Genetic Analysis of Intermittent Access Ethanol Consumption in Diversity Outbred (DO) and Progenitor Mouse Strains

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Intermittent ethanol access (IEA) progressively increases voluntary oral ethanol consumption in mice, and models ethanol consumption seen in humans with alcohol use disorder (AUD). Here we analyzed genetic contributions to IEA using the diversity outbred (DO) mouse model. DO mice (Jackson Laboratories) result from a complex cross of 8 progenitor strains (129S1/SvlmJ, A/J, C57BL/6J, CAST/EiJ, NOD/ShiLtJ, NZO/HiLtJ, PWK/PhJ and WSB/EiJ) chosen to maximize genetic variance within resulting crosses. Initial IEA (every-other day access) and daily ethanol access with a 3-bottle choice model (water, 15% and 30% v/v ethanol) in progenitor strains showed marked strain x drinking paradigm differences in ethanol consumption ranging from 1.2-37.7 g/kg/24 hours with IEA heritability exceeding 0.65. IEA and anxiety trait analyses were then conducted for 640 DO mice with 4 weeks of IEA consumption followed by genotyping for 143,000 SNP markers using gigaMUGA arrays (Neogen, Lansing, MI) and collection of brain and peripheral tissue for RNA-seq analysis. R/QTL2 control trait genetic analysis confirmed a large quantitative trait locus (LOD≥90) for albino coat color on mouse Chr 7 at ~87.5 Mb with a 1 LOD support interval of 0.4 Mb. Initial genetic analysis of ethanol consumption behavior across an initial 200 DO mice showed a provisional QTL on Chr 6 (LOD>6) with full analysis of all 600 animals ongoing. These studies sho that genetic analysis of IEA ethanol consumption in DO mice, together with ongoing whole genome expression studies, are a powerful approach for high resolution mapping of genetic loci influencing progressive ethanol consumption and identifying associated gene expression networks and novel candidates for future therapeutic or mechanistic studies. *Supported by NIAAA grants P50AA022537 AND R01AA020634 TO MFM.*