Article

Mapping genomic loci implicates genes and synaptic biology in schizophrenia

https://doi.org/10.1038/s41586-022-04434-5

Received: 12 August 2020

Accepted: 10 January 2022

Published online: 8 April 2022

Check for updates

Schizophrenia has a heritability of 60–80%[1], much of which is attributable to common risk alleles. Here, in a two-stage genome-wide association study of up to 76,755 individuals with schizophrenia and 243,649 control individuals, we report common variant associations at 287 distinct genomic loci. Associations were concentrated in genes that are expressed in excitatory and inhibitory neurons of the central nervous system, but not in other tissues or cell types. Using fine-mapping and functional genomic data, we identify 120 genes (106 protein-coding) that are likely to underpin associations at some of these loci, including 16 genes with credible causal non-synonymous or untranslated region variation. We also implicate fundamental processes related to neuronal function, including synaptic organization, differentiation and transmission. Fine-mapped candidates were enriched for genes associated with rare disruptive coding variants in people with schizophrenia, including the glutamate receptor subunit *GRIN2A* and transcription factor *SP4*, and were also enriched for genes implicated by such variants in neurodevelopmental disorders. We identify biological processes relevant to schizophrenia pathophysiology; show convergence of common and rare variant associations in schizophrenia and neurodevelopmental disorders; and provide a resource of prioritized genes and variants to advance mechanistic studies.

Schizophrenia typically manifests in late adolescence or early adulthood[1] and is associated with reduced life expectancy, increased risk of suicide[2], serious physical illnesses[3] and substantial health and social costs. Treatments are at least partially effective in most people, but many have chronic symptoms, and adverse treatment effects are common[4]. There is a need for new therapeutic targets to be discovered, but this process is impeded by our limited understanding of pathophysiology.

Much of the between-individual variation in risk is genetic, and involves large numbers of common alleles[5], rare copy number variants (CNVs)[6] and rare coding variants[7,8]. A previous genome-wide association study (GWAS) reported 176 genomic loci containing common alleles associated with schizophrenia[9] but the causal variants that drive these associations and the biological consequences of these variants are largely unknown. To increase our understanding of the contribution of common variants to schizophrenia, we performed what is to our knowledge the largest GWAS of the disorder to date and analysed the findings to prioritize variants, genes and biological processes that contribute to pathogenesis.

Association meta-analysis

We performed a primary GWAS in 74,776 individuals with schizophrenia (hereafter, cases) and 101,023 control individuals, followed by an extended GWAS, which included additional data for the most significant single-nucleotide polymorphisms (SNPs) (Methods). In the primary GWAS, we combined by meta-analysis (i) individual genotypes from a core Psychiatric Genomics Consortium (PGC) dataset of 90 cohorts of European (EUR) and East Asian (ASN) ancestry from the PGC, totalling 67,390 cases and 94,015 controls; and (ii) summary-level data from 7,386 cases and 7,008 controls from 9 cohorts of African American (AA) and Latino (LAT) ancestry[10]. We analysed up to 7,585,078 single-nucleotide polymorphisms (SNPs) with a minor allele frequency (MAF) greater than or equal to 1% in 175,799 individuals of whom 74.3% were EUR, 17.5% ASN, 5.7% AA and 2.5% LAT (see 'Case–control sample descriptions' in the Supplementary Information). This primary GWAS identified 313 independent SNPs (linkage disequilibrium (LD) $r^2 < 0.1$) that exceeded genome-wide significance ($P < 5 \times 10^{-8}$) (Extended Data Fig. 1, Supplementary Table 1), spanning 263 distinct loci.

In the extended GWAS, we meta-analysed the primary GWAS results with summary statistics from deCODE genetics (1,979 cases, 142,626 controls) for index SNPs with $P < 10^{-5}$ and identified 342 linkage-disequilibrium-independent significant SNPs (Supplementary Table 2) located in 287 loci (Supplementary Table 3, Supplementary Figs. 1, 2). Comparisons with the 128 associations (108 loci) we reported in 2014 are provided (Supplementary Note); one association (rs3768644; chr2:72.3 Mb) is no longer supported[11].

Separate GWASs for male and female individuals had a genetic correlation (r_g) that was statistically indistinguishable from 1 ($r_g = 0.992$, standard error (s.e.) = 0.024). These and other analyses (Supplementary Note) show that common variant genetic liability to schizophrenia is essentially identical in male and female individuals despite reported sex differences in age at onset, symptom profile, course and outcome[12].

Heritability and polygenic prediction

In the EUR sample, the SNP-based heritability (h^2_{SNP}) (that is, the proportion of variance in liability attributable to all measured SNPs)

A list of authors and their affiliations appears online. ✉e-mail: sripke@broadinstitute.org; WaltersJT@cardiff.ac.uk; ODonovanMC@cardiff.ac.uk

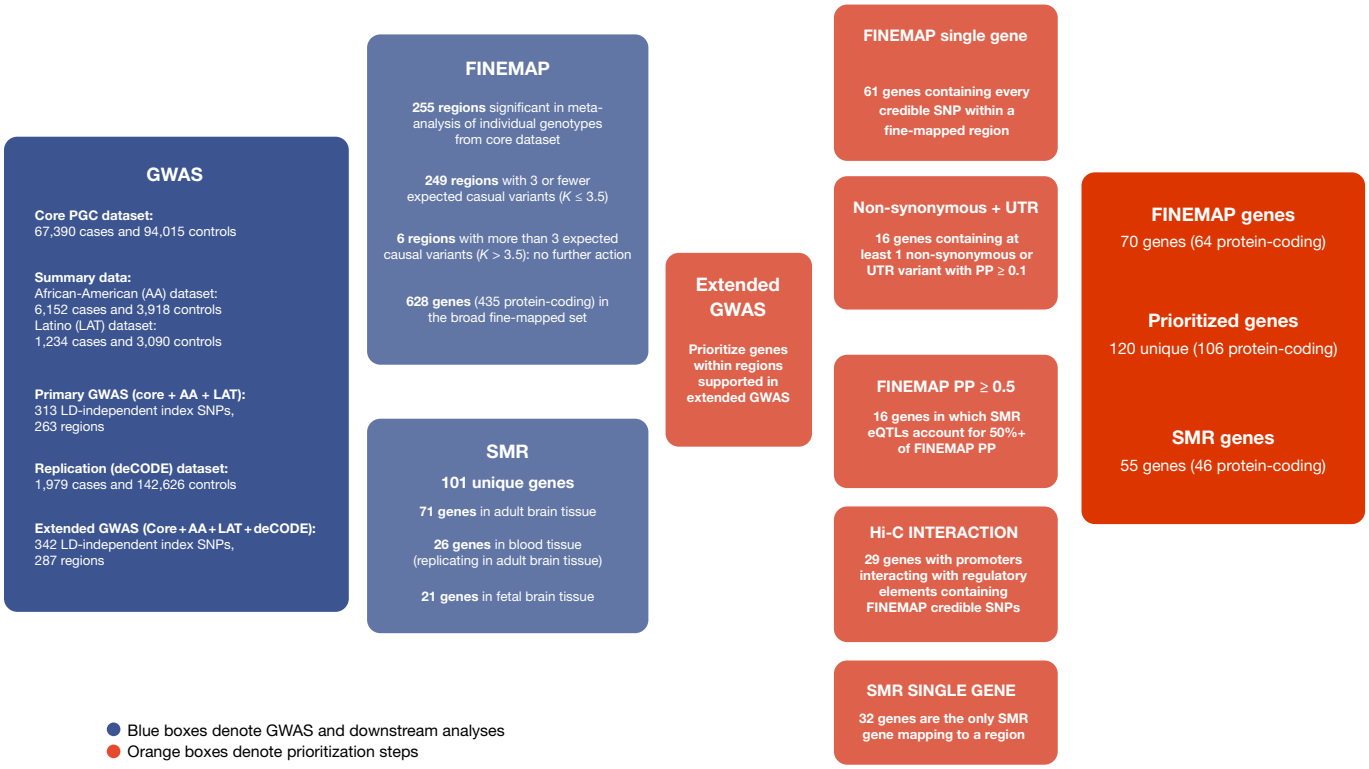


Fig. 1 | Overview of GWAS and gene prioritization. Flow diagram summarizing GWAS, fine-mapping (FINEMAP) and SMR analyses and how these informed gene prioritization.

was estimated[13] to be 0.24 (s.e. = 0.007). Using the all-ancestry primary GWAS as the discovery sample, polygenic risk score (PRS) analysis explained a median of 0.073 of variance in liability (SNPs with GWAS $P < 0.05$), and 0.024 when restricted to genome-wide significant SNPs. For almost all cohorts, PRS had more explanatory power when based on risk alleles derived from the larger combined ancestry GWAS than risk alleles from the matched ancestry GWAS; given the ancestry-specific sample sizes, unsurprisingly[9], this effect was strongest for the non-EUR samples (Extended Data Fig. 2, Supplementary Table 5).

PRS explained most variance in liability in cohorts of European ancestry (again a result of the ancestry composition of the GWAS[9]) and in samples that are likely to include the most severe cases (hospitalized individuals or those treated with clozapine) (Supplementary Note). However, even in EUR cohorts, the median area under the receiver operating characteristic curve (AUROC) is only 0.72, meaning that the liability explained is insufficient for predicting diagnosis in the general population. Nevertheless, as a quantitative estimate of liability to schizophrenia, PRS has applications in research, and in those contexts, PRS can index substantial differences in liability between individuals in the primary GWAS. Compared to the lowest centile of PRS, the highest centile of PRS has an odds ratio for schizophrenia of 39 (95% confidence interval (CI) 29–53), and 5.6 (CI 4.9–6.5) when the top centile is compared with the remaining 99% of individuals (Supplementary Table 6). An extended discussion of heritability and polygenic prediction is provided in the Supplementary Note.

Post-GWAS processing

We next performed several secondary analyses in the core PGC dataset in which individual genotypes were available based on fully aligned quality control and imputation procedures, and where the data in the Haplotype Reference Consortium (HRC) reference dataset allowed us to account for linkage disequilibrium.

Gene set enrichments

Tissue and cell types

Genes with relatively high specificity for bulk expression in every tested region of human brain[14] were significantly enriched for associations (Extended Data Fig. 3). Comparison with our previous studies[11,15] shows an increasingly clear contrast between the enrichments in brain and non-brain tissues. More strongly than in previous studies[16], from human single-cell expression data[17], we found that associations were enriched in genes with high expression in excitatory glutamatergic neurons from the cerebral cortex and hippocampus (pyramidal CA1 and CA3 cells, and granule cells of dentate gyrus) and in cortical inhibitory interneurons (Fig. 4a). In mouse single-cell RNA sequencing (RNA-seq) data[16], we found similar patterns of enrichments in genes, with high expression in excitatory glutamatergic pyramidal neurons from the cortex and hippocampus (Fig. 4b) and in inhibitory cortical interneurons. We also found that associations were enriched in inhibitory medium spiny neurons, the main cells of the striatum.

In support of these findings, similar results were obtained using a different dataset of 265 cell types in the mouse central and peripheral nervous system[18]. Very strong enrichments were again seen for genes expressed in excitatory glutamatergic neurons of the cortex (especially the deep layers) and hippocampus, but also for those expressed in the amygdala (Supplementary Fig. 3). Highly significant enrichments were also seen for other neuronal populations, including, as above, inhibitory medium spiny neurones in the striatum, but also both excitatory and inhibitory neurons from the midbrain, thalamus and hindbrain, and inhibitory cells from the hippocampus. There was little evidence for enrichment of genes with highly specific expression in glia or microglia. Overall, the findings across all the datasets are consistent with the hypothesis that schizophrenia is primarily a disorder of neuronal function, but they do not suggest that pathology is restricted to a defined region of the brain.

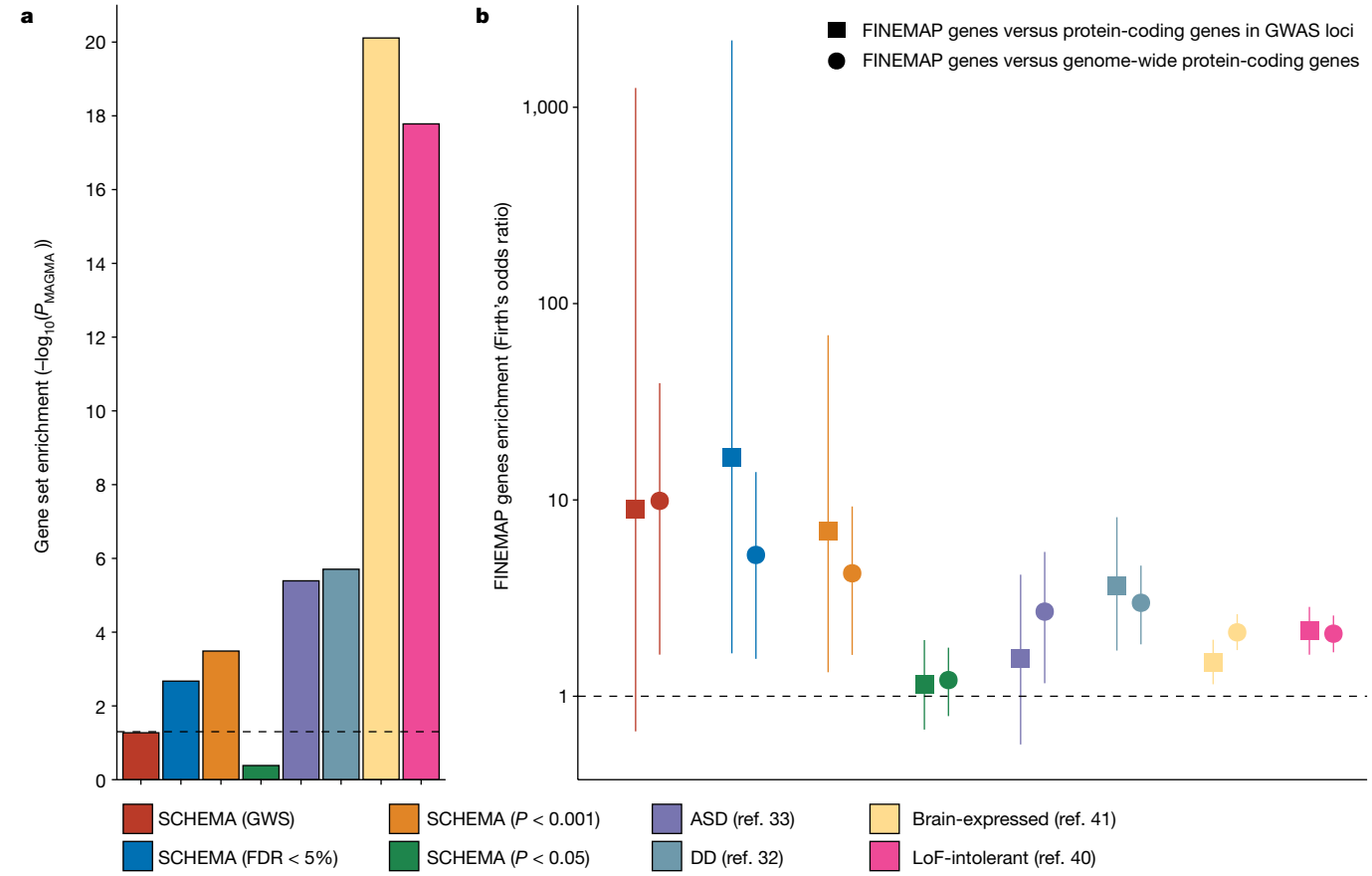


Fig. 2 | Gene set enrichment tests at the genome-wide level and for protein-coding genes that contain FINEMAP credible SNPs. Gene sets tested were retrieved from sequencing studies of schizophrenia[30], ASD[34] and developmental disorders (DD)[33]. Sets representing genes that are intolerant to loss-of function mutations[41] (LoF-intolerant) and brain-expressed genes[42] are also shown. **a**, MAGMA gene set enrichment analysis. Dotted line indicates nominal significance ($P = 0.05$). **b**, Logistic regression (with Firth's bias reduction method) showing the odds ratio (and 95% CI) for association between protein-coding genes that contain at least 1 credible FINEMAP SNP ($n = 418$ after excluding genes with no LoF-intolerance data) and genes from the sets indicated. Odds ratios are relative to protein-coding genes within GWAS $K \leq 3.5$ loci (1,283 genes; squares) or across the genome excluding the extended MHC[43] (19,547 genes; circles). Dotted line indicates no enrichment.

Ontologies

Of 7,315 Gene Ontology (GO) classifications, 24 were associated with schizophrenia (Supplementary Table 7). All were relevant to neuronal function, including development, differentiation and synaptic transmission, and involved multiple cellular components, including ion channels, synapses and both axon and dendritic annotations. Using the curated ontology of the SynGO consortium[19], we further examined the synaptic signal and found that conditionally significant annotations were mainly within postsynaptic terms (Supplementary Tables 8, 9), although enrichment was also found for genes involved in synaptic organization and signalling.

Gene prioritization

To facilitate biological interpretation and laboratory follow-up, we sought to prioritize specific variants and genes that are most likely to explain associations using a combination of fine-mapping, transcriptomic analysis and functional genomic annotations. The initial steps in these procedures were necessarily based on 293 index SNPs (255 loci) that attained significance in the core PGC dataset (Methods, Supplementary Table 10); we then focused on the loci that remained significant in the full extended GWAS to maximize robustness (Fig. 1).

Fine-mapping

We performed stepwise analyses (Supplementary Note), conditioning associations in loci on their index SNP (and any subsequent conditionally independent associations) to identify regions that contained independent signals (conditional $P < 10^{-6}$). This analysis supported the existence of independent associations in around 10% of loci (Supplementary Table 10b).

We also used the Bayesian fine-mapping method implemented in FINEMAP[20] to infer the most likely number of distinct causal variants driving our GWAS results. FINEMAP was based on 255 regions determined by the linkage disequilibrium clumping procedure (Supplementary Table 11e), after merging clumps if their boundaries physically overlapped and excluding the extended major histocompatibility complex (MHC) region (Methods). For regions predicted to contain three or fewer causal variants ($n = 249$; Fig. 1, Supplementary Tables 11a, b), we extracted from FINEMAP the posterior probability (PP) of being causal for every SNP across the region, and constructed credible sets of SNPs that cumulatively capture 95% of the regional PP (Supplementary Note).

