Name: Emma Johnson Email: emma.c.johnson@wustl.edu

Evidence for Antagonistic Pleiotropy With Respect to Substance Use Behaviors

Emma C Johnson, Arpana Agrawal

Department of Psychiatry, Washington University School of Medicine, Saint Louis, MO, USA

Antagonistic pleiotropy occurs when an allele confers opposing effects on fitness (e.g., fitness-increasing effect on one trait, fitness-decreasing effect on another trait), and there is evidence that antagonistic pleiotropy may be widespread among polygenic disorders. Substance use disorders (SUDs) are associated with accelerated biological aging and earlier mortality, suggesting that genetic variants associated with SUDs may be under negative selection pressures. Antagonistic pleiotropy may contribute to the maintenance of genetic variation underlying substance use phenotypes, but this has not been thoroughly explored. We estimated genetic correlations between the number of children born (NEB; N=785,604), age at menopause (AMP; N=201,323), and several substance use phenotypes: smoking initiation (N=805,431), cannabis ever-use (CanUse; N=162,082), drinks per week (DPW; N=666,978), tobacco use disorder (N =495,005), cannabis use disorder (CanUD; N=886,025), problematic alcohol use (PAU; N=903,147), and opioid use disorder (N=639,063). Significant genetic correlations with NEB ranged from rg=0.08 to 0.31, while correlations with AMP ranged from rg=-0.14 to -0.11. Notably, the genetic correlations with NEB for PAU and CanUD were significantly stronger (pdiff<0.003) than their non-diagnostic counterparts (DPW and CanUse). Using genomic SEM, we found that a latent factor representing shared genetic liability to SUDs was significantly associated with NEB, even when covarying for risk tolerance. Our results suggest that alleles associated with greater liability for substance use behaviors are associated with reproductive advantage in terms of number of children born, but are also associated with earlier age at menopause, suggesting an evolutionary tradeoff. Forthcoming analyses will explore alternative evolutionary mechanisms and sex-specific effects.