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. I only have several concerns as the following:

Major Revisions

1, The DMR analysis strategy should be revised. Since the sample size is too small, only DMR with large difference can be detected with high confidence. The present yes/no strategy would only detected some false positive signals. Meanwhile, the present study did not arrange technique negative control in the experiments, these false positive would be more serious. I found that similar study had ever been published in Clinical Epigenetics, such as Zhao et al. Clinical Epigenetics 2014, 6:18 or Zhao et al. Clinical Epigenetics 2014, 6:30. Maybe, this is also the reason why the difference of the BSP assay were not significant in Figure 3A. Actually, I preferred to take the right and left regions of the Figure 3A and 3B as the significant DMR. Could you provided the P-value for the right and left regions in Figure 3A and 3B? Whether these two regions were significantly different between cases and controls?

Minor Revision,

1, Is there any miRNAs, ncRNAs in the DMR regions? The author should be check it again. Meanwhile, the signals or information of ENCODE in the main DMR regions should be provided in the manuscript or as the supplementary.

2, The most important contribution of the study were that large number potential epigenetic variations were found to be aberrant in Crohn's disease-associated fibrosis and several variations were validated by further experiments, therefore, a clear table should be provided to show the reader the most important 20 or 50 aberrant DMR and their expression.

3, I do not quite understand the logic of the following sentence in the manuscript “Based on reported DNA methylome analyses in cancer and other fibrotic diseases, the number, size and genome-wide distribution of DMRs in fibrotic HIF strongly suggest that this epigenetic modification has an important role in intestinal fibrosis”.

4, Please check the characters in Line 33, page 11

5, In the line 25, page 14, the author mentioned “ENCODE”, however, the result for the encode analysis were not shown in the whole manuscript?

6, Additional file 1, 2 and so on which were involved with the table, should be provided as the Excel or txt files. eanwhile, in the Additional file 1, the average enrichment level should be provided for cases and controls.

7, In the Figure 2, the font size for the gene label were too small. Something should be done here.

8, The demographic information’s for the samples should be included in the manuscript, such as gender, age and other important information.