Rapid #: -19320621

CROSS REF ID: **6121369**

LENDER: **LHL4CRLRM :: Main Library**

BORROWER: **HUL :: Widener Library**

TYPE:	Article CC:CCL
JOURNAL TITLE:	Nature
USER JOURNAL TITLE:	Nature
ARTICLE TITLE:	Schizophrena Working Group of the Psychiatric Genomics Consortium
ARTICLE AUTHOR:	
VOLUME:	511
ISSUE:	7510
MONTH:	July
YEAR:	2014
PAGES:	421-427
ISSN:	0028-0836
OCLC #:	

Processed by RapidX: 7/25/2022 2:15:18 PM

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ARTICLE

doi:10.1038/nature13595

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

Schizophrenia is a highly heritable disorder. Genetic risk is conferred by a large number of alleles, including common alleles of small effect that might be detected by genome-wide association studies. Here we report a multi-stage schizophrenia genome-wide association study of up to 36,989 cases and 113,075 controls. We identify 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, 83 of which have not been previously reported. Associations were enriched among genes expressed in brain, providing biological plausibility for the findings. Many findings have the potential to provide entirely new insights into aetiology, but associations at *DRD2* and several genes involved in glutamatergic neurotransmission highlight molecules of known and potential therapeutic relevance to schizophrenia, and are consistent with leading pathophysiological hypotheses. Independent of genes expressed in brain, associations were enriched among genes expressed in tissues that have important roles in immunity, providing support for the speculated link between the immune system and schizophrenia.

Schizophrenia has a lifetime risk of around 1%, and is associated with substantial morbidity and mortality as well as personal and societal costs[1–3]. Although pharmacological treatments are available for schizophrenia, their efficacy is poor for many patients[4]. All available antipsychotic drugs are thought to exert their main therapeutic effects through blockade of the type 2 dopaminergic receptor[5,6] but, since the discovery of this mechanism over 60 years ago, no new antipsychotic drug of proven efficacy has been developed based on other target molecules. Therapeutic stasis is in large part a consequence of the fact that the pathophysiology of schizophrenia is unknown. Identifying the causes of schizophrenia is therefore a critical step towards improving treatments and outcomes for those with the disorder.

High heritability points to a major role for inherited genetic variants in the aetiology of schizophrenia[7,8]. Although risk variants range in frequency from common to extremely rare[9], estimates[10,11] suggest half to a third of the genetic risk of schizophrenia is indexed by common alleles genotyped by current genome-wide association study (GWAS) arrays. Thus, GWAS is potentially an important tool for understanding the biological underpinnings of schizophrenia.

To date, around 30 schizophrenia-associated loci[10–23] have been identified through GWAS. Postulating that sample size is one of the most important limiting factors in applying GWAS to schizophrenia, we created the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC). Our primary aim was to combine all available schizophrenia samples with published or unpublished GWAS genotypes into a single, systematic analysis[24]. Here we report the results of that analysis, including at least 108 independent genomic loci that exceed genome-wide significance. Some of the findings support leading pathophysiological hypotheses of schizophrenia or targets of therapeutic relevance, but most of the findings provide new insights.

108 independent associated loci

We obtained genome-wide genotype data from which we constructed 49 ancestry matched, non-overlapping case-control samples (46 of European and three of east Asian ancestry, 34,241 cases and 45,604 controls) and 3 family-based samples of European ancestry (1,235 parent affected-offspring trios) (Supplementary Table 1 and Supplementary Methods). These comprise the primary PGC GWAS data set. We processed the genotypes from all studies using unified quality control procedures followed by imputation of SNPs and insertion-deletions using the 1000 Genomes Project reference panel[25]. In each sample, association testing was conducted using imputed marker dosages and principal components (PCs) to control for population stratification. The results were combined using an inverse-variance weighted fixed effects model[26]. After quality control (imputation INFO score ≥ 0.6, MAF ≥ 0.01, and successfully imputed in ≥ 20 samples), we considered around 9.5 million variants. The results are summarized in Fig. 1. To enable acquisition of large samples, some groups ascertained cases via clinician diagnosis rather than a research-based assessment and provided evidence of the validity of this approach (Supplementary Information)[11,13]. Post hoc analyses revealed the pattern of effect sizes for associated loci was similar across different assessment methods and modes of ascertainment (Extended Data Fig. 1), supporting our *a priori* decision to include samples of this nature.

For the subset of linkage-disequilibrium-independent single nucleotide polymorphisms (SNPs) with $P < 1 \times 10^{-6}$ in the meta-analysis, we next obtained results from deCODE genetics (1,513 cases and 66,236 controls of European ancestry). We define linkage-disequilibrium-independent SNPs as those with low linkage disequilibrium ($r^2 < 0.1$) to a more significantly associated SNP within a 500-kb window. Given high linkage disequilibrium in the extended major histocompatibility complex (MHC) region spans ~8 Mb, we conservatively include only a single MHC SNP to represent this locus. The deCODE data were then combined with those from the primary GWAS to give a data set of 36,989 cases and 113,075 controls. In this final analysis, 128 linkage-disequilibrium-independent SNPs exceeded genome-wide significance ($P \leq 5 \times 10^{-8}$) (Supplementary Table 2).

As in meta-analyses of other complex traits which identified large numbers of common risk variants[27,28], the test statistic distribution from our GWAS deviates from the null (Extended Data Fig. 2). This is consistent with the previously documented polygenic contribution to schizophrenia[10,11]. The deviation in the test statistics from the null ($\lambda_{GC} = 1.47, \lambda_{1000} = 1.01$) is only slightly less than expected ($\lambda_{GC} = 1.56$) under a polygenic model given fully informative genotypes, the current sample size, and the lifetime risk and heritability of schizophrenia[29].

*A list of authors and affiliations appears at the end of the paper.