For 33 regions, the 95% credible set contained 5 or fewer SNPs (Supplementary Table 11c) and for 9, only a single SNP. We highlight rs4766428 (PP > 0.99) which is the only credible SNP in a locus that contains 25 genes and is located within *ATP2A2*. Mutations in *ATP2A2*

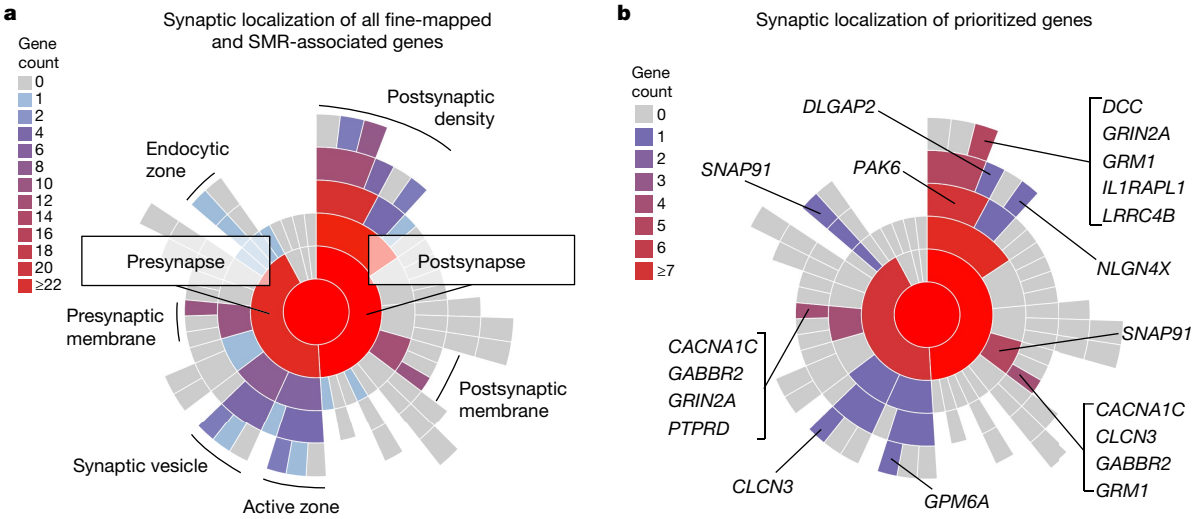


Fig. 3 | Mapping of all fine-mapped and SMR-associated genes, and prioritized genes, to synaptic locations using SynGO. Sunburst plots depict synaptic locations starting with the synapse (centre), pre- and postsynaptic locations in the first ring and child terms (that is, terms that are subsets of the adjacent inner ring) in subsequent rings. The number of genes in each term is indicated by the colour scheme in the legend. **a**, FINEMAP/SMR genes are protein-coding genes tagged by at least one credible SNP identified by FINEMAP and/or associated using SMR ($n = 470$), of which $n = 58$ are SynGO-annotated, 51 to cellular components. **b**, Prioritized genes (Extended Data Table 1; $n = 106$), of which 15 are SynGO-annotated, 14 to cellular components.

cause Darier disease[21], which co-segregates with bipolar disorder in several multiplex pedigrees and is associated with bipolar disorder and schizophrenia at a population level[22]. *ATP2A2* encodes a sarcoplasmic or endoplasmic reticulum calcium pump, suggesting that its role in schizophrenia pathogenesis may be through regulating neuronal levels of cytoplasmic calcium. The probable relevance of calcium metabolism is also suggested by enrichment for associations in and around voltage-gated calcium channels (Supplementary Tables 3, 7).

We denote as our broad fine-map set 628 genes (435 protein-coding) that contained at least one credible SNP (Fig. 1a). At a genome-wide level, genes that are expressed in the brain, and that are relatively intolerant to loss-of-function mutations, are known to be enriched for schizophrenia associations, and this was confirmed here (Fig. 2a). Protein-coding genes in the broad fine-map set were enriched for these properties compared to the other protein-coding genes within the associated regions (Fig. 2b), consistent with genes in this set having an increased probability of influencing liability to schizophrenia. To identify the most credible causal genes, we prioritized those mapping to the 287 loci that were genome-wide significant in our extended GWAS that also contained (a) at least one non-synonymous or untranslated region (UTR) variant with a PP > 0.1; (b) the entire credible set (Supplementary Tables 13, 14). These protein-coding genes had a greater-than-threefold enrichment for loss-of-function intolerance compared with other protein-coding genes within the loci that were not tagged by credible SNPs (Supplementary Table 15, Supplementary Note), supporting our strategy to delimit credible causal genes.

Among the 70 FINEMAP prioritized genes (64 protein-coding) were 16 genes (protein-coding by definition) based on non-synonymous or UTR variants (Supplementary Table 13). These include *SLC39A8*, in which rs13107325—previously a moderately high credible SNP[23]—is now strongly supported as causal (PP > 0.99). Other non-synonymous variants with a high PP were found in genes with minimal functional characterization, including *THAP8* and *WSCD2*, and in two genes that encode E3 ubiquitin ligases, *PJA1* and *CUL9*. Missense and UTR variants prioritized interferon regulatory factor 3 (*IRF3*), and the transcription factor *KLF6* was highlighted by three variants in the 3′-UTR. Finally, we identified 61 genes (55 protein-coding) in which the 95% credible set was restricted to a single gene (Supplementary Table 14).

Prioritization by gene expression

To detect GWAS associations that are credibly explained by expression quantitative trait loci (eQTLs)—that is, variants that influence gene expression—we used summary-based Mendelian randomization (SMR)[24] to find evidence that GWAS signals co-localize with eQTLs (from adult brain[25], fetal brain[26] or whole blood[27]) and the HEIDI test[24] to then reject co-localizations due to linkage disequilibrium between distinct schizophrenia-associated and eQTL variants (Supplementary Table 16). To retain brain relevance, we considered only findings from the blood that were replicated in the brain. After removing duplicates identified in multiple tissues (Supplementary Table 17a–c), we identified 101 SMR-implicated genes (Supplementary Table 17d); the use of alternative methodologies supported the robustness of the SMR findings (Supplementary Note, Supplementary Table 17e).

We used three approaches to prioritize genes from these 101 candidates (Supplementary Note, Supplementary Tables 17f, g, 18). We identified (i) 32 genes as the single SMR-implicated gene at the locus or through conditional analysis of a locus containing multiple candidates; (ii) 16 genes in which the putatively causal eQTLs captured 50% or more of the FINEMAP posterior probability; and (iii) 29 genes in which chromatin conformation analysis (Hi-C analysis of adult and fetal brain) suggested that a promoter of that gene interacted with a putative regulatory element containing a FINEMAP credible SNP[28].

After removing duplicates, 55 genes were prioritized by SMR or SMR-Hi-C (Supplementary Table 12), of which 46 were protein-coding. Genes in which putatively causal eQTLs captured a particularly high FINEMAP PP (greater than 95%) (Supplementary Table 17g) included: *ACE*, which encodes angiotensin-converting enzyme—the target of a major class of anti-hypertensive drugs (underexpressed in schizophrenia); *DCLK3*, which encodes a neuroprotective kinase[29] (underexpressed in schizophrenia); and *SNAP91* (discussed below; overexpressed in schizophrenia).

Combining all approaches, FINEMAP and SMR, we prioritized 120 genes, of which 106 are protein-coding (Fig. 1, Extended Data Table 1).

Prioritized genes at the synapse

Following the findings from the genome-wide enrichment tests, we examined prioritized genes in the context of synaptic location and

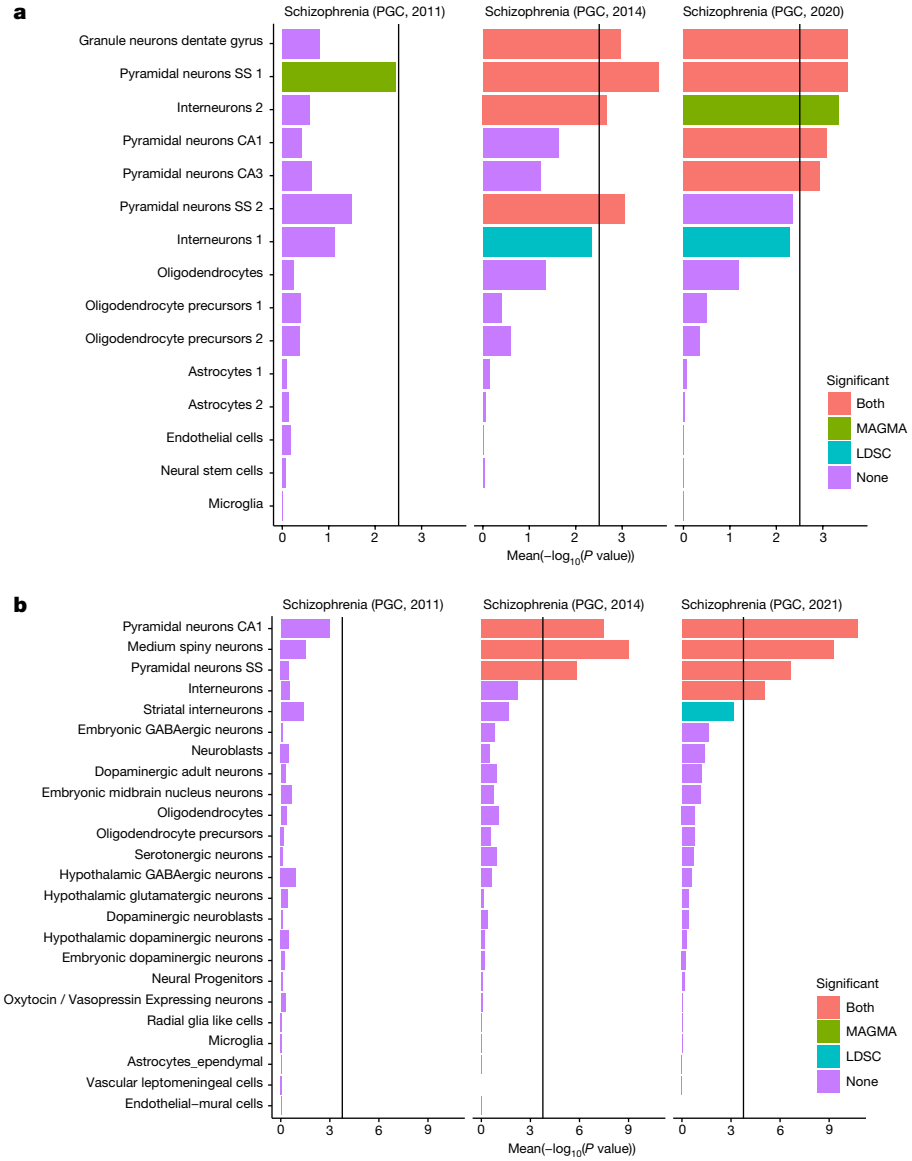


Fig. 4 | Associations between schizophrenia and cell types from multiple brain regions in human and mouse. a, **b**, The mean of the evidence ($-\log_{10}$ *P* value) obtained from two methods (MAGMA and LDSC) for testing GWAS data for enrichment of associations in genes with high expression in cell types. 15 human cell types (derived from single nuclei) from the cortex and hippocampus (**a**) and 24 cell types (derived from single-cell RNA-seq) from 5 different brain regions in mouse (cortex, hippocampus, striatum, midbrain and hypothalamus) and from specific enrichments of oligodendrocytes, serotonergic neurons, dopaminergic neurons and cortical parvalbuminergic interneurons (**b**). Bar colour indicates whether the cell type is significantly associated with both methods, one method or none. The black vertical line represents the significance threshold corrected for the total number of cell types tested in each analysis. Results obtained for previous iterations of schizophrenia GWAS12,18 are shown for comparison. Pyramidal SS, pyramidal neurons from the somatosensory cortex; pyramidal CA1/CA3, pyramidal neurons from the CA1/CA3 region of the hippocampus. Where types of cell (such as interneurons) formed sub-clusters in the source data, these are designated by the suffix 1 or 2.

function in the SynGO database[19] (Fig. 3). Of the 106 proteins encoded, 15 have synaptic annotations (Supplementary Table 19): 7 postsynaptic, 5 both pre- and postsynaptic, 2 presynaptic, and 1 gene not mapped to any specific compartment.

These results are consistent with the genome-wide enrichment tests that point to postsynaptic pathology. However, many prioritized genes had additional locations, suggesting that presynaptic pathology may also be involved. The encoded proteins map to 16 unique biological terms in the hierarchy (Supplementary Table 19), but there are specific themes. Multiple genes encode receptors and ion channels, including voltage-gated calcium and chloride channels (*CACNA1C* and *CLCN3*), metabotropic receptors (glutamate (*GRM1*) and GABA (*GABBR2*)), and the ligand-gated *N*-methyl-D-aspartate (NMDA) receptor subunit (*GRIN2A*). Others encode proteins that have a role in endocytosis (*SNAP91*), synaptic organization and differentiation (*DLGAP2*, *LRRC4B*, *GPM6A*, *PAK6* and *PTPRD*; this group also includes *PTPRD*, a receptor protein tyrosine phosphatase presynaptic organizer that trans-synaptically interacts with multiple postsynaptic cell adhesion molecules, for example, IL1RAPL1) and modulation of chemical transmission (*MAPK3*, *DCC*, *CLCN3* and *DLGAP2*). The diversity of synaptic proteins identified in this study suggests that multiple functional interactions of schizophrenia risk converge on synapses. It remains to be determined whether these interactions occur at a limited set of specific synapse types, or whether the diversity points to several types in different brain regions.

Convergence of common and rare variants

The Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium identified 32 genes with damaging ultra-rare mutations associated with schizophrenia (false discovery rate (FDR) < 0.05), including 10 at exome-wide significance[30]. We found that both sets of genes were enriched for common variant associations, as were more weakly associated SCHEMA genes down to uncorrected $P < 0.001$ (Fig. 2a, Supplementary Tables 20, 21). Moreover, within associated loci, protein-coding genes that contained one or more FINEMAP credible SNPs were enriched for SCHEMA genes relative to other protein-coding genes (Fig. 2b, Supplementary Table 21). There are rare variant overlaps in liability to schizophrenia, autism spectrum disorder (ASD) and developmental disorder[8,31,32]. We found that genes in which rare variants increase risk of ASD and developmental disorder[33,34] are also enriched for schizophrenia common variant associations. Moreover, they are also enriched among genes that contain FINEMAP credible SNPs (Fig. 2, Supplementary Tables 20, 21).

Convergences between rare variants and fine-mapped GWAS signals have been previously observed in other traits[35,36], suggesting that genes that are most strongly implicated by fine-mapping and which have additional support from rare variant data are compelling candidates. Of the 10 exome-wide significant genes identified by SCHEMA[37], two were prioritized candidates from fine-mapping: *GRIN2A*, which encodes a glutamatergic NMDA receptor subunit; and *SP4*, a transcription factor that is highly expressed in the brain, which is regulated by NMDA transmission and also regulates NMDA receptor abundance[38]. Two other genes supported by SCHEMA at FDR < 0.05 had strong support from fine-mapping: *STAG1*, which is involved in controlling chromosome segregation and regulating gene expression; and *FAM120A*, which encodes an RNA-binding protein. SNPs mapping to these genes had cumulative FINEMAP PPs of 0.88 and 0.72, respectively (Supplementary Table 11b). The prioritized fine-mapped set also contained four genes implicated in developmental disorder: a transcriptional regulator (*BCL11B*); the well-known *CACNA1C*[39]; and genes mentioned elsewhere in this paper (*GRIN2A* and *SLC39A8*). Genes that encode additional transcriptional regulators are also of note; *RERE*, *FOXP1* and *MYT1L*. *RERE* was prioritized by SMR and is associated with developmental disorder. *FOXP1* and *MYT1L* are associated with both developmental disorder and ASD and met our fine-mapping prioritization criteria in the core PGC dataset (Supplementary Table 12).

Discussion

We have performed the largest—to our knowledge—GWAS of schizophrenia so far and in doing so, have identified a substantial increase in the number of associated loci. We show that genes we prioritize within associated loci by fine-mapping are enriched for those with an increased burden of rare deleterious mutations in schizophrenia, and identify *GRIN2A*, *SP4*, *STAG1* and *FAM120A* as specific genes in which the convergence of rare and common variant associations strongly supports their pathogenic role in the disorder. Notably, this convergence also implies that the pathogenic relevance of altered function of these genes extends beyond the small proportion of cases that carry rare mutations. We also show that common variant schizophrenia associations are enriched at genes that are implicated in neurodevelopmental disorders, suggesting that the increasing power of rare variant studies of those disorders could be used to further prioritize genes from GWAS studies. Exploiting this, in addition to *GRIN2A* we identify *BCL11B*, *CACNA1C*, *RERE*, *FOXP1*, *MYT1L* and *SLC39A8* as genes with strong support.

Enrichment of common variant associations was restricted to genes that are expressed in neurons of the central nervous system—both excitatory and inhibitory—and that have roles in fundamental biological processes related to neuronal function. This indicates that neurons are the most important site of pathology in schizophrenia. We also show that genes with high relative specificity for expression in almost all tested brain regions are enriched for genetic association. This suggests that abnormal neuronal function in schizophrenia is not confined to a small number of brain structures, which in turn might explain its diverse psychopathology, association with a broad range of cognitive impairments and lack of regional specificity in neuroimaging measures[1].

Disrupted neuronal function in schizophrenia is unlikely to be restricted to the synapse, but the concentration of associations in genes with pre- and postsynaptic locations, and with functions related to synaptic organization, differentiation and transmission, point to the pathophysiological importance of these neuronal compartments and their attendant functions. This is further supported by studies showing substantial effects on schizophrenia risk of CNVs[40] and rare damaging coding variants in genes with similar functions, including some of the same genes[30]. Genomic studies, therefore, converge in highlighting these areas of biology as targets for research that aims for a mechanistic understanding of schizophrenia. The large number of prioritized genes and variants identified here offer an empirically supported resource for that endeavour.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-022-04434-5.

1. Owen, M. J., Sawa, A. & Mortensen, P. B. Schizophrenia. *Lancet* **388**, 86–97 (2016).
2. Plana-Ripoll, O. et al. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. *Lancet* **394**, 1827–1835 (2019).
3. Momen, N. C. et al. Association between mental disorders and subsequent medical conditions. *N. Engl. J. Med.* **382**, 1721–1731 (2020).
4. Jääskeläinen, E. et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr. Bull.* **39**, 1296–1306 (2013).
5. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748–752 (2009).
6. Pocklington, A. J. et al. Novel findings from CNVs implicate inhibitory and excitatory signaling complexes in schizophrenia. *Neuron* **86**, 1203–1214 (2015).
7. Singh, T. et al. The contribution of rare variants to risk of schizophrenia in individuals with and without intellectual disability. *Nat. Genet.* **49**, 1167–1173 (2017).
8. Rees, E. et al. De novo mutations identified by exome sequencing implicate rare missense variants in *SLC6A1* in schizophrenia. *Nat. Neurosci* **23**, 179–184 (2020).
9. Lam, M. et al. Comparative genetic architectures of schizophrenia in East Asian and European populations. *Nat. Genet.* **51**, 1670–1678 (2019).
10. Bigdeli, T. B. et al. Contributions of common genetic variants to risk of schizophrenia among individuals of African and Latino ancestry. *Mol. Psychiatry* **25**, 2455–2467 (2020).
11. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
12. Räsänen, S., Pakaslahti, A., Syvälahti, E., Jones, P. B. & Isohanni, M. Sex differences in schizophrenia: a review. *Nord. J. Psychiatry* **54**, 37–45 (2000).
13. Zeng, J. et al. Widespread signatures of natural selection across human complex traits and functional genomic categories. *Nat. Commun.* **12**, 1164 (2021).
14. Aguet, F. et al. Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017).
15. Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* **43**, 969–978 (2011).
16. Skene, N. G. et al. Genetic identification of brain cell types underlying schizophrenia. *Nat. Genet.* **50**, 825–833 (2018).
17. Habib, N. et al. Massively parallel single-nucleus RNA-seq with DroNc-seq. *Nat. Methods* **14**, 955–958 (2017).
18. Zeisel, A. et al. Molecular architecture of the mouse nervous system. *Cell* **174**, 999–1014 (2018).
19. Koopmans, F. et al. SynGO: an evidence-based, expert-curated knowledge base for the synapse. *Neuron* **103**, 217–234 (2019).
20. Benner, C. et al. FINEMAP: efficient variable selection using summary data from genome-wide association studies. *Bioinformatics* **32**, 1493–1501 (2016).
21. Sakuntabhai, A. et al. Mutations in *ATP2A2*, encoding a Ca^{2+} pump, cause Darier disease. *Nat. Genet.* **21**, 271–277 (1999).

