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

Supplementary Tables

Supplementary Figures

Supplementary Note

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

Nature Genetics: doi:10.1038/ng.2711

SUPPLEMENTARY TABLES

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**	**6.0e-15**	**0.0071**	0.072	**1.5e-14**
literature[d] **λ_{1st}**	M-A: 2.1[1], Offspring[2,e]: 2.4,5.2,4.5,6.0 Sib[2,e]: 3.9,3.7,3.9,5.0	M-A[f]: 1.5	Parent[3]: 2.9 Sibling[3]: 2.6 Sibling (ASD/ADHD)[6]: 2.4	Parent[4,g]: > 1	M-A[5,h]: 3.1,2.7
literature r_g	0.60[2,i]	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 to Supplementary Table 1 on next page

Nature Genetics: doi:10.1038/ng.2711

SNP-h^2 SNP-heritability on the liability scale, r_g SNP genetic correlation, λ_{1st}-cov : increased risk to 1st degree relatives attributable to SNPs calculated from the SNP-coheritability and *K* values, i.e. genetic covariance = SNP-coheritability , λ_{1st}-r_g increased risk to 1st degree relatives calculated from the SNP-r_g, *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^2 estimated 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 1st-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 1st degree relatives of BPD1 child probands 2) Risk of ADHD in 1st degree relatives of BPD1 adult probands 3) Risk of BPD1 in 1st degree relatives of ADHD adult probands 4) Risk of BPD1 in 1st 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.

Nature Genetics: doi:10.1038/ng.2711

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

Nature Genetics: doi:10.1038/ng.2711

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: 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.

Nature Genetics: doi:10.1038/ng.2711

Supplementary Table 4. Genomic partitioning by minor allele frequency (MAF) of SNPs for SCZ/BPD analysis

		h^2 (SE)		r_g (SE)	Covariance OR coheritability (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

Nature Genetics: doi:10.1038/ng.2711

Supplementary Table 5. Univariate and bivariate analyses for sub-cohorts

A: Univariate analyses for sub-cohorts

Sub-cohort	SNPs	Cases	Controls	h^2_{cc} (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).

Nature Genetics: doi:10.1038/ng.2711

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 co-heritability 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

Nature Genetics: doi:10.1038/ng.2711

Supplementary Table 6. Bivariate analyses between psychiatric disorders and Crohn's Disease (CD) control

Trait 1/ trait 2	SNPs	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	covarianceOR co-heritability 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	9143/7091	0.18 (0.01)	0.23 (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.

Nature Genetics: doi:10.1038/ng.2711

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 co-heritability 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 co-heritability 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, r_g 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]).

Nature Genetics: doi:10.1038/ng.2711

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

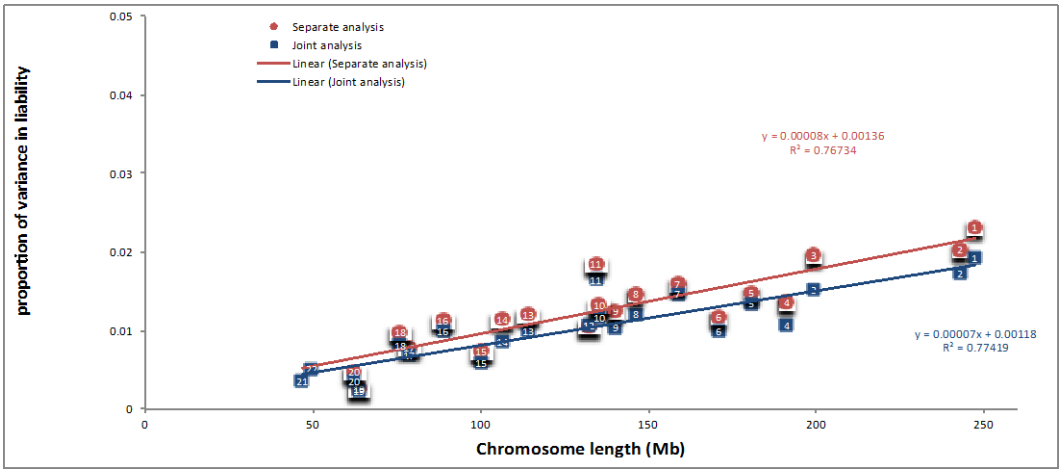
f. We used the estimates from the non-hierarchical data since we could not account for censoring in the hierarchical data. From their Table 3 hierarchical diagnosis RR= 11.9/8.9.

Odds ratios and relative risks are considered interchangeable.

