



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 74272

Title: Genome-wide methylation profiling of early colorectal cancer using an Illumina Infinium Methylation EPIC BeadChip

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05776245

Position: Peer Reviewer

Academic degree: BSc, MSc

Professional title: Academic Research, Research Scientist, Teaching Assistant

Reviewer's Country/Territory: Poland

Author's Country/Territory: China

Manuscript submission date: 2021-12-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-15 14:35

Reviewer performed review: 2022-01-15 19:37

Review time: 5 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 Grade E: Do not publish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
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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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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
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SPECIFIC COMMENTS TO AUTHORS

Dear Authors, an interesting methylome study with small comparison of the used chip to alternative techniques at the end of the manuscript. I have some suggestions although there are little or no major flaws in my opinion. One suggestion that would definitely strengthen the findings is to validate the obtained elements using e.g. RNA-seq. As you mentioned in the paper, most of the DMSs were located within gene body (64.1%) so the identification of specific genes is possible and the methylation results could be complemented with expression changes on transcriptome level. The choice of a few best DMSs from volcano plot and their following validation as mentioned above would be appreciated. Except that, below are my comments regarding the current content: (1) Make sure that space is present when needed, sometimes it is not present e.g. between a word and successive part in brackets (Abstract, Aim section, "EPIC BeadChip(850K)"). Please check throughout the entire paper. (2) Minor changes in English are required, examples are: (a) Methods in Abstract, second sentence: if "were performed" then it should be "analyses", not "analysis"; selected " differentially methylated sites" (optionally with hyphen between first two words), not "differential"; to further "discover", not "discovery". Please check the entire paper as I believe the "differential" was present here and there. (3) Sometimes, the two (or more) sentences could be merged into one, examples are: "While the incidence of CRC is insidious, and the early manifestation is not obvious. Early effective screening is of great significance to reduce its morbidity and mortality"; "The data (IDAT files) were mainly analyzed using the ChAMP package in R. And we used β values (range, 0-1) to represent DNA methylation level. The β values were calculated from the intensity ratio of the methylated signals to the total



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(methylated and unmethylated) signals for each site". (4) Please do not begin the sentence with "And", examples: "And CRC usually develops from its precancerous lesion, colorectal adenoma", "And we used β values (range, 0-1) to represent DNA methylation level"; "And DNA methylation is an important epigenetic alteration led to expression silencing of tumor-related genes, and many abnormal methylations have been found in genomic DNA of tumor cells, which are also reflected in plasma ctDNA". (5) Consider changing "different histological subtypes" into "various histological subtypes" to avoid "different" repetition in the sentence. (6) Do not add dot when referring to objects like figures or tables within a text e.g. Table.1, Figure 2. C, standardize it preferably to "Figure 1" or "Table 1". (7) Why numbers in this sentence are marked with red? "Their ages ranged from 52 to 79 years old, with the average age of 63 years old". (8) Make sure you did not miss any words in sentences, example: "Then Qubit ssDNA HS Assay Kit (Invitrogen, USA, Q32854) and Qubit 3.0 fluorescence quantizer (Thermo Fisher, USA) for DNA quantitative analysis after bisulfite conversion". At first, the beginning could be "subsequently" instead of "then", and moreover assay kit as well as fluorometer WERE USED for quantitative analysis. (9) EPIC BeadChip was described in Results as the one having 866895 CpG sites. Because of that, I believe that "8,66,895" in Introduction is incorrect form (comma should not be between "8" and "6"). (10) Please describe the abbreviations used for groups in Figure 1A (Ca, P). Moreover, legends in Figure 2A/C/D could be larger (same as in Figure 1A/B). In description of Figure 2, there is subfigure "E" instead of "D" (same in the first paragraph of Results). Two "GpGs" instead of "CpGs" are present in the manuscript. (11) The part "There were also differences in the distribution in gene structure elements" - should the second "in" be changed to "of"? (12) In gene ontology, BP stands for "biological process", not "biologic". Please correct it. (13) In Results, it was mentioned that DAVID resource was used for GO/KEGG enrichment analysis, while such detail was not mentioned in Methods. Please correct. (14) Some



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words are started with capital letter while it should not. Examples are "Binding" in "sphingolipid Binding" and "Enrichment" in "KEGG pathway Enrichment analysis" or "Pathway" in "MAPK signaling Pathway". Please double-check the entire paper. (15) Starting the sentence using "Such as" in "Such as Calcium signaling Pathway, Rap1 signaling Pathway and PI3K-Akt signaling pathway, MAPK signaling Pathway, cell adhesion pathway and metabolic pathway, which were all important biological pathways in tumor research" is inappropriate. Please change it to e.g. "Examples are". (16) Although the information about 25ng used for this methylation chip could be mentioned at the end of Discussion (so to compare with other methods using 3-5ug; I understood your intention), such data must also be put in Methods while currently it is not.



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Reviewer's code: 03479334

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Chief Physician

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2021-12-19

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-22 07:13

Reviewer performed review: 2022-01-26 12:53

Review time: 4 Days and 5 Hours

Scientific quality	<input checked="" 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 type="checkbox"/> Grade E: Do not publish
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SPECIFIC COMMENTS TO AUTHORS

Good work