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Genetic Correlation Profile of Schizophrenia Mirrors Epidemiological Results and Suggests Link Between Polygenic and Rare Variant (22q11.2) Cases of Schizophrenia

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New methods in genetics research, such as linkage disequilibrium score regression (LDSR), quantify overlap in the common genetic variants that influence diverse phenotypes. It is becoming clear that genetic effects often cut across traditional diagnostic boundaries. Here, we introduce genetic correlation analysis (using LDSR) to a nongeneticist audience and report transdisciplinary discoveries about schizophrenia. This analytical study design used publically available genome wide association study (GWAS) data from approximately 1.5 million individuals. Genetic correlations between schizophrenia and 172 medical, psychiatric, personality, and metabolomic phenotypes were calculated using LDSR, as implemented in LDHub in order to identify known and new genetic correlations. Consistent with previous research, the strongest genetic correlation was with bipolar disorder. Positive genetic correlations were also found between schizophrenia and all other psychiatric phenotypes tested, the personality traits of neuroticism and openness to experience, and cigarette smoking. Novel results were found with medical phenotypes: schizophrenia was negatively genetically correlated with serum citrate, positively correlated with inflammatory bowel disease, and negatively correlated with BMI, hip, and waist circumference. The serum citrate finding provides a potential link between rare cases of schizophrenia (strongly influenced by 22q11.2 deletions) and more typical cases of schizophrenia (with polygenic influences). Overall, these genetic correlation findings match epidemiological findings, suggesting that common variant genetic effects are part of the scaffolding underlying phenotypic comorbidity. The "genetic correlation profile" is a succinct report of shared genetic effects, is easily updated with new information (eg, from future GWAS), and should become part of basic disease knowledge about schizophrenia.

Key words: polygenic/22q11.2/personality/BMI/citrate/smoking

Introduction

As scientists and clinicians, we want to understand why schizophrenia exists, and how it is best treated and prevented. This is not an easy task. Even setting aside—for the sake of simplicity—heterogeneity among people with schizophrenia, we still seek a more thorough understanding of the biological, environmental, psychological, and social processes that contribute to schizophrenia. A foundation upon which to understand schizophrenia requires understanding of comorbidity and the genetic factors that influence comorbidity. Regarding the field's understanding of *genetic* factors influencing comorbidity (across all of medicine), a noteworthy development occurred in 2015 with the publication of the linkage disequilibrium score regression (LDSR) method.[1] As described more fully below, LDSR affords substantially broader investigation of shared genetic effects than ever before, hence the motivation for the present study. The goals of this report are 2-fold. First, we aim to contextualize LDSR among other methods that are informative about shared genetic effects among phenotypes (eg, twin/family studies, polygenic risk scoring[2,3] [PRS], and genome-wide complex trait analysis[4] [GCTA]). Second, we apply LDSR to schizophrenia and 172 phenotypes to generate a genetic correlation profile of schizophrenia. This genetic correlation profile should be viewed as a dynamic report which can be augmented with new results (as described below), and it provides fundamental information about the phenotype of schizophrenia.

What Is LDSR and Why Is This Analysis Possible Now?

LDSR[1] is one of multiple methods used to estimate the magnitude and direction of shared genetic effects between phenotypes (eg, shared genetic influences on

schizophrenia and bipolar disorder). Other leading methods are twin/family studies, PRS,[2,3] and GCTA.[4] Whereas twin and family studies have been used to assess shared genetic effects for decades, methods requiring genome-wide molecular genetic data (LDSR, GCTA, and PRS) have been developed in the last 10 years with the advent of genome-wide association studies (GWAS), and in particular, the public availability of the results from GWAS, which are referred to as GWAS results or summary statistics. See figure 1 for a glossary of genetics terms and reference articles about GWAS. A thorough discussion of the similarities and differences among methods used to assess shared genetic effects (also referred to as genetic correlations, co-heritability, and genetic overlap) is beyond the scope of this report, but we briefly review the major strengths and limitations of these methods (see figure 2 for a visual overview). Regarding statistical approaches, GCTA is a mixed linear model approach that quantifies the proportion of phenotypic variance explained by genetic variants, using individual-level genotype and phenotype data. LDSR is a regression based approach that estimates genetic correlations by quantifying deviation of chi-square statistics from expectation under the null, and it uses only summary statistics. See Yang et al[5] for a more thorough comparison of these approaches.

Twin and Family Studies. *Twin and family studies* use information about phenotypes and family relationships (most commonly, monozygotic and dizygotic twin status) to infer the relative importance of genetic factors in the population being studied (heritability). Bivariate twin studies can be used to quantify genetic effects shared between 2 phenotypes. Though classical twin studies do not use molecular genetic data, their design is elegant in that it captures (without measurement error) all inherited genetic effects, including common, rare, and complicated genetic variations that are not accurately captured by genotyping arrays (also known as GWAS chips). The major limitation of twin studies is that the 2 phenotypes must be measured on the same participants, thereby dramatically decreasing the practical potential of applying twin studies to large numbers of phenotype pairs.

Polygenic Risk Scoring. First developed in 2007[2] and widely popularized in 2009,[3] PRS, is a method that leverages the results of large scale GWAS (ie, the discovery or training sample), to construct individual-level metrics of genetic risk which can then be tested for correlation to phenotypes of interest (ie, in the target or testing sample). For example, researchers can use the summary statistics (ie, the GWAS results) from the best-powered GWAS of schizophrenia to date[6] (currently, the 2014 publication reporting 108 genomic regions associated with schizophrenia) to construct—in independent samples—individual-level metrics of genetic risk for schizophrenia. The main outcome from a PRS analysis is typically the amount of phenotypic variance explained in a phenotype of interest, in the target sample. This metric is informative about the *existence* of shared genetic effects, but it does not provide a direct estimate of the *magnitude* of shared genetic effects between 2 phenotypes. A benefit of PRS is that the target sample size may be much smaller than the discovery sample. On the other hand, the need for individual level genotype data makes this method more time consuming (and impossible when individual level genotype data are not available). PRS is therefore less widely applicable than LDSR (which requires only summary statistics, as noted below).

