**Response to Reviewer 1**

We thank you for your helpful comments. We respond to each comment, in turn, below. Changes to the manuscript has been made according to your suggestion.

**Your comment 1:**

First, unsuccessful or incomplete capture reactions might have resulted in the sequencing of non-methylated DNA fragments, leading to inconsistencies in or the absence of methylation enrichment in their sample.

**Our response:**

Yes, it is really good question and you are quite right. The MethyCap-seq based genome-wide DNA methylation profile greatly dependent on the efficiency and accuracy of the capture procedure. Unsuccessful and incomplete capture would bring the bias of the DNA methylation status in genomes. However, we have set several quality controls to guarantee the quality of the DNA methylation profile. For example, 1) 2)

**Your comment 2:**

Second, poor sequencing library complexity and CpG coverage often limits the statistical power to call differential methylation, affecting ultimately the reproducibility of the dataset. Explain.

How was the quality control experiment performed?

**Our response:**

Yes, it is really good question and you are quite right. We have provided quality control as the supplementary materials.

**Your comment 3:**

A schematic representation of work-flow adopted for primary and secondary data analysis must be included. This will help the reader to get an over-view of the exercises performed.

**Our response:**

it is really good suggestion. We have provided a schematic representation in the manuscript.

**Your comment 4:**

First, the principal objective and aim of the study is ill defined in the introduction. I strongly believe that inclusion of the same in the last paragraph of introduction will strengthen the rationale of the study.

**Our response:**

it is really good suggestion. We have provided a description at the end of the introduction as the following:

In present study, Ten PC tissue and corresponding adjacent tissue samples were pooled separately followed by MethylCap-seq based DNA methylation profile identification process. The methylation profiles of various genomic regions and elements were characterized, including gene-associated CGIs, non-gene-associated CGIs (orphan CGIs), CpG shores and gene promoters without CGIs. Differential methylation status between pancreatic cancers and normal tissues were tested in terms of above genomic regions, therefore, large number of pancreatic cancer specific hyper and hypo-methylated regions were identified. Gene Ontology and KEGG pathway analysis to these aberrantly methylated were conducted to discover aberrant functional modules in the development of pancreatic cancer. The methylation profile constructed by MethylCap-seq was validated by comprehensive procedures based on different techniques and in different samples. Additionally, the regulation role of aberrant methylation of orphan CGIs on the RNA expression was validated by MSRE-qPCR and RT-qPCR in pancreatic cancer cell lines before and after the treatment of 5-Aza-2’-deoxycytidine.

**Your comment 5:**

Second, what is translational utility of the work? This has to go a step-beyond explaining the importance of using the methylational profile as biomarker. Specifics must be provided for a few clusters only. A couple of lines on which specific experimental maneuvers will be necessary before these can be utilized in a clinical setting, must be included in the end segment of discussion. This will help to significantly elevate the impact of the article.

**Our response:**

**Response to Reviewer 2**

Thank you for your insightful comments. We respond to each of them, in turn, below. All changes in the manuscript are highlighted in yellow.

Major comments

1. In Figs. 1A-G, all data should be shown for both PC and PN to see if there is a clear difference in the methylation pattern.

**Our response:**

Yes, it is really good question.

2. In Fig. 2A, it is difficult to see which part of the gene locus is methylated or not. The authors should modify this figure.

**Our response:**

3. As shown in table S15, change in methylation pattern is seen in only a subset of PC. Therefore, the authors should analyze whether the change in the methylation pattern is related to clinical profiles of PC.

**Our response:**

4. The authors state that ‘the methylation status of DLX4, ELAVL2, IRX1, PITX2, SIM2, TBX5, and TFAP2C was subsequently validated in tissue samples’. However, the data is not shown and the authors should show the data.

**Our response:**

5. In table 2, the authors listed gene ontology enriched in differentially methylated genes in PC. Although it is interesting, it does not show whether genes involved in regulation of tumorigenesis are identified or not. The authors should also make a list of genes that may be involved in tumor suppression or promotion.

**Our response:**

Yes, it is really good idea. What a pity, up to now, we do not know such bioinformatics analysis tools or database which can provide whether a gene is involved in tumor suppression or promotion or not. However, we do want to give a positive reply to your question. We proposed the following text mining process to give a gene list which is related both with cancer and methylation.

First, we collect all the articles in the Pubmed which containing the item of cancer or tumor in title and containing the item of methylation in title. We found 2637 articles which met the above criterion. Then, we extract the abstract of these 2248 abstracts. We find 35 of 349 aberrant methylation genes in our list were found in the database which indicates the methylation statuses of these genes were related with cancer development, diagnosis or prognosis. If we do the similar procedure with the database collected as the criterion of cancer or tumor and methylation in abstract. 14200 abstracts were collected and 82 of 349 aberrant methylation genes in our list were found in the database. These 35 and 82 genes were showed in the file of cancer.tumor.methylationl.title.gene.txt and cancer.tumor.methylationl.abstract.gene.txt, respectively.

6. In Fig. 3C, Orphan7-1 data is not clear. The authors should modify this picture.

**Our response:**

Minor comments

There are numbers of typos (for example, p. 6 line 37, ‘Four candidate DMR genes which included...’, the number should be ‘six’). The authors should carefully check and correct them.

**Our response:**