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Cross-species functional validation of overlapping GWAS candidates between tobacco smoking in human and socially acquired nicotine IVSA in rats

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We exploit *C. elegans* for the cross-species functional validation of vulnerable target associated with nicotine dependence. Although Genome-wide association studies (GWAS) have successfully identified SNPs associated with complex diseases, rapid functional validation of candidates and their signaling-related pathways have not been effectively accomplished.

We determined nicotine seeking by nicotine-Conditioned Cue Preference (CCP), adapted from the Conditioned-Place Preference paradigm. We demonstrated that worms exhibited the recapitulation of the pivotal features of nicotine-dependent behaviors in mammals, where nicotine-induced increased dopamine mediates nicotine motivated behavior. We identified the nicotine-elicited cue preference is mediated by nicotinic acetylcholine receptors in worms. In addition, dopamine is required for the development of CCP by conditioning between nicotine and conditioned stimulus.

We tested GWAS candidates for tobacco smoking in human and socially acquired nicotine intravenous nicotine self-administration (IVSA) in rats, provided by P50 pilot project; NIDA, P50DA037844. The loss of function and knock-out (KO) strains of *Cacna2d3* and *Mef2c* orthologues were tested for CCP. We also tested KO strain of *Cacna2d2* orthologue, which is closely related to *Cacna2d3* in the same family and shared the human smoking phenotypes. The orthogonal test exhibited a delayed and impaired development of nicotine-conditioned cue preference, endorsing the rat GWAS results. We expanded the usage of the CCP assay to aversion-resistant seeking assay for measurement of compulsive nicotine seeking and applied it to the GWAS candidates for the test. The functional validation of the orthogonal test showed orthologues of *Cacna2d2, Cacna2d3* and *Mef2c* have a role in nicotine-motivated behavior in *C. elegans*.