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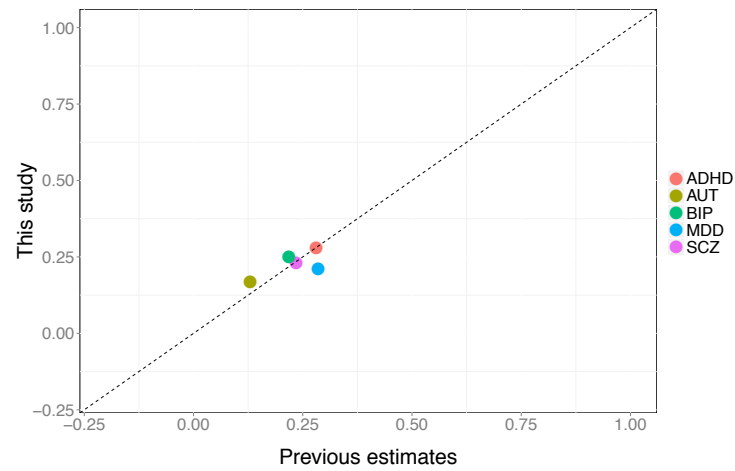
Supplemental Data

Joint Analysis of Psychiatric Disorders Increases Accuracy of Risk Prediction for Schizophrenia, Bipolar Disorder, and Major Depressive Disorder

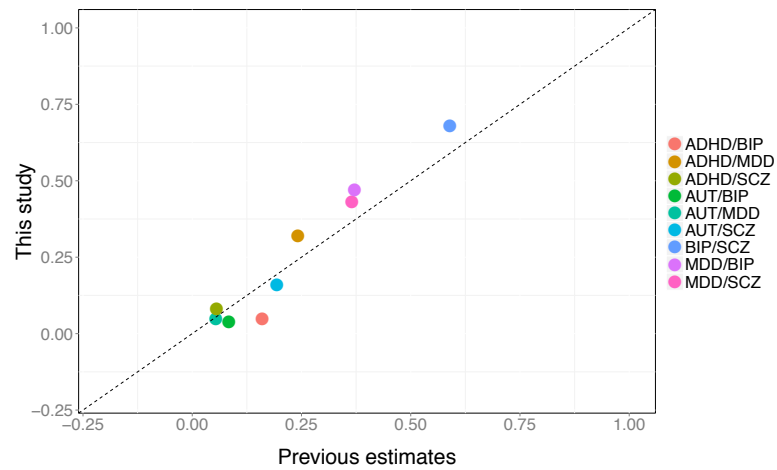
Robert Maier, Gerhard Moser, Guo-Bo Chen, Stephan Ripke, Cross disorder Working group of the Psychiatric Genomics Consortium, William Coryell, James B. Potash, William A. Scheftner, Jianxin Shi, Myrna M. Weissman, Christina M. Hultman, Mikael Landén, Douglas F. Levinson, Kenneth S. Kendler, Jordan W. Smoller, Naomi R. Wray, and S. Hong Lee

Supplementary data

A. Heritability



B. Genetic correlations



C. SNP-coheritability

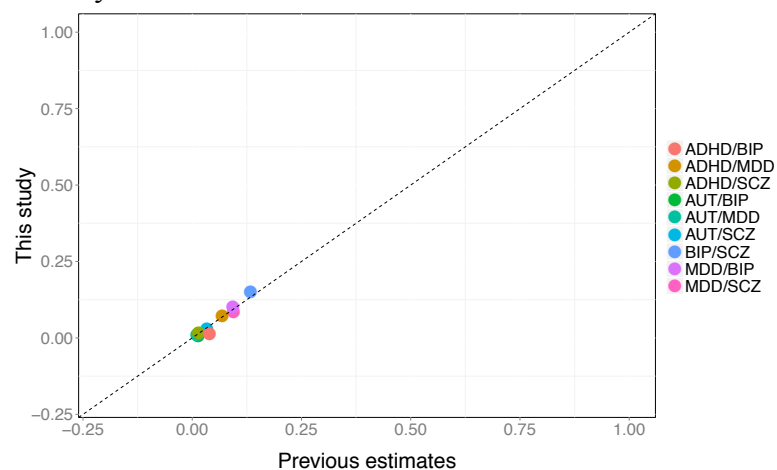


Figure S1. Previous estimates (Lee et al. 2013) plotted against estimates from this study for 5 psychiatric disorders. Both studies and the previous utilised the same data. However, the previous estimates used a bivariate model and so overlapping and closely related samples were excluded on a pairwise basis. In this study overlapping

samples and closely related samples were removed across all 5 disorders generating small samples per disease. A. SNP-heritability (correlation coefficient between previous and current estimates = 0.69); B. Genetic correlations (correlation coefficient between previous and current estimates = 0.98); C. SNP-coheritability (correlation coefficient between previous and current estimates = 0.98)

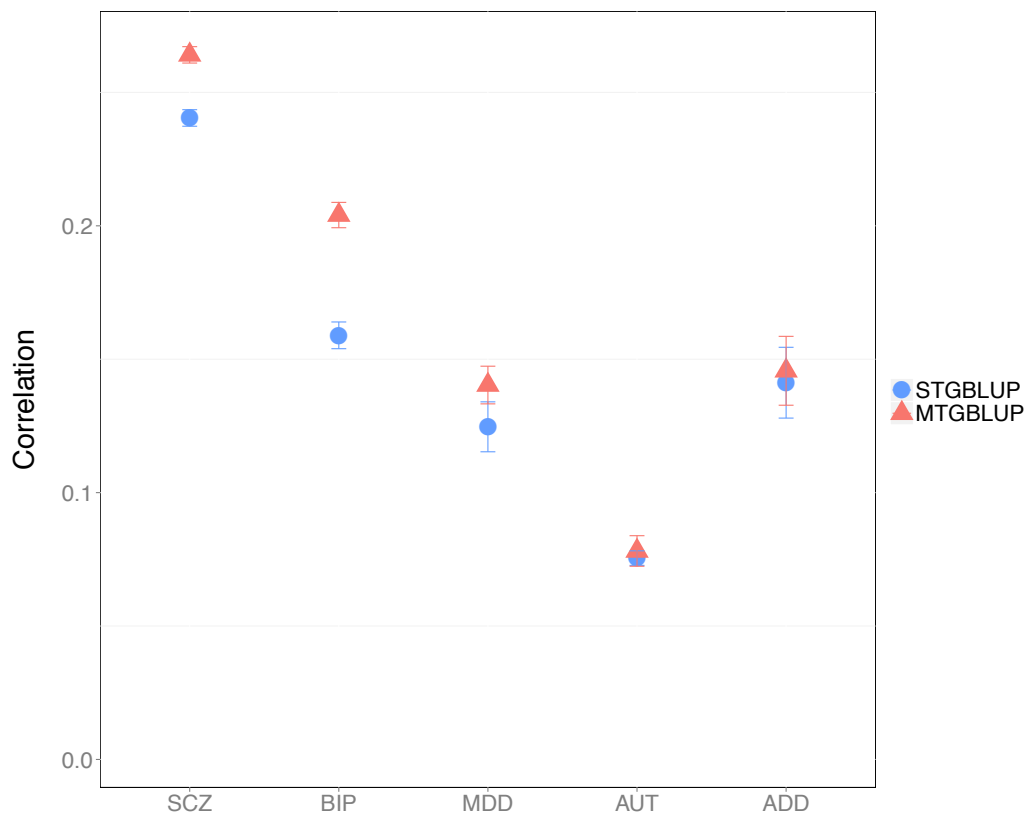
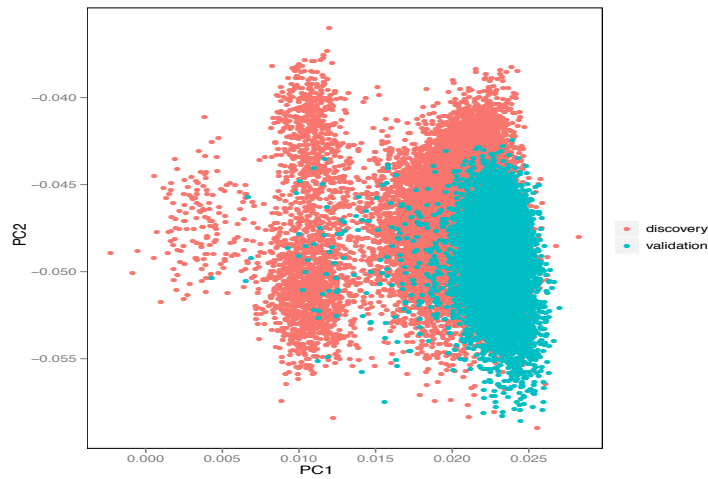
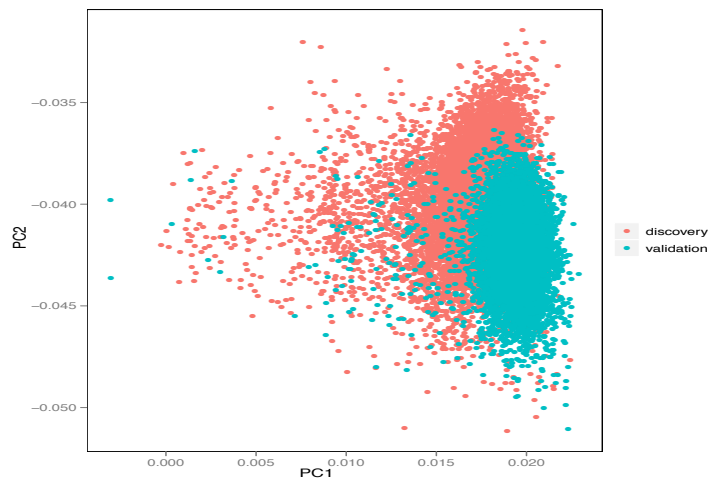


