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Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs

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Most psychiatric disorders are moderately to highly heritable. The degree to which genetic variation is unique to individual disorders or shared across disorders is unclear. To examine shared genetic etiology, we use genome-wide genotype data from the Psychiatric Genomics Consortium (PGC) for cases and controls in schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD). We apply univariate and bivariate methods for the estimation of genetic variation within and covariation between disorders. SNPs explained 17–29% of the variance in liability. The genetic correlation calculated using common SNPs was high between schizophrenia and bipolar disorder (0.68 ± 0.04 s.e.), moderate between schizophrenia and major depressive disorder (0.43 ± 0.06 s.e.), bipolar disorder and major depressive disorder (0.47 ± 0.06 s.e.), and ADHD and major depressive disorder (0.32 ± 0.07 s.e.), low between schizophrenia and ASD (0.16 ± 0.06 s.e.) and non-significant for other pairs of disorders as well as between psychiatric disorders and the negative control of Crohn's disease. This empirical evidence of shared genetic etiology for psychiatric disorders can inform nosology and encourages the investigation of common pathophysiologies for related disorders.

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The current classification of psychiatric disorders reflects clinical syndromes with largely unknown etiology and is based on historical descriptions provided by prominent clinicians over the last 125 years. Family (including twin and adoption) studies provide consistent evidence that genetic factors are involved in these syndromes[1]. In principle, family studies allow quantification of the shared genetic etiology of disorders, through the estimation of heritability (the proportion of variance in liability attributable to additive genetic factors), and the genetic correlation between them. However, difficulties in ascertaining samples of sufficient size mean that there are few estimates of genetic correlations. Nonetheless, family studies suggest correlated familial genetic liabilities to bipolar disorder and schizophrenia[2,3], bipolar disorder and major depressive disorder[2,3], and ASD and ADHD[4–6] (**Supplementary Table 1**). Phenotypic and genetic overlap has also been suggested for ASD and schizophrenia[7–11], ASD and bipolar disorder[9], bipolar disorder and ADHD[12], and major depressive disorder and ADHD[13]. Some of these relationships have been supported by recent evidence of shared molecular risk factors[14–16], but the extent of these relationships remains unclear, given the small proportion of risk associated with individually identified variants.

The genomics era provides new opportunities to explore the shared genetic etiology of disorders. Genome-wide association studies (GWAS) assess common genetic polymorphisms (for example, SNPs) at several hundred thousand positions in the genome. The experimental paradigm of GWAS involves the identification of individual variants associated with case-control status[17]. However, these data can also be used to estimate the total variance in liability explained by SNPs (SNP heritability, h^2_{SNP}) through the estimation of genetic similarities (relationships) between cases and controls using SNP genotypes[18,19]. The pairwise genetic relationships that contribute to the estimate are very small, but the large number of pairwise relationships in a case-control sample generates estimates with reasonable precision. The h^2_{SNP} value is an estimate of the total variance in liability to disease explained by SNPs together. Genetic variation is estimated when case-case pairs and control-control pairs are, on average, more similar across the genome than case-control pairs. The h^2_{SNP} value is a lower bound for total narrow-sense heritability, as the former cannot include contributions from causal variants not tagged by the measured SNPs, mostly less common and rare causal variants. A bivariate extension[20] of these genome-wide methods estimates the genetic correlation ($r_{g\ SNP}$) explained by SNPs between case-control samples collected independently for two disorders (Online Methods). The correlation is positive when the cases of one disorder show higher genetic similarity to the cases of the other disorder than they do to their own controls. A negative correlation is possible if the cases of one disorder are less similar across the genome to the cases of another disorder than they are to controls of the other disorder. A genetic correlation of zero is estimated if the genome-wide relationship between cases of one disorder is the same with the cases as with the controls of another disorder. As a correlation, a high $r_{g\ SNP}$ value is achieved when the covariance term between the traits is similar in magnitude to the variance terms. Therefore, we also report the SNP-based coheritability of pairs of disorders, which is the covariance between disorders on the liability scale and allows comparison of the shared liability attributable to SNPs on the same scale as h^2_{SNP}. Here we apply univariate and bivariate methods to the five disorders of the PGC—schizophrenia[21], bipolar disorder[22], major depressive disorder[23], ASD[24,25] and ADHD[26]—analyzed in the

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PGC Cross-Disorder Group association study[25], together with additional ADHD data sets[27–30] (**Table 1**).

RESULTS

SNP heritabilities for the five disorders

In our linear mixed model, we estimate the variance in case-control status explained by SNPs[18] (heritability on the observed scale; CC estimates in **Table 1**). Cases in case-control samples are highly ascertained compared to in the population, and, because the cohorts for different disorders had different proportions of cases, CC estimates were difficult to interpret and compare. For this reason, we report h^2_{SNP} values on the liability scale, in which a linear transformation[18] is applied based on a user-specified estimate of the risk of the disorder in the study base population (disorder risk, *K*). For each disorder, we considered three values of *K* (**Table 1**), and we converted h^2_{SNP} values to predicted risk to first-degree relatives ($\lambda_{1st\ SNP}$) given *K*. We benchmarked the $\lambda_{1st\ SNP}$ risk values to risk to first-degree relatives (λ_{1st}), consistent with estimates of heritability reported from family studies given *K*. Our estimates of $\lambda_{1st\ SNP}$ values were robust, and our estimates of h^2_{SNP} values were reasonably robust, to the likely range of *K* values and show that a key part of the heritabilities or familial risk estimated from family studies is associated with common SNPs. Twice the standard error of estimates approximates the magnitude of the parameter that is possible to detect as being significantly different from zero, given the available sample sizes[31].

