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# The Functional Role of a Human Polymorphism (rs2304297) in the 3'-UTR of the CHRNA6 Gene in Nicotine-Induced Locomotion and Anxiety in Adolescent Sprague Dawley Rats

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A single nucleotide polymorphism (SNP), rs2304297, in the human 3'-untranslated region (UTR) of the alpha(α)6 nicotinic acetylcholine receptor (nAChR) subunit gene (CHRNA6), is associated with enhanced smoking during adolescence in humans. The α6 nAChR subunit exhibits peak expression during adolescence in dopaminergic neurons of the ventral tegmental area and substantia nigra in rodents. Studies using α6 genetic animal models and pharmacological approaches provide evidence that α6-containing (*) nAChRs mediate nicotine-induced locomotor activity, anxiety, and self-administration. To study the role of the human CHRNA6 3'-UTR SNP *in vivo*, our lab generated a humanized rodent line via CRISPR/Cas9 genomic engineering. Using our new genetic animal model, our current studies test the functional role of the SNP in adolescent locomotor response and anxiety-like behavior following acute and sub-chronic nicotine exposure. We hypothesize that the CHRNA6 SNP will interact with nicotine to enhance locomotion and anxiolytic behavior in male and female humanized 3'-UTR CHRNA6 rats. Our results illustrate sub-chronic, but not acute, nicotine exposure leads to genotype- and sex-dependent enhancement of locomotion. For anxiety-like behavior, we observe genotype-dependent effects for acute nicotine exposure and genotype- and sex-dependent effects for sub-chronic nicotine versus saline exposure. Taken together, our data illustrate that the SNP is functional in our humanized 3'-UTR CHRNA6 rats and highlight the complexity of genetics, environment, and sex in studying substance use.