Figure S2. Prediction accuracy of MTGBLUP and STGBLUP for five psychiatric disorders in the within-study validation of PCG. Results are based on 5 replicates. Error bars are \pm empirical standard error. Prediction accuracy is measured as the mean of the correlation coefficient between the true disease status and the predicted genomic risk score in the validation data.

A. Schizophrenia



B. Bipolar disorder

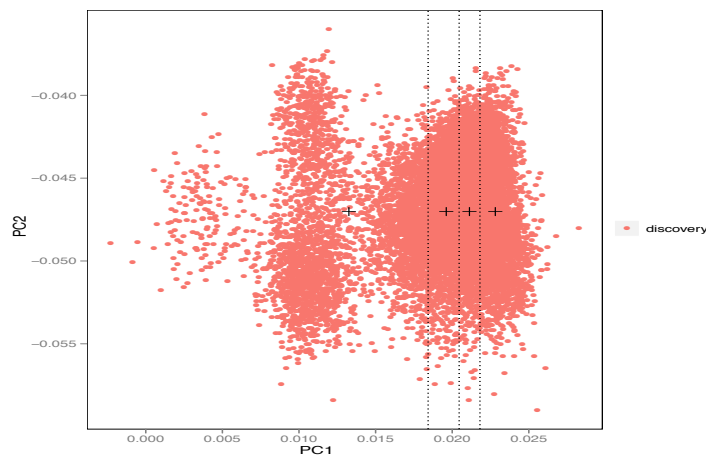


C. Major depressive disorder

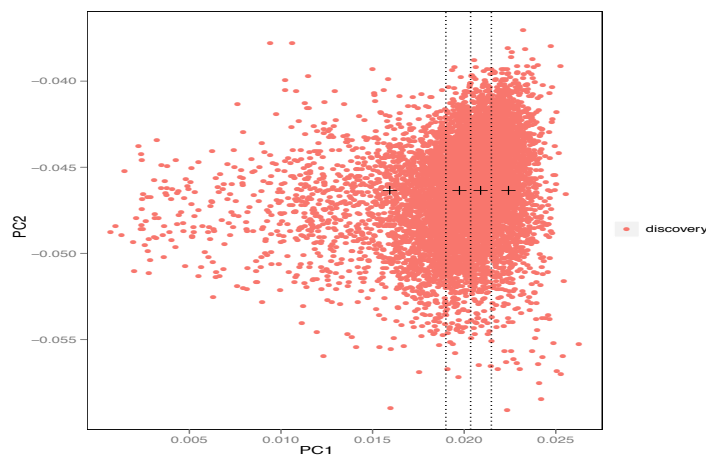


Figure S3. Principal component analysis based on the projected PC from POPRES for SCZ (A), BIP (B) and MDD (C). The same SNPs were selected from the discovery and validation set and used to project PC in each disorder. The number of SNPs used was 745,631 for SCZ, 645,237 for BIP and 673,109 for MDD.

A. Schizophrenia



B. Bipolar disorder



C. Major depressive disorder

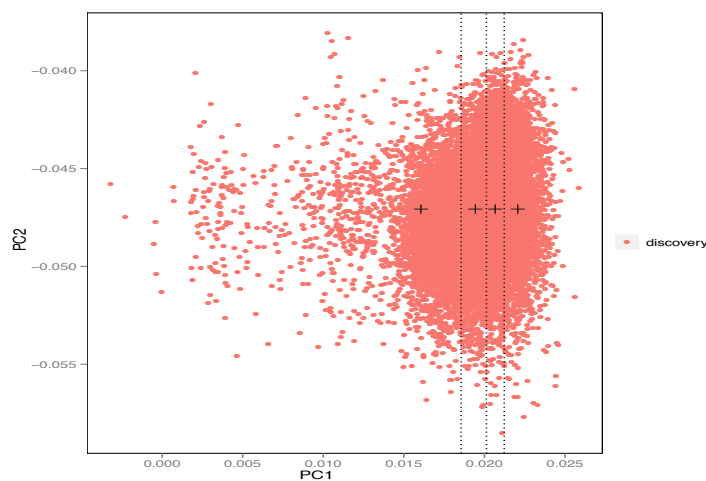
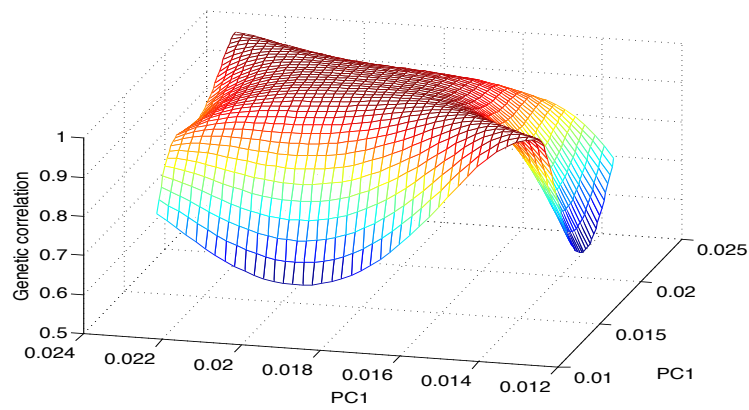
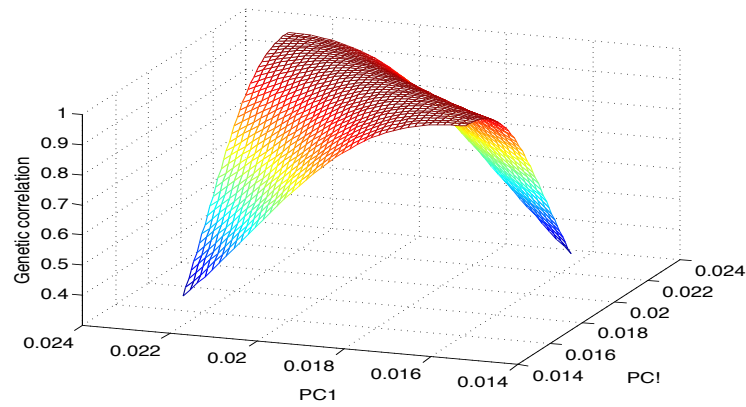


Figure S4. Principal component analysis based on the projected PC from POPRES for the discovery sample of SCZ (A), BIP (B) and MDD (C). The number of SNPs used to project PC was 745,705 for all three disorders. The dashed lines are 25%, 50% and 75% quartiles of the first principal component in the discovery sample (four population classes) and the plus sign is the mean (of PC1) of each population class. The four population classes for each trait were used in the reaction norm model (Appendix B).

