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A CHROMOSOMAL CONNECTOME FOR PSYCHIATRIC AND METABOLIC RISK VARIANTS IN ADULT DOPAMINERGIC NEURONS

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Midbrain dopaminergic neurons (MDN) represent 0.0005% of the brain's neuronal population, mediate cognition and reward functions, and food intake and metabolism, and are posited to underlay neurobiological dysfunction of schizophrenia (SCZ), a severe neuropsychiatric disorder that is characterized not only by psychosis, but also by multifactorial medical co-morbidities, including metabolic disorders and substance dependence, that contribute to markedly increased morbidity and mortality. We investigated the genomic interaction of psychosis and other medical disorders, including metabolic disorders, previously constrained by investigations limited to the 'linear' genome, by exploring the MDN's 'spatial genome', including chromosomal contact landscapes as a critical layer of cell type-specific epigenomic regulation. Low input Hi-C protocols were applied to 5-10x10^3 dopaminergic and other cell-specific nuclei collected by fluorescence-activated nuclei sorting from adult human midbrain. The Hi-C reconstructed MDN spatial genome resulted in multiple 'Euclidean hotspots' of clustered chromatin domains harboring risk sequences for SCZ and elevated body mass index (BMI). Inter- and intrachromosomal contacts interconnecting SCZ and BMI risk sequences showed massive enrichment for brain- specific expression quantitative trait loci (eQTL), with gene ontologies, regulatory motifs and proteomic interactions related to adipogenesis and lipid regulation, dopaminergic neurogenesis and neuronal connectivity and reward and addiction related pathways. More broadly, our NIDA/PsychENCODE sponsored Hi-C study offers a novel cell type-specific genomic approach for studying psychiatric and medical co-morbidities constrained by limited genetic overlap on the linear genome.