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Genetic correlation between smoking behaviors and schizophrenia

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Abstract

Nicotine dependence is highly comorbid with schizophrenia, and the etiology of the comorbidity is unknown. To determine whether there is a genetic correlation of smoking behavior with schizophrenia, genome-wide association study (GWAS) meta-analysis results from five smoking phenotypes (ever/never smoker (N=74,035), age of onset of smoking (N=28,647), cigarettes smoked per day (CPD, N=38,860), nicotine dependence (N=10,666), and current/former smoker (N=40,562)) were compared to GWAS meta-analysis results from schizophrenia (N=79,845) using linkage disequilibrium (LD) score regression. First, the SNP heritability (h^2_g) of each of the smoking phenotypes was computed using LD score regression (ever/never smoker h^2_g =0.08, age of onset of smoking h^2_g=0.06, CPD h^2_g=0.06, nicotine dependence h^2_g=0.15, current/former smoker h^2_g=0.07, p<0.001 for all phenotypes). The SNP heritability for nicotine dependence was statistically higher than the SNP heritability for the other smoking phenotypes (p<0.0005 for all two-way comparisons). Next, a statistically significant (p<0.05) genetic correlation was observed between schizophrenia and three of the five smoking phenotypes (nicotine dependence r_g=0.14, CPD r_g=0.12, and ever/never smoking r_g=0.10). These results suggest that there is a component of common genetic variation that is shared between smoking behaviors and schizophrenia.

Keywords

genetic correlation; schizophrenia; nicotine dependence

Introduction

Severe mental illness and nicotine dependence frequently co-occur. Individuals suffering from schizophrenia have much higher rates of smoking than the general population (Hartz et al., 2014) and smokers are more likely to suffer from schizophrenia (Gage et al., 2014; Gurillo et al., 2015; Myles et al., 2012; Sorensen et al., 2011; Zammit et al., 2003). Furthermore, much of the morbidity and premature mortality in individuals with schizophrenia can be attributed to smoking-related diseases (Brady et al., 1993; Colton and Manderscheid, 2006; Crump et al., 2013; Drake and Wallach, 1989; Olfson et al., 2015; Parks et al., 2006).

Given the severe public health consequences of the comorbidity of schizophrenia with nicotine dependence, understanding the etiology of this comorbidity is clinically important. Currently, schizophrenia is diagnosed and treated independently of nicotine dependence. Prognostically, there is already evidence that schizophrenia with comorbid nicotine dependence is more severe and has worse outcomes than schizophrenia without comorbid nicotine dependence (Gage et al., 2014; Sorensen et al., 2011; Tsoi et al., 2013; Zammit et al., 2003).

There are three non-exclusive models to explain the comorbidity between nicotine dependence and schizophrenia (Gage and Munafo, 2015a): (1) smoking may lead to the onset of schizophrenia; (2) schizophrenia may cause the development of nicotine dependence (self-medication, for example); and (3) there may be common underlying risk factors, environmental and genetic, that predispose to both schizophrenia and nicotine dependence. Recently, there has been growing evidence to suggest a causal pathway from smoking to schizophrenia. Studies have found that smoking prospectively predicts risk for schizophrenia (Gage et al., 2014; Kendler et al., 2015). Further, the observed association did not arise from smoking onset during the prodromal period of schizophrenia and demonstrated a clear dose-response relationship (Kendler et al., 2015).

There is new evidence that nicotine dependence and schizophrenia share contributory genetic factors. Recently, the Psychiatric Genetics Consortium identified 128 independent loci that contribute to risk of developing schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Interestingly, one locus recently identified as contributing to schizophrenia is the chromosome 15q24 locus, which contains the α5-α3-β4 nicotinic receptor subunit genes and is the strongest genetic contributor to nicotine dependence (Hancock et al., 2015; TAG, 2010). Although this is promising evidence of shared genetic factors between nicotine dependence and schizophrenia, because the analysis did not adjust for smoking, the finding may be due to confounding from smoking. A different study found positive associations both between nicotine dependence and polygenic risk scores for schizophrenia, and between schizophrenia and polygenic risk scores for cotinine levels (Chen et al., 2016). These complimentary analyses support the hypothesis that nicotine dependence and schizophrenia have shared genetic factors.

