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review for "Regions of very low H3K27me3 partition the Drosophila genome into topological domains"

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The manuscript “Regions of very low H3K27me3 partition the *Drosophila* genome into topological domains” aims to investigate the mechanisms that partition the genome into TADs and the nature of domain boundaries. The authors investigated the *Drosophila* genome and identified two distinct domains: D domains which have very low H3K27me3 and E domains containing mid-to-high levels of H3K27me3. The D domains correlate with the boundaries of TADs, while the E domains generally correlate with TADs.

To understand the features of *Drosophila* genome, they first used whole genome analysis (ChIP-seq) to identify the histone modification states (H3K27me3) and found that the genome can be separated into two domains: D domains and E domains. Then they investigated the genomic features of the D domain and suggested that D domains contain housekeeping genes and are enriched in a subset of architectural proteins. Used the Hi-C, they found that D and E domains are topologically distinct: E domains generally correspond to TADs, having long-range interactions. Whereas D domains corresponds to boundaries with short-range interactions.

This work would be a good reference and guide for other researchers in the community as it would open up many new avenues of research. While different experiments and many data in this manuscript provide the argument for the nature of domain boundaries, additional experiments and clarifications would put forth a stronger argument and allow for easier interpretation of the results.

Major points:

1. The whole genome data in this manuscript are from different cell types. Especially when comparing different architectural proteins in the D domains (Figure 2), some factors are from Kc cells, the others are from S2 cells and the H3K27me3 is from primary spermatocyte. It would be more convincing if they can show the data from the same cell types. Or if they could provide some data that there is no variation between different cell types.

2. In figure 1: the 20-24h embryos have higher H3k27me3 level than 1st instar larvae, which is not consistent with the conclusion that there is a general developmental increase in H3K27me3 levels outside Pc domains.

Minor points:

1. For the ChIP-seq data in this paper, the scales were different among the different samples. It would

be more convincing if all the ChIP-seq data are in same scales and still have the same pattern but not just be background.

2. In figure 2, the authors showed that HAT and HDAC both bind to the same sites, it would be nice if the authors could give more introduction about how HAT and HDAT bind to same sites to regulate histone acetylation.

3. In figure 3, the y axis (300kb) of panel A is confusing, we cannot find any information in the manuscript regarding it.

4. In figure 4, the authors did not give much information about non-housekeeping genes in D domains, so it is a little bit confusing why they compared housekeeping versus non-housekeeping genes in panel E. They suggested that CTCF is widely distributed with D domain, but also enriched at TSS. Additional clarification would be helpful for interpretation of the results.

5. Figure 6 provides a good model for summary of the paper. However, it would be good if the authors can show more genome-wide examples of D-D interactions.