22. Cederlöf, M. et al. The association between Darier disease, bipolar disorder, and schizophrenia revisited: a population-based family study. *Bipolar Disord.* **17**, 340–344 (2015).
23. Pardiñas, A. F. et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat. Genet.* **50**, 381–389 (2018).
24. Zhu, Z. et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–487 (2016).
25. Gandal, M. J. et al. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science* **362**, eaat8127 (2018).
26. O'Brien, H. E. et al. Expression quantitative trait loci in the developing human brain and their enrichment in neuropsychiatric disorders. *Genome Biol.* **19**, 194 (2018).
27. Võsa, U. et al. Large-scale *cis*- and *trans*-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat. Genet.* **53**, 1300–1310 (2021).
28. Wang, D. et al. Comprehensive functional genomic resource and integrative model for the human brain. *Science* **362**, eaat8464 (2018).
29. Galvan, L. et al. The striatal kinase DCLK3 produces neuroprotection against mutant huntingtin. *Brain* **141**, 1434–1454 (2018).
30. Singh, T. et al. Rare coding variants in 10 genes confer substantial risk for schizophrenia. *Nature* https://doi.org/10.1038/s41586-022-04556-w (2022).
31. Rees, E. et al. Analysis of intellectual disability copy number variants for association with schizophrenia. *JAMA Psychiatry* **73**, 963–969 (2016).
32. Fromer, M. et al. De novo mutations in schizophrenia implicate synaptic networks. *Nature* **506**, 179–184 (2014).
33. Kaplanis, J. et al. Evidence for 28 genetic disorders discovered by combining healthcare and research data. *Nature* **586**, 757–762 (2020).
34. Satterstrom, F. K. et al. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell* **180**, 568–584 (2020).
35. Luo, Y. et al. Exploring the genetic architecture of inflammatory bowel disease by whole-genome sequencing identifies association at *ADCY7*. *Nat. Genet.* **49**, 186–192 (2017).
36. Cheng, Y. et al. Rare genetic variants affecting urine metabolite levels link population variation to inborn errors of metabolism. *Nat. Commun.* **12**, 964 (2021).
37. Singh, T., Neale, B. M. & Daly, M. J. Exome sequencing identifies rare coding variants in 10 genes which confer substantial risk for schizophrenia. Preprint at https://doi.org/10.1101/2020.09.18.20192815 (2020).
38. Priya, A., Johar, K. & Wong-Riley, M. T. T. Specificity protein 4 functionally regulates the transcription of NMDA receptor subunits GluN1, GluN2A, and GluN2B. *Biochim. Biophys. Acta* **1833**, 2745–2756 (2013).
39. Ripke, S. et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.* **45**, 1150–1159 (2013).
40. Kirov, G. et al. De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. *Mol. Psychiatry* **17**, 142–153 (2012).
41. Lek, M. et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* **536**, 285–291 (2016).
42. Fagerberg, L. et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol. Cell. Proteomics* **13**, 397–406 (2014).
43. Stephens, R. et al. Gene organisation, sequence variation and isochore structure at the centromeric boundary of the human MHC. J. Mol. Biol. 291, 789–799 (1999).

Vassily Trubetskoy[1,452], Antonio F. Pardiñas[2,452], Ting Qi[3,4], Georgia Panagiotaropoulou[1], Swapnil Awasthi[1], Tim B. Bigdeli[5,6,7], Julien Bryois[8], Chia-Yen Chen[9,10,11], Charlotte A. Dennison[2], Lynsey S. Hall[2], Max Lam[12,13,14], Kyoko Watanabe[15], Oleksandr Frei[16,17,18], Tian Ge[11,12,19], Janet C. Harwood[2], Frank Koopmans[20], Sigurdur Magnusson[21], Alexander L. Richards[2], Julia Sidorenko[3], Yang Wu[3], Jian Zeng[3], Jakob Grove[22,23,24], Minsoo Kim[25], Zhiqiang Li[26,27], Georgios Voloudakis[28], Wen Zhang[28,29], Mark Adams[30], Ingrid Agartz[16,31,32], Elizabeth G. Atkinson[10,12], Esben Agerbo[22,33], Mariam Al Eissa[34], Margot Albus[35], Madeline Alexander[36], Behrooz Z. Alizadeh[37,38], Köksal Alptekin[39,40], Thomas D. Als[22,23,24], Farooq Amin[41], Volker Arolt[42], Manuel Arrojo[43], Lavinia Athanasiu[16,17], Maria Helena Azevedo[44], Silviu A. Bacanu[45], Nicholas J. Bass[34], Martin Begemann[46], Richard A. Belliveau[12], Judit Bene[47], Beben Benyamin[48,49,50], Sarah E. Bergen[8], Giuseppe Blasi[51], Julio Bobes[52,53,54], Stefano Bonassi[55], Alice Braun[1], Rodrigo Affonseca Bressan[56,57], Evelyn J. Bromet[58], Richard Bruggeman[37,59], Peter F. Buckley[60], Randy L. Buckner[61], Jonas Bybjerg-Grauholm[22,62], Wiepke Cahn[63,64], Murray J. Cairns[65,66,67], Monica E. Calkins[68], Vaughan J. Carr[69,70,71], David Castle[72,73], Stanley V. Catts[74,75], Kimberley D. Chambert[12], Raymond C. K. Chan[76,77], Boris Chaumette[78,79], Wei Cheng[80], Eric F. C. Cheung[81], Siow Ann Chong[13,82], David Cohen[83,84,85], Angèle Consoli[83,84], Quirino Cordeiro[86], Javier Costas[87], Charles Curtis[88,89], Michael Davidson[90], Kenneth L. Davis[91], Lieuwe de Haan[92,93], Franziska Degenhardt[94], Lynn E. DeLisi[19,95], Ditte Demontis[22,23,24], Faith Dickerson[96], Dimitris Dikeos[97], Timothy Dinan[98,99], Srdjan Djurovic[100,101], Jubao Duan[102,103], Giuseppe Ducci[104], Frank Dudbridge[105], Johan G. Eriksson[106,107,108], Lourdes Fañanás[109,110], Stephen V. Faraone[111], Alessia Fiorentino[34], Andreas Forstner[94,112], Josef Frank[113], Nelson B. Freimer[114,115], Menachem Fromer[116], Alessandra Frustaci[117], Ary Gadelha[56,57], Giulio Genovese[12], Elliot S. Gershon[118], Marianna Giannitelli[83,84], Ina Giegling[119], Paola Giusti-Rodríguez[120], Stephanie Godard[121], Jacqueline I. Goldstein[10], Javier González Peñas[110,122], Ana González-Pinto[110,123], Srihari Gopal[124], Jacob Gratten[3,125], Michael F. Green[126,127], Tiffany A. Greenwood[128], Olivier Guillin[129,130,131], Sinan Gülöksüz[132,133], Raquel E. Gur[68], Ruben C. Gur[68], Blanca Gutiérrez[134], Eric Hahn[135], Hakon Hakonarson[136], Vahram Haroutunian[91,137,138], Annette M. Hartmann[119], Carol Harvey[72,139], Caroline Hayward[140], Frans A. Henskens[141], Stefan Herms[142], Per Hoffmann[142], Daniel P. Howrigan[10,143], Masashi Ikeda[144], Conrad Iyegbe[145], Inge Joa[146], Antonio Julià[147], Anna K. Kähler[8], Tony Kam-Thong[148], Yoichiro Kamatani[149,150], Sena Karachanak-Yankova[151,152], Oussama Kebir[78], Matthew C. Keller[153], Brian J. Kelly[141], Andrey Khrunin[154], Sung-Wan Kim[155], Janis Klovins[156], Nikolay Kondratiev[157], Bettina Konte[119], Julia Kraft[1,158], Michiaki Kubo[159], Vaidutis Kučinskas[160], Zita Ausrele Kučinskiene[160], Agung Kusumawardhani[161], Hana Kuzelova-Ptackova[162], Stefano Landi[163], Laura C. Lazzeroni[164,165], Phil H. Lee[12,166], Sophie E. Legge[2], Douglas S. Lehrer[167], Rebecca Lencer[42], Bernard Lerer[168], Miaoxin Li[169], Jeffrey Lieberman[170], Gregory A. Light[128,171], Svetlana Limborska[154], Chih-Min Liu[172,173], Jouko Lönnqvist[174,175], Carmel M. Loughland[176], Jan Lubinski[177], Jurjen J. Luykx[132,178,179,180], Amy Lynham[2], Milan Macek Jr[181], Andrew Mackinnon[182,183], Patrik K. E. Magnusson[8], Brion S. Maher[184], Wolfgang Maier[185], Dolores Malaspina[91,186], Jacques Mallet[187], Stephen R. Marder[188], Sara Marsal[147], Alicia R. Martin[10,12,189], Lourdes Martorell[190], Manuel Mattheisen[23,191,192,193], Robert W. McCarley[194,454], Colm McDonald[195], John J. McGrath[33,196,197], Helena Medeiros[198,199], Sandra Meier[191,200], Bela Melegh[201], Ingrid Melle[16,17], Raquelle I. Mesholam-Gately[19,202], Andres Metspalu[203], Patricia T. Michie[204], Lili Milani[203], Vihra Milanova[205], Marina Mitjans[46], Espen Molden[206,207], Esther Molina[208], María Dolores Molto[110,209,210], Valeria Mondelli[89,211], Carmen Moreno[110,122], Christopher P. Morley[212], Gerard Muntané[190,213], Kieran C. Murphy[214], Inez Myin-Germeys[215], Igor Nenadić[216,217], Gerald Nestadt[218], Liene Nikitina-Zake[156], Cristiano Noto[56,57], Keith H. Nuechterlein[126], Niamh Louise O'Brien[34], F. Anthony O'Neill[219], Sang-Yun Oh[220,221], Ann Olincy[222], Vanessa Kiyomi Ota[57,223], Christos Pantelis[139,224,225,226], George N. Papadimitriou[97], Mara Parellada[110,122], Tiina Paunio[227,228], Renata Pellegrino[136], Sathish Periyasamy[196,229], Diana O. Perkins[230], Bruno Pfuhlmann[231], Olli Pietiläinen[12,232,233], Jonathan Pimm[34], David Porteous[234], John Powell[235], Diego Quattrone[88,89,236], Digby Quested[237,238], Allen D. Radant[239,240], Antonio Rampino[51], Mark H. Rapaport[241], Anna Rautanen[148], Abraham Reichenberg[91], Cheryl Roe[242], Joshua L. Roffman[243], Julian Roth[244], Matthias Rothermundt[42], Bart P. F. Rutten[132], Safaa Saker-Delye[245], Veikko Salomaa[246], Julio Sanjuan[110,210,247], Marcos Leite Santoro[57,223], Adam Savitz[124], Ulrich Schall[66,248], Rodney J. Scott[65,66,249], Larry J. Seidman[19,202], Sally Isabel Sharp[34], Jianxin Shi[250], Larry J. Siever[91,251], Engilbert Sigurdsson[252,253], Kang Sim[254,255,256], Nora Skarabis[1], Petr Slominsky[154], Hon-Cheong So[257,258], Janet L. Sobell[198], Erik Söderman[32], Helen J. Stain[259,260], Nils Eiel Steen[17,261], Agnes A. Steixner-Kumar[46], Elisabeth Stögmann[262], William S. Stone[263,264], Richard E. Straub[265], Fabian Streit[113], Eric Strengman[266], T. Scott Stroup[170], Mythily Subramaniam[13,82], Catherine A. Sugar[126,267], Jaana Suvisaari[246], Dragan M. Svrakic[268], Neal R. Swerdlow[128], Jin P. Szatkiewicz[120], Thi Minh Tam Ta[269,270], Atsushi Takahashi[271], Chikashi Terao[271], Florence Thibaut[272,273], Draga Toncheva[151,274], Paul A. Tooney[65,66,67], Silvia Torretta[51], Sarah Tosato[275], Gian Battista Tura[276], Bruce I. Turetsky[68], Alp Üçok[277], Arne Vaaler[278,279], Therese van Amelsvoort[89,132], Ruud van Winkel[132,280], Juha Veijola[281,282], John Waddington[283], Henrik Walter[1], Anna Waterreus[284,285], Bradley T. Webb[45], Mark Weiser[286], Nigel M. Williams[2], Stephanie H. Witt[113], Brandon K. Wormley[45], Jing Qin Wu[287], Zhida Xu[288], Robert Yolken[289], Clement C. Zai[290,291], Wei Zhou[27], Feng Zhu[292,293], Fritz Zimprich[262], Eşref Cem Atbaşoğlu[186,294], Muhammad Ayub[295], Christian Benner[233], Alessandro Bertolino[51], Donald W. Black[296], Nicholas J. Bray[2], Gerome Breen[88], Nancy G. Buccola[297], William F. Byerley[298], Wei J. Chen[299,300], C. Robert Cloninger[268], Benedicto Crespo-Facorro[301,302], Gary Donohoe[195], Robert Freedman[222], Cherrie Galletly[303,304,305], Michael J. Gandal[25], Massimo Gennarelli[306,307], David M. Hougaard[22,62], Hai-Gwo Hwu[173,308], Assen V. Jablensky[285], Steven A. McCarroll[12], Jennifer L. Moran[12,243], Ole Mors[22,309], Preben B. Mortensen[22,33], Bertram Müller-Myhsok[310,311,312], Amanda L. Neil[313], Merete Nordentoft[22,314], Michele T. Pato[315,316], Tracey L. Petryshen[166], Matti Pirinen[233,317,318], Ann E. Pulver[218], Thomas G. Schulze[193,319,320,321], Jeremy M. Silverman[91,251], Jordan W. Smoller[12,166], Eli A. Stahl[116,322,323], Debby W. Tsuang[239,240], Elisabet Vilella[190], Shi-Heng Wang[324], Shuhua Xu[325,326,327], Indonesia Schizophrenia Consortium*, PsychENCODE, Psychosis Endophenotypes International Consortium, The SynGO Consortium, Rolf Adolfsson[328], Celso Arango[110,122], Bernhard T. Baune[42,225,226], Sintia Iole Belangero[57,223], Anders D. Børglum[22,23,24], David Braff[128,171], Elvira Bramon[329], Joseph D. Buxbaum[91], Dominique Campion[129,130], Jorge A. Cervilla[330], Sven Cichon[331,332,333], David A. Collier[334], Aiden Corvin[335], David Curtis[336,337], Marta Di Forti[88,89,236], Enrico Domenici[338], Hannelore Ehrenreich[46], Valentina Escott-Price[2,339], Tõnu Esko[203,322], Ayman H. Fanous[7,340,341], Anna Gareeva[342,343], Micha Gawlik[244], Pablo V. Gejman[102,103], Michael Gill[335], Stephen J. Glatt[344], Vera Golimbet[157], Kyung Sue Hong[345], Christina M. Hultman[8], Steven E. Hyman[12,232], Nakao Iwata[144], Erik G. Jönsson[32,261], René S. Kahn[63,91], James L. Kennedy[290,291], Elza Khusnutdinova[342,343], George Kirov[2], James A. Knowles[346,347], Marie-Odile Krebs[78], Claudine Laurent-Levinson[83,84], Jimmy Lee[348,349], Todd Lencz[14,350,351], Douglas F. Levinson[164], Qingqin S. Li[124], Jianjun Liu[352,353], Anil K. Malhotra[14,350,351], Dheeraj Malhotra[354], Andrew McIntosh[30], Andrew McQuillin[34], Paulo R. Menezes[355], Vera A. Morgan[284,285], Derek W. Morris[195], Bryan J. Mowry[196,229], Robin M. Murray[89], Vishwajit Nimgaonkar[356], Markus M. Nöthen[94], Roel A. Ophoff[114,357,358], Sara A. Paciga[359], Aarno Palotie[233,360,361], Carlos N. Pato[315,316], Shengying Qin[27,362], Marcella Rietschel[113], Brien P. Riley[45], Margarita Rivera[363,364], Dan Rujescu[119], Meram C. Saka[294], Alan R. Sanders[102,103], Sibylle G. Schwab[365,366], Alessandro Serretti[367], Pak C. Sham[368,369,370], Yongyong Shi[26,27], David St Clair[371], Hreinn Stefánsson[21], Kari Stefansson[21], Ming T. Tsuang[372,373], Jim van Os[145,374], Marquis P. Vawter[375], Daniel R. Weinberger[266], Thomas Werge[376,377,378,379], Dieter B. Wildenauer[380], Xin Yu[381,382], Weihua Yue[381,382,383], Peter A. Holmans[2], Andrew J. Pocklington[2], Panos Roussos[28,384], Evangelos Vassos[88,89,385], Matthijs Verhage[386,387], Peter M. Visscher[3], Jian Yang[3,4,388], Danielle Posthuma[387], Ole A. Andreassen[16,17], Kenneth S. Kendler[45], Michael J. Owen[2], Naomi R. Wray[3,196], Mark J. Daly[10,143,233], Hailiang Huang[10,12,189], Benjamin M. Neale[10,12], Patrick F. Sullivan[8,120,230], Stephan Ripke[1,10,361,453] ✉, James T. R. Walters[2,453] ✉, Michael C. O'Donovan[2,453] ✉ & Schizophrenia Working Group of the Psychiatric Genomics Consortium*

