

Transcriptomic and Methyloomic Architecture of Polygenic Risk for Opioid Use Disorder

Our prior work has demonstrated the value of integrating epigenomic and transcriptomic data to identify molecular correlates of opioid exposure in human brain tissue. In an analysis of 160 post-mortem dorsolateral prefrontal cortex (dlPFC) samples, we examined DNA methylation using the Illumina Infinium MethylationEPIC BeadChip and gene expression using RNA-seq. This work identified 13 CpG sites that surpassed a relaxed false discovery rate. We also observed modest evidence of accelerated methylation age in opioid-exposed individuals. In parallel, differential expression analyses identified 16 genes at $FDR < .1$, with NPAS4 emerging as the top downregulated transcript in opioid samples, consistent with prior evidence implicating this gene in addiction-related neurobiology. Although these findings highlight several biologically plausible targets, the limited concordance across prior studies underscores the need for larger, more integrative analyses. Building on this foundation, we investigated the transcriptomic and methyloomic architecture of opioid use disorder (OUD) polygenic risk by testing how inherited liability to OUD is reflected in coordinated patterns of gene expression and DNA methylation in the dlPFC. This approach moves beyond case-control contrasts to identify molecular signatures associated with genetic susceptibility itself, helping to clarify how polygenic risk shapes regulatory pathways relevant to opioid dependence.

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