A. Schizophrenia



B. Bipolar disorder



C. Major depressive disorder

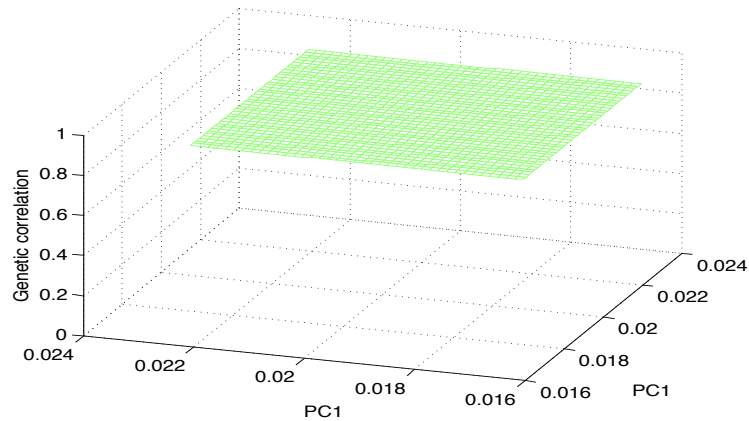
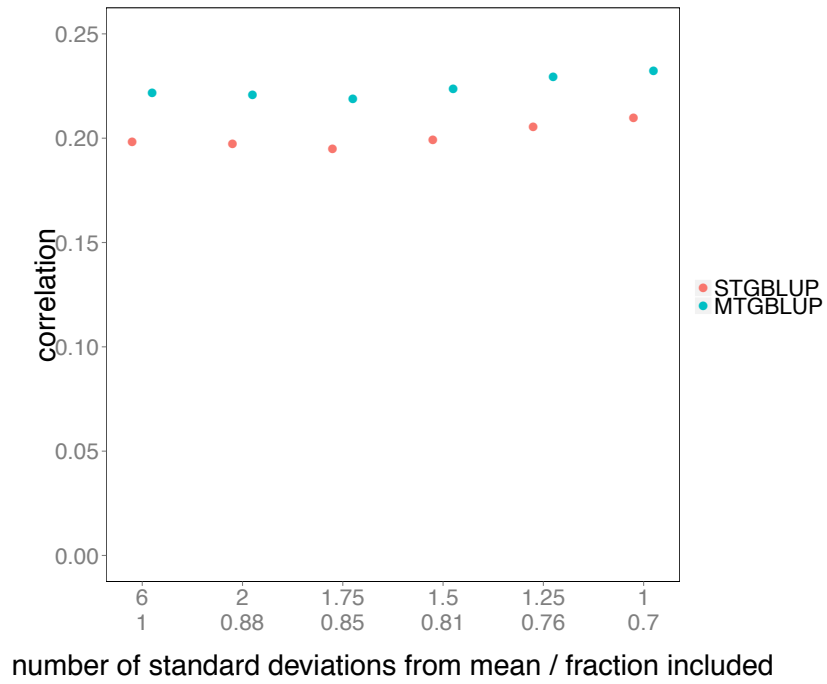
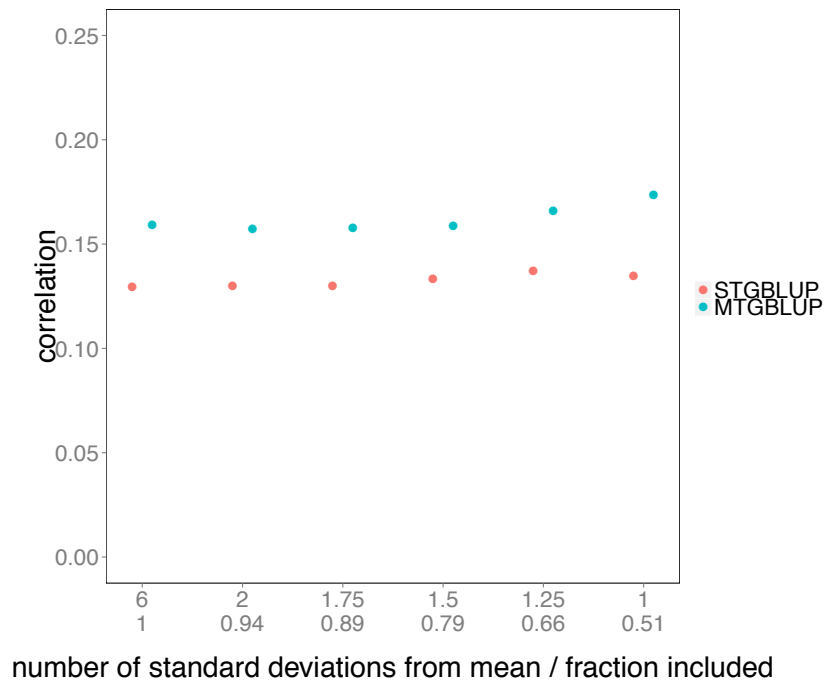


Figure S5. Genetic correlation pattern across different ancestry principal components estimated from the reaction norm model (Appendix B). Order of polynomial (see Table S9): A. $k=3$ for SCZ, B. $k=2$ for BIP, C. $k=1$ for MDD.

A. SCZ



B. BIP



C. MDD

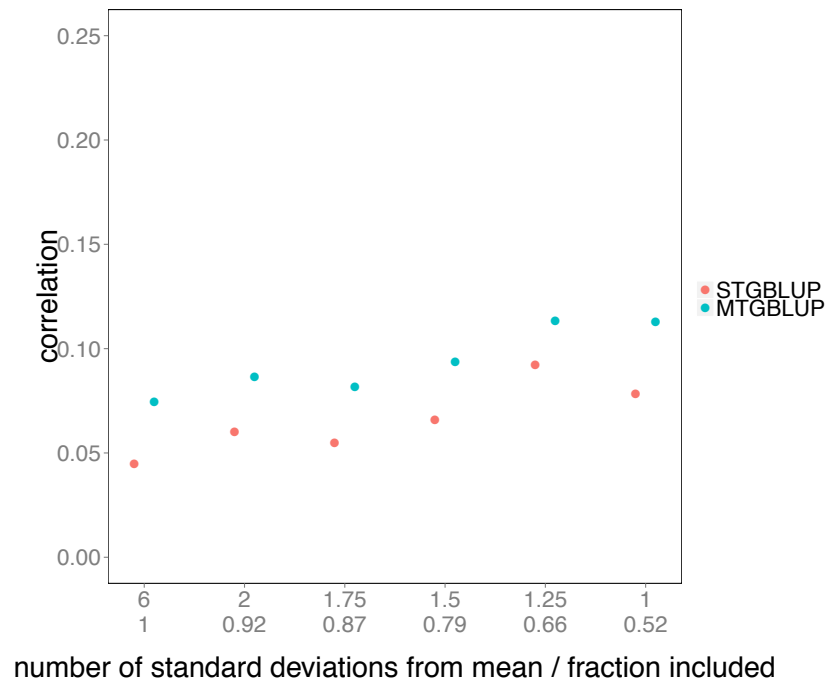


Figure S6. Effect of excluding population outliers on the prediction accuracy from MTGBLUP and STGBLUP. Outliers are defined as points ± 6 , 2, 1.75, 1.5, 1.25 and 1 SD from the mean for both the first and second principal components in the independent (A) SCZ, (B) BIP, (C) MDD samples.