SNP coheritabilities and SNP correlations ($r_{g\ SNP}$)

The relationships between disorders were expressed as SNP-based coheritabilities (**Fig. 1**). The $r_{g\ SNP}$ value was high between schizophrenia and bipolar disorder at 0.68 (0.04 standard error (s.e.)), moderate between schizophrenia and major depressive disorder at 0.43 (0.06 s.e.), bipolar disorder and major depressive disorder at 0.47 (0.06 s.e.), and ADHD and major depressive disorder at 0.32 (0.07 s.e.), low between schizophrenia and ASD at 0.16 (0.06 s.e.) and non-significant for other pairs of disorders (**Supplementary Table 1**). The $r_{g\ SNP}$ value for correlation is expected to be equal to the r_g value from family studies only if genetic correlation is the same across the allelic frequency spectrum and if the linkage disequilibrium (LD) between genotyped and causal variants is similar for both disorders. The sample size for ASD was the smallest but still could detect correlations of >|0.18| different from zero in bivariate analyses with all other disorders.

Our results provide empirical evidence that schizophrenia, bipolar disorder and major depressive disorder have shared genetic etiology. Because some schizophrenia and bipolar disorder cohorts were collected in the same clinical environments, we investigated the possible impact of the non-independent collection of schizophrenia and bipolar disorder samples sets but found no significant change in the estimates related to this (**Supplementary Table 2**). The correlation between schizophrenia and ASD was significant but small (0.16, 0.06 s.e.; $P = 0.0071$). In general, our analyses suggested that, whereas common genetic variants contribute to both childhood-onset disorders (ASD and ADHD) and disorders usually diagnosed after childhood (schizophrenia, bipolar disorder and major depressive disorder), the sharing of common variants between these groups is modest.

The pattern of our results (in which pairs of disorders demonstrated genetic overlap) was consistent with polygenic profile score[32] results from PGC cross-disorder analyses[25]. The profile score method uses SNP associations from one disorder to construct a linear predictor in another disorder. The profile scores explained small but significant

Table 1 Univariate analyses: sample description, SNP-based heritabilities and recurrence risk to first-degree relatives

	Schizophrenia	Bipolar disorder	Major depressive disorder	ASD	ADHD
SNPs (imputed)	915,354	995,971	962,093	982,100	917,066
Cases	9,087	6,704	9,041	3,303	4,163
Controls	12,171	9,031	9,381	3,428[a]	12,040[a]
N cohorts					
	17	11	9	8	8
Primary reference	21	22	23	24,25	26–30
CC (s.e.)	0.41 (0.015)	0.44 (0.021)	0.18 (0.017)	0.31 (0.046)	0.25 (0.020)
Disorder risk for the study-based population (disorder risk, *K*)[b]					
K	0.01	0.01	0.15	0.01	0.05
h^2_{SNP} (s.e.)	0.23 (0.008)	0.25 (0.012)	0.21 (0.021)	0.17 (0.025)	0.28 (0.023)
$\lambda_{1st\text{-}SNP}$ (s.e)	2.10 (0.05)	2.23 (0.08)	1.27 (0.03)	1.75 (0.14)	1.71 (0.07)
λ_{1st}	8.8	9.6	1.5	8.7	3.5
Lower bound for disorder risk (*K*)					
K	0.004	0.007	0.1	0.001	0.03
h^2_{SNP} (s.e.)	0.19 (0.007)	0.23 (0.010)	0.19 (0.018)	0.11 (0.017)	0.24 (0.020)
$\lambda_{1st\text{-}SNP}$ (s.e)	2.14 (0.06)	2.25 (0.08)	1.31 (0.03)	1.79 (0.15)	1.77 (0.07)
λ_{1st}	14.4	11.7	1.7	29.4	4.5
Upper bound for disorder risk (*K*)					
K	0.012	0.015	0.2	0.015	0.08
h^2_{SNP} (s.e.)	0.24 (0.009)	0.27 (0.013)	0.23 (0.023)	0.19 (0.028)	0.32 (0.026)
$\lambda_{1st\text{-}SNP}$ (s.e)	2.10 (0.05)	2.20 (0.07)	1.24 (0.02)	1.74 (0.13)	1.65 (0.06)
λ_{1st}	8.0	7.7	1.4	7.0	2.8
Heritability estimated from twin/family studies[61]					
h^2	0.81	0.75	0.37	0.80	0.75

CC is the SNP-based heritability estimated on case-control scale. h^2_{SNP} is the SNP-based heritability on liability scale, given assumed *K*. All estimates of h^2_{SNP} are highly significantly different from zero. $\lambda_{1st\text{-}SNP}$ is the recurrence risk to first-degree relatives calculated from h^2_{SNP} and *K*. λ_{1st} is the recurrence risk to first-degree relatives calculated from h^2 from twin and/or family studies and *K*.

