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Genetic and phenotypic characterization of different modes of lifetime tobacco use in the All of Us Research Program

Nearly all genetic studies of tobacco use have focused on cigarette smoking, despite other popular modes of tobacco use. Different modes of tobacco use may reflect varied environmental and genetic influences and differentially correlate with health outcomes. We performed genome-wide association studies (GWAS) of five modes of tobacco use in the All of Us Research Program v. 8: lifetime use of e-nicotine products, cigars, tobacco in a hookah, smokeless tobacco products, or at least 100 cigarettes. Each GWAS was performed within groups of participants who were most genetically similar to people of European, Admixed American, and African ancestry, followed by cross-ancestry meta-analyses.

Phenotypic differences in age and sex were found across tobacco use modes. The genome-wide cross-ancestry meta-analyses of cigarette, cigar, e-nicotine products, and smokeless tobacco use identified 87, 1, 4, and 1 genome-wide risk loci, respectively; no variants reached genome-wide significance for hookah use. Gene-based analyses revealed several significant genes shared across multiple modes of use: THSD7B, significant across cigarette, e-nicotine, and cigar use meta-analyses, and the EUR ancestry GWAS of e-nicotine use; NCAM1, significant in both meta-analyses and the EUR ancestry GWAS of cigarette and e-nicotine use.

Smokeless tobacco, e-nicotine products, and cigarette use showed the strongest genetic correlations with each other (rg=0.83–0.93), whereas cigar and hookah use were also strongly correlated (rg=0.86). Genetic correlations with psychiatric, personality, and other phenotypes diverged significantly, such that cigarette, e-nicotine, and smokeless tobacco use consistently showed positive genetic correlations with risk for psychiatric disorders, negative urgency, and neuroticism, while cigar use and hookah use showed null to weak genetic correlations with psychiatric phenotypes and were positively correlated with sensation seeking. Notably, hookah use was uniquely positively correlated with educational attainment. Our findings reveal important phenotypic and genetic distinctions between modes of tobacco use.

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