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The Use of Chromosome Substitution Strains to Identify Genetic Modifiers that Alter the Impact of *Chrna5* Deletion on Oral Nicotine Intake in Mice.

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The gene *CHRNA5/Chrna5* has strongly been implicated in nicotine use and dependence in both humans and animal models. Rodent models have shown that deletion or knockdown of *Chrna5* typically leads to increased intravenous as well as elevated oral nicotine consumption. However, we found that *Chrna5* deletion had no effect on oral nicotine consumption when introgressed onto an A/J background. This finding indicates that the A/J genome may possess genetic modifiers that eliminate the *Chrna5* deletion-dependent enhanced nicotine consumption that is seen on other genetic backgrounds. To begin to identify the A/J modifiers that alter the effect of *Chrna5* deletion on nicotine consumption, we assessed oral nicotine intake in a panel of C57BL/6 x A/J chromosome substitution strains (CSS) in which we introduced the *Chrna5* knockout (KO) allele. Results indicate that there are genetic modifiers on A/J chromosomes 1, 2, 5 and 11 and potential sex-dependent modifiers on chromosomes 8 and 15. All identified modifiers led to decreased nicotine intake in the CSS-*Chrna5* KO mice to levels at or below those of C57BL/6 wildtype controls. During the modifier screen we also detected a robust main effect of chromosome 17 on nicotine intake that was independent of *Chrna5* genotype. Mice possessing A/J chromosome 17 consumed twice as much nicotine as their *Chrna5* genotype matched counterparts possessing a C57BL/6 chromosome 17. Experiments to narrow the potential modifier and main effect alleles are underway. Identification of these alleles may lead to novel therapeutic targets for nicotine dependence.