Genome-Wide Complex Trait Analysis. *GCTA*[4] affords estimation of heritability from molecular genetic data and also can be used to estimate shared genetic effects. Genotypic and phenotypic similarities are assessed using restricted maximum likelihood. Notably, heritability estimates from GCTA (denoted h^2_{SNP}) and LDSR are reliably lower than heritability estimates from twin studies (denoted h^2_{twin}). This discrepancy is sometimes misinterpreted as evidence that heritability estimates are incorrect or unreliable. In reality, this discrepancy is expected because, as noted above, twin studies capture, without measurement error, the effects of all inherited genetic variation. In contrast, molecular genetic methods currently use only common variant data, and further many variants are imputed and are therefore known to be measured imperfectly. Combined with knowledge about the highly polygenic nature of all psychiatric phenotypes, it is therefore unsurprising that h^2_{SNP} estimates are reliably lower than h^2_{twin} estimates. Regarding GCTA estimates of shared genetic effects, such estimates have smaller standard errors than estimates from LDSR (an advantage of GCTA), but the disadvantage of GCTA is that individual level genotype data are required (and such data are often not available from consortia or individual groups).

Linkage Disequilibrium Score Regression. *LDSR, also called LDSC* is a regression based method, which can be used to estimate sample overlap and population stratification,[7] to estimate heritability, and to estimate shared genetic effects[1] (ie, genetic correlations between phenotypes, the subject of this report). While accounting for the effects of linkage disequilibrium, LDSR quantifies the similarity in test statistics for 2 phenotypes, to yield estimates of genetic correlations. GCTA and LDSR yield similar estimates for heritability and for shared genetic effects. Whereas GCTA is applied to individual level genotype and phenotype data, LDSR is applied to summary statistics from GWAS, and this permits application to a many more phenotypes. The other major advantage of LDSR is that any level of overlap among participants in samples is permissible. The LDSR method estimates a term (the intercept), which reflects the degree of sample overlap and/or population stratification.[1,7] Thus, the

Complex genetic phenotype (aka polygenic phenotype) – a trait or diagnosis influenced by approximately thousands of genetic variants and by environmental factors. Examples include obesity, height, major depressive disorder, and schizophrenia.

Common genetic variants – genetic polymorphisms (i.e. known DNA variations) that have a minor allele frequency (MAF) of at least 5%.

SNPs – single nucleotide polymorphisms are places in the genome at which one nucleotide (i.e. A, T, G, or C) is known to be variable, such that one of the other three nucleotides is also found at the same location. SNPs often have rs numbers (e.g. rs6265) that serve as their names.

Allele – one form of a polymorphism. For example, the SNP rs6265 has two alleles G and A. Possible *genotypes* for rs6265 are GG, GA, and AA. The less common allele (in a given population) is referred to as the *minor* allele, and the more common allele is the *major* allele.

GWAS - genome-wide association study – a study type used to test for systematic relationships between a phenotype and specific alleles.

Linkage Disequilibrium (LD) – is a term used to describe known patterns of correlation across alleles.

LDSR – Linkage Disequilibrium Score Regression is the statistical method used in this report. It can provide estimates of heritability and genetic correlations, and it uses GWAS summary statistics as input.

Summary statistics (aka GWAS results) – The primary output of a GWAS is a results file, which typically has millions of rows. It provides association statistics for each genetic variant (one per row). Odds ratios (or betas), standard errors, and p-values are some of the statistics provided for each variant. The term 'summary statistics' (from a GWAS) distinguishes this type of dataset from the individual level genotype data that were used in the GWAS.

Data resources – By 'data resource' we refer to datasets, which are often publically available, that are necessary for genomic analyses. For example, this analysis uses the data resources of GWAS results (173 sets of results) and also uses information about patterns of LD across the genome.

Bivariate GCTA – a method used to assess shared genetic effects. It is slightly more statistically powerful than LDSR, but cannot be applied to summary statistics, and therefore it cannot be as widely applied as LDSR.

Ancestry (relevance to LDSR) – quantification of ancestry is standard in genomic analyses. Allele frequencies and combinations of alleles vary with ancestry, and this is why LSDR can only be applied within relatively homogeneous ancestry groups. Given historical bias toward European ancestry populations in genetics research and method development that first focused on non-admixed groups (e.g. European-ancestry individuals) LDSR can only be widely applied to European-ancestry individuals until data resources from more diverse ancestry groups (e.g. African Americans and Latinos) are available.

Articles about GWAS results – for further information, these articles may be useful:

Visscher, P. M., Brown, M. A., McCarthy, M. I. & Yang, J. (2012) Five years of GWAS discovery. *American Journal of Human Genetics*, 90, 7–24.

Visscher, P. M. et al. (2017) 10 Years of GWAS Discovery: Biology, Function, and Translation. *American Journal of Human Genetics*, 101, 5–22.

Duncan, L.E. & Keller, M.C. (2011) A Critical Review of the First Ten Years of Candidate Gene by Environment Interaction Research in Psychiatry. *Am. J. of Psych., 168(10), 1041-1049.*

Fig. 1. Glossary of genetics terms provides definitions of terms in manuscript and additional references about GWAS results.

