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Epigenome-wide association study of alcohol consumption in N=8161 individuals and relevance to alcohol use disorder pathophysiology

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Growing evidence suggests that alcohol consumption is strongly associated with alterations in DNA methylation. Identification of alcohol-associated methylomic variation might provide novel insights into pathophysiology and novel treatment targets for alcohol use disorder (AUD).

We performed the largest single-cohort epigenome-wide association study (EWAS) of alcohol consumption to date (N=8161) and cross validated findings in AUD populations with relevant endophenotypes, as well as alcohol-related animal models.

2504 CpGs sites were significantly associated with alcohol consumption with the five leading probes located in SLC7A11 (p=7.75 x 10-108), JDP2 (p=1.44 x 10-56), GAS5 (p=2.71 x 10-47), TRA2B (p=3.54 x 10-42) and SLC43A1 (p=1.18 x 10-40). Two sample Mendelian randomization confirmed the causal relationship of consumption on AUD risk (IVW p=5.37 x 10-09). A methylation-based predictor of alcohol consumption was able to discriminate AUD cases in two independent cohorts (p=6.32 x 10-38 and p=5.41 x 10-14). The top EWAS probe cg06690548, located in the cystine/glutamate transporter SLC7A11, was replicated in an independent cohort of AUD and control participants (N=615) and showed strong hypomethylation in AUD (p<10-17). Decreased CpG methylation at this probe was associated with clinical AUD phenotypes. SLC7A11 expression was increased in AUD post-mortem brain and in liver tissue from alcohol exposed rats.

Our EWAS and subsequent validation of the top probe in AUD suggest a strong role of abnormal glutamate signaling mediated by methylomic variation in SLC7A11. Our data are intriguing given the prominent role of glutamate signaling in brain and liver and might provide an important target for therapeutic intervention.