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Maps of chromatin conformation in the cerebral cortex

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Motivation and Aim: Chromosome conformation capture (3C) methods have launched tremendous progress in our understanding of chromatin organization. At the higher end of chromatin organization, interphase chromosomes form distinct territories called chromosome territories; small and active chromosomes tend to locate at the center of the nucleus, whereas inactive and heterochromatic regions are located in the nuclear periphery [1–3]. Using the Hi-C technique, Lieberman-Aiden et al. demonstrated that chromatin is spatially segregated into two compartments [4]. Follow-up studies with higher data resolution revealed that individual chromosomes are partitioned into topologically associating domains (TADs), which are highly conserved across cell types and species. At the lower level of chromatin organization, long-range chromatin loops were identified within TADs from super-resolution 3C-based sequencing data [5, 6]. Despite this progress, Hi-C experiments in the brain tissue remain challenging, which is why, among hundreds of publicly available Hi-C datasets, only a few papers describe chromatin architecture in the human brain [7–12], two of these papers still being on bioRxiv. Even fewer studies analyze the adult brain, as the fetal brain is easier to work with. In this work, we aim to comprehensively describe chromatin architecture in the adult brain and link chromatin organization features with functional properties of the brain at the molecular level.

Methods and Algorithms: We used FACS flow cytometry to sort neurons (NeuN+ cells) and glia (NeuN- cells), two main types of cells in the brain, allowing to determine the chromosome conformation separately for each cell type. We then applied Hi-C method to produce genome-wide chromatin conformation maps separately in neurons and glial cells, according to the Hi-C protocol that we have recently optimized for the mouse brain tissue [13]. Each Hi-C library was sequenced to 150–200 mln. paired-end reads per replicate and the resulting Hi-C data were binned at 50, 25, and 20-kb resolution to choose the most suitable Hi-C map resolution for each level of chromatin architecture. We also performed RNA-seq experiments in the same samples.

Results: In agreement with current understanding of chromatin organization in mammals, our Hi-C interaction maps of cerebral cortex demonstrate multiple architectural levels: interchromosomal contacts, A/B compartments, TADs, and point-scale interactions. Further, we comprehensively analyze chromatin organization at all levels of chromosome architecture, starting from interchromosomal interactions and finishing by chromatin loops. In addition, we analyze gene expression data accessed using RNA-seq experiments in the same cortex area to obtain integrated information about transcription and chromatin architecture, and subsequently suggest possible

mechanisms linking chromatin conformation features with molecular functioning of the brain.

Conclusion: Our new data on the 3D organization of chromatin in the brain allows filling one of the few remaining gaps in an overall picture of the molecular organization of the brain.

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