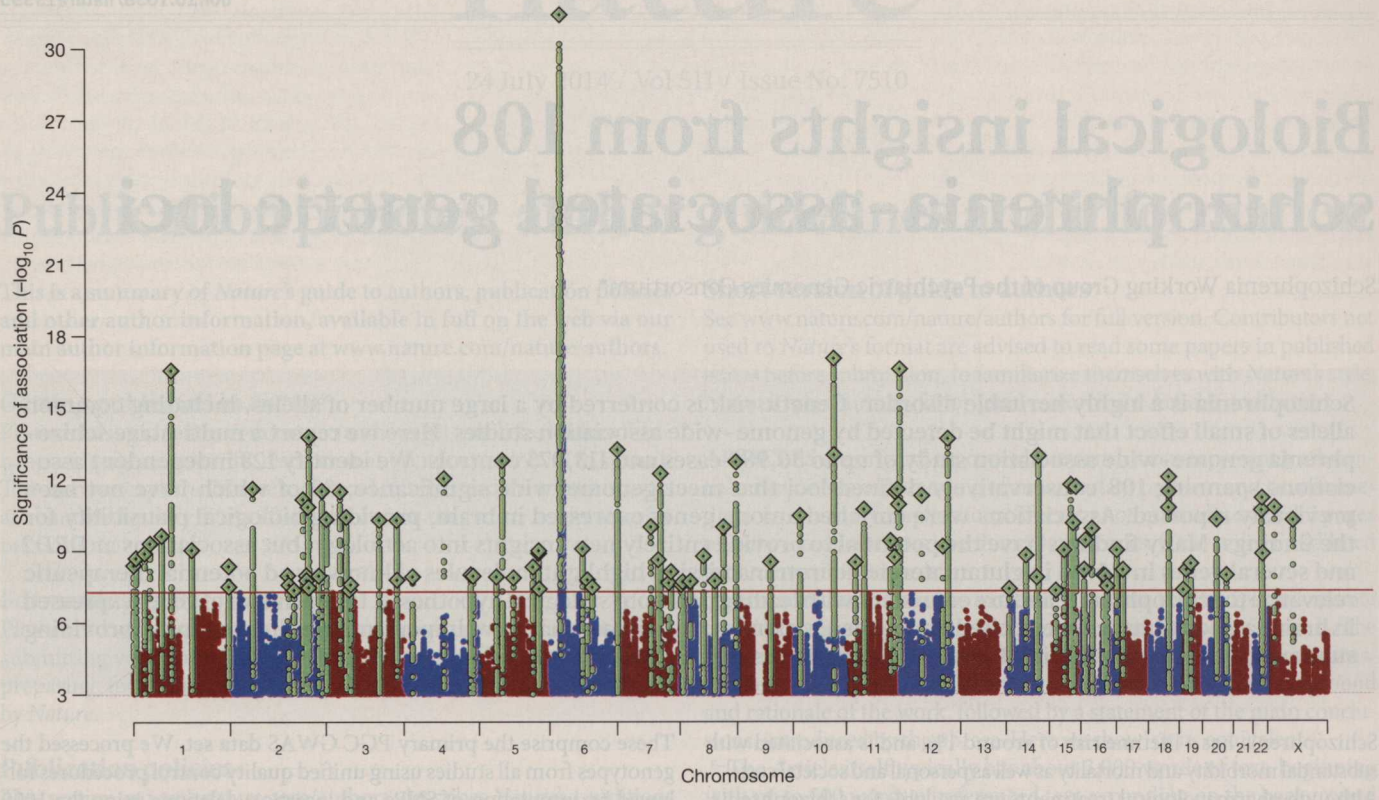

Figure 1 | Manhattan plot showing schizophrenia associations. Manhattan plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). The *x* axis is chromosomal position and the *y* axis is the significance ($-\log_{10} P$; 2-tailed) of association derived by logistic regression. The red line shows the genome-wide significance level (5×10^{-8}). SNPs in green are in linkage disequilibrium with the index SNPs (diamonds) which represent independent genome-wide significant associations.

Additional lines of evidence allow us to conclude the deviation between the observed and null distributions in our primary GWAS indicates a true polygenic contribution to schizophrenia. First, applying a novel method[30] that uses linkage disequilibrium information to distinguish between the major potential sources of test statistic inflation, we found our results are consistent with polygenic architecture but not population stratification (Extended Data Fig. 3). Second, the schizophrenia-associated alleles at 78% of 234 linkage-disequilibrium-independent SNPs exceeding $P < 1 \times 10^{-6}$ in the case-control GWAS were again overrepresented in cases in the independent samples from deCODE. This degree of consistency between the case-control GWAS and the replication data is highly unlikely to occur by chance ($P = 6 \times 10^{-19}$). The tested alleles surpassed the $P < 10^{-6}$ threshold in our GWAS before we added either the trios or deCODE data to the meta-analysis. This trend test is therefore independent of the primary case-control GWAS. Third, analysing the 1,235 parent-proband trios, we again found excess transmission of the schizophrenia-associated allele at 69% of the 263 linkage-disequilibrium-independent SNPs with $P < 1 \times 10^{-6}$ in the case-control GWAS. This is again unlikely to occur by chance ($P = 1 \times 10^{-9}$) and additionally excludes population stratification as fully explaining the associations reaching our threshold for seeking replication. Fourth, we used the trios trend data to estimate the expected proportion of true associations at $P < 1 \times 10^{-6}$ in the discovery GWAS, allowing for the fact that half of the index SNPs are expected to show the same allelic trend in the trios by chance, and that some true associations will show opposite trends given the limited number of trio samples (Supplementary Methods). Given the observed trend test results, around 67% (95% confidence interval: 64–73%) or $n = 176$ of the associations in the scan at $P < 1 \times 10^{-6}$ are expected to be true, and therefore the number of associations that will ultimately be validated from this set of SNPs will be considerably more than those that now meet genome-wide significance. Taken together, these analyses indicate that the observed deviation of test statistics from the null primarily represents polygenic association signal and the considerable excess of associations at the tail of extreme significance largely correspond to true associations.

Independently associated SNPs do not translate to well-bounded chromosomal regions. Nevertheless, it is useful to define physical boundaries for the SNP associations to identify candidate risk genes. We defined an associated locus as the physical region containing all SNPs correlated at $r^2 > 0.6$ with each of the 128 index SNPs. Associated loci within 250 kb of each other were merged. This resulted in 108 physically distinct associated loci, 83 of which have not been previously implicated in schizophrenia and therefore harbour potential new biological insights into disease aetiology (Supplementary Table 3; regional plots in Supplementary Fig. 1). The significant regions include all but 5 loci previously reported to be genome-wide significant in large samples (Supplementary Table 3).

Characterization of associated loci

Of the 108 loci, 75% include protein-coding genes (40%, a single gene) and a further 8% are within 20 kb of a gene (Supplementary Table 3). Notable associations relevant to major hypotheses of the aetiology and treatment of schizophrenia include *DRD2* (the target of all effective antipsychotic drugs) and many genes (for example, *GRM3*, *GRIN2A*, *SRR*, *GRIA1*) involved in glutamatergic neurotransmission and synaptic plasticity. In addition, associations at *CACNA1C*, *CACNB2* and *CACNA1I*, which encode voltage-gated calcium channel subunits, extend previous findings implicating members of this family of proteins in schizophrenia and other psychiatric disorders[11,13,31,32]. Genes encoding calcium channels, and proteins involved in glutamatergic neurotransmission and synaptic plasticity have been independently implicated in schizophrenia by studies of rare genetic variation[33–35], suggesting convergence at a broad functional level between studies of common and rare genetic variation. We highlight in the Supplementary Discussion genes of particular interest within associated loci with respect to current hypotheses of schizophrenia

aetiology or treatment (although we do not imply that these genes are necessarily the causal elements).

For each of the schizophrenia-associated loci, we identified a credible causal set of SNPs (for definition, see Supplementary Methods)[36]. In only 10 instances (Supplementary Table 4) was the association signal credibly attributable to a known non-synonymous exonic polymorphism. The apparently limited role of protein-coding variants is consistent both with exome sequencing findings[33] and with the hypothesis that most associated variants detected by GWAS exert their effects through altering gene expression rather than protein structure[37,38] and with the observation that schizophrenia risk loci are enriched for expression quantitative trait loci (eQTL)[39].

