Page 7: [1] Deleted **Shantao** **2/3/17 12:08 PM**

[STL2MG: What's the EncodeCA results on DHS when comparing cancer/normal cell lines?

Also I am not very sure whether we should fight back on this. If we say DHS region shift only adds second-order effect, then how do we rationalize mutation rate change? Chromatin remodelers participating in DNA repair? Then why particularly high mutation rate in open chromatin region?
I feel we could just step back and agree with the referee. Then it is just a language game: we call DHS as "open chromatin regions in normal state". We will then have a convincing rational on the mechanism and still show the results are still meaningful.]

Page 9: [2] Deleted **Shantao** **2/5/17 10:38 PM**

The effect of NEAT1 is not minor. Patients generally have good prognosis in our pRCC cohort, thus affects the power of our survival analysis. However, in the revision, we looked at the TCGA ccRCC cohort. Although lacking WGS data to find genomic alteration, we found NEAT1 is overexpressed in about 6% of the cohort. NEAT1 higher expression is significantly associated with shorter overall survival time (OS). NEAT1 is tightly co-expressed with MALAT1, which is another noticeable lncRNA in cancer.

Additionally, we are a part of the currently ongoing PCAWG study (PanCancer Analysis of Whole Genomes). During revision, we quickly looked at the NEAT1 mutation stats in the PCAWG RCC dataset. 21/144(14.58%) of the samples carry mutations in NEAT1, a frequency agrees with the one from our cohort. Confirmed hypermutation in a larger, high-quality dataset further supports our results. Unfortunately, we are not able to publish results based on PCAWG data at this moment.

In the revised manuscript, we include the new analyses we have done on NEAT1 to support its role in pRCC.