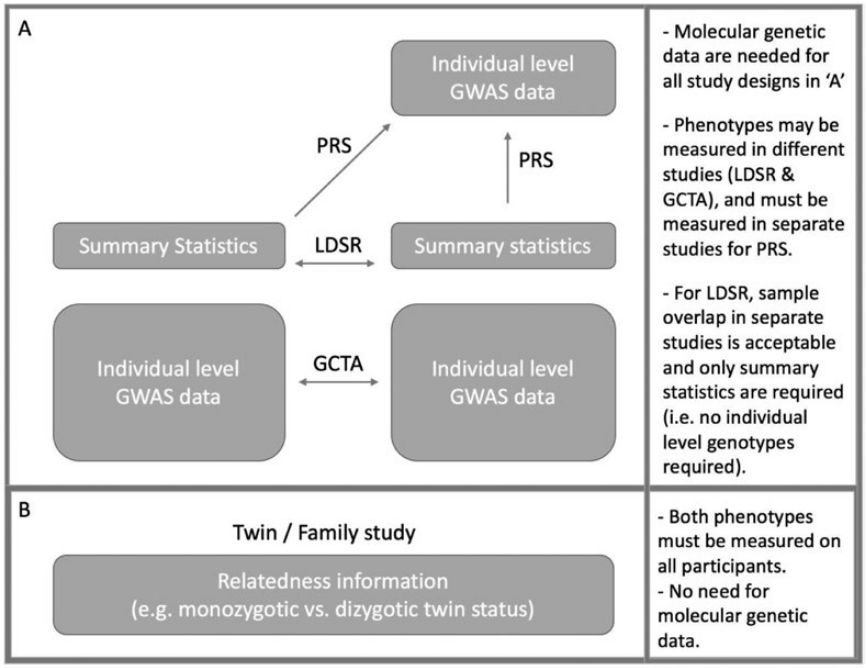

Fig. 2. Methods of assessing shared genetic effects. (A) Molecular genetic methods for detecting shared genetic effects include polygenic risk scoring (PRS), linkage disequilibrium score regression (LDSR, used in this report), and genome-wide complex trait analysis (GCTA). (B) Twin (and family) studies do not require molecular genetic data. Shaded gray boxes denote the type of genetically informative data used by the study type (PRS, LDSR, GCTA, and twin/family are the 4 study types). Arrows denote the types of information used in each molecular genetic method. For example, PRS uses summary statistics from a discovery sample to construct polygenic scores using individual level GWAS data in the target sample (unidirectional arrow). GCTA requires individual level GWAS data for both phenotypes (bidirectional arrow). Brief notes about methods are given in the right column.

degree of sample overlap is estimated by LDSR, and therefore unbiased estimates of genetic correlation can be obtained even in the presence of sample overlap (ie, an advantage over other methods that do not account for sample overlap).

What Is a Genetic Correlation Profile, and Why Is It a Dynamic Report?

In this report, we provide a genetic correlation profile of schizophrenia (in figure 3), which affords rapid understanding of the direction and magnitude of shared genetic effects between schizophrenia and other phenotypes. In essence, the genetic correlation profile reveals the scaffolding underlying comorbidity between schizophrenia and other phenotypes. The genetic correlation profile reported here provides the most current overview of phenotypes that are likely to share common variant genetic effects with schizophrenia. Additional phenotypes will likely be identified in the future. The genetic correlation profile is easily updated with new information (eg, as GWAS of more phenotypes become available), and amenable to refinement of point estimates (as statistical power and scope of genomic investigations increases, see "Discussion" section for details). Thus, the genetic correlation profile here provides the most comprehensive genetic correlation information on schizophrenia available to date, and we also recommend that it be conceptualized as a dynamic report, which should see modest expansion and refinement in the future.

Motivation for the Present Report

Advances in genomics research in the past 5 years have revealed a high level of pleiotropy (ie, shared genetic effects) across medical and other phenotypes. Multiple lines of evidence also make it clear that many thousands of genetic variants typically influence complex genetic phenotypes (including psychiatric disorders). As noted by Schorck et al[8] and others, there is much work to be done to discover the precise nature of shared genetic effects. Nevertheless, we are now able to use publically available data and the LDSR method to gain a novel perspective on the biological underpinnings of schizophrenia by calculating genetic correlations between schizophrenia and 172 diverse phenotypes (including psychiatric, personality, health, and anthropomorphic phenotypes).

Methods

This is an analytical investigation, which did not use new data from participants, but rather GWAS results from previous investigations. Using suitable data (see below), we ran the regression analysis used by LDSR to estimate

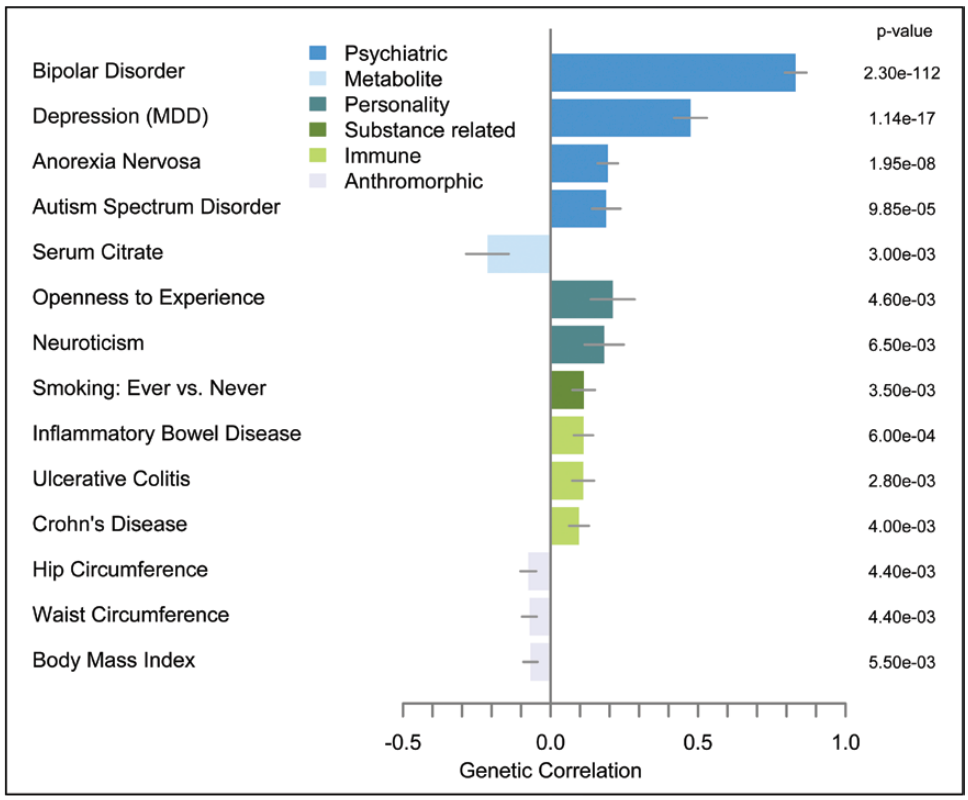

Fig. 3. Genetic correlation profile for schizophrenia. Colored bars depict genetic correlations with schizophrenia, which have a theoretical range from −1 to 1. Ticks at bar ends denote ±1 standard error. Uncorrected *P*-values are displayed on the right.

genetic correlations between schizophrenia and 172 other phenotypes. The analysis was conducted in LDHub. The schizophrenia GWAS data used in this report are the GWAS summary statistics from the European ancestry subset (N = 74 626) of the best-powered GWAS of schizophrenia published to date.[6] Consistent with modern GWAS procedures, we used imputed data (imputation to 1000Genomes[9]), and we filtered for variants with high imputation quality scores (INFO > 0.9) and minor allele frequency >5%. Regarding phenotypes to be tested for potential genetic correlations to schizophrenia, we used the phenotypes in the LDHub database because, to the best of our knowledge, it has the largest collection of GWAS results suitable for LDSR genetic correlation analysis. Our goal was to identify suspected and novel genetic correlations, hence our use of an inclusive list of phenotypes.