To try to identify eQTLs that could explain associations with schizophrenia, we merged the credible causal set of SNPs defined above with eQTLs from a meta-analysis of human brain cortex eQTL studies ($n = 550$) and an eQTL study of peripheral venous blood ($n = 3{,}754$)[40] (Supplementary Methods). Multiple schizophrenia loci contained at least one eQTL for a gene within 1 Mb of the locus (Supplementary Table 4). However, in only 12 instances was the eQTL plausibly causal (two in brain, and nine in peripheral blood, one in both). This low proportion suggests that if most risk variants are regulatory, available eQTL catalogues do not yet provide power, cellular specificity, or developmental diversity to provide clear mechanistic hypotheses for follow-up experiments.

The brain and immunity

To further explore the regulatory nature of the schizophrenia associations, we mapped the credible sets ($n = 108$) of causal variants onto sequences with epigenetic markers characteristic of active enhancers in 56 different tissues and cell lines (Supplementary Methods). Schizophrenia associations were significantly enriched at enhancers active in brain (Fig. 2) but not in tissues unlikely to be relevant to schizophrenia (for example, bone, cartilage, kidney and fibroblasts). Brain tissues used to define enhancers consist of heterogeneous populations of cells. Seeking greater specificity, we contrasted genes enriched for expression in neurons and glia using mouse ribotagged lines[41]. Genes with strong expression in multiple cortical and striatal neuronal lineages were enriched for associations, providing support for an important neuronal pathology in schizophrenia (Extended Data Fig. 4) but this is not statistically more significant than, or exclusionary of, contributions from other lineages[42].

Schizophrenia associations were also strongly enriched at enhancers that are active in tissues with important immune functions, particularly B-lymphocyte lineages involved in acquired immunity (CD19 and CD20 lines, Fig. 2). These enrichments remain significant even after excluding the extended MHC region and regions containing brain enhancers (enrichment P for CD20 $< 10^{-6}$), demonstrating that this finding is not an artefact of correlation between enhancer elements in different tissues and not driven by the strong and diffuse association at the extended MHC. Epidemiological studies have long hinted at a role for immune dysregulation in schizophrenia, the present findings provide genetic support for this hypothesis[43].

To develop additional biological hypotheses beyond those that emerge from inspection of the individual loci, we further undertook a limited mining of the data through gene-set analysis. However, as there is no consensus methodology by which such analyses should be conducted, nor an established optimal significance threshold for including loci, we sought to be conservative, using only two of the many available approaches[44,45] and restricting analyses to genes within genome-wide significant loci. Neither approach identified gene-sets that were significantly enriched for associations after correction for the number of pathways tested (Supplementary Table 5) although nominally significantly enrichments were observed among several predefined candidate pathways (Extended Data Table 1). A fuller exploratory analysis of the data will be presented elsewhere.

Overlap with rare mutations

CNVs associated with schizophrenia overlap with those associated with autism spectrum disorder (ASD) and intellectual disability[9], as do genes

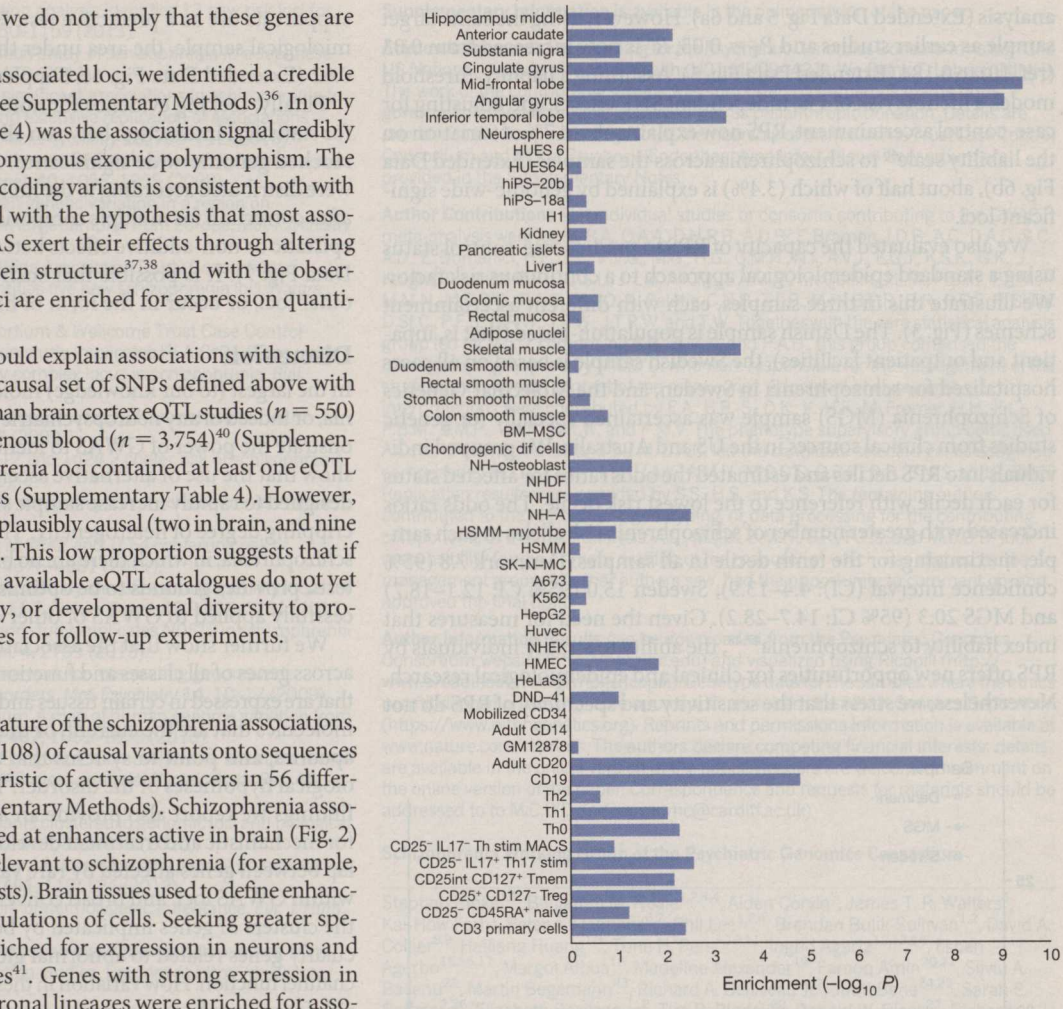

Figure 2 | Enrichment in enhancers of credible SNPs. Cell and tissue type specific enhancers were identified using ChIP-seq data sets (H3K27ac signal) from 56 cell line and tissue samples (y axis). We defined cell and tissue type enhancers as the top 10% of enhancers with the highest ratio of reads in that cell or tissue type divided by the total number of reads. Enrichment of credible causal associated SNPs from the schizophrenia GWAS was compared with frequency matched sets of 1000 Genomes SNPs (Supplementary Methods). The x axis is the $-\log_{10} P$ for enrichment. P values are uncorrected for the number of tissues or cells tested. A $-\log_{10} P$ of roughly 3 can be considered significant after Bonferroni correction. Descriptions of cell and tissue types at the Roadmap Epigenome website (http://www.roadmapepigenomics.org).

with deleterious *de novo* mutations[34]. Here we find significant overlap between genes in the schizophrenia GWAS associated intervals and those with *de novo* non-synonymous mutations in schizophrenia ($P = 0.0061$) (Extended Data Table 2), suggesting that mechanistic studies of rare genetic variation in schizophrenia will be informative for schizophrenia more widely. We also find evidence for overlap between genes in schizophrenia GWAS regions and those with *de novo* non-synonymous mutations in intellectual disability ($P = 0.00024$) and ASD ($P = 0.035$), providing further support for the hypothesis that these disorders have partly overlapping pathophysiologies[9,34].

