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Behavioral And Expression Genetics Identification Of Genes Modulating Progressive Ethanol Consumption In Diversity Outbred Mice

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Background and Purpose: Alcohol use disorder (AUD) involves progression from occasional ethanol consumption to compulsive excessive intake and is strongly influenced by genetic variance. Here we used the intermittent ethanol access (IEA) model and a high-resolution complex mouse genetic resource, diversity outbred (DO) mice, to identify genetic loci contributing to progressive ethanol consumption. High priority candidate genes were ranked using RNAseq and cross-species bioinformatics.

Methods: DO male mice (n=640) were studied with 3-bottle choice (15 or 30% v/v ethanol, and water) IEA ethanol consumption for 4 weeks. Control animals received only water. Brain regions were collected for RNAseq analysis and mice genotyped at >140k markers. Behavioral QTL (bQTL) analysis was performed using R/qtl2. RNAseq analysis of prefrontal cortex and nucleus accumbens used genotyping by RNAseq (GBRS) to identify haplotype-specific expression and expression QTL (eQTL).

Results: DO mice showed a highly significant progressive increase in ethanol consumption across weeks of access. R/qtl2 analysis identified 3 genome-wide significant loci ($p<0.01$), and several suggestive loci (LOD>6) with support intervals of 1.05-3.8 Mb. GBRS RNAseq cis-eQTL, haplotype analysis and bioinformatics identified candidate genes, including a highly significant single candidate for progressive ethanol consumption on proximal Chr4 that has also been implicated in responses to psychostimulants.

Conclusion: Study of progressive ethanol consumption in DO mice identified significant bQTL for ethanol consumption. Expression genetics and cross-species bioinformatics identified a tractable list of high priority candidate genes for future mechanistic and behavioral studies. *Supported by NIAAA grant P50AA022537.*