[1]Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany. [2]MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK. [3]Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia. [4]School of Life Sciences, Westlake University, Hangzhou, China. [5]Department of Psychiatry and the Behavioral Sciences, SUNY Downstate Medical Center, New York, NY, USA. [6]Institute for Genomic Health, SUNY Downstate Medical Center, New York, NY, USA. [7]Department of Psychiatry, Veterans Affairs New York Harbor Healthcare System, New York, NY, USA. [8]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [9]Biogen, Cambridge, MA, USA. [10]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [11]Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA. [12]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA. [13]Research Division, Institute of Mental Health, Singapore, Republic of Singapore. [14]Division of Psychiatry Research, Zucker Hillside Hospital, Glen Oaks, NY, USA. [15]Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. [16]NORMENT Centre, Division of Mental Health and Addiction, University of Oslo, Oslo, Norway. [17]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. [18]Center for Bioinformatics, Department of Informatics, University of Oslo, Oslo, Norway. [19]Department of Psychiatry, Harvard Medical School, Boston, MA, USA. [20]Department of Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognitive Research, Faculty of Science, Amsterdam Neuroscience, Vrije Universiteit, Amsterdam, The Netherlands. [21]deCODE Genetics, Amgen, Reykjavik, Iceland. [22]The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark. [23]Department of Biomedicine and Centre for Integrative Sequencing (iSEQ), Aarhus University, Aarhus, Denmark. [24]Center for Genomics and Personalized Medicine, Aarhus, Denmark. [25]Department of Psychiatry, Semel Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA. [26]Affiliated Hospital of Qingdao University and Biomedical Sciences Institute of Qingdao University (Qingdao Branch of SJTU Bio-X Institutes), Qingdao University, Qingdao, China. [27]Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Collaborative Innovation Center for Brain Science, Shanghai Jiao Tong University, Shanghai, China. [28]Department of Psychiatry, Pamela Sklar Division of Psychiatric Genomics, Friedman Brain Institute, Department of Genetics and Genomic Science and Institute for Data Science and Genomic Technology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [29]Department of Genetics and Genomic Sciences and Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [30]Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK. [31]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway. [32]Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet and Stockholm Health Care Services, Stockholm Region, Stockholm, Sweden. [33]National Centre for Register-based Research, Aarhus University, Aarhus, Denmark. [34]Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, London, UK. [35]Comedicum Lindwurmhof, Munich, Germany. [36]Center for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, MA, USA. [37]University Medical Center Groningen, University Center for Psychiatry, Rob Giel Research Center, University of Groningen, Groningen, The Netherlands. [38]Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [39]Department of Psychiatry, Dokuz Eylül University School of Medicine, Izmir, Turkey. [40]Department of Neuroscience, Dokuz Eylül University Graduate School of Health Sciences, Izmir, Turkey. [41]Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, USA. [42]Department of Psychiatry, University of Münster, Münster, Germany. [43]Servizo de Psiquiatría, Complexo Hospitalario Universitario de Santiago de Compostela, Servizo Galego de Saúde (SERGAS), Santiago de Compostela, Spain. [44]Institute of Medical Psychology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal. [45]Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. [46]Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen, Germany. [47]Department of Medical Genetics, Medical School, University of Pécs, Pécs, Hungary. [48]Australian Centre for Precision Health, University of South Australia Cancer Research Institute, University of South Australia, Adelaide, South Australia, Australia. [49]UniSA Allied Health and Human Performance, University of South Australia, Adelaide, South

Australia, Australia. [50]South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia. [51]Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', Bari, Italy. [52]Área de Psiquiatría-Universidad de Oviedo, Hospital Universitario Central de Asturias (HUCA), Asturias, Spain. [53]Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Asturias, Spain. [54]Centro de Investigación Biomédica en Red de Salud Mental, Oviedo, Asturias, Spain. [55]Unit of Clinical and Molecular Epidemiology, IRCCS San Raffaele Roma and San Raffaele University, Rome, Italy. [56]Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil. [57]Laboratory of Integrative Neuroscience, Universidade Federal de São Paulo, São Paulo, Brazil. [58]Department of Psychiatry and Behavioural Health, Stony Brook University, Stony Brook, NY, USA. [59]Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands. [60]Health Science Center, University of Tennessee, Memphis, TN, USA. [61]Department of Psychology, Harvard University, Cambridge, MA, USA. [62]Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark. [63]University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands. [64]Altrecht, General Menthal Health Care, Utrecht, The Netherlands. [65]School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, New South Wales, Australia. [66]Hunter Medical Research Institute, Newcastle, New South Wales, Australia. [67]Centre for Brain and Mental Health Research, University of Newcastle, Newcastle, New South Wales, Australia. [68]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. [69]School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia. [70]Department of Psychiatry, Monash University, Melbourne, Victoria, Australia. [71]Neuroscience Research Australia, Sydney, New South Wales, Australia. [72]Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia. [73]St Vincent's Hospital, Melbourne, Victoria, Australia. [74]Brain and Mind Centre, The University of Sydney, Sydney, New South Wales, Australia. [75]School of Medicine, University of Queensland, Herston, Queensland, Australia. [76]Institute of Psychology, Chinese Academy of Science, Beijing, China. [77]Department of Psychology, University of Chinese Academy of Sciences, Beijing, China. [78]INSERM U1266, Institute of Psychiatry and Neuroscience of Paris, Université de Paris, GHU Paris Psychiatrie & Neurosciences, Paris, France. [79]Department of Psychiatry, McGill University, Montreal, Québec, Canada. [80]Department of Computer Science, University of North Carolina, Chapel Hill, NC, USA. [81]Castle Peak Hospital, Hong Kong, China. [82]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Republic of Singapore. [83]Faculté de Médecine Sorbonne Université, Groupe de Recherche Clinique no. 15 - Troubles Psychiatriques et Développement (PSYDEV), Department of Child and Adolescent Psychiatry, Hôpital Universitaire de la Pitié-Salpêtrière, Paris, France. [84]Centre de Référence des Maladies Rares à Expression Psychiatrique, Department of Child and Adolescent Psychiatry, AP-HP Sorbonne Université, Hôpital Universitaire de la Pitié-Salpêtrière, Paris, France. [85]Institut des Systèmes Intelligents et de Robotique (ISIR), CNRS UMR7222, Faculté des Sciences et Ingénierie, Sorbonne Université, Paris, France. [86]Department of Psychiatry, Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil. [87]Instituto de Investigación Sanitaria (IDIS) de Santiago de Compostela, Complexo Hospitalario Universitario de Santiago de Compostela (CHUS), Servizo Galego de Saúde (SERGAS), Santiago de Compostela, Spain. [88]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [89]National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, London, UK. [90]University of Nicosia Medical School, Nicosia, Cyprus. [91]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [92]Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands. [93]Arkin, Institute for Mental Health, Amsterdam, The Netherlands. [94]Institute of Human Genetics, University of Bonn, Bonn, Germany. [95]Cambridge Health Alliance, Cambridge, MA, USA. [96]Sheppard Pratt Health System, Baltimore, MD, USA. [97]First Department of Psychiatry, Medical School, National and Kapodistrian University of Athens, Eginition Hospital, Athens, Greece. [98]Department of Psychiatry and Neurobehavioural Sciences, University College Cork, Cork, Ireland. [99]APC Microbiome Ireland, University College Cork, Cork, Ireland. [100]NORMENT Centre, Department of Clinical Science, University of Bergen, Bergen, Norway. [101]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. [102]Center for Psychiatric Genetics, NorthShore University HealthSystem, Evanston, IL, USA. [103]Department of Psychiatry and Behavioral Neurosciences, The University of Chicago, Chicago, IL, USA. [104]Department of Mental Health, ASL Rome 1, Rome, Italy. [105]Department of Health Sciences, University of Leicester, Leicester, UK. [106]Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [107]Folkhälsan Research Center, Helsinki, Finland. [108]Department of Obstetrics and Gynecology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Republic of Singapore. [109]Department of Evolutionary Biology, Ecology and Environmental Sciences, Faculty of Biology, University of Barcelona, Barcelona, Spain. [110]Centro de Investigación Biomédica en Red en Salud Mental (CIBERSAM), Madrid, Spain. [111]Departments of Psychiatry and Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA. [112]Centre for Human Genetics, University of Marburg, Marburg, Germany. [113]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany. [114]Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA. [115]Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA. [116]Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [117]Barnet, Enfield and Haringey Mental Health NHS Trust, St Ann's Hospital, London, UK. [118]Departments of Psychiatry and Human Genetics, University of Chicago, Chicago, IL, USA. [119]Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria. [120]Department of Genetics, University of North Carolina, Chapel Hill, NC, USA. [121]Departments of Psychiatry and Human and Molecular Genetics, INSERM, Institut de Myologie, Hôpital de la Pitiè-Salpêtrière, Paris, France. [122]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, Madrid, Spain. [123]BIOARABA Health Research Institute, OSI Araba, University Hospital, University of the Basque Country, Vitoria, Spain. [124]Neuroscience Therapeutic Area, Janssen Research and Development, Titusville, NJ, USA. [125]Mater Research Institute, University of Queensland, Brisbane, Queensland, Australia. [126]Department of Psychiatry and Biobehavioral Sciences, Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA. [127]VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA. [128]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. [129]INSERM, Rouen, France. [130]Centre Hospitalier du Rouvray, Rouen, France. [131]UFR Santé, Université de Rouen Normandie, Rouen, France. [132]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands. [133]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA. [134]Department of Psychiatry, Faculty of Medicine and Biomedical Research Centre (CIBM), University of Granada, Granada, Spain. [135]Department of Psychiatry, Charité - Universitätsmedizin, Berlin, Germany. [136]Children's Hospital of Philadelphia, Leonard Madlyn Abramson Research Center, Philadelphia, PA, USA. [137]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [138]Mental Illness Research Clinical and Education Center (MIRECC), JJ Peters VA Medical Center, New York, NY, USA. [139]NorthWestern Mental Health, Melbourne, Victoria, Australia. [140]MRC Human Genetics Unit, University of Edinburgh, Institute of Genetics and Cancer, Western General Hospital, Edinburgh, UK. [141]School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia. [142]Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland. [143]Broad Institute of MIT and Harvard, Cambridge, MA, USA. [144]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake Aichi, Japan. [145]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [146]Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, Stavanger, Norway. [147]Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona, Spain. [148]Roche Pharma Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffman-La Roche, Basel, Switzerland. [149]Laboratory of Complex Trait Genomics, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan. [150]Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [151]Department of Medical Genetics, Medical University, Sofia, Bulgaria. [152]Department of Genetics, Faculty of Biology, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria. [153]Institute for Behavioural Genetics, University of Colorado Boulder, Boulder, CO, USA. [154]Institute of Molecular Genetics of National Research Centre "Kurchatov Institute", Moscow, Russia. [155]Department of Psychiatry, Chonnam National University Medical School, Gwangju, Korea. [156]Latvian Biomedical Research and Study Centre, Riga, Latvia. [157]Mental Health Research Center, Moscow, Russian Federation. [158]Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany. [159]RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [160]Faculty of Medicine, Vilnius University, Vilnius, Lithuania. [161]Psychiatry Department, University of Indonesia - Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. [162]Department of Psychiatry, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic. [163]Dipartimento di Biologia, Universita' di Pisa, Pisa, Italy. [164]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA. [165]Department of Biomedical Data Science, Stanford University, Stanford, CA, USA. [166]Psychiatric and Neurodevelopmental Genetics Unit, Department of Psychiatry and Center for Genomic Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [167]Department of Psychiatry, Wright State University, Dayton, OH, USA. [168]Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel. [169]Zhongshan School of Medicine and Key Laboratory of Tropical Diseases Control (SYSU), Sun Yat-sen University, Guangzhou, China. [170]Department of Psychiatry, Columbia University, New York, NY, USA. [171]VISN 22, Mental Illness Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, CA, USA. [172]Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan. [173]Neurobiology and Cognitive Science Center, National Taiwan University, Taipei, Taiwan. [174]Mental Health Unit, Department of Public Health Solutions, National Institute for Health and Welfare, Helsinki, Finland. [175]Department of Psychiatry, University of Helsinki, Helsinki, Finland. [176]Hunter New England Health and University of Newcastle, Newcastle, New South Wales, Australia. [177]Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, Szczecin, Poland. [178]Department of Psychiatry, UMC Utrecht Brain Center, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands. [179]Department of Translational Neuroscience, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands. [180]Second Opinion Outpatient Clinic, GGNet Mental Health, Warnsveld, The Netherlands. [181]Department of Biology and Medical Genetics, 2nd Faculty of Medicine and University Hospital Motol, Prague, Czech Republic. [182]Black Dog Institute, University of New South Wales, Randwick, New South Wales, Australia. [183]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia. [184]Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA. [185]Department for Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn, Bonn, Germany. [186]Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [187]Asfalia Biologics, iPEPS-ICM, Hôpital Universitaire de la Pitié-Salpêtrière, Paris, France. [188]Semel Institute for Neurosciene, University of California Los Angeles, Los Angeles, CA, USA. [189]Department of Medicine, Harvard Medical School, Boston, MA, USA. [190]Hospital Universitari Institut Pere Mata, IISPV, Universitat Rovira i Virgili, CIBERSAM, Reus, Spain. [191]Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada. [192]Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada. [193]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany. [194]VA Boston Health Care System, Brockton, MA, USA. [195]Centre for Neuroimaging, Cognition and Genomics (NICOG), National University of Ireland Galway, Galway, Ireland. [196]Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia. [197]Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Brisbane, Queensland, Australia. [198]Department of Psychiatry and the Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. [199]College of Medicine, SUNY Downstate Health Sciences University, New York, NY, USA. [200]Department of Biomedicine, Aarhus University, Aarhus, Denmark. [201]Department of Medical Genetics, University of Pécs, School of Medicine, Pécs, Hungary. [202]Massachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Boston, MA, USA. [203]Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia. [204]School of Psychology, University of Newcastle, Newcastle, New South Wales, Australia. [205]Psychiatric Clinic,

Alexandrovska University Hospital, Sofia, Bulgaria. [206]Department of Pharmacy, University of Oslo, Oslo, Norway. [207]Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway. [208]Department of Nursing, Faculty of Health Sciences and Biomedical Research Centre (CIBM), University of Granada, Granada, Spain. [209]Department of Genetics, Faculty of Biological Sciences, Universidad de Valencia, Valencia, Spain. [210]Biomedical Research Institute INCLIVA, Valencia, Spain. [211]Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK. [212]Departments of Public Health and Preventive Medicine, Family Medicine, and Psychiatry and Behavioral Sciences, State University of New York, Upstate Medical University, Syracuse, NY, USA. [213]Institut de Biologia Evolutiva (UPF-CSIC), Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra, PRBB, Barcelona, Spain. [214]Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland. [215]Department for Neurosciences, Center for Contextual Psychiatry, KU Leuven, Leuven, Belgium. [216]Cognitive Neuropsychiatry Laboratory, Department of Psychiatry and Psychotherapy, Philipps Universität Marburg, Marburg, Germany. [217]Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany. [218]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [219]Centre for Public Health, Institute of Clinical Sciences, Queen's University Belfast, Belfast, UK. [220]Department of Statistics and Applied Probability, University of California at Santa Barbara, Santa Barbara, CA, USA. [221]Computational Research Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA. [222]Department of Psychiatry, University of Colorado Denver, Aurora, CO, USA. [223]Department of Morphology and Genetics, Laboratorio de Genetica, Universidade Federal de São Paulo, São Paulo, Brazil. [224]Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health, Melbourne, Victoria, Australia. [225]The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia. [226]Department of Psychiatry, Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia. [227]Department of Public Health Solutions, Genomics and Biomarkers Unit, National Institute for Health and Welfare, Helsinki, Finland. [228]Department of Psychiatry and SleepWell Research Program, Faculty of Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland. [229]Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia. [230]Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA. [231]Clinic of Psychiatry and Psychotherapy, Weißer Hirsch, Dresden, Germany. [232]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA. [233]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. [234]Centre for Genomic and Experimental Medicine, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, UK. [235]Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [236]South London and Maudsley NHS Mental Health Foundation Trust, London, UK. [237]Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK. [238]Department of Psychiatry, University of Oxford, Oxford, UK. [239]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA. [240]VA Puget Sound Health Care System, Seattle, WA, USA. [241]Huntsman Mental Health Institute, Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, USA. [242]SUNY Upstate Medical University, Syracuse, NY, USA. [243]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [244]Department of Psychiatry, Psychosomatics and Psychotherapy, Julius-Maximilians-Universität Würzburg, Würzburg, Germany. [245]Généthon, Evry, France. [246]THL–Finnish Institute for Health and Welfare, Helsinki, Finland. [247]Department of Psychiatry, School of Medicine, University of Valencia, Hospital Clínico Universitario de Valencia, Valencia, Spain. [248]Priority Centre for Brain and Mental Health Research, University of Newcastle, Mater Hospital, McAuley Centre, Newcastle, New South Wales, Australia. [249]Division of Molecular Medicine, NSW Health Pathology North, Newcastle, New South Wales, Australia. [250]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. [251]James J. Peters VA Medical Center, Bronx, NY, USA. [252]Faculty of Medicine, University of Iceland, Reykjavik, Iceland. [253]Department of Psychiatry, Landspitali University Hospital, Reykjavik, Iceland. [254]West Region, Institute of Mental Health, Singapore, Singapore. [255]Yoo Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [256]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. [257]School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong, China. [258]Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong, China. [259]School of Social and Health Sciences, Leeds Trinity University, Leeds, UK. [260]TIPS - Network for Clinical Research in Psychosis, Stavanger University Hospital, Stavanger, Norway. [261]NORMENT Centre, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [262]Department of Neurology, Medical University of Vienna, Vienna, Austria. [263]Harvard Medical School Department of Psychiatry at Beth Israel Deaconess Medical Center, Boston, MA, USA. [264]Massachusetts Mental Health Center, Boston, MA, USA. [265]Lieber Institute for Brain Development, Baltimore, MD, USA. [266]Department of Medical Genetics, University Medical Centre Utrecht, Utrecht, The Netherlands. [267]Department of Biostatistics, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA, USA. [268]Department of Psychiatry, Washington University, St Louis, MO, USA. [269]Department of Psychiatry, Charité – Universitätsmedizin Berlin, Berlin, Germany. [270]Berlin Institute of Health (BIH), Berlin, Germany. [271]Laboratory for Statistical and Translational Genetics, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. [272]Université de Paris, Faculté de Médecine, Hôpital Cochin-Tarnier, Paris, France. [273]INSERM U1266, Institut de Psychiatrie et de Neurosciences, Paris, France. [274]Bulgarian Academy of Science, Sofia, Bulgaria. [275]Department of Neuroscience, Biomedicine and Movement Sciences, Section of Psychiatry, University of Verona, Verona, Italy. [276]Psychiatry Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. [277]Department of Psychiatry, Faculty of Medicine, Istanbul University, Istanbul, Turkey. [278]Division of Mental Health, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway. [279]Department of Mental Health, Norwegian University of Science and Technology, Trondheim, Norway. [280]Department of Neurosciences, Center for Clinical Psychiatry, KU Leuven, Leuven, Belgium. [281]Department of Psychiatry, Research Unit of Clinical Neuroscience, University of Oulu, Oulu, Finland. [282]Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland. [283]Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. [284]Neuropsychiatric Epidemiology Research Unit, School of Population and Global Health, University of Western Australia, Perth, Western Australia, Australia. [285]Centre for Clinical Research in Neuropsychiatry, University of Western Australia, Perth, Western Australia, Australia. [286]Sheba Medical Center, Tel Hashomer, Israel. [287]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia. [288]Department of Psychiatry, GGz Centraal, Utrecht, The Netherlands. [289]Stanley Neurovirology Laboratory, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [290]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. [291]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. [292]Department of Psychiatry, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. [293]Center for Translational Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. [294]Department of Psychiatry, School of Medicine, Ankara University, Ankara, Turkey. [295]Department of Psychiatry, Queens University Kingston, Kingston, Ontario, Canada. [296]Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA. [297]School of Nursing, Louisiana State University Health Sciences Center, New Orleans, LA, USA. [298]Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA. [299]Center for Neuropsychiatric Research, National Health Research Institutes, Zhunan Town, Taiwan. [300]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan. [301]University of Sevilla, CIBERSAM IBiS, Seville, Spain. [302]Hospital Universitario Virgen del Rocio, Department of Psychiatry, Universidad del Sevilla, Seville, Spain. [303]Discipline of Psychiatry, Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia. [304]Ramsay Health Care (SA) Mental Health, Adelaide, South Australia, Australia. [305]Northern Adelaide Local Health Network, Adelaide, South Australia, Australia. [306]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy. [307]Genetic Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. [308]Department of Psychiatry, College of Medicine and National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan. [309]Psychosis Research Unit, Aarhus University Hospital, Aarhus, Denmark. [310]Max Planck Institute of Psychiatry, Munich, Germany. [311]Munich Cluster for Systems Neurology, Munich, Germany. [312]Department of Health Data Science, University of Liverpool, Liverpool, UK. [313]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia. [314]Mental Health Services in the Capital Region of Denmark, Mental Health Center Copenhagen, University of Copenhagen, Copenhagen, Denmark. [315]Rutgers University, Robert Wood Johnson Medical School, New Brunswick, NJ, USA. [316]Rutgers University, New Jersey Medical School, Newark, NJ, USA. [317]Department of Mathematics and Statistics, University of Helsinki, Helsinki, Finland. [318]Department of Public Health, University of Helsinki, Helsinki, Finland. [319]Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA. [320]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany. [321]Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University, Baltimore, MD, USA. [322]Program in Medical and Population Genetics, The Broad Institute of MIT and Harvard, Cambridge, MA, USA. [323]Regeneron Genetics Center, Orange, CA, USA. [324]College of Public Health, China Medical University, Taichung, Taiwan. [325]State Key Laboratory of Genetic Engineering and Ministry of Education (MOE) Key Laboratory of Contemporary Anthropology, Collaborative Innovation Center of Genetics and Development, Human Phenome Institute, School of Life Sciences, Fudan University, Shanghai, China. [326]School of Life Science and Technology, ShanghaiTech University, Shanghai, China. [327]Center for Excellence in Animal Evolution and Genetics, Chinese Academy of Sciences, Kunming, China. [328]Department of Clinical Sciences, Psychiatry, Umeå University, Umeå, Sweden. [329]Division of Psychiatry, Department of Mental Health Neuroscience, University College London, London, UK. [330]Department of Psychiatry, San Cecilio University Hospital, University of Granada, Granada, Spain. [331]Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland. [332]Department of Biomedicine, University of Basel, Basel, Switzerland. [333]Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany. [334]Eli Lilly and Company, Windlesham, UK. [335]Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin, Ireland. [336]UCL Genetics Institute, University College London, London, UK. [337]Centre for Psychiatry, Queen Mary University London, London, UK. [338]Department of Cellular, Computational and Integrative Biology, University of Trento, Trento, Italy. [339]Dementia Research Institute, Cardiff University, Cardiff, UK. [340]Department of Psychiatry, Phoenix VA Healthcare System, Phoenix, AZ, USA. [341]Banner-University Medical Center, Phoenix, AZ, USA. [342]Department of Human Molecular Genetics of the Institute of Biochemistry and Genetics of the Ufa Federal Research Center of the Russian Academy of Sciences (IBG UFRC RAS), Ufa, Russia. [343]Federal State Educational Institution of Highest Education Bashkir State Medical University of Public Health Ministry of Russian Federation (BSMU), Ufa, Russia. [344]Psychiatric Genetic Epidemiology and Neurobiology Laboratory (PsychGENe lab), Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA. [345]Department of Psychiatry, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea. [346]Department of Psychiatry and Zilkha Neurogenetics Institute, Keck School of Medicine at University of Southern California, Los Angeles, CA, USA. [347]Department of Cell Biology, State University of New York, Downstate Health Sciences University, New York, NY, USA. [348]Department of Psychosis, Institute of Mental Health, Singapore, Singapore. [349]Neuroscience and Mental Health, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. [350]Institute of Behavioral Science, Feinstein Institutes for Medical Research, Manhasset, NY, USA. [351]Department of Psychiatry, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA. [352]Human Genetics, Genome Institute of Singapore, A*STAR, Singapore, Singapore. [353]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [354]Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffman-La Roche, Basel, Switzerland. [355]Department of Preventative Medicine, Faculdade de Medicina FMUSP, University of São Paulo, São Paulo, Brazil. [356]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA. [357]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA. [358]Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands. [359]Early Clinical Development, Pfizer Worldwide Research and Development, Groton, CT, USA. [360]Analytic and Translational Genetics Unit, Department of Medicine, Department of Neurology and Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [361]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA. [362]Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