[a]Some cohorts include cases and pseudocontrols, where pseudocontrols are the genomic complements of the cases derived from genotyping of proband-parent trios. [b]Used in **Figures 1** and **3** **Supplementary Tables 1–8**.

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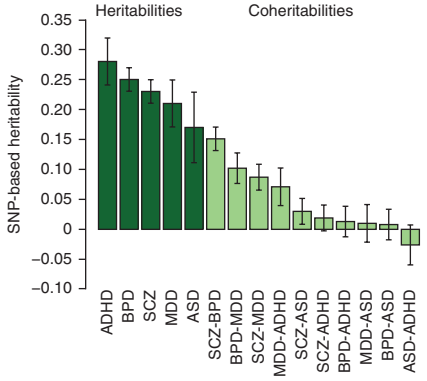

Figure 1 Evidence for genome-wide pleiotropy between psychiatric disorders. Proportion of variance in liability (SNP-based heritability) and proportion of covariance in liability between disorder (SNP-based coheritability) for five major psychiatric disorders. The 95% error bars represent the estimates ± 1.96 s.e. SCZ, schizophrenia; MDD, major depressive disorder; BPD, bipolar disorder.

proportions of the variance[25], expressed as Nagelkerke's R^2 (maximum of 2.5% between schizophrenia and bipolar disorder). To achieve high R^2 values requires accurate estimation of the effect sizes of individual SNPs and depends on the size of the discovery sample. In contrast, our approach uses SNPs to estimate genome-wide similarities between pairs of individuals, resulting in unbiased estimates of the relationships between disorders, with larger sample sizes generating smaller standard errors for the estimates. Our estimates were on the liability scale, allowing direct comparison to genetic parameters estimated in family studies, whereas a genetic interpretation of Nagelkerke's R^2 values is less straightforward[33].

Genomic partitioning of SNP heritabilities and coheritabilities

The heritabilities explained by SNPs can be partitioned according to SNP annotation by the estimation of genetic similarity matrices from multiple, non-overlapping SNP sets. For the five disorders and the five disorder pairs showing significant SNP correlation, we partitioned the h^2_{SNP} and SNP-based coheritabilities explained by functional annotation, allocating SNPs to one of three sets: (i) SNPs in genes preferentially expressed in the central nervous system (CNS+)[34,35], (ii) SNPs in other genes and (iii) SNPs not in genes, with genes defined by 50-kb boundaries extending from their start and stop positions. The SNPs in the CNS+ gene set represented 0.20 of the total set, both in number and megabases of DNA. However, the proportion of the variance explained by SNPs attributable to this SNP set was significantly greater than 0.20 for schizophrenia (0.30; $P = 7.6 \times 10^{-8}$) and bipolar disorder (0.32; $P = 5.4 \times 10^{-6}$) and for schizophrenia and bipolar disorder coheritability (0.37; $P = 8.5 \times 10^{-8}$) (**Fig. 2** and **Supplementary Table 3**). For other disorders or pairs of disorders, the estimates explained by CNS+ SNPs did not differ from the values expected by chance (**Supplementary Table 3**), although their large standard errors suggest that we cannot address this question with precision. For data from the schizophrenia and bipolar disorder pair, we also partitioned the heritabilities explained by SNPs by minor allele frequency (MAF) (**Supplementary Table 4**) and by chromosome (**Supplementary Fig. 1**). The high standard errors on estimates limited interpretation, but the results are consistent with a polygenic architecture comprising many common variants of small effect dispersed throughout the genome. The MAF partitioning suggests that a key part of the variance explained by SNPs is attributable to common causal variants (this was investigated in detail for schizophrenia[35]), but the low contribution to the total variance explained by SNPs with MAF of <0.1 reflects, at least in part, under-representation of SNPs with low MAFs in the analysis (minimum MAF = 0.01) relative to those present in the genome.

Within-disorder heterogeneity

To benchmark the estimates of genetic sharing across disorders, we estimated sharing between data subsets for the same disorder. We split the data for each disorder into two or three independent sets and estimated h^2_{SNP} values for each subset and the SNP-based coheritability between each pair of subsets within a disorder (**Fig. 3a** and **Supplementary Table 5**). The estimates of h^2_{SNP} from the data subsets were typically higher than the h^2_{SNP} estimate from the combined sample; we note that published estimates from individual cohorts of bipolar disorder[18], major depressive disorder[36] and ASD[37] were also higher. Because both traits in these data subset bivariate analyses are for the same disorder, the SNP-based coheritability is also an estimate of h^2_{SNP} for the disorder, but these estimates were generally lower than the estimates of SNP-based heritability from individual data subsets. These results generated SNP-based correlations that were less than 1, sometimes significantly so (**Supplementary Table 5**). The SNP-based correlation between schizophrenia and bipolar disorder (0.68, 0.04 s.e.) was of comparable magnitude to the SNP-based correlations between bipolar disorder data sets (0.63, 0.11 s.e.; 0.88, 0.09 s.e.; and 0.55, 0.10 s.e.; **Fig. 3a,b**, SNP-based coheritabilities), adding further weight to the conclusion that schizophrenia and bipolar disorder may be part of the same etiological spectrum.

