October 7, 2016

EIF3F Genetics of Substance Abuse

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Abstract

With the support of NIDA (DA021409), we have cloned the eukaryotic translation initiation factor 3 subunit F (EIF3F) as the first allele-selective and stressor-sensitive transcription factor for the human dopamine transporter gene (*hDAT* or *SLC6A3*). EIF3F binds to allele B of an intronic dinucleotide polymorphism (DNPi A/B) of *hDAT*. Secondary analyses of dbGaP GWAS datasets show that single nucleotide polymorphisms (SNPs) next to DNPi interact significantly with the EIF3F gene in Caucasian substance abuse (meta-analysis *P*-values are down to 3.9×10^{-15} with odds ratios between 0.17 and 6.5 by logistic regression). In a mouse study, one copy deletion of the EIF3F gene blunts cocaine self-administration selectively. Based on these genetic and other neuropharmacologic findings, a current dopaminergic model integrating genetics with stress effects will be presented.