Evidence of shared genetic factors between nicotine dependence and schizophrenia would imply a common etiology between the two disorders. There is new evidence that polygenic

risk scores for nicotine dependence and related phenotypes predict schizophrenia, and that polygenic risk scores for schizophrenia predict nicotine dependence and related phenotypes (Chen et al., 2016). However, additional studies are needed to clarify this relationship.

One approach to determining whether shared genetic factors contribute to multiple phenotypes is to estimate the genetic correlation between the phenotypes using linkage disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). Using known LD between single nucleotide polymorphisms (SNPs), the intercept computed from LD score regression can be included in GWAS analyses as a powerful correction factor for the inflation of test statistics (Bulik-Sullivan et al., 2015b). In addition, the formula for LD score regression can be permuted to compute the genetic correlation between phenotypes based on GWAS results, termed genetic correlation (Bulik-Sullivan et al., 2015a).

LD score regression has been used to show genetic correlation between multiple psychiatric phenotypes (Bulik-Sullivan et al., 2015a), which included observed positive genetic correlation between age of onset of smoking and cigarettes per day ($p<0.05$). However, to our knowledge, the genetic correlation between the full complement of smoking behaviors (including nicotine dependence) and schizophrenia has not been fully characterized. In this study, we use LD score regression to evaluate the genetic correlation between multiple smoking phenotypes and schizophrenia.

Methods

Smoking phenotypes

To evaluate the genetic correlation between smoking phenotypes and schizophrenia, five different smoking phenotypes were used (Table 1). Ever/never smoker was coded as a dichotomous phenotype, with ever smokers typically defined as having smoked 100 cigarettes lifetime (Tobacco and Genetics Consortium, 2010). Age of onset of smoking was a continuous phenotype that was log transformed for analysis, and was defined as the age of onset of regular smoking (Tobacco and Genetics Consortium, 2010). Cigarettes per day (CPD) was coded as a continuous phenotype and is correlated with nicotine dependence (Tobacco and Genetics Consortium, 2010). The phenotype of nicotine dependence was measured only among ever smokers and was defined by the Fagerström Test for Nicotine Dependence (FTND), a six item questionnaire designed to assess the intensity of physical addiction to nicotine, with scores ranging from 0 to 10 (Heatherton et al., 1991). Nicotine dependence was then classified into mild (FTND score 0–3), moderate (FTND score 4–6), or severe (FTND score 7–10), as has been done in previous research (Hancock et al., 2015). Current/former smoker was coded as a dichotomous phenotype, where current smokers reported at interview that they presently smoked and former smokers had quit smoking at least 1 year before interview (Tobacco and Genetics Consortium, 2010). The phenotypes of age of onset, cigarettes per day, nicotine dependence, and current/former smokers included only ever smokers. Schizophrenia was also coded as a dichotomous phenotype based on meeting DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Data

The computation of genetic correlation in LD score regression uses GWAS results from European ancestry meta-analysis studies for each phenotype (references in Table 1). The GWAS for nicotine dependence included eight studies from a meta-analysis of FTND (Hancock et al., 2015): Environment and Genetics in Lung Cancer Etiology Study (N=3,006, dbGaP accession number phs000093.v2.p2) (Landi et al., 2009; Landi et al., 2008); Collaborative Genetic Study of Nicotine Dependence (COGEND, N=1935 recruited from wave 1 and N=292 from wave 2, dbGaP accession number phs000092.v1.p1) (Bierut et al., 2007); Chronic Obstructive Pulmonary Disease Gene Study (N=2,211, dbGaP accession number phs000765.v1.p2) (Regan et al., 2010); UW-TTURC (N=1,534, dbGaP accession number phs000404.v1.p1) (Baker et al., 2007); Study of Addiction: Genetics and Environment (excluding COGEND participants, N=843, dbGaP accession number phs000092.v1.p1) (Rice et al., 2012); GAIN (N=774, dbGaP accession number phs000021.v3.p2) (Manolio et al., 2007); nonGAIN (N=671, dbGaP accession number phs000167.v1.p1) (Manolio et al., 2007); and the Dental Caries Study (N=243, dbGaP accession number phs000095.v2.p1) (Shaffer et al., 2011). Published GWAS results for schizophrenia, and four Tobacco and Genetics (TAG) Consortium analyses of smoking-related behaviors were downloaded from the Psychiatric Genetics Consortium website (https://www.med.unc.edu/pgc/results-and-downloads).

