Interrogating the 3D Structure of the Genome in Human and Chimpanzee Tissues

THE UNIVERSITY OF CHICAGO

Ittai Eres, Kevin Luo, Joyce Hsiao, and Yoav Gilad
Department of Human Genetics, University of Chicago

INTRODUCTION

Over the last several decades, a growing body of evidence has suggested that heritable variation in gene expression plays a crucial role in phenotypic divergence between species[1-5]. Previous work in the Gilad lab has yielded a panel of integration-free human and chimpanzee induced pluripotent stem cells (iPSCs)[6], providing a model system for studying changes in gene regulation underlying the observed expression differences between the two species.

Studies in mice, flies, and yeast have revealed that expression divergence between species is primarily driven by mutations in cis-regulatory elements (CREs), rather than trans elements[7]. Cis-regulatory elements operate in an allele-specific manner, typically on the same chromosome, but not necessarily on the most proximal gene. Hence, connecting CREs to their target gene(s) is critical for understanding species-specific differences in regulation of gene expression. Hi-C combines proximity ligation with high-throughput next-generation sequencing to find DNA-DNA contacts genome-wide, connecting CREs with their target(s)[8]. By collecting in situ Hi-C[9] data from a panel of 4 human and 4 chimpanzee iPSCs, and integrating expression data previously collected from the same individuals, this study interrogates how and to what extent variation in 3-dimensional genome structure correlates with variation in gene expression in primates.
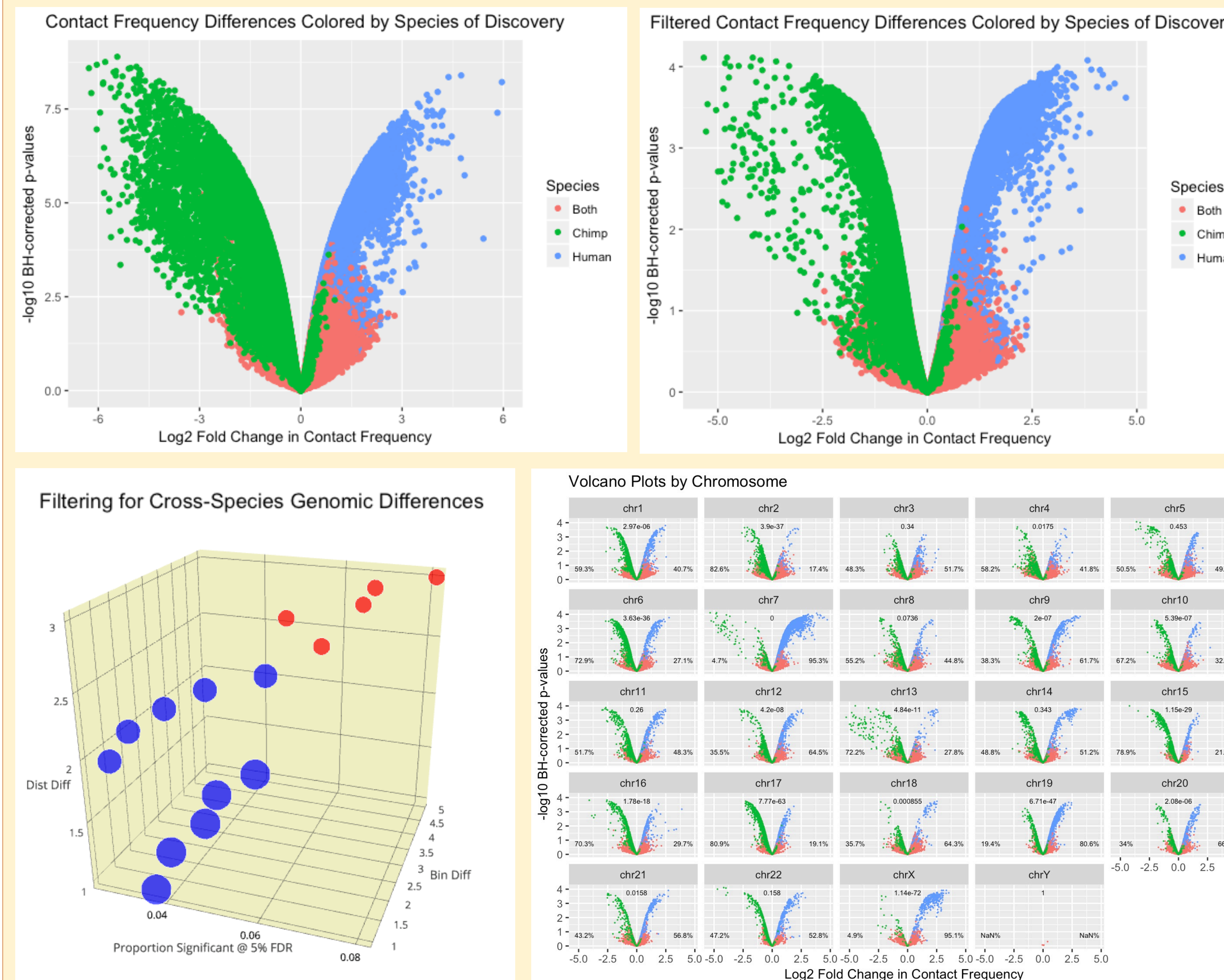
ANALYSIS PIPELINE
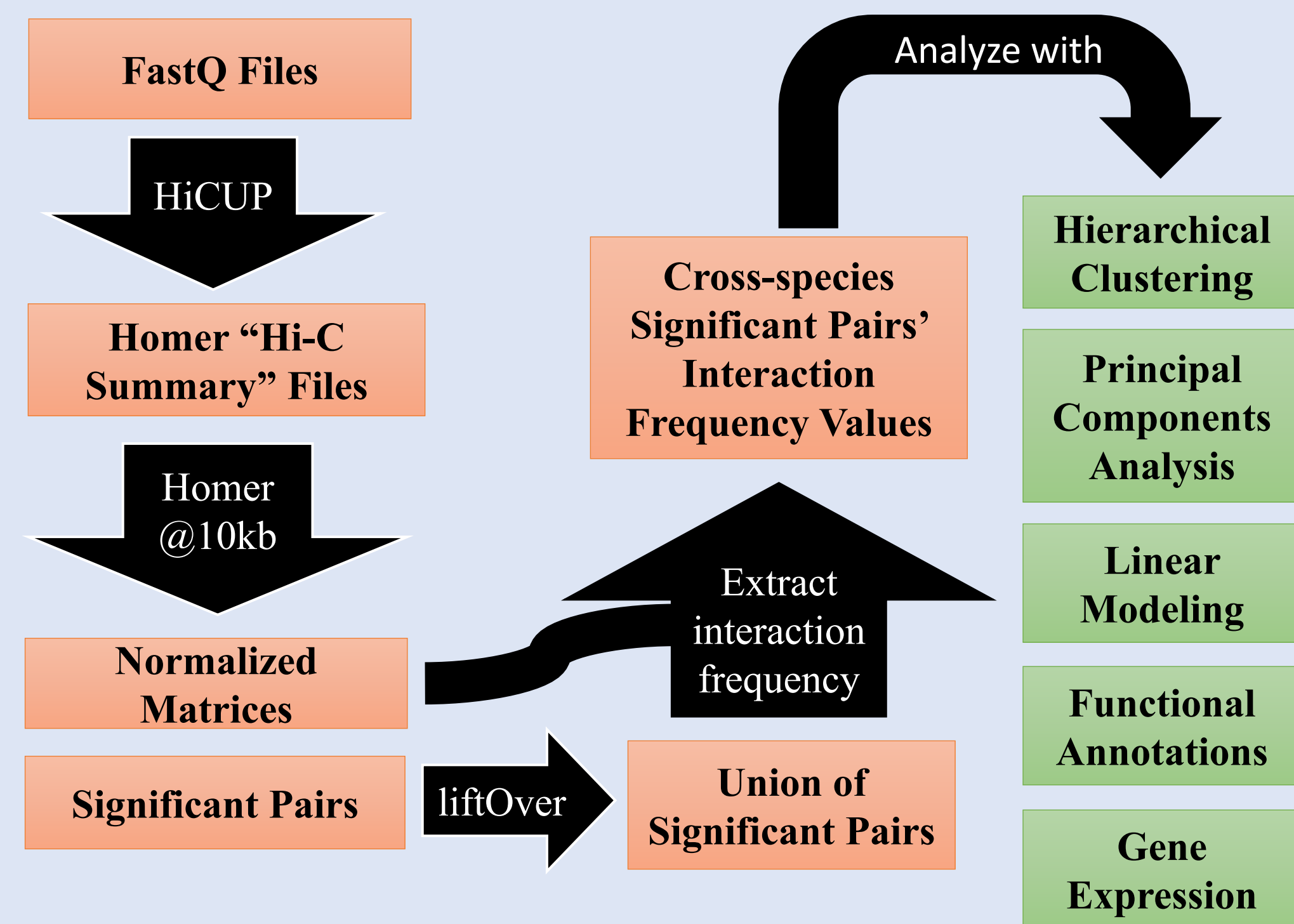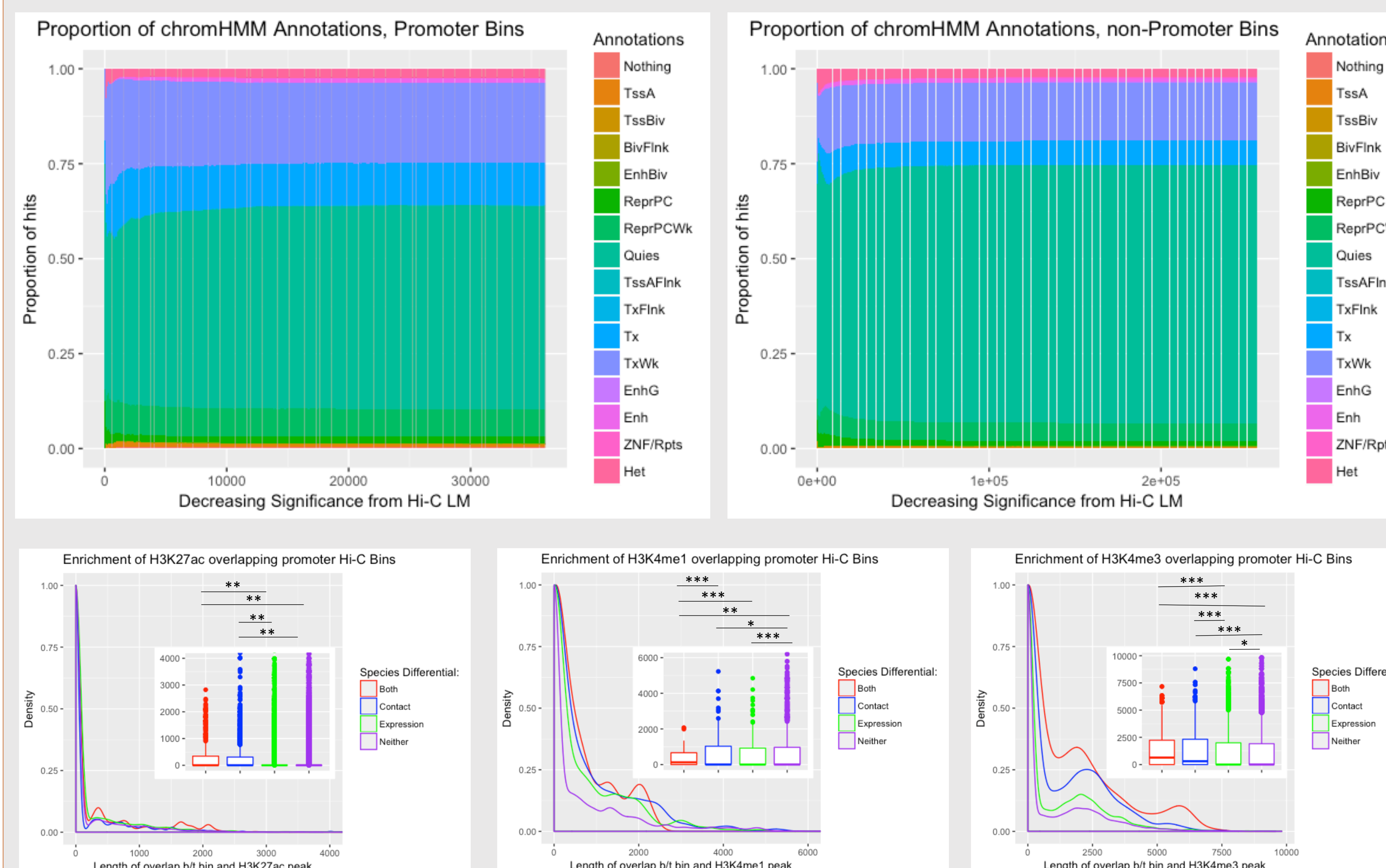

