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 XXX(Journal name).

Colorectal cancer (CRC) is the third leading cause of cancer related deaths. Even CRC in both incidence and mortality are higher in all kinds of cancer, adenoma stage provide an excellent opportunity to prevent its cancerization and get excellent survival. A large number of studies were focusing on CRC, while a part of them treated adenoma as middle stage lacking of further specific study. Actually, colorectal adenoma has different pathologic stages (low-grade adenoma and high-grade adenoma), and no research has compared the different adenomas of different stages at Whole-genome DNA methylation level. Alterations of genome-wide DNA methylation is the hallmark of human cancers and was demonstrated to be early event of tumorigenesis. However, the DNA methylation changes during the normal to low-grade and high-grade adenoma have not been fully exploited. Besides, alterations on low-grade adenoma maybe potential diagnostic biomarker. Therefore, the comprehensive understanding to the genome-wide DNA methylation profile for colorectal cancer, especially the early stage pre-cancerous lesions (low-grade adenoma and high-grade adenoma), will provide important resources for cancer early diagnosis and candidate biomarkers for cell-free DNA methylation research. In this study, we firstly treated adenoma as two stages, and identified dynamic DNA methylation change of colorectal low and high-grade adenoma. We conducted enrichment analysis to DMRs to inquiry potential DNA methylation influenced functional difference in adenoma initiation and development stages. Moreover, we found the performance of hyper-DMSs (different methylation sites) are better than hypo-DMSs’ for the colorectal adenoma and cancer prediction. Finally, we described one functional methylation biomarker, *ADHFE1*, for colorectal adenoma and cancer, the AUC of ROC curve of which can reach to 0.97 with specificity and sensitivity as 0.95 and 0.96.

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

Sincerely, for the authors,

Shigang Ding, M.D.

Department of Gastroenterology, Peking University Third Hospital, Beijing 100191, China

Tel: XXXX

Email: dingshigang222@163.com

Changqing Zeng, Ph.D.

Key Laboratory of Genomic and Precision Medicine, Beijing Institute of Genomics

Chinese Academy of Sciences, Beijing, 100101,

Tel: (010) 8409-7818

Email: [czeng@big.ac.cn](mailto:czeng@big.ac.cn)