[363]Department of Biochemistry and Molecular Biology II, Faculty of Pharmacy, University of Granada, Granada, Spain. [364]Institute of Neurosciences, Biomedical Research Center (CIBM), University of Granada, Granada, Spain. [365]Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, New South Wales, Australia. [366]Illawarra Health and Medical Research Institute, Wollongong, New South Wales, Australia. [367]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy. [368]Centre for PanorOmic Sciences, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China. [369]State Key Laboratory of Brain and Cognitive Sciences, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China. [370]Department of Psychiatry, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China. [371]Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK. [372]Center for Behavioral Genomics, Department of Psychiatry, University of California San Diego, La Jolla, CA, USA. [373]Institute of Genomic Medicine, University of California San Diego, La Jolla, CA, USA. [374]University Medical Center Utrecht, Department of Psychiatry, Utrecht, The Netherlands. [375]Department of Psychiatry and Human Behavior, School of Medicine, University of California Irvine, Irvine, CA, USA. [376]Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark. [377]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. [378]Center for GeoGenetics, GLOBE Institute, University of Copenhagen, Copenhagen, Denmark. [379]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Copenhagen, Denmark. [380]School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, Western Australia, Australia. [381]Peking University Sixth Hospital, Peking University Institute of Mental Health, Beijing, China. [382]National Clinical Research Center for Mental Disorders, NHC Key Laboratory of Mental Health (Peking University) and Chinese Academy of Medical Sciences Research Unit, Beijing, China. [383]PKU–IDG/McGovern Institute for Brain Research, Peking University, Beijing, China. [384]Mental Illness Research, Education, and Clinical Center (VISN 2 South), James J. Peters VA Medical Center, New York, NY, USA. [385]Oxford Health NHS Foundation Trust, Oxford, UK. [386]Department of Clinical Genetics, Center for Neurogenomics and Cognitive Research, University Medical Center Amsterdam, Amsterdam, The Netherlands. [387]Department of Functional Genomics, Faculty of Exact Science, Center for Neurogenomics and Cognitive Research, VU University Amsterdam and VU Medical Center, Amsterdam, The Netherlands. [388]Westlake Laboratory of Life Sciences and Biomedicine, Hangzhou, China. [452]These authors contributed equally: Vassily Trubetskoy, Antonio F. Pardiñas. [453]These authors jointly supervised this work: Stephan Ripke, James T. R. Walters, Michael C. O'Donovan. [454]Deceased: Robert W. McCarley. ✉e-mail: sripke@broadinstitute.org; WaltersJT@cardiff.ac.uk; ODonovanMC@cardiff.ac.uk

Indonesia Schizophrenia Consortium

Nan Dai[389,390], Qin Wenwen[389,390], D. B. Wildenauer[389,390], Feranindhya Agiananda[391], Nurmiati Amir[391], Ronald Antoni[391], Tiana Arsianti[391], Asmarahadi Asmarahadi[391], H. Diatri[391], Prianto Djatmiko[391], Irmansyah Irmansyah[391], Siti Khalimah[391], Irmia Kusumadewi[391], Profitasari Kusumaningrum[391], Petrin R. Lukman[391], Martina W. Nasrun[391], N. S. Safyuni[391], Prasetyawan Prasetyawan[391], G. Semen[391], Kristiana Siste[391], Heriani Tobing[391], Natalia Widiasih[391], Tjhin Wiguna[391], D. Wulandari[391], None Evalina[391], A. J. Hananto[391], Joni H. Ismoyo[391], T. M. Marini[391], Supiyani Henuhili[391], Muhammad Reza[391] & Suzy Yusnadewi[391]

[389]Western Australian Institute for Medical Research and Centre for Medical Research, University of Western Australia, Nedlands, Western Australia, Australia. [390]School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, Western Australia, Australia. [391]Department of Psychiatry, University of Indonesia, Jakarta, Indonesia.

PsychENCODE

Alexej Abyzov[392], Schahram Akbarian[393], Allison Ashley-Koch[394], Harm van Bakel[393], Michael Breen[393], Miguel Brown[395], Julien Bryois[396], Becky Carlyle[397], Alex Charney[393], Gerard Coetzee[398], Gregory Crawford[394], Stella Dracheva[393], Prashant Emani[397], Peggy Farnham[398], Menachem Fromer[143], Timur Galeev[397], Mike Gandal[399], Mark Gerstein[397], Gina Giase[400], Kiran Girdhar[393], Fernando Goes[401], Kay Grennan[395], Mengting Gu[397], Brittney Guerra[397], Gamze Gursoy[397], Gabriel Hoffman[393], Thomas Hyde[265], Andrew Jaffe[265], Shan Jiang[400], Yan Jiang[393], Amira Kefi[400], Yunjung Kim[402], Robert Kitchen[397], James A. Knowles[403], Fides Lay[398], Donghoon Lee[397], Mingfeng Li[397], Chunyu Liu[242], Shuang Liu[397], Eugenio Mattei[404], Fabio Navarro[397], Xinghua Pan[397], Mette A. Peters[405], Dalila Pinto[393], Sirisha Pochareddy[397], Damon Polioudakis[399], Michael Purcaro[404], Shaun Purcell[393], Henry Pratt[404], Tim Reddy[394], Suhn Rhie[398], Panagiotis Roussos[393], Joel Rozowsky[397], Stephan Sanders[406], Nenad Sestan[397], Anurag Sethi[397], Xu Shi[397], Annie Shieh[400], Vivek Swarup[399], Anna Szekely[397], Daifeng Wang[397], Jonathan Warrell[397], Sherman Weissman[397], Zhiping Weng[407], Kevin White[408], Jennifer Wiseman[393], Heather Witt[398], Hyejung Won[399], Shannon Wood[398], Feinan Wu[397], Xuming Xu[397], Lijing Yao[398] & Peter Zandi[401]

[392]Mayo Clinic, Rochester, MN, USA. [393]Mount Sinai, New York, NY, USA. [394]Duke University, Durham, NC, USA. [395]University of Chicago, Chicago, IL, USA. [396]Karolinska Institutet, Stockholm, Sweden. [397]Yale University, New Haven, CT, USA. [398]University of Southern California, Los Angeles, CA, USA. [399]University of California Los Angeles, Los Angeles, CA, USA. [400]University of Illinois at Chicago, Chicago, IL, USA. [401]Johns Hopkins University, Baltimore, MD, USA. [402]University of North Carolina - Chapel Hill, Chapel Hill, NC, USA. [403]SUNY Downstate Medical Center, New York, NY, USA. [404]University of Massachusetts, Amherst, MA, USA. [405]Sage Bionetworks, Seattle, WA, USA. [406]University of California San Francisco, San Francisco, CA, USA. [407]University of Massachusetts Medical School, Worcester, MA, USA. [408]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.

Psychosis Endophenotypes International Consortium

Maria J. Arranz[409,410], Steven Bakker[178], Stephan Bender[411,412], Elvira Bramon[409,413], David A. Collier[88,334], Benedicto Crepo-Facorro[110,414], Jeremy Hall[415], Conrad Iyegbe[409], René Kahn[178], Stephen Lawrie[416], Cathryn Lewis[409], Kuang Lin[409], Don H. Linszen[417], Ignacio Mata[110,414], Andrew McIntosh[416], Robin M. Murray[409], Roel A. Ophoff[418], Jim van Os[419,420], John Powell[409], Dan Rujescu[421,422] & Muriel Walshe[409]Matthias Weisbrod[412]

[409]King's College London, London, UK. [410]Fundació de Docència i Recerca Mútua de Terrassa, Universitat de Barcelona, Barcelona, Spain. [411]Child and Adolescent Psychiatry, University of Technology Dresden, Dresden, Germany. [412]Section for Experimental Psychopathology, General Psychiatry, Heidelberg, Germany. [413]Institute of Cognitive Neuroscience, University College London, London, UK. [414]University Hospital Marqués de Valdecilla, Instituto de Formación e Investigación Marqués de Valdecilla, University of Cantabria, Santander, Spain. [415]Neuroscience and Mental Health Research Institute, Division of Psychiatry and Clinical Neuroscience, Cardiff University, Cardiff, UK. [416]Division of Psychiatry, University of Edinburgh, Edinburgh, UK. [417]Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. [418]Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA. [419]Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, The Netherlands. [420]Institute of Psychiatry, King's College London, London, UK. [421]Department of Psychiatry, University of Halle, Halle, Germany. [422]Department of Psychiatry, University of Munich, Munich, Germany.

The SynGO Consortium

Tilmann Achsel[423], Maria Andres-Alonso[424], Claudia Bagni[423], Àlex Bayés[425], Thomas Biederer[426], Nils Brose[427], Tyler C. Brown[12], John Jia En Chua[428], Marcelo P. Coba[429], L. Niels Cornelisse[430], Arthur P. H. de Jong[431], Jaime de Juan-Sanz[432], Daniela C. Dieterich[433,434], Guoping Feng[12,435], Hana L. Goldschmidt[436], Eckart D. Gundelfinger[434], Casper Hoogenraad[437], Richard L. Huganir[436], Steven E. Hyman[12,438], Cordelia Imig[439], Reinhard Jahn[440], Hwajin Jung[441], Pascal S. Kaeser[442], Eunjoon Kim[441], Frank Koopmans[387], Michael R. Kreutz[424], Noa Lipstein[443], Harold D. MacGillavry[431], Robert Malenka[444], Peter S. McPherson[445], Vincent O'Connor[446], Rainer Pielot[433,434], Timothy A. Ryan[447], Dnyanada Sahasrabudhe[387], Carlo Sala[448], Morgan Sheng[12], Karl-Heinz Smalla[433,434], August B. Smit[449], Thomas C. Südhof[450], Paul D. Thomas[451], Ruud F. Toonen[387], Jan R. T. van Weering[430], Matthijs Verhage[387] & Chiara Verpelli[448]

[423]Department of Fundamental Neurosciences, University of Lausanne, Lausanne, Switzerland. [424]RG Neuroplasticity, Leibniz Institute for Neurobiology, Magdeburg, Germany. [425]Molecular Physiology of the Synapse Laboratory, Biomedical Research Institute Sant Pau, Barcelona, Spain. [426]Department of Neurology, Yale School of Medicine, New Haven, CT, USA. [427]Department of Molecular Neurobiology, Max Planck Institute of Experimental Medicine, Göttingen, Germany. [428]LSI Neurobiology Programme, National University of, Singapore, Singapore. [429]Zilkha Neurogenetic Institute and Department of Psychiatry and Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. [430]Functional Genomics section, Department of Human Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam University Medical Center, Amsterdam, The Netherlands. [431]Cell Biology, Neurobiology and Biophysics, Department of Biology, Faculty of Science, Utrecht University, Utrecht, The Netherlands. [432]Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, Inserm, CNRS, APHP, Hôpital de la Pitié Salpêtrière, Paris, France. [433]Institute for Pharmacology and Toxicology, Medical Faculty Otto-von-Guericke University Magdeburg, Magdeburg, Germany. [434]Leibniz Institute for Neurobiology (LIN), Magdeburg, Germany. [435]McGovern Institute for Brain Research, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology (MIT), Cambridge, MA, USA. [436]Solomon H. Snyder Department of Neuroscience, Kavli Neuroscience Discovery Institute, The Johns Hopkins University School of Medicine, Baltimore, MD, USA. [437]Department of Neuroscience, Genentech, South San Francisco, CA, USA. [438]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA. [439]Department of Neuroscience, University of Copenhagen, Copenhagen, Denmark. [440]Laboratory of Neurobiology, Max-Planck Institute for Biophysical Chemistry, Göttingen, Germany. [441]Center for Synaptic Brain Dysfunctions, Institute for Basic Science (IBS), Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, South Korea. [442]Department of Neurobiology, Harvard Medical School, Boston, MA, USA. [443]Department of Molecular Physiology and Cell Biology, Leibniz-Forschungsinstitut für Molekulare Pharmakologie, Berlin, Germany. [443]Nancy Pritzker Laboratory, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA. [445]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Québec, Canada. [446]Biological Sciences, University of Southampton, Southampton, UK. [447]Department of Biochemistry, Weill Cornell Medicine, New York, NY, USA. [448]CNR Neuroscience Institute, Milan, Italy. [449]Department of Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. [450]Department of Molecular and Cellular Physiology, Howard Hughes Medical Institute, Stanford University, Stanford, CA, USA. [451]Division of Bioinformatics, Department of Preventive Medicine, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA, USA.