REGULATORY LANDSCAPES SEPARATE SPECIES
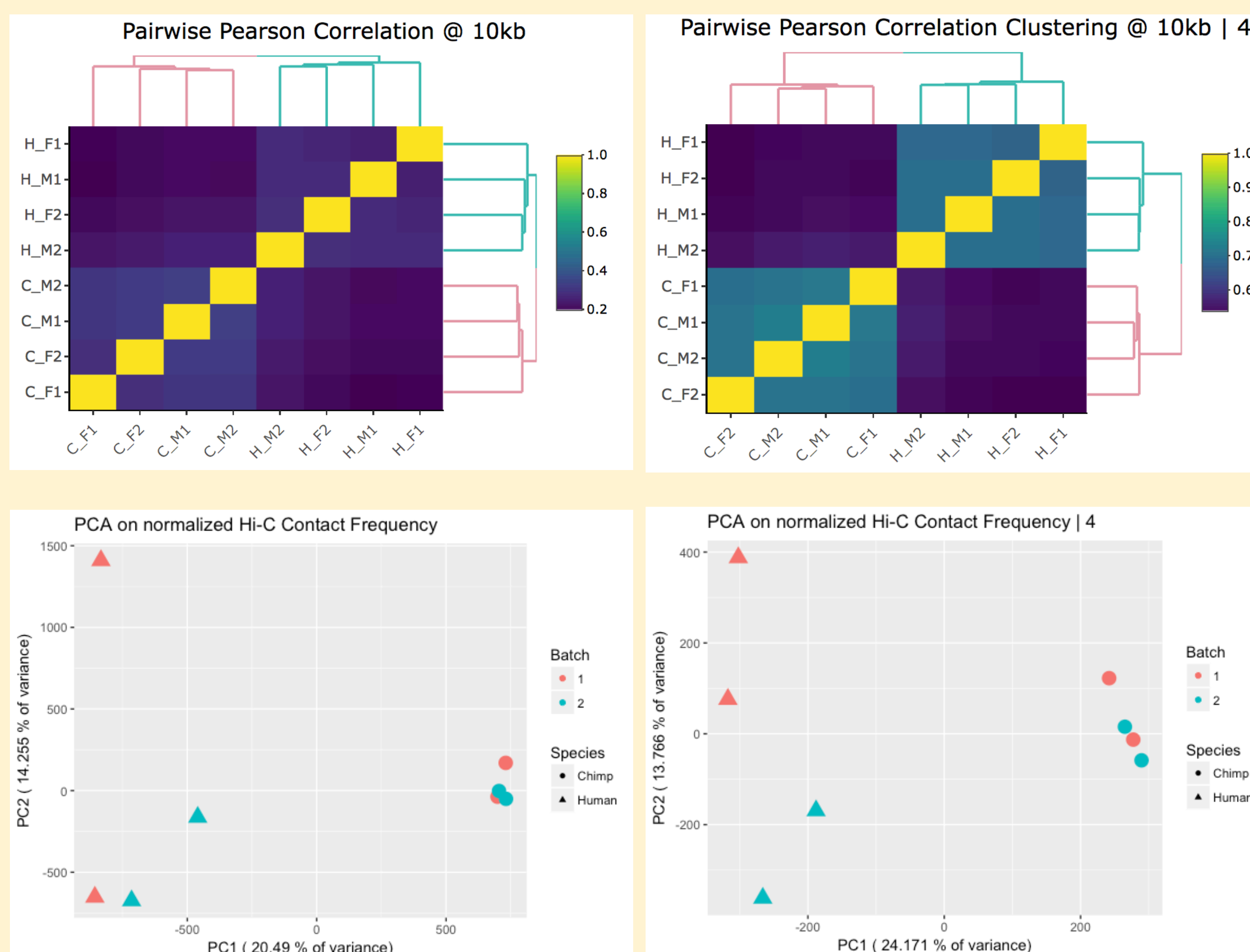
LINEAR MODELING REVEALS LARGE-SCALE CHROMOSOMAL DIFFERENCES IN REGULATION