GWAS results for the 172 phenotypes from LDHub met the following criteria: imputation to at least HapMap 2 reference panel, heritability z-score greater than 2, and predominately European ancestry. The range of sample sizes for these GWAS studies was 5422 (attention deficit hyperactivity disorder) to 232 101 (waist circumference), with mean sample size of 37 440 and median sample size of 21 241. The number of SNPs from the 172 studies ranged from 453 218 to 12 716 084 (mean = 8 549 581, median = 11 760 646 SNPs). For specific information about each phenotype and the corresponding GWAS, see supplemental table S1.

Genetic correlation analysis was performed using LDSR software,[1] as implemented in the LDHub platform[10] to estimate genetic correlations between schizophrenia and 172 phenotypes (http://ldsc.broadinstitute.org). Correction for testing 172 genetic correlations was conducted using Benjamini and Hochberg[11] false discovery rate (FDR) as implemented in R[12] (*P*.adjust function) with FDR adjusted $P < .1$ as the significance threshold. This implies that 90% of results are likely to be correct. We also used the Benjamini and Yekutieli[13] correction approach, which accounts for positive dependence among tests. In figure 2, we omit, for clarity, redundant phenotypes passing our significance threshold (ie, 2 alternative parameterizations of BMI and a cross-disorder psychiatric phenotype, which includes the schizophrenia samples used in this investigation).

Results

Significant genetic correlations between schizophrenia and diverse phenotypes are provided in figure 2. The strongest genetic correlations were to the psychiatric phenotypes of bipolar disorder (genetic correlation [r_g] = .83, standard error [SE] = .04, raw *P*-value [*P*] = 2.3×10^{-112}, FDR adjusted *P*-value [FDR.*P*] = 1.33×10^{-110})

and major depressive disorder (r_g = .47, SE = .06, $P = 1.1 \times 10^{-17}$, FDR.$P = 4.92 \times 10^{-16}$). Anorexia nervosa (r_g = .19, SE = .03, $P = 2.0 \times 10^{-8}$, FDR.$P = 6.73 \times 10^{-7}$) and autism spectrum disorder (r_g = .19, SE = .05, $P = 9.9 \times 10^{-5}$, FDR.$P = 2.84 \times 10^{-3}$) were also positively correlated with schizophrenia, as were the personality dimensions of openness to experience (r_g = .21, SE = .07, $P = 4.6 \times 10^{-3}$, FDR.$P = 5.31 \times 10^{-2}$) and neuroticism (r_g = .18, SE = .07, $P = 6.5 \times 10^{-3}$, FDR.$P = 6.61 \times 10^{-2}$). Other positive correlations were to smoking status of ever vs never (r_g = .11, SE = .04, $P = 3.5 \times 10^{-3}$, FDR.$P = 5.31 \times 10^{-2}$) and to the immune phenotypes of ulcerative colitis (r_g = .11, SE = .04, $P = 2.8 \times 10^{-3}$, FDR.$P = 5.19 \times 10^{-2}$), Crohn's Disease (r_g = .10, SE = .03, $P = 4.0 \times 10^{-3}$, FDR.$P = 5.31 \times 10^{-2}$), and inflammatory bowel disease (r_g = .11, SE = .03, $P = 6.0 \times 10^{-4}$, FDR.$P = 1.48 \times 10^{-2}$), the latter of which relied on a GWAS of ulcerative colitis and Crohn's disease cases combined, and compared to controls.

Citrate level, as measured in serum by nuclear magnetic resonance (NMR) assay, was negatively genetically correlated with schizophrenia (r_g = −.21, SE = .07, $P = 3.0 \times 10^{-3}$, FDR.$P = 5.19 \times 10^{-2}$). Anthropomorphic measures relevant to metabolic syndrome were also negatively genetically correlated with schizophrenia: hip circumference (r_g = −.08, SE = .03, $P = 4.4 \times 10^{-3}$, FDR.$P = 5.31 \times 10^{-2}$), waist circumference (r_g = −.07, SE = .03, $P = 4.4 \times 10^{-3}$, FDR.$P = 5.31 \times 10^{-2}$), and body mass index (BMI, r_g = −.07, SE = .02, $P = 5.5 \times 10^{-3}$, FDR.$P = 5.95 \times 10^{-2}$). Other parameterizations of BMI were also negatively correlated with schizophrenia (eg, obesity class 1), but were omitted from figure 2 to reduce redundancy. After correction of *P*-values using the more stringent Benjamini and Yekutieli approach,[13] only psychiatric (for bipolar disorder, major depressive disorder, anorexia nervosa, and autism spectrum disorder) and inflammatory bowel disease genetic correlations remained significant, see supplementary table 1 for details.

Discussion

The genetic correlation profile reported here provides the most comprehensive readout ever available of the phenotypes that share genetic influences with schizophrenia. These results are akin to those from epidemiology (regarding comorbidity), but are also mechanistically informative given that the cause (common genetic variation) is known. In the following sections, we discuss specific results, limitations, and future directions.

