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Wan Chai, Hong Kong, China

ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 8847
Title: RELATIONSHIP BETWEEN METHYLATION WITH ENDOSCOPIC AND HISTOLOGICAL INFLAMMATION IN ULCERATIVE COLITIS AND CROHN'S COLITIS PATIENTS WITH INCREASED RISK FOR NEOPLASIA
Reviewer code: 02462691
Science editor: Wen, Ling-Ling
Date sent for review: 2014-01-10 22:17
Date reviewed: 2014-01-13 13:38

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[Y] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
This is a study to further elucidate the clinical role of two methylation markers in high risk patients with UC and Crohn's colitis. Despite limited by sample size, the study provides useful data that consolidate the pathological role of these markers. Further studies with larger cohorts are needed. Some specific comments are as below: 1. Molecular biomarkers are predicted in the near future to complement if not replace the poorly sensitive and non-specific endoscopic/histologic criteria to diagnose pre-neoplastic lesions in the GI tract (for example in gastric precancerous lesions associated with H. pylori, reference: Maran S et al. World J Gastroenterol 2013; 19: 3615-22). The marker especially SLIT2 therefore merits further study in IBD-associated dysplasia including DALM. 2. For active disease, it is very common to confuse histologically with dysplasia even with experienced pathologists. Therefore, it is important for authors to clarify their definitions for dysplasia and how the confusions were resolved if any. 3. Sample size was a limitation, and authors may need to clarify why they could not recruit more during the study period. This clearly affected the results of longitudinal analysis with non-significant p-values. 4. Table 1 was confusing. Rather than number and % as headings, would UC vs Crohn's more useful? Also, legend for FC-QPOCT was not provided. There were 2 reported figures for medications which I do not understand what they represent. 5. Table 5 was not provided despite being mentioned in the manuscript. 6. Can authors explain the differential findings between SLIT2 and TGFB2?

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Reviewer code: 00041288
Science editor: Wen, Ling-Ling
Date sent for review: 2014-01-10 22:17
Date reviewed: 2014-01-16 13:47

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
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COMMENTS TO AUTHORS
This study evaluates the association between methylation of SLIT2 and TGFB2 promoters and the histologic and endoscopic activity of ulcerative colitis (UC) and Crohns colitis (CC) patients with an increased risk for dysplasia. 38 patients underwent colonoscopy with biopsies, and 23 of these had follow-up endoscopic evaluation within 1 year. SLIT2 methylation was significantly more frequent in patients with endoscopic and histologic evidence of acute inflammation. TGFB2 methylation significantly correlated with endoscopic activity only. Methylation was found to be present significantly more often at the distal colon for both genes. Multivariate analysis showed that inflammation status was independently associated with SLIT2 methylation. At follow-up evaluation, endoscopic remission was protective for methylation. Overall, this is a good study that attempts to identify IBD patients that are at an increased risk for colonic dysplasia and neoplasia. The authors have previously published on the methylation of SLIT2 and TGFB2; and their role as markers to discriminate between tumor and adjacent mucosa in inflammatory bowel disease (IBD) patients. Haven said this, the study has several limitations and the manuscript requires revision. - The introduction needs to be shortened. Focus on the association between methylation and IBD-dysplasia; and the aim of the study. - "Increased risk for dysplasia/CAC" needs to be better defined. References are required. - Why was more than 8 years used as a cut-off? - A reference is required for the histologic activity parameters. - The type of medical treatment these patients were receiving should be mentioned in the text. Plus, the authors should mention if IBD treatment modifies SLIT2/TGFB2 expression and/or methylation in any way. - The authors protocol for endoscopic

surveillance and biopsy technique should be described. - How many endoscopists and pathologists participated in the study, and how did the authors control for interobserver variability? - "Distal colon" should be better defined. Were any rectal specimens taken? - Was there any correlation between methylation and the patients clinical status? - Median time to the "longitudinal evaluation" should be added. - Were there any variations between UC and CC patients? - Significant English language revision is required. - Tables need to be more focused. They are quite confusing. Try to shorten the legends. NS should be replaced with the actual P value obtained. The P values should be added as a 4th column in Table 2. Erase supplemental tables. - The authors should expand on why no correlation was found between SLIT2 and TGFB2. - Limitations of the study should be pointed-out in the discussion: non-prospective patient accrual, low patient numbers, no comparison to other methylation markers or healthy controls, and lack of long-term follow-up.

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Reviewer code: 01799104
Science editor: Wen, Ling-Ling
Date sent for review: 2014-01-10 22:17
Date reviewed: 2014-01-22 12:39

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[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
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COMMENTS TO AUTHORS
Interesting study concerning relationship between promotor methylation status and activity of IBD. Although the authors discussed why they only chose SLIT2 and TGFB2 and explain shortly why distal lesion had more specific results, is there any clinical implication for IBD patients? Did their patients with methylation become colorectal cancer at their follow up? There has no Table 5 in the manuscript of which the authors mentioned in longitudinal analysis of results. Meanwhile, the manuscript needs rewriting in accordance with the format of WJG.