs less resources compared to WGS. (3) Format: There are 1 table and 5 figures; (4) References: A total of 21 references are cited, including 8 references published in the last 3 years; (5) Self-cited references: There are 0 self-cited references; (6) References recommendations: The authors have cited proper references. 2. Language evaluation: Classification: Grade B. 3 Academic norms and rules: The authors provided the Non-Native Speakers of English Editing Certificate, Biostatistics Review Certificate, Institutional Review Board Approval Form, and STROBE Statement. 4. Supplementary comments: The topic has not previously been published in the WJG. Funding and Foundation acknowledgements: National Natural Science Foundation of China Grants 81900015 and 81741103, Shanghai Science and Technology Committee Grant 19411971300, Funded by Jin Lei Pediatric Endocrinology Growth Research Fund for Young Physicians (PEGRF) (NO. PEGRF201809004), and the Shanghai Plan for Women and Children's Health Service Capacity Construction (Enhancing the Service Capacity of Shanghai Women and Children Health Care Institutions). 5. Issues raised: Please add "Article Highlight" section due to a clinical research article. 6. Re-Review: Required. 7. Recommendation: Conditional acceptance

We appreciate the Science editor’s comments and suggestions. We have responded to Reviewer #1 about the cost effectiveness and feasibility of WGS compared to WES above. We have also added “ARTICLE HIGHLIGHTS” section in the revised manuscript as required.

(2) **Company editor-in-chief:** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. We appreciate the Company editor-in-chief’s comments and have revised the manuscript as required and marked yellow in “Abstract”.

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