Polygenic risk score profiling

Previous studies have shown that risk profile scores (RPS) constructed from alleles showing modest association with schizophrenia in a discovery GWAS can predict case-control status in independent samples, albeit with low sensitivity and specificity[10,11,16]. This finding was robustly confirmed in the present study. The estimate of Nagelkerke R^2 (a measure of variance in case-control status explained) depends on the specific target data set and threshold (P_T) for selecting risk alleles for RPS

analysis (Extended Data Fig. 5 and 6a). However, using the same target sample as earlier studies and $P_T = 0.05$, R^2 is now increased from 0.03 (ref. 10) to 0.184 (Extended Data Fig. 5). Assuming a liability-threshold model, a lifetime risk of 1%, independent SNP effects, and adjusting for case-control ascertainment, RPS now explains about 7% of variation on the liability scale[46] to schizophrenia across the samples (Extended Data Fig. 6b), about half of which (3.4%) is explained by genome-wide significant loci.

We also evaluated the capacity of RPS to predict case-control status using a standard epidemiological approach to a continuous risk factor. We illustrate this in three samples, each with different ascertainment schemes (Fig. 3). The Danish sample is population-based (that is, inpatient and outpatient facilities), the Swedish sample is based on all cases hospitalized for schizophrenia in Sweden, and the Molecular Genetics of Schizophrenia (MGS) sample was ascertained specially for genetic studies from clinical sources in the US and Australia. We grouped individuals into RPS deciles and estimated the odds ratios for affected status for each decile with reference to the lowest risk decile. The odds ratios increased with greater number of schizophrenia risk alleles in each sample, maximizing for the tenth decile in all samples: Denmark 7.8 (95% confidence interval (CI): 4.4–13.9), Sweden 15.0 (95% CI: 12.1–18.7) and MGS 20.3 (95% CI: 14.7–28.2). Given the need for measures that index liability to schizophrenia[47,48], the ability to stratify individuals by RPS offers new opportunities for clinical and epidemiological research. Nevertheless, we stress that the sensitivity and specificity of RPS do not support its use as a predictive test. For example, in the Danish epidemiological sample, the area under the receiver operating curve is only 0.62 (Extended Data Fig. 6c, Supplementary Table 6).

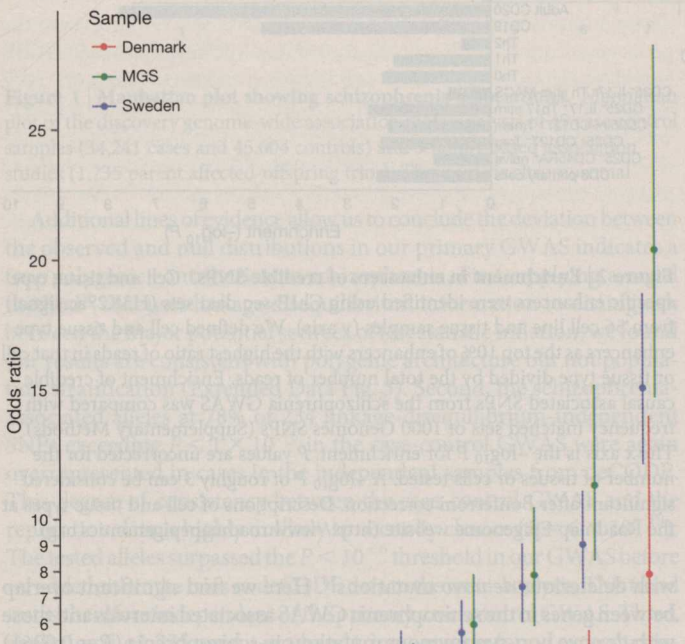

Figure 3 | Odds ratio by risk score profile. Odds ratio for schizophrenia by risk score profile (RPS) decile in the Sweden (Sw1-6), Denmark (Aarhus), and Molecular Genetics of Schizophrenia studies (Supplementary Methods). Risk alleles and weights were derived from 'leave one out' analyses in which those samples were excluded from the GWAS meta-analysis (Supplementary Methods). The threshold for selecting risk alleles was $P_T < 0.05$. The RPS were converted to deciles (1 = lowest, 10 = highest RPS), and nine dummy variables created to contrast deciles 2-10 to decile 1 as the reference. Odds ratios and 95% confidence intervals (bars) were estimated using logistic regression with PCs to control for population stratification.

Finally, seeking evidence for non-additive effects on risk, we tested for statistical interaction between all pairs of 125 autosomal SNPs that reached genome-wide significance. *P* values for the interaction terms were distributed according to the null, and no interaction was significant after correction for multiple comparisons. Thus, we find no evidence for epistatic or non-additive effects between the significant loci (Extended Data Fig. 7). It is possible that such effects could be present between other loci, or occur in the form of higher-order interactions.

Discussion

In the largest (to our knowledge) molecular genetic study of schizophrenia, or indeed of any neuropsychiatric disorder, ever conducted, we demonstrate the power of GWAS to identify large numbers of risk loci. We show that the use of alternative ascertainment and diagnostic schemes designed to rapidly increase sample size does not inevitably introduce a crippling degree of heterogeneity. That this is true for a phenotype like schizophrenia, in which there are no biomarkers or supportive diagnostic tests, provides grounds to be optimistic that this approach can be successfully applied to GWAS of other clinically defined disorders.

We further show that the associations are not randomly distributed across genes of all classes and function; rather they converge upon genes that are expressed in certain tissues and cellular types. The findings include molecules that are the current, or the most promising, targets for therapeutics, and point to systems that align with the predominant aetiological hypotheses of the disorder. This suggests that the many novel findings we report also provide an aetiologically relevant foundation for mechanistic and treatment development studies. We also find overlap between genes affected by rare variants in schizophrenia and those within GWAS loci, and broad convergence in the functions of some of the clusters of genes implicated by both sets of genetic variants, particularly genes related to abnormal glutamatergic synaptic and calcium channel function. How variation in these genes impact function to increase risk for schizophrenia cannot be answered by genetics, but the overlap strongly suggests that common and rare variant studies are complementary rather than antagonistic, and that mechanistic studies driven by rare genetic variation will be informative for schizophrenia.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

Received 6 March; accepted 18 June 2014.
Published online 22 July 2014.

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Supplementary Information is available in the online version of the paper.

