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Genomic and Transcriptomic Splicing Associations in Opioid and Alcohol Use Disorder

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Genes associated with substance use (SU) and substance use disorders (SUDs) are increasingly being identified. Yet, the exact mechanisms by which these increase risk for SU and SUD is not fully understood. Alternative mRNA splicing has been observed for neuropsychiatric traits, but less so for substances like alcohol and opioids, which pose a significant public health burden. We assessed the biological interplay between alternative splicing and genetics for alcohol- and opioid-use disorder in different brain tissues (e.g., dorsal–lateral prefrontal cortex (dlPFC), nucleus accumbens (NAc)) of humans and model organisms. Higher polygenic risk for alcohol use disorder (AUD) predicted alternative mRNA splicing changes in brain tissue of individuals with AUD. We identified 714 differentially spliced genes and 6,463 splicing quantitative trail loci (sQTLs) that were enriched in genomic regions that regulate transcription (i.e., enhancers & DNase I hypersensitive sites). Many of the differentially spliced genes associated with AUD were correlated with primate models of chronic alcohol consumption. For opioid use disorder (OUD), we found 788 differentially spliced genes across brain regions, which mostly demonstrated tissue specific effects, but a functionally characterized splicing change in the clathrin and AP-2-binding (CLAP) domain of the Bridging Integrator 1 (BIN1) gene was significantly linked to OUD across all brain regions. There was limited evidence to suggest that genetic variation within and around alternative mRNA splicing regions were linked to genetic predisposition for OUD. Altogether, our studies underscore the substantial yet complex contribution of alternative mRNA splicing in the pathophysiology of AUD and OUD.