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

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2013 Nature Genetics 45, 984-994

This is the reformatted manuscript submitted - prior to publication in its final form
at doi: 10.1038/ng.2711

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Abstract

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.

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 estim-ation of genetic

similarities (relation-ships) 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 heritabil-ity, 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 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 pro-portions 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 λ_{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 λ_{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 coherit-abilities (**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 proportions of the variance [25], expressed

Table 1

Univariate analyses: sample description, SN**P-based heritabilities and recurrence risk to first-degree relatives**

	Schizophrenia	**Bipolar disorder**	**Major depressive dis.**	**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*. λ1st 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**

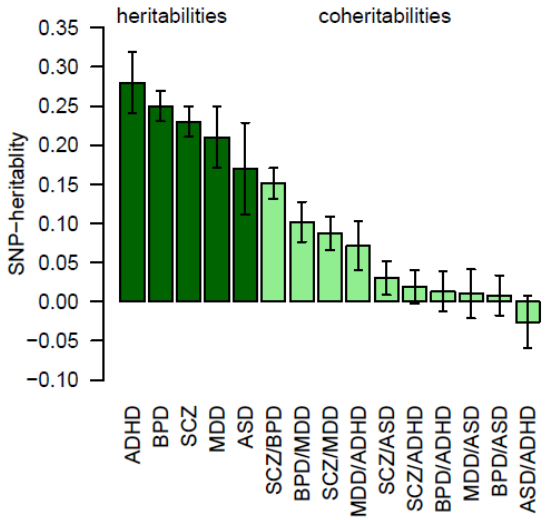

Figure 1 Evidence for genome-wide pleiotropy between psychiatric disorders. Proportion of variance in liability (SNP-based heritability) and proportion of covariance in liability between disorder (SNP-based coheritability) for five major psychiatric disorders. The 95% error bars represent the estimates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

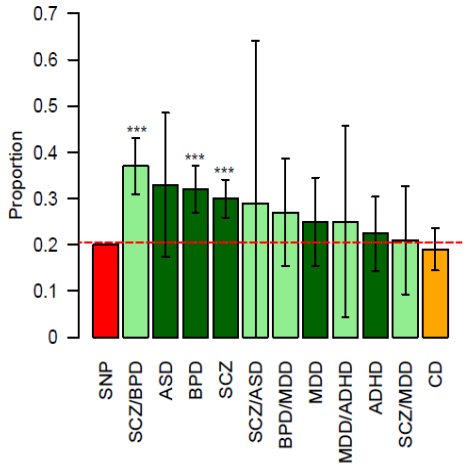

Figure 2 Genomic partitioning of SNP-based heritability and SNP-based coheritability by annotation. Shown is the proportion of SNPs attributable to genes in the CNS+ set (red), the proportion of SNP-based heritability attributable to SNPs in the CNS+ set (dark green), the proportion of SNP-based coheritability 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.

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 SNPs to estimate genome-wide similar-ities between pairs of individuals, resulting in unbiased estimates of the relationships between disorders, with larger sample sizes generating smaller stand-ard errors for the estimates. Our estim-ates 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].depends on the size of the discovery sample. In contrast, our approach uses

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; $P = 5.4$

× 10^{-6}) and for schizophrenia and bipolar disorder coheritability (0.37; P = 8.5 × 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*SNP2 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 sets35, 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 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 methodology18, we emphasized that any factors making SNP genotypes of cases more similar to those of other cases and making the genotypes

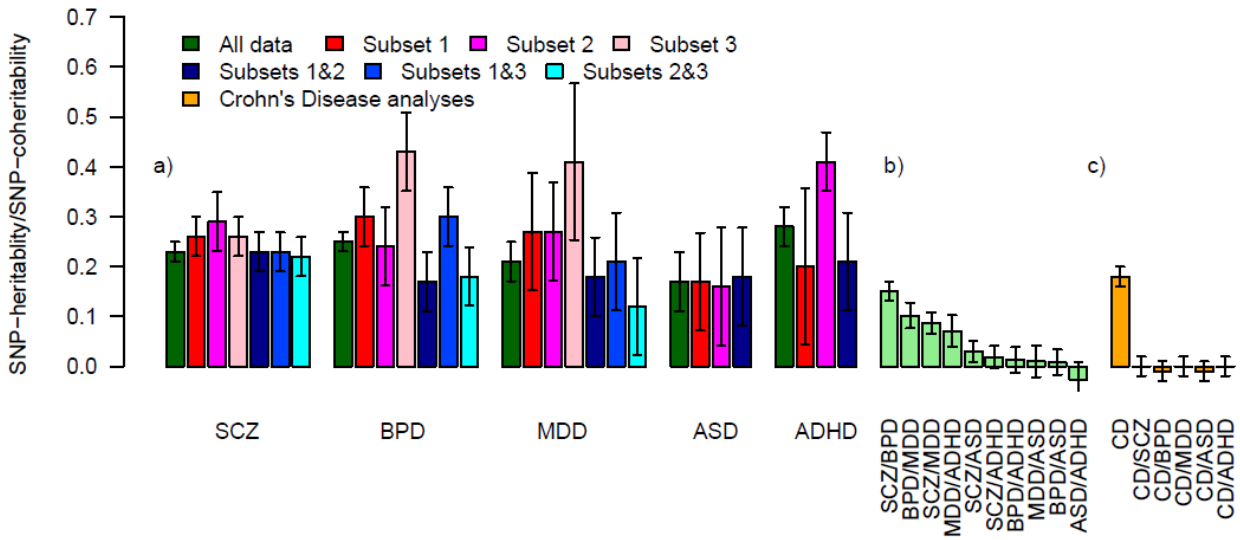

Figure 3 SNP-based heritabilities and coheritabilities. (**a**) For each disorder, SNP-based heritabilities are estimated from univariate analyses of the full data set (dark green) or of sample subsets (red and pink bars). These heritabilities are also estimated from bivariate analyses in which different 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.

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 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 size51. 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 compari-son 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 SNPs32 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 co-aggregation 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-versa10). 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 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 schizo-phrenia[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/.

