Reviewer's report

Title: Tight Associations Between Transcription Promoter Type and Epigenetic Variation in Histone Positioning and Modification

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The authors have identified an interesting, counter-intuitive phenomenon, namely the organization of histones on broad promoters in contrast to narrow, peaked promoters. However, the subsequent data analysis does not adequately explore the new territory their observation opens up. The analysis relies too much on average profiles and does not examine the behavior of features on individual promoters in sufficient depth.

* What landmark of the broad promoters was used to align promoters to produce the average profile? What it the best method?

* The observation of Sp1 positioning is largely predicted by the results of [7] and so it not particularly novel here.

* What fraction of broad promoters exhibit the observed pattern?

* The TATA-box and CpG island association is not novel - should not be presented.

* In measuring the statistical difference between modified histone patterns on broad and narrow promoters, it is important to take account of the fact that many narrow promoters are not heavily modified (as mentioned in [37]). This lack of modification, means that the average level on narrow promoters is likely to be lower. Measures of significance, should then focus on measuring the amount of organization and/or the number of promoters exhibiting the pattern.

* What does the section on modification add to the argument? If the nucleosomes are aligned, then the default assumption is that the modified histones will also be aligned.

* The nucleosome stability analysis does not appear to account for nucleosomes being removed with gene induction. If a nucleosome is present in one

condition, but then is removed in the other, then the author's method will try to connect the missing nucleosome with its neighbor which will yield large distances. We note that in the plot there appears to be missing probability mass in the induced condition which suggests nucleosomes are measured as moving long distances, when in fact they may be disappearing.

* CpG islands - A bold claim like this would be strengthened by comparison with a more modern definition of CpG islands, e.g., those that use methylation to identify functional CpG islands. Furthermore, others have observed that CpG islands are less occupied by nucleosomes. This is not inconsistent with the strong nucleosome pattern observed in this paper. The strong pattern may be derived from a small population of broad promoters. The authors should determine whether the pattern they observe is from a large fraction of promoters or just a few. Also, how to the patterns relate to the underlying CpG island? Figure 4 indicates that the observed effect may be due to CpG islands, rather than the broad-vs-peak distinction, especially if the identification of CpG islands is faulty.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.