Acknowledgements Core funding for the Psychiatric Genomics Consortium is from the US National Institute of Mental Health (U01 MH094421). We thank T. Lehner (NIMH). The work of the contributing groups was supported by numerous grants from governmental and charitable bodies as well as philanthropic donation. Details are provided in the Supplementary Notes. Membership of the Wellcome Trust Case Control Consortium and of the Psychosis Endophenotype International Consortium are provided in the Supplementary Notes.

Author Contributions The individual studies or consortia contributing to the GWAS meta-analysis were led by R.A., O.A.A., D.H.R.B., A.D.B., E. Bramon, J.D.B., A.C., D.A.C., S.C., A.D., E. Domenici, H.E., T.E., P.V.G., M.G., H.G., C.M.H., N.I., A.V.J., E.G.J., K.S.K., G.K., J. Knight, T. Lencz, D.F.L., Q.S.L., J. Liu, A.K.M., S.A.M., A. McQuillin, J.L.M., P.B.M., B.J.M., M.M.N., M.C.O'D., R.A.O., M.J.O., A. Palotie, C.N.P., T.L.P., M.R., B.P.R., D.R., P.C.S, P. Sklar. D.St.C., P.F.S., D.R.W., J.R.W., J.T.R.W. and T.W. Together with the core statistical analysis group led by M.J.D. comprising S.R., B.M.N. and P.A.H., this group comprised the management group led by M.C.O'D. who were responsible for the management of the study and the overall content of the manuscript. Additional analyses and interpretations were contributed by E.A., B.B.-S., D.K., K.-H.F., M. Fromer, H.H., P.L., P.B.M., S.M.P., T.H.P., N.R.W. and P.M.V. The phenotype supervisory group comprised A.C., A.H.F., P.V.G., K.K.K. and B.J.M. D.A.C. led the candidate selected genes subgroup comprised of M.J.D., E. Dominici, J.A.K., A.M.H., M.C.O'D, B.P.R., D.R., E.M.S. and P. Sklar. Replication results were provided by S.S., H.S. and K.S. The remaining authors contributed to the recruitment, genotyping, or data processing for the contributing components of the meta-analysis. A.C., M.J.D., B.M.N., S.R., P.F.S. and M.C.O'D. took responsibility for the primary drafting of the manuscript which was shaped by the management group. All other authors saw, had the opportunity to comment on, and approved the final draft.

Author Information Results can be downloaded from the Psychiatric Genomics Consortium website (http://pgc.unc.edu) and visualized using Ricopili (http://www.broadinstitute.org/mpg/ricopili). Genotype data for the samples where the ethics permit deposition are available upon application from the NIMH Genetics Repository (https://www.nimhgenetics.org). Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details are available in the online version of the paper. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to to M.C.O'D. (odonovanmc@cardiff.ac.uk).

Schizophrenia Working Group of the Psychiatric Genomics Consortium

Stephan Ripke[1,2], Benjamin M. Neale[1,2,3,4], Aiden Corvin[5], James T. R. Walters[6], Kai-How Farh[1], Peter A. Holmans[6,7], Phil Lee[1,2,4], Brendan Bulik-Sullivan[1,2], David A. Collier[8,9], Hailiang Huang[1,3], Tune H. Pers[3,10,11], Ingrid Agartz[12,13,14], Esben Agerbo[15,16,17], Margot Albus[18], Madeline Alexander[19], Farooq Amin[20,21], Silviu A. Bacanu[22], Martin Begemann[23], Richard A. Belliveau Jr[2], Judit Bene[24,25], Sarah E. Bergen[2,26], Elizabeth Bevilacqua[2], Tim B. Bigdeli[22], Donald W. Black[27], Richard Bruggeman[28], Nancy G. Buccola[29], Randy L. Buckner[30,31,32], William Byerley[33], Wiepke Cahn[34], Guiqing Cai[35,36], Dominique Campion[37], Rita M. Cantor[38], Vaughan J. Carr[39,40], Noa Carrera[6], Stanley V. Catts[39,41], Kimberly D. Chambert[2], Raymond C. K. Chan[42], Ronald Y. L. Chen[43], Eric Y. H. Chen[43,44], Wei Cheng[45], Eric F. C. Cheung[46], Siow Ann Chong[47], C. Robert Cloninger[48], David Cohen[49], Nadine Cohen[50], Paul Cormican[5], Nick Craddock[6,7], James J. Crowley[51], David Curtis[52,53], Michael Davidson[54], Kenneth L. Davis[36], Franziska Degenhardt[55,56], Jurgen Del Favero[57], Ditte Demontis[17,58,59], Dimitris Dikeos[60], Timothy Dinan[61], Srdjan Djurovic[14,62], Gary Donohoe[5,63], Elodie Drapeau[36], Jubao Duan[64,65], Frank Dudbridge[66], Naser Durmishi[67], Peter Eichhammer[68], Johan Eriksson[69,70,71], Valentina Escott-Price[6], Laurent Essioux[72], Ayman H. Fanous[73,74,75,76], Martilias S. Farrell[51], Josef Frank[77], Lude Franke[78], Robert Freedman[79], Nelson B. Freimer[80], Marion Friedl[81], Joseph I. Friedman[36], Menachem Fromer[1,2,4,82], Giulio Genovese[2], Lyudmila Georgieva[6], Ina Giegling[81,83], Paola Giusti-Rodríguez[51], Stephanie Godard[84], Jacqueline I. Goldstein[1,3], Vera Golimbet[85], Srihari Gopal[86], Jacob Gratten[87], Lieuwe de Haan[88], Christian Hammer[23], Marian L. Hamshere[6], Mark Hansen[89], Thomas Hansen[17,90], Vahram Haroutunian[36,91,92], Annette M. Hartmann[81], Frans A. Henskens[39,93,94], Stefan Herms[55,56,95], Joel N. Hirschhorn[3,11,96], Per Hoffmann[55,56,95], Andrea Hofman[55,56], Mads V. Hollegaard[97], David M. Hougaard[97], Masashi Ikeda[98], Inge Joa[99], Antonio Julià[100], René S. Kahn[34], Luba Kalaydjieva[101,102], Sena Karachanak-Yankova[103], Juha Karjalainen[78], David Kavanagh[6], Matthew C. Keller[104], James L. Kennedy[105,106,107], Andrey Khrunin[108], Yunjung Kim[51], Janis Klovins[109], James A. Knowles[110], Bettina Konte[81], Vaidutis Kucinskas[111], Zita Ausrele Kucinskiene[111], Hana Kuzelova-Ptackova[112], Anna K. Kähler[26], Claudine Laurent[19,113], Jimmy Lee Chee Keong[47,114], S. Hong Lee[87], Sophie E. Legge[6], Bernard Lerer[115], Miaoxin Li[43,44,116], Tao Li[117], Kung-Yee Liang[118], Jeffrey Lieberman[119], Svetlana Limborska[108], Carmel M. Loughland[39,120], Jan Lubinski[121], Jouko Lönnqvist[122], Milan Macek Jr[112], Patrik K. E. Magnusson[26], Brion S. Maher[123], Wolfgang Maier[124], Jacques Mallet[125], Sara Marsal[100], Manuel Mattheisen[17,58,59,126], Morten Mattingsdal[14,127], Robert W. McCarley[128,129], Colm McDonald[130], Andrew M. McIntosh[131,132], Sandra Meier[77], Carin J. Meijer[88], Bela Melegh[24,25], Ingrid Melle[14,133], Raquelle I. Mesholam-Gately[128,134], Andres Metspalu[135], Patricia T. Michie[39,136], Lili Milani[135], Vihra Milanova[137], Younes Mokrab[8], Derek W. Morris[5,63], Ole Mors[17,58,138], Kieran C. Murphy[139], Robin M. Murray[140], Inez Myin-Germeys[141], Bertram Müller-Myhsok[142,143,144], Mari Nelis[135], Igor Nenadic[145], Deborah A. Nertney[146], Gerald Nestadt[147], Kristin K. Nicodemus[148], Liene Nikitina-Zake[109], Laura Nisenbaum[149], Annelie Nordin[150], Eadbhard O'Callaghan[151], Colm O'Dushlaine[2], F. Anthony O'Neill[152], Sang-Yun Oh[153], Ann Olincy[79], Line Olsen[17,90], Jim Van Os[141,154], Psychosis Endophenotypes International Consortium[155], Christos Pantelis[39,156],

