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DNA Methylation Signatures of Alcohol Use Disorder – a Large-Scale Meta-Analysis in the PGC-SUD Epigenetics Working Group

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Alcohol Use Disorder (AUD) is a major public health challenge contributing to morbidity and mortality worldwide. Despite a growing body of research exploring the role of DNA methylation (DNAm) in the pathophysiology of AUD, findings have been inconsistent and difficult to replicate across cohorts. This study aimed to address these challenges by conducting a large-scale meta-analysis of epigenome-wide association studies (EWAS) to identify reliable and reproducible epigenetic markers of AUD.

Seven cohorts with blood DNA methylation data from 3,745 individuals (1,315 with AUD) contributed to this meta-analysis under the framework of the PGC SUDs Epigenetics Working Group. Data was processed using standardized QC and EWAS scripts. The association of AUD status with DNAm was evaluated using robust linear models in each cohort and a fixed effects meta-analysis was performed on summary statistics. Differentially methylated regions (DMRs) were identified using comb-p and gene ontology overrepresentation analysis was performed with clusterProfiler.

We identified 282 epigenome-wide significant CpG sites associated with AUD after Bonferroni correction, with the strongest hypomethylation in cg03546163 (FKBP5) and hypermethylation in MIR9-3HG. Meta-analysis results replicated findings from individual cohorts. On a regional level, we identified 324 DMRs enriched for metabolic and GTPase signaling pathways.
This meta-analysis represents one of the largest epigenetic studies of AUD to date and provides valuable insights into molecular mechanisms underlying AUD. By elucidating the role of DNAm in

AUD, our study paves the way for future research aimed at developing epigenetic biomarkers for diagnosis, prognosis, and treatment response in individuals with AUD.