Submitter Name: Stella Dracheva
Submitted email: stella.dracheva@mssm.edu

Extensive cell type-specific epigenetic reorganization of the *OPRM1* locus in primate evolution

Alexey Kozlenkov[1,2*], Junhao Li[3], Yasmin L. Hurd[2], Eran A. Mukamel[3], and Stella Dracheva[1,2,]

[1]James J. Peters VA Medical Center; [2] Friedman Brain Institute and Department of Psychiatry, Icahn School of Medicine at Mount Sinai; [3] Dept. of Cognitive Science, University of California

We performed genome-wide transcriptomic (RNA-seq) and epigenomic (H3K27ac ChIP-seq) analyses of the two main cortical neuronal subtypes [glutamatergic projection neurons (Glu) and GABAergic interneurons] in human, chimpanzee and rhesus macaque and identified multiple genes with concordant changes in gene expression and epigenetic regulation.

In particular, *OPRM1* that encodes *mu* opioid receptor showed human- and Glu-specific concordant enrichment in expression and the H3K27ac signal, which was detected for both promoters and enhancers, and was supported by multiple features of the *OPRM1* regulatory domain. The *OPRM1* locus exemplified a "re-specification" evolutionary event, as it contains an enhancer that is human-specific in Glu but rhesus-specific in GABA. This re-specification was manifested in GABA-specific expression of *OPRM1* in rhesus, but not in human. Conversely, *OPRM1* contains multiple human- and Glu-specific enhancers. Thus, *OPRM1* locus shows strong evidence for extensive cell type-specific evolutional reorganization of its regulatory landscape coupled with concordant changes in gene expression.

We also found human- and GABA-specific concordant changes in expression and regulation for *PENK* that encodes the precursor of delta opioid receptor ligand, proenkephalin, and for *SLC17A8* that encodes vesicular glutamate transporter 3. *SLC17A8* has been implicated in anxiety and cocaine abuse. Altogether, these evolutionary findings suggest human-specific modification of cellular and molecular pathways implicated in drug abuse. Understanding how gene expression and regulation changed over the evolutionary divergence of primates will help to identify the cellular and molecular substrates of drug addiction and will guide the choice of models to study this disorder.