George N. Papadimitriou[60], Sergi Papiol[23], Elena Parkhomenko[36], Michele T. Pato[110], Tiina Paunio[157,158], Milica Pejovic-Milovancevic[159], Diana O. Perkins[160], Olli Pietiläinen[158,161], Jonathan Pimm[53], Andrew J. Pocklington[6], John Powell[140], Alkes Price[3,162], Ann E. Pulver[147], Shaun M. Purcell[82], Digby Quested[163], Henrik B. Rasmussen[17,90], Abraham Reichenberg[36], Mark A. Reimers[164], Alexander L. Richards[6], Joshua L. Roffman[30,32], Panos Roussos[82,165], Douglas M. Ruderfer[6,82], Veikko Salomaa[71], Alan R. Sanders[64,65], Ulrich Schall[39,120], Christian R. Schubert[166], Thomas G. Schulze[77,167], Sibylle G. Schwab[168], Edward M. Scolnick[2], Rodney J. Scott[39,169,170], Larry J. Seidman[128,134], Jianxin Shi[171], Engilbert Sigurdsson[172], Teimuraz Silagadze[173], Jeremy M. Silverman[36,174], Kang Sim[47], Petr Slominsky[108], Jordan W. Smoller[2,4], Hon-Cheong So[43], Chris C. A. Spencer[175], Eli A. Stahl[3,82], Hreinn Stefansson[176], Stacy Steinberg[176], Elisabeth Stogmann[177], Richard E. Straub[178], Eric Strengman[179,34], Jana Strohmaier[77], T. Scott Stroup[119], Mythily Subramaniam[47], Jaana Suvisaari[122], Dragan M. Svrakic[48], Jin P. Szatkiewicz[51], Erik Söderman[12], Srinivas Thirumalai[180], Draga Toncheva[103], Sarah Tosato[181], Juha Veijola[182,183], John Waddington[184], Dermot Walsh[185], Dai Wang[86], Qiang Wang[117], Bradley T. Webb[22], Mark Weiser[54], Dieter B. Wildenauer[186], Nigel M. Williams[6], Stephanie Williams[51], Stephanie H. Witt[77], Aaron R. Wolen[164], Emily H. M. Wong[43], Brandon K. Wormley[22], Hualin Simon Xi[187], Clement C. Zai[105,106], Xuebin Zheng[188], Fritz Zimprich[177], Naomi R. Wray[87], Kari Stefansson[176], Peter M. Visscher[87], Wellcome Trust Case-Control Consortium 2[189], Rolf Adolfsson[150], Ole A. Andreassen[14,133], Douglas H. R. Blackwood[132], Elvira Bramon[190], Joseph D. Buxbaum[35,36,91,191], Anders D. Børglum[17,58,59,138], Sven Cichon[55,56,95,192], Ariel Darvasi[193], Enrico Domenici[194], Hannelore Ehrenreich[23], Tõnu Esko[3,11,96,135], Pablo V. Gejman[64,65], Michael Gill[5], Hugh Gurling[53], Christina M. Hultman[26], Nakao Iwata[98], Assen V. Jablensky[39,102,186,195], Erik G. Jönsson[12,14], Kenneth S. Kendler[196], George Kirov[6], Jo Knight[105,106,107], Todd Lencz[197,198,199], Douglas F. Levinson[19], Qingqin S. Li[86], Jianjun Liu[188,200], Anil K. Malhotra[197,198,199], Steven A. McCarroll[2,96], Andrew McQuillin[53], Jennifer L. Moran[2], Preben B. Mortensen[15,16,17], Bryan J. Mowry[87,201], Markus M. Nöthen[55,56], Roel A. Ophoff[38,80,34], Michael J. Owen[6,7], Aarno Palotie[2,4,161], Carlos N. Pato[110], Tracey L. Petryshen[2,128,202], Danielle Posthuma[203,204,205], Marcella Rietschel[77], Brien P. Riley[196], Dan Rujescu[81,83], Pak C. Sham[43,44,116], Pamela Sklar[82,91,165], David St Clair[206], Daniel R. Weinberger[178,207], Jens R. Wendland[166], Thomas Werge[17,90,208], Mark J. Daly[1,2,3], Patrick F. Sullivan[26,51,160] & Michael C. O'Donovan[6,7]