Table S1. Comparison of prediction accuracy (Correlation) and regression coefficient (Regression) from MTGBLUP and STGBLUP for five psychiatric disorders in the within-study validation of PCG

	Correlation	Regression
	Schizophrenia	
STGBLUP	0.240 (0.003)	1.011 (0.022)
MTGBLUP	0.264 (0.003)	1.019 (0.019)
	Bipolar disorder	
STGBLUP	0.159 (0.005)	1.091 (0.054)
MTGBLUP	0.204 (0.005)	0.971 (0.025)
	Major depression	
STGBLUP	0.125 (0.009)	1.078 (0.054)
MTGBLUP	0.140 (0.007)	0.930 (0.038)
	Autism Spectrum Disorders	
STGBLUP	0.075 (0.003)	0.965 (0.080)
MTGBLUP	0.078 (0.006)	0.884 (0.054)
	ADHD	
STGBLUP	0.141 (0.013)	1.144 (0.052)
MTGBLUP	0.146 (0.013)	1.116 (0.050)

Correlation and regression coefficients and empirical standard errors (in brackets) are calculated based on 5 replicates.

Table S2. Prediction accuracy for schizophrenia (SCZ), bipolar disorder (BIP) and major depressive disorder (MDD) in independent validation data sets when using the second annotation model.

	Correlation			Regression		
	SCZ	BIP	MDD	SCZ	BIP	MDD
STGBLUP-SAI	0.199	0.130	0.048	0.787	0.746	0.323
MTGBLUP-SAI	0.222	0.160	0.076	0.817	0.718	0.470

MTGBLUP-SAI or STGBLUP-SAI: in the SAI model SNPs are grouped into schizophrenia / autism / intellectual disability (SAI) candidate genes sets. Prediction accuracy is given as the correlation coefficient between the true disease status and the predicted genomic risk score in the validation data.

Table S3. Comparison of the fit of standard model with the SAI-annotation model for STGBLUP, MTGBLUP and MTGBLUP.

		SCZ	BIP	MDD
x_1	x_2	p-values from LRT		
STGBLUP	STGBLUP-SAI	0.18	0.18	0.070
MTGBLUP	MTGBLUP-SAI	0.22	0.71	0.54
STGBLUP	MTGBLUP-SAI	1.2e-24	9.7E-15	0.0083

Likelihood ratio LR = -2 [$\log L(x_1)$ - $\log L(x_1 + x_2)$]

Table S4. SNP-heritability and genetic correlation between discovery and validation set from bivariate analyses for SCZ, BIP and MDD

Trait 1/ trait 2	Cases T1/T2	Controls T1/T2	Trait 1 h^2 (SE)	Trait 2 h^2 (SE)	r_g (SE)	p-value
SCZ discovery/ SCZ validation	8826/ 4068	6106/ 5471	0.23 (0.01)	0.21 (0.02)	0.80 (0.05)	7.3E-51
BIP discovery/ BIP validation	5867/ 2029	3328/ 5338	0.21 (0.02)	0.22 (0.02)	0.75 (0.08)	7.3E-17
MDD discovery/ MDD validation	8770/ 822	6506/ 467	0.28 (0.02)	0.11 (0.25)	0.51 (0.64)	0.84

h^2 is SNP-heritability on the liability scale. r_g is genetic correlation between discovery/validation set. P-value is for testing if r_g is different from 1, indicating heterogeneity for a lower p-value.

Table S5. Reaction norm model to test heterogeneity across populations classified by the first ancestry principal component

Polynomial order k	log L	Number of parameters	LR	p-value
SCZ				
1	3830.01	5	0.00	1
2	3836.61	7	13.20	0.0014
3	3840.55	10	21.07	0.00078
4	3841.36	14	22.69	0.0069
BIP				
1	2342.89	5	0.00	1
2	2349.27	7	12.76	0.0017
3	2351.64	10	17.49	0.0037
4	2352.77	14	19.75	0.019
MDD				
1	3326.17	5	0.00	1
2	3326.39	7	0.42	0.81
3	3328.24	10	4.14	0.53
4	3330.98	14	9.61	0.38

Populations are classified by the first ancestry principal component. Schizophrenia (p-value=0.00078) and bipolar disorder (p-value=0.0017) show a significant evidence for heterogeneity across different populations.

Table S6. Additional required sample size of STGBLUP to achieve the same prediction accuracy as MTGBLUP and MTGBLUP-CNS.

	SCZ	BIP	MDD
MTGBLUP	4660 (3110 – 6270)	5550 (2830 – 8640)	10940 (730 – 24440)
MTGBLUP-CNS	5080 (3520 – 6690)	6220 (3380 – 9380)	11550 (1220 – 25300)

Values in brackets are Ninety-five percent confidence interval (CI) is in bracket.

Table S7. Comparison of prediction accuracy (correlation) and regression coefficient (regression) from bivariate GBLUP (BVGBLUP)

model	Dependent variable	correlation	regression
BVGBLUP (SCZ, BIP)	SCZ	0.220	0.822
BVGBLUP (SCZ, BIP)	BIP	0.156	0.705
BVGBLUP (SCZ, MDD)	SCZ	0.201	0.785
BVGBLUP (SCZ, MDD)	MDD	0.071	0.461
BVGBLUP (BIP, MDD)	BIP	0.133	0.682
BVGBLUP (BIP, MDD)	MDD	0.040	0.263

Table S8. Results of model comparison between bi-variate (BVGBLUP) and multi-trait GBLUP (MTGBLUP).

x1	x2	Dependent variable	p-value
BVGBLUP (SCZ, BIP)	MTGBLUP	SCZ	1.9E-03
BVGBLUP (SCZ, BIP)	MTGBLUP	BIP	7.4E-03
BVGBLUP (SCZ, MDD)	MTGBLUP	SCZ	1.9E-23
BVGBLUP (SCZ, MDD)	MTGBLUP	MDD	0.50
BVGBLUP (BIP, MDD)	MTGBLUP	BIP	2.5E-14
BVGBLUP (BIP, MDD)	MTGBLUP	MDD	0.00056

Likelihood ratio LR = -2 [logL(x1) - logL(x1+x2)]

Cross disorder Working group of the Psychiatric Genomics Consortium:

Devin Absher¹, Ingrid Agartz^{2,3}, Huda Akil⁴, Farooq Amin⁵, Ole A Andreassen^{2,6}, Adebayo Anjorin⁷, Richard Anney⁸, Dan E Arking⁹, Philip Asherson¹⁰, Maria H Azevedo¹¹, Lena Backlund¹², Judith A Badner¹³, Anthony J Bailey¹⁴, Tobias Banaschewski¹⁵, Jack D Barchas¹⁶, Michael R Barnes¹⁷, Thomas B Barrett¹⁸, Nicholas Bass⁷, Agatino Battaglia¹⁹, Michael Bauer²⁰, Mònica Bayés²¹, Frank Bellivier^{22,23}, Sarah E Bergen^{24,25,26}, Wade Berrettini²⁷, Catalina Betancur^{28,29}, Thomas Bettecken³⁰, Joseph Biederman³¹, Elisabeth B Binder³⁰, Donald W Black³², Douglas H R Blackwood³³, Cinnamon S Bloss^{34,35}, Michael Boehnke^{36,37}, Dorret I Boomsma^{38,39}, Gerome Breen^{10,40}, René Breuer⁴¹, Richard Bruggeman⁴², Nancy G Buccola⁴³, Jan K Buitelaar⁴⁴, William E Bunney⁴⁵, Joseph D Buxbaum⁴⁶, William F Byerley^{47,48}, Sian Caesar⁴⁹, Wiepke Cahn⁵⁰, Rita M Cantor⁵¹, Miguel Casas^{52,53}, Aravinda Chakravarti⁹, Kimberly Chambert²⁴, Khalid Choudhury⁷, Sven Cichon^{54,55}, C Robert Cloninger⁵⁶, David A Collier¹⁰, Edwin H Cook⁵⁷, Hilary Coon⁵⁸, Bru Cormand^{59,60}, Paul Cormican⁸, Aiden Corvin⁸, William H Coryell³², Nicholas Craddock^{61,62}, David W Craig⁶³, Ian W Craig¹⁰, Jennifer Crosbie⁶⁴, Michael L Cuccaro⁶⁵, David Curtis⁶⁶, Darina Czamara^{30,67}, Mark J Daly^{24,68}, Susmita Datta⁶⁹, Geraldine Dawson^{70,71}, Richard Day⁷², Eco J De Geus^{38,39}, Franziska Degenhardt^{54,73}, Bernie Devlin⁷⁴, Srdjan Djurovic^{2,75}, Gary J Donohoe⁸, Alysa E Doyle⁷⁶, Jubao Duan⁷⁷, Frank Dudbridge⁷⁸, Eftichia Duketis⁷⁹, Richard P Ebstein⁸⁰, Howard J Edenberg^{81,82}, Josephine Elia^{27,83}, Sean Ennis⁸⁴, Bruno Etain^{22,23,85,86}, Ayman Fanous^{87,88}, Stephen V Faraone^{89,90}, Anne E Farmer¹⁰, I Nicol Ferrier⁹¹, Matthew Flickinger^{36,37}, Eric Fombonne^{92,93}, Tatiana Foroud⁸², Josef Frank⁴¹, Barbara Franke⁴⁴, Christine Fraser^{61,62}, Robert Freedman⁹⁴, Nelson B Freimer⁹⁵, Christine M Freitag⁷⁹, Marion Friedl⁹⁶, Louise Frisén¹², Louise Gallagher⁸, Pablo V Gejman⁷⁷, Lyudmila Georgieva^{61,62}, Elliot S Gershon¹³, Daniel H Geschwind^{97,98}, Ina Giegling⁹⁶, Michael Gill⁸, Scott D Gordon⁹⁹, Katherine Gordon-Smith^{49,61}, Elaine K Green¹⁰⁰, Tiffany A Greenwood¹⁰¹, Dorothy E Grice^{102,103}, Magdalena Gross¹⁰⁴, Detelina Grozeva⁶¹, Weihua Guan^{36,37,105}, Hugh Gurling⁷, Lieuwe De Haan¹⁰⁶, Jonathan L Haines¹⁰⁷, Hakon Hakonarson^{108,109}, Joachim Hallmayer¹¹⁰, Steven P Hamilton⁴⁷, Marian L Hamshere^{61,111}, Thomas F Hansen^{112,113}, Annette M Hartmann⁹⁶, Martin Hautzinger¹¹⁴, Andrew C Heath⁵⁶, Anjali K Henders⁹⁹, Stefan Herms^{54,55}, Ian B Hickie¹¹⁵, Maria Hipolito¹¹⁶, Susanne Hoefels¹⁰⁴, Peter A Holmans^{61,111}, Florian Holsboer³⁰, Witte J Hoogendijk¹¹⁷, Jouke-Jan Hottenga^{38,39}, Christina M Hultman²⁶, Vanessa Hus¹¹⁸, Andrés Ingason^{112,113}, Marcus Ising³⁰, Stéphane Jamain^{22,23,85,86}, Ian Jones^{61,62}, Lisa Jones⁴⁹, Anna K Kähler²⁶, René S Kahn⁵⁰, Radhika Kandaswamy⁷, Matthew C Keller¹¹⁹, John R Kelsoe^{101,120}, Kenneth S Kendler^{88,121,122}, James L Kennedy¹²³, Elaine Kenny⁸, Lindsey Kent¹²⁴, Yunjung Kim¹²⁵, George K Kirov^{61,62}, Sabine M Klauck¹²⁶, Lambertus Klei⁷⁴, James A Knowles¹²⁷, Martin A Kohli³⁰, Daniel L Koller⁸², Bettina Konte⁹⁶, Ania Korszun¹²⁸, Lydia Krabbendam¹²⁹, Robert Krasucki⁷, Jonna Kuntsi¹⁰, Phoenix Kwan^{36,37}, Mikael Landén^{26,130}, Niklas Långström²⁶, Mark Lathrop¹³¹, Jacob Lawrence⁷, William B Lawson¹¹⁶, Marion Leboyer^{22,23,85,86}, David H Ledbetter¹³², Phil H Lee²⁵, Todd Lencz^{133,134,135}, Klaus-Peter Lesch^{136,137}, Douglas F Levinson¹³⁸, Cathryn M Lewis¹⁰, Jun Li¹³⁹, Paul Lichtenstein²⁶, Jeffrey A Lieberman¹⁴⁰, Dan-Yu Lin¹⁴¹, Don H Linszen¹⁴², Chunyu Liu¹⁴³, Falk W Lohoff²⁷, Sandra K Loo^{95,144}, Catherine Lord¹⁴⁵, Jennifer K Lowe^{97,98}, Susanne Lucae³⁰, Donald J MacIntyre³³, Pamela AF Madden⁵⁶, Elena Maestrini¹⁴⁶, Patrik KE Magnusson²⁶, Pamela B Mahon¹⁴⁷, Wolfgang Maier¹⁰⁴, Anil K Malhotra^{133,134,135}, Shrikant M Mane¹⁴⁸, Christa

