Submitter Name: Xusheng Wang
Submitted email: Xusheng.wang@und.edu

Genetic Architecture of Protein Expression in Rat Brain

Ling Li[1], Zhiping Wu[2], Ariana Mancieri[2], He Huang[1], Alyssa Erickson[1], Michal Pravenec[3], Junmin Peng[2], Robert W. Williams[4], Xusheng Wang[1]

[1]Department of Biology, University of North Dakota, Grand Forks, ND 58202, USA
[2]Department of Structural Biology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[3]Institute of Physiology of the Czech Academy of Sciences, 142 00, Praha 4, Czech Republic
[4]Department of Genetics, Genomics and Informatics, University of Tennessee Health Science Center, 19S Manassas St, Memphis, TN, 38163, USA

Genetic variation in protein expression has been implicated in almost all common diseases and complex traits, including substance use disorders (SUD) and addiction. However, the fundamental genetic architecture and variation of protein expression has received much less attention than that of mRNA expression or classical phenotypic traits. In this study, we performed a systematic characterization of the genetic architecture of protein expression in the rat brain. This study is an essential prelude of work on the proteomic impact of SUD. By using tandem mass tag (TMT)-based quantitative mass-spectrometry (MS) technology, we identified and quantified 8,231 proteins of SHR/Olalpcv (RRID:RGD_631848) and BN-Lx/Cub (RRID:RGD_61117), and of 19 of their HXB/BXH progeny inbred strains. Differential expression (DE) analysis identified 402 proteins with significant differences in protein expression between the parents (log fold change > 1 and $p < 0.01$). These proteins are involved in chemokine signaling pathway, regulation of protein deubiquitination, and axonal development. We detected 222 *cis*-acting quantitative trait loci (pQTLs) that strongly modulate protein levels in brain at a false discovery rate of 5%. For example, we identified a locus in the upstream of *CYP2D4*—a protein involved in pain and opiate responses—that is strongly associated with variation in its protein expression (q value = 2.3×10^{-9}). The deep proteomic data provide a rich resource for understanding the genetic control of protein modulation in rat brain and over the next few years—on the impact of SUD on protein levels in whole brain and mesocorticolimbic systems and on differential responses to drugs of abuse.