The estimates of heritability from both univariate (**Fig. 3a**, red and pink bars) and bivariate (**Fig. 3a**, blue bars) analyses are more heterogeneous for bipolar disorder, major depressive disorder and ADHD than they are for schizophrenia and ASD. Several factors could explain why SNP-based heritabilities from univariate analyses of a single data set could generate higher estimates than bivariate analyses of independent data sets[35], including loss of real signal or dilution of artifacts. Loss of real signal might occur because individual cohorts are more homogeneous, both phenotypically (for example, owing to

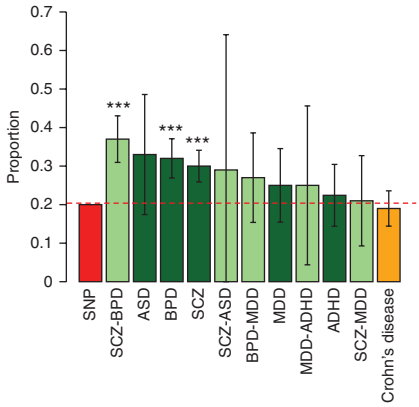

Figure 2 Genomic partitioning of SNP-based heritability and SNP-based coheritability by annotation. Shown is the proportion of SNPs attributable to genes in the CNS+ set (red), the proportion of SNP-based heritability attributable to SNPs in the CNS+ set (dark green), the proportion of SNP-based coheritability attributable to SNPs in the CNS+ set (light green) and the proportion of SNP-based heritability for Crohn's disease attributed to SNPs in the CNS+ set (orange). The 95% error bars represent the estimates ± 1.96 s.e. $^{***}P < 1 \times 10^{-5}$ in a test of whether the proportion of heritability explained by SNPs was equal to the proportion of SNP for the CNS+ set.

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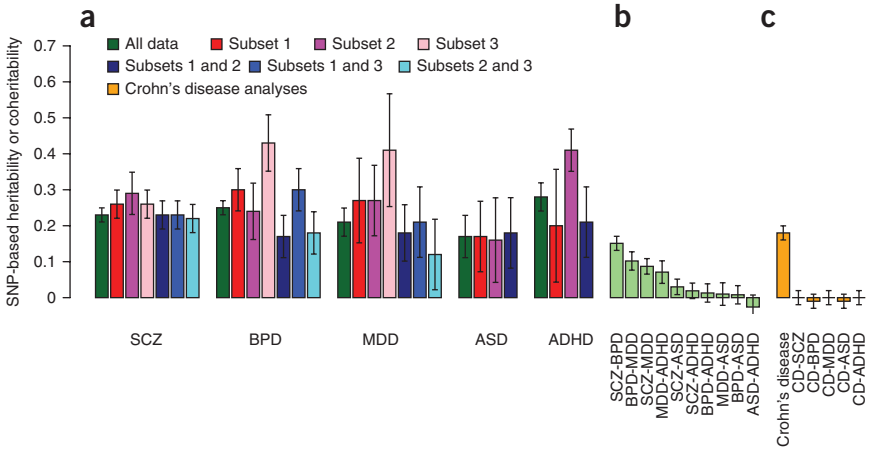

Figure 3 SNP-based heritabilities and coheritabilities. (**a**) For each disorder, SNP-based heritabilities are estimated from univariate analyses of the full data set (dark green) or of sample subsets (red and pink bars). These heritabilities are also estimated from bivariate analyses in which different subsets of the same disorder comprise the two traits (blue). Test of the heterogeneity of estimates, *P* value for Cochran's *Q*: schizophrenia, 0.3; bipolar disorder, 1×10^{-6}; major depressive disorder, 4×10^{-3}; ADHD, 9×10^{-6}; ASD, 0.99; Higgins' I^2: schizophrenia, 21%; bipolar disorder, 86%; major depressive disorder, 71%; ADHD, 91%; ASD, 0%). (**b**) For comparison, the coheritabilities using the full data sets reported in **Figure 1** are shown. (**c**) As a negative control, estimates of coheritabilities with Crohn's disease, a disease not expected to be genetically related to psychiatric disorders, are shown. We estimated 95% error bars using ± 1.96 s.e.