LD Score regression

LD patterns across the genome enable the calculation of genetic correlations between traits. This is because the observed association for a SNP is a product of both its own contribution toward a phenotype and the association of the SNPs that are in LD with it (Yang et al., 2011). Because SNPs in regions of high LD tag a greater proportion of the genome than SNPs in regions of low LD, SNPs in regions of high LD will have stronger associations than SNPs found in regions of low LD. Thus, by using the known LD structure of a reference SNP panel, the SNP heritability of a single phenotype or the genetic correlation of two phenotypes can be computed using LD score regression (Bulik-Sullivan et al., 2015a; Lee et al., 2016).

To estimate SNP heritability (h^2_g) and genetic correlation (r_g), we used the software and protocol from the Bulik-Sullivan et al. study (2015a) (http://www.github.com/bulik/ldsc) and applied it to our datasets. To control for imputation quality, only those SNPs found in HapMap3 with a 1000 Genomes EUR MAF>0.01 were included (integrated_phase1_v3.20101123). Next, insertions and deletions (indels) and structural variants were removed along with strand-ambiguous SNPs. LD scores and weights were downloaded from the Broad institute (http://www.broadinstitute.org/~bulik/eur_ldscores/). An unconstrained intercept was used in the regression model. The code created for this study is available at https://github.com/achorton/LDSC_for_Hartz_et_al.

Results

The first step was to estimate the heritability of the smoking phenotypes. The univariate SNP heritability, the proportion of phenotypic variance explained by GWAS SNPs, was evaluated

for each smoking phenotype (Table 2). All the smoking phenotypes have statistically significant SNP heritability ($p<0.001$). The phenotype with the highest magnitude of estimated SNP heritability (15%) was nicotine dependence. This is approximately double the estimated SNP heritability for the other smoking phenotypes (estimates ranging 6%–8%), suggesting that nicotine dependence, as defined using FTND, has higher SNP heritability than the other smoking phenotypes ($p<0.0005$, for all two-way comparisons).

Next, we looked at the genetic correlation between the smoking phenotypes and schizophrenia. The genetic correlation, defined here as the proportion of common genetic variation that is shared by two phenotypes, was evaluated between the smoking phenotypes and schizophrenia. Significant genetic correlation was observed between schizophrenia and three of the five smoking phenotypes ($p<0.05$): ever/never smoker (r_g 0.10), CPD (r_g 0.12), and nicotine dependence (r_g 0.14). The values for ever/never smoker and age of onset are slightly different from those published previously (Bulik-Sullivan et al., 2015a) because the prior study did not use the same schizophrenia GWAS results.

Discussion

The results of this study show that (1) common genetic variation explains more phenotypic variance for nicotine dependence relative to other smoking phenotypes (i.e. higher SNP heritability), and (2) there is a component of common genetic variation that is shared between smoking behaviors and schizophrenia (i.e. nonzero genetic correlation).

LD score regression has identified multiple diseases that have shared genetic factors with schizophrenia (Bulik-Sullivan et al., 2015a). Of these, bipolar disorder (r_g=0.79) and depression (r_g=0.51) have the highest genetic correlations. The next tier of genetic correlations include other psychiatric disorders (Attention Deficit Hyperactivity Disorder r_g=0.23, Anorexia r_g=0.19, Autism Spectrum Disorders r_g=0.14) and autoimmune disorders (Crohn's Disease r_g=0.13, Ulcerative Colitis r_g=0.13). Our observed genetic correlations between schizophrenia and smoking behaviors fit into this second tier (ranging from 0.14 for nicotine dependence to 0.10 for ever/never smoking). This suggests that smoking behaviors should be included when leveraging other phenotypes to investigate the genetic etiology of schizophrenia.

Our findings of higher SNP heritability for nicotine dependence (as measured by FTND) relative to other smoking phenotypes is consistent with observations of differential GWAS associations for different smoking phenotypes (Chen et al., 2012; Hancock et al., 2015; Rice et al., 2012). For example, variants in the *CHRNA6/CHRNB3* region are more strongly associated with FTND-based nicotine dependence than CPD (Rice et al., 2012). In contrast, FTND-based nicotine dependence and CPD were equally associated with genetic variants in the *CHRNA5/CHRNA3/CHRNB4* region (Chen et al., 2012). This highlights the complexity of the relationship between smoking behavior and genetics.