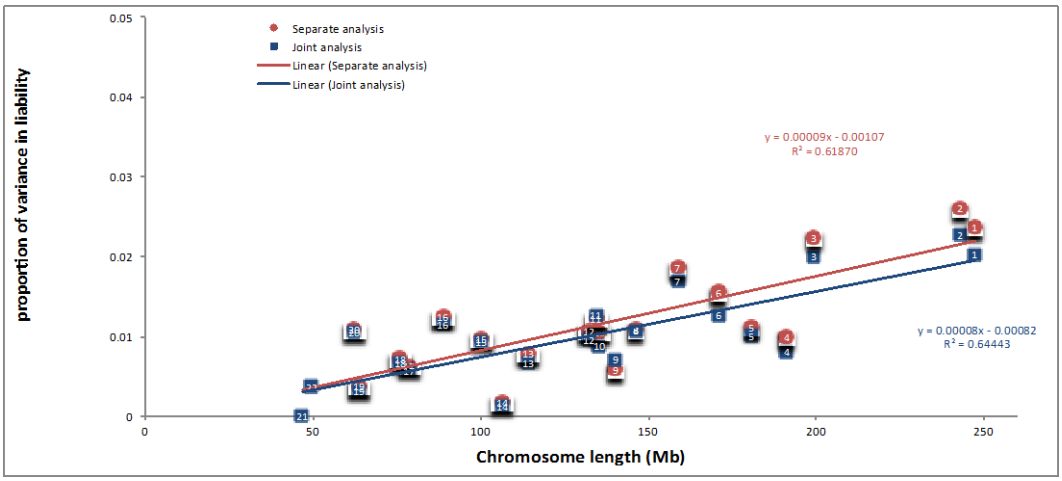
Nature Genetics: doi:10.1038/ng.2711

SUPPLEMENTARY FIGURES

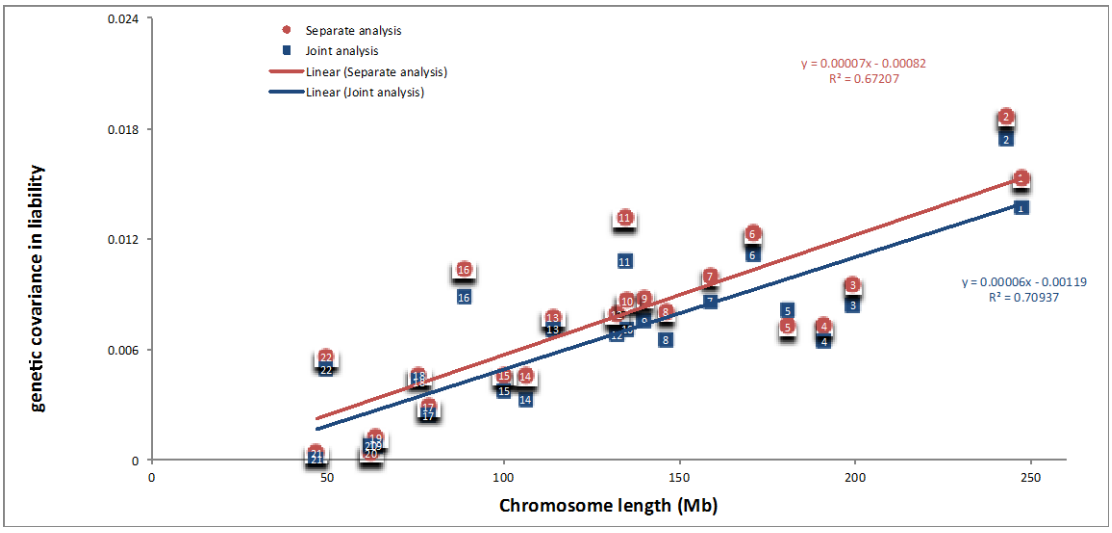
A. Proportion of variance in liability (SNP-heritability) explained by SNPs from each chromosome for SCZ from a SCZ/BPD bivariate analysis.



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

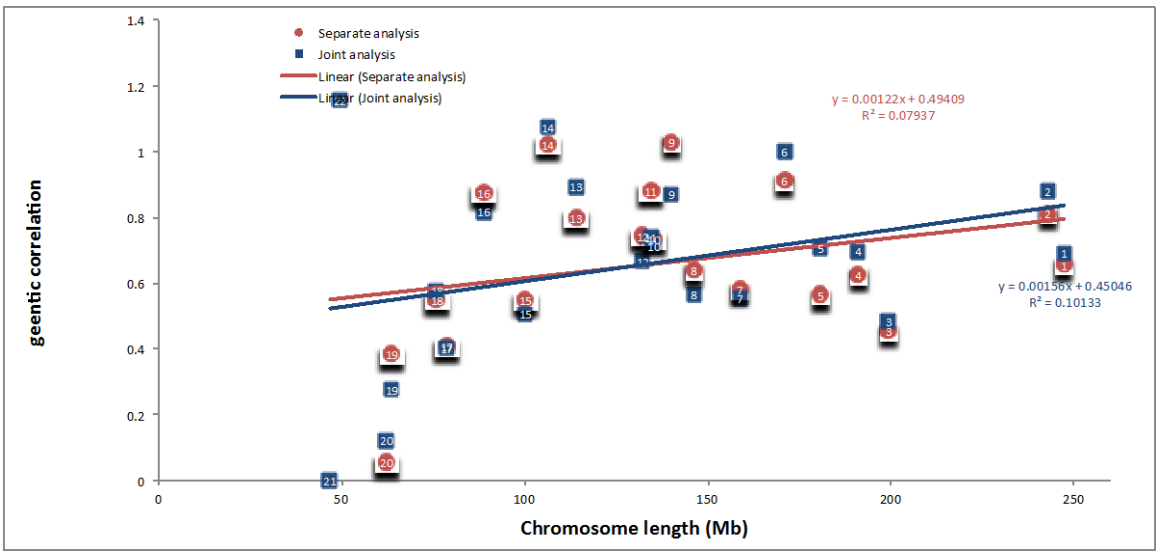


C. Proportion of covariance in liability (SNP-coheritability) explained by SNPs from each chromosome SCZ/BPD



Nature Genetics: doi:10.1038/ng.2711

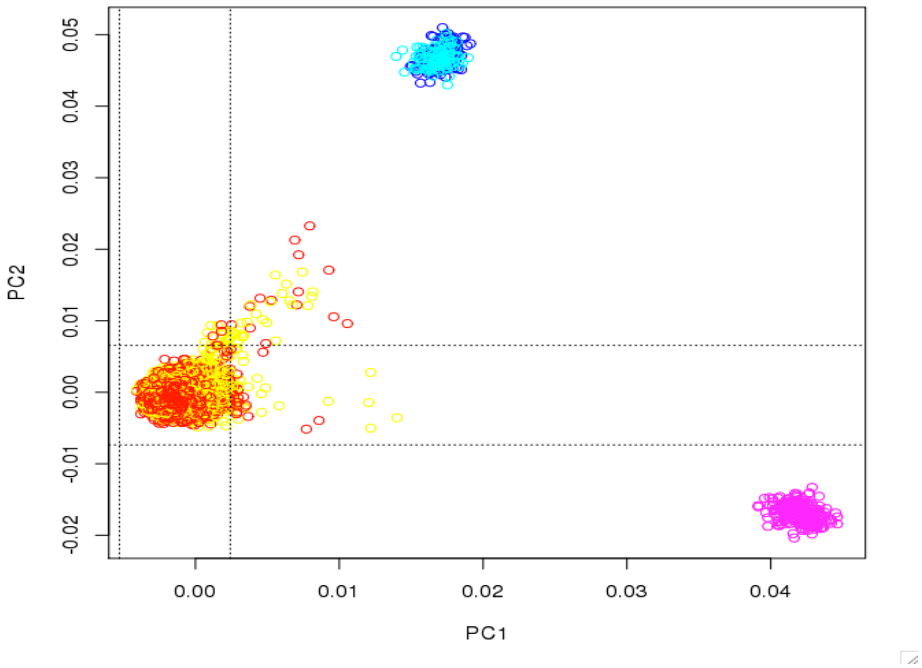
D. SNP genetic correlation between SCZ/BPD