Specific Results

Psychiatric and Personality. Positive genetic correlations between schizophrenia and all other psychiatric disorders (in this study) are consistent with the original report of the LDSR method,[1] with co-heritability estimates using an alternative statistical method (bivariate GCTA), and with family studies.[14,15] Cross-disorder genetic effects on psychiatric phenotypes have been reported extensively,[1,16] and serve as positive controls for these LDSC analyses, given widespread knowledge of consistently demonstrated shared genetic effects between schizophrenia and other psychiatric disorders. Though not available for this analysis, a recent PTSD genetic study also reported a positive genetic correlation between schizophrenia and PTSD.[17]

The broad consistency of genetic correlation results across psychiatric disorders notwithstanding, there is still variability in point estimates from different methods and from specific datasets to which methods have been applied. Specifically, for the genetic correlation between schizophrenia and bipolar disorder, our point estimate of .84 is the highest of available estimates. This value is not significantly different from the point estimate of .79 from the original LDSR report.[1] Other estimates of genetic correlation from LDSR and GCTA (for a subset of samples suitable for use with GCTA) yielded genetic correlation of ~.7 for both methods (values extracted from figure 1 in the LDSR paper).[1] Family studies yielded estimates of .68 and .60.[14,15] In sum, the range of estimates for genetic correlation between schizophrenia and bipolar disorder is .60–.84; a range that is not uncommon for application of even the same method to different studies. Thus, a reasonable interpretation is that the genetic correlation between the 2 disorders is high. At a minimum it is moderate, and future studies (as described in the "Limitations" section) may help to clarify the reasons for variability in point estimates of genetic correlation.

Regarding practical interpretation of the risks for psychiatric disorders to relatives of individuals with particular diagnoses, it is important to keep in mind that schizophrenia and bipolar disorder are both infrequent in the population. Consequently, high genetic risk (eg, high heritability and high genetic correlation) do not confer rates of diagnoses anywhere near as high as naïve interpretation of heritability or genetic correlations might suggest. For example, Lichtenstein and colleagues conducted a population-based examination of schizophrenia and bipolar disorder in Sweden. They found that—if one parent had schizophrenia—the relative risk of schizophrenia for a child was 9.9, and the relative risk of bipolar disorder for a child was 5.2. Thus, despite high heritability for schizophrenia and high genetic correlation with bipolar disorder, it is still true that only a minority of even first-degree relatives will develop either of these disorders.

Personality correlates of schizophrenia have been widely studied, and 3 personality variables were available for this genetic analysis (neuroticism, openness to experience, and conscientiousness).[18] Phenotypic (nongenetic) meta-analysis revealed a positive correlation between neuroticism and schizophrenia,[19] which is consistent with the genetic correlations reported here. However,

phenotypic and genetic correlations diverge for openness to experience,[19] with the former negative and the latter positive. Our result could be a false positive, but more interesting explanations are also possible. Consistent with our finding, Power et al[20] found that polygenic risk for schizophrenia (and bipolar disorder) is predictive of artistic occupations in the general population. Openness to experience is the personality dimension most closely related to art and aesthetics.[18,21,22] Recently, another study used these data, plus additional privately available data, and also found a positive correlation between schizophrenia and openness to experience.[23] Further, delusions are by definition unconventional beliefs, and individuals high on openness to experience are more likely to hold unconventional beliefs. Taken together, these findings point to shared genetic influences on schizophrenia, creative professions, and openness to experience.

Novel and Potentially Mechanistically Relevant: Serum Citrate. We observed a modest but significant negative genetic correlation between serum citrate level and schizophrenia. Citrate metabolism is not widely discussed as being relevant to schizophrenia. Yet previous results suggest possible mechanistic relevance. In a small study, Xuan et al[24] conducted serum metabolomic profiling, and citrate was the top metabolite in a classification model separating people with schizophrenia from controls. The direction of effect (reduced citrate in schizophrenia) is consistent with the negative genetic correlation reported here. Further, 2 reports have suggested that altered citrate metabolism could play a role in the pathophysiology of 22q11.2 deletion syndrome, which is detected in around 0.3% of individuals with schizophrenia but which increases risk of schizophrenia in carriers by around 30-fold.[25,26] Stoffel et al[27] found that the mitochondrial citrate transporter gene (*SLC20A3*/*SLC25A1*) maps to the smallest known deletion in the 22q11.2 region reported in a person with schizophrenia. Napoli et al[28] characterized diverse molecular correlates of 22q11.2del as a mitochondrial citrate transporter-dependent signature. Further, it is known that insufficiency of the SLC25A1 gene causes citrate to accumulate in mitochondria but to decrease in cytosol and urine, with symptoms improving when citrate is administered therapeutically.[29] The symptoms of this rare condition (autosomal recessive mitochondrial citrate carrier deficiency) include neurodevelopmental deficits and seizures, which occur at rates higher than chance in schizophrenia.[30–33] Thus, it is possible that defects in citrate metabolism are relevant to the rare form of schizophrenia seen in 22q11.2 deletion carriers and also the more common forms with polygenic influences.

The negative genetic correlation between schizophrenia and citrate level (reported here) relies on large samples (schizophrenia N = 74 626, citrate N = 24 770) using a method (genotyping of genomic DNA) that is not influenced by the usual confounders of biological studies of patients (eg, age, time of day, smoking, medication effects). Conversely, studies of citrate levels in large numbers of schizophrenia patients under appropriate conditions would be difficult and expensive to carry out—so the findings to date come from small studies that have received little attention. The convergence of findings across the 3 available types of evidence—negative genetic correlation, lower serum levels, and greatly increased risk in individuals with only one copy of the citrate transporter gene (in which mutations are known to reduce citrate levels)—suggests that a role for deficient citrate metabolism in schizophrenia deserves a closer look. This type of convergence is precisely the goal of examining genetic correlation profiles of complex genetic phenotypes.

Smoking. The rate of smoking among individuals with schizophrenia is remarkably high compared to the general population, with an overall OR of 5.9 from a meta-analysis of worldwide studies.[34] Shared genetic effects have long been postulated[35] and some evidence from linkage studies suggested shared rare variant effects on these phenotypes.[36] Recently, PRS revealed a genetic relationship between schizophrenia and nicotine dependence,[37] and Hartz et al[38] recently reported a positive genetic correlation between schizophrenia and smoking phenotypes, consistent with this report. Together these findings affirmatively answer longstanding questions about whether or not shared genetic effects contribute to the high comorbidity between smoking and schizophrenia.