use of the same assessment protocols) and genetically (for example, because LD between causal variants and analyzed SNPs might be higher within than between cohorts). Artifacts could also generate consistent differences in case genotypes relative to control genotypes within case-control data sets. In the derivation of our methodology[18], we emphasized that any factors making SNP genotypes of cases more similar to those of other cases and making the genotypes of controls more similar to those of other controls would produce SNP-based heritability. The fitting as covariates of principal components derived from the SNP data corrects both for population stratification and for genotyping artifacts, but residual population stratification could remain, although this bias should be small[38]. Partitioning SNP-based heritability by chromosome in analyses where each chromosome was fitted individually compared to analyses where all chromosomes were fitted jointly is an empirical strategy to assess residual stratification[35,39], and we found no evidence of this type of stratification here (**Supplementary Fig. 1**). Stringent quality control (as applied here) helps to remove artifacts, but artifactual differences between cases and controls might remain, particularly for data sets in which cases and controls have been genotyped independently[40]. As more data sets accumulate, the contributions from artifacts are diluted because the random directional effects of artifacts (including population stratification) are not consistent across data sets. For this reason, significant SNP-based coheritabilities between subsets of the same disorder are unlikely to reflect artifacts and provide a lower bound for SNP-based heritability.

Pseudocontrols

One strategy adopted in GWAS to guard against artifacts from population stratification is to genotype family trio samples (cases and their parents) and then analyze the data as a case-control sample, with controls generated as genomic complements of the cases (pseudocontrols). ADHD subset 1 and most of the ASD sample comprised case-pseudocontrol samples and, consistent with this strategy limiting the impact of artifacts from population stratification or genotyping, it is noted that the lowest SNP-based heritability for the five psychiatric disorders was for ASD and that the estimate of SNP-based heritability was lower for ADHD subset 1 than for ADHD subset 2. However, under a polygenic model, assortative mating[41] or preferential ascertainment of multiplex families could diminish the expected mean difference in liability between pseudocontrols and cases[37], which would result in an underestimation of SNP-based heritability from case-pseudocontrol compared to case-control analyses and would also result in nonzero estimates of SNP-based heritability from pseudocontrol-control analyses, as shown in analysis of ASD data[37].

SNP-based coheritabilities with Crohn's disease

As a negative control analysis, we conducted bivariate analyses between each of the PGC data sets and Crohn's disease samples from the International IBD Genetics Consortium (IIBDGC)[42]. Although onset of major depressive disorder is not uncommon after diagnosis with Crohn's disease[43] and although gastrointestinal pathology is a common comorbidity with ASD[44], there is no strong evidence of a familial relationship between psychiatric disorders and Crohn's disease. Despite substantial h^2_{SNP} values for Crohn's disease (0.19, 0.01 s.e.), none of the SNP-based coheritabilities with the psychiatric disorders differed significantly from zero (**Fig. 3c**, **Supplementary Table 6** and **Supplementary Note**). Lastly, genomic partitioning by annotation of the variance in Crohn's disease explained by SNPs showed, as expected, no excess of variance attributable to SNPs in the CNS+ gene set (**Fig. 2**). Our results provide no evidence of common genetic pleiotropy in Crohn's disease and ASD, consistent with a non-genetic, for example, microbial[45], explanation for the comorbidity of gastrointestinal symptoms in ASD.

Potential impact of misclassification of disorders

Misclassification among disorders could inflate estimates of genetic correlation and/or coheritability[46]. Indeed, some level of misclassification in psychiatric disorders is expected. For example, longitudinal studies[47,48] of first admissions with psychosis showed that, with long-term follow-up, ~15% of subjects initially diagnosed with bipolar disorder were rediagnosed with schizophrenia, whereas ~4% of schizophrenia diagnoses were reclassified as bipolar disorder. Cases selected for GWAS contributing to PGC are more likely to have achieved a stable diagnosis compared to first-admission cases. However, assuming these levels of misclassification, the genetic correlation between bipolar disorder and schizophrenia for true diagnoses is still high, estimated[46] to be 0.55. Likewise, because a modest proportion of cases diagnosed with major depressive disorder, when followed over time, ultimately meet criteria for bipolar disorder[49], our estimated genetic correlation between these two disorders may be modestly inflated by misclassification. However, if moderate-to-high genetic correlations between the major adult disorders are true, then overlapping symptoms and misdiagnosis among these disorders might be expected. The $r_{g\,SNP}$ value between schizophrenia and major

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depressive disorder is also unlikely to reflect misdiagnosis because misclassification between these disorders is rare[49]. Excluding 5 of the 18 PGC schizophrenia cohorts containing schizoaffective disorder cases[21] (**Supplementary Table 7**) or major depressive disorder cohorts ascertained from community rather than clinical settings (**Supplementary Table 8**) had little impact on $r_{g\,SNP}$ estimates.