L Martin¹³², Nicholas G Martin⁹⁹, Manuel Mattheisen^{73,113,149,150}, Keith Matthews⁷²,
 Morten Mattingsdal^{2,151}, Steven A McCarroll²⁴, Kevin A McGhee³³, James J
 McGough¹⁵², Patrick J McGrath¹⁴⁰, Peter McGuffin¹⁰, Melvin G McInnis¹⁵³, Andrew
 McIntosh^{33,154}, Rebecca McKinney¹⁰¹, Alan W McLean^{33,154}, Francis J McMahon¹⁵⁵,
 William M McMahon⁵⁸, Andrew McQuillin⁷, Helena Medeiros¹²⁷, Sarah E
 Medland⁹⁹, Sandra Meier⁴¹, Ingrid Melle^{2,6}, Fan Meng⁴, Jobst Meyer¹⁵⁶, Christel M
 Middeldorp^{38,39}, Lefkos Middleton¹⁵⁷, Vihra Milanova¹⁵⁸, Ana Miranda¹⁵⁹, Anthony P
 Monaco^{160,161}, Grant W Montgomery⁹⁹, Jennifer L Moran²⁴, Daniel Moreno-De-
 Luca¹⁶², Gunnar Morken^{163,164}, Derek W Morris⁸, Eric M Morrow^{165,166}, Valentina
 Moskvina^{61,111}, Bryan J Mowry^{167,168}, Pierandrea Muglia¹⁶⁹, Thomas W
 Mühleisen^{54,73,170}, Bertram Müller-Myhsok^{30,67}, Michael Murtha¹⁷¹, Richard M
 Myers¹, Inez Myin-Germeys¹²⁹, Benjamin M Neale^{24,68}, Stan F Nelson⁹⁵, Caroline M
 Nievergelt¹⁰¹, Ivan Nikolov^{61,62}, Vishwajit Nimgaonkar^{172,173}, Willem A Nolen¹⁷⁴,
 Markus M Nöthen^{54,73}, John I Nurnberger^{82,175}, Evaristus A Nwulia¹¹⁶, Dale R
 Nyholt⁹⁹, Michael C O'Donovan^{61,62}, Colm O'Dushlaine²⁴, Robert D Oades¹⁷⁶, Ann
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 Paterson^{181,182}, Carlos N Pato¹²⁷, Michele T Pato¹²⁷, Brenda W Penninx^{39,183,184},
 Michele L Pergadia⁵⁶, Margaret A Pericak-Vance⁶⁵, Roy H Perlis^{24,25}, Benjamin S
 Pickard^{33,154}, Jonathan Pimm⁷, Joseph Piven⁷¹, Danielle Posthuma^{185,186,187}, James B
 Potash³², Fritz Poustka⁷⁹, Peter Propping⁷³, Shaun M Purcell^{24,68,188}, Vinay Puri⁷,
 Digby J Quested¹⁸⁹, Emma M Quinn⁸, Josep Antoni Ramos-Quiroga^{52,53}, Henrik B
 Rasmussen^{112,113}, Soumya Raychaudhuri^{24,68}, Karola Rehnström¹⁸⁰, Andreas Reif¹⁹⁰,
 Marta Ribasés^{52,191}, John P Rice¹⁹², Marcella Rietschel⁴¹, Stephan Ripke^{24,68}, Kathryn
 Roeder¹⁹³, Herbert Roeyers¹⁹⁴, Lizzy Rossin²⁴, Aribert Rothenberger¹⁹⁵, Guy
 Rouleau¹⁹⁶, Douglas Ruderfer¹⁸⁸, Dan Rujescu⁹⁶, Alan R Sanders⁷⁷, Stephan J
 Sanders^{162,171,197,198}, Susan L Santangelo^{199,200}, Russell Schachar⁶⁴, Martin Schalling¹²,
 Alan F Schatzberg²⁰¹, William A Scheftner²⁰², Gerard D Schellenberg²⁰³, Stephen W
 Scherer²⁰⁴, Nicholas J Schork^{34,205}, Thomas G Schulze^{147,206}, Johannes Schumacher⁷³,
 Markus Schwarz²⁰⁷, Edward Scolnick²⁴, Laura J Scott^{36,37}, Joseph A Sergeant²⁰⁸,
 Jianxin Shi²⁰⁹, Paul D Shilling¹⁰¹, Stanley I Shyn²¹⁰, Jeremy M Silverman¹⁰³, Pamela
 Sklar¹⁸⁸, Susan L Slager²¹¹, Susan L Smalley^{95,144}, Johannes H Smit^{183,184}, Erin N
 Smith^{34,205}, Jordan W Smoller^{24,25}, Edmund JS Sonuga-Barke^{194,212}, David St Clair²¹³,
 Matthew State^{162,171,197}, Michael Steffens²¹⁴, Hans-Christoph Steinhausen^{215,216,217},
 John S Strauss²¹⁸, Jana Strohmaier⁴¹, T Scott Stroup²¹⁹, Patrick F Sullivan¹²⁵, James
 Sutcliffe²²⁰, Peter Szatmari^{221,222,223}, Szabocls Szelinger⁶³, Anita Thapar^{61,62}, Srinivasa
 Thirumalai²²⁴, Robert C Thompson⁴, Alexandre A Todorov⁵⁶, Federica Tozzi¹⁶⁹, Jens
 Treutlein⁴¹, Jung-Ying Tzeng²²⁵, Manfred Uhr³⁰, Edwin JCG van den Oord²²⁶, Gerard
 Van Grootheest^{183,184}, Jim Van Os¹²⁹, Astrid M Vicente^{227,228,229}, Veronica J
 Vieland²³⁰, John B Vincent²¹⁸, Peter M Visscher^{167,231}, Christopher A
 Walsh^{232,233,234,235}, Thomas H Wassink³², Stanley J Watson⁴, Lauren A Weiss⁴⁷,
 Myrna M Weissman²³⁶, Thomas Werge^{112,113,237}, Thomas F Wienker²³⁸, Durk
 Wiersma⁴², Ellen M Wijsman^{239,240}, Gonneke Willemsen^{38,183}, Nigel Williams^{61,62}, A
 Jeremy Willsey^{171,197}, Stephanie H Witt⁴¹, Naomi R Wray¹⁶⁷, Wei Xu¹⁸², Allan H
 Young^{91,241}, Timothy W Yu²⁴², Stanley Zammit^{61,62}, Peter P Zandi²⁴³, Peng
 Zhang^{36,37,153}, Frans G Zitman²⁴⁴, Sebastian Zöllner^{36,37,153}

¹HudsonAlpha Institute of Biotechnology, Huntsville, Alabama, USA. ²KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ³Department of Research, Diakonhjemmet Hospital, Oslo, Norway. ⁴Molecular Psychiatry Laboratory, Molecular and Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, Michigan, USA. ⁵Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Emory University, Atlanta, Georgia, USA. ⁶Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. ⁷Mental Health Sciences Unit, University College London, London, UK. ⁸Department of Psychiatry, Trinity College Dublin, Dublin, Ireland. ⁹McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. ¹⁰MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, The Institute of Psychiatry, King's College London, London, UK. ¹¹Faculty of Medicine, University of Coimbra, Coimbra, Portugal. ¹²Department of Molecular Medicine and Surgery, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden. ¹³Department of Psychiatry, University of Chicago, Chicago, Illinois, USA. ¹⁴Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada. ¹⁵Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. ¹⁶Department of Psychiatry, Weill Medical College, Cornell University, New York, New York, USA. ¹⁷GlaxoSmithKline, London, UK. ¹⁸Portland Veterans Affairs Medical Center, Portland, Oregon, USA. ¹⁹Stella Maris Institute for Child and Adolescent Neuropsychiatry, Calambrone, Pisa, Italy. ²⁰Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Dresden, Germany. ²¹Centro Nacional de Análisis Genómico (CNAG), Parc Científic de Barcelona (PCB), Barcelona, Spain. ²²Institut National de la Santé et de la Recherche Médicale (INSERM) U955, Psychiatrie Génétique, Créteil, France. ²³ENBREC (European Network of Bipolar Research Expert Centres) Group, Fondation FondaMental, Créteil, France. ²⁴Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. ²⁵Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. ²⁶Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ²⁷Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA. ²⁸INSERM U952, Paris, France. ²⁹Université Pierre et Marie Curie, Paris, France. ³⁰Max Planck Institute of Psychiatry, Munich, Germany. ³¹Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA. ³²Department of Psychiatry, University of Iowa, Iowa City, Iowa, USA. ³³Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK. ³⁴The Scripps Translational Science Institute, La Jolla, California, USA. ³⁵Scripps Health, La Jolla, California, USA. ³⁶Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA. ³⁷Center for Statistical Genetics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA. ³⁸Department of Biological Psychology, VU University, Amsterdam, The Netherlands. ³⁹Neuroscience Campus Amsterdam, Amsterdam, The Netherlands. ⁴⁰National Institute of Health Research (NIHR) Biomedical Research Centre for Mental Health, South London, London, UK and Maudsley National Health Service (NHS) Trust and Institute of Psychiatry, London, UK. ⁴¹Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim,

Germany.⁴²Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.⁴³School of Nursing, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA.