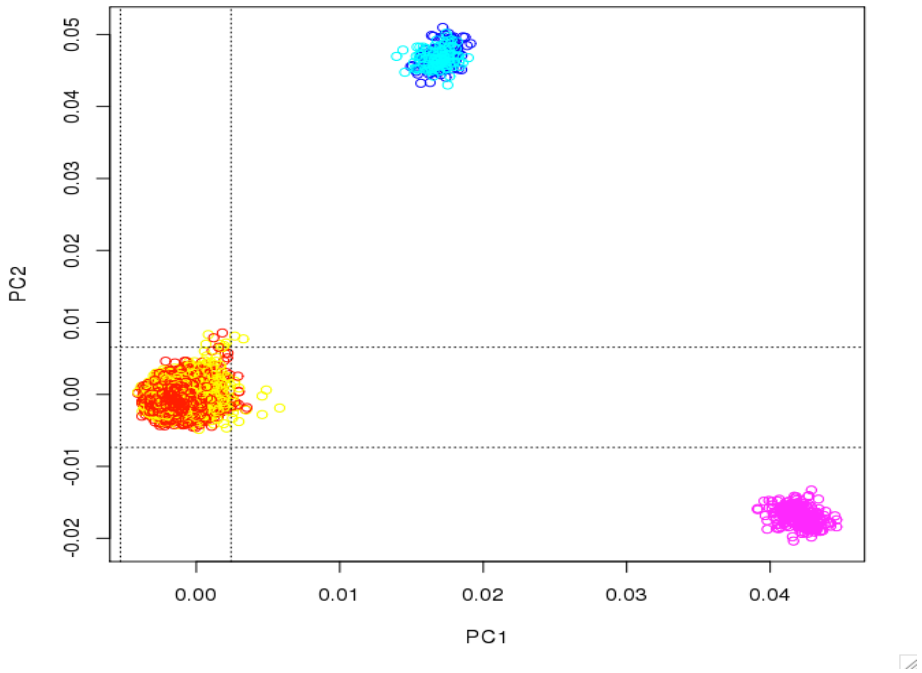
Supplementary Figure 1. Chromosome partitioning of genetic variance for schizophrenia (A), bipolar disorder (B), genetic covariance between schizophrenia and bipolar disorder (C) and genetic correlation between schizophrenia and bipolar disorder (D) from a bivariate analysis fitting 22 chromosomes.

Nature Genetics: doi:10.1038/ng.2711

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

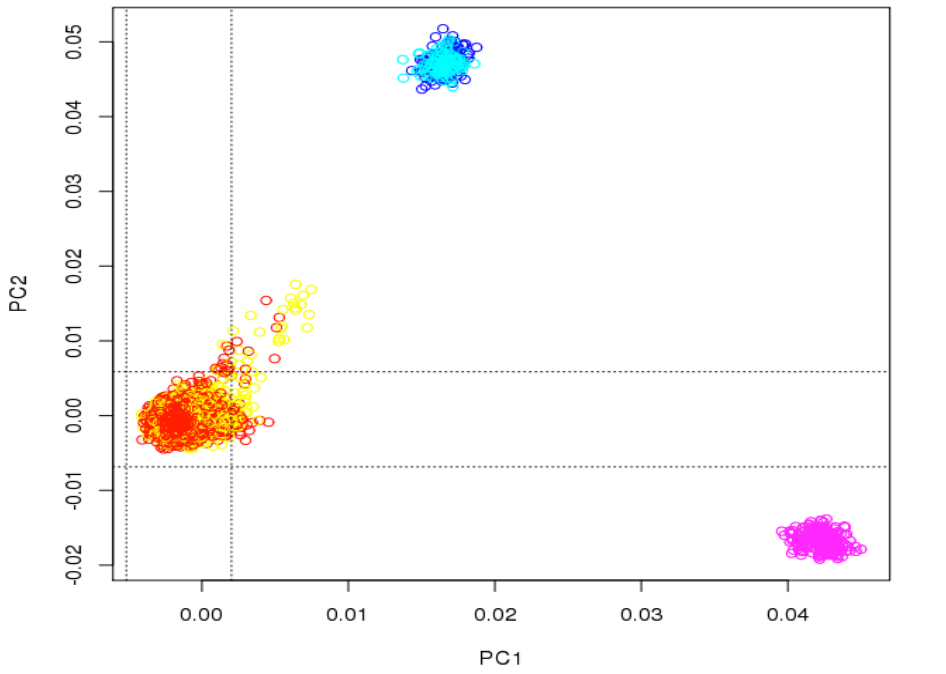


B: SCZ after relatedness cut-off < 0.05 (9087 case and 12171 controls)

