

Submitter Name: Sandhya Chandrasekaran
Submitter email: sandhya.chandrasekaran@icahn.mssm.edu
PI Name (if different): Schahram Akbarian
PI email (if different): schahram.akbarian@mssm.edu

Neuron-specific regulation of chromosomal megadomains in the mammalian brain implicated in endogenous retroviral silencing

Sandhya Chandrasekaran^{1,2}, Sergio Espeso-Gil^{1,2}, Yong-Hwee Eddie Loh³, Behnam Javidfar^{1,2}, Bibi Kassim^{1,2}, Yuhao Dong⁴, Yueyan Zhu⁴, Lucy King Bicks^{1,2}, Prashanth Rajarajan^{1,2}, Cyril Peter^{1,2}, Esperanza Agullo-Pascual², Marina Iskhakova¹, Molly Estill², Li Shen², Yan Jiang⁴, Schahram Akbarian^{1,2}

¹Department of Psychiatry, Icahn School of Medicine at Mount Sinai; ²Department of Neuroscience, Icahn School of Medicine at Mount Sinai; ³Health Science Libraries, University of Southern California; ⁴Institutes of Brain Science, Fudan University

Repeat-rich sequence blocks, considered major determinants for 3D folding and structural genome organization in the nuclei of all higher eukaryotes, are critically involved in a range of genomic functions. However, the relationship between the 3D genome (3DG) and DNA repeat organization in brain cells, with potential implications for neuronal health and function, remains unexplored. Here, we show that megabase-scale chromatin domain organization in adult mouse cerebral cortex is linked to specific multiple retrotransposon superfamilies, comprising the vast majority of 'mobile' DNA elements in the murine genome. We identify a neuronal megadomain subtype, termed B2, comprising loci enriched with endogenous retroviral (ERV2) elements and silenced in a neuron-specific fashion. Comparative chromosomal conformation mapping in wild-derived *SPRET/EiJ* and inbred *C57/BL6J* mouse strains revealed strain-specific configurations tracking the dramatic phylogenetic accumulation of ERV2s within the genomic landscape of *C57/BL6J* inbred lines, with ongoing *de novo* integrations of ERV2s preferentially within B2 domains. Neuronally depleting *Kmt1e/Setdb1* histone methyltransferase, critical to the KMT1E-KAP1-zinc finger and retrotransposon silencer complex, triggered megabase-scale disintegration and rewiring of chromosomal interactions among B2 domains; this was associated with the loss of retrotransposon silencing coupled with severe neuroinflammation and activation of cellular stress genes. Strikingly, the endomembrane system of susceptible *Setdb1*-deficient neurons was hijacked for provirus assembly, generating provirus-like particles. Our findings provide the first example of how 3DG compartmentalization in the mature mouse brain is critically shaped by mobile DNA elements in strictly cell-type fashion, uncovering a distinct heterochromatic regulome in neurons which, upon perturbation, could robustly unleash ERV proviruses.