CYFIP2 mediated control of cocaine induced neuroadaptations in mice

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Using an unbiased forward genetic approach utilizing mouse substrains, we identified *Cyfip2* as a key regulator of acute and sensitized cocaine responses. We identified a mutation in CYFIP2 (S968F) that exists in all C57BL/6N substrains, including mice that are being produced in the international Knockout Mouse Project. CYFIP2 and its paralog CYFIP1 control neuronal function through at least two distinct pathways, FMRP and the WAVE regulatory complex. Both pathways have been shown to regulate behavior through control of neuronal connectivity and plasticity. Misregulation of neuronal plasticity in the mesolimbic system is thought to play a key role in the transition to addiction. Neuronal plasticity falls into two broad categories - functional plasticity in synaptic function and physiology (LTP/LTD) and structural plasticity of cellular architecture (dendritic spines, cell size). Here, we further explore the mechanism through which CYFIP2 mediates addiction relevant phenotypes using genetic, genomic, electrophysiology, and behavioral methods.

Using CRISPR/Cas9 mediated engineering of C57BL/6NJ and C57BL/6J substrains, we definitively show that the S968F variant is the causative mutation leading to acute and sensitized cocaine response changes. We extend our behavior analysis to show that *Cyfip2* regulates intravenous self-administration (IVSA) of cocaine, and voluntary alcohol drinking. Using electrophysiology, we test whether *Cyfip2* can regulate synaptic and intrinsic plasticity in the nucleus accumbens shell. Using genomic analysis, we explore changes in gene regulatory and co-expression networks in the mesolimbic circuit during cocaine sensitization. Finally, we constructed an allelic series through ten generations of backcrosses to change the genetic background of the *Cyfip2* deletion allele. A careful examination of these Müller's Morphs revealed that the S968F variant behaves like a hypermorph, a dominant gain of function mutation. Combined with recently published structural data from the Rosen Lab (UTSW), we postulate that this mutation leads to hyperactivated Rac signaling. Combined these data show that CYFIP2 regulates reward behaviors from multiple drugs of abuse through control of actin-remodeling complex and its associated changes in neuronal plasticity.