Archival Report

Biological Psychiatry

Association Between Substance Use Disorder and Polygenic Liability to Schizophrenia

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ABSTRACT

BACKGROUND: There are high levels of comorbidity between schizophrenia and substance use disorder, but little is known about the genetic etiology of this comorbidity.

METHODS: We tested the hypothesis that shared genetic liability contributes to the high rates of comorbidity between schizophrenia and substance use disorder. To do this, polygenic risk scores for schizophrenia derived from a large meta-analysis by the Psychiatric Genomics Consortium were computed in three substance use disorder datasets: the Collaborative Genetic Study of Nicotine Dependence (ascertained for tobacco use disorder; n = 918 cases; 988 control subjects), the Collaborative Study on the Genetics of Alcoholism (ascertained for alcohol use disorder; n = 643 cases; 384 control subjects), and the Family Study of Cocaine Dependence (ascertained for cocaine use disorder; n = 210 cases; 317 control subjects). Phenotypes were harmonized across the three datasets and standardized analyses were performed. Genome-wide genotypes were imputed to the 1000 Genomes reference panel.

RESULTS: In each individual dataset and in the mega-analysis, strong associations were observed between any substance use disorder diagnosis and the polygenic risk score for schizophrenia (mega-analysis pseudo-R^2 range 0.8–3.7%; minimum $p = 4 \times 10^{-23}$).

CONCLUSIONS: These results suggest that comorbidity between schizophrenia and substance use disorder is partially attributable to shared polygenic liability. This shared liability is most consistent with a general risk for substance use disorder rather than specific risks for individual substance use disorders and adds to increasing evidence of a blurred boundary between schizophrenia and substance use disorder.

Keywords: Genetics, Polygenic risk score, Schizophrenia, Substance dependence, Substance use disorder

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Schizophrenia and substance use disorder frequently co-occur in the same individual (1–6). This increased comorbidity can be explained through several nonexclusive mechanisms (7) (Figure 1): 1) schizophrenia may cause the development of substance use disorder (8); 2) substance use disorder may lead to the onset of schizophrenia (9); or 3) there may be common underlying risk factors, environmental and genetic, that predispose to both schizophrenia and substance use disorder (10,11). With the publication of large meta-analyses of genome-wide association studies, polygenic risk scores (PRSs) now can be used to measure the shared genetic liability between schizophrenia and substance use disorder, which can lead to better understanding of potential mechanisms for these comorbid conditions.

PRSs represent aggregated effects across the many loci associated with a disorder at p value thresholds that accommodate tens of thousands of single nucleotide polymorphisms, thereby approximating additive genetic variance (12). PRSs are generated using a discovery genetic association study of one disorder (e.g., schizophrenia meta-analysis) and can be applied to compute the phenotypic variance explained by the score in a new independent sample. For example, PRSs were used to show that schizophrenia has underlying shared genetic liability with bipolar disorder (12–17) and major depressive disorder (16). Importantly, a growing number of studies have begun to investigate shared genetic liability between schizophrenia and patterns of substance use. We recently found a statistically significant association between general liability for substance use disorder and polygenic risk for cross-disorder psychopathology (18). In addition, recent studies have described common genetic risk factors between schizophrenia and cannabis use (19,20) and evidence for shared genetic factors between schizophrenia and smoking-related phenotypes (21,22).

Despite recent progress, to our knowledge there has been no comprehensive and systematic examination of the association between polygenic liability to schizophrenia and substance use disorder, which has been carefully assessed for licit and illicit substances. For these analyses, we leverage studies systematically ascertained for substance use disorder to

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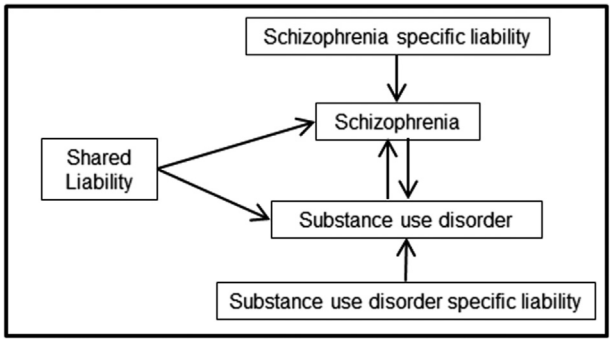

Figure 1. Model of liability leading to the comorbidity between schizophrenia and substance use disorder.

determine whether the schizophrenia PRSs are associated with these substance use disorders.

