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Genetic Analysis of Intermittent Access Ethanol Consumption in Diversity Outbred (DO) Mice

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Intermittent ethanol access (IEA) progressively increases voluntary oral ethanol consumption in mice, and models human ethanol consumption seen with alcohol use disorder (AUD). Here we analyzed genetic contributions to IEA using diversity outbred (DO) mice originating from 8 progenitor mouse strains chosen to maximize genetic diversity (Churchill et al., Mammalian Genome 23:713, 2012). DO mice also have reduced recombination intervals allowing fine mapping of traits. We studied IEA (M-W-F, 24 h access; 3-bottle choice with water, 15% and 30% v/v ethanol) for 640 DO mice with 4 weeks of ethanol access followed by genotyping for 143,000 SNP markers and collection of brain tissue for RNA-seq analysis. Total ethanol consumption showed a broad distribution (0.5-40 g/kg/24h) with population increases in consumption from first week vs. last week (5.99 vs. 7.57 g/kg/24h, $p<2.75 \times 10^{-11}$). Behavioral QTL analysis (R/QTL2) identified 10 genome-wide significant or suggestive QTL with LOD ≥ 6. QTL support intervals were generally <2Mb, allowing high resolution mapping of candidate genes. For example, the support interval for a Chr11 last-week total consumption (Chr11:49.96-51.5 Mb) contained 62 genes with only 14 having associated SNPs with haplotype patterns matching founder effects on the phenotype. Ongoing RNAseq analysis of prefrontal cortex for 240 DO mice will identify brain cis-expression QTL (cis-eQTL) as high priority candidate genes and expression network analysis for correlation with behavioral phenotypes. These studies hold high promise for identifying novel genes and gene networks contributing to progressive ethanol consumption. *Supported by NIAAA grants P50AA022537 AND R01AA020634 TO MFM.*