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NEWS AND COMMENTARY

Connecting the dots, genome-wide association studies in substance use

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The recent genome-wide association (GWA) meta-analysis of lifetime cannabis use by the International Cannabis Consortium marks a milestone in the study of the genetics of cannabis use.[1] Similar milestones for the genetics of substance use were the GWA meta-analyses of four smoking related traits,[2] of coffee consumption[3] and of alcohol consumption.[4] Combined, 315 981 partly overlapping individuals were genotyped, phenotyped and their data analyzed in genetic association studies, reflecting a huge communal effort by the substance use/addiction genetics community. These genome-wide association study (GWAS) efforts considered different stages of substance use: lifetime use (ever versus never use) was analyzed for cannabis and smoking, quantity of use (in users) was analyzed for coffee, alcohol, and smoking and age of initiation and cessation were analyzed for smoking. There are other GWA efforts and publications in the realm of addiction (see ref. 5), but here we limit ourselves to the largest meta-analyses per substance in order to maximize power. The GWA meta-analyses of substance-related traits identified many substance-specific genetic variants of moderate to small effect, which provided insight in the genetic etiology of substance use and its comorbidities.

There are substantial phenotypic correlations among use of different substances, and both twin and polygenic risk prediction studies have shown that these phenotypic correlations are partly due to common genetic influences.[6, 7] Here we estimate genetic correlations (r_g) between substance use-related variables based on the GWA summary statistics. These estimates of r_g are based on all polygenic effects captured by single nucleotide polymorphisms. We used the recently developed linkage disequilibrium (LD) score regression method to estimate the proportion of covariance between traits that is due to single nucleotide polymorphisms, based on the expected relationship between LD and strength of association under a polygenic model.[8,9]

The genetic correlation matrix revealed important information about common versus substance-specific genetic effects as well as specific patterns of cross-substance comorbidity (Figure 1). The substantial negative correlation between smoking cessation and smoking initiation reveals that the genes that predispose to initiation are negative predictors of success at cessation. Likewise, the genes that predispose individuals to smoke more cigarettes per day are negative predictors of successful cessation. Age at first cigarette is only associated with smoking initiation, not with cigarettes per day or smoking cessation. Interestingly, high genetic correlations are also observed across substance, between cannabis initiation and smoking initiation ($r_g = 0.83$, se = 0.148), but also between quantity of nicotine consumption (cigarettes per day) and quantity of coffee consumed (cups per day) ($r_g = 0.44$, se = 0.151), between coffee consumed and nicotine consumption ($r_g = 0.38$, se = 0.16), and between alcohol consumption (alcohol per week) and cigarettes per day ($r_g = 0.44$, se = 0.17). Most significant cross-substance correlations reflect genetic correlations within stage. However, both coffee per day and cigarettes per day are negatively associated with successful smoking cessation, indicating that frequent use, irrespective of substance, is genetically related to more problematic use of a different substance.