Acknowledgments

This research was directly supported by the Australian Research Council (FT0991360 and DE130100614) and the Australian National Health and Medical Research Council (613608, 1011506 and 1047956). The PGC Cross-Disorder Group is supported by National Institute of Mental Health (NIMH) grant U01 MH085520. Statistical analyses were carried out on the Genetic Cluster Computer (see URLs), which is financially supported by the Netherlands Scien-tific Organization (NOW; 480-05-003; principal investigator D.P.) along with a supplement from the Dutch Brain Foundation and VU University. data, without which this research would not be possible; grant numbers are listed in primary PGC publications or in the Supplementary Note Numerous (>100) grants from government agencies along with substantial private and foundation support worldwide enabled the collection of phenotype and genotype**.**

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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 contrib-uted 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 IIBDGC42 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 individ-uals had a genome-wide similarity relation-ship 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

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

where **y** is a vector of case (**y** = 1) or control (**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, **g** is the vector of random additive genetic effects based on aggregate SNP information and **e** is a vector of random error effects. **X** is an incidence matrix for the fixed effects relating these effects to individuals. The variance structure of phenotypic observations is

$$\mathbf{V(y) = V = A}\sigma^2_{\mathbf{g}} \mathbf{+ I}\sigma^2_{\mathbf{e}}$$

where s^2_g is additive genetic variance tagged by the SNPs, s^2_e is error variance, **A** is the realized similarity relationship matrix estimated from SNP data[19] and **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 hSNP2. 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 $\chi 2$ 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' $I2$ (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 ascertain-ment strategy) and the population, which might differ between cohorts. We consid-ered lower and upper bounds for *K* in **Table 1** to cover the range of possible values. $r_{g\ SNP}$ 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

$$\mathbf{Y} = \mathbf{X\beta} + \sum_{t=1}^{n} \boldsymbol{g}_t + \mathbf{e}$$

with

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

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 schizo-phrenia[35]. All methods have been imple-mented into the freely available GCTA software[65].

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Supplementary Information

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

Supplementary Tables

Supplementary Figures

Abbreviations:

SCZ- schizophrenia, BPD- bipolar disorder, MDD – major depressive disorder, ASD- autism spectrum disorders, ADHD- attention deficit hyperactivity disorder, CD-Crohn's Disease

Supplementary Table 1. Bivariate analyses

	Trait 1/ Trait 2				
	SCZ/BPD	**SCZ/MDD**	**SCZ/ASD**	**SCZ/ADHD**	**BPD/MDD**
SNPs	909307	885448	896627	778235	938610
Cases	9032/6664	9051/8998	9111/3226	9013/4108	6665/8997
Controls	7980/5258	10385/7823	12146/3308	10115/9936	7408/7680
SNP-h^2 Trait 1[a]	0.22 (0.01)	0.21 (0.01)	0.23 (0.01)	0.23 (0.01)	0.23 (0.01)
SNP-h^2 Trait 2[a]	0.22 (0.01)	0.19 (0.02)	0.16 (0.02)	0.23 (0.02)	0.20 (0.02)
Covariance[b]	0.151 (0.010)	0.087 (0.011)	0.030 (0.011)	0.019 (0.011)	0.102 (0.013)
SNP-r_g (SE)	0.68 (0.04)	0.43 (0.06)	0.16 (0.06)	0.08 (0.05)	0.47 (0.06)
λ_{1st}-cov(SE)	1.7 (0.05)	1.2 (0.05)	1.2 (0.03)	1.1 (0.03)	1.2 (0.00)
λ_{1st}-r_g	4.7	1.6	1.5	1.2	1.6
p[c]	**<e-16** M-A: 2.1[1], Offspring[2,e]: 2.4,5.2,4.5,6.0	**6.0e-15** M-A [f]: 1.5	**0.0071** Parent[3]: 2.9 Sibling[3]: 2.6	0.072 Parent [4,g]: > 1	**1.5e-14**
literature[d] λ_{1st}	Sib[2,e]: 3.9,3.7,3.9,5.0		Sibling ASD/ADHD)[6]: 2.4		M-A[5,h]: 3.1,2.7
literature r_g	0.60[2,j]	N/A	N/A	N/A	0.65[7,j]

	Trait 1/ Trait 2				
	BPD/ASD	**BPD/ADHD**	**MDD/ASD**	**MDD/ADHD**	**ASD/ADHD**
SNPs	952858	834238	927731	813902	827620
Cases	6704/3207	6656/4099	9031/3239	8936/4098	3156/4181
Controls	9030/3294	7041/9873	9370/3331	8668/11233	3254/12022
SNP-h^2 Trait 1[a]	0.24 (0.01)	0.21 (0.01)	0.20 (0.02)	0.19 (0.02)	0.15 (0.03)
SNP-h^2 Trait 2[a]	0.17 (0.03)	0.26 (0.02)	0.17 (0.03)	0.26 (0.02)	0.25 (0.02)
Covariance[b]	0.008 (0.013)	0.013 (0.013)	0.010 (0.016)	0.071 (0.016)	-0.026 (0.017)
SNP-r_g (SE)	0.04 (0.06)	0.05 (0.05)	0.05 (0.09)	0.32 (0.07)	-0.13 (0.09)
λ_{1st}-cov(SE)	1.0 (0.04)	1.0 (0.05)	1.0 (0.03)	1.2 (0.04)	0.9 (0.04)
λ_{1st}-r_g	1.1	1.1	1.1	1.3	<1
p[c]	p = 0.53	p = 0.31	p = 0.53	**p = 6.8e-06**	p = 0.13
literature[d] λ_{1st}	parent[3]: 1.9 sibling[3]:2.5	M-A BPD I[8,k]: 2.8,2.6,2.2,2.1	N/A	M-A[9,l] 1.6, 1.9	N/A
literature r_g	N/A	N/A	N/A	Q[10,m]: 0.78, 0.67	0.87[11] Q[12]:"56% of phenotypic correlation of 0.63 attributable to shared genetic influences" Q[13]: male 0.41 Q[13]: fem 0.23 Q[14]: male 0.57 Q[14]: fem 0.56 Q[15]: 0.72

(Notes on the next page)

SNP-h^2-SNP-heritability on the liability scale, *rg* SNP genetic correlation, $\lambda_{1st\text{-}cov}$: increased risk to 1st degree relatives attributable to SNPs calculated from the SNP-coheritability and *K* values, i.e. genetic covariance = SNP-coheritability , $\lambda_{1st\text{-}rg}$ increased risk to 1st degree relatives calculated from the SNP-rg, *K* values and heritability estimates from family studies listed in Table 1. This provides a benchmark for comparison with literature estimates under the assumption that the genetic correlation is the same across the allelic spectrum.

Abbreviations: M-A: meta-analysis, Q: quantitative scores, N/A to our knowledge.

a: The estimates of SNP-h^2estimated from the bivariate analyses differ slightly from the univariate estimates, because the sample sets differ (overlapping samples, removed and QC based on pairwise relationship), SNP sets differ (imputation R2 > 0.6 in all imputation cohorts in the analysis), as well as because the maximum likelihood estimate in the bivariate analysis will optimize based on information from both disorders.
b: Covariance or SNP-coheritability
c: p values of H0: SNP-coheritability = 0.
d: Where possible we have selected meta-analyses or large studies. Note that these estimates may reflect but genetic and environmental factors that increase risk to relatives
e: The four estimates from this study of national records in Sweden are 1) risk of SCZ in relative when proband has BPD 2) risk of BPD in relative when proband has SCZ 3) risk of SCZ in adopted away relatives when proband has BPD, 4) risk of BPD in adopted away relatives when proband has SCZ
f: See supplementary Table 9.
g: Small study of 29 children who were 1_{st}-degree relatives of SCZ and 30 healthy controls
h: 3.1= Risk of BPD in relatives of probands with unipolar disorder (MDD)/Risk of BPD in controls 2.2%/0.7%, 2.7=Risk of unipolar disorder(MDD) in relatives of probands with BPD/Risk of MDD in controls 14.1%/5.2%.
i: Swedish national study
j: 67 twin pairs proband with BPD and 177 twin pairs proband with unipolar disorder (MDDD).
k: The meta-analysis study considered only bipolar disorder 1 (BPDI). The four estimates are: 1) Risk of ADHD in 1_{st} degree relatives of BPD1 child probands 2) Risk of ADHD in 1_{st} degree relatives of BPD1 adult probands 3) Risk of BPD1 in 1_{st} degree relatives of ADHD adult probands 4) Risk of BPD1 in 1_{st} degree relatives of ADHD child probands
l: 1.6 = 13.2% rate of depression in relatives of ADHD children/ 8.2% rate of depression in relatives of control children. 1.9 = 12.4% of children of depressed parents had ADHD/6.6% of children of control parents had ADHD
m: 645 twin pairs, birth cohort, genetic correlation based on quantitative scores of hyperactivity and mood.

