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What, Where and How: Decoding Addiction GWAS with Mouse Data Resources

Substance use disorders are among the most complex and heterogeneous conditions in human medicine, shaped by genetic, environmental, and developmental factors. While genome-wide association studies (GWAS) have identified a growing number of risk variants, interpreting their effects requires biological context that human studies alone cannot provide. Mouse genetics, and the wealth of experimental data it affords, offers a powerful complementary resource to functionally characterize, model, and interpret human variant effects.

Model organism genetics can address the core questions GWAS cannot answer — what, where, and how a variant influences addiction-related behavioral processes — through interoperable resources that enable bidirectional translation across species. VoICE (Variants with Inferred Conserved Effects), a weighted graph of 32 billion relationships among variants, transcripts, genes, and regulatory regions, identifies the human genes regulated by GWAS variants and reveals the convergent genetic signal in mice by identifying mouse variants that regulate orthologous genes. Traits co-regulated by these same variants, identified via the Mouse Phenome Database Trait Regulatory Network, pinpoint the behavioral assays and phenotypic endpoints associated with the variant's biological effect and inform preclinical study design.

Effective translation to a preclinical study requires selecting a strain whose genetic background best resembles the human disease state. Because the phenotypic impact of a variant depends on the resilience of the underlying biological network, which varies considerably across genetic backgrounds, this choice is critical — particularly prior to genetic manipulation. Strain Recommender prioritizes 650+ strain backgrounds according to predicted vulnerability to the human disease state, correctly predicting strain effects for 5,578 of 5,890 (94.7%) diseases and 2,424 of 2,598 (93.3%) rare diseases in a global retrospective validation study.

Together, these tools support the full preclinical modeling pipeline: prioritizing candidate genes, variants, and regulatory targets; selecting the strain background that best models human disease; and determining the behavioral endpoints that reflect preclinical efficacy.

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