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GWAS on socially acquired nicotine IVSA in heterogeneous stock rats highlights genes implicated in human smoking behavior

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Cigarette smoking remains the leading cause of preventable disease and death in the United States. We previously established socially acquired nicotine intravenous self-administration in adolescent rats as a model of voluntary nicotine consumption. Stable intravenous nicotine infusion required the social transmission of a nicotine associated odor cue in this model. Further, multiple lines of evidence indicated that nicotine was the primary reinforcer. Using over 1400 heterogeneous stock rats, we conducted a genome-wide association study using this model. We analyzed over 60 traits and found 30 QTL that reached genome-wide significance, including seven for the number of licks on the active spout, eight for nicotine infusion, and one for reinstatement of nicotine seeking. We compared these results with those from human smoking-related GWAS, which identified 33 genes implicated in both species. Many of these overlapped genes were associated with similar phenotypes. For example, a locus on rat chr1 (278.5 Mb) was associated with the number of licks on the active spout in the first session. Four out of 99 genes under this loci (*Shtn1*, *Vti1a*, *Hspa12a*, and *Nrap*) had homologs associated with smoking initiation in human GWAS. One locus on rat chr16 (83.9Mb) was associated with the number of licks on the active spout and nicotine infusion for sessions 5 and 7, and the total number of nicotine infusions. One gene in this region, *Tex29*, has a human homolog that was associated with lifetime cigarette consumption. These overlapping genes may help elucidate the molecular mechanism of nicotine addiction.