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## **The role of *a priori*-identified addiction and smoking gene sets in smoking behaviors**

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Smoking is a leading cause of death, and genetic factors contribute to an individual's risk for smoking and nicotine addiction. The goal of this study was to identify and compare evidence for two sets of genes previously prioritized for their possible role in risk. Two addiction-related gene sets, the Smokescreen Genotyping Array and the nicotinic acetylcholine receptors, were curated by experts in the field based on *a priori* biological knowledge, but previous studies examining these gene sets were limited in size. We performed a gene set-based association and heritable enrichment study using the largest available GWAS summary statistics for smoking behaviors. We assessed smoking initiation, cigarettes per day, smoking cessation, and age of smoking initiation. Individual genes within each gene set were significantly associated with various smoking behaviors. Both the Smokescreen and the nicotinic acetylcholine sets of genes were significantly associated with cigarettes per day, smoking initiation, and smoking cessation. Age of initiation was only associated with the Smokescreen gene set. While both sets of genes were enriched for heritability of these traits, they each account for only a small proportion of the genetic variance (2-12%). These two gene sets are associated with smoking behaviors, but collectively account for a limited amount of the genetic and phenotypic variation of these complex traits, consistent with their high polygenicity. Importantly, this work confirms that additional genome-wide approaches and integration of other 'omics data will be needed to fully account for the genetic variation in smoking phenotypes.