Supplementary Table 2.

Bivariate analysis for SCZ/BPD limiting data sets to those that have been collected totally independently.

Trait 1/ trait 2	SNPs	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	Covariance OR coherit-ability SE)
SCZ/BPD	909307	6968/5589	5392/4445	0.23 (0.01)	0.23 (0.02)	0.59 (0.05)	0.14 (0.01)

h^2- SNP-heritability on the liability scale, r_g SNP genetic correlation

SCZ data sets included: ISC- Aberdeen, ISC-Cardiff (Bulgarian), ISC-Dublin, ISC-Edinburgh, ISC-Portugal, ISC-SW1, ISC-SW2, MGS, SGENE-Copenhagen, SGENE-Munich, SGENE-UCLA, Zucker Hillside.

SCZ data sets excluded: Cardiff UK, CATIE, ISC-London, SGENE-Bonn, SGENE-TOP3 (data set names as in[16])

BPD data sets included: BOMA, GSK, STEP1, STEP2, TOP, UCL, Pritzker, and WTCCC

BPD data sets excluded: GAIN/BiGS, Dublin, Edinburgh (data set names as in[17])

Supplementary Table 3.

Genomic partitioning by annotation

Estimated proportion of variance in liability (SNP-heritability, h^2) explained by SNPs in CNS+ genes other genes and non-genes for the five disorders from univariate analyses and SNP - coheritability from bivariate analyses for the 5 pairs of disorders with significant genome-wide SNP correlations in Supplementary Table 2.

			h^2(SE) accounted for by SNPs attributed to: *h*			
			No. SNPs			
	Cases	Controls	CNS+ (2725 Genes	Other 14804 genes	Not	Proportion in CNS+(SE) p-value
SCZ	9087	12171	0.071 (0.005) 195044	0.079 (0.006) 355562	0.076 (0.006) 364748	0.30(0.021) **7.6 e-08**
BPD	6704	9031	0.078 (0.007) 213226	0.103 (0.009) 387545	0.065 (0.008) 395200	0.32(0.026) **5.4e-06**
MDD	9041	9381	0.053 (0.011) 206133	0.079 (0.014) 373115	0.081 (0.014) 381845	0.25 (0.049) 0.32
ASD	3303	3428	0.055 (0.014) 209785	0.047 (0.017) 381897	0.066 (0.018) 390418	0.33 (0.080) 0.10
ADHD	4163	12040	0.063 (0.013) 197342	0.096 (0.016) 357278	0.122 (0.016) 362446	0.22 (0.041) 0.54
SCZ/BPD	9032/6664	7980/5258	0.055 (0.005) 193601	0.043 (0.006) 353120	0.052 (0.007) 362586	0.37 (0.031) **8.5e-08**
SCZ/MDD	9051/8998	10385/7823	0.018 (0.006) 188535	0.029 (0.007) 343565	0.039 (0.008) 353348	0.21 (0.060) 0.92
BPD/MDD	6665/8997	7408/7680	0.028 (0.007) 200626	0.029 (0.009) 364387	0.045 (0.009) 373597	0.27 (0.059) 0.23
SCZ/ASD	9111/3226	12146/3308	0.009 (0.006) 190530	0.013 (0.008) 348023	0.009 (0.008) 358074	0.29 (0.179) 0.53
MDD/ADHD	8936/4098	8668/11233	0.018 (0.008) 173665	0.024 (0.010) 315210	0.028 (0.011) 325027	0.25 (0.105) 0.63
CD	5054	11496	0.033 (0.005) 216951	0.124 (0.006) 393544	0.027 (0.006) 397565	0.19 (0.023) 0.40

The p-values test H0: proportion of variance explained by SNPs in CNS+ genes = v, where v is the proportion of SNPs in the analysis attributed to the CNS+ genes.

Supplementary Table 4.

Genomic partitioning by minor allele frequency (MAF) of SNPs for SCZ/BPD analysis

		h^2 (SE)		rg (SE)	Covariance OR coherit-ability (SE)
MAF	no. SNP	SCZ	BPD		
<0.1	156900	0.02 (0.01)	0.02 (0.01)	0.59 (0.34)	0.004 (0.002)
0.1<<0.2	208042	0.06 (0.01)	0.04 (0.01)	0.62 (0.17)	0.011 (0.003)
0.2<<0.3	190274	0.05 (0.01)	0.05 (0.01)	0.70 (0.15)	0.014 (0.003)
0.3<<0.4	180764	0.05 (0.01)	0.05 (0.01)	0.68 (0.16)	0.013 (0.003)
0.4<<0.5	173327	0.05 (0.01)	0.05 (0.01)	0.77 (0.14)	0.016 (0.002)
Sum	909307	0.22	0.21		

h^2_{SNP}-heritability on the liability scale, r_g SNP genetic correlation

Supplementary Table 5
Univariate and bivariate analyses for sub-cohorts
A: Univariate analyses for sub-cohorts

Sub---cohort	SNPs	Cases	Controls	h^2_{ccc}(SE) observed scale case/control	h^2(SE) liability scale	h^2(SE) liability scale
		SCZ			K=0.01	K=0.005
Sub1	915354	3220	3445	0.49 (0.04)	0.27 (0.02)	0.23 (0.02)
Sub2	915354	2571	2419	0.55 (0.06)	0.31 (0.03)	0.26 (0.03)
Sub3	915354	3296	6307	0.44 (0.03)	0.27 (0.02)	0.23 (0.02)
		BPD			K=0.01	K=0.005
Sub1	995971	2465	4058	0.49 (0.05)	0.30 (0.03)	0.25 (0.02)
Sub2	995971	2540	2058	0.44 (0.07)	0.24 (0.04)	0.21 (0.03)
Sub3	995971	1699	2915	0.73 (0.06)	0.43 (0.04)	0.37 (0.03)
		MDD			K=0.15	K=0.07
Sub1	962093	3077	3420	0.22 (0.05)	0.27 (0.06)	0.21 (0.04)
Sub2	962093	3785	3289	0.23 (0.04)	0.27 (0.05)	0.22 (0.04)
Sub3	962093	2179	2672	0.34 (0.06)	0.41 (0.08)	0.32 (0.06)
		ADHD			K=0.05	
Sub1	917066	1736	1766	0.23 (0.09)	0.20 (0.08)	
Sub2	917066	2427	10274	0.30 (0.03)	0.41 (0.03)	
		ASD			K=0.01	
Sub1	982100	1893	1888	0.31 (0.08)	0.17 (0.05)	
Sub2	982100	1540	1540	0.29 (0.10)	0.16 (0.06)	

