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Pleiotropic genes for resting-state brain functional connectivity and nicotine addiction

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Background and significance: Tobacco dependence is a complex and heritable behavior and a chief modifiable risk factor for cancer, pulmonary, cardio-and-cerebrovascular disorders. Genetic factors account for >50% of the variation in nicotine dependence related traits in population studies. Neuroimaging studies showed brain alterations in both gray and white matter for nicotinic addiction, however, the pathway from genes to brain alternations to nicotine addiction remained unclear.

Hypothesis and Methods: We hypothesize that risk genes impact nicotine addiction partially via modifying functional connectivity (FC) change inside the brain. A first step to understand this hypothesized pathway is to identify the pleiotropic genes associated with both brain FC and nicotine addiction. In this study, we combine genetic, resting-state functional MRI (fMRI) and smoking related behavior data from UK Biobank with expression quantitative trait loci (eQTL) data from

Genotype-Tissue Expression (GTEx) to conduct transcriptomic-wide association studies (TWAS) on brain regional FC and smoking phenotypes and identify pleiotropic genes associated with both traits. Existing statistical methods that follow intersection-union tests (IUT) to detect pleiotropic genes are over-conservative for high-dimensional regional FC phenotypes. We consider a multivariate method to test for pleiotropy to account for the correlation between regional FC phenotypes and reduce multiple testing burden.

Results: We found genes previously reported to be associated with nicotine addiction also highly associated with brain FC in several brain regions of interest, which are worth further investigation.