In this manuscript, Dr. Li and colleagues investigated the DNA methylation difference between lung cancer and normal, as well as the drug-related toxicity (DRT) caused by Capecitabine in a small Chinese population (N=21). It is a quite interesting data since there is no any methylation 850K methylation data were generated in Chinese lung cancer population. However, the data/bioinformatics analysis were two naive and the authors just tried to repeat known knowledge rather than to identify novel knowledge. I suggest the authors could conduct a deep analysis to the data and make further validation to the most important findings. I only have several tiny concerns for the authors to think about again and make further response.

**Major Compulsory Revisions**

1. The authors claim the 21 patients were enrolled for the treatment of capecitabine, However, the authors didn’t show whether the patients were treated with other drugs which is very important confounders for the data analysis. The authors should check another important confounder which is BMI.
2. Obviously, the authors provided a bioinformatics paper since there is no any further validation to the current result. Therefore, I suggest the authors could complete the whole analysis, including DMR and DCNV analysis based on ChAMP package.
3. In the Figure 1, the authors shown Tissue and Chip is the top 2 variation sources, However, in the method section, the authors have apply BMIQ to adjusted the Chip effect, I am wondering why Chip is still the No 2 variation source.
4. In Figure 1B, what’s the difference between the TN on the top right and bottom right? Meanwhile, what’s the difference between the TN on the right and bottom right in Figure 1C?
5. Figure 1E should be gave more explicit legend. It is difficult to understand Figure 1E.
6. The authors could give more information how to make the conclusion chip-to-chip variation did not interact with tissue variation with Figure 1A
7. The author mentioned “results suggested that hypomethylation was the main transformation of cancer generation”. Actually it is known truth for quite long ago. Cancer is shown genome-wide hypomethylation and hypermethylated in CpG-regions.
8. For Figure 4, it is too good to be truth. The high AUC totally caused by the over-fitting since the variable number is larger than sample size.
9. The authors can compare the enriched Ontology or KEGG pathway with previous methylation research in CRC and check how much of them are repeated and then make a discussion in the discussion section.
10. Manhattan plot and qqplot is the most important Figures for this study. These two figures should be considered as the Figure 1.
11. Raw data including IDAT, Beta or M matrix should be deposited in the GEO database.

Minor Revisions:

1. In the study, multiple tests were conducted and I am think multiple test correction should be considered, at least in the discussion section.
2. In table 1, the P-value column is not easy to be understood since it is not very clear which one is reference, for example, row of Gestational diabetes
3. All the ROC and AUC Figures can move to supplementary since they didn’t provide too much information.
4. All the Gene-enrichment analyses Figures can moved to supplementary while the most important figure is Manhattan plot and qqplot.