DISCUSSION

Our results show direct, empirical, quantified molecular evidence for an important genetic contribution to the five major psychiatric disorders. The h^2_{SNP} estimates for each disorder—schizophrenia, 0.23 (0.01 s.e.), bipolar disorder, 0.25 (0.01 s.e.), major depressive disorder, 0.21 (0.02), ASD, 0.17 (0.02 s.e.) and ADHD, 0.28 (0.02 s.e.)—are considerably less than the heritabilities estimated from family studies (**Table 1**). Yet, they show that common SNPs make an important contribution to the overall variance, implying that additional individual, common SNP associations can be discovered as sample size increases[50]. h^2_{SNP} values are a lower bound for narrow-sense heritability because they exclude contributions from some causal variants (mostly rare variants) not associated with common SNPs. Although SNP-based heritability estimates are similar for major depressive disorder and other disorders, much larger sample sizes will be needed, as high risk for a disorder implies lower power for equal sample size[51]. The h^2_{SNP} values are all lower than those reported for height (0.45, 0.03 s.e.)[39], but the estimates are in the same ballpark as those reported for other complex traits and diseases using the same quality control pipeline, such as for body mass index (BMI) (0.17, 0.03 s.e.)[39], Alzheimer's disease (0.24, 0.03 s.e.), multiple sclerosis (0.30, 0.03 s.e.) and endometriosis (0.26, 0.04 s.e.)[40].

Our results show molecular evidence of the sharing of genetic risk factors across key psychiatric disorders. Traditionally, quantification of the genetic relationship between disorders has been thwarted by the need for cohorts of families or twins assessed for multiple disorders. Problems of achieving genetically informative samples of sufficient size and without associated ascertainment biases for the rarer psychiatric disorders have meant that few studies have produced meaningful estimates of genetic correlations. Notably, our estimates of heritability and genetic correlation are made using very distant genetic relationships between individuals, both within and between disorders, so that shared environmental factors are unlikely to contaminate our estimates. Likewise, our estimates are unlikely to be confounded by non-additive genetic effects, as the coefficients of non-additive genetic variance between very distant relatives are negligible[52].

The estimates of SNP-based genetic correlation ($r_{g\,SNP}$) between disorders reflect the genome-wide pleiotropy of variants tagged by common SNPs, and whether these are the same as correlations across the allelic frequency spectrum may differ between pairs of disorders. For example, a high $r_{g\,SNP}$ value but a low genetic correlation estimated from family studies (r_g) could indicate that the same common variants contribute to genetic susceptibility for both disorders, although the diagnostic-specific variants are less common variants. For this reason, the comparison of $r_{g\,SNP}$ with r_g estimated from family studies is not straightforward. Nonetheless, we benchmark our estimates in this way, calculating the increased risk of disorder B in first-degree relatives of probands with disorder A ($\lambda_{A,B}$) from the r_g SNP value to allow comparison with literature values (**Supplementary Table 1**). A meta-analysis[53] reported increased risk of bipolar disorder in first-degree relatives of probands with schizophrenia compared to first-degree relatives of control probands ($\lambda_{SCZ,BPD}$) of 2.1, which implies a maximum genetic correlation between the disorders of 0.3 (assuming that the disorder risks for schizophrenia and bipolar disorder are both 1% and their heritabilities are 81% and 75%, respectively; **Table 1**). However, a large-scale Swedish family and adoption study[54] estimated the genetic correlation between schizophrenia and bipolar disorder to be +0.60, similar to that found here. Profiling scoring analysis using genome-wide SNPs[32] was the first method to clearly demonstrate a genetic relationship based on molecular data, but quantification as a genetic correlation was not reported. The evidence of shared genetic risk factors for schizophrenia and bipolar disorder was strengthened by our analyses of the CNS+ gene set in which we saw a clear enrichment in variants shared by these two disorders.

Our finding of a substantial $r_{g\,SNP}$ of +0.43 between schizophrenia and major depressive disorder is notable and contrary to conventional wisdom about the independence of familial risk for these disorders. However, because major depressive disorder is common, even a high genetic correlation implies only modest incremental risk. Assuming the disorder risks and heritabilities for schizophrenia and major depressive disorder given in **Table 1**, then the genetic correlation between them of 0.43 predicts increased risk of major depressive disorder in first-degree relatives of probands with schizophrenia compared to first-degree relatives of control probands ($\lambda_{SCZ,MDD}$) of 1.6. In fact, meta-analysis of five interview-based research studies of families are broadly consistent with our results ($\lambda_{SCZ,MDD}$ = 1.5, 95% confidence interval (CI) = 1.2–1.8; **Supplementary Table 9**), suggesting that familial coaggregation of major depressive disorder and schizophrenia reflects genetic effects rather than resulting from living in a family environment that includes a severely ill family member. If replicated by future work, our empirical molecular genetic evidence of a partly shared genetic etiology for schizophrenia and major depressive disorder would have key nosological and research implications, incorporating major depressive disorder as part of a broad psychiatric genetic spectrum. A shared genetic etiology for bipolar disorder and major depressive disorder has been shown in family studies[2,3], but the $r_{g\,SNP}$ value of 0.47 was lower than the estimate of 0.65 from a twin study[55].

Our results show a small but significant $r_{g\,SNP}$ value between schizophrenia and ASD. A lower genetic correlation between schizophrenia and ASD than between schizophrenia and bipolar disorder is consistent with Swedish national epidemiological studies, which reported higher odds ratios in siblings for schizophrenia and bipolar disorder[54] than for schizophrenia and ASD[9]. These results imply a modest overlap of common genetic etiological processes in these two disorders, consistent with emerging evidence from the discovery of copy number variants, in which both shared variants (for example, 15q13.3, 1q2.1 and 17q12 deletions[56,57]) and mutations in the same genes although with different variants (deletions associated with schizophrenia and duplications associated with autism and vice-versa[10]). The small ASD sample size thwarted attempts at further explorative partitioning of the SNP-based coheritability for schizophrenia and ASD.

