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Validating novel human GWAS hits for problematic alcohol use and consumption using genetic mouse models

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Recent well-powered human genome-wide association studies (GWAS) have identified numerous novel genetic variants associated with alcohol consumption and problematic use. To utilize this genetic information most effectively, it is necessary to follow up on these findings using model systems to determine *whether and how* these genes affect alcohol-related behaviors. Mutant mouse lines provide a first step to determine whether individual gene manipulations are sufficient to alter alcohol consumption and to begin to explore the underlying mechanisms of action. Here, we investigated the role of the candidate gene *Fut2,* which has been associated with both problematic alcohol use and alcohol consumption in humans, in two different models of alcohol drinking in mice. Heterozygous knockout mice and wild type littermates were tested for alcohol Drinking in the Dark (DID), followed by intermittent access escalation of drinking. Genotype did not affect binge-like intake during the DID test, but mice heterozygous for the *Fut2* knockout showed less escalation of drinking during week 1 of the intermittent access test. However, no genotype differences were seen in weeks 2 or 3, with all mice ultimately reaching the same level of intake. These findings highlight the complexity of translating genetic findings between humans and model organisms, even for phenotypes that may appear to be similar across species (e.g. alcohol consumption). In ongoing experiments, we are continuing to evaluate *Fut2* and other candidate genes for their effects on a wide variety of alcohol-relevant phenotypes in mice to determine how these genes may increase risk of problematic alcohol use.