Editorial

Novel Methodologies and the Need for Big Data in Nicotine and Tobacco Genetics Research

Tobacco use is a complex polygenic disorder and continues to be the leading cause of preventable death worldwide. The present issue highlights seven original investigations that address some of the complexities and gaps in the state of the science with innovative methods.

Do and Maes conducted a systematic review of gene-environment (GxE) interaction investigations that identified 16 studies with at least one statistically-significant GxE interaction. Due to heterogeneity of phenotypes and endpoints, no meta-analyses were possible. Melroy-Greif and colleagues examined a panel of single nucleotide polymorphisms (SNPs) in genes for nicotinic acetylcholine receptors and interacting genes in 9141 European-ancestry (EA) and 3947 African-ancestry smokers. Although nominal ($p < .05$) associations were reported for nicotine dependence and cigarettes per day, none were robust to correction for multiple comparisons.

Two studies examined genetic influences on tobacco use phenotypes during childhood and adolescence. In a first of its kind investigation, Maes and colleagues conducted an integrated mega-analysis of longitudinal twin studies between 1983 and 2007 in over 19,000 same-sex and opposite-sex twin pairs from the United States, Europe, and Australia. The results demonstrated remarkable consistency of findings across sexes and cultures for a decay of shared environmental effects on smoking initiation with age and increased liability of additive genetic factors on tobacco use by late adolescence. Pugach and colleagues investigated the potential protective effects of haplotypes of five single nucleotide polymorphisms tagging the CHRNA3-A6 and CHRNA5-A3-B4 gene clusters in a longitudinal sample of $N = 480$ EA adolescent smokers, using classification tree analyses. Although the baseline Nicotine Dependence Syndrome Scale was the strongest predictor, the CHRN3-A6 rs2304297 and CHRNA5-A3-B4 haplotype C rs6495308 SNPs were also predictive of 6-year daily smoking.

Two studies explored new phenotypes and their relationship with candidate gene variants. Richmond-Rakerd and colleagues introduced a novel “tobacco use problems” phenotype using factor analysis in 1942 EA smokers and 255 Native-American smokers. They subsequently examined associations between SNPs most strongly related to the new measure with cigarettes per day from the chromosome 15q25 gene cluster, CYP2A6, and CYP2B6 genes. Although three SNPs (rs938682, rs1051730, and rs16969968) were associated with cigarettes per day, none were associated with tobacco use problems. Stevens and colleagues investigated a novel “difficulty of quitting smoking” phenotype by defining “easy quitters” as having achieved >1-year abstinence after their first quit attempt and “difficult quitters” as reporting 10 or more quit attempts in 3000 smokers (stage 1), replicated in 2600 (stage 2) non-EA smokers from an independent sample. None of the SNPs in stage 2 had a $p$-value level below the adjusted Bonferroni $p$-value of .0045, but three SNPs (HTR1B rs6298, NR4A2 rs834829, and CYP2A6 rs8192729) were robustly statistically significant in combined sample analyses.

Risso and colleagues investigated the relationship between SNPs in the TAS2R38 bitter taste receptor gene and smoking menthol cigarettes in the first study of its kind in 718 African Americans, who are more likely to smoke menthol cigarettes than other ethnic/racial groups. There was an allele-dose effect of the presence of the TAS2R38 “taster” PAV haplotype, such that menthol cigarette smoking was less frequent in individuals possessing two or more copies of the PAV haplotype. These results confirm those previously reported in EA smokers and have important public health implications. In addition, a polygenic risk score based on the 11 nominal SNPs identified with statistical trend in stage 1, was significantly associated with the difficult quitting phenotype in stage 2—albeit with a small effect size.

These studies present a range of innovative approaches to filling important gaps in translation but also expose the persistent challenges of limited sample sizes, particularly for non-European study populations, the need for open and “big” data to enable large-scale, unbiased meta-research, and the need for evidence of clinical utility in a field justified by public health and clinical endpoints.

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References