[1]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [2]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142, USA. [3]Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142, USA. [4]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [5]Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin 8, Ireland. [6]MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff CF24 4HQ, UK. [7]National Centre for Mental Health, Cardiff University, Cardiff CF24 4HQ, UK. [8]Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey GU20 6PH, UK. [9]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, UK. [10]Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, DK-2800, Denmark. [11]Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, Massachusetts 02115, USA. [12]Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, SE-17176 Stockholm, Sweden. [13]Department of Psychiatry, Diakonhjemmet Hospital, 0319 Oslo, Norway. [14]NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, 0424 Oslo, Norway. [15]Centre for Integrative Register-based Research, CIRRAU, Aarhus University, DK-8210 Aarhus, Denmark. [16]National Centre for Register-based Research, Aarhus University, DK-8210 Aarhus, Denmark. [17]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark. [18]State Mental Hospital, 85540 Haar, Germany. [19]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California 94305, USA. [20]Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia 30033, USA. [21]Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia 30322, USA. [22]Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia 23298, USA. [23]Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen 37075, Germany. [24]Department of Medical Genetics, University of Pécs, Pécs H-7624, Hungary. [25]Szentagothai Research Center, University of Pécs, Pécs H-7624, Hungary. [26]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm SE-17177, Sweden. [27]Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, Iowa 52242, USA. [28]University Medical Center Groningen, Department of Psychiatry, University of Groningen NL-9700 RB, The Netherlands. [29]School of Nursing, Louisiana State University Health Sciences Center, New Orleans, Louisiana 70112, USA. [30]Athinoula A. Martinos Center, Massachusetts General Hospital, Boston, Massachusetts 02129, USA. [31]Center for Brain Science, Harvard University, Cambridge, Massachusetts 02138, USA. [32]Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [33]Department of Psychiatry, University of California at San Francisco, San Francisco, California 94143, USA. [34]University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, 3584 Utrecht, The Netherlands. [35]Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [36]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [37]Centre Hospitalier du Rouvray and INSERM U1079 Faculty of Medicine, 76301 Rouen, France. [38]Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, California 90095, USA. [39]Schizophrenia Research Institute, Sydney NSW 2010, Australia. [40]School of Psychiatry, University of New South Wales, Sydney NSW 2031, Australia. [41]Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, St Lucia QLD 4072, Australia. [42]Institute of Psychology, Chinese Academy of Science, Beijing 100101, China. [43]Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. [44]State Key Laboratory for Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China. [45]Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina 27514, USA. [46]Castle Peak Hospital, Hong Kong, China. [47]Institute of Mental Health, Singapore 539747, Singapore. [48]Department of Psychiatry, Washington University, St. Louis, Missouri 63110, USA. [49]Department of Child and Adolescent Psychiatry, Assistance Publique Hopitaux de Paris, Pierre and Marie Curie Faculty of Medicine and Institute for Intelligent Systems and Robotics, Paris 75013, France. [50]Blue Note Biosciences, Princeton, New Jersey 08540, USA [51]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599-7264, USA. [52]Department of Psychological Medicine, Queen Mary University of London, London E1 1BB, UK. [53]Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London WC1E 6JJ, UK. [54]Sheba Medical Center, Tel Hashomer 52621, Israel. [55]Department of Genomics, Life and Brain Center, D-53127 Bonn, Germany. [56]Institute of Human Genetics, University of Bonn, D-53127 Bonn, Germany. [57]Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, B-2610 Antwerp, Belgium. [58]Centre for Integrative Sequencing, iSEQ, Aarhus University, DK-8000 Aarhus C, Denmark. [59]Department of Biomedicine, Aarhus University, DK-8000 Aarhus C, Denmark. [60]First Department of Psychiatry, University of Athens Medical School, Athens 11528, Greece. [61]Department of Psychiatry, University College Cork, Co. Cork, Ireland. [62]Department of Medical Genetics, Oslo University Hospital, 0424 Oslo, Norway. [63]Cognitive Genetics and Therapy Group, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Co. Galway, Ireland. [64]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois 60637, USA. [65]Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, Illinois 60201, USA. [66]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK. [67]Department of Child and Adolescent Psychiatry, University Clinic of Psychiatry, Skopje 1000, Republic of Macedonia. [68]Department of Psychiatry, University of Regensburg, 93053 Regensburg, Germany. [69]Department of General Practice, Helsinki University Central Hospital, University of Helsinki P.O. Box 20, Tukholmankatu 8 B, FI-00014, Helsinki, Finland [70]Folkhälsan Research Center, Helsinki, Finland, Biomedicum Helsinki 1, Haartmaninkatu 8, FI-00290, Helsinki, Finland. [71]National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland. [72]Translational Technologies and Bioinformatics, Pharma Research and Early Development, F. Hoffman-La Roche, CH-4070 Basel, Switzerland. [73]Department of Psychiatry, Georgetown University School of Medicine, Washington DC 20057, USA. [74]Department of Psychiatry, Keck School of Medicine of the University of Southern California, Los Angeles, California 90033, USA. [75]Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298, USA. [76]Mental Health Service Line, Washington VA Medical Center, Washington DC 20422, USA. [77]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg , D-68159 Mannheim, Germany. [78]Department of Genetics, University of Groningen, University Medical Centre Groningen, 9700 RB Groningen, The Netherlands. [79]Department of Psychiatry, University of Colorado Denver, Aurora, Colorado 80045, USA. [80]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California 90095, USA. [81]Department of Psychiatry, University of Halle, 06112 Halle, Germany. [82]Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, New York 10029, USA. [83]Department of Psychiatry, University of Munich, 80336, Munich, Germany. [84]Departments of Psychiatry and Human and Molecular Genetics, INSERM, Institut de Myologie, Hôpital de la Pitiè-Salpêtrière, Paris 75013, France. [85]Mental Health Research Centre, Russian Academy of Medical Sciences, 115522 Moscow, Russia. [86]Neuroscience Therapeutic Area, Janssen Research and Development, Raritan, New Jersey 08869, USA. [87]Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, QLD 4072, Australia. [88]Academic Medical Centre University of Amsterdam, Department of Psychiatry, 1105 AZ Amsterdam, The Netherlands. [89]Illumina, La Jolla, California, California 92122, USA. [90]Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Mental Health Services Copenhagen, DK-4000, Denmark. [91]Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [92]J. J. Peters VA Medical Center, Bronx, New York, New York 10468, USA. [93]Priority Research Centre for Health Behaviour, University of Newcastle, Newcastle NSW 2308, Australia. [94]School of Electrical Engineering and Computer Science, University of Newcastle, Newcastle NSW 2308, Australia. [95]Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel CH-4058, Switzerland. [96]Department of Genetics, Harvard Medical School, Boston, Massachusetts, Massachusetts 02115, USA. [97]Section of Neonatal Screening and Hormones, Department of Clinical Biochemistry, Immunology and Genetics, Statens Serum Institut, Copenhagen DK-2300, Denmark. [98]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi,470-1192, Japan. [99]Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, 4011 Stavanger, Norway. [100]Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona 08035, Spain. [101]Centre for Medical Research, The University of Western Australia, Perth WA6009, Australia. [102]The Perkins Institute for Medical Research, The University of Western Australia, Perth WA6009, Australia. [103]Department of Medical Genetics, Medical University, Sofia 1431, Bulgaria. [104]Department of Psychology, University of Colorado Boulder, Boulder, Colorado 80309, USA. [105]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario M5T 1R8, Canada. [106]Department of Psychiatry, University of Toronto, Toronto, Ontario M5T 1R8, Canada. [107]Institute of Medical Science, University of Toronto, Toronto, Ontario M5S 1A8, Canada. [108]Institute of Molecular Genetics, Russian Academy of Sciences, Moscow 123182, Russia. [109]Latvian Biomedical Research and Study Centre, Riga, LV-1067, Latvia. [110]Department of Psychiatry and Zilkha Neurogenetics Institute, Keck School of Medicine at University of