Immune Phenotypes. Immune hypotheses about schizophrenia are many, and genetic results would be most useful if they help arbitrate among them, extend them, or at least apply to certain hypotheses and not others. The present findings of positive genetic correlations between schizophrenia and inflammatory bowel disease (including Crohn's disease and ulcerative colitis, together and separate) add to the body of literature linking autoimmune diseases with increased rates of schizophrenia[39,40] and extend them by implicating shared genetic risk for schizophrenia and inflammatory bowel disease. Various infections have been implicated in the subsequent development of schizophrenia[39–42] and other autoimmune phenotypes have also been linked to schizophrenia (eg, multiple sclerosis[43] and autoimmune hepatitis, and see Benros et al. for comorbidity estimates from a national population sample[39]). When suitable GWAS are available for these phenotypes, it will be possible to determine if they also share genetic influences with schizophrenia.

It is also important to be clear about which immune hypotheses cannot be interpreted in light of these genetic correlation results. Landmark discoveries about schizophrenia include the strong MHC genetic association to schizophrenia[6] (on chromosome 6) and the specific discovery of complement component 4 (C4)'s relevance to

schizophrenia.[44] The present results are independent of these findings. A notable feature of the MHC region (which contains C4) is that it has the longest LD in the human genome. As such, variants in the MHC region are statistical outliers and are therefore removed from LDSC genetic correlation analyses. Thus, MHC[6] and C4 results[44] are distinct findings from those reported here; the present results pertain to the remainder of the genome. An idea emerging from these findings, however, is that traditionally immune machinery may be used in alternative ways in the brain, and perturbed in schizophrenia.

Anthropomorphic Traits Relevant to Metabolic Syndrome. The final group of genetic correlations we discuss—between schizophrenia and BMI, waist, and hip circumference—illustrates the potential for this method to clarify underlying causes when mechanistic understanding is complicated by side effects of medications. Schizophrenia is associated with early mortality, some of which is attributable to metabolic syndrome, which can be precipitated by anti-psychotic medications.[45–48] Individuals with schizophrenia are commonly overweight, and many treatment providers have come to associate schizophrenia with weight-related conditions. There is also suggestion that individuals with schizophrenia are predisposed to metabolic syndrome. While this may be the case for certain features of the syndrome, the present results suggest that the opposite is true: those with schizophrenia are genetically predisposed to lower BMI, hip, and waist circumference. It is possible that this expectation is an artifact of medication effects, although lifestyle and chronic stress may also play a role. Epidemiological research showing *lower* than average BMI among medication naïve individuals,[49,50] and those before diagnosis of schizophrenia,[51–53] is consistent with this conclusion and was predicted by the genetic correlation results presented here. With regard to stigma that accompanies both the diagnosis of schizophrenia and high BMI, it may be clinically meaningful for treatment providers to be even more aware of the causes of weight gain (ie, oftentimes medication) such that increased weight is not ascribed to personal failings of the patient, or considered inherent to the disorder. The genetic correlation reported here is also consistent with the success of a previous investigation to identify additional schizophrenia risk variants.[54]

Limitations

A major goal of this report is to present a transformative genomics method to a broad audience. As we noted above, the results presented here are consistent with previous genetic correlation estimates and consistent with epidemiological findings, suggesting that these results are generally true. Nevertheless understanding of limitations is necessary for proper interpretation of results and thus, we devote considerable space to this topic. Limitations can be grouped into categories of estimation, ancestry, and certainty of interpretation (including multiple testing correction).

Estimation. We report genome-wide estimates of shared genetic effects, based on common genetic variation only (SNPs with MAF >5%, threshold selected per LDSR method guidelines). The genetic correlation estimates for particular pairs of phenotypes will be misleading if rare variant effects are not shared in the same manner as common variant effects. For example, considering schizophrenia and bipolar disorder, the true genetic correlation between these 2 phenotypes may be higher (if rare variant effects are shared to a greater degree than common variant effects) or lower (if rare variant effects are shared to a lesser degree). Currently, it is known that common variants determine sizeable amounts of phenotypic variability among polygenic phenotypes.[55] Further, there is no a priori reason to expect systematic differences between rare and common variants in terms of their shared influences on particular pairs of phenotypes. Thus, genetic correlation estimates based on common genetic variations (as reported here) may prove to be reasonable estimates of overall genetic correlations, but more rare variant studies are needed to test this hypothesis.

Regarding estimation of common variant genetic correlations, improvements on the LDSR method class (including GCTA) have been proposed.[56] Optimizations exploit variability in heritability across the genome. When such improvements are available for genetic correlation analyses, it will be useful to re-estimate genetic correlations with schizophrenia. Imprecision in estimation of genetic correlations is one of the relative weaknesses of LDSR (as compared to GCTA), and some false positives and false negatives are possible. Variable power across the GWAS of the 172 phenotypes in this report means that we had better power to detect certain genetic correlations than others. False negatives are particularly likely when power is low in one or both of the component GWAS. The effect of low power is less precise estimates of genetic correlations, but low power does not lead to biased estimates of genetic correlations. On an obvious but related point, we cannot detect genetic correlations with phenotypes that are unavailable for analysis. Taken together, these points suggest that there are likely to be additional phenotypes that share genetic correlations with schizophrenia (eg, other autoimmune phenotypes).

Another consideration relevant to estimation of overall genetic correlations is that such estimates undoubtedly mask variability across individual loci. For example, a particular locus might have opposing effects on 2 phenotypes, despite overall positive genetic correlation.[43] Thus, the determination of pleiotropy for individual risk variants must be accomplished separately,[57] and genetic correlations reported here will be underestimates, to the

extent that the direction of shared effects is not consistent across all loci.[8] Finally, genetic correlation results apply to *populations* and not *individuals*. Just as heritability estimates are not informative about the degree to which a given individual's phenotype is due to genetics, phenotypic pairings within an individual that match (or fail to match) the overall genetic correlation cannot—at this time—be ascribed to genetic effects.

Ancestry. Allele frequencies and patterns of alleles vary according to ancestry. Given practical limitations, we used only European ancestry data, and consequently these results are only strictly generalizable to European ancestry individuals. This problem of strict generalizability is one facing all of medical genetics because genetic studies have been primarily conducted in European ancestry individuals.[58] Though there is no a priori reason to expect global ancestry-based differences in genetic correlation patterns, the problem of biased representation is important from an equity standpoint, can be medically relevant,[59] and is a high priority for future research.

