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# Nicotine plus cue-induced reinstatement is enhanced in adolescent Sprague-Dawley rats containing the Human 3'UTR polymorphism (rs2304297) in the alpha(α)6 nicotinic acetylcholine receptor subunit

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**Background:** 34 million adults in the United States are current smokers, a majority began smoking during adolescence. Large-scale human candidate gene studies have indicated a genetic variant in the alpha(α)6 nicotinic acetylcholine receptor subunit (nAChR), encoded by *Chrna6*$^{C123G}$, may play a key role in adolescent smoking. We hypothesize the *Chrna6*$^{C123G}$ polymorphism, rs2304297, selectively enhances nicotine + cue-induced reinstatement, but not nicotine- or cue-only reinstatement in GG (risk) versus CC (non-risk) allele carriers. **Methods:** Genetically modified adolescent rats were food trained under a fixed-ratio one (FR1) schedule of reinforcement and progressively increased to FR5TO20. Animals were implanted with catheters and began nicotine self-administration (15 µg/kg/infusion) at FR5. Upon reaching stable responding, reinforced behavior was extinguished by removal of drug and cues. Reinstatement testing began for cue only, nicotine only, and nicotine + cue in a randomized order. Animals were returned to extinction conditions 2 days minimum between testing. **Results:** No genotype effects are observed for food reinforcement during acquisition at FR5 or progressive ratio schedule of reinforcement. All animals show a preference for reinforced versus non-reinforced responding. CC and GG-allele carriers exhibit equivalent nicotine reinforcement and extinction. GG versus CC rats exhibit potentiated nicotine + cue induced reinstatement. **Conclusions:** Our findings indicate the GG risk allele carriers exhibit enhanced nicotine + cue-induced reinstatement at a low nicotine dose without altering natural food reward, nicotine reinforcement, cue-or nicotine-only reinstatement. Understanding the role of functional human genetic variants in nicotine seeking among adolescents is key for development of future prevention and intervention strategies.