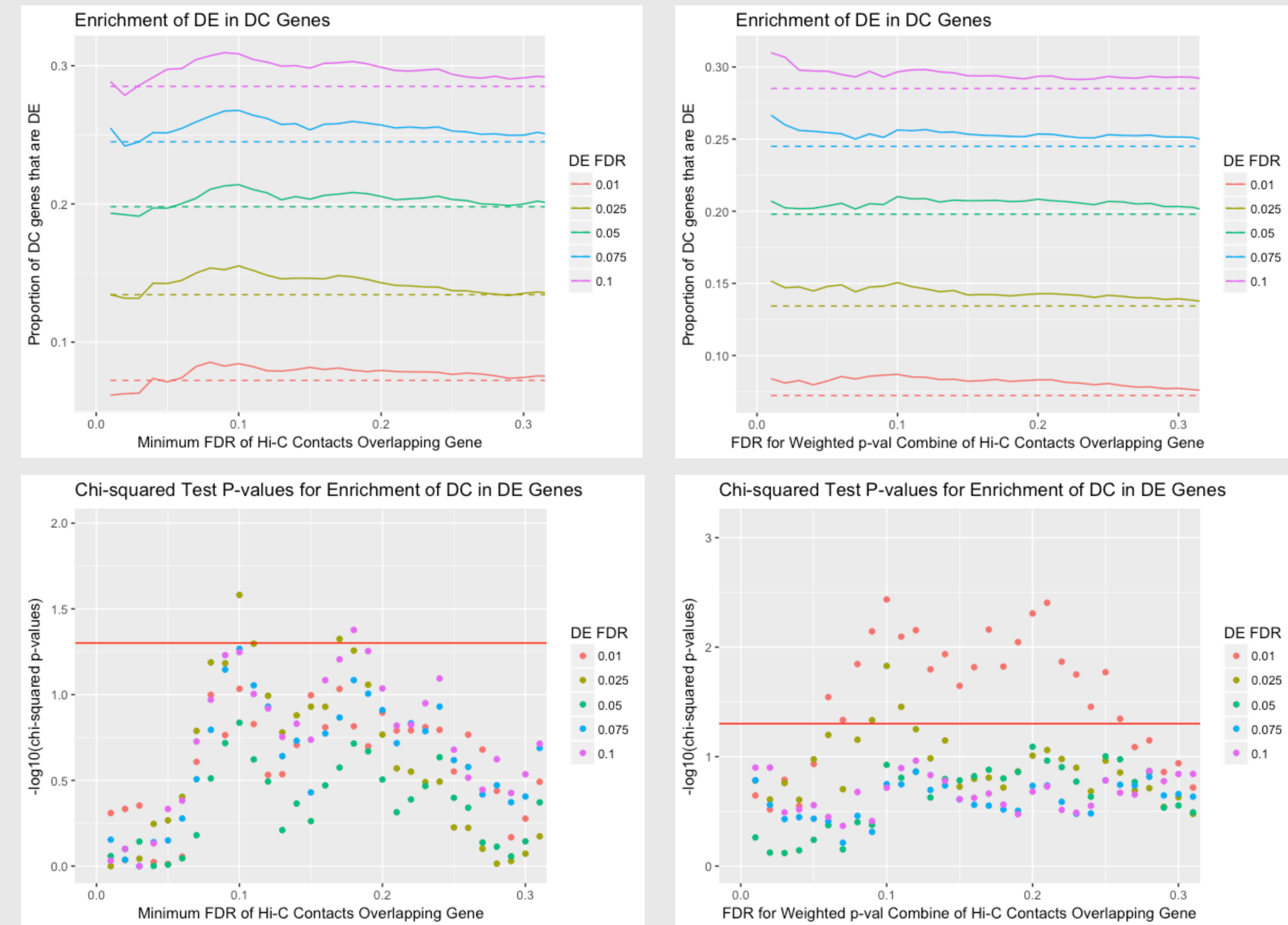
$$Y = \beta_0 + \beta_{sp}s + \beta_{sx}x + \beta_{btc}b + \varepsilon_i$$
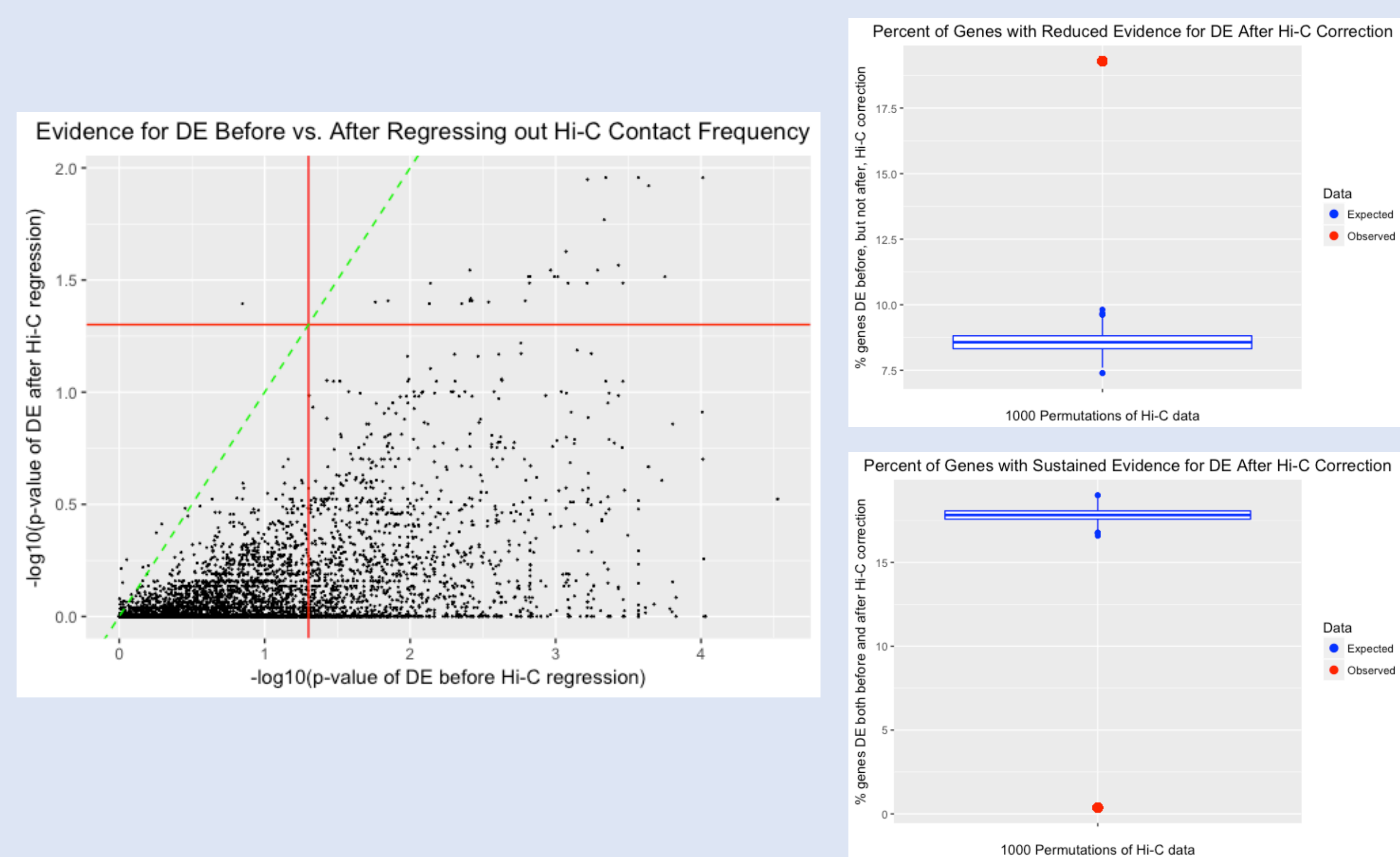

