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The alternative splicing and alternative polyadenylation transcriptional landscape of the HXB/BXH recombinant inbred rat panel and its role in predisposition to voluntary alcohol consumption

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Post transcriptional phenomena are powerful mechanisms by which eukaryotes expand their genetic diversity. For instance, researchers estimate that 95-100% and 70% or more of genes in humans undergo alternative splicing and alternative polyadenylation, respectively. These splicing events produce distinct RNA molecules, which in turn yield distinct protein isoforms and/or influence RNA stability, translation, nuclear export, and RNA/protein cellular localization. Due to their pervasiveness and impact, we hypothesized that alternative splicing and alternative polyadenylation in brain play a role in predisposition to voluntary alcohol consumption. Using a subset of the Hybrid Rat Diversity Panel, we generated over one terabyte of brain RNA sequencing data (total RNA) and identified novel splice variants (via StringTie) and alternative polyadenylation sites (via aptardi) to determine the transcriptional landscape in these animals. After establishing an analysis pipeline to ascertain high quality transcripts, brain transcript levels were associated with voluntary alcohol consumption in the two-bottle choice paradigm. For genes that were previously associated with this trait, we were able to distinguish between isoforms to provide further information about the role of candidate transcripts for the trait. We also identified candidate transcripts for genes not previously associated with alcohol consumption, potentially due to improved annotation of all isoforms composing the gene. Overall, we established a pipeline for including alternative splicing and alternative polyadenylation in the transcriptome and demonstrate how their inclusion provides rich information for elucidating the genetic architecture of complex traits such as alcohol consumption. Sponsored by NIAAA (R24AA013162, F31AA027430), NIDA (P30DA044223), and the Banbury Fund.