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Cross-Species Prioritization of Genomic Loci for Drug Addiction: An Example Using Alcohol Consumption

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Alcohol use disorder (AUD) is a persistent disease present in approximately 9% of the US population. Prior studies suggest that AUD related phenotypes, such as dependence and vulnerability are genetically influenced (h^2=40-60%), but no single gene or robust set of genes have been identified. The polygenic architecture of alcohol related traits complicates the localization and identification of susceptibility loci. The integration of gene expression and functional experimentation evidence across species may facilitate human-based association analyses to the extent that co-regulated sets of genes reflect systems under regulation by repeated drug exposure. The present study investigates how highly connected genes related to alcohol consumption in humans, Drosophila, mice and rats, contribute to individual differences in alcohol consumption (AC) in humans. We examine a new pipeline to assess the ability of genes identified from expression-QTL (eQTL) studies in model-organisms to prioritize genes for AC. eQTL-based gene sets were derived from GeneWeaver. Over 14,000 genes were initially identified across all AUD phenotypes, and 2,538 specifically for AC. These genes were then ranked, and systematically examined as joint predictors of alcohol consumption in the UKBiobank (N=146,244) and dbGAP sample (N=6615) to identify sets of SNPs in a subset of genes that are highly connected to AC. Partitioning of the heritability of alcohol dependence, indicated that one-half of the observed effects were attributable to the identified gene set. Notably, effects reduced as the number of SNPs included in the gene set were restricted by the number of times a gene was observed across multiple studies.