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Investigating Genetic Susceptibility to Tobacco Smoking at rs16969968 based on Age at Onset of Regular Smoking

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Smoking quantity, measured in cigarettes per day (CPD), has been associated with the nonsynonymous single nucleotide polymorphism rs16969968 in several studies, and early age of onset of smoking (AOS) is linked to heavier smoking. Previous studies reported an increased genetic risk of heavy smoking in individuals with the rs16969968 risk allele who began smoking at an earlier age, but this genotype-AOS interaction has yet to be replicated in a large, independent sample. Using 130,626 unrelated individuals from the UK Biobank study population, we directly tested for rs16969968-AOS interaction effects on CPD, using formal GxE interaction association model as well as assessing if rs16969968 effect size estimates differed between early and late AOS individuals. We analyzed log10-transformed CPD as well as light vs. heavy smokers (<10 and >20 CPD, respectively, n=61,218). While we found strong main effects of both rs16969968 and AOS, consistent with published literature, we found no significant rs16969968-by-AOS interaction ($p>0.2$). We did find a small but statistically significant difference in allele effect size estimates (non-overlapping 95% CIs) on heavy vs. light smoking when the association was stratified by early and late AOS, as previously reported. We conclude that there is only equivocal support for an interaction between rs16969968 age of smoking initiation, and if present, only a slight difference in allele effect size in early vs. late initiation smokers. However, this suggests that efforts to reduce adolescent smoking should remain a public policy goal.