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, Please collect genome-wide DNA methylation and gene expression data from GEO or arrayexpress (such as RRBS, MBD-seq or BS-seq data in ESCA) to find the evidence that genome-wide methylation and gene expression data were supporting to the present discovery. In addition, TCGA has provided large number of ESCA data, the methylation and gene expression status for NKD2 should be descripted.

2, please provide the reason how to select the genomic region to conduct the methylation detection. There are at least two CpG islands, which one to choose? In addition, why choose CpG Island, rather than CpG shore or CpG shelf?

3, Any GWAS evidence shown NKD2 were related with ESCA? If there is no any such evidence, how to interpret such phenomenon?

4, please read this paper “DNA demethylation by 5-aza-2′-deoxycytidine is imprinted, targeted to euchromatin, and has limited transcriptional consequences” and discuss the 5-aza section of the study.