Dr. Brian Lacy, Dr. Brennan Spiegel, and Editorial Board 1 Sep. 2019

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On behalf of all authors, please consider our submitted research article entitled “Genome-wide methylation of colorectal adenoma analysis reveals potential early diagnosis biomarkers” for publication on *The American Journal of Gastroenterology*.

Colorectal cancer (CRC) is the third leading cause of cancer related deaths. Identification and application of early biomarkers to discover the cancer cells become one of most effective approaches to increase the overall survival probabilities. Recent evidences demonstrated DNA methylation showed promising early diagnosis and tissue-of-origin mapping ability with circulating cell-free DNA (cfDNA). In the past decades, large number of DNA methylation biomarker researches have been conducted in colorectal cancer, however, all these research are based on colorectal cancer samples in which the studies assume early methylation aberrant are maintained during pre-clinical stage to cancer stage. In this study, we collected two distinct colorectal adenoma samples, which could represent early colorectal cancers, which included low-grade adenoma (LGA) and high-grade adenoma (HGA). To the best of our knowledge, it is the first genome-wide DNA methylation research to LGA and HGA in which we compared the methylation patterns between LGA, HGA and CRC. Alterations of genome-wide DNA methylation is the hallmark of human cancers and was demonstrated to be early event of tumorigenesis. We found the of genome-wide hypo-methylation actually happened as early as LGA and HGA stage indicating LGA maybe the best candidate to identify early diagnostic biomarkers. We believe that the comprehensive understanding to the genome-wide DNA methylation profile for the early stage pre-cancerous lesions (LGA and HGA), will provide important resources for cancer early diagnosis and candidate biomarkers for cfDNA methylation research. Enrichment analysis were conducted to differential methylation regions (DMRs) and we found nervous system and signal transduction associated pathways were significantly enriched. Finally, we described one functional methylation biomarker, *ADHFE1*, for colorectal adenoma and cancer. We found the AUC of ROC curve reached to 0.97 with specificity and sensitivity as 0.95 and 0.96. Overall, we believe our innovative study provided an opportunity to identify early diagnostic biomarkers and the better understanding to the pathology of the colorectal carcinoma.

This manuscript has not been submitted elsewhere and all authors declare no conflicts of interest. Thank you for your consideration.

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