⁴⁴Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Centre, Nijmegen, The Netherlands.⁴⁵Department of Psychiatry and Human Behavior, University of California– Irvine, Irvine, California, USA. ⁴⁶Seaver Autism Center for Research and Treatment, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA⁴⁷Department of Psychiatry, University of California, San Francisco, San Francisco, California, USA. ⁴⁸NCIRE (Northern California Institute of Q Research and Education), San Francisco, California, USA. ⁴⁹Department of Psychiatry, Birmingham University, Birmingham, UK.⁵⁰Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center, Utrecht, The Netherlands.⁵¹David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA. ⁵²Department of Psychiatry, Hospital Universitari Vall d’Hebron, CIBERSAM (Centro de Investigación Biomédica en el Area de Salud Mental), Barcelona, Spain. ⁵³Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain.⁵⁴Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. ⁵⁵Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland. ⁵⁶Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA. ⁵⁷Department of Psychiatry, Institute for Juvenile Research, University of Illinois, Chicago, Illinois, USA⁵⁸Department of Psychiatry, University of Utah, Salt Lake City, Utah, USA. ⁵⁹Departament de Genètica, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain. ⁶⁰Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain.⁶¹Medical Research Council (MRC) Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK.⁶²Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, UK. ⁶³The Translational Genomics Research Institute, Phoenix, Arizona, USA.⁶⁴Neurosciences and Mental Health Program, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.⁶⁵John P. Hussman Institute for Human Genomics, University of Miami, Miami, Florida, USA. ⁶⁶East London NHS Foundation Trust, Queen Mary, University of London, London, UK. ⁶⁷Munich Cluster for Systems Neurology (SyNergy), Munich, Germany.⁶⁸Analytic and Translational Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA. ⁶⁹Genetics Institute, University College London, London, UK. ⁷⁰Autism Speaks, New York, New York, USA. ⁷¹Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.⁷²Division of Neuroscience, Medical Research Institute, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK. ⁷³Institute of Human Genetics, University of Bonn, Bonn, Germany. ⁷⁴Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.⁷⁵Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. ⁷⁶Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA. ⁷⁷Department of Psychiatry and Behavioral Sciences, NorthShore University Health System and University of Chicago, Evanston, Illinois, USA. ⁷⁸Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK.

⁷⁹Department of Child and Adolescent Psychiatry, Psychosomatics and

Psychotherapy, JW Goethe University Frankfurt, Frankfurt, Germany.⁸⁰Psychology Department, National University of Singapore, Singapore.⁸¹Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana, USA.⁸²Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA.⁸³AI Dupont Hospital for Children, University of Pennsylvania, Philadelphia, Pennsylvania, USA.⁸⁴School of Medicine, Medical Science University College, Dublin, Ireland.⁸⁵Université Paris Est, Faculté de Médecine, Créteil, France.⁸⁶AP-HP, Hôpital H Mondor–A Chenevier, Département de Psychiatrie, Créteil, France.⁸⁷Department of Psychiatry, Georgetown University School of Medicine, Washington, DC, USA.⁸⁸Virginia Institute of Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA.⁸⁹Department of Psychiatry, State University of New York (SUNY) Upstate Medical University, Syracuse, New York, USA.⁹⁰Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, New York, USA.⁹¹Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK.⁹²Department of Psychiatry, Oregon Health & Science University, Portland, Oregon, USA.⁹³Institute for Development & Disability, Oregon Health & Science University, Portland, Oregon, USA.⁹⁴Department of Psychiatry, University of Colorado Denver, Aurora, Colorado, USA.⁹⁵Center for Neurobehavioral Genetics, University of California, Los Angeles, Los Angeles, California, USA.⁹⁶Department of Psychiatry, University of Halle, Halle, Germany.⁹⁷Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA.⁹⁸Center for Autism Research and Treatment, Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA.⁹⁹Queensland Institute of Medical Research, Brisbane, Queensland, Australia.¹⁰⁰Department of Biomedical and Biological Sciences, Plymouth University, Plymouth, UK.¹⁰¹Department of Psychiatry, University of California, San Diego, La Jolla, California, USA.¹⁰²Division of Tics, OCD and Related Disorders, Icahn School of Medicine at Mount Sinai, New York, New York, USA.¹⁰³Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA.¹⁰⁴Department of Psychiatry, University of Bonn, Bonn, Germany.¹⁰⁵Division of Biostatistics, University of Minnesota, Minneapolis, Minnesota, USA.¹⁰⁶Department of Psychiatry, Academic Medical Centre, University of Amsterdam The Netherlands.¹⁰⁷Center for Human Genetics Research, Vanderbilt University Medical Center, Nashville, Tennessee, USA.¹⁰⁸The Center for Applied Genomics, Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.¹⁰⁹Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA.¹¹⁰Department of Psychiatry, School of Medicine, Stanford University, Stanford, California, USA.¹¹¹Biostatistics and Bioinformatics Unit, Cardiff University, Cardiff, UK.¹¹²Institute of Biological Psychiatry, Copenhagen University Hospital, Roskilde, Denmark.¹¹³The Lundbeck Initiative for Integrative Psychiatric Research, iPSYCH, Roskilde, Denmark.¹¹⁴Department of Clinical and Developmental Psychology, Eberhard Karls University of Tübingen, Tübingen, Germany.¹¹⁵Brain and Mind Research Institute, University of Sydney, Sydney, New South Wales, Australia.¹¹⁶Department of Psychiatry and Behavioral Sciences, Howard University College of Medicine, Washington, DC, USA.¹¹⁷Department of Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands.¹¹⁸Department of Psychology, University of Michigan, Ann Arbor, Michigan, USA.¹¹⁹Department of Psychology, University of Colorado, Boulder,

Colorado, USA.¹²⁰Department of Psychiatry, Special Treatment and Evaluation Program (STEP), Veterans Affairs San Diego Healthcare System, San Diego, California, USA.¹²¹Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, USA.¹²²Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA.¹²³Psychiatric Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada.¹²⁴School of Medicine, University of St Andrews, St Andrews, UK.¹²⁵Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.¹²⁶Division of Molecular Genome Analysis, German Cancer Research Center (DKFZ), Heidelberg, Germany.¹²⁷Department of Psychiatry, Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.¹²⁸Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK.¹²⁹Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, Maastricht, The Netherlands.¹³⁰Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden.¹³¹Centre National de Genotypage, Evry, France.¹³²Geisinger Health System, Autism and Developmental Medicine Institute, Danville, Pennsylvania, USA.¹³³Department of Psychiatry, Division of Research, The Zucker Hillside Hospital Division of the North Shore, Long Island Jewish Health System, Glen Oaks, New York, USA.¹³⁴Center for Psychiatric Neuroscience, The Feinstein Institute of Medical Research, Manhasset, New York, USA.¹³⁵Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, USA.¹³⁶Division of Molecular Psychiatry, ADHD Clinical Research Unit, Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany.¹³⁷Department of Psychiatry and Psychology, School for Mental Health and Neuroscience (MHENS), Maastricht University, Maastricht, The Netherlands.¹³⁸Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA.¹³⁹Department of Human Genetics, University of Michigan, Ann Arbor, Michigan, USA.¹⁴⁰New York State Psychiatric Institute, Columbia University, New York, New York, USA.¹⁴¹Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.¹⁴²Department of Psychiatry, Academic Medical Centre University of Amsterdam, Amsterdam, The Netherlands.¹⁴³Department of Psychiatry, Institute of Human Genetics, University of Illinois at Chicago, Chicago, Illinois, USA.¹⁴⁴Department of Psychiatry and Biobehavioral Science, University of California, Los Angeles, Los Angeles, California, USA.¹⁴⁵Center for Autism and the Developing Brain, Weill Cornell Medical College, White Plains, New York, USA.¹⁴⁶Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy.¹⁴⁷Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, Maryland, USA.¹⁴⁸Yale Center for Genome Analysis, Orange, Connecticut, USA.¹⁴⁹Department of Biomedicine, Aarhus University, Aarhus, Denmark.¹⁵⁰Department of Genomic Mathematics, University of Bonn, Bonn, Germany.¹⁵¹Sørlandet Hospital, Kristiansand, Norway.¹⁵²Child and Adolescent Psychiatry, Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA.¹⁵³Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, USA.¹⁵⁴Molecular Medicine Centre, University of Edinburgh, Edinburgh, UK.¹⁵⁵National Institute of Mental Health, US National Institutes of Health, Bethesda, Maryland, USA.¹⁵⁶Department of Neurobehavioral Genetics, Trier University, Trier, Germany.¹⁵⁷Neuroepidemiology and Ageing Research, School of Public Health,

