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Computational Genetic Discovery for SUD

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We developed a computational method for mouse genetic analysis. A causative genetic factor is identified by correlating the pattern of observable physiological differences among mouse strains with the pattern of genetic variation in a genome map covering 43 inbred strains (21M SNPs). This method has identified the genetic basis for 25 clinically important biomedical responses. As one example, based upon a genetic finding, we demonstrated that administration of a commonly used 5-HT_3 antagonist (ondansetron) prevented experimentally induced opiate withdrawal symptoms in mice and human subjects. Babies born to mothers taking opiates develop a severe opiate withdrawal syndrome after birth; and a multi-center clinical trial is now testing whether ondansetron can prevent this from developing in at risk neonates.

We are developing computational methods that enable genetic factors affecting substance use disorders (SUD) to be discovered and experimentally characterized. We analyzed a publicly available database, which contains 213,000 responses in panels of inbred mouse strains. To analyze this massive dataset, 'AI' methodology is used to analyze corresponding genetic, transcriptional and metabolomic data; and natural language processing is used for automated literature analysis. These computational tools are now being used to identify genes/pathways mediating SUD by analyzing customized datasets measuring fifteen SUD-related responses (cocaine, oxycodone, nicotine) in inbred strains; and corresponding SUD-induced transcriptional and metabolomic changes in brain. We use a high efficiency method for engineering specific allelic changes into the genome of inbred strains, and the engineered lines are used to experimentally test the effect of an identified genetic factor.