November 2, 2022

Dear Editors,

My co-authors and I are writing to submit the manuscript entitled “Variation in histone configurations correlates with gene expression across nine inbred strains of mice”, as a research article for *Genome Research.*

The manuscript describes the diversity of epigenomic modifications in a survey of hepatocytes derived from nine inbred mouse strains. Although the variation in epigenomic modifications across cell types has been well explored, variation across genetically distinct individuals not been well documented. To fill this gap in knowledge, we investigated the variation in epigenetic modifications across these genetically distinct mice. We examined four histone modifications—H3K4me1, H3K4me3, H3K27me3, and H3K27ac—as well as DNA methylation in hepatocytes. Using ChromHMM, we identified 14 chromatin states made up of unique combinations of the four histone marks. The occurrence of these states varied widely across the surveyed strains. Further, we showed that the states were correlated with inter-strain variation in gene expression both in terms of state abundance and spatial distribution along the gene body. In contrast, DNA methylation did not vary across the strains and was not associated with inter-strain variation in gene expression.

To further investigate the relationship between chromatin state and gene expression, we imputed local chromatin state and DNA methylation status into a population of Diversity Outbred (DO) mice. We then mapped gene expression using genetic haplotype, imputed chromatin state, imputed methylation status, or local SNPs. Mapping with imputed local chromatin state explained almost as much variance in gene expression as haplotype, and significantly more than SNPs. Imputed DNA methylation status explained the least amount of variation in DO gene expression. This result suggests that expression quantitative trait loci (eQTL) in a genetically diverse population may be mediated in large part through local histone modifications. Thus, variation in epigenetic modifications across individuals may play a significant role in regulation of gene expression, as well as the emergence of health and disease derived from this regulation.

Significantly, in addition to explaining expression variance, mapping with histone modifications provides a high-resolution method for annotating functional elements in the genome using naturally occuring variation. In this manuscript, we identifed two putative enhancer regions within the gene *Pkd2* based on inter-strain epigenetic variation and correlation with inter-strain gene expression.

With this manuscript, we provide a unique data set consisting of gene expression, and multiple epigenomic modifications in hepatocytes across nine commonly used inbred strains of mouse. The raw and processed data are hosted on Gene Expression Omnibus (accession: GSE213968). These data provide an important resource that will aid in the investigation of genetically determined epigenomic variation, and the functional annotation of the mouse genome.

We believe that this manuscript will be of interest to geneticists working in model organism populations. The manuscript includes main text, seven figures, and five supplementary figures. No author has any financial, personal, or professional interests that could be construed to have influenced the paper. Thank you for your consideration of this manuscript.

Sincerely,