Targeted sequencing identifies genetic polymorphisms of flavin-containing monooxygenase genes that contribute to the risk of nicotine dependence in European and African Americans

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Smoking is a leading cause of preventable death. Early studies based on samples of twins have linked the lifetime smoking practices to genetic predisposition. Three protein families are involved nicotine pharmacokinetics: liver cytochrome P450 enzymes (CYPs), flavin-containing monooxygenases (FMOs) and uridinediphosphate glucuronosyltransferase enzymes (UGTs). The flavin-containing monooxygenase (FMO) protein family consists of a group of enzymes that metabolize drugs and xenobiotics. Five forms of FMOs are found in human and have been designated FMO1-FMO5. Among these FMO genes, part of the nicotine inhaled during smoking can be broken down to N′-oxide by flavin-containing monooxygenase 3 (encoded by FMO3)

In this study, we investigated whether the potential susceptible genes of the FMO gene family confer risk to nicotine dependence via deep targeted sequencing in 2,820 study subjects comprising of 1,583 nicotine dependent cases and 1,237 controls from Europeans and African Americans. Study subjects were recruited from Collaborative Genetics Study of Nicotine Dependence (COGEND) and the Genetic Study of Nicotine Dependence in African Americans (AAND). We assessed the study subjects' smoking behavior using the Fagerström test for nicotine dependence (FTND). The nicotine dependence patients were defined as current smokers with FTND score equal or greater than 4, and controls were defined as having FTND score of 0 or 1 and have smoked at least 100 cigarettes in their lifetime. Specifically, we focused on the two genomic segments including FMO1, FMO3 and the pseudo gene FMO6P, and investigated the potential association between FMO genes and nicotine dependence. We identified different clusters of significant common variants in European (with the most significant SNP rs6674596, P=0.0004, OR=0.67, MAF_EA=0.14) and in African Americans (with the most significant SNP rs6608453, P=0.001, OR=0.64, MAF_AA=0.1). Most of the significant variants identified were SNPs located within introns.