In this manuscript, Dr. Liu and colleagues conducted a genome-wide 5-hydroxymethylcytosine analysis to gastric adenocarcinoma in different status: remote normal, adjacent normal and primary cancer tissues. The study confirmed previous findings: genome-wide of loss-of-5hmC. The study was performed rigorously and the findings are interesting. However, the manuscript was not well prepared, especially for the data analysis. The following comments hope to be helpful to improve the study. I suggest the authors provided as many supplementary as possible and update the manuscript with deep revision.

**Major Compulsory Revisions**

1. I suggest remove the conclusion “Intriguingly, there were more red bins than blue bins in the comparison of peripheral tissues to normal tissue (Figure 1C), suggesting that the 5hmC abundance could potentially increase in peripheral tissues; however, we did not detect a significant difference by dot blot”. You can not infer the genome-wide 5hmC with the number of the red and blue bins since for each bin the weight might be different.
2. The author did not mention whether the genome-wide 5mC has been done for gastric adenocarcinoma? And what’s the consistence between 5mC data and 5hmC data?
3. “Tumor, Peripheral and Normal tissues from the same individual were grouped together to adjust for any within-subject effects” Why “Peripheral and “N”ormal use upper case? There are too many low-level mistakes in the manuscript, please check it carefully in the next version.
4. “Sites with p-values smaller than 0.01 were considered significantly different as DhMRs”. Here it is “Sites” or “Regions”? Same things happened in lots of place in the manuscript, please check it carefully. In addition, why 0.01 was applied? Why not conduct multiple test correction?
5. It is interesting analysis: the 1344 (83.5%) DhMRs from the T/N gain-of-5hmC DhMRs overlapped with the P/N gain of 5hmC DhMRs, suggesting similar 5hmC changes in both tumor and peripheral tissues. However, since the significance is based on 0.01, the detail number loss its corresponding values.
6. In the “DhMRs overlap with the previously identified super-enhancers” section, please do the enrichment analysis to CpGI, promoter, exon, intron and some other common features at the same time and show the corresponding values.
7. Antibody providing company in dot blot assay should be provide and the catalog. Same with other assays. How many duplicates for dot analysis and how much of the variants for dot analysis in duplicate samples?
8. The manuscript is not well prepared. Since it is a bioinformatics manuscript, as many as supplementary material to the details of the analysis will be helpful for the reader. However, in this manuscript, none of the supplementary files was prepared.
9. ChIP-seq and motif identification is based on public dataset or based on your own data? It should be clearly mentioned. When do the motif enrichment analysis, I suggest to do it in loss-of-5hmc and gain-of-5hmc separately. The information to motif analysis was too limited, we provide more information to readers.
10. The author should confirm the relationship between 5hmC DMR and gene expression in their samples.
11. It is great that the authors submit the raw data to GEO, however, the fastq should be submit to SRA database.
12. The basic information to the clinical samples should be provided, such as race, gender, stage, age etc.