

Name: Z. Carl Lin

Email: zlin@mclean.harvard.edu

Human Epistatic Mechanisms in Polysubstance Use Disorders

Z. Carl Lin¹, Pei-Hong Shen², Allison J. Cash¹, Juan Zhao³, Kefu Liu⁴, Hui Sun²

¹Laboratory of Psychiatric Neurogenomics, McLean Hospital, Belmont, MA 02478, USA

²Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

³Aerospace Center Hospital, Beijing, China

⁴School of Life Sciences, Central South University, Changsha, China

Humans are a unique species by carrying not only human-specific chromosomal sequences, human-specific genetic variants but also human-specific genes. Furthermore, these genetics function in various ways, including monogenetic/additive, intergenic and intragenic epistasis mechanisms which may contribute to disease pathways. Such information manifests the necessity to elucidate human genetic mechanisms for various diseases including polysubstance use disorders (PUDs). We have examined both epistatic and transcriptional mechanisms for PUDs. First, we have meta-analyzed in single nucleotide polymorphisms (SNP)-based dbGaP datasets epistases among forty-six candidate genes which were selected based on findings from not only GWAS, but also pharmacological, imaging and molecular signaling approaches. This focused analysis revealed extensive and absolute genome-wide significances (AGWS, P-values<10⁻²⁰) for epistases via SNP-SNP interactions including top interactions with P-values around 10⁻⁶⁴ in males. Similarly, we examined genetic roles of known human-specific genes and found that a human-specific gene interacting selectively with dopaminergic genes again as the top interactions at AGWS in males. Finally, we interrogated intragenic epistasis of SLC6A3, the gene for dopamine transporter, and collected supporting evidence for epistasis in in vitro transcription and brain region-dependent PET-imaging signals. These significant epistases confirmed interacting dopamine signal and gender-dependence in PUDs, shedding light on molecular biology of polygenic risks in such complex disorders.

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