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Genetic regulation of personalized opioid response in cerebral organoids

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There has been a surge in neonatal abstinence syndrome (NAS) due to dramatic increases in prenatal opioid exposure, a consequence of the ongoing opioid epidemic in the United States. *In-utero* drug exposure is associated with increased risk of NAS and multiple adverse outcomes. Independent of socioeconomic status, children exposed to opioids *in-utero* and in the neonatal period are at greater risk for later cognitive, language, attention, and visual problems and poorer academic performance. The variability in outcomes, for comparable exposures, implicates a role of gene-by-environment interactions for these neurological phenotypes. Deconstructing the interplay between environment exposures, genetic variation, and cell-specific molecular features is a principle challenge to understanding personalized opioid responses. To address this, we are differentiating human neural precursors and cerebral organoids (with and without opioids exposure) from iPSC lines reprogrammed from 54 donors with high-depth phased whole genome sequence. We will integrate genetic variation with diverse molecular (scRNA-seq, ATAC-seq, BruUV-seq) and cellular (live imaging and micro-electrode assays) features to produce a dense catalog of quantitative trait loci (QTL) that can illuminate the cell types, genes, and regulatory elements associated with personalized opioid-linked neuronal outcomes. Using association summary statistics from these opioid-response QTL maps, we will perform scans across large cohorts (e.g. UK Biobank) to identify cell types and genes associated with diverse adult biology. Collectively, these results will provide a genetic catalog that maps the cell-specific molecular landscape of neuronal effects from developmental opioid exposure to adult disease outcomes and will be a platform for novel gene discovery.