Cell type and Brain Region-specific Impact of Nicotine Use-associated Genetic Variation

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Nicotine use has an enormous impact on health and wellbeing across the world. Recent genome-wide association studies (GWAS) have begun to identify an increasing number of genomic loci associated with the predisposition to nicotine use, with many more loci implicated with lower confidence. The majority of the genetic variants associated with complex brain disorders, including substance use, are likely to be located in non-coding cis regulatory elements (CREs), and not within protein-coding genes.

Here, we aim to understand the molecular mechanisms underlying nicotine-use predisposition by comparing CRE annotations of human brain, both published and unpublished, a to recent GWAS for nicotine use. We began by compiling a database of CREs identified by ChIP-Seq for the histone modification H3K27ac in the roadmap epigenome project, which includes 7 brain regions. To identify which cell types within the brain are likely to be involved, we used fluorescence-activated sorting of nuclear markers to isolate the nulcei neurons, microglia, and other glial cells from 5 post-mortem human brain samples. On each of those fractions, we performed ChIP-Seq for H3K27ac. The resulting CRE database of brain regions and cell types was compared to a well-powered (>300,000 subjects) GWAS for nicotine use published by the UK Biobank. As predicted, we found several brain regions, including the caudate, showed an enrichment for nicotine use-associated mutations. Additionally, the neuron-specific CREs showed a substantial enrichment relative to microglia and other glia ($p<10^{-6}$), suggesting that most nicotine-use associated mutations impact neuron function.

To interpret how nicotine-use associated mutations impact regulatory elements, we have built multi-task convolutional neural network models that link genome sequence to cell type-specific and brain region-specific regulatory element activity. These models provide testable hypotheses for how nicotine-use associated mutations disrupt the regulatory code.