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Systematic Functional Mapping of Transcription Factor Variants Relevant to Substance Use Disorders Using Deep Mutational Scanning

Transcriptional regulation plays a central role in neuronal adaptation to substance exposure, yet the functional consequences of genetic variation within transcription factors (TFs) involved in substance use disorders (SUD) remain largely unresolved. Many variants identified in sequencing studies are classified as variants of uncertain significance (VUS), and their functional impact on transcriptional regulation remains poorly characterized. Such variation may alter how cells respond to substance exposure.

To better understand how genetic variation alters TF function, we use a Deep Mutational Scanning (DMS) platform that enables parallel functional assessment of thousands of coding variants. Our system introduces both TF coding sequences and their corresponding DNA response elements using a lentiviral design. TF activity is measured through a transcriptional reporter in which binding to the response element drives fluorescence expression, allowing direct quantification of TF-DNA regulatory activity, and variant effects are quantified by Sort-seq. This platform enables high-throughput functional testing of TF variants.

We previously established this framework and are now expanding it to additional TFs, including IRF3, SRF, and NFkB1, to systematically characterize variant effects across different regulatory contexts. Our goal is to generate functional maps that help resolve VUS and clarify how genetic variation in transcriptional regulators may contribute to differential susceptibility or resilience in substance-related disorders.

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