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Genetic Architecture and Adolescent Social Stress Shape Anxiety-Related Behaviors and Nicotine Sensitivity in BXD Mice

Adolescence is a critical developmental window characterized by neural circuit maturation, which both enhances behavioral adaptability and creates vulnerability to environmental stressors. Social stress during this period is a primary risk factor for adverse psychiatric outcomes. This study investigates how adolescent social instability stress (SIS) and genetic background interact to influence anxiety-related behaviors and acute nicotine sensitivity in a subset of BXD recombinant inbred mouse strains. We observed marked strain differences in spontaneous exploration of the elevated plus maze (EPM) and locomotor responses to acute nicotine. These phenotypes were moderately heritable, with R^2 values ranging from 0.39 to 0.45 for anxiety-like behavior and 0.41 to 0.73 for nicotine-induced hypolocomotion. Notably, the magnitude of initial versus extended responses to nicotine was not interdependent, suggesting distinct genetic regulation of these phases. SIS significantly modified both anxiety-related behaviors and nicotine-induced locomotor profiles in a strain-dependent manner, highlighting a Gene x Environment (GxE) interaction. To explore the underlying biological mechanisms, we queried 26 candidate genes, identifying 1,056 SNVs across the BXD strains with 34 missense variants clustering on specific chromosomes. These variants represent potential functional drivers of the observed behavioral diversity. Our findings suggest that genetic architecture fundamentally shapes how adolescent stress modulates drug susceptibility. These results provide insight into the individual risk factors for mental health and substance use disorders, emphasizing the importance of genetic background in translating environmental stress into behavioral phenotypes.

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