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GWAS of Neuroimaging Derived Subtypes of Alcohol Use Disorder

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Background: Alcohol use disorder (AUD) presents with substantial heterogeneity.
Rational: Attempts to distinguish SUDs such as AUD by clinical features alone have had limited translational success.

Hypothesis: Objective biomarkers, like those derived from neuroimaging, will help parse AUD heterogeneity based on biology.

Methods. We developed neuroimaging derived cortical thickness biotypes of AUD in the European subset of the UK biobank (N=22,321) and conducted GWAS of biotype membership vs. controls (i.e., AUD biotype 1 vs. controls from biotype 2 and non-affected individuals). We also conducted GWAS contrasting biotypes in all individuals with neuroimaging data (N = 32,287). Results: Differences in regional cortical thickness within the salience network (e.g., regions) differentiated two AUD biotypes from controls. AUD biotype 1 was characterized by greater cortical thickness and biotype 2 had less cortical thickness, within the salience network. GWAS of biotype 1 (vs controls) identified one suggestive hit (rs60657889, p = 5.93e-08). GWAS contrasting the two biotypes revealed two significant hits including lead variant rs12355217 on FAM107B, (P=1.77e-09), a gene known to influence neurological pathways.

Discussion. Using a data-forward approach, we can parse heterogeneity in AUD and discover potential genetic pathways contributing to heterogeneity. Future analyses will examine loci from a joint analysis of biotypes with the largest GWAS of problematic alcohol use using a multivariate GWAS (N=1,079,947) and conduct multi-ancestry fine-mapping to determine likely causal variants. Finally, genetic correlations and drug repurposing analyses will determine the clinical and pharmacotherapeutic separability of brain-imaging derived biotypes.