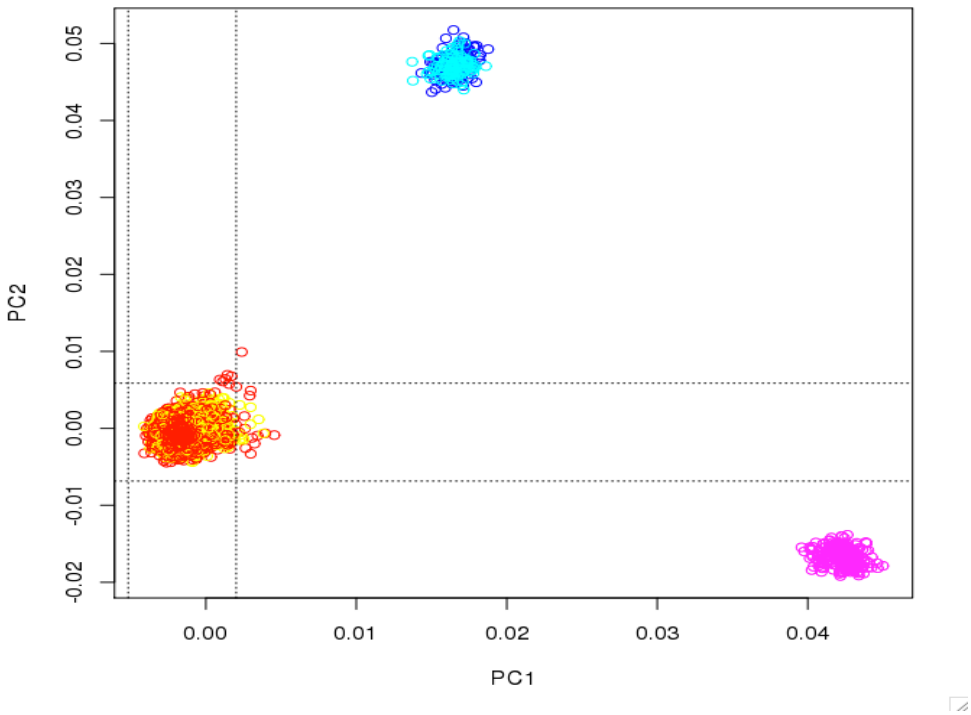


Nature Genetics: doi:10.1038/ng.2711

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

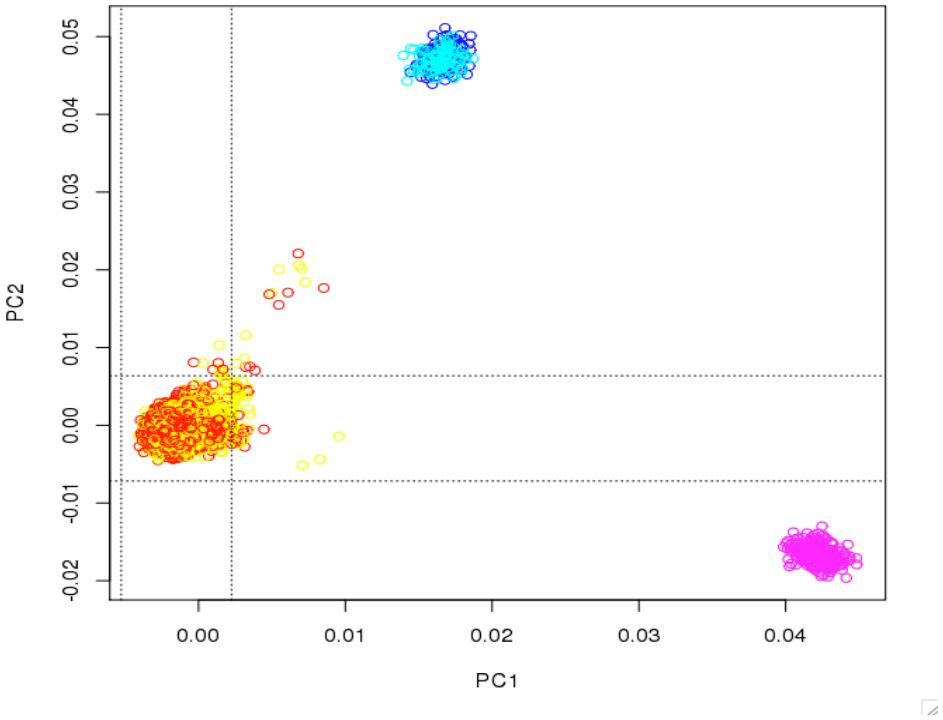


D: BPD after relatedness cut-off < 0.05 (6704 case and 9031 controls)