Schizophrenia Working Group of the Psychiatric Genomics Consortium

Vassily Trubetskoy[1,452], Antonio F. Pardiñas[2,452], Georgia Panagiotaropoulou[1], Swapnil Awasthi[1], Tim B. Bigdeli[5,6,7], Charlotte A. Dennison[2], Lynsey S. Hall[2], Max Lam[12,13,14], Oleksandr Frei[16,17,18], Alexander L. Richards[2], Jakob Grove[22,23,24], Zhiqiang Li[26,27], Mark Adams[30], Ingrid Agartz[16,31,32], Elizabeth G. Atkinson[10,12], Esben Agerbo[22,33], Mariam Al Eissa[34], Margot Albus[35], Madeline Alexander[36], Behrooz Z. Alizadeh[37,38], Köksal Alptekin[39,40], Thomas D. Als[22,23,24], Farooq Amin[41], Volker Arolt[42], Manuel Arrojo[43], Lavinia Athanasiu[16,17], Maria Helena Azevedo[44], Silviu A. Bacanu[45], Nicholas J. Bass[34], Martin Begemann[46], Richard A. Belliveau[12], Judit Bene[47], Beben Benyamin[48,49,50], Sarah E. Bergen[8], Giuseppe Blasi[51], Julio Bobes[52,53,54], Stefano Bonassi[55], Alice Braun[1], Rodrigo Affonseca Bressan[56,57], Evelyn J. Bromet[58], Richard Bruggeman[37,59], Peter F. Buckley[60], Randy L. Buckner[61], Jonas Bybjerg-Grauholm[22,62], Wiepke Cahn[63,64], Murray J. Cairns[65,66,67], Monica E. Calkins[68], Vaughan J. Carr[69,70,71], David Castle[72,73], Stanley V. Catts[74,75], Kimberley D. Chambert[12], Raymond C. K. Chan[76,77], Boris Chaumette[78,79], Wei Cheng[80], Eric F. C. Cheung[81], Siow Ann Chong[13,82], David Cohen[83,84,85], Angèle Consoli[83,84], Quirino Cordeiro[86], Javier Costas[87], Charles Curtis[88,89], Michael Davidson[90], Kenneth L. Davis[91], Lieuwe de Haan[92,93], Franziska Degenhardt[94], Lynn E. DeLisi[19,95], Ditte Demontis[22,23,24], Faith Dickerson[96], Dimitris Dikeos[97], Timothy Dinan[98,99], Srdjan Djurovic[100,101], Jubao Duan[102,103], Giuseppe Ducci[104], Johan G. Eriksson[106,107,108], Lourdes Fañanás[109,110], Stephen V. Faraone[111], Alessia Fiorentino[34], Andreas Forstner[94,112], Josef Frank[113], Nelson B. Freimer[114,115], Menachem Fromer[116], Alessandra Frustaci[117], Ary Gadelha[56,57], Giulio Genovese[12], Elliot S. Gershon[118], Marianna Giannitelli[83,84], Ina Giegling[119], Paola Giusti-Rodríguez[120], Stephanie Godard[121], Jacqueline I. Goldstein[10], Javier González Peñas[110,122], Ana González-Pinto[110,123], Srihari Gopal[124], Jacob Gratten[3,125], Michael F. Green[126,127], Tiffany A. Greenwood[128], Olivier Guillin[129,130,131], Sinan Gülöksüz[132,133], Raquel E. Gur[68], Ruben C. Gur[68], Blanca Gutiérrez[134], Eric Hahn[135], Hakon Hakonarson[136], Vahram Haroutunian[91,137,138], Annette M. Hartmann[119], Carol Harvey[72,139], Caroline Hayward[140], Frans A. Henskens[141], Stefan Herms[142], Per Hoffmann[142], Daniel P. Howrigan[10,143], Masashi Ikeda[144], Conrad Iyegbe[145], Inge Joa[146], Antonio Julià[147], Anna K. Kähler[8], Tony Kam-Thong[148], Yoichiro Kamatani[149,150], Sena Karachanak-Yankova[151,152], Oussama Kebir[78], Matthew C. Keller[153], Brian J. Kelly[141], Andrey Khrunin[154], Sung-Wan Kim[155], Janis Klovins[156], Nikolay Kondratiev[157], Bettina Konte[119], Julia Kraft[1,158], Michiaki Kubo[159], Vaidutis Kučinskas[160], Zita Ausrele Kučinskiene[160], Agung Kusumawardhani[161], Hana Kuzelova-Ptackova[162], Stefano Landi[163], Laura C. Lazzeroni[164,165], Phil H. Lee[12,166], Sophie E. Legge[2], Douglas S. Lehrer[167], Rebecca Lencer[42], Bernard Lerer[168], Miaoxin Li[169], Jeffrey Lieberman[170], Gregory A. Light[128,171], Svetlana Limborska[154], Chih-Min Liu[172,173], Jouko Lönnqvist[174,175], Carmel M. Loughland[176], Jan Lubinski[177], Jurjen J. Luykx[132,178,179,180], Amy Lynham[2], Milan Macek Jr[181], Andrew Mackinnon[182,183], Patrik K. E. Magnusson[8], Brion S. Maher[184], Wolfgang Maier[185], Dolores Malaspina[91,186], Jacques Mallet[187], Stephen R. Marder[188], Sara Marsal[147], Alicia R. Martin[10,12,189], Lourdes Martorell[190], Manuel Mattheisen[23,191,192,193], Robert W. McCarley[194,454], Colm McDonald[195], John J. McGrath[33,196,197], Helena Medeiros[198,199],

Sandra Meier[191,200], Bela Melegh[201], Ingrid Melle[16,17], Raquelle I. Mesholam-Gately[19,202], Andres Metspalu[203], Patricia T. Michie[204], Lili Milani[203], Vihra Milanova[205], Marina Mitjans[46], Espen Molden[206,207], Esther Molina[208], María Dolores Molto[110,209,210], Valeria Mondelli[89,211], Carmen Moreno[110,122], Christopher P. Morley[212], Gerard Muntané[190,213], Kieran C. Murphy[214], Inez Myin-Germeys[215], Igor Nenadić[216,217], Gerald Nestadt[218], Liene Nikitina-Zake[156], Cristiano Noto[56,57], Keith H. Nuechterlein[126], Niamh Louise O'Brien[34], F. Anthony O'Neill[219], Sang-Yun Oh[220,221], Ann Olincy[222], Vanessa Kiyomi Ota[57,223], Christos Pantelis[139,224,225,226], George N. Papadimitriou[97], Mara Parellada[110,122], Tiina Paunio[227,228], Renata Pellegrino[136], Sathish Periyasamy[196,229], Diana O. Perkins[230], Bruno Pfuhlmann[231], Olli Pietiläinen[12,232,233], Jonathan Pimm[34], David Porteous[234], John Powell[235], Diego Quattrone[88,89,236], Digby Quested[237,238], Allen D. Radant[239,240], Antonio Rampino[51], Mark H. Rapaport[241], Anna Rautanen[148], Abraham Reichenberg[91], Cheryl Roe[242], Joshua L. Roffman[243], Julian Roth[244], Matthias Rothermundt[42], Bart P. F. Rutten[132], Safaa Saker-Delye[245], Veikko Salomaa[246], Julio Sanjuan[110,210,247], Marcos Leite Santoro[57,223], Adam Savitz[124], Ulrich Schall[66,248], Rodney J. Scott[65,66,249], Larry J. Seidman[19,202], Sally Isabel Sharp[34], Jianxin Shi[250], Larry J. Siever[91,251], Kang Sim[254,255,256], Nora Skarabis[1], Petr Slominsky[154], Hon-Cheong So[257,258], Janet L. Sobell[198], Erik Söderman[32], Helen J. Stain[259,260], Nils Eiel Steen[17,261], Agnes A. Steixner-Kumar[46], Elisabeth Stögmann[262], William S. Stone[263,264], Richard E. Straub[265], Fabian Streit[113], Eric Strengman[266], T. Scott Stroup[170], Mythily Subramaniam[13,82], Catherine A. Sugar[126,267], Jaana Suvisaari[245], Dragan M. Svrakic[268], Neal R. Swerdlow[128], Jin P. Szatkiewicz[120], Thi Minh Tam Ta[269,270], Atsushi Takahashi[271], Chikashi Terao[271], Florence Thibaut[272,273], Draga Toncheva[151,274], Paul A. Tooney[65,66,67], Silvia Torretta[51], Sarah Tosato[275], Gian Battista Tura[276], Bruce I. Turetsky[68], Alp Üçok[277], Arne Vaaler[278,279], Therese van Amelsvoort[89,132], Ruud van Winkel[132,280], Juha Veijola[281,282], John Waddington[283], Henrik Walter[1], Anna Waterreus[284,285], Bradley T. Webb[45], Mark Weiser[286], Nigel M. Williams[2], Stephanie H. Witt[113], Brandon K. Wormley[45], Jing Qin Wu[287], Zhida Xu[288], Robert Yolken[289], Clement C. Zai[290,291], Wei Zhou[27], Feng Zhu[292,293], Fritz Zimprich[262], Eşref Cem Atbaşoğlu[186,294], Muhammad Ayub[295], Alessandro Bertolino[51], Donald W. Black[296], Nicholas J. Bray[2], Gerome Breen[88], Nancy G. Buccola[297], William F. Byerley[298], Wei J. Chen[299,300], C. Robert Cloninger[268], Benedicto Crespo-Facorro[301,302], Gary Donohoe[195], Robert Freedman[222], Cherrie Galletly[303,304,305], Massimo Gennarelli[306,307], David M. Hougaard[22,62], Hai-Gwo Hwu[173,308], Assen V. Jablensky[285], Steven A. McCarroll[12], Jennifer L. Moran[12,243], Ole Mors[22,309], Preben B. Mortensen[22,33], Bertram Müller-Myhsok[310,311,312], Amanda L. Neil[313], Merete Nordentoft[22,314], Michele T. Pato[315,316], Tracey L. Petryshen[166], Ann E. Pulver[218], Thomas G. Schulze[193,319,320,321], Jeremy M. Silverman[91,252], Jordan W. Smoller[12,166], Eli A. Stahl[116,322,323], Debby W. Tsuang[239,240], Elisabet Vilella[190], Shi-Heng Wang[324], Shuhua Xu[325,326,327], Rolf Adolfsson[328], Celso Arango[110,122], Bernhard T. Baune[42,225,226], Sintia Iole Belangero[57,223], Anders D. Børglum[22,23,24], David Braff[128,171], Elvira Bramon[329], Joseph D. Buxbaum[91], Dominique Campion[129,130], Jorge A. Cervilla[330], Sven Cichon[331,332,333], David A. Collier[334], Aiden Corvin[335], David Curtis[336,337], Marta Di Forti[88,89,236], Enrico Domenici[338], Hannelore Ehrenreich[46], Valentina Escott-Price[2,339], Tõnu Esko[203,322], Ayman H. Fanous[7,340,341], Anna Gareeva[342,343], Micha Gawlik[244], Pablo V. Gejman[102,103], Michael Gill[335], Stephen J. Glatt[344], Vera Golimbet[157], Kyung Sue Hong[345], Christina M. Hultman[8], Steven E. Hyman[12,232], Nakao Iwata[144], Erik G. Jönsson[32,261], René S. Kahn[63,91], James L. Kennedy[290,291], Elza Khusnutdinova[342,343], George Kirov[2], James A. Knowles[346,347], Marie-Odile Krebs[78], Claudine Laurent-Levinson[83,84], Jimmy Lee[352,353], Todd Lencz[14,350,351], Douglas F. Levinson[164], Qingqin S. Li[124], Jianjun Liu[352,353], Anil K. Malhotra[14,350,351], Dheeraj Malhotra[354], Andrew McIntosh[30], Andrew McQuillin[34], Paulo R. Menezes[355], Vera A. Morgan[284,285], Derek W. Morris[195], Bryan J. Mowry[196,229], Robin M. Murray[89], Vishwajit Nimgaonkar[356], Markus M. Nöthen[94], Roel A. Ophoff[114,357,358], Sara A. Paciga[359], Aarno Palotie[233,360,361], Carlos N. Pato[315,316], Shengying Qin[27,362], Marcella Rietschel[113], Brien P. Riley[45], Margarita Rivera[363,364], Dan Rujescu[119], Meram C. Saka[294], Alan R. Sanders[102,103], Sibylle G. Schwab[365,366], Alessandro Serretti[367], Pak C. Sham[368,369,370], Yongyong Shi[26,27], David St Clair[371], Ming T. Tsuang[372,373], Jim van Os[145,374], Marquis P. Vawter[375], Daniel R. Weinberger[265], Thomas Werge[376,377,378,379], Dieter B. Wildenauer[380], Xin Yu[381,382], Weihua Yue[381,382,383], Peter A. Holmans[2], Panos Roussos[28,384], Evangelos Vassos[88,89,385], Danielle Posthuma[387], Ole A. Andreassen[16,17], Kenneth S. Kendler[45], Michael J. Owen[2], Naomi R. Wray[3,196], Mark J. Daly[10,143,233], Hailiang Huang[10,12,189], Benjamin M. Neale[10,12], Patrick F. Sullivan[8,120,230], Stephan Ripke[1,10,361,453], James T. R. Walters[2,453] & Michael C. O'Donovan[2,453]

Methods

Ethics

The study protocols were approved by the institutional review board at each centre involved with recruitment. Informed consent and permission to share the data were obtained from all individuals, in compliance with the guidelines specified by the institutional review boards pf the recruiting centres. Genotyping of samples recruited in mainland China were processed and analysed by Chinese groups on Chinese local servers, to comply with the Human Genetic Resources Administrative Regulations.

Overview of samples

Details of each of the samples (including sample size, ancestry and whether included in the previous publication by the PGC) are given in the 'Case–control sample descriptions' section of the Supplementary Information. The core PGC dataset included 90 cohorts for which we had individual-level genotype data fully processed under a uniform pipeline. This core dataset contains genotypes on 161,405 unrelated individuals; 67,390 cases of schizophrenia or schizoaffective disorder and 94,015 control individuals, equivalent in power to 73,189 of each. A parent–proband trio is considered to comprise one case and one control. Approximately half (31,914 cases and 47,176 controls) of the samples were not included in the previous GWAS of the PGC[11]. Around 80% of the probands (53,386 cases and 77,258 controls) were of European (EUR) ancestry, and the remainder (14,004 cases and 16757 controls) were of East Asian (ASN) ancestry[9]. We also included in the primary GWAS summary statistics from 9 cohorts comprising African American (AA; 6,152 cases 3918 controls) and Latino (LAT; 1,234 cases, 3,090 controls) participants; the combined sample is equivalent in power to 6,551 each of cases and controls. A total of 1,249 linkage-disequilibrium-independent ($r^2 > 0.1$) variants showing evidence for association ($P < 1 \times 10^{-5}$) were further meta-analysed with an additional dataset of 1,979 cases and 142,626 controls of European ancestry obtained from deCODE genetics; thus, the final analysis represents 320,404 diploid genomes.

Association analysis

Technical quality control of the 90 cohorts that comprise the primary PGC sample. Technical quality control was performed on the core PGC cohorts separately according to standards developed by the PGC[44] including SNP missingness < 0.05 (before sample removal); subject missingness < 0.02; autosomal heterozygosity deviation ($|F_{het}| < 0.2$); SNP missingness < 0.02 (after sample removal); difference in SNP missingness between cases and controls < 0.02; and SNP Hardy–Weinberg equilibrium (HWE: $P > 10^{-6}$ in controls or $P > 10^{-10}$ in cases). For family-based cohorts we excluded individuals with more than 10,000 Mendelian errors and SNPs with more than 4 Mendelian errors. For X-chromosomal genotypes we applied an additional round of the above quality control to the male and female subgroups separately.

Genomic quality control, principal component analysis and relatedness checking in the core PGC dataset. We performed principal component analysis (PCA) for all 90 cohorts separately using SNPs with high imputation quality (INFO > 0.8), low missingness (<1%), MAF > 0.05 and in relative linkage equilibrium (LD) after 2 iterations of LD pruning ($r^2 < 0.2$, 200 SNP windows). We removed well known long-range-LD areas (MHC and chr8 inversion). Thus, we retained between 57,000 and 95,000 autosomal SNPs in each cohort. SNPs present in all 90 cohorts ($n = 7{,}561$) were used for robust relatedness testing using PLINK v.1.9[45]; pairs of subjects with PIHAT > 0.2 were identified and one member of each pair removed at random, preferentially retaining cases and trio members over case–control members.

To control for false positive associations due to inflated test statistics we evaluated the effectiveness of the primary technical and genomic quality control parameters on the genome-wide inflation of test statistics using the lambda GC (median)[46] and as necessary made the quality control parameters more stringent until this value was between 1.0 and 1.4 (before inclusion of principal components as covariates) and/or between 1.0 and 1.15 after inclusion of PCA covariates. In addition, we applied loose PCA filters for strongly stratified datasets even if we did not observe strong inflation of test statistics so as to retrieve reliable test statistics (see Supplementary Fig. 4). As the core PGC cohorts came from many distinct centres, countries and continents, various measures (for example, tightening of the technical quality control parameters and/or genomic quality control) had to be taken in an iterative process to achieve this goal.

Supplementary Table 22 lists detailed per-cohort exclusion numbers for individuals in the non-Asian samples. The Asian cohorts were sufficiently homogeneous as they did not show marked population structure in PCAs. The exclusion numbers for individuals during technical quality control are in most cohorts low. For six cohorts (marked in yellow in Supplementary Table 22) it was necessary to exclude more than 100 cases during genomic quality control so that Lambda GC fell within the window mentioned above. Supplementary Figure 4 gives details about this process and explains why the excluded cases could not be used with the presently available control cohorts for this manuscript.

Imputation of the core PGC dataset. Genotype imputation of case control cohorts was performed using the pre phasing/imputation stepwise approach implemented in EAGLE 2 (ref. [47]) or MINIMAC3 (ref. [48]) (with 132 genomic windows of variable size and default parameters). The imputation reference consisted of 54,330 phased haplotypes with 36,678,882 variants from the publicly available HRC reference, release 1.1[49] Chromosome X imputation was conducted using individuals who passed quality control for the autosomal analysis. Chromosome X imputation and association analysis was performed separately for male and female individuals. For trio-based cohorts, families with multiple (*N*) affected offspring were split into *N* parent offspring trios, duplicating the parental genotype information. Trios were phased with SHAPEIT 3 (ref. [50]). We created pseudo-controls based on the non-transmitted alleles from the parents. Phased case–pseudo-control genotypes were then taken forward to the IMPUTE4 algorithm[51] into the above HRC reference panel.

Association and meta-analysis. In each individual cohort, association testing was based on an additive logistic regression model using PLINK[52]. As covariates we used a subset of the first 20 principal components (PCA), derived within each cohort. By default, we included the first four PCAs and thereafter every PCA that was nominally significantly associated ($P < 0.05$) to case–control status. PCAs in trios were only used to remove extreme ancestry outliers. We conducted a meta-analysis of the results (including the nine cohorts comprising African American and Latino participants) using a standard error inverse-weighted fixed effects model. For chromosome X, gene dosages in male individuals were scored 0 or 2; in female individuals, 0/1/2. We summarized the associations as number of independently associated index SNPs. Index SNPs were LD-independent and had $r^2 < 0.1$ within 3-Mb windows. We recorded the left and rightmost variant with $r^2 < 0.1$ to an index SNP to define an associated clump. To define loci, we added a 50-kb window on each side of the LD clump and combined overlapping LD clumps into a single locus.

Owing to the strong signal and high linkage disequilibrium in the MHC, only one SNP was kept from the extended MHC region (chr6: 25–35 Mb).

We additionally examined the X chromosome for evidence of heterogeneity between the sexes and X chromosome dosage compensation using methods described previously[53] (Supplementary Note). To minimize possible confounding effects of ancestry on effect sizes by sex, we restricted this analysis to those of European ancestry.

We obtained summary association results from deCODE genetics for 1,228 index SNPs ($P < 1 \times 10^{-5}$) based on 1,979 cases and 142,626 control individual of European ancestry. Genotyping was carried out at deCODE Genetics. We used this sample to establish that SNP associations from the primary GWAS replicated en masse in an independent sample (see Supplementary Note) by showing that the directions of effect of index SNPs differed from the null hypothesis of randomly oriented effects and also comparing the expected number of same direction effects with those if all associations were true, taking into account the discovery magnitude of effect and the replication effect estimate precision (Supplementary Note).

The summary statistics from deCODE were combined with those from our primary GWAS dataset using an inverse variance-weighted fixed effects model. In a similar manner to the discovery meta-analysis (see above), we merged overlapping LD clumps to a total of 287 distinct genomic regions (5 on the X chromosome) with at least one genome-wide significant signal.

