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Transcriptome-Wide Association Studies Leveraging Biomarker Data Offer Etiologic Insights Into Tobacco Smoking and Schizophrenia

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Smoking and schizophrenia (SCZ) are comorbid and highly heritable (~50-80%). While crucial for genetic discovery, large genome-wide association studies (GWAS) typically use self-reported phenotypes and do not model gene expression effects. To address these gaps, we conducted a transcriptome-wide association study (TWAS) of cotinine, the major metabolite of nicotine and a biomarker of smoking heaviness, using summary statistics from our cotinine GWAS in >5,000 European ancestry smokers. We then performed a TWAS of SCZ in ~130,000 Europeans using summary statistics from the PGC's wave 3 SCZ GWAS data release. We used S-PrediXcan, GTEx brain and liver transcriptomic data, and a within-tissue Bonferroni P-value correction (0.05/# genes). The cotinine TWAS yielded five significant genes: ADAMTS7 (in nucleus accumbens and cortex), CRABP1 (in frontal cortex), HYKK (in liver), PSMA4 (in liver and cortex), and RP11-344P13.6 (in nucleus accumbens). Notably, CRABP1 and RP11-344P13.6 were not significant in the cotinine GWAS. CRABP1 (cellular retinoic acid binding protein-1) is located ~220kb 5' of the CHRNA5-A3-B4 cluster on chromosome 15 and was previously found in GWAS of nicotine dependence, self-reported cigarettes/day, and pulmonary function. The SCZ TWAS yielded 279 significant genes; the top overall association was for MSH5 in putamen. One gene, HYKK (hydroxylysine kinase), was significant in both the cotinine TWAS (P=2.48e-10 in liver) and SCZ TWAS (P=1.71e-6 in liver and P=1.35e-6 in anterior cingulate cortex). Our findings highlight two novel genes associated with an established biomarker of smoking and the potential importance of variable HYKK expression in the shared etiology of smoking and schizophrenia.