

Project 6: Genomics Analysis of Social Stress and Individual Variation in Ethanol Drinking

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Recent studies in our laboratory on ethanol 2-bottle choice drinking with C54BL/6 inbred mice have documented exceedingly consistent, substantial individual variation in daily drinking behavior. This individual variation in ethanol drinking is modified by environmental factors, including formation of social hierarchy through group housing with non-siblings. This variation in drinking is not seen for saccharin or total fluid intake. Initial microarray studies done on individual animals have identified expression patterns highly correlated with this drinking behavior. It is our hypothesis that stress (isolation, social hierarchy) has created long-lasting influences altering drinking behavior in these genetically identical animals. This offers a unique opportunity to finely dissect molecular mechanisms underlying difference in drinking behavior generated by environmental influences, particularly in regard to social interactions. We predict our results will partially overlap with drinking behavior-related gene networks identified by “traditional” genetic approaches as well as identify novel modulators of drinking behavior not discernable in studies on populations. We will conduct five specific aims. Aim 1 will further characterize our behavioral model to determine the stability of the variation in individual drinking behavior induced by group housing. Aim 2 will characterize whether individual variation in drinking behavior correlates with behavioral or neurochemical measures of anxiety and stress. These studies will include assessment of plasma corticosterone levels and brain regional levels of corticotrophin releasing factor (CRF) and the neurosteroid, allopregnanolone. Aim 3 will use whole genome microarray studies to identify gene expression patterns correlating with drinking behavior or social stressors such as group housing or isolation housing. Aim 4 will refine microarray data using bioinformatic resources through the INIA-Stress bioinformatics core and collaborations with Drs. Chesler, Langston and Williams. Candidate genes will be selected through a multivariate ranking scheme and expression verified by Q-rtPCR, Western blotting and immunocytochemistry. Candidates selected from our microarray studies will also be used to determine if the same genes show correlations with stress or drinking behavior in mouse samples from Dr. Biggio (project 9) and primates (Dr. Grant, Project 2). In Aim 5, these genes will be used to predict drinking behavior or drinking responses to social stress in mouse lines derived from the BXD recombinant inbred panel or other mouse resources from this INIA. Finally, these candidate genes will be behaviorally verified by generating null mouse lines from genetrapped ES cells (via the Knock Core, Dr. Delpire) or using viral vectors to deliver gene constructs to target brain regions followed by behavioral studies. These studies might thus identify genes or networks of genes that cause human alcohol consumption to vary across individuals, leading some to excessive alcohol intake and risk for alcoholism.