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Large-scale deep sequencing meta-analysis of alcohol and tobacco use: Effects of rare variation

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ABSTRACT:

Alcohol and tobacco use are moderately heritable behaviors ($h^2 \approx 0.50$), and genome-wide association studies (GWAS) have identified a large number of common variants, each with small effect and uncertain direct causality. Much of the remaining missing heritability for complex traits is thought to be attributable to rare variation (minor allele frequency [MAF] < 0.01). However, such investigations using deep whole-genome sequencing (WGS) require large samples and have not yet been conducted for substance use and dependence. Therefore, the current study sought to test whether rare variants were associated with measures of alcohol and tobacco use and addiction. Study phenotypes included a measure of drinks consumed per week, as well as smoking initiation, age of smoking initiation, cigarettes smoked per day, and smoking cessation. Deep whole-genome sequences were obtained for ~155,000 samples as part of the Trans-Omics for Precision Medicine (TOPMed) consortium, and this dataset was used as a reference panel to impute genotypes for ~500,000 individuals in UK Biobank, a large-scale richly-phenotyped biomedical and research database. Whole-exome sequences (WES) were also obtained for ~200,000 UK Biobank participants. Planned analyses are ongoing at this time, and include a rare variant meta-analysis of TOPMed WGS, UK Biobank genome-wide array data imputed to TOPMed, and UK Biobank WES, as well as rare-variant gene-based tests. This study will allow for well-powered discovery of rare variants and genes associated with alcohol and tobacco use and inform our understanding of their biological etiology.

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