

## AN INFLUENTIAL NOVEL TRANSCRIPT IN A SYSTEMS GENETIC MODEL OF ALCOHOL CONSUMPTION

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We have previously used a network approach to identify candidate transcriptional networks that influence levels of alcohol consumption. Combining brain RNA-Seq and microarray data from the panel of HXB/BXH recombinant inbred rat strains and five pairs of rat strains selected for high and low levels of alcohol consumption, and applying QTL, correlation and weighted gene coexpression network analysis (WGCNA), a module of coexpressed transcripts was found to be significantly correlated with the predisposition of the rats to consume varying levels of alcohol in a two bottle choice paradigm (Saba et al., 2015). The hub gene (most highly connected gene) in this module is an unannotated transcript that is similar to a transcript found in mouse and human. Based on its sequence, the transcript is likely to be a long non-coding RNA (lncRNA). To ascertain the role of this transcript in alcohol consumption, we used CRISPER-Cas9 technology in Wistar rats to disrupt the third exon of the transcript. We compared the levels of alcohol consumption in wild-type, heterozygous and homozygous “knockout” male and female rats in a two-bottle choice paradigm. Both male homozygous and heterozygous knockout rats consumed significantly more alcohol compared to wild-type littermates indicating that two copies of the transcript are necessary for normal levels of alcohol consumption. Disruption of the transcript did not affect alcohol drinking by female rats. These results confirm a role of the putative lncRNA as a sex-specific modulator of alcohol consumption in rats. Furthermore, we identified wide-spread transcriptional consequences of disrupting this lncRNA using RNA sequencing, including changes in other transcripts within the original candidate transcriptional system that influenced alcohol consumption. Long non-coding transcripts are important regulators of transcription, and the identification of this particular transcript provides the first instance of an lncRNA being directly involved in modulating levels of alcohol consumption. Supported by NIAAA (R24AA013162 and INIA Project) and the Banbury Fund.