Increased nicotine response in iPSC-derived human neurons carrying the CHRNA5 N398 allele

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Genetic variation in nicotinic receptor alpha 5 (*CHRNA5*) has been associated with increased risk of addiction-associated phenotypes in human yet little is known the underlying neural basis. Induced pluripotent stem cells (iPSCs) were derived from donors homozygous for either the major (D398) or the minor (N398) allele of the nonsynonymous single nucleotide polymorphism (SNP), rs16969968, in *CHRNA5*. To understand the impact of these nicotinic receptor variants in humans, we differentiated these iPSCs to dopamine (DA) or glutamatergic neurons and then tested their functional properties and response to nicotine. Results show that N398 variant human DA neurons differentially express genes associated with ligand receptor interaction and synaptic function. While both variants exhibited physiological properties consistent with mature neuronal function, the N398 neuronal population responded more actively with an increased excitatory postsynaptic current response upon the application of nicotine in both DA and glutamatergic neurons. Glutamatergic N398 neurons responded to lower nicotine doses (0.1 □M) with greater frequency and amplitude but they also exhibited rapid desensitization, consistent with previous analyses of N398-associated nicotinic receptor function. This study offers a proof-of-principle for utilizing human neurons to study gene variants contribution to addiction.