K lifetime probability of disorder.
Subset membership using the cohort names given in the primary PGC publications.
SCZ
Sub1: ISC-Aberdeen, ISC-Cardiff, ISC-Dublin, ISC-Edinburgh, ISC-London, ISC-Portugal, ISC-SW1, ISC-SW2
Sub2: MGS
Sub3: SGENE-Bonn, SGENE-CH, SGENE-MUN, SGENE-TOP3, SGENE-UCLA, Cardiff, CATIE, Zucker Hillside
BPD
Sub1: BOMA, GSK, TOP, UCL, Edinburgh, Dublin
Sub2: GAIN&BIGS, STEP1, STEP2, Pritzer
Sub3: WTCCC
MDD
Sub1: GAIN, MDD2000-QIMR_610, MDD2000-QIMR_317
Sub2: GenRed, STAR*D, RADIANT (UK)
Sub3: RADIANT(GER)+Bonn/Mann., MPIP, GSK
ADHD
Sub1: CHOP, IMAGE, PUWMa included in [18] and a Canadian cohort[19] (all trio samples used to generate cases and pseudo controls)
Sub2: IMAGEII from[18] and samples from UK[20], Germany[21] and Spain (genotyped on Illumina Omni1 and with clinical cohort described in [22]) (all case-control samples).
ASD
Sub1: AGP, AGP2
Sub2: CHOP, Finland, JHU, MonBos, SSC in two imputation cohorts (Illumina Infinium 1Mv3 (duo) and Illumina Infinium 1Mv1).

B: Bivariate analyses for sub-cohorts

Trait 1/ Trait 2	SNPs	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	Covariance OR coherit-ability SE)
			SCZ, K=0.01				
Sub1/Sub2	915354	3220/2571	3445/2419	0.26 (0.02)	0.29 (0.03)	0.84 (0.09)	0.23 (0.02)
Sub1/Sub3	915354	3220/3296	3445/6307	0.26 (0.02)	0.27 (0.02)	0.89 (0.07)	0.23 (0.02)
Sub2/Sub3	915354	2571/3296	2419/6307	0.30 (0.03)	0.26 (0.02)	0.79 (0.08)	0.22 (0.02)
			BPD, K =0.01				
Sub1/Sub2	99597	2465/2540	4058/2058	0.30 (0.03)	0.24 (0.04)	0.63 (0.11)	0.17 (0.03)
Sub1/Sub3	99597	2465/1699	4058/2915	0.28 (0.03)	0.42 (0.04)	0.88 (0.09)	0.30 (0.03)
Sub2/Sub3	99597	2540/1699	2058/2915	0.24 (0.04)	0.43 (0.04)	0.55 (0.10)	0.18 (0.03)
			MDD, K=0.15				
Sub1/Sub2	962093	3077/3785	3420/3289	0.27 (0.06)	0.27 (0.05)	0.65 (0.16)	0.18 (0.04)
Sub1/Sub3	962093	3077/2179	3420/2672	0.27 (0.06)	0.41 (0.07)	0.63 (0.16)	0.21 (0.05)
Sub2/Sub3	962093	3785/2179	3289/2672	0.27 (0.05)	0.40 (0.07)	0.38 (0.14)	0.12 (0.05)
			ADHD, K=0.05				
Sub1/Sub2	917066	1736/2427	1766/10274	0.21 (0.07)	0.41 (0.03)	0.71 (0.17)	0.21 (0.05)
			ASD, K=0.01				
Sub1/Sub2	982100	1893/1410	1888/1540	0.16 (0.05)	0.15 (0.06)	1.17 (0.34)	0.18 (0.05)

h^2 SNP-heritability on the liability scale, r_g SNP genetic correlation

Supplementary Table 6.

Bivariate analyses between psychiatric disorders and Crohn's Disease (CD) control

a: This analysis used the CD sample (WCD) from the Wellcome Trust Case Control Consortium[23] (WTCCC) and Subsets 1 and 2 from BPD. Bipolar subset 3 (BPD3) was the WTCCC BPD sample. Since WCD and BPD3 use the same controls, the significant covariance between BP1 & BP3 and BP2 & BP3 compared to no covariance for BPD1+BPD2 & WCD reflects genome-wide genetic similarity between the BPD cases. In all our analyses highly related individuals are excluded so that in the CD/BPD analysis WTCCC controls are randomly shared between the CD and BPD sets.

Trait 1/ Trait 2	SNPs	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	Covariance OR coherit-ability SE)
CD/SCZ	899550	4793/9074	9125/10224	0.18 (0.01)	0.23 (0.01)	-0.01 (0.03)	0.00 (0.01) p = 0.70
CD/BPD	960646	4810/6688	09143/7091	0.18 (0.01)	.23 (0.01)	-0.05 (0.04)	-0.01 (0.01) p = 0.22
CD/MDD	942496	4827/9019	10600/8896	0.18 (0.01)	0.20 (0.02)	0.02 (0.05)	0.00 (0.01) p = 0.70
CD/ASD	954950	5019/3180	11491/3271	0.19 (0.01)	0.16 (0.03)	-0.07 (0.06)	-0.011 (0.01) p = 0.31
CD/ADHD	843722	4839/4166	9501/10193	0.16 (0.01)	0.26 (0.02)	-0.02 (0.05)	0.00 (0.01) p = 0.71
WCD/BPD[a]	960646	1671/4996	1494/5685	0.24 (0.03)	0.21 (0.02)	0.03 (0.08)	0.01 (0.02) p = 0.74

a: This analysis used the CD sample (WCD) from the Wellcome Trust Case Control Consortium[23] (WTCCC) and Subsets 1 and 2 from BPD. Bipolar subset 3 (BPD3) was the WTCCC BPD sample. Since WCD and BPD3 use the same controls, the significant covariance between BP1 & BP3 and BP2 & BP3 compared to no covariance for BPD1+BPD2 & WCD reflects genome-wide genetic similarity between the BPD cases. In all our analyses highly related individuals are excluded so that in the CD/BPD analysis WTCCC controls are randomly shared between the CD and BPD sets.

Supplementary Table 7.

Bivariate analysis for SCZ/BPD and SCZ/MDD excluding SCZ cohorts that include some schizoaffective disorder cases

Trait 1/ Trait 2	SNPs	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	Covariance OR coherit-ability SE)
SCZ/BPD	909307	5308/6664	5623/5258	0.25 (0.01)	0.22 (0.01)	0.68 (0.05)	0.16 (0.01)
SCZ/MDD	909307	5316/8998	7810/7823	0.25 (0.01)	0.22 (0.02)	0.38 (0.06)	0.09 (0.01)

Cohorts excluded from SCZ (cohort names given in the primary PGC publication[16])
ISC-Portugal, MGS, SGENE-CH, SGENE-TOP3, Zucker Hillside

Supplementary Table 8.