METHODS AND MATERIALS

Datasets

Three datasets were used for these analyses (Table 1). The datasets were all ascertained for substance dependence, validated by assessments used for DSM-IV diagnoses (23). However, the updated terminology from DSM-5 is substance use disorder (24), the union of DSM-IV substance dependence and DSM-IV substance abuse (25). For consistency, we use DSM-5 terminology throughout this article. The Collaborative Genetic Study of Nicotine Dependence (COGEND) (26–30) was ascertained for tobacco use disorder, the Collaborative Study on the Genetics of Alcoholism (COGA) (31–35) was ascertained for alcohol use disorder, and the Family Study of Cocaine Dependence (FSCD) (36) was ascertained for cocaine use disorder. Individuals from each of the three datasets were used to comprise the Study of Addiction: Genetics and Environment (SAGE) (37) (database of Genotypes and Phenotypes [dbGaP] accession number phs000092.v1.p1). Additional participants from the COGEND study were subsequently added to the SAGE study (dbGaP accession number phs000404.v1.p1). For this study, we restricted analyses to self-reported non-Hispanic individuals of European descent (N = 3676) because this is the population used to derive PRSs for schizophrenia. Ancestry was confirmed through principal component analyses. All studies were approved by their respective local institutional review boards, and all participants provided informed consent.

Recruitment

COGEND. COGEND was initiated to detect and characterize genes that alter risk for tobacco use disorder. Community-based recruitment enrolled subjects with tobacco use disorder and smoking control subjects without tobacco use disorder in St. Louis, Missouri, and Detroit, Michigan, between 2002 and 2007. All participants were between 25 and 44 years of age and spoke English. Subjects with tobacco use disorder were defined as current smokers with a Fagerström Test for Nicotine Dependence score ≥4 (26). Control status was defined as smoking ≥100 cigarettes lifetime but with a lifetime Fagerström Test for Nicotine Dependence score ≤1. Other substance use disorder diagnoses or comorbid disorders were not used as exclusionary criteria.

COGA. COGA, initiated in 1989, is a large-scale family study, with its primary aim being the identification of genes that contribute to susceptibility for alcohol use disorder. Participants were recruited from seven sites across the United States. Probands with alcohol use disorder were recruited from treatment facilities. Family members of the probands were recruited and comparison families were drawn from the same communities. A case-control sample of biologically unrelated individuals was drawn from COGA subjects (dbGaP accession number phs000125.v1.p1). All cases met DSM-IV criteria for alcohol dependence, and controls were defined as individuals who consumed alcohol but did not meet any definition of alcohol dependence or alcohol abuse, nor did they meet any DSM-IIIR or DSM-IV definition of abuse or dependence for other drugs (except nicotine).

FSCD. FSCD was initiated in 2000 with the primary goal of increasing understanding of the familial and nonfamilial antecedents and consequences of cocaine use disorder (38). Individuals with cocaine dependence defined by DSM-IV criteria were systematically recruited from chemical dependency treatment units in the greater St. Louis metropolitan area. Community-based control participants were identified and matched by age, race, gender, and residential ZIP code.

Table 1. Participant Characteristics by Study

	COGEND: Tobacco Use Disorder		COGA: Alcohol Use Disorder		FSCD: Cocaine Use Disorder	
Ascertainment	Cases	Control Subjects	Cases	Control Subjects	Cases	Control Subjects
n	918	988	801	442	210	317
Female, %	53	69	30	74	48	52
Average Age, Years (SD)	37 (5)	36 (5)	43 (11)	50 (12)	33 (9)	34 (9)
Tobacco Use Disorder, %	100	0	71	28	71	8
Alcohol Use Disorder, %	18	7	100	0	100	22
Cannabis Use Disorder, %	13	4	29	0	7	63
Cocaine Use Disorder, %	11	3	38	0	100	0

COGA, Collaborative Study on the Genetics of Alcoholism; COGEND, Collaborative Genetic Study of Nicotine Dependence; FSCD, Family Study of Cocaine Dependence.