The observed genetic correlation between smoking behaviors and schizophrenia suggests that shared genetic variation contributes to the comorbidity between schizophrenia and smoking behaviors. Shared genetic variation could contribute either directly to the disorders

(pleiotropy), or may be mediated (for example, genetic variation contributes to nicotine dependence, which then contributes to schizophrenia). As discussed in the introduction, there is a growing amount of evidence that nicotine dependence contributes to schizophrenia (Gage et al., 2014; Kendler et al., 2015). However, LD score regression cannot distinguish the difference between pleiotropy or mediation (or, most likely, a combination of pleiotropy and mediation). Therefore, future studies are necessary to dissect the mechanism of association. For example, pleiotropy can be explored for a genetic locus associated with both nicotine dependence and schizophrenia by stratifying the schizophrenia sample into never smokers and ever smokers (Wium-Andersen et al., 2015).

An inherent limitation of genetic correlation estimates using LD score regression is that they capture only shared *common* genetic variation between two phenotypes, and therefore the estimates are typically much lower than traditional measures of heritability. For example, the estimated heritability from twin studies of nicotine dependence is 59% (Li, 2006), relative to our GWAS heritability estimate of 15%, and the estimated heritability of smoking initiation is 50% (Li et al., 2003), relative to our GWAS heritability estimate of 8%. The discrepancy between traditional heritability measures and GWAS heritability is due to the fact that these estimates are based on GWAS data, filtered to include only SNPs with minor allele frequency greater than 0.01. In addition, the effects of the SNPs must all be in the same direction; SNPs that contribute to both phenotypes, but have opposite effect sizes will reduce the genetic correlation estimates. These limitations, however, do not bias the methodology, but instead reduce the power of the methodology. Therefore, the observed associations are likely sound.

A potential confounder of these analyses is smoking behavior itself: because individuals with schizophrenia are more likely to smoke than controls (Hartz et al., 2014), some of the GWAS associations for schizophrenia may, in fact, be associations with smoking behavior. Because (1) there is a significant proportion of individuals with schizophrenia who do not smoke, and (2) we are looking at composite GWAS results rather than individual SNPs, it is unlikely that this confounder biases the findings.

This study supports literature suggesting that genetic factors contribute to the comorbidity between smoking and schizophrenia (Chen et al., 2016; Gage and Munafo, 2015b), highlighting the importance of further research in order to better understand the complex relationship between these two disorders. The combination of a differential prognosis in schizophrenia for those with and without nicotine dependence and evidence of shared etiology suggests that perhaps optimal treatment for schizophrenia differs, depending on whether there is comorbid nicotine dependence.

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Table 1

GWAS meta-analysis results used for computation of LD score regression

	N	Coding	Reference
Ever/Never smoked	74,035	Dichotomous	(Tobacco and Genetics Consortium, 2010)
Age of onset of smoking	28,647	Continuous, log transform	(Tobacco and Genetics Consortium, 2010)
Cigarettes per day (CPD)	38,860	Continuous	(Tobacco and Genetics Consortium, 2010)
Nicotine Dependence	10,666	3 level: mild, moderate, severe	(Hancock et al., 2015)
Current/Former smoker	40,562	Dichotomous	(Tobacco and Genetics Consortium, 2010)
Schizophrenia	79,845	Dichotomous	(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014)

Table 2

SNP heritability of smoking phenotypes and genetic correlation estimates with schizophrenia

	Univariate SNP heritability (h^2_g)		Genetic Correlation with Schizophrenia (r_g)	
	Estimate (95% CI)	P	Estimate	P
Ever/Never Smoked	0.08 (0.06–0.09)	1E-27	0.10	0.009
Age of onset of smoking	0.06 (0.03–0.09)	0.0004	0.14	0.08
Cigarettes Per Day	0.06 (0.03–0.09)	0.0002	0.12	0.05
Nicotine Dependence	0.15 (0.07–0.24)	0.0008	0.14	0.04
Current/former Smoker	0.07 (0.05–0.09)	9E-10	−0.03	0.68