Bivariate analysis for BPD/MDD excluding MDD community-based samples

Trait 1/ Trait 2	SNPs	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	Covariance OR coherit-ability SE)
BPD/MDD	938610	6665/5916	7408/4169	0.23 (0.01)	0.23 (0.04)	0.54 (0.08)	0.12 (0.02)

h^2_{SNP}-heritability on the liability scale, rg SNP genetic correlation

MDD data sets included: GenRed, GSK, MPIP, RADIANT (GER) + Bonn/Mannheim, RADIANT (UK), STAR*D.

MDD data sets excluded: GAIN (partly a community-based sample), MDD2000-QIMR_610, MDD200-QIMR_317. (Data set names as in [24]).

Supplementary Table 9.

Meta-analysis of the relative risk (odds ratio) for schizophrenia and MDD (unipolar disorder) among first-degree relatives of schizophrenic probands in controlled family studies

	MDD
Iowa Family Study[25]	0.9 (0.6-1.4)[a]
NIMH[26]	2.2 (1.2-3.2)[a]
Danish Adoption Study[27]	1.8 (0.6-4.9)[a]
Roscommon Family Study[28]	1.7 (1.2-2,6)[a]
Mainz Family Study[29]	1.7 (1.1-2.6)[a]
Finnish Adoption Study[30]	0.6 (0.2-1.6)[b]
New York Study[31]	1.0 (0.4-1.9)[c]
Bonn-Mainz multi-generation study[32]	2.6 (1.4-4.1)[d]
New York High Risk Study[33]	1.0 (0.5-2.1)[e]
Copenhagen High Risk Study[34]	1.3 (0.6-3.0)[f]
Washington University St Louis Study[35]	1.1 (0.2-5.9)[g]
Meta-analysis	1.5 (1.2-1.8)

a. As reported in [32]

b. Relative risk (RR) based on offspring with either depressive disorder with psychosis or nonpsychotic depression RR = ((2+4)/137) / ((1+13)/192)

c. RR uses N affected as reported in their Table 1 and age-adjusted N from their footnote. RR = (17/329.2) / (18/337.4)

d. RR uses age-adjusted prevalences from their Table 3 and N from their Table 2. RR = (22.4 / 8.5)

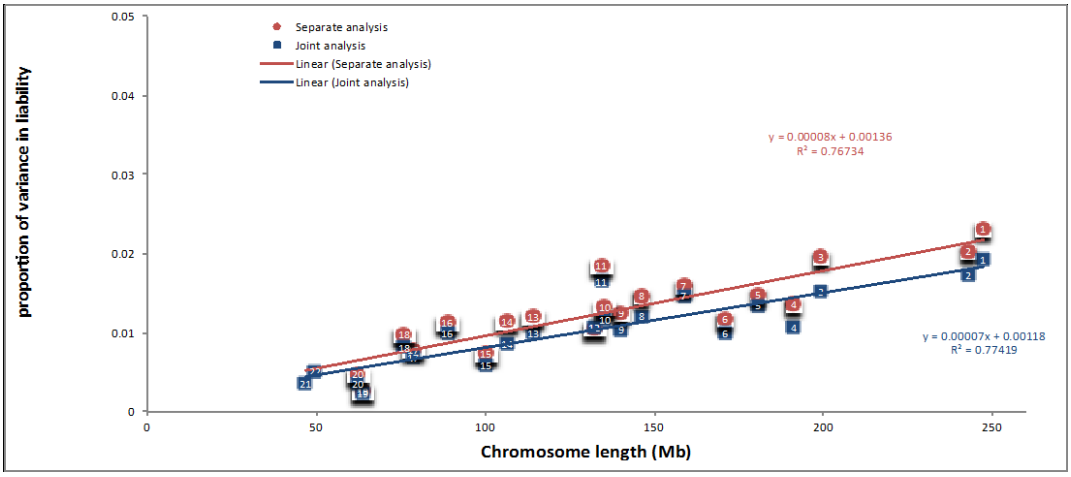
e. RR = (1.2+26.2) / (0+27.2) from their Table 2, psychotic and non-psychotic major depression

f. We used the estimates from the non-hierarchical data since we could not account for censoring in the hierarchical data. From their Table 3 hierarchical diagnosis RR= 11.9 / 8.9.

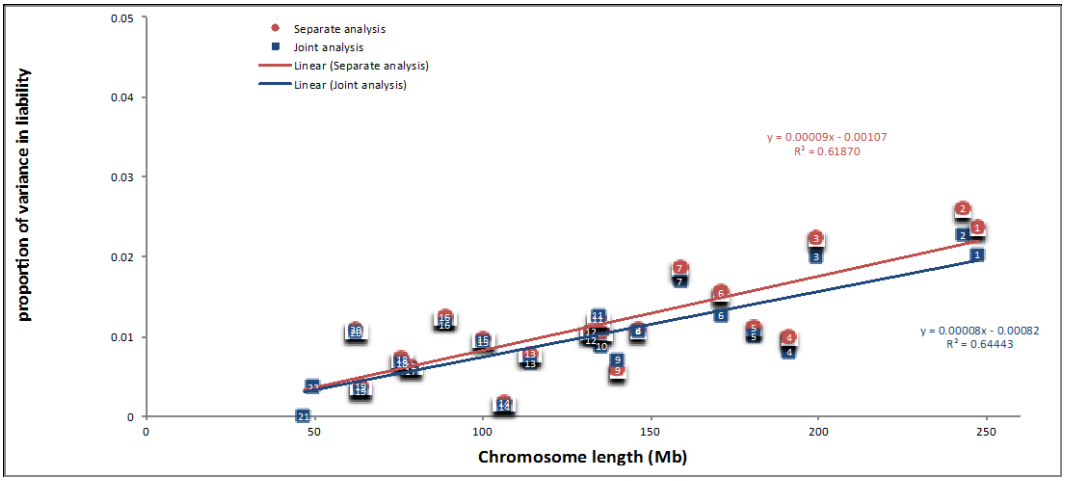
Odds ratios and relative risks are considered interchangeable.

