Comments to the Authors,  
  
This manuscript "Silencing NKD2 by promoter region hyper-methylation promotes esophageal cancer progression by activating Wnt signaling" reported a comprehensive description to the epigenetic abnormal of NKD2 and its regulation role in esophageal cancer was related to one of most important cancer relevant signal pathway of Wnt. The study was performed rigorously and the findings sound very interesting. What's more, it would be an exciting example to explore the mechanism of the epigenetic silence of gene expression and then caused cancer development. The biological and biomedical evidence provided by the authors has been very solid. In general, I'd recommend publication if the authors can address the following concerns and to strengthen the reproducible and creditable of the manuscript.  
  
Major Compulsory Revisions  
  
1, I am glad the authors find these public GEO data and made the analysis eventually. However, the authors didn’t provide enough result to the analysis. How about the methylation status and gene expression of NKD2 in ESCA and adjacent tissue from TCGA dataset? Why not put these result as a supplementary Figure since they will provide more evidence to support your discovery? There are so many CpG sites in the NKD2 and in TCGA beadchip, which one were enrolled to do the methylation-expression correlation analysis? Can you provide the whole methylation profile based on TCGA from promoter to 3-UTR for ESCA and Normal samples? Is there any scatter-plot for the methylation and expression relationship?   
  
2, Although the authors have provided the primer sequence, please provide the genomic position for your primers and PCR regions so that the reader can do further validation to your result accurately. Another question is there are two CpG island on the promoter region of NKD2, do you think both of them should be detected?

3, As we all know, methylation status was influenced by smoking, drug consumption. How to eliminate the effect of confounders in present study? It would be better to give some discussion in the last section of the manuscript.

4, 5-AZA treatment would change the genome-wide DNA methylation profile, how to contribute the gene expression change of NKD2 were caused by the hypo-methylation of the methylation status of the interested region? Is there any possibility from gene-gene interaction or some other reasons? More directly technique should be applied to get the direct evidence.