Genome-wide mapping of ethanol sensitivity in the Diversity Outbred mouse population

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A strong predictor for the development of alcohol use disorders (AUDs) is altered sensitivity to the intoxicating effects of alcohol. Individual differences in the initial sensitivity to alcohol are controlled at least in part by genetic factors. Mice offer a powerful tool for elucidating the genetic basis of behavioral and physiological traits relevant to AUDs; but conventional experimental crosses have only been able to identify large chromosomal regions rather than specific genes. Genetically diverse, highly recombinant mouse populations allow for the opportunity to observe a wider range of phenotypic variation, offer greater mapping precision, and thus increase the potential for efficient gene identification. We have taken advantage of the newly developed Diversity Outbred (DO) mouse population to identify and map narrow quantitative trait loci (QTL) associated with ethanol sensitivity. We phenotyped 778 JAX Diversity Outbred mice (DO) for three measures of ethanol sensitivity: ataxia, hypothermia, and loss of the righting response (LORR). We genotyped a subset of these mice at ~150k markers across the genome and performed high precision QTL mapping using the R program DOQTL. A paired samples t-test indicated that on average, there was a significant and robust decrease in pre-ethanol performance as compared to post-ethanol performance on the Rotarod latency to fall, $t(786) = 26.6$, $p < 0.0001$, $d = .95$. A repeated-measures ANOVA indicated that following ethanol administration, subjects showed significant changes in body temperature over time, $F(3.02, 2352.90) = 1098.30$, $p < 0.0001$, $\eta_p^2 = 0.59$. During LORR testing, the majority of subjects (87.7%) both lost and regained the righting reflex during the testing period, with duration of LORR ranging from 0 minutes to the cut-off time of 180 minutes ($M = 75.9$, $SD = 52.9$). Importantly, we observed tremendous variation in all three traits which enables genetic mapping of naturally occurring genetic variation that is associated with trait variation. We identified four significant QTLs associated with ethanol sensitivity on chromosomes 1, 9, 10, & 16 (-log10pvalue > 6.1). The high genetic precision and phenotypic diversity in the DO may facilitate discovery of previously undetectable mechanisms underlying predisposition to develop AUDs. With the inclusion of RNA-Seq and other molecular profiling we will be able to apply a systems genetic strategy to construct the network of correlations that

exist between DNA sequence, gene expression values and ethanol-related phenotypes. This information can in turn be used to identify alleles that contribute to AUDs in humans, elucidate causative biological mechanisms, or assist in the development of putative treatment strategies.