SUPPLEMENTARY FIGURES

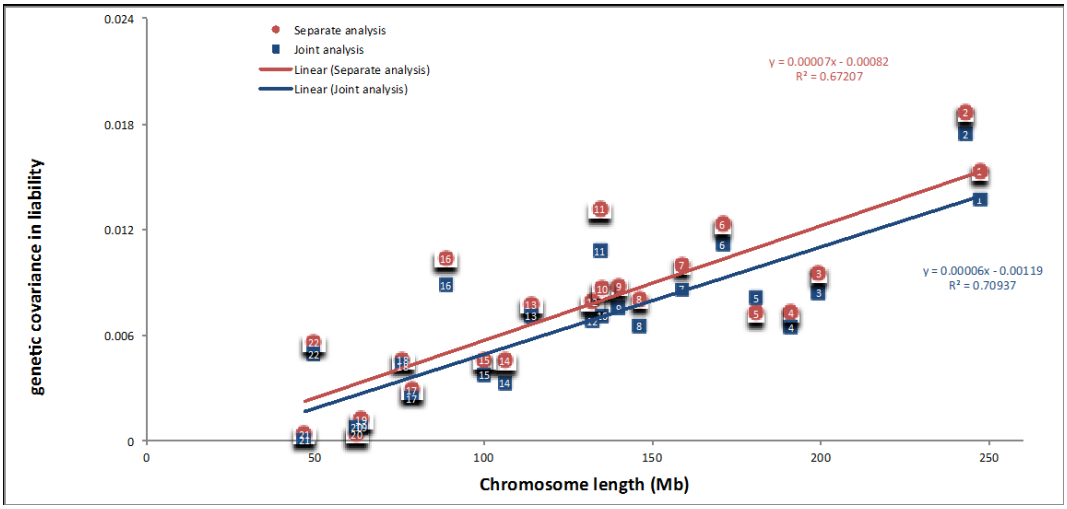
A. Proportion of variance in liability (SNP-heritability) explained by SNPs from each chromosome for SCZ from a SCZ/BPD bivariate analysis.



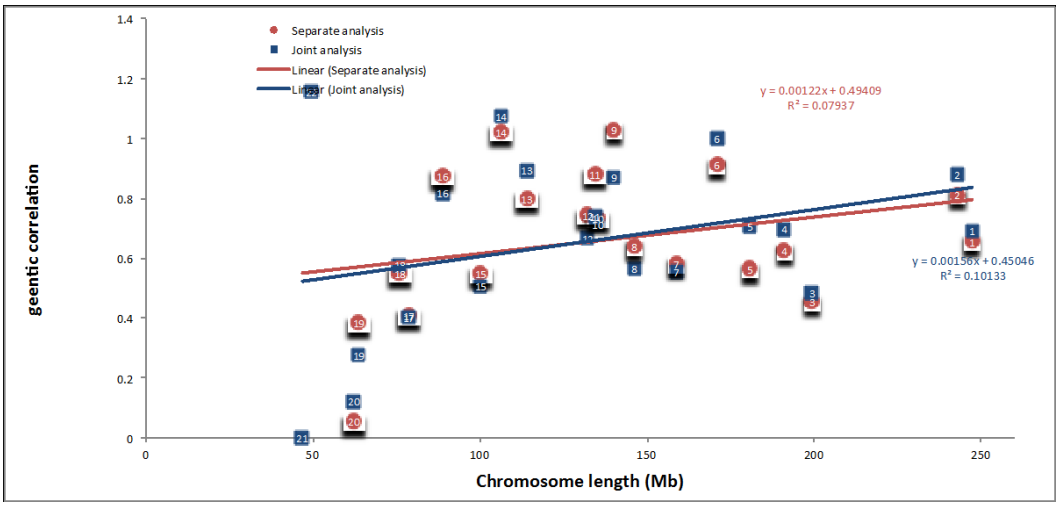
B. Proportion of variance in liability (SNP-heritability) explained by SNPs from each chromosome for BPD from a SCZ/BPD bivariate analysis-



C. Proportion of covariance in liability (SNP-coheritability) explained by SNPs from each chromosome SCZ/BPD

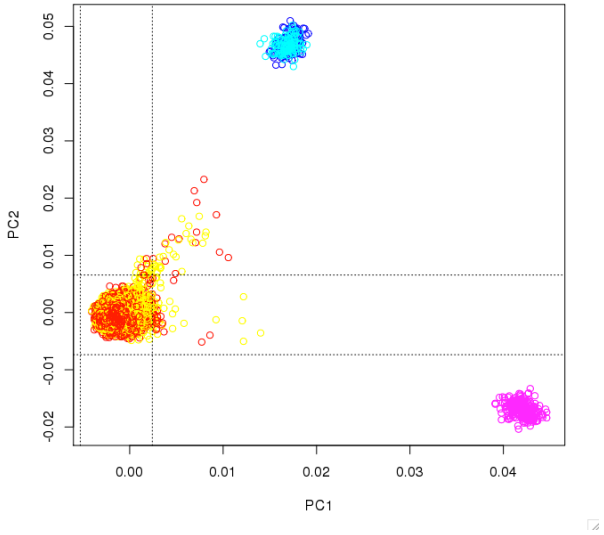


D. SNP genetic correlation between SCZ/BPD

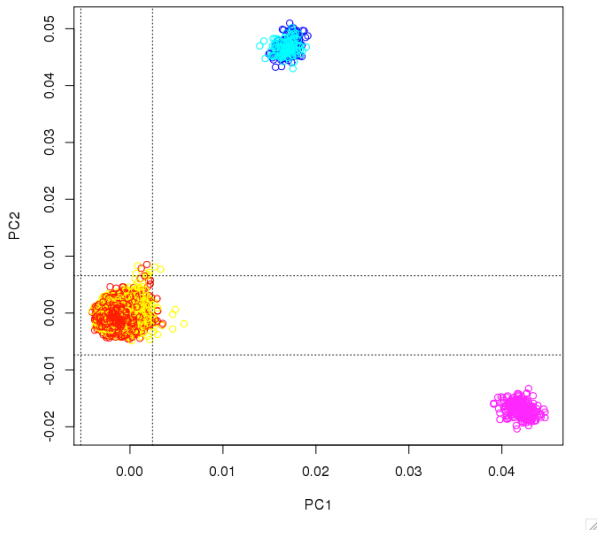


Supplementary Figure 1. Chromosome partitioning of genetic variance for schizophrenia (A), bipolar disorder (B), genetic covariance between schizophrenia and bipolar disorder (C) and genetic correlation between schizophrenia and bipolar disorder (D) from a bivariate analysis fitting 22 chromosomes.

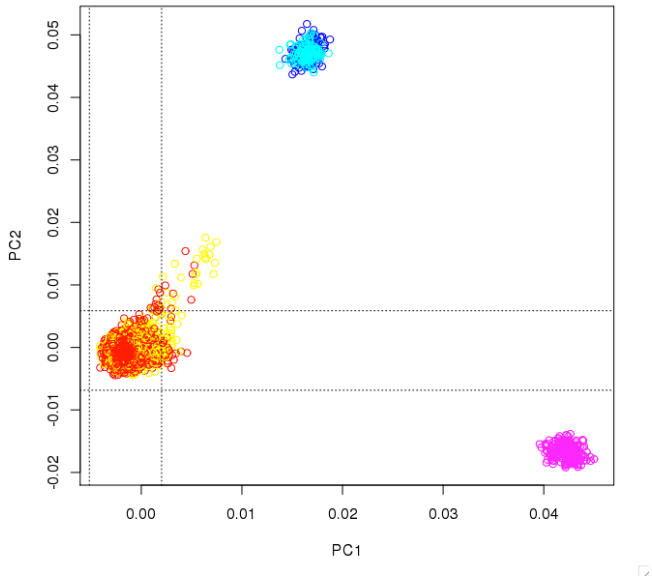
A. SCZ before relatedness cut-off < 0.05 (9431 cases and 12848 controls). The number of individuals outside the bounds of CEU ± 6 s.d. (dotted lines) is 33.