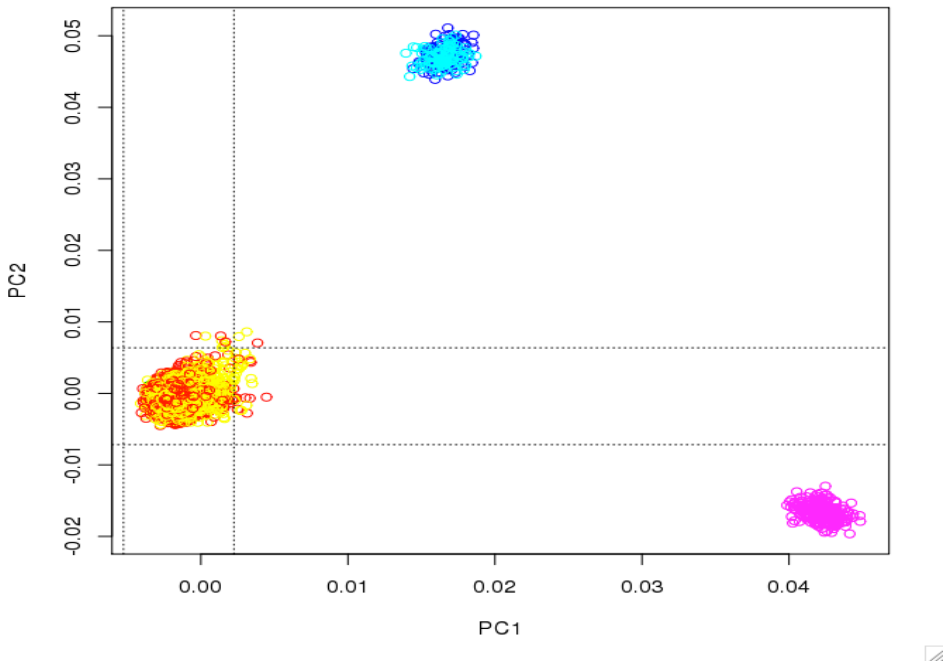


Nature Genetics: doi:10.1038/ng.2711

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

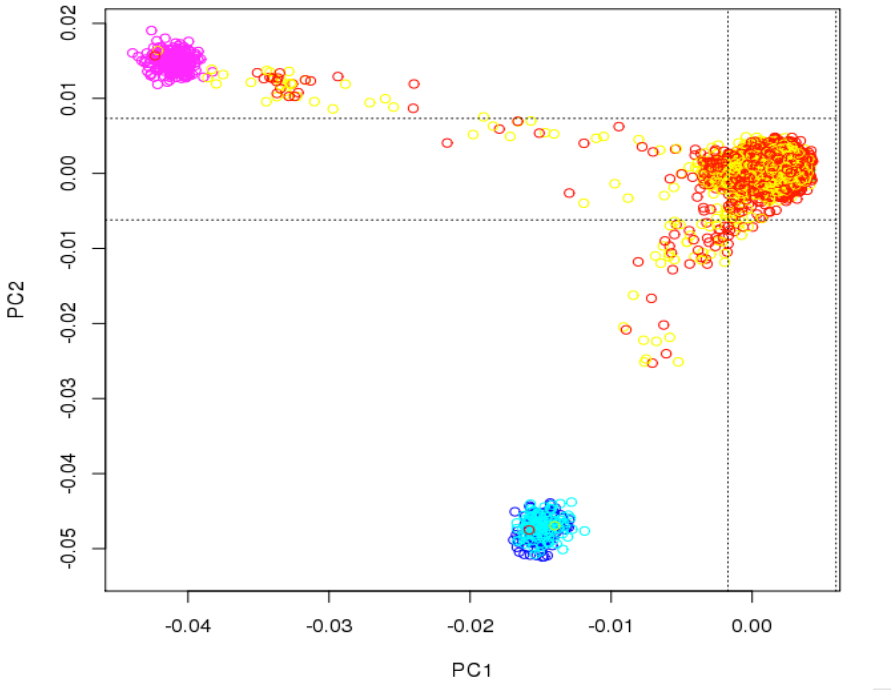


F: MDD after relatedness cut-off < 0.05 (9041 cases 9381 controls)

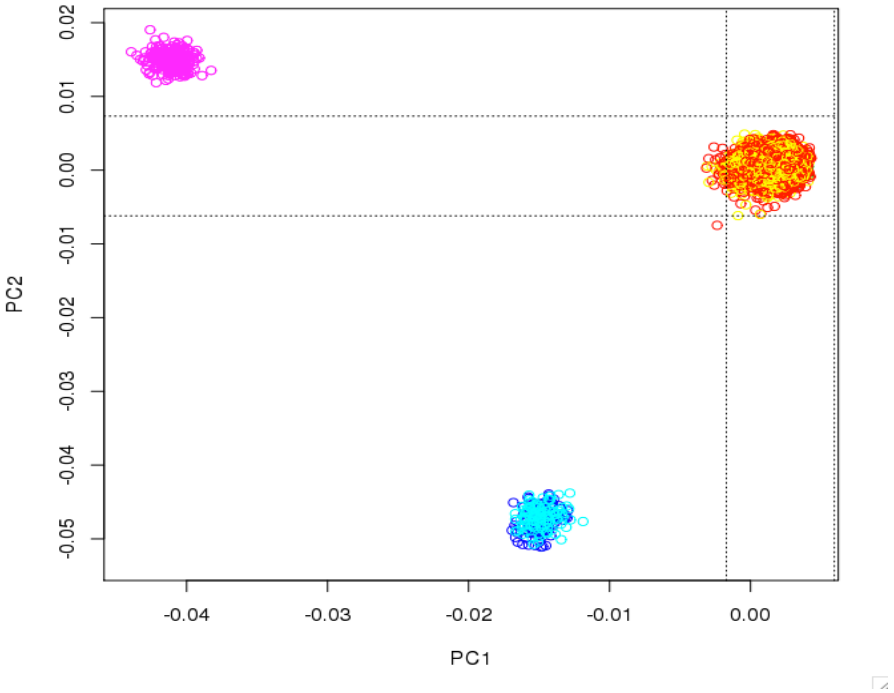


Nature Genetics: doi:10.1038/ng.2711

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

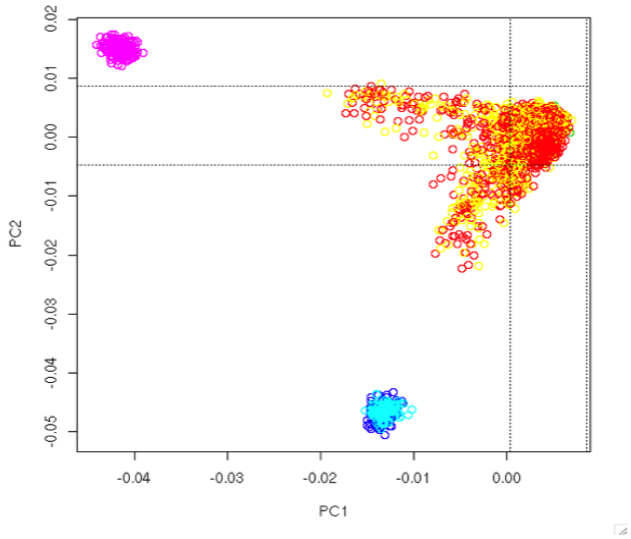


H: ADHD after relatedness cut-off < 0.05 4163 cases and 12040 controls)

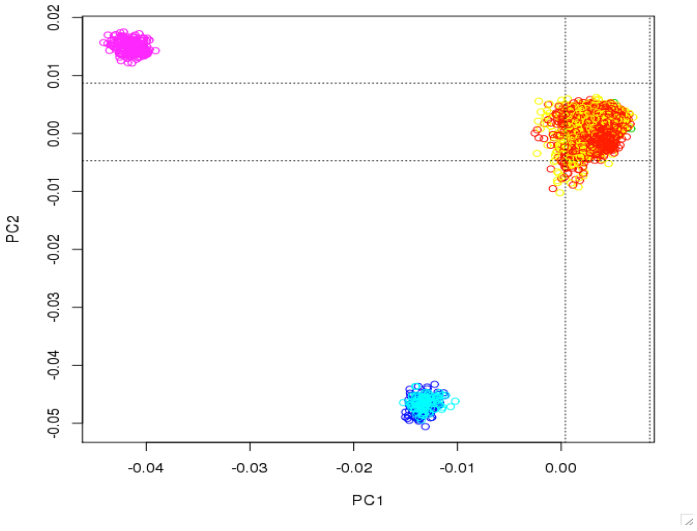


Nature Genetics: doi:10.1038/ng.2711

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)

Nature Genetics: doi:10.1038/ng.2711

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.