The pattern of correlations observed implies a genetic model for substance use where both substance-specific and stage-specific genetic effects play a role. GWA meta-analyses of smoking, alcohol, cannabis and coffee use have shed light on the specific genetic effects for each substance. Here we show substance- and stage-specific GWAS results can be leveraged to elucidate the genetic architecture of substance use vulnerability in general. The next generation of large well-powered substance use GWA studies should systematically target all stages of use, for a broad spectrum of substances (e.g., cocaine and sugar rich foods) or addictive behavior (e.g., gambling, gaming and compulsive Internet use). Such an effort can aid in distinguishing between genes that are substance specific from genes that contribute to a specific stage of use, irrespective of substance or addictive behavior.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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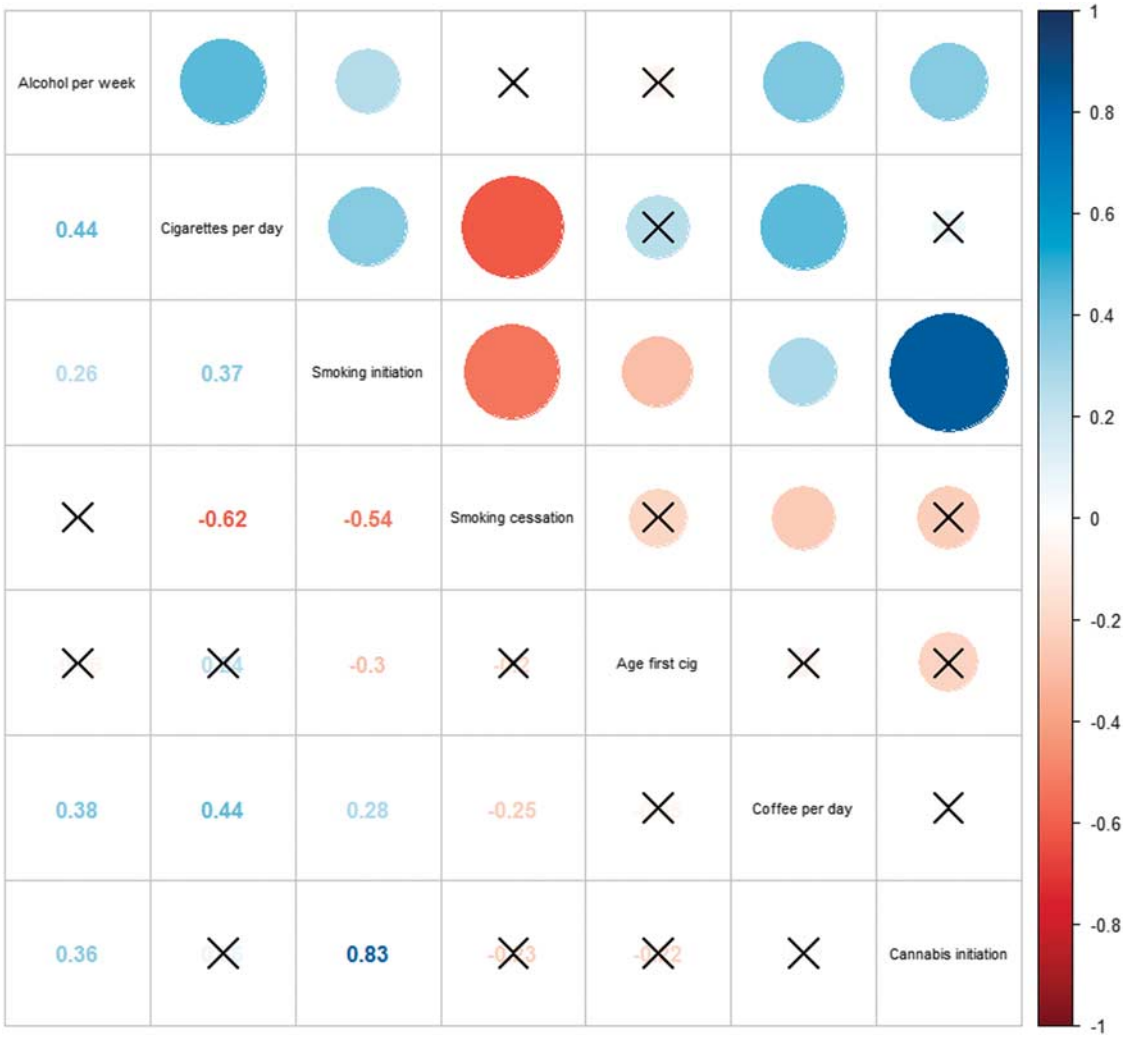

Figure 1. Genetic correlations between seven substance use related variables estimated by linkage disequilibrium score regression. 'X' denotes correlations that did not reach false discovery rate-adjusted $P < 0.05$. Above the diagonal correlations are depicted visually: larger circles indicate stronger correlations, blue colors indicate positive correlations and red colors negative correlations. Below the diagonal the estimated genetic correlations are shown. Correlations are based on results of the largest meta-analyses to date for smoking,[2] alcohol use,[4] coffee[3] and cannabis.[1] Two genetic correlations were also published in (refs 1 and 10).

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