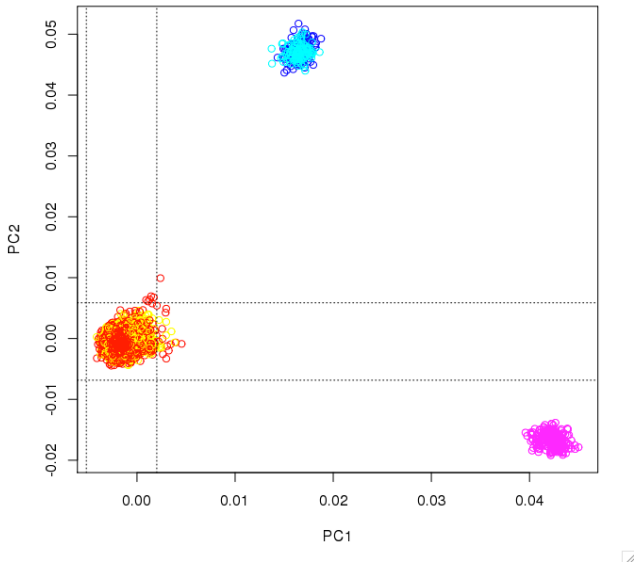
B: SCZ after relatedness cut-off < 0.05 (9087 case and 12171 controls)



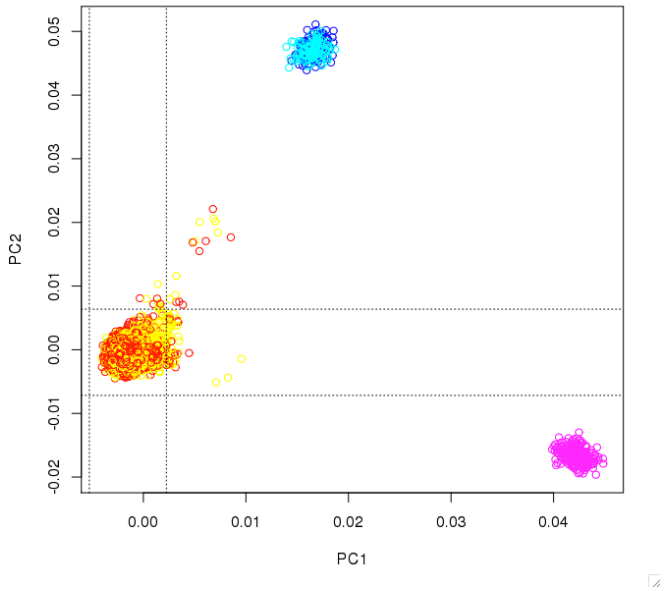
C: BPD before relatedness cut-off < 0.05 (8275 cases and 10532 controls). The number of individuals outside the bounds of CEU ± 6 s.d. (dotted lines) is 28.



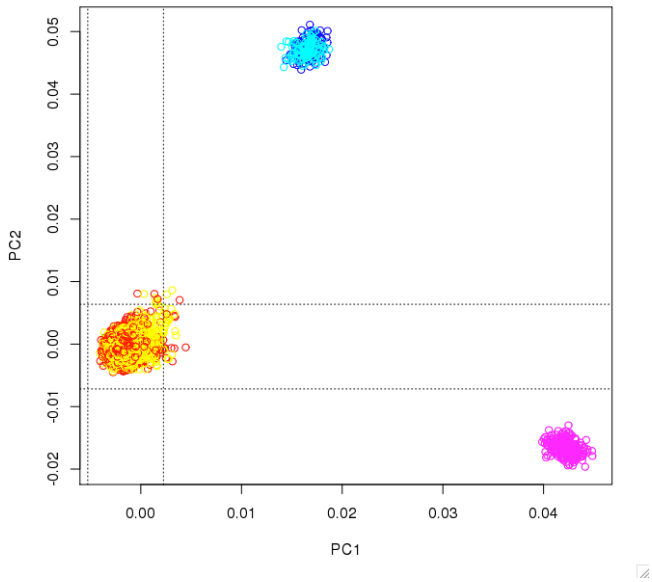
D: BPD after relatedness cut-off < 0.05 (6704 case and 9031 controls)



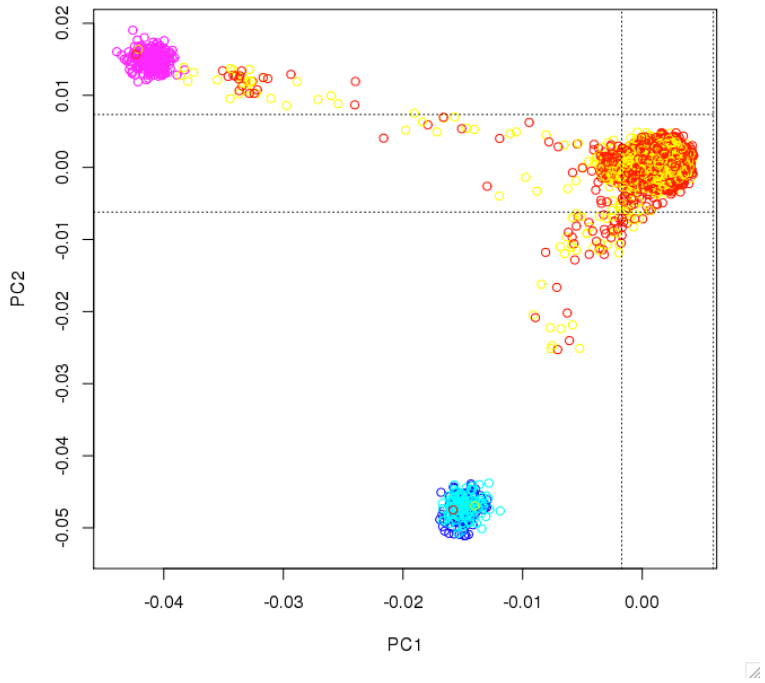
E: MDD before relatedness cut-off < 0.05 (9322 cases and 10306 controls). The number of individuals outside the bounds of CEU ± 6 s.d. (dotted lines) is 43.



