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Genome-Wide Analysis of Methylome in the Mouse Brain Reveals Epigenetic Regulation of Alcohol Use Disorder

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Epigenetic regulation of gene expression has been previously associated with alcohol use disorder (AUD). However, the epigenetic mechanism mediating AUD remains largely unclear. In this study, we investigate a potential link between epigenetic regulation through DNA methylation and AUD. DNA methylation regulates gene expression by recruiting proteins involved in gene repression or by inhibiting the binding of transcription factor(s) to DNA, especially in the regulation of Allele-Specific Expression (ASE). We profiled genome-wide methylome in the two inbred mouse strains, C57BL/6J (B6) and DBA/2J (D2) using Oxford Nanopore long-read sequencing technology. We detected millions of methylation events and 1,465 differentially methylated regions (DMRs) between B6 and D2. Of the 1,465 identified DMRs, we found 449 DMRs associated with 307 genes with ASE, and 207 DMRs with 136 imprinted genes, respectively. We also identified 61 DMRs in the promoter and intergenic regions of 50 well documented AUD genes. A few notable AUD genes with DMRs in their regulatory regions include *Aldh2, Creb1, Gabbr1,* and *Gabbr2*. Overall, our findings highlight the role of epigenetic regulation of gene expression in AUD, leading to a deeper understanding of genetic basis of AUD.