

Deciphering gene regulatory effects of opioid use disorder risk variants through allelic-specific DNA methylation mapping in glial cells

Background.

Genome-wide association studies (GWAS) have identified multiple risk loci for opioid use disorder (OUD); however, the majority of associated variants reside in non-coding regions, posing significant challenges for biological interpretation. A growing body of evidence indicates that psychiatric risk variants frequently exert their effects through gene regulatory mechanisms. Allelic-specific DNA methylation (ASM) - a regulatory mechanism in which genetic variation influences local epigenetic states in a cis-dependent manner - remains underexplored in this context, despite its potential to alter gene expression and mediate genotype-to-phenotype relationships. Glial cells are central to neuroinflammation, synaptic modulation, and reward circuitry, processes strongly implicated in the pathophysiology of OUD. Here, we mapped ASM in glial cells, linking OUD GWAS risk variants to functional regulatory consequences and revealing cell-type-specific epigenetic mechanisms that may underlie genetic susceptibility to OUD.

Methods.

We performed whole-genome sequencing on human postmortem orbitofrontal cortex (OFC) tissue from 22 donors using a novel 6-base genomics technology that enables simultaneous quantification of epigenomic and genomic variation within the same sample. ASM was quantified by comparing DNA methylation levels between phased haplotypes using Fisher's tests. To evaluate potential functional mechanisms, we further assessed the overlap between ASM-associated genetic variants and GWAS signals for opioid misuse, as well as expression quantitative trait loci (eQTLs).

Results.

We identified more than 8 million ASM sites distributed across the genome. Sites shared across all samples were broadly distributed throughout the genome, including within a well-characterized imprinted region on chromosome 21. Among OUD cases, donors carrying a risk haplotype in PDE4B - a gene previously implicated in opioid susceptibility - exhibited reduced cis DNA methylation, consistent with a more transcriptionally permissive chromatin state. Notably, these haplotypes did not overlap with known eQTLs for PDE4B, suggesting that ASM may capture regulatory variation not detected by transcriptomic approaches alone.

Conclusion.

Our findings suggest that a subset of GWAS risk variants for OUD may exert their regulatory effects through ASM rather than through classical eQTL mechanisms, underscoring the complementary value of epigenomic approaches in interpreting non-coding genetic risk. These results highlight the importance of integrating ASM and other epigenomic regulatory layers as potential mediators of GWAS variant effects, particularly in disease-relevant cell types such as glia.

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