SPECIES DIFFERENTIAL CONTACTS (DC) ARE ENRICHED FOR ACTIVE REGULATORY MARKS

DIFFERENTIALLY EXPRESSED (DE) GENES ARE ENRICHED FOR DIFFERENTIAL CONTACTS

DIFFERENTIAL CONTACTS MAY BE A DRIVER OF DIFFERENTIAL EXPRESSION

REFERENCES

1. Britten, R.J. and E.H. Davidson, Repetitive and non-repetitive DNA sequences and a speculation on the origins of evolutionary novelty. Q Rev Biol, 1971. 46(2): p. 111-38.
2. King, M., and A. Wilson. Evolution at Two Levels in Humans and Chimpanzees. Science, 1975. 188(4184): p. 107-16.
3. Carroll, Sean B. Evolution at Two Levels: On Genes and Form. PLoS Biology, 2005. 3(7): p. 1159-1166
4. Gilad, Y., et al. Expression profiling in primates reveals a rapid evolution of human transcription factors. Nature, 2006. 440(7081): p. 242-5.
5. Wray, G.A., The evolutionary significance of cis-regulatory mutations. Nat Rev Genet, 2007. 8(3): p. 206-16.
6. Gallego Romero, Irene et al. A Panel of Induced Pluripotent Stem Cells from Chimpanzees: A Resource for Comparative Functional Genomics. eLife, 2015. 4: e07103.
7. Tirosh, I. and N. Barkai. Inferring regulatory mechanisms from patterns of evolutionary divergence. Mol Syst Biol, 2011. 7: p. 530.
8. Lieberman-Aiden, E. et al. Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome. Science, 2009. 326(5950): p. 289-93.
9. Rao, Suhas S.p., et al. A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping. Cell, 2014. 159(7): p. 1665-680.