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Integrative mouse genetic analysis illuminates human GWAS of multiple substance use

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Genome-wide association studies in humans reveal variants of potential impact on substance use disorder, but understanding when, where and how those variants play a role in phenomena as complex as substance use disorders requires extensive downstream follow up. This is the case even when the affected biological process or pathway is readily apparent, as the higher order behavioral effects and their role in SUD is less obvious. Thousands of biobehavioral traits characterized in mouse population studies provide a rich backdrop of information with which to interpret these effects. The challenges in tapping into this information reside in data heterogeneity within and across species. We built and applied a set of interconnected services including Mouse Phenome Database (MPD), VariantGraphDB, GenomeMuster and others to address these problems and applied the tools to the interpretation of variants associated with multiple substance use disorders in people. The variants were extrapolated across species to orthologous target genes and their regulatory variants. Over 390 mouse neurobehavioral measurements in MPD were associated with these variants using a genome-wide association metanalysis in mice. Integration across the multiple populations and measurements was performed via available in GenomeMuster imputed genome sequences for widely used inbred mouse strains, recombinant inbred panels and heterogeneous stock populations. Trait aggregation was assisted through the use of the expanded Vertebrate Trait and Mammalian Phenotype Ontology terms available for annotation of addiction related traits in model organisms. By comparing human variant associations to the mouse multi-trait associations, specific variant roles in addiction-related phenomena can be identified.