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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.

1. 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

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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 the 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. 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 schizophrenia and both the age of onset of smoking and cigarettes smoked 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.

2. Methods

2.1. 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).

2.2. 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 = 3006, 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 = 2211, dbGaP accession number phs000765.v1.p2) (Regan et al., 2010); UW-TTURC (N = 1534, 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).

2.3. 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

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)

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