

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Pharmacology and Therapeutics

**Manuscript NO:** 55669

**Title:** The Role of Telomere Shortening in Anticipation of Inflammatory Bowel Disease

**Reviewer's code:** 03478404

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Romania

**Author's Country/Territory:** United States

**Manuscript submission date:** 2020-03-28

**Reviewer chosen by:** Ruo-Yu Ma (Quit in 2020)

**Reviewer accepted review:** 2020-04-06 08:46

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**Review time:** 5 Days and 8 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<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
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	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**

1. The authors of this limited study concluded that “telomere shortening appeared unlikely to be involved in mechanisms of possible genetic anticipation in IBD”. However, they included only three IBD families, 24 patients of European descent (eight parent-child pairs affected by IBD). 2. Abstract: It should clearly state that only 11 individuals with IBD were included, of the 24 subjects. 3. Core Tip: too long – it should have a maximum of 100 words. 4. Introduction: background well presented; length appropriate. A. Page 4 – „which has an increased risk of colon cancer” - please insert that the overall risk of cancer is increased, not only colon cancer. B. Please formulate clearly the „Aim of the study” (or, preferably, primary and secondary objectives). 5. Material and Methods: A. When was this study carried out? The authors wrote “beginning in 1990”, but IRB Initial Approval Date appears as 5/18/2010. When did it end? B. Study families: Please replace the term of “indeterminate colitis”. It has been replaced many years ago by the term “IBD Unclassified” (IBD-U). C. Please specify what criteria/guidelines were used for the diagnosis of CD, UC and IBDU in these three families. Since 1990, many guidelines changed, according to the more recent scientific findings. D. No MRE was performed at all? E. This paragraph “Material and Methods” has only two sub-paragraphs : “Study families” and “statistical analysis”. “Study families” should be divided in study design (maybe including the questionnaire – even as supplementary material), families, IBD diagnosis, genetic analysis etc. 6. Results: A. Clinical characteristics of patient population: Please replace the old term of IC with IBDU. Again – Importance of the criteria used to classify/diagnose CD, UC and IBDU. Please mention. B. Please replace subtitle “Children were younger at diagnosis than their parents” with „Children’s age at diagnosis”. C. The following sentence is incomplete; „The mean age of parents at diagnosis was 40+/-17 and the mean age 21+/-13, p<.0014.” D. Comparison of disease extent in parent-child pairs: Data are presented in Table 1.

However, we cannot get anything from it, since only old classical therapies were used. E. Table 1: Patient Characteristics: please remove IC and replace with IBDU. Most patients were treated with steroids and/or 5ASA. Only 3 received thiopurines. No other medication? What about Metotrexate (in Crohn's), Biologics? When were these patients treated? As per the current guidelines, 5ASA is generally not effective in CD, only in very selected patients with very mild inflammation. Those mentioned patients (Table 1) had complicated behaviour: B2 or B3. Why 5ASA then? F. Family with UC: The text mentions that "All the affected members of second family underwent total colectomy for disease refractory to medical therapy with the youngest member requiring surgery at only 6 years of age." But, what therapy? Only steroids, 5ASA and thiopurine are mentioned in Table 1 (thiopurine in two patients). I would have liked a Discussion about this family, with such a severe UC, however since no proper therapy was administered, what to expect? These are probably very old data, therefore we cannot apply them to our daily basis, with so many possibilities of biologic agents used as therapy. G. Testing TL: "No associations were found between TL in lymphocytes and granulocytes and anticipation of the age at onset observed in successive generations". Not useful study for practice. H. Genetic variants detected by WES: "WES did not detect any rare frameshift, nonsense or missense coding variants in genes shared by these three families for either dominant or recessive modes of inheritance." Not bringing any info that should be important. 7. Discussion paragraph is extremely flimsy, almost unbelievable for a manuscript. Main limitation: very few patients: 11 with IBD. Three families – 1 with CD, 2 with UC (and IBDU). 8. References very old: nothing from 2020, 2019, just 1 from 2018, none from 2018, 2017. Most of the other references are quite old. At the end of the used references, we still find 5 references (still very old), not included (numbered 1 to 5). Maybe the authors did not submit the last version of their paper. Very superficial. 9. Copyright License Agreement – not signed and written. Why? 10. IRB



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Approval Date: Principal Investigator: Florin Stelaru - does not appear in the manuscript at all. Is this the same study? 11. Signed Informed Consent Form(s) or Document(s). The name of the PI - Theodore M Bayless does not appear in the manuscript at all. In the end of the paper, we learn that this study was "In Memoriam". The date of expiration on this signed consent form is 1997. We should be very careful with this study. 12. The manuscript is not prepared according to the WJG rules. No ORCID number of authors, no required format, etc.

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<b>Scientific quality</b>	<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
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#### **SPECIFIC COMMENTS TO AUTHORS**

According to the following publication [Lee JC, Bridger S, McGregor C, Macpherson AJ, Jones JE. Why children with inflammatory bowel disease are diagnosed at a younger age than their affected parent. *Gut*. 1999;44:808-11. doi: 10.1136/gut.44.6.808. PMID: 10323881; PMCID: PMC1727524], "There was no evidence of genetic anticipation or genomic imprinting of age at diagnosis in this sample of IBD families. Ascertainment bias is responsible for the age differences at diagnosis between affected parents and children". Another publication [Faybush EM, Blanchard JF, Rawsthorne P, Bernstein CN. Generational differences in the age at diagnosis with Ibd: genetic anticipation, bias, or temporal effects. *Am J Gastroenterol*. 2002;97(3):636-640. doi:10.1111/j.1572-0241.2002.05542.x] also suggested that "There is a tendency for children to be younger than their parents at the time of diagnosis of familial IBD, and that this difference in mean age at diagnosis is almost doubled for grandparent/grandchild pairs. However, we conclude that these differences are most likely due to a bias based on length of follow-up or recent multigenerational temporal changes in the risk of IBD, or both". How the authors could explain the above statements. The authors also stated that "The study represents the first evaluation of telomere length defects in IBD". However, there were actually relevant data published previously [Risques RA, Lai LA, Brentnall TA, Li L, Feng Z, Gallaher J, Mandelson MT, Potter JD, Bronner MP, Rabinovitch PS. Ulcerative colitis is a disease of accelerated colon aging: evidence from telomere attrition and DNA damage. *Gastroenterology*. 2008;135:410-8. doi: 10.1053/j.gastro.2008.04.008.. PMID: 18519043; PMCID: PMC2574910].