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Collaborative Cross RIS as a Mouse Model to Identify Genetic Polymorphisms that Modify Alcohol-Related Outcomes

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The limited genetic diversity of many mouse strains reduces their utility to identify novel polymorphisms affecting alcohol vulnerability. The Collaborative Cross (CC) recombinant inbred strains were derived from eight inbred and wild-derived strains to recapitulate the diversity of human genetic heterozygosity. They represent a novel discovery tool for genetic research on alcohol and addiction. We report here alcohol-related phenotypes for 12 CC strains. All mice consume a fixed-nutrient diet (AIN-93G) to reveal gene × nutrient × alcohol interactions. C57Bl/6J serves as reference strain. To date, five CC strains have exceptional alcohol responses. Alcohol clearance varies widely: 30-min after single alcohol gavage (3 g/kg), mean BACs range from 80 mg/dl (two strains) to >350 mg/dl (one strain) [mean for C57Bl/6J, 220 mg/dl]. Two strains die from cerebral aneurysm within 60min following a single oral dose (3g/kg). Testing of alcohol preference (two-bottle reverse choice) is underway. For PAE (3g/kg daily, GD8.5-19.5), one strain has a 37% fetal malformation rate; a second develops fatal PAE-dependent preeclampsia. Basal stress responses vary widely and mean body temperature change (assessed using stress-induced hyperthermy) ranges from -0.2°C to +1°C. Despite consuming identical diets, strains exhibit gene-nutrient interactions that modify fertility, food intake, body composition (NMR), and adiposity. These data affirm that the CC RIS are a powerful discovery tool to identify candidate genetic influences upon alcohol outcomes. Their exceptional diversity complements existing RIS, and their deep sequencing and extensive SNP maps accelerates identification of polymorphisms affecting alcohol vulnerability. [Supported by the UNC-NRI.]