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From All of Us to All of Mus: Using human rare variant association scores to prioritize inbred mouse strains as complex, reproducible preclinical models for substance use disorders

Conventional mouse models often fail to capture the complexity of human disease, limiting clinical translation. Models based on single gene mutations are background-dependent and cannot fully represent polygenic conditions like substance use disorders (SUD). Selecting the optimal preclinical model from hundreds of available inbred strains is time-intensive and impractical without a data-driven approach.

We developed Strain Recommender, a data-driven approach that prioritizes over 600 mouse inbred strains based on resemblance to a human disease state. Leveraging RVAS summary statistics from the All of Us Research Program- a large-scale NIH initiative that has identified more than 275 million previously unreported genetic variants from a diverse U.S. cohort- Strain Recommender harnesses allelic state data from 657 mouse strains in GenomeMUSter and the genetic diversity of Diversity Outbred (J:DO) mice to prioritize inbred backgrounds most likely to be vulnerable or resistant to SUD.

To validate Strain Recommender predictions, we compared addiction-related behavioral data of Collaborative Cross (CC) strains, collected by the Center for Systems Neurogenetics of Addiction (CSNA). Strains predicted to be vulnerable based on All of Us RVAS summary statistics consistently exhibited higher impulsivity, anxiety-related responses, novelty-seeking behavior, and locomotor activity, as well as enhanced behavioral response to cocaine and impaired reversal learning, compared to strains predicted to be resistant.

These findings demonstrate that Strain Recommender can effectively prioritize preclinical mouse models with improved translational relevance for SUD research. By integrating large-scale human genomic data with mouse genetic diversity, this approach supports more efficient model selection for multi-substance and substance-specific disorders, with broad implications for understanding addiction biology and accelerating the development of therapeutics, interventions, and prevention strategies.

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