

Submitter Name: Tianzhou Ma  
Submitted email: [tma0929@umd.edu](mailto:tma0929@umd.edu)

## **White matter integrity and nicotine dependence in smokers: evaluating vertical and horizontal pleiotropy**

Zhenyao Ye<sup>1\*</sup>, Chen Mo<sup>1\*</sup>, Kathryn Hatch<sup>1</sup>, Song Liu<sup>4</sup>, Si Gao<sup>1</sup>, Elliot Hong<sup>1</sup>, Peter Kochunov<sup>1‡</sup>,  
Shuo Chen<sup>1,2‡</sup>, Tianzhou Ma<sup>3‡</sup>

<sup>1</sup> Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, Baltimore, Maryland, United States of America

<sup>2</sup> Division of Biostatistics and Bioinformatics, Department of Epidemiology and Public Health, School of Medicine, University of Maryland, Baltimore, Maryland, United States of America

<sup>3</sup> Department of Epidemiology and Biostatistics, School of Public Health, University of Maryland, College Park, Maryland, United States of America

<sup>4</sup> Department of Computer Science and Technology, Qilu University of Technology, Jinan, Shandong, China

\*These authors contributed equally to this work

‡ Corresponding authors: [tma0929@umd.edu](mailto:tma0929@umd.edu) (TM); [shuochen@som.umaryland.edu](mailto:shuochen@som.umaryland.edu) (SC); [pkochunov@mprc.umaryland.edu](mailto:pkochunov@mprc.umaryland.edu)

Nicotine addiction and smoking are complex behaviors with strong genetic underpinnings. The genetic predispositions for nicotine addiction may act through cerebral white matter (WM) that shows short- and long-term changes in smokers consistent with positive and negative reinforcement mechanisms. We hypothesized that vertical genetic pleiotropic pathways may be responsible for the links between genes, nicotine addiction and cerebral WM integrity. We tested this hypothesis using individual genetic factors, WM integrity measured by fractional anisotropy (FA), and smoking/nicotine dependence measured by cigarettes per day (CPD) in a large epidemiological sample collected UK Biobank. We performed genome-wide association study (GWAS) to identify genetic factors associated with smoking and nicotine dependence, that were also associated with WM integrity. We then evaluated two competing vertical pathways: genes → WM integrity → smoking severity vs. genes → smoking severity → WM integrity, and a horizontal pleiotropy pathway where genetic factors independently affect both smoking severity and WM integrity. Ten variants associated with both smoking status and FA measures and 20 variants associated with CPD and FA were identified. Impact of *SARDH* variants on smoking status was modulated by FA measures over multiple brain regions. This gene is involved in the tolerance effect on nicotine by catalyzing the oxidative demethylation of sarcosine. Variants in *IREB2* exerted vertical pleiotropy effects on FA measures through CPD. These variants were reported as risk factors for both neurodegeneration and smoking-induced diseases. The genetic predisposition to smoking acts through vertical pleiotropy pathways to maintain nicotine addiction through changes in cerebral WM.