Comments to the Authors,

This manuscript studied the methylation landscape of 37 drug metabolizing enzymes genes in some liver cancer and normal tissues to discover the relationship between the variations of DNA methylation with the gene expression. The authors found DNA methylation contributed to inter- and intra-individual drug metabolism differences mediated by gene expression regulation and alternative splicing. The study was performed rigorously and the findings are interesting. However, the manuscript needs more careful editing. In general, I'd recommend publication if the authors can address the following concerns.

**Major Compulsory Revisions**

1. In figure 1, the selection strategy of CpG probe should be mentioned. For example, 15 CpG and 8 CpG were found in CYP3A4 and TSS region in the annotation of MH450K, however, there are only 3 of them were listed in the figure 1. In additional, 22 CpG loci of BMP4 in Figure 2 were found and only 7 of them were showed in Figure 1.

2. Beta-range value was applied to measure the variability of the methylation inter and intra individuals, however, this statistic is unstable in array dataset. For example, how to recognize the maximum and minimum from outlier. Another independent statistic should be test in the study to show the stability of the conclusion.

3. More housekeeping gene (>=5) should be evaluated in the study to check the result in Figure 3. What’s more, is there any evidence for the statement that “We expected that the control genes would show the least variation because the expression of these genes should be tightly regulated by DNA methylation on their promoter CpG islands”?

**Minor Essential Revisions**

1,In the manuscript, the authors mentioned “6 control genes” for several time, However, except ACTB and BMP4, what the other 4 genes are?

2,In the page of 14, line 16-17, how to get the conclusion that “These results suggested that DNA methylation acted as a “driver”, but not “passenger”. Which part of evidence from the study can make such conclusion or inference?

3, In the section of “Classification of DME genes based on their DNA methylation landscape”, what happened to the genes which showed high variation in normal tissue without negative correlation of gene expression? Also, there are so other genes which are not belong to any of the group.

4, In the section of “DME genes regulated by DNA methylation in adult livers”, the detail correlation or relationship between DNA methylation and gene expression should be provided. The thing I am worry about is that the significant association would be disappear after the multiple test correction?

5, In the page 11, line 2-3, A threshold of 0.5 were used, Is there any previous research which had ever used this threshold or the authors create it for the first time? The scientific reasonability should be interpreted carefully.

6, In the section of “DME genes regulated by DNA methylation in adult livers” and “DME genes regulated by DNA methylation in 3 hepatoma cell lines”, 7 and 5 genes were considered to be regulated by DNA methylation. However, only one gene were shared by the two list. How to interpret this situation?

7, in the page of 13, line 3-8, DME genes without CpGI in the promoter region were found to have higher variation than genes with CpGI in the promoter. Is this a specific feature for DME gene or a general pattern for any kinds of gene family? The type-II error should be provided for this test.

8, In the section of “DNA methylation and alternative splicing of UGT1A isoforms”, statistic significance should be provided rather than descript the higher or decrease with the visual.

9, Taking advantage published GEO dataset could provide more power to discover or validate the present hypothesis, however, as showed in Clinical Epigenetics 2014, 6:5 doi:10.1186/1868-7083-6-5, such integration should be careful since the batch effect. The author should be make some discussion about this problem in the discussion section.

10, For my personal concern, What’s the most urgent scientific question in the field of the paper. What’s the plan for the next step in concerns of clinical practices?

**Discretionary Revisions**

1, the figures should be rebuilt, the font size, circle size. they should be more comfortable.