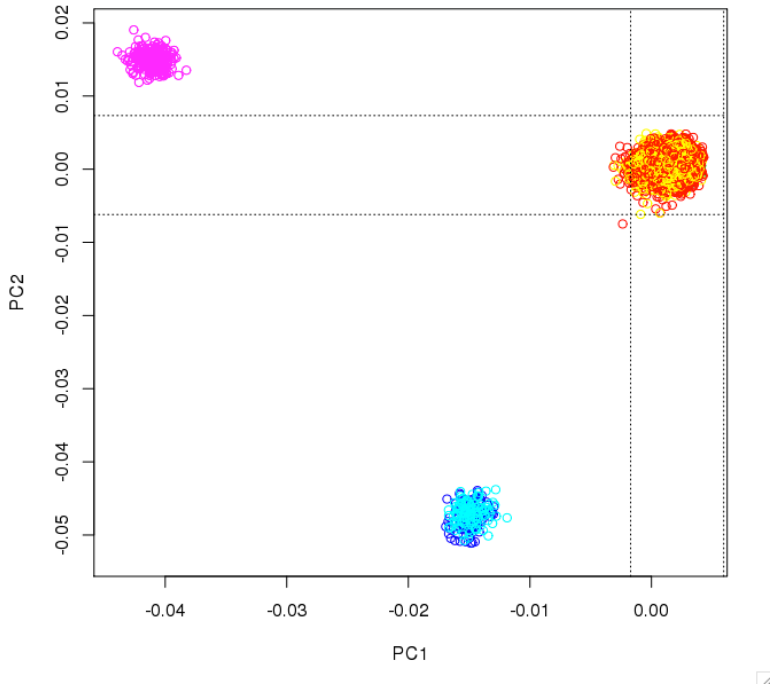
F: MDD after relatedness cut-off < 0.05 (9041 cases 9381 controls)



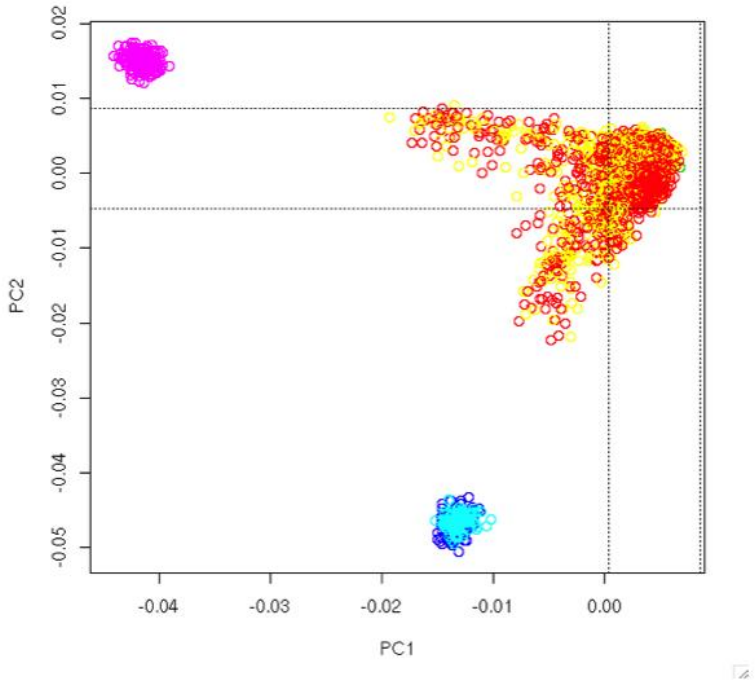
G: ADHD before relatedness cut-off < 0.05 (4607 cases and 12659). The number of individuals outside the bounds of CEU ± 6 s.d. (dotted lines) is 38.



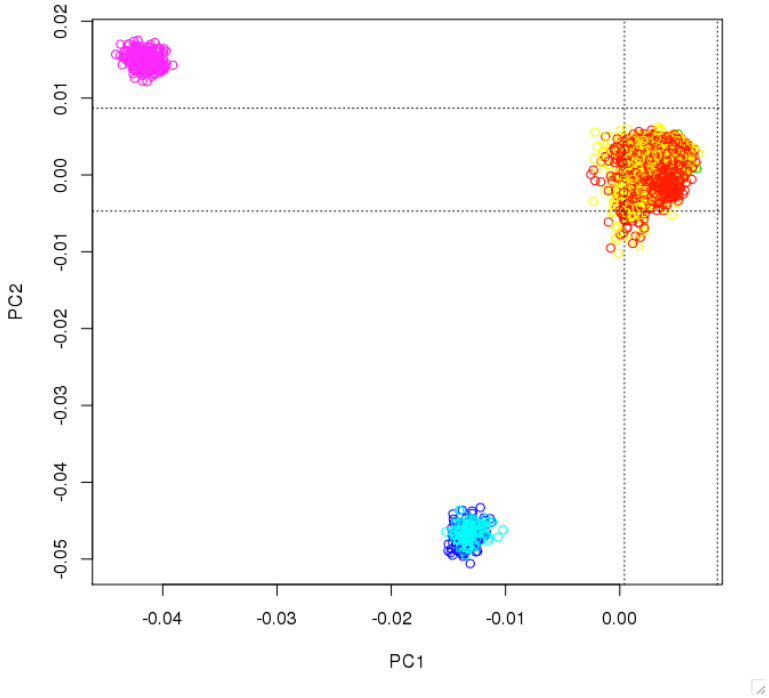
H: ADHD after relatedness cut-off < 0.05 4163 cases and 12040 controls)



I: ASD before relatedness cut-off < 0.05 (3661 cases and 4040 controls). Excluding the 144 outliers does not change the estimate of SNP heritability.



J: ASD after relatedness cut-off < 0.05 (3381 cases and 3508 controls)



Supplementary Figure 2. Principal Component Analysis for each disorder. Mapped with HapMap3 samples. Pink: YRI, Blues: CHB and JPT, Yellow and red: SCZ cases and controls, Green: CEU (usually hidden behind cases and controls)

SUPPLEMENTARY NOTE

Supplementary acknowledgements.

Numerous (>100) grants from government agencies along with substantial private and foundation support world-wide enabled the phenotype and genotype data collection without which this research would be not be possible; the grants are listed in the primary PGC publications.

The ADHD Spanish cohort has not yet been included in a PGC publication. Their acknowledgements are:

Financial support was received from "Instituto de Salud Carlos III" (PI11/00571, PI11/01629), "Fundació La Marató de TV3" (092330/31, 092010), "Ministerio de Economía y Competitividad, Spain" (SAF2012-33484), "Fundación Alicia Koplowitz" and "Agència de Gestió d'Ajuts Universitaris i de Recerca-AGAUR" (2009GR00971). Marta Ribasés is a recipient of a Miguel Servet contract form the "Instituto de Salud Carlos III", Spain. Genotyping services were provided by the Spanish "Centro Nacional de Genotipado" (CEGEN; www.cegen.org).

Darina Czamara was supported by the Deutsche Forschungsgemeinschaft (German Research Foundation) within the framework of the Munich Cluster for Systems Neurology (EXC 1010 SyNergy)

Frank Bellivier acknowledges grant funding from Banque de cellules (Pr Jamel Chelly), APHP, Hopital Cochin, Paris, France

This study makes use of data generated by the Wellcome Trust Case-Control Consortium. A full list of the investigators who contributed to the generation of the WTCCC data is available from www.wtccc.org.uk. Funding for the WTCCC project was provided by the Wellcome Trust under award 076113.

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