Certainty/Multiple Testing Correction. The final topic relevant to interpreting these results is the certainty with which these genetic correlations can be reported. We've used a relatively lenient threshold for declaring notable genetic correlations (FDR.$P < .1$). We do so because of the high level of correspondence between genetic correlation results and phenotypic comorbidity (as reported here and in other applications of LDSR[1]), which lends support to multiple a priori hypotheses. Further, individual results included in this analysis have recently been reported in separate publications with more data and additional analyses (eg, about schizophrenia and smoking[38] and personality[23]), supporting the veracity of these findings. Finally, there is high potential for mechanistically relevant findings in this nonclinical report. Our contention is that these factors shift the decision about how to correct for multiple statistical tests in favor of maximizing true positives and minimizing false negatives. However, these findings require replication in adequately powered samples, and replication is particularly important for the genetic correlations that did not surpass the most stringent corrections for multiple testing.

Finally, many of the genetic correlations reported here may be described as small in magnitude, and readers may wonder what to make of genetic correlations in the range of ~0.1–0.2. Drawing upon the GWAS literature more broadly, Visscher et al[60] note that even single risk variants for complex genetic diseases (with small magnitude effect sizes) can indicate important disease processes and mechanisms of drug action. Likewise, a small genetic correlation may be indicative of the presence of a mechanistically important process shared between 2 phenotypes. Alternatively, if only a subset of cases of schizophrenia shares a particular biological influence with another phenotype, then the magnitude of the genetic correlation may be small for the broader class of schizophrenia cases. Indeed, one promising avenue for future investigations with genetic correlation profiles is in distinguishing varying psychosis syndromes. Such analyses will become tractable as sample sizes for GWAS of schizophrenia syndromes increase and achieve adequate statistical power (with a guideline for adequate power being h^2_{SNP} z-score >4).

Future Directions

These results suggest a variety of specific future directions. For one, we argue that genetic correlation profiles, as reported here, provide fundamental information relevant to understanding schizophrenia and should become part of basic disease knowledge in the way that epidemiological findings are today. Another use of genetic correlation analysis will become increasingly informative as GWAS results accrue. GWAS results for medication responses, additional GWAS of metabolites, and GWAS of mechanistic variables will yield results that are informative about the genetic underpinnings of biological mechanisms. LDSR then offers a unique opportunity: these mechanistic variables may be screened for relevance to schizophrenia, but without measuring each of the mechanistic variables in schizophrenia samples (thereby leveraging resources and enabling mechanistic investigations that would likely never be completed in large patient samples). The ability of LDSR to reveal shared genetic effects across non-overlapping samples offers valuable possibilities, which could ultimately aid treatment design and mechanistic classification of schizophrenia subphenotypes (eg, comparing genetic profiles for cases of schizophrenia with predominately negative symptoms vs predominately positive symptoms).

In sum, we report the magnitude and direction of genetic correlations between schizophrenia and 172 phenotypes. These findings support known genetic relationships between schizophrenia and psychiatric disorders, and they extend our understanding of the relationships between schizophrenia and personality, smoking, immune, and weight-related phenotypes. They highlight the potential for genetic correlation analysis to identify novel mechanistic relationships (citrate example), and suggest the potential for a link between rare instances of schizophrenia due to 22q11.2 deletion syndrome and typical polygenic instances. More broadly, we begin to see the genetic scaffolding underlying phenotypic comorbidities with schizophrenia, and with it the potential for deeper understanding of this complex genetic phenotype.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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References

1. Bulik-Sullivan B, Finucane HK, Anttila V, et al.; ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3. An atlas of genetic correlations across human diseases and traits. *Nat Genet*. 2015;47:1236–1241.
2. Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Res*. 2007;17:1520–1528.
3. Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460:748–752.
4. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet*. 2011;88:76–82.
5. Yang J, Zeng J, Goddard ME, Wray NR, Visscher PM. Concepts, estimation and interpretation of SNP-based heritability. *Nat Genet*. 2017;49:1304–1310.
6. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511:421–427.
7. Bulik-Sullivan BK, Loh PR, Finucane HK, et al.; Schizophrenia Working Group of the Psychiatric Genomics Consortium. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet*. 2015;47:291–295.
8. Schork AJ, Wang Y, Thompson WK, Dale AM, Andreassen OA. New statistical approaches exploit the polygenic architecture of schizophrenia—implications for the underlying neurobiology. *Curr Opin Neurobiol*. 2016;36:89–98.
9. 1000 Genomes Project Consortium, Abecasis GR, Auton A, et al. An integrated map of genetic variation from 1,092 human genomes. *Nature*. 2012;491:56–65.
10. Zheng J, Erzurumluoglu AM, Elsworth BL, et al.; Early Genetics and Lifecourse Epidemiology (EAGLE) Eczema Consortium. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics*. 2017;33:272–279.
11. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995;57:289–300.
12. Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. 2005. ISBN 3-900051-07-0. http://www.R-project.org. Accessed October 4, 2013.
13. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann Stat*. 2001;29:1165–1188.
14. Cardno AG, Owen MJ. Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. *Schizophr Bull*. 2014;40(3):504–515 doi:10.1093/schbul/sbu016.
15. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet*. 2009;373:234–239.
16. Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45:984–994.
17. Duncan LE, Ratanatharathorn A, Aiello AE, et al. Largest GWAS of PTSD (N=20070) yields genetic overlap with schizophrenia and sex differences in heritability. *Mol Psychiatry*. 2017. doi:10.1038/mp.2017.77.
18. Costa PT, McCrae RR. Four ways five factors are basic. *Personal Individ Differ*. 1992;13:653–665.
19. Ohi K, Shimada T, Nitta Y, et al. The five-factor model personality traits in schizophrenia: A meta-analysis. *Psychiatry Res*. 2016;240:34–41.
20. Power RA, Steinberg S, Bjornsdottir G, et al. Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. *Nat Neurosci*. 2015;18:953–955.

