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Roles of alternative splicing in alcohol use disorder

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Alterations in pre-mRNA splicing have been linked to a range of neuropsychiatric conditions, including addiction. In this study, we designed a Mendelian randomization-based model to identify skipped exons that contribute to AUD risk. Genotypes and RNA-seq data from the CommonMind Consortium were used as the training dataset to develop predictive models linking individual genotypes to exon skipping in the prefrontal cortex. We applied these models to data from the Collaborative Studies on Genetics of Alcoholism to examine the association between the imputed cis-regulated splicing outcome and the AUD-related traits. We identified 27 exon skipping events that were predicted to affect AUD risk; six of these were replicated in the Australian Twin-family Study of Alcohol Use Disorder. In addition to disease risk, by examining transcriptome data from multiple brain regions of 142 independent subjects, we found elevated level of aberrant intron retention (aIR) in the AUD brains. The host genes of these aIRs were enriched in multiple neuronal and glial cell types. In addition, we found AUD-associated aIRs tends to be longer. We hypothesized that long introns potentiate the formation of double-stranded RNA, which may trigger neuroinflammation and immune responses. We performed immunofluorescent staining of dsRNA in brain tissues from alcohol-preferring P rats, and observed higher dsRNA signals in the brain tissues of P rats consuming alcohol. In summary, our study underscores the critical roles of alternative splicing in AUD, influencing both the disease risk and the biological responses to alcohol exposure.