Nature Genetics: doi:10.1038/ng.2711

International Inflammatory Bowel Disease Genetics Consortium Members

Clara Abraham[1], Jean-Paul Achkar[2], Tariq Ahmad[3], Leila Amininejad[4], Ashwin N Ananthakrishnan[5], Vibeke Andersen[6], Carl A Anderson[7], Jane M Andrews[8], Vito Annese[9,10], Leonard Baidoo[11], Tobias Balschun[12], Peter A Bampton[13], Jeffrey C Barrett[7], Alain Bitton[14], Gabrielle Boucher[15], Stephan Brand[16], Steven R Brant[17], Carsten Büning[18], Judy H Cho[19], Sven Cichon[20], Isabelle Cleynen[21], Ariella Cohain[22], Mauro D'Amato[23], Mark J Daly[24], Dirk DeJong[25], Kathy L Devaney[5], Martine DeVos[26], Marla Dubinsky[27], Richard H Duerr[28,29], Cathryn Edwards[30], David Ellinghaus[12], Jonah Essers[31], Lynnette R Ferguson[32], Denis Franchimont[4], Andre Franke[12], Karin Fransen[33,34], Richard Gearry[35], Michel Georges[36], Christian Gieger[37], Jürgen Glas[14], Philippe Goyette[15], Hakon Hakonarson[38], Talin Haritunians[39], Ailsa Hart[40], Chris Hawkey[41], Matija Hedl[1], Xinli Hu[42], Ken Y Hui[19], Luke Jostins[7], Tom H Karlsen[43], Subra Kugathasan[44], Limas Kupcinskas[45], Anna Latiano[46], Debby Laukens[26], Ian C Lawrance[47], James C Lee[48], Charlie W Lees[49], Edouard Louis[50], Gillian Mahy[51], John Mansfield[52], Christopher G Mathew[53], Dermot P McGovern[54], Mitja Mitrovic[55], Angharad R Morgan[32], Craig Mowat[56], William Newman[57], Kaida Ning[1], Orazio Palmieri[46], Miles Parkes[48], Cyriel Y Ponsioen[58], Uros Potocnik[59], Natalie J Prescott[60], Graham Radford-Smith[61,62], Soumya Raychaudhuri[42], Miguel Regueiro[11], John D Rioux[15], Stephan Ripke[63,64], Jerome I Rotter[39], Richard K Russell[65], Jeremy D Sanderson[66], Miquel Sans[67], Jack Satsangi[49], Eric E Schadt[22], Stefan Schreiber[68], L Philip Schumm[69], Yashoda Sharma[1], Mark S Silverberg[70], Lisa A Simms[61], Sarah L Spain[71], Jurgita Sventoraityte[45], Stephan R Targan[72], Kent D Taylor[72], Emilie Theatre[73], Mark Tremelling[74], Severine Vermeire[53], Hein W Verspaget[75], Rinse K Weersma[25], Zhi Wei[76], Cisca Wijmenga[34], David C Wilson[77], Juliane Winkelmann[78], Ramnik J Xavier[5], Sebastian Zeissig[79], Bin Zhang[22], Hongyu Zhao[80]

Department of Internal Medicine, Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut, USA. [1]Department of Internal Medicine, Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut, USA. [2]Department of Gastroenterology & Hepatology, Digestive Disease Institute, Cleveland Clinic, and Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA. [3]Peninsula College of Medicine and Dentistry, Exeter, UK. [4]Erasmus Hospital, Free University of Brussels, Department of Gastroenterology, Brussels, Belgium. [5]Massachusetts General Hospital, Harvard Medical School, Gastroenterology Unit, Boston, Massachusetts, USA. [6]Viborg Regional Hospital, Medical Department, Viborg, Denmark. [7]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK. [8]Inflammatory Bowel Disease Service, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, and School of Medicine, University of Adelaide, Adelaide, Australia. [9]Unit of Gastroenterology, Istituto di Ricovero e Cura a Carattere Scientifico-Casa Sollievo della Sofferenza (IRCCS-CSS) Hospital, San Giovanni Rotondo, Italy .[10]Azienda Ospedaliero Universitaria (AOU) Careggi, Unit of Gastroenterology SOD2, Florence, Italy. [11]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA. [12]Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany. [13]Department of Gastroenterology and Hepatology, Flinders Medical Centre and School of Medicine, Flinders University, Adelaide, Australia. [14]Division of Gastroenterology, McGill University Health Centre, Royal Victoria Hospital, Montréal, Québec, Canada. [15]Université de Montréal and the Montreal Heart Institute, Research Center, Montréal, Québec, Canada. [16]Department of Medicine II, University Hospital Munich-Grosshadern, Ludwig-Maximilians-University, Munich, Germany. [17]Meyerhoff Inflammatory Bowel Disease Center, Department of Medicine, School of Medicine, and Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA. [18]Department of Gastroenterology, Charit, Campus Mitte, UniversitŠtsmedizin Berlin, Berlin, Germany. [19]Department of Genetics, Yale School of Medicine, New Haven, Connecticut, USA. [20]Department of Genomics, Life & Brain Center, University Hospital Bonn, Bonn, Germany.[21]Department of Pathophysiology, Gastroenterology section, KU Leuven, Leuven, Belgium. [22]Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York City, New York, USA. [23]Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. [24]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA. [25]Department of Gastroenterology and Hepatology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands. [26]Ghent University Hospital, Department of Gastroenterology and Hepatology, Ghent, Belgium. [27]Department of Pediatrics, Cedars Sinai Medical Center, Los Angeles, California, USA. [28]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh School of Medicine. [29]Department of Human Genetics, University of Pittsburgh Graduate School of Public Health, Pittsburgh,Pennsylvania, USA. [30]Torbay Hospital, Department of Gastroenterology, Torbay, Devon, UK.[31]Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA. [32]School of Medical Sciences, Faculty of Medical & Health Sciences, The University of Auckland, Auckland, New Zealand. [33]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA . [34]University of Groningen, University Medical Center

