**The CHRNA5 variant rs16969968 alters how dopaminergic function changes during progression toward nicotine addiction and during nicotine withdrawal**

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Nicotine is the principal psychoactive component in tobacco smoke that drives continued addiction through its action on neuronal nicotinic acetylcholine receptors (nAChR). A number of genome-wide association (GWAS) and candidate gene-based studies investigating the genetic variants associated with nicotine dependence and smoking-related phenotypes have highlighted the *CHRNA5/A3/B4*gene cluster on chromosome 15, which encodes the α5, α3, and β4 nAChR subunits, respectively. Several polymorphisms were identified, including a missense variant in *CHRNA5* (rs16969968; G>A) that creates a D398N amino acid change, with the minor "A" allele representing the risk allele for nicotine dependence.

Although the action of nicotine and neuroadaptations caused by long-term nicotine exposure are beginning to be delineated at both the synaptic and behavioral levels, there are still few data available on the specific role of the α5-containing nAChRs during the nicotine addiction process. We used electrophysiology, fast-scan cyclic voltammetry and *in vivo* microdialysis approaches to directly investigate nicotinic influences over midbrain circuit controls that are altered during the progression toward addiction and during withdrawal, focusing on the α5 subunit and the rs16969968 SNP in particular.

Our results indicate that the D398N mutation leads to profound changes in dopaminergic cell activity and VTA nAChR function at baseline, during chronic nicotine exposure, and during short-term and prolonged withdrawal. The data provide insight into the cellular and circuit-based changes associated with the rs16969968 SNP and help to explain why the polymorphism increases vulnerability to nicotine dependence.

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