Nicotine Dependence Associated with Functional Variation in FMO3

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A common haplotype of the *flavin-containing monooxygenase* gene *FMO3* is associated with aberrant mRNA splicing, a two-fold reduction in *in vivo* nicotine *N*-oxidation and reduced nicotine dependence. We determined the effects of common variants in *FMO3* on plasma levels of nicotine-*N*-oxide in 170 European Americans administered deuterated nicotine. The polymorphism rs2266780 (E308G) was associated with *N*-oxidation of both orally administered and ad libitum smoked nicotine. *In vitro*, the FMO3 G308 variant was not associated with reduced activity, but rs2266780 was strongly associated with aberrant *FMO3* mRNA splicing in both liver and brain. Surprisingly, in treatment-seeking European American smokers (n=1558) this allele was associated with reduced nicotine dependence, specifically with a longer time to first cigarette, but not with reduced cigarette consumption. Since *N*-oxidation accounts for only a small percentage of hepatic nicotine metabolism we hypothesized that *FMO3* genotype affects nicotine metabolism in the brain or that nicotine-*N*-oxide itself has pharmacological activity. We demonstrated nicotine *N*-oxidation in human brain, mediated by FMO3 and FMO1, and show that nicotine-*N*-oxide modulates human α4β2 nicotinic receptor activity *in vitro*. These results indicate possible mechanisms for associations between *FMO3* genotype and smoking behaviors, and suggest nicotine *N*-oxidation as a novel target to enhance smoking cessation.