Nature Genetics: doi:10.1038/ng.2711

Groningen, Department of Genetics, Groningen, The Netherlands. [35]Department of Medicine, University of Otago, and Department of Gastroenterology, Christchurch Hospital, Christchurch, New Zealand. [36] Unit of Animal Genomics, Groupe Interdisciplinaire de Genoproteomique Appliquee (GIGA-R) and Faculty of Veterinary Medicine, University of Liege, Liege, Belgium. [37] Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany. [38]Center for Applied Genomics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA. [39]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA. [40]St Mark's Hospital, Watford Road, Harrow, Middlesex, HA1 3UJ. [41]Nottingham Digestive Diseases Centre, Queens Medical Centre, Nottingham NG7 1AW, UK.[42]Division of Rheumatology Immunology and Allergy, Brigham and Women's Hospital, Boston, Massachusetts, USA. [43]Research Institute of Internal Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway . [44]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA. [45]Kaunas University of Medicine, Department of Gastroenterology, Kaunas, Lithuania. [46]Unit of Gastroenterology, Istituto di Ricovero e Cura a Carattere Scientifico-Casa Sollievo della Sofferenza (IRCCS-CSS) Hospital, San Giovanni Rotondo, Italy. [47]School of Medicine and Pharmacology, The University of Western Australia, Fremantle, Australia. [48]Inflammatory Bowel Disease Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK. [49]Gastrointestinal Unit, Molecular Medicine Centre, University of Edinburgh, Western General Hospital, Edinburgh, UK. [50]Division of Gastroenterology, Centre Hospitalier Universitaire, Universite de Liege, Liege, Belgium. [51] Department of Gastroenterology, The Townsville Hospital, Townsville, Australia. [52]Institute of Human Genetics, Newcastle University, Newcastle upon Tyne, UK. [53]Division of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium. [54]Cedars-Sinai F.Widjaja Inflammatory Bowel and Immunobiology Research Institute and Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA. [55]University of Maribor, Faculty of Medicine, Center for Human Molecular Genetics and Pharmacogenomics, Maribor, Slovenia and University Medical Center Groningen, Department of Genetics, Groningen, The Netherlands. [56]Department of Medicine, Ninewells Hospital and Medical School, Dundee, UK. [57]Genetic Medicine, MAHSC, University of Manchester, Manchester, UK. [58] Academic Medical Center, Department of Gastroenterology, Amsterdam, The Netherlands. [59] University of Maribor, Faculty of Medicine, Center for Human Molecular Genetics and Pharmacogenomics, Maribor and University of Maribor, Faculty for Chemistry and Chemical Engineering, Maribor, Slovenia. [60]King's College London School of Medicine, Guy's Hospital, Department of Medical and Molecular Genetics, London, UK. [61]Inflammatory Bowel Diseases, Genetics and Computational Biology, Queensland Institute of Medical Research, Brisbane, Australia. [62] Department of Gastroenterology, Royal Brisbane and Womens Hospital, and School of Medicine, University of Queensland, Brisbane, Australia. [63] Analytic and Translational Genetics Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA . [64]Broad Institute of MIT and Harvard, Cambridge, MA, USA. [65]Royal Hospital for Sick Children, Paediatric Gastroenterology and Nutrition, Glasgow, UK. [66]Guy's & St. Thomas' NHS Foundation Trust, St Thomas' Hospital, Department of Gastroenterology, London, UK. [67]Department of Gastroenterology, Hospital Clinic/Institut d'Investigaci— Biomedica August Pi i Sunyer (IDIBAPS). [68]Christian-Albrechts-University, Institute of Clinical Molecular Biology,and Department for General Internal Medicine, Christian-Albrechts-University, Kiel, Germany. [69]Department of Health Studies, University of Chicago, Chicago, Illinois, USA. [70]Mount Sinai Hospital Inflammatory Bowel Disease Centre, University of Toronto, Toronto, Ontario, Canada. [71]Department of Medical and Molecular Genetics, King's College London School of Medicine, Guy's Hospital, London, UK.[72]Cedars-Sinai F.Widjaja Inflammatory Bowel and Immunobiology Research Institute, Los Angeles, California, USA. [73]Unit of Animal Genomics, Groupe Interdisciplinaire de Genoproteomique Appliquee (GIGA-R) and Faculty of Veterinary Medicine, University of Liege,and Division of Gastroenterology, Centre Hospitalier Universitaire, Universite de Liege, Liege, Belgium. [74] Norfolk and Norwich University Hospital. [75]Department of Gastroenterology, Leiden University Medical Center, Leiden, The Netherlands. [76]Department of Computer Science, New Jersey Institute of Technology, Newark, NJ 07102, USA. [77]Royal Hospital for Sick Children, Paediatric Gastroenterology and Nutrition, Glasgow, UK and Child Life and Health, University of Edinburgh, Edinburgh, Scotland, UK. [78]Institute of Human Genetics and Department of Neurology, Technische Universität München, Munich, Germany. [79]Department for General Internal Medicine, Christian-Albrechts-University, Kiel, Germany. [80]Department of Biostatistics, School of Public Health, Yale University, New Haven, Connecticut, USA.

Nature Genetics: doi:10.1038/ng.2711

References

1 Van Snellenberg, J. X. & de Candia, T. Meta-analytic evidence for familial coaggregation of schizophrenia and bipolar disorder. *Arch. Gen. Psychiatry* **66**, 748-755 (2009).

2 Lichtenstein, P. *et al.* Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**, 234-239 (2009).

3 Sullivan, P. F. *et al.* Family history of schizophrenia and bipolar disorder as risk factors for autism *Archives of General Psychiatry* **69**, 1099-1103 (2012).

4 Keshavan, M. S., Sujata, M., Mehra, A., Montrose, D. M. & Sweeney, J. A. Psychosis proneness and ADHD in young relatives of schizophrenia patients. *Schizophr Res* **59**, 85-92 (2003).

