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Integrating past, present and future mouse and human population genetics of addiction using multi-trait meta-analyses to identify conserved human polysubstance use genes

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Complex diseases, like addiction, are characterized by multi-faceted biological responses to the environment, interventions, drug(s) and mechanisms specific to each drug's pharmacology. Thus, a multi-faceted analysis is required to understand the genetic basis of addiction. While single studies are often subject to idiosyncratic procedures and conditions and many lack the statistical power to identify casual variants of disease, meta-analysis provides the statistical framework to combine shared signal and pool power across studies. Data harmonization across the phenotypes and genotypes represented in these studies, while often challenging, is required to apply meta-analysis techniques. The Mouse Phenome Database contains expertly curated studies mapped to ontology terms, providing the common semantic reference necessary to harmonize measurements of different aspects of the disease. Genetic variants in study populations are anchored by GenomeMUSter, a new comprehensive genotype resource for inbred strains, with a novel pipeline that integrates outbred populations. We leverage these phenomic and genomic resources to identify the causal genetic variants of addiction-related traits in the mouse. For each variant, we identify the conditions under which the effect exists, whether the effect is broad or specific to drug, sex or other factors. We link addiction-related variants in the mouse to addiction in humans with the variant mapping graph database. With this approach, we identified polysubstance mouse variants and working with members of the PGC-SUD, identified those associated with genetic variation in polysubstance use in humans. This work is supported by NIH DA028420 and by The Jackson Laboratory, The Cube Initiative Program Fund.