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QTL Mapping of Genetic Modifiers of Oral Nicotine Consumption in *Chrna5* Null Mutant Mice

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Previously, we used the panel of C57BL/6J-Chr#A/J/NAJ chromosome substitution strains (CSS) in which we had introgressed the *Chrna5* null mutation to screen for genetic modifiers of the effect of *Chrna5* deletion on oral nicotine consumption. Results indicated that CSS strains CSS1, CSS5 and CSS11 significantly reduced nicotine intake while CSS17 substantially increased nicotine intake in *Chrna5* null mutant mice. To narrow the chromosomal regions responsible for the modifier effects, we used an F2 intercross to perform QTL analysis in CSS1, CSS11 and CSS17 mice. Two significant QTL were detected in CSS1 mice (Chr1: 98.05 Mbp, LOD = 5.65, CI = 87.07-131.05 Mbp; Chr1 162.05 Mbp, LOD = 3.67, CI = 139.87-168.05 Mbp).

Significant QTL were also identified in CSS11 (Chr11: 79.14 Mbp, LOD = 5.78, CI = 69.19-89.3 Mbp) and CSS17 (Chr17: 29.43 Mbp, LOD = 6.63, CI = 19.43-36.43 Mbp). RNA sequencing from frontal cortex and striatum also was performed in the CSS1 F2 mice. In frontal cortex, 18 of the top 50 transcripts that correlated with nicotine consumption exhibited eQTLs on chromosome 1, including 12 cis and 6 trans eQTLs. In striatum, 22 of the top 50 correlated transcripts had chromosome 1 eQTLs, with 3 cis and 19 trans eQTLs. Enrichment analysis (DAVID) identified postsynaptic membrane, ER, heat shock protein and MAP/JUN kinase as the top enriched categories for striatum. Mitochondrial related categories represented 3 of the top 5 enriched clusters for striatum while processes related to ribosomes and RNA processing made up the other 2 clusters.