Imperial College London, London, UK. ¹⁵⁸Department of Psychiatry, First Psychiatric Clinic, Alexander University Hospital, Sofia, Bulgaria. ¹⁵⁹Department of Developmental and Educational Psychology, University of Valencia, Valencia, Spain. ¹⁶⁰Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK. ¹⁶¹Office of the President, Tufts University, Medford, Massachusetts, USA. ¹⁶²Department of Psychiatry, Yale University, New Haven, Connecticut, USA. ¹⁶³Department of Psychiatry, St. Olavs Hospital, Trondheim, Norway. ¹⁶⁴Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway. ¹⁶⁵Department of Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, Rhode Island, USA. ¹⁶⁶Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, USA. ¹⁶⁷The University of Queensland, Queensland Brain Institute, Brisbane, Queensland, Australia. ¹⁶⁸Queensland Centre for Mental Health Research, Wacol, Queensland, Australia. ¹⁶⁹Neurosciences Centre of Excellence in Drug Discovery, GlaxoSmithKline Research and Development, Verona, Italy. ¹⁷⁰Life & Brain Center, University of Bonn, Bonn, Germany. ¹⁷¹Child Study Center, Yale University, New Haven, Connecticut, USA. ¹⁷²Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania, USA. ¹⁷³Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA. ¹⁷⁴Department of Psychiatry, Groningen University Medical Center, Groningen, The Netherlands. ¹⁷⁵Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana, USA. ¹⁷⁶Clinic for Child and Adolescent Psychiatry and Psychotherapy, University of Duisburg-Essen, Essen, Germany. ¹⁷⁷Research and Clinical Training Department, Pediatric Hospital, Centro Hospitalar e Universitário Coimbra, Coimbra, Portugal. ¹⁷⁸Department of Human Genetics, University of California, Los Angeles, Los Angeles, California, USA. ¹⁷⁹Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands. ¹⁸⁰Sanger Institute, Hinxton, Cambridge, UK. ¹⁸¹Program in Genetics and Genomic Biology, The Hospital for Sick Children, Toronto, Ontario, Canada. ¹⁸²Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada. ¹⁸³EMGO+ (ExtraMuraalGeneeskundig Onderzoek) Institute for Health and Care Research, Amsterdam, The Netherlands. ¹⁸⁴Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands. ¹⁸⁵Department of Functional Genomics, VU University, Amsterdam, The Netherlands. ¹⁸⁶Department of Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands. ¹⁸⁷Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands. ¹⁸⁸Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA. ¹⁸⁹Academic Department of Psychiatry, University of Oxford, Oxford, UK. ¹⁹⁰Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Goethe-University Frankfurt, Frankfurt am Main, Germany. ¹⁹¹Psychiatric Genetics Unit, Vall d'Hebron Research Institute, Barcelona, Spain. ¹⁹²Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA. ¹⁹³Department of Statistics, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA. ¹⁹⁴Department of Experimental Clinical & Health Psychology, Ghent University, Ghent, Belgium. ¹⁹⁵Child and Adolescent Psychiatry, University Medicine Göttingen, Göttingen, Germany. ¹⁹⁶Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada. ¹⁹⁷Department of Genetics, Yale University, New Haven, Connecticut, USA. ¹⁹⁸Program on Neurogenetics, Yale University, New Haven, Connecticut, USA. ¹⁹⁹Department of Psychiatry, Maine Medical Center, Portland, Maine,

USA.²⁰⁰ Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA.²⁰¹ Department of Psychiatry and Behavioral Science, Stanford University School of Medicine, Palo Alto, California, USA.²⁰² Rush Ambulatory Behavioral Health, Rush University Medical Center, Chicago, Illinois, USA.²⁰³ Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.²⁰⁴ The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, Ontario, Canada.²⁰⁵ The Scripps Research Institute, La Jolla, California, USA.²⁰⁶ Department of Psychiatry & Psychotherapy, University of Göttingen, Göttingen, Germany.²⁰⁷ Psychiatric Center Nordbaden, Wiesloch, Germany.²⁰⁸ Department of Clinical Neuropsychology, VU University, Amsterdam, The Netherlands.²⁰⁹ Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA.²¹⁰ Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington, USA.²¹¹ Mayo Clinic, Rochester, Minnesota, USA.²¹² Developmental Brain & Behaviour Laboratory, Academic Unit of Psychology, University of Southampton, Southampton, UK.²¹³ Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK.²¹⁴ Research Department, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany.²¹⁵ Research Unit of Child and Adolescent Psychiatry, Aalborg University Hospital, Aalborg, Denmark.²¹⁶ Clinical Psychology and Epidemiology, University of Basel, Basel, Switzerland.²¹⁷ Department of Child and Adolescent Psychiatry, University of Zurich, Zurich, Switzerland.²¹⁸ Molecular Neuropsychiatry and Development Laboratory, Centre for Addiction and Mental Health, Toronto, Ontario, Canada.²¹⁹ Department of Psychiatry, Columbia University, New York, New York, USA.²²⁰ Vanderbilt Brain Institute, Vanderbilt University, Nashville, Tennessee, USA.²²¹ Department of Psychiatry, University of Toronto, Toronto, Ontario Canada.²²² Neurosciences and Mental Health Program, Hospital for Sick Children, Toronto, Ontario Canada.²²³ Centre for Addiction and Mental Health, Toronto, Ontario, Canada.²²⁴ Oxford Health NHS Foundation Trust, Marlborough House Secure Unit, Milton Keynes, UK.²²⁵ Bioinformatics Research Center, North Carolina State University, Raleigh, North Carolina, USA.²²⁶ Center for Biomarker Research and Personalized Medicine, Virginia Commonwealth University, Richmond, Virginia, USA.²²⁷ Instituto Nacional de Saude Dr Ricardo Jorge, Lisbon, Portugal.²²⁸ BioFIG—Center for Biodiversity, Functional and Integrative Genomics, Campus da FCUL, Campo Grande, Lisbon, Portugal.²²⁹ Instituto Gulbenkian de Ciência, Lisbon, Portugal.²³⁰ Battelle Center for Mathematical Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA.²³¹ The University of Queensland, Diamantina Institute, Brisbane, Queensland, Australia.²³² Howard Hughes Medical Institute, Children's Hospital Boston, Boston, Massachusetts, USA.²³³ Division of Genetics, Children's Hospital Boston, Boston, Massachusetts, USA.²³⁴ Department of Neurology, Harvard Medical School Center for Life Sciences, Boston, Massachusetts, USA.²³⁵ Department of Pediatrics, Harvard Medical School Center for Life Sciences, Boston, Massachusetts, USA.²³⁶ Columbia University College of Physicians and Surgeons, New York, New York, USA.²³⁷ Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark.²³⁸ Institute of Medical Biometry, University of Bonn, Bonn, Germany.²³⁹ Department of Biostatistics, University of Washington, Seattle, Washington, USA.²⁴⁰ Department of Medicine, University of Washington, Seattle, Washington, USA.²⁴¹ Centre for Affective Disorders, Institute of Psychiatry, King's College London, London, UK.²⁴² Division of Genetics, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, USA.²⁴³ Department of Mental Health, Johns Hopkins University, Baltimore,

Maryland, USA.²⁴⁴Department of Psychiatry, Leiden University Medical Center,
Leiden, The Netherlands.