The lack of overlap between ADHD and ASD is unexpected and is not consistent with family and data linkage studies, which indicate that the two disorders share genetic risk factors[5,6,58,59]. Some rare copy number variants are seen in both disorders[16]. As noted above, the use of pseudocontrols for many of the ASD and ADHD cohorts may affect all results for these disorders. Ideally, we would investigate the impact of pseudocontrols, given the hierarchical diagnostic system (autism but not autism spectrum is an exclusion criterion for most ADHD data sets), on estimates of SNP-based coheritability, but the small ASD sample size prohibits such analyses. We also found no overlap between ADHD and bipolar disorder, despite support from meta-analysis results of an increased risk for ADHD in relatives of individuals with bipolar disorder I (a subtype of bipolar disorder with

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more extreme manic symptoms than the other major bipolar disorder subtype) and an increased risk for bipolar disorder I in relatives of individuals with ADHD[12]. These findings could mean that the familial link between the two disorders is mediated by environmental risk factors or that shared genetic factors are not part of the common allelic spectrum. Alternatively, the etiological link between ADHD and bipolar disorder might be limited to bipolar disorder I or early-onset bipolar disorder[12], which, therefore, is difficult for us to detect. Our finding of genetic overlap between ADHD and major depressive disorder is consistent with evidence from studies showing increased rates of ADHD in the families of depressed probands and increased rates of depression in families of probands with ADHD[12,13].

Our results should be interpreted in the context of four potentially important methodological limitations. First, any artifacts that make SNP genotypes more similar between cases than between cases and controls could inflate estimates of SNP-based heritability[18], but to a much lesser extent for SNP-based coheritability. Second, the sample sizes varied considerably across the five disorders. Although h^2_{SNP} values are expected to be unbiased, estimates from smaller samples are accompanied by larger standard errors, blurring their interpretation. Third, although applying similar diagnostic criteria, the clinical methods of ascertainment and the specific study protocols, including which specific interview instruments were employed, varied across sites. We cannot now determine the degree to which our results might have been influenced by between-site differences in the kinds of patients seen or in their assessments. Fourth, by combining samples from geographic regions, contributions from less common associated variants specific to particular populations are diluted compared to what would have been achieved if the same sample size had been ascertained from a single homogeneous population.

In summary, we report SNP-based heritabilities that are significantly greater than zero for all five disorders studied. We have used the largest psychiatric GWAS data sets currently available, and our results provide key pointers for future studies. Our results demonstrate that the dearth of significant associations from psychiatric GWAS so far, particularly for major depressive disorder, ASD and ADHD, reflects lack of power to detect common associated variants of small effect rather than the absence of such variants. Hence, as sample sizes increase, the success afforded to other complex genetic diseases[50] in increasing the understanding of their etiologies is achievable for psychiatric disorders, as is already being shown for schizophrenia[60]. We also provide evidence of substantial sharing of the genetic risk variants tagged by SNPs between schizophrenia and bipolar disorder, bipolar disorder and major depressive disorder, schizophrenia and major depressive disorder, ADHD and major depressive disorder, and, to a lesser extent, between schizophrenia and ASD. Our results will likely contribute to the efforts now under way to base psychiatric nosology on a firmer empirical footing. Furthermore, they will encourage investigations into shared pathophysiologies across disorders, including potential clarification of common therapeutic mechanisms.

URLs. PGC, https://pgc.unc.edu/; Genetic Cluster Computer, http://www.geneticcluster.org/; GCTA, http://www.complextraitgenomics.com/software/gcta/.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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The authors declare no competing financial interests.

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ONLINE METHODS

Data and quality control. A summary of the data available for analysis is listed in **Table 1** and comprise data used in the PGC–Cross-Disorder Group analysis[25] together with newly available ADHD samples[27–30]. Data upload to the PGC central server follows strict guidelines to ensure local ethics committee approval for all contributed data (PGC; see URLs). Data from all study cohorts were processed through the stringent PGC pipeline[25]. Imputation of autosomal SNPs used CEU (Utah residents of Northern and Western European ancestry) and TSI (Toscani in Italia) HapMap Phase 3 data as the reference panel[21]. For each analysis (univariate or bivariate), we retained only SNPs that had MAF of >0.01 and imputation R^2 of >0.6 in all contributing cohort subsamples (imputation cohorts). Different quality control strategies were investigated in detail for the raw and PGC imputed genotyped data of the International Schizophrenia Consortium, a subset of the PGC schizophrenia sample[35]. The Crohn's disease samples from IIBDGC[42] were processed through the same quality control and imputation pipeline as the PGC data, generating a data set of 5,054 cases and 11,496 controls from 6 imputation cohorts.