21. George JM, Zhou J. When openness to experience and conscientiousness are related to creative behavior: an interactional approach. *J Appl Psychol*. 2001;86:513–524.
22. McCrae RR. Creativity, divergent thinking, and openness to experience. *J Pers Soc Psychol*. 1987;52:1258–1265.
23. Lo MT, Hinds DA, Tung JY, et al. Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nat Genet*. 2017;49:152–156.
24. Xuan J, Pan G, Qiu Y, et al. Metabolomic profiling to identify potential serum biomarkers for schizophrenia and risperidone action. *J Proteome Res*. 2011;10:5433–5443.
25. Rees E, Walters JT, Georgieva L, et al. Analysis of copy number variations at 15 schizophrenia-associated loci. *Br J Psychiatry*. 2014;204:108–114.
26. Karayiorgou M, Morris MA, Morrow B, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Natl Acad Sci U S A*. 1995;92:7612–7616.
27. Stoffel M, Karayiorgou M, Espinosa R III, Beau MM. The human mitochondrial citrate transporter gene (SLC20A3) maps to chromosome band 22q11 within a region implicated in DiGeorge syndrome, velo-cardio-facial syndrome and schizophrenia. *Hum Genet*. 1996;98:113–115.
28. Napoli E, Tassone F, Wong S, et al. Mitochondrial citrate transporter-dependent metabolic signature in the 22q11.2 deletion syndrome. *J Biol Chem*. 2015;290:23240–23253.
29. Mühlhausen C, Salomons GS, Lukacs Z, et al. Combined D2-/L2-hydroxyglutaric aciduria (SLC25A1 deficiency): clinical course and effects of citrate treatment. *J Inherit Metab Dis*. 2014;37:775–781.
30. Censits DM, Ragland JD, Gur RC, Gur RE. Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. *Schizophr Res*. 1997;24:289–298.
31. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468:187–193.
32. Hyde TM, Weinberger DR. Seizures and schizophrenia. *Schizophr Bull*. 1997;23:611–622.
33. Chang YT, Chen PC, Tsai IJ, et al. Bidirectional relation between schizophrenia and epilepsy: a population-based retrospective cohort study. *Epilepsia*. 2011;52:2036–2042.
34. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res*. 2005;76:135–157.
35. Leonard S, Mexal S, Freedman R. Smoking, genetics and schizophrenia: evidence for self medication. *J Dual Diagn*. 2007;3:43–59.
36. Faraone SV, Su J, Taylor L, Wilcox M, Van Eerdewegh P, Tsuang MT. A novel permutation testing method implicates sixteen nicotinic acetylcholine receptor genes as risk factors for smoking in schizophrenia families. *Hum Hered*. 2004;57:59–68.
37. Chen J, Bacanu SA, Yu H, et al.; Cotinine meta-analysis group; FTND meta-analysis group. Genetic relationship between schizophrenia and nicotine dependence. *Sci Rep*. 2016;6:25671.
38. Hartz SM, Horton AC, Hancock DB, et al. Genetic correlation between smoking behaviors and schizophrenia. *Schizophr Res*. 2017. doi:10.1016/j.schres.2017.02.022.
39. Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry*. 2011;168:1303–1310.
40. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. *Schizophr Bull*. 2014;40:181–191.
41. Boksa P. Maternal infection during pregnancy and schizophrenia. *J Psychiatry Neurosci*. 2008;33:183–185.
42. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry*. 2010;167:261–280.
43. Andreassen OA, Harbo HF, Wang Y, et al.; Psychiatric Genomics Consortium (PGC) Bipolar Disorder and Schizophrenia Work Groups; International Multiple Sclerosis Genetics Consortium (IMSGC). Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. *Mol Psychiatry*. 2015;20:207–214.
44. Sekar A, Bialas AR, de Rivera H, et al.; Schizophrenia Working Group of the Psychiatric Genomics Consortium. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530:177–183.
45. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLoS One*. 2014;9:e94112.
46. Citrome L, Holt RI, Walker DJ, Hoffmann VP. Weight gain and changes in metabolic variables following olanzapine treatment in schizophrenia and bipolar disorder. *Clin Drug Investig*. 2011;31:455–482.
47. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. *Early Interv Psychiatry*. 2016;10:193–202.
48. Martínez-Ortega JM, Funes-Godoy S, Díaz-Atienza F, Gutiérrez-Rojas L, Pérez-Costillas L, Gurpegui M. Weight gain and increase of body mass index among children and adolescents treated with antipsychotics: a critical review. *Eur Child Adolesc Psychiatry*. 2013;22:457–479.
49. Verma SK, Subramaniam M, Liew A, Poon LY. Metabolic risk factors in drug-naive patients with first-episode psychosis. *J Clin Psychiatry*. 2009;70:997–1000.
50. Juutinen J, Hakko H, Meyer-Rochow VB, Räsänen P, Timonen M; Study-70 Research Group. Body mass index (BMI) of drug-naïve psychotic adolescents based on a population of adolescent psychiatric inpatients. *Eur Psychiatry*. 2008;23:521–526.
51. Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Height, weight and body mass index in early adulthood and risk of schizophrenia. *Acta Psychiatr Scand*. 2006;114:49–54.
52. Sørensen HJ, Gamborg M, Sørensen TIA, Baker JL, Mortensen EL. Childhood body mass index and risk of schizophrenia in relation to childhood age, sex and age of first contact with schizophrenia. *Eur Psychiatry*. 2016;34:64–69.
53. Zammit S, Rasmussen F, Farahmand B, et al. Height and body mass index in young adulthood and risk of schizophrenia: a longitudinal study of 1 347 520 Swedish men. *Acta Psychiatr Scand*. 2007;116:378–385.
54. Andreassen OA, Djurovic S, Thompson WK, et al. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. *Am J Hum Genet*. 2013;92:197–209.

55. Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. *Am J Hum Genet*. 2012;90:7–24.
56. Speed D, Cai N, Johnson MR, Nejentsev S, Balding DJ; UCLEB Consortium. Reevaluation of SNP heritability in complex human traits. *Nat Genet*. 2017;49:986–992.
57. Pickrell JK, Berisa T, Liu JZ, Ségurel L, Tung JY, Hinds DA. Erratum: Detection and interpretation of shared genetic influences on 42 human traits. *Nat Genet*. 2016;48:1296.
58. Bustamante CD, Burchard EG, De la Vega FM. Genomics for the world. *Nature*. 2011;475:163–165.
59. Petrovski S, Goldstein DB. Unequal representation of genetic variation across ancestry groups creates healthcare inequality in the application of precision medicine. *Genome Biol*. 2016;17:157.
60. Visscher PM, Wray NR, Zhang Q, et al. 10 Years of GWAS discovery: biology, function, and translation. *Am J Hum Genet*. 2017;101:5–22.