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Neuron-specific RNA-binding Protein ELAVL2 and Post-transcriptional Gene Regulation in Substance Use Disorders

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Genetic polymorphisms mapping to the embryonic lethal and abnormal vision-like 2 (*ELAVL2*) gene have been repeatedly identified as significant markers in large-cohort genome-wide association studies (GWAS) for different substance use disorders (SUDs), and psychiatric phenotypes often comorbid with SUDs. However, molecular mechanisms by which *ELAVL2* might be involved in these addiction-relevant phenotypes remain unknown. *ELAVL2* is expressed exclusively in neurons and encodes an RNA-binding protein that functions in post-transcriptional gene regulation (PTGR), e.g., alternative polyadenylation that generates RNA isoforms with distinct 3'-untranslated regions (3'-UTR). We hypothesized that ELAVL2 was associated with SUD phenotypes through (post-)transcriptional regulation of SUD risk genes.

We performed enhanced crosslinking and immunoprecipitation sequencing (eCLIP-seq) to identify transcriptome-wide ELAVL2-RNA-bound sites, and RNA-seq after ELAVL2 knock-down to identify differential gene expression, splicing and polyadenylation in human iPSC-derived neurons. We found that the majority (74%) of eCLIP-seq-identified ELAVL2-bound sites mapped to 3'-UTRs, and most ELAVL2-bound genes displayed changes in polyadenylation (n=963, compared to 66 for splicing and 8 for RNA levels) after ELAVL2 knock-down. Finally, ELAVL2-bound sites overlapped with genetic loci identified by SUD GWAS designed to identify genes which might contribute to SUDs through ELAVL2-mediated PTGR. We identified 61 ELAVL2-bound genes including *NCAM1*, *CTNND1*, and *FTO*, which have been identified in GWAS for opioid and alcohol use disorders, and/or nicotine addiction. All of these genes displayed changes in polyadenylation after ELAVL2 knock-down.

Our results demonstrated that ELAVL2 regulates many SUD risk genes through PTGR, suggesting a PTGR mechanism of SUD pathophysiology that needs to be further studied.