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Highly rearranged chromosomes reveal uncoupling between genome topology and gene expression

Chromatin topology is intricately linked to gene expression, yet its functional requirement remains unclear. We comprehensively assessed the interplay between genome topology and gene expression using highly rearranged chromosomes (balancers) spanning ~75% of the Drosophila genome. Using transheterozyte (balancer/wild-type) embryos, we measured allele-specific changes in genome topology and gene expression in cis, whilst minimizing trans effects. Through genome sequencing, we resolved eight large nested inversions, smaller inversions, duplications, and thousands of deletions. These extensive rearrangements caused many changes to chromatin topology at the level of long-range loops, TADs and promoter interactions, yet these are not predictive of changes in expression. Gene expression is generally not altered around inversion breakpoints, indicating that mis-appropriate enhancer-promoter activation is a rare event. Similarly, shuffling or fusing TADs, changing intra-TAD connections and disrupting long-range inter-TAD loops, does not alter expression for the majority of genes. Our results suggest that properties in addition to genome topology ensure productive enhancer-promoter interactions.

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