Abstract: The use of nicotine and tobacco products are a major public health concern, with an exponential rise in the rate of electronic cigarette use among teens. Since developmental nicotine exposure can enhance drug consumption later in life, studying the molecular mechanisms mediating adolescent nicotine use is especially important. Large-scale human candidate gene studies reveal that a common genetic variant in the alpha(α)6 nicotinic acetylcholine receptor subunit (nAChR) (encoded by the Chrna6C123G gene, rs2304297) plays a vital role in adolescent nicotine/tobacco use. The findings represent one of the most consistent and replicable genomic loci in predicting nicotine/tobacco use in humans. The localization of the α6 nAChR subunit in ventral tegmental area (VTA) dopaminergic neurons suggest that modifications in its quantity and/or function influence the effects on motivational neurocircuitry. The functional effects of Chrna6C123G genetic variant are supported through a luciferase reporter assay illustrating microRNA (miRNA) -dependent mechanisms influencing protein expression. However, the in vivo functional consequences of the Chrna6C123G genetic variant at the behavioral or molecular level are unknown, which represents a critical gap in knowledge. To address this gap, my laboratory has engineered a genetically humanized Chrna6C123G mutant rat line. The humanized line replicates the genetic variation in humans needed to functionally validate the role of the Chrna6C123G polymorphism in adolescent nicotine use during adolescence and adulthood. Thus, the overall objective for this application is to identify the role of the Chrna6C123G genetic variant in nicotine use. The central hypothesis is that α6 nAChRs perpetuate nicotine self-administration, with adolescence particularly at risk. To test this hypothesis, the current proposal delineates the role of the polymorphism in nicotine self-administration. The acquisition of such knowledge is essential to the development of improved prevention and intervention strategies for tobacco addiction.