Submitter Name: Andreas Pfenning
Submitted email: apfenning@cmu.edu

Addiction-associated genetic variants implicate cell type- and region-specific cis-regulatory elements in addiction neurobiology

Chaitanya Srinivasan[1], BaDoi Phan[1,2], Easwaran Ramamurthy[1], Alyssa Lawler[3], Michael Kleyman[1], Irene Kaplow[1], Ashley Brown[1], Morgan Wirthlin[1], Erin Zhang[1], Aydin Alikaya[4], Jing He[4,] Esin Ozturk[5], Molly Johnson[5], William Stauffer[4], Leah Byrne[5], Andreas Pfenning[1,3]

[1]Department of Computational Biology, School of Computer Science, Carnegie Mellon University; [2]Medical Scientist Training Program, School of Medicine, University of Pittsburgh; [3]Department of Biological Sciences, Mellon College of Sciences, Carnegie Mellon University; [4]Department of Neurobiology, School of Medicine, University of Pittsburgh; [5]Department of Ophthalmology, School of Medicine, University of Pittsburgh

Recent large genome-wide association studies (GWAS) have identified multiple confident risk loci linked to addiction-associated phenotypes. Genetic variants from complex behavioral and neurological traits, including addiction, tend to lie within non-coding cis-regulatory elements (CRE). We leverage the high degree of cell type-specificity of CREs to hypothesize that addiction-associated genetic variants lying in CREs of some cell types, but not others, might play functional role in the process of addiction.

We applied LD score regression to intersect addiction-associated variants with cell type- and region-specific CREs from human, mouse, and macaque to predict cell populations and circuits of addiction. We find that addiction-associated variants enrich in NeuN+ nuclei from human dorsolateral prefrontal cortex, orbitofrontal cortex, putamen, and the nucleus accumbens (Fullard *et al.* 2018), and excitatory and inhibitory neurons of human occipital cortex (Lake *et al*. 2018). We note concordant enrichment in orthologous CREs specific to mouse bulk striatum as well as mouse excitatory and VIP+ cortical neurons from INTACT sorted nuclei (Mo *et al.* 2015). We find further concordant enrichment within orthologous non-coding regions around medium spiny neurons and interneuron sub-types marker genes of the macaque striatal cell populations. Lastly, machine-learning models trained on sequences of cell type-specific CREs predict the impact of addiction-associated variants on CRE function.

The enrichments patterns that we find within cell type- and region-specific CREs across species point to the conservation of neural circuits and translatable inferences of studying addiction genetics in model organisms.