In each analysis, individuals were excluded to ensure that all cases and controls were completely unrelated in the classical sense, so that no pairs of individuals had a genome-wide similarity relationship greater than 0.05 (equivalent to about second cousins). This procedure removed ancestry outliers (over and above those already removed in the PGC quality control pipeline; **Supplementary Fig. 2**) and ensured that overlapping control sets were allocated randomly between disorders in the bivariate analyses. Exact numbers of cases and controls used in each analysis are listed in **Supplementary Tables 1–8**.

Linear mixed model for estimation of SNP-based heritability and coheritability. We used the methods presented in Lee *et al.*[18,35]. Briefly, we estimated the variance in case-control status explained by all SNPs using a linear mixed model

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{g} + \mathbf{e}$$

where $\mathbf{y}$ is a vector of case ($\mathbf{y} = 1$) or control ($\mathbf{y} = 0$) status (the observed scale), β is a vector for fixed effects of the overall mean (intercept), sex, sample cohort and 20 ancestry principal components, $\mathbf{g}$ is the vector of random additive genetic effects based on aggregate SNP information and $\mathbf{e}$ is a vector of random error effects. $\mathbf{X}$ is an incidence matrix for the fixed effects relating these effects to individuals. The variance structure of phenotypic observations is

$$\mathbf{V}(\mathbf{y}) = \mathbf{V} = \mathbf{A}\sigma_g^2 + \mathbf{I}\sigma_e^2$$

where σ_g^2 is additive genetic variance tagged by the SNPs, σ_e^2 is error variance, $\mathbf{A}$ is the realized similarity relationship matrix estimated from SNP data[19] and $\mathbf{I}$ is an identity matrix. All variances were estimated on the observed case-control scale and were transformed to the liability scale, which requires specification of the disorder risk K to estimate h^2_{SNP}. Risk to first-degree relatives was calculated from K and h^2_{SNP} on the basis of the liability threshold model[62].

The bivariate analyses used a bivariate extension of equation (1) (ref. 20). The two traits were measured in different individuals, but the equations were related through the genome-wide similarities estimated from SNPs. Genetic and residual variances for the traits were estimated as well as the genetic covariance σ_{g12}. The genetic correlation coefficient (r_g) was calculated by $(\sigma_{g12}/(\sigma_{g1}\sigma_{g2}))$ and is approximately the same on the observed case-control scale as on the liability scale[20] and so does not depend on specifications of K. The covariance σ_{g12} can be transformed to the liability scale, accounting for assumed disorder risks and proportions of cases and controls in the samples of each disorder[20], and it equals the coheritability[52] $r_g h_1 h_2$. We used the approximated χ^2 test statistic (estimate/s.e.)^2 to test whether estimates were significantly different from zero. We checked that this simple approximation agreed well with the more formal and computer-intensive likelihood ratio test for several examples. Heterogeneity of SNP-based heritabilities was tested using Cochran's Q (ref. 63) and Higgins' I^2 (ref. 64) values, acknowledging potential non-independence of the six estimates (three subsets plus three subset pairs).

Disorder risk for the study-based population (disorder risk, *K*). Estimates of h^2_{SNP} and SNP-based coheritability from the linear model are on the case-control scale and so depend partly on the proportion of cases and controls in the sample. Transformation to the liability scale allowed benchmarking of h^2_{SNP} to estimates of heritability from family studies, and the transformation accounts for the proportion of cases in the sample and depends on the assumed disorder risk (K). The appropriate choice of K depends on the definitions of both the phenotype (including ascertainment strategy) and the population, which might differ between cohorts. We considered lower and upper bounds for K in **Table 1** to cover the range of possible values. $r_{g\,\mathrm{SNP}}$ estimates are independent of scale and hence are not dependent on the choice of K.

Genome-partitioning linear mixed model. We partitioned the variance explained by the SNPs in several ways. For example, for the univariate linear model

$$\mathbf{y} = \mathbf{X}\beta + \sum_{t=1}^{n} g_t + \mathbf{e}$$

with

$$\mathbf{V} = \sum_{t=1}^{n} \mathbf{A}_t \sigma^2_{g_t} + \mathbf{I}\sigma_e^2$$

where n is the number of subsets from any non-overlapping partitioning of SNPs; $n = 22$ for the joint analysis by chromosome, $n = 5$ for the analysis by MAF bin and $n = 3$ for the analysis of SNP by gene annotation in which SNPs were classed as CNS+ genes (2,725 genes representing 547 Mb), SNPs in other genes (14,804 genes representing 1,069 Mb) and the remaining SNPs not in genes. Gene boundaries were set at ± 50 kb from the 5′ and 3′ UTRs of each gene, and CNS+ genes were the four sets identified by Raychaudhuri *et al.*[34] (one set comprised genes expressed preferentially in the brain compared to other tissues, and the other three sets comprised genes annotated to be involved in neuronal activity, learning and synapses). The CNS+ set was found to explain more of the SNP-based heritability than expected by chance for schizophrenia[35]. All methods have been implemented into the freely available GCTA software[65].

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