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A gene-by-gene interaction analysis of rs16969968 and genome-wide loci on cigarettes per day in the UK Biobank

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Genes coding for the neuronal nicotinic acetylcholine receptor genes emerged as the top replicable associations with smoking behaviors from GWAS a little over a decade ago. In particular, a non-synonymous single nucleotide polymorphism (SNP) in *CHRNA5*, rs16969968, leads to an amino acid change (D398N) which affects the pharmacological response of the receptor. We aim to identify other variants/genes that may interact with SNP rs16969968. Using the UK Biobank, we performed a genome-wide rs16969968-by-SNP interaction analysis for cigarettes per day. Both raw (M=18.22, SD=10.16) and log-transformed (M=1.20, SD=0.25) cigarette per day scores from 116,257 unrelated current and former smokers were evaluated. No genome-wide significant interactions between rs16969968 and genome-wide SNPs were detected for this phenotype. Simulations revealed that even with a large sample size such as UK Biobank, the power to detect SNPxSNP interactions at the genome-wide level remains limited. As a secondary analysis, we conducted a gene-by-SNP interaction analysis of daily cigarette use using MAGMA. Two genes on chromosome 20 (*TMEM230*, *PCNA*) reached genome-wide significance ($p<2.64e-06$) for the rs16969968-by-gene interaction term. Currently, we are conducting a competitive gene set analysis to determine if genes involved in the nicotinic pathway interact with rs16969869 more strongly than the rest of the genome to influence daily cigarette usage. Results from this work provide insight regarding possible GxG mechanisms that underlie smoking behaviors, which may inform future functional studies of the underlying biology.