Comments to the Authors,

The study conducted an integrated Omics study to Crohn's disease-associated fibrosis. Genome-wide DNA methylation and transcriptome were explored with MBD-seq and RNA-seq in 3 pairs of Crohn's disease-associated fibrosis samples. Large number of potential differential methylation regions (DMR) and differential expressed gene (DMG) were identified. Several genes were validated with BSP and RT-PCR with solid result. The study was performed rigorously and the findings are interesting. What’s more, the study were conducted timely which provided important insight of the contribution from DNA methylation to to Crohn's disease-associated fibrosis. In the previous revision, the authors has removed parts of my concerns, However, I was still have several question to the study.

1, Is there any previous study has been conducted to investigate the genome-wide DNA methylation of Crohn's disease? What’s the heterogeneity of this disease? If the heterogeneity is very high, I really don’t believe 3 sample would represent the real differential methylation change of Crohn's disease. What’s worse, the control samples were collected from patients with Diverticulitis. Is there any significant difference of genome-wide DNA methylation between with Diverticulitis patients with normal colons? In addition, age, gender, nutrition and drug consumption also would influence the DNA methylation profile. I don’t believe 3 samples would represent variation and the heterogeneity of Crohn's disease. I suggest the author to increase the microarray to 12 vs 12 which is most acceptable in present methylation study.

2, Can you provide the cluster analysis or PCA analysis to the genome-wide DNA methylation and gene expression to show the relationship between these 6 samples?

3, In the Figure 3,for gene PTGIS the left figure showed CD6 have higher methylation level, however, in the right panel, CD6 have lowest methylation level in BSP, how to interpret this phenomenon?

4, I highly recommend the authors to move Supplementary Table 3 to the main body of the manuscript.