Polygenic prediction

We estimated the cumulative contribution of SNPs to polygenic risk of schizophrenia using a series of leave-one-out polygenic prediction analyses based on LD clumping and *P*-value thresholding ($P + T$)[5] (also known as $C + T$) using PLINK[52]. For calculating polygenic scores, we included the most significant SNP for any pair of SNPs within <500 kb and with LD $r^2 > 0.1$. We included only those with MAF > 1%. We considered a range of *P*-value thresholds; 5×10^{-8}, 1×10^{-6}, 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 5×10^{-2}, 1×10^{-1}, 2×10^{-1}, 5×10^{-1} and 1.0. We performed logistic regression analysis within each case–control sample, to assess the relationship between case status and PRS ($P + T$) quantiles. The same principal components used for each GWAS were used as covariates for this analysis. Whenever the number of controls at a quantile was less than five times the number of covariates[54], or if the higher bound for the PRS odds ratio (OR) became infinity, Firth's penalized likelihood method was used to compute regression statistics, as implemented in the R package 'logistf'[55]. ORs from these calculations were then meta-analysed using a fixed-effects model in the R package 'metafor'[56]. To ensure stability of the estimates, meta-analysis was conservatively restricted to case–control samples that contained more than 10 individuals in the top 1% PRS, with at least one of them being a control. Analogous analyses were conducted to assess the ORs between individuals at the top and bottom quantiles. To assess the performance of PRS as a predictor of schizophrenia case status, we calculated liability R^2, Nagelkerke's R^2 following a previous report[57] and a combined AUROC. Both liability R^2 and Nagelkerke's R^2 included any principal components marginally associated with the outcome within each cohort, in the baseline model. AUROC was estimated using the non-parametric meta-analysis implemented in the R package 'nsROC'[58]. Polygenic score analysis of the African American and Latino cohorts were conducted by the authors of the study reporting those datasets[10].

Secondary analyses in the core PGC dataset

Some of the secondary analyses (gene set enrichments, conditional SNP association analyses, fine-mapping) necessitate access to individual-level data and require identical quality control and imputation procedures and/or an accurate linkage disequilibrium reference panel, meaning that these analyses could only be reliably performed in a subset of the dataset. The following analyses focused on the core PGC dataset, for which these conditions are met.

Gene set enrichment

Tissue and cell types. We collected bulk RNA-seq data across 53 human tissues (GTEx v.8, median across samples)[14]; from a study of 19,550 nuclei from frozen adult human post-mortem hippocampus and prefrontal cortex representing 16 different cell types[17]; from a study of around 10,000 single cells from 5 mouse brain regions (cortex, hippocampus, hypothalamus, midbrain and striatum, in addition to specific enrichments for oligodendrocytes, dopaminergic neurons, serotonergic neurons and cortical parvalbuminergic interneurons) that identified 24 cell types[16]; and from a study of around 500,000 single cells from the mouse nervous system (19 regions) that identified 265 cell types[18].

Datasets were processed uniformly[59]. First, we calculated the mean expression for each gene for each type of data if these statistics were not provided by the authors. We used the pre-computed median expression (transcripts per million (TPM)) across individuals for the GTEx tissues (v.8). For the GTEx dataset, we excluded tissues with fewer than 100 samples, merged tissues by organ (with the exception of brain tissues) and excluded non-natural tissues (for example, Epstein–Barr virus (EBV)-transformed lymphocytes) and testis (outlier in hierarchical clustering), resulting in 37 tissues. Genes without unique names and genes not expressed in any cell types were excluded. We scaled the expression data to 1 million unique molecular identifiers (UMIs) or TPM for each cell type (or tissue). After scaling, we excluded non-protein-coding genes, and, for mouse datasets, genes that had no expert curated 1:1 orthologues between mouse and human (Mouse Genome Informatics, The Jackson Laboratory, version 22 November 2016). We then calculated a metric of gene expression specificity by dividing the expression of each gene in each cell type (or tissue) by the total expression of that gene in all cell types (or tissues), leading to values ranging from 0 to 1 for each gene (0 meaning that the gene is not expressed in that cell type (or tissue); 1 meaning that 100% of the expression of that gene is performed in that cell type (or tissue)). We selected the 10% most-specific genes per cell type (or tissue) with an expression level of at least 1 TPM, or 1 UMI per million, for downstream analyses and used MAGMA v.1.08[60] to test whether they were enriched for genetic associations. We performed a one-sided test as we were only interested in enrichments for genetic associations (in contrast with depletions). We also applied partitioned linkage disequilibrium score regression (LDSC) as described[61] to the top 10% genes for each cell type for heritability enrichment. We selected the one-sided coefficient *z*-score *P* value as a measure of the association of the cell type/tissue with schizophrenia.

Ontology gene sets. Gene set analyses were performed using MAGMA v.1.08[60]. Gene boundaries were retrieved from Ensembl release 92 (GRCh37) using the 'biomaRt' R package[62] and expanded by 35 kb upstream and 10 kb downstream to include probable regulatory regions[63]. Gene-wide *P* values were calculated from European and Asian summary statistics separately using the SNP-wise 'mean' Imhof method, and meta-analysed within the software. Linkage disequilibrium reference data files were from the European and East Asian populations of the HRC[64]. Within each gene set analysis, *P* values were corrected for multiple testing using the Bonferroni procedure Specifically, we tested the following gene sets. (i) Gene Ontology: 7,315 sets extracted from the GO database (http://geneontology.org/, accession date: 09 November 2020) curated to include only annotations with experimental or phylogenetic supporting evidence. (ii) SynGO ontology: described elsewhere[19], this collection was analysed as two subsets; 'biological process' (135 gene sets) and 'cellular component' (60 gene sets). We controlled for a set of 10,360 genes with detectable expression in brain tissue measured as fragments per kilobase of transcript per million mapped reads (FPKM)[65] to detect synaptic signals above signals simply reflecting the property of brain expression. Exploiting the hierarchical structure of SynGO, gene sets were reconstructed using a 'roll-up' method, in which parent categories contained all genes annotated to child categories. For stepwise conditional testing[23], we prioritized the most-specific child annotations[66] (that is, the lowest possible level) as regression covariates.

Conditional SNP association analyses

We performed stepwise conditional analyses of 248 loci that were genome-wide significant in the core PGC dataset looking for

independent associations. We performed association testing and meta-analysis across each locus, adding the allele dosages of the index SNP as a covariate. Where a second SNP had a conditional P value of less than 1×10^{-6}, we considered this as evidence for a second signal and repeated the process adding this as an additional covariate. We repeated this until no additional SNPs in the region achieved $P < 1 \times 10^{-6}$. We also searched for long range dependencies. Here we tested all the pairs of independent signals for conditional independence (Supplementary Note).

Fine-mapping

We used FINEMAP[20] to fine-map regions defined by LD clumps ($r^2 > 0.1$), excluding the MHC locus owing to its complex LD structure. Clumps that overlapped (without adding the additional 50 kb used to define physically distinct loci) were combined. As fine-mapping requires data from all markers in the region[67] we only performed fine-mapping on regions that attained genome-wide significance in the core PGC GWAS. In total, we attempted to fine-map 255 non-overlapping regions (Supplementary Table 11e). Further details about the fine-mapping process are provided in the Supplementary Note.

SMR analysis, FUSION and EpiXcan

We used SMR[24] as our primary method to identify SNPs that might mediate association with schizophrenia through effects on gene expression. The significance for SMR is set at the Bonferroni-corrected threshold of $0.05/M$, in which M is the number of genes with significant eQTLs tested for a given tissue. Significant SMR associations imply co-localization of the schizophrenia associations with eQTL. We applied the HEIDI test[24] to filter out SMR associations ($P_{HEIDI} < 0.01$) due to linkage disequilibrium between schizophrenia-associated variants and eQTLs. *cis*-eQTL summary data were from three studies: fetal brain ($n = 120$)[26], adult brain (n = around 1,500)[25] and blood (n = around 32,000)[68]. Linkage disequilibrium data required for the HEIDI test[24] were estimated from the Health and Retirement Study (HRS)[69] (n = 8,557). We included only genes with at least one *cis*-eQTL at $P_{eQTL} < 5 \times 10^{-8}$, excluding those in MHC regions because of the complexity of this region. For blood, we included only genes with eQTLs in brain. This left 7,803 genes in blood, 10,890 genes in prefrontal cortex and 754 genes in fetal brain for analysis (see Supplementary Note for further details). SMR was performed using data from the primary GWAS. The results were then filtered to exclude significant SMR implicated genes in which the eQTLs did not map within our definition of an associated locus in the extended GWAS meta-analysis of our primary GWAS dataset and the dataset provided by deCODE genetics.

For genomic regions in which there were multiple genes that showed significant SMR associations, we attempted to resolve these with conditional analysis using GCTA-COJO[70,71]. We selected the top-associated *cis*-eQTL for one gene (or a set of genes sharing the same *cis*-eQTL) ran a COJO analysis in the schizophrenia GWAS data and the eQTL data for each of the other genes conditioning on the selected top *cis*-eQTL. We then reran the SMR and HEIDI analyses using these conditional GWAS and eQTL results.

We used FUSION[72] and EpiXcan[73] as tests of robustness of the SMR results. Details are supplied in the Supplementary Note as are our approaches to prioritizing SMR-associated genes.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

Summary statistics for the 'extended', 'core', ancestry-specific and sex-stratified analyses are available at https://www.med.unc.edu/pgc/download-results/scz/. Genotype data are available for a subset of cohorts, including dbGAP accession numbers and/or restrictions, as described in the 'Case–control sample descriptions' section of the Supplementary Information.

Code availability

Core analysis code for RICOPILI can be found at https://sites.google.com/a/broadinstitute.org/ricopili/. This wraps PLINK (https://www.cog-genomics.org/plink2/), EIGENSOFT (https://www.hsph.harvard.edu/alkes-price/software/), Eagle2 (https://alkesgroup.broadinstitute.org/Eagle/), Minimac3 (https://genome.sph.umich.edu/wiki/Minimac3), SHAPEIT3 (https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html), METAL (https://genome.sph.umich.edu/wiki/METAL_Documentation) and LDSR (https://github.com/bulik/ldsc). For downstream analyses, FINEMAP can be found at http://christianbenner.com/, and our utility for meta-analysing cohort-specific LD matrices can be found at https://github.com/Pintaius/LDmergeFM. MAGMA can be found at https://ctg.cncr.nl/software/magma and the GO gene sets and automated curation pipeline are provided in https://github.com/janetcharwood/pgc3-scz_wg-genesets. SMR is available at https://cnsgenomics.com/software/smr/ and SbayesS at https://cnsgenomics.com/software/gctb/.

44. Lam, M. et al. RICOPILI: Rapid Imputation for COnsortias PIpeLIne. *Bioinformatics* **36**, 930–933 (2019).
45. Purcell, S., Neale, B., Todd-Brown, K., Thomas, L. & Ferreira, M. A. PLINK: a toolset for whole-genome association and population-based linkage analysis. *Am. J. Hum. Genet.* **81**, 559–575 (2007).
46. Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997–1004 (1999).
47. Reference-based phasing using the Haplotype Reference Consortium panel. *Nat. Genet.* **48**, 1443–1448 (2016).
48. Das, S. et al. Next-generation genotype imputation service and methods. *Nat. Genet.* **48**, 1284–1287 (2016).
49. The Haplotype Reference Consortium. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
50. O'Connell, J. et al. Haplotype estimation for biobank-scale data sets. *Nat. Genet.* **48**, 817–820 (2016).
51. Bycroft, C. et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
52. Chang, C. C. et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).
53. Lee, J. J. et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* **50**, 1112–1121 (2018).
54. Vittinghoff, E. & McCulloch, C. E. Relaxing the rule of ten events per variable in logistic and cox regression. *Am. J. Epidemiol.* **165**, 710–718 (2007).
55. Heinze, G. & Ploner, M. *A SAS macro, S-PLUS library and R package to perform logistic regression without convergence problems*. Technical report 2/2004 https://cemsiis.meduniwien.ac.at/fileadmin/user_upload/_imported/fileadmin/msi_akim/CeMSIIS/KB/programme/tr2_2004.pdf (Medical University of Vienna, 2004).
56. Viechtbauer, W. Conducting meta-analyses in R with the metafor package. *J. Stat. Softw.* **36**, 1–48 (2010).
57. Lee, S. H., Goddard, M. E., Wray, N. R. & Visscher, P. M. A better coefficient of determination for genetic profile analysis. *Genet. Epidemiol.* **36**, 214–224 (2012).
58. Martínez-Camblor, P. Fully non-parametric receiver operating characteristic curve estimation for random-effects meta-analysis. *Stat. Methods Med. Res.* **26**, 5–20 (2017).
59. Bryois, J. et al. Genetic identification of cell types underlying brain complex traits yields insights into the etiology of Parkinson's disease. *Nat. Genet.* **52**, 482–493 (2020).
60. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).
61. Finucane, H. K. et al. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat. Genet.* **50**, 621–629 (2018).
62. Durinck, S., Spellman, P. T., Birney, E. & Huber, W. Mapping identifiers for the integration of genomic datasets with the R/ Bioconductor package biomaRt. *Nat. Protoc.* **4**, 1184–1191 (2009).
63. Maston, G. A., Evans, S. K. & Green, M. R. Transcriptional regulatory elements in the human genome. *Annu. Rev. Genomics Hum. Genet.* **7**, 29–59 (2006).
64. A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).
65. Genovese, G. et al. Increased burden of ultra-rare protein-altering variants among 4,877 individuals with schizophrenia. *Nat. Neurosci.* **19**, 1433–1441 (2016).
66. Merico, D., Isserlin, R., Stueker, O., Emili, A. & Bader, G. D. Enrichment map: a network-based method for gene-set enrichment visualization and interpretation. *PLoS One* **5**, e13984 (2010).
67. Benner, C. et al. Prospects of fine-mapping trait-associated genomic regions by using summary statistics from genome-wide association studies. *Am. J. Hum. Genet* **101**, 539–551 (2017).
68. Võsa, U. et al. Large-scale *cis*- and *trans*-eQTL analysis identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nat. Genet.* **53**, 1300–1310 (2021).

69. Sonnega, A. et al. Cohort profile: The Health and Retirement Study (HRS). *Int. J. Epidemiol.* **43**, 576–585 (2014).
70. Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76–82 (2011).
71. Yang, J. et al. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* **44**, 369–375 (2012).
72. Gusev, A. et al. Integrative approaches for large-scale transcriptome-wide association studies. *Nat. Genet.* **48**, 245–252 (2016).
73. Zhang, W. et al. Integrative transcriptome imputation reveals tissue-specific and shared biological mechanisms mediating susceptibility to complex traits. *Nat. Commun.* **10**, 3834 (2019).

Acknowledgements The National Institute of Mental Health (USA) provides core funding for the PGC under award no. U01MH109514. The content is the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The work of the contributing groups was supported by numerous grants from governmental and charitable bodies as well as philanthropic donation (details in Supplementary Note). We acknowledge a substantial contribution from P. Sklar (deceased) as one of the PGC principal investigators, and E. Scolnick, whose support for this study was vital. We acknowledge the Wellcome Trust Case Control Consortium for the provision of control genotype information. Membership of the Psychosis Endophenotypes International Consortium, the SynGO consortium, the PsychENCODE Consortium, the eQTLGen consortium, the BIOS Consortium and the Indonesia Consortium are provided in the author list. We are grateful to C. Hopkins for illustrations. The work at Cardiff University was additionally supported by Medical Research Council Centre grant no. MR/L010305/1 and program grant no. G0800509. S. Xu also gratefully acknowledges the support of the National Natural Science Foundation of China (NSFC) grants (31525014, 91731303, 31771388, 31961130380 and 32041008), the UK Royal Society-Newton Advanced Fellowship (NAF\R1\191094), the Key Research Program of Frontier Sciences (QYZDJ-SSW-SYS009) and the Strategic Priority Research Program (XDB38000000) of the Chinese Academy of Sciences, and the Shanghai Municipal Science and Technology Major Project (2017SHZDZX01). O. A. Andreassen was supported by the Research Council of Norway (283798, 262656, 248980, 273291, 248828, 248778, 223273); KG Jebsen Stiftelsen, South-East Norway Health Authority, EU H2020 no. 847776. B. Melegh was supported in part by the National Scientific Research Program (NKFIH) K 138669. S. V. Faraone is supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 602805, the European Union's Horizon 2020 research and innovation programme under grant agreements 667302 and 728018 and NIMH grants 5R01MH101519 and U01 MH109536-01. S. I. Belangero was supported by FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), grant numbers: 2010/08968-6; 2014/07280-1 2011/50740-5 (including R. A. Bressan). The Singapore team (J. Lee, J. Liu, K. Sim, S. A. Chong and M. Subramanian) acknowledges the National Medical Research Council Translational and Clinical Research Flagship Programme (grant no.: NMRC/TCR/003/2008). M. Macek was supported by LM2018132, CZ.02.1.01/0.0/0.0/18_046/0015515 and IP6003 –VZFNM00064203. C. Arango has been funded by the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (SAM16PE07CP1, PI16/02012, PI19/024), co-financed by ERDF Funds from the European Commission, 'A way of making Europe', CIBERSAM, Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds, European Union Seventh Framework Program and European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking (grant agreement no 115916, project PRISM; and grant agreement no. 777394, project AIMS-2-TRIALS), Fundación Familia Alonso and Fundación Alicia Koplowitz. E. Bramon acknowledges support from the National Institute of Health Research UK (grant NIHR200756); Mental Health Research UK John Grace QC Scholarship 2018; an ESRC collaborative award 2020; BMA Margaret Temple Fellowship 2016; Medical Research Council New Investigator Award (G0901310); MRC Centenary Award (G1100583); MRC project grant G1100583; National Institute of Health Research UK post-doctoral fellowship (PDA/02/06/016); NARSAD Young Investigator awards 2005 and 2008; Wellcome Trust Research Training Fellowship; Wellcome Trust Case Control Consortium awards (085475/B/08/Z, 085475/Z/08/Z); European Commission Horizon 2020 (747429); NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and King's College London; and NIHR Biomedical Research Centre at University College London Hospitals NHS Foundation Trust and University College London (UCLH BRC - Mental Health Theme). D. Molto is funded by the European Regional Development Fund (ERDF)–Valencian Community 2014–2020, Spain. E. G. Atkinson was supported by the NIMH K01MH121659.