5 Smoller, J. W. & Finn, C. T. Family, twin, and adoption studies of bipolar disorder. *Am. J. Med. Genet. C Semin. Med. Genet.* **123**, 48-58 (2003).

6 Mortensen, P. B., Pedersen, M. G. & Pedersen, C. B. Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychol Med* **40**, 201-210, doi:10.1017/S0033291709990419 (2010).

7 McGuffin, P. *et al.* The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch. Gen. Psychiatry* **60**, 497-502 (2003).

8 Faraone, S. V., Biederman, J. & Wozniak, J. Examining the Comorbidity Between Attention Deficit Hyperactivity Disorder and Bipolar Disorder: A Meta-Analysis of Family-Genetic Studies. *American Journal of Psychiatry* **169**, 1256-1266 (2012).

9 Faraone, S. V. & Biederman, J. Do attention deficit hyperactivity disorder and major depression share familial risk factors? *The Journal of nervous and mental disease* **185**, 533-541 (1997).

10 Cole, J., Ball, H. A., Martin, N. C., Scourfield, J. & McGuffin, P. Genetic overlap between measures of hyperactivity/inattention and mood in children and adolescents. *J. Am. Acad. Child Adol. Psychiatry* **48**, 1094-1101 (2009).

11 Lichtenstein, P., Carlstrom, E., Rastam, M., Gillberg, C. & Anckarsater, H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am. J. Psychiatry* **167**, 1357-1363, doi:10.1176/appi.ajp.2010.10020223 (2010).

12 Mulligan, A. *et al.* Autism symptoms in Attention-Deficit/Hyperactivity Disorder: a familial trait which correlates with conduct, oppositional defiant, language and motor disorders. *J.. Autism Dev. Disord.* **39**, 197-209 (2009).

13 Taylor, M. J. *et al.* Developmental associations between traits of autism spectrum disorder and attention deficit hyperactivity disorder: a genetically informative, longitudinal twin study. *Psychol Med*, 1-12, doi:10.1017/S003329171200253X (2012).

14 Ronald, A., Simonoff, E., Kuntsi, J., Asherson, P. & Plomin, R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J. Child Psychol. Psychiatry Allied Disciplines* **49**, 535-542 (2008).

15 Reiersen, A. M., Constantino, J. N., Grimmer, M., Martin, N. G. & Todd, R. D. Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. *Twin research and human genetics : the official journal of the International Society for Twin Studies* **11**, 579-585, doi:10.1375/twin.11.6.579 (2008).

16 Ripke, S. *et al.* Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* **43**, 969-976 (2011).

17 Sklar, P. *et al.* Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat. Genet.* **43**, 977-983 (2011).

18 Neale, B. M. *et al.* Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **49**, 884-897 (2010).

19 Lionel, A. C. *et al.* Rare copy number variation discovery and cross-disorder comparisons identify risk genes for ADHD. *Sci. Transl. Med.* **3**, 95ra75 (2011).

20 Hamshere, M. *et al.* Identifying common genetic variants for ADHD that have phenotypic and clinical meaning: are there any? *submitted* (2012).

21 Hinney, A. *et al.* Genome-wide association study in German patients with attention deficit/hyperactivity disorder. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **156B**, 888-897 (2011).
22 Ribases, M. *et al.* Exploration of 19 serotoninergic candidate genes in adults and children with attention-deficit/hyperactivity disorder identifies association for 5HT2A, DDC and MAOB. *Molecular psychiatry* **14**, 71-85, doi:10.1038/sj.mp.4002100 (2009).
23 Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661-678 (2007).
24 Psychiatric GWAS Consortium Major Depressive Disorder. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol. Psychiatry* (2012).
25 Tsuang, M. T., Winokur, G. & Crowe, R. R. Morbidity Risks of Schizophrenia and Affective-Disorders among 1st Degree Relatives of Patients with Schizophrenia, Mania, Depression and Surgical Conditions. *Brit J Psychiat* **137**, 497-504, doi:Doi 10.1192/Bjp.137.6.497 (1980).
26 Gershon, E. S. *et al.* A controlled family study of chronic psychoses. Schizophrenia and schizoaffective disorder. *Arch. Gen. Psychiatry* **45**, 328-336 (1988).
27 Kendler, K. S., Gruenberg, A. M. & Kinney, D. K. Independent Diagnoses of Adoptees and Relatives as Defined by Dsm-Iii in the Provincial and National Samples of the Danish Adoption Study of Schizophrenia. *Arch Gen Psychiat* **51**, 456-468 (1994).
28 Kendler, K. S. *et al.* The Roscommon Family Study. IV. Affective illness, anxiety disorders, and alcoholism in relatives. *Arch. Gen. Psychiatry* **50**, 952-960 (1993).
29 Maier, W. *et al.* Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. *Archives of general psychiatry* **50**, 871-883 (1993).
30 Tienari, P. *et al.* Genetic boundaries of the schizophrenia spectrum: Evidence from the Finnish adoptive family study of schizophrenia. *American Journal of Psychiatry* **160**, 1587-1594, doi:Doi 10.1176/Appi.Ajp.160.9.1587 (2003).
31 Baron, M. *et al.* A Family Study of Schizophrenic and Normal Control Probands - Implications for the Spectrum Concept of Schizophrenia. *American Journal of Psychiatry* **142**, 447-455 (1985).
32 Maier, W. *et al.* The dichotomy of schizophrenia and affective disorders in extended pedigrees. *Schizophr Res* **57**, 259-266 (2002).
33 Erlenmeyer-Kimling, L. *et al.* The New York High-Risk Project. Prevalence and comorbidity of axis I disorders in offspring of schizophrenic parents at 25-year follow-up. *Archives of general psychiatry* **54**, 1096-1102 (1997).
34 Parnas, J. *et al.* Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. Results from the Copenhagen High-Risk Study. *Archives of general psychiatry* **50**, 707-714 (1993).
35 Coryell, W. & Zimmerman, M. The heritability of schizophrenia and schizoaffective disorder. A family study. *Archives of general psychiatry* **45**, 323-327 (1988).