Southern California, Los Angeles, California 90089, USA. [111]Faculty of Medicine, Vilnius University, LT-01513 Vilnius, Lithuania. [112]Department of Biology and Medical Genetics, 2nd Faculty of Medicine and University Hospital Motol, 150 06 Prague, Czech Republic. [113]Department of Child and Adolescent Psychiatry, Pierre and Marie Curie Faculty of Medicine, Paris 75013, France. [114]Duke-NUS Graduate Medical School, Singapore 169857. [115]Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel. [116]Centre for Genomic Sciences, The University of Hong Kong, Hong Kong, China. [117]Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chengdu, 610041 Sichuan, China. [118]Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland 21205, USA. [119]Department of Psychiatry, Columbia University, New York, New York 10032, USA. [120]Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle NSW 2300, Australia. [121]Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, 70-453 Szczecin, Poland. [122]Department of Mental Health and Substance Abuse Services; National Institute for Health and Welfare, P.O. BOX 30, FI-00271 Helsinki, Finland. [123]Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland 21205, USA. [124]Department of Psychiatry, University of Bonn, D-53127 Bonn, Germany. [125]Centre National de la Recherche Scientifique, Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurodégénératifs, Hôpital de la Pitié Salpêtrière, 75013 Paris, France. [126]Department of Genomics Mathematics, University of Bonn, D-53127 Bonn, Germany. [127]Research Unit, Sørlandet Hospital, 4604 Kristiansand, Norway. [128]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115, USA. [129]VA Boston Health Care System, Brockton, Massachusetts 02301, USA. [130]Department of Psychiatry, National University of Ireland Galway, Co. Galway, Ireland. [131]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh EH16 4SB, UK. [132]Division of Psychiatry, University of Edinburgh, Edinburgh EH16 4SB, UK. [133]Division of Mental Health and Addiction, Oslo University Hospital, 0424 Oslo, Norway. [134]Massachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Boston, Massachusetts 02114, USA. [135]Estonian Genome Center, University of Tartu, Tartu 50090, Estonia. [136]School of Psychology, University of Newcastle, Newcastle NSW 2308, Australia. [137]First Psychiatric Clinic, Medical University, Sofia 1431, Bulgaria. [138]Department P, Aarhus University Hospital, DK-8240 Risskov, Denmark. [139]Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin 2, Ireland. [140]King's College London, London SE5 8AF, UK. [141]Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, 6229 HX Maastricht, The Netherlands. [142]Institute of Translational Medicine, University of Liverpool, Liverpool L69 3BX, UK. [143]Max Planck Institute of Psychiatry, 80336 Munich, Germany. [144]Munich Cluster for Systems Neurology (SyNergy), 80336 Munich, Germany. [145]Department of Psychiatry and Psychotherapy, Jena University Hospital, 07743 Jena, Germany. [146]Department of Psychiatry, Queensland Brain Institute and Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, St Lucia QLD 4072, Australia. [147]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA. [148]Department of Psychiatry, Trinity College Dublin, Dublin 2, Ireland. [149]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, 46285 Indiana, USA. [150]Department of Clinical Sciences, Psychiatry, Umeå University, SE-901 87 Umeå, Sweden. [151]DETECT Early Intervention Service for Psychosis, Blackrock, Co. Dublin, Ireland. [152]Centre for Public Health, Institute of Clinical Sciences, Queen's University Belfast, Belfast BT12 6AB, UK. [153]Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, California 94720, USA. [154]Institute of Psychiatry, King's College London, London SE5 8AF, UK. [155]A list of authors and affiliations appear in the Supplementary Information. [156]Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne, Vic 3053, Australia. [157]Department of Psychiatry, University of Helsinki, P.O. Box 590, FI-00029 HUS, Helsinki, Finland. [158]Public Health Genomics Unit, National Institute for Health and Welfare, P.O. BOX 30, FI-00271 Helsinki, Finland [159]Medical Faculty, University of Belgrade, 11000 Belgrade, Serbia. [160]Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina 27599-7160, USA. [161]Institute for Molecular Medicine Finland, FIMM, University of Helsinki, P.O. Box 20FI-00014, Helsinki, Finland [162]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA. [163]Department of Psychiatry, University of Oxford, Oxford, OX3 7JX, UK. [164]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia 23298, USA. [165]Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [166]PharmaTherapeutics Clinical Research, Pfizer Worldwide Research and Development, Cambridge, Massachusetts 02139, USA. [167]Department of Psychiatry and Psychotherapy, University of Gottingen, 37073 Göttingen, Germany. [168]Psychiatry and Psychotherapy Clinic, University of Erlangen, 91054 Erlangen, Germany. [169]Hunter New England Health Service, Newcastle NSW 2308, Australia. [170]School of Biomedical Sciences, University of Newcastle, Newcastle NSW 2308, Australia. [171]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland 20892, USA. [172]University of Iceland, Landspitali, National University Hospital, 101 Reykjavik, Iceland. [173]Department of Psychiatry and Drug Addiction, Tbilisi State Medical University (TSMU), N33, 0177 Tbilisi, Georgia. [174]Research and Development, Bronx Veterans Affairs Medical Center, New York, New York 10468, USA. [175]Wellcome Trust Centre for Human Genetics, Oxford OX3 7BN, UK. [176]deCODE Genetics, 101 Reykjavik, Iceland. [177]Department of Clinical Neurology, Medical University of Vienna, 1090 Wien, Austria. [178]Lieber Institute for Brain Development, Baltimore, Maryland 21205, USA. [179]Department of Medical Genetics, University Medical Centre Utrecht, Universiteitsweg 100, 3584 CG, Utrecht, The Netherlands. [180]Berkshire Healthcare NHS Foundation Trust, Bracknell RG12 1BQ, UK. [181]Section of Psychiatry, University of Verona, 37134 Verona, Italy. [182]Department of Psychiatry, University of Oulu, P.O. Box 5000, 90014, Finland. [183]University Hospital of Oulu, P.O. Box 20, 90029 OYS, Finland. [184]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland. [185]Health Research Board, Dublin 2, Ireland. [186]School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth WA6009, Australia. [187]Computational Sciences CoE, Pfizer Worldwide Research and Development, Cambridge, Massachusetts 02139, USA. [188]Human Genetics, Genome Institute of Singapore, A*STAR, Singapore 138672. [189]A list of authors and affiliations appear in the Supplementary Information. [190]University College London, London WC1E 6BT, UK. [191]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [192]Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, 52428 Juelich, Germany. [193]Department of Genetics, The Hebrew University of Jerusalem, 91905 Jerusalem, Israel. [194]Neuroscience Discovery and Translational Area, Pharma Research and Early Development, F. Hoffman-La Roche, CH-4070 Basel, Switzerland. [195]Centre for Clinical Research in Neuropsychiatry, School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Medical Research Foundation Building, Perth WA6000, Australia. [196]Virginia Institute for Psychiatric and Behavioral Genetics, Departments of Psychiatry and Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia 23298, USA. [197]The Feinstein Institute for Medical Research, Manhasset, New York 11030, USA. [198]The Hofstra NS-LIJ School of Medicine, Hempstead, New York 11549, USA. [199]The Zucker Hillside Hospital, Glen Oaks, New York 11004, USA. [200]Saw Swee Hock School of Public Health, National University of Singapore, Singapore 117597, Singapore. [201]Queensland Centre for Mental Health Research, University of Queensland, Brisbane 4076, Queensland, Australia. [202]Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [203]Department of Child and Adolescent Psychiatry, Erasmus University Medical Centre, Rotterdam 3000, The Netherlands. [204]Department of Complex Trait Genetics, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, Amsterdam 1081, The Netherlands. [205]Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam 1081, The Netherlands. [206]University of Aberdeen, Institute of Medical Sciences, Aberdeen AB25 2ZD, UK. [207]Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, USA. [208]Department of Clinical Medicine, University of Copenhagen, Copenhagen 2200, Denmark.