Author contributions The management group for this paper was led by M.O.D. and J.T.R.W., with S.R. responsible for primary analytic matters supported by B.M.N. and M.J.D. The management group comprised a subset of the principal investigators of the component studies, bioinformaticians and analysts and was responsible for study design, conduct, management, primary and final interpretation; this group included O.A.A., B.T.B., S.I.B., A.D.B., D.B., E.B., S.C., A. Corvin, D. Curtis, M.J.D., M.D.F., E.D., H.E., A.H.F., P.V.G., M. Gill, S.J.G., K.S.H., H. Huang, N.I., R.S.K., K.S.K., J.A.K., J. Lee, T.L., D.F.L., J. Liu, A. McIntosh, A. McQuillin, V.A.M., D.W.M., B.J.M., B.M.N., M.O.D., R.A.O., M.J.O., A.P., D. Posthuma, S.Q., B.P.R., S.R., D.R., S.G.S., A. Serretti, Y.S., E.A.S., P.F.S., M.T.T., M.P.V., J.T.R.W., D.R.W., T.W., N.R.W., X.Y. and W.Y. GWAS meta-analyses: S.A., G.P., S.R. and V.T. Replication data: S. Magnusson, H.S. and K. Stefansson (deCODE). African American and Latino sample analyses: E.G.A., T.B., G.G., S.R. and V.T. Bioinformatics: J. Bryois, J.C.H., A.F.P., A.J.P., D. Posthuma, P.F.S., K.W. and the SynGO consortium. Comparison of male and female individuals: S.R., J. Sidorenko, V.T. and P.M.V. Heritability and polygenic prediction: O.A.A., O.F., T.G., H. Huang, B.M.N., M.O.D., A.F.P., A.L.R., S.R., V.T., J.T.R.W., N.R.W. and J.Z. Phenotype stratification: C.A.D. and E. Vassos. Cellular and tissue analysis: J. Bryois, M.O.D., D. Posthuma, P.F.S., J.T.R.W. and K.W. Gene Ontology: J.C.H., M.O.D., A.F.P., A.J.P., D. Posthuma, J.T.R.W. and K.W. Fine-mapping: C.B., M.J.D., H. Huang, M. Lam, M.O.D., G.P., A.F.P., M.P., S.R. and J.T.R.W. SMR: L.S.H., M.O.D., T.Q., N.R.W., Y.W. and J.Y. Hi-C: D. Posthuma, A.L.R., P.F.S., J.T.R.W. and K.W. Other transcriptome-wide association studies: M.J.G., L.S.H., M. Kim, P.R., G.V. and W. Zhang. Integration of fine-mapping, gene expression, Hi-C informatics and rare variants: L.S.H., M.O.D., A.F.P., T.Q., A.L.R., P.F.S., J.T.R.W., N.R.W., Y.W. and J.Y. SynGO: F.K., M.O.D., A.F.P., A.B.S., M.V. and J.T.R.W. Additional statistical advice: P.A.H. The remaining authors contributed to the recruitment, phenotyping, genotyping or data processing for the contributing components of the meta-analysis, or provided other forms of functional annotation data. Primary drafting and editing of the manuscript were coordinated by S.R., J.T.R.W. and M.O.D. The primary draft sections were written by J. Bryois, C.Y.C., C.A.D., L.S.H., H. Huang, B.M.N., M.O.D., M.J.O., A.F.P., A.J.P., S.R., A.B.S, P.F.S., V.T., E. Vassos, M.V., J.T.R.W., N.R.W. and J.Y. Additional edits were from O.A.A., M.J.D. and K.S.K. Numerous other authors provided edits, comments and suggestions, and all authors saw and approved the contents of the manuscript. The Chair of the PGC is P.F.S. and the Schizophrenia Working Group of the PGC is led by M.O.D. and J.T.R.W.

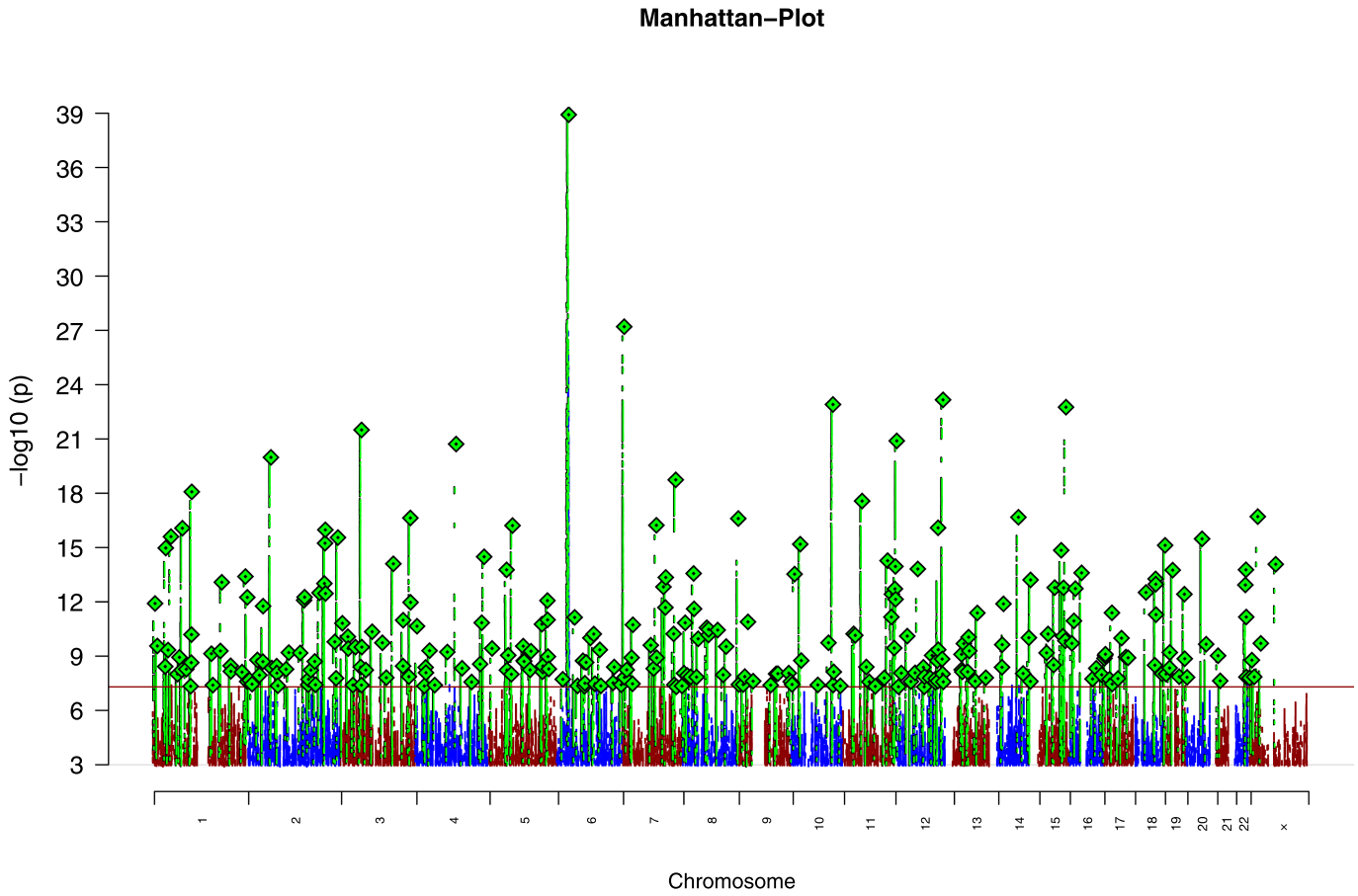
Competing interests A. Palotie is a member of Astra Zeneca's Genomics Advisory Board. V. Salomaa has consulted for Novo Nordisk and Sanofi and has ongoing research collaboration with Bayer (both unrelated to the present study). M. F. Green is a paid consultant for AiCure, Biogen, Lundbeck and Roche, is a member of the Scientific Board of Cadent, and has received research funds from Forum. G. A. Light has consulted to Astellas, Forum, and Neuroverse. K. Nuechterlein has research support from Janssen, Genentech and Brain Plasticity, and has also consulted for Astellas, MedinCell, Takeda, Teva, Genentech, Otsuka, Janssen and Brain Plasticity. D. Cohen has reported past consultation for or the receipt of honoraria from Otsuka, Shire, Lundbeck, Roche and Janssen. M. J. Daly is a founder of Maze Therapeutics and on the scientific advisory board of Neumora Therapeutics. A. K. Malhotra is a consultant to Genomind, InformedDNA and Concert Pharmaceuticals. R. A. Bressan has received research grants from Janssen, has been a forum consultant for Janssen, Sanof and Roche and is on the speakers' bureau for Ache, Janssen, Sanofi and Torrent. C. Noto was on the speakers' bureau and/or has acted as a consultant for Janssen and Daiichi-Sankyo in the last 12 months. C. Pantelis has, for the last three years, served on an advisory board for Lundbeck and received honoraria for talks presented at educational meetings organized by Lundbeck. D. A. Collier is a full-time employee and stockholder of Eli Lilly and Company. M. C. O'Donovan is supported by a collaborative research grant from Takeda Pharmaceuticals. M. J. Owen is supported by a collaborative research grant from Takeda Pharmaceuticals. J. T. R. Walters is supported by a collaborative research grant from Takeda Pharmaceuticals. A. J. Pocklington is supported by a collaborative research grant from Takeda Pharmaceuticals. S. R. Marder has consulted for the following companies: Roche, Sunovion, Lundbeck, Boeringer-Ingelheim, Acadia and Merck. S. Gopal is a full time employee and shareholder in Johnson & Johnson (AMEX: JNJ). A. Savitz is an employee of Janssen Research & Development and owns stock or stock options in the company. Q. S. Li is an employee of Janssen Research & Development and owns stock or stock options in the company. T. Kam-Thong is an employee of F. Hoffman-La Roche. A. Rautanen is an employee of F. Hoffman-La Roche. D. Malhotra is an employee of F. Hoffman-La Roche. S. A. Paciga is an employee of Pfizer. O. A. Andreassen is a consultant for HealthLytix, and received speaker's honorarium from Lundbeck. S. V. Faraone has received income, potential income, travel expenses continuing education support and/or research support from Akili Interactive Labs, Arbor, Genomind, Ironshore, Ondosis, Otsuka, Rhodes, Shire/Takeda, Sunovion, Supernus, Tris and Vallon. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of attention deficit hyperactivity disorder. In previous years, he received support from Alcobra, Avekshам, CogCubed, Eli Lilly, Enzymotec, Impact, Janssen, KemPharm, Lundbeck/Takeda, McNeil, Neurolifesciences, Neurovance, Novartis, Pfizer and Vaya. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health; Oxford University Press: Schizophrenia: The Facts; and Elsevier: ADHD: Non-Pharmacologic Interventions. He is also Program Director of https://adhdinadults.com/. C. Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. K. Alptekin has received grants and honoraria for consulting work, lecturing and research from Abdi İbrahim, Abdi İbrahim Otsuka, Janssen, Ali Raif and TUBITAK.

Additional information

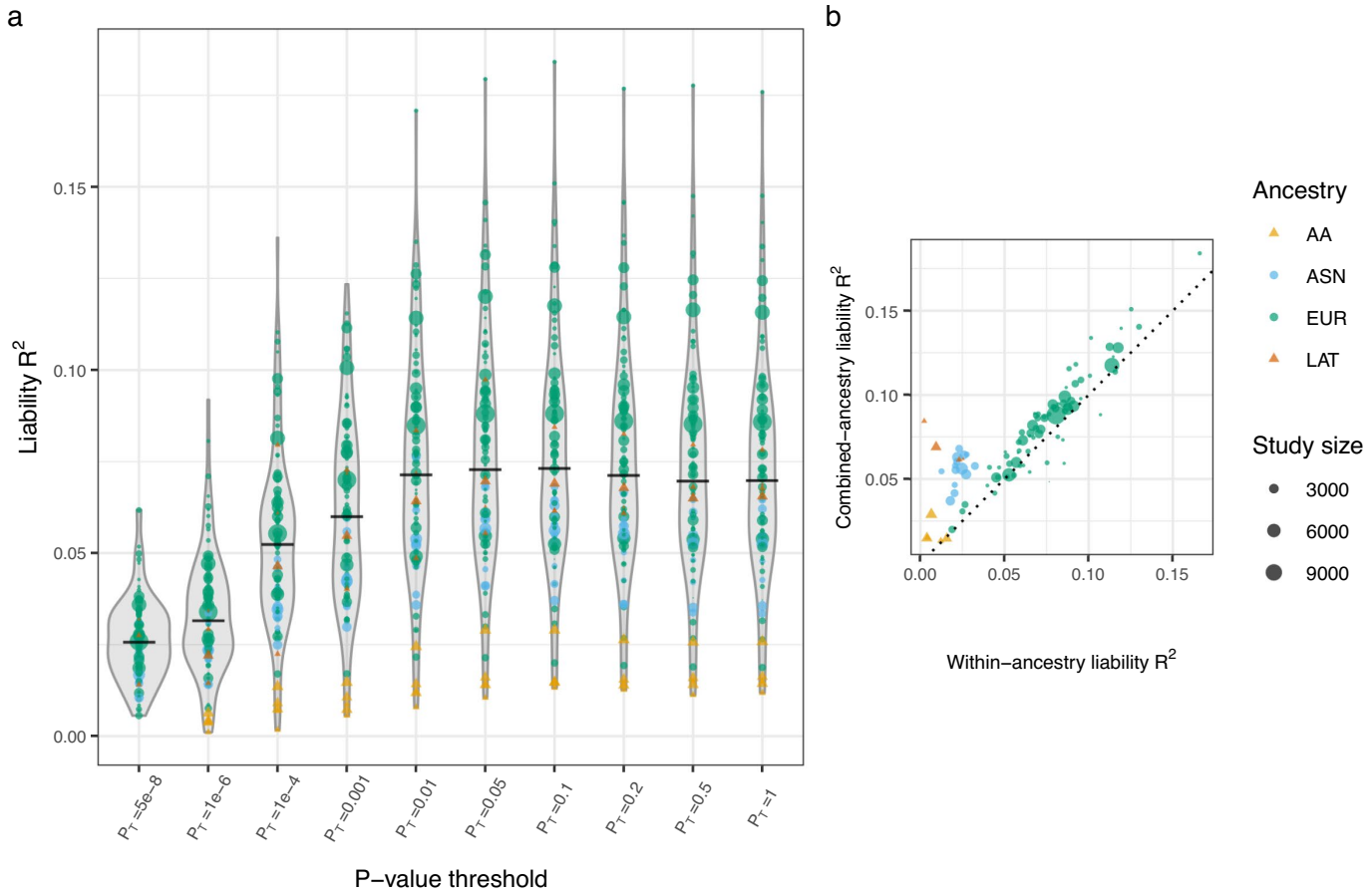
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41586-022-04434-5.

Correspondence and requests for materials should be addressed to Stephan Ripke, James T. R. Walters or Michael C. O'Donovan.

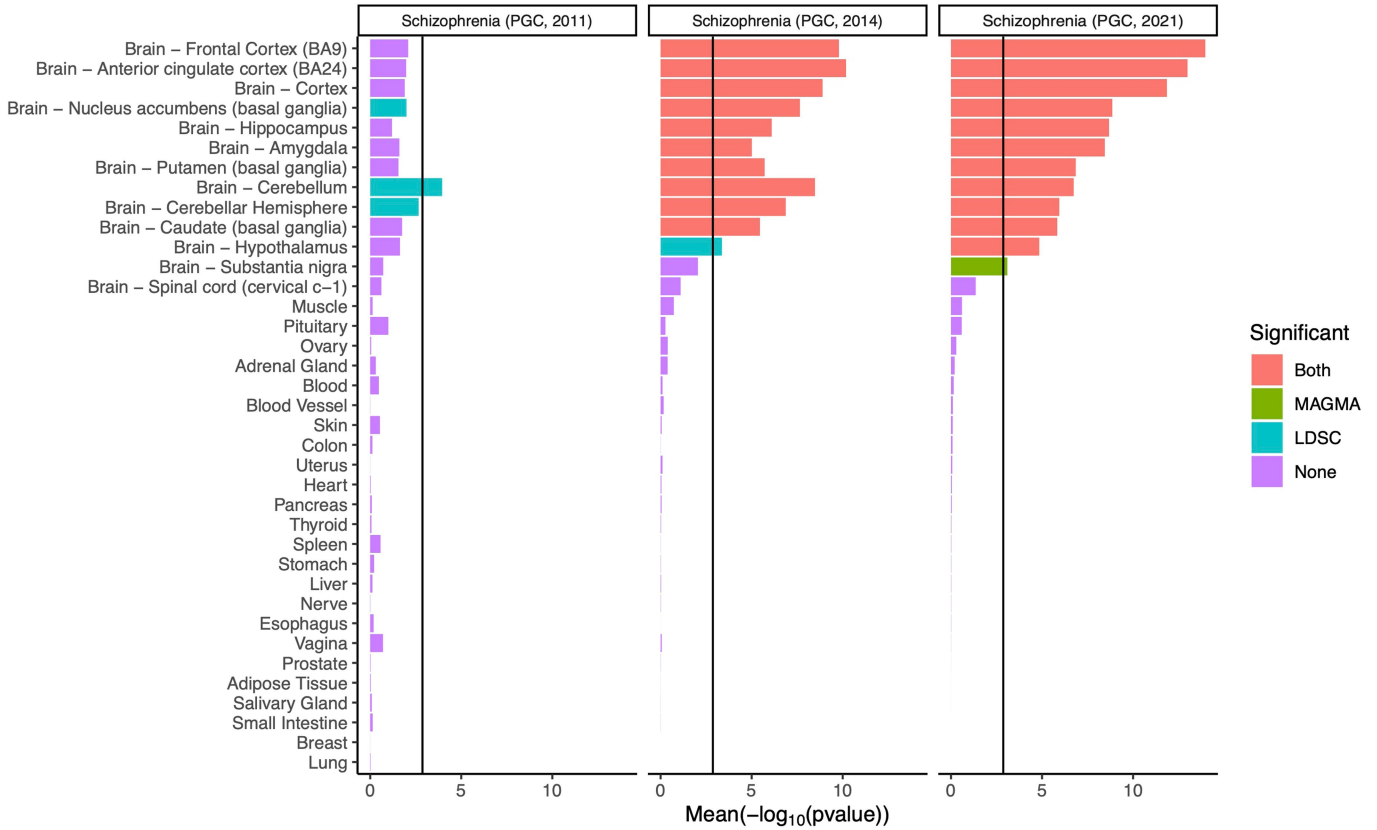
Peer review information *Nature* thanks Paul O'Reilly and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.



Extended Data Fig. 1 | Primary GWAS Manhattan plot. The *x* axis indicates chromosomal position and the *y* axis is the significance of association ($-\log_{10}(P)$). The red line represents genome-wide significance level (5×10^{-8}). SNPs in green are in linkage disequilibrium (LD; $r_2 > 0.1$) with index SNPs (diamonds) which represent LD-independent genome-wide significant associations.



Extended Data Fig. 2 | Polygenic risk prediction. a, Distributions of liability scale R^2 across 98 left-out-cohorts for polygenic risk scores built from SNPs with different p-value thresholds. Distributions of liability R^2 (assuming schizophrenia life-time risk of 1%) are shown for each p-value threshold, with point size representing size of the left-out cohort and colour representing ancestry. The median liability R^2 is represented as a horizontal black line. **b**, Liability R^2 of predicted and observed phenotypes in left-out cohorts using variants with p-value threshold p = 0.05, from the fixed effect meta-analysis of variant effects, unadjusted for multiple comparisons. The polygenic risk scores are derived from two separate sets of leave-one-out GWAS meta-analyses: *y* axis R^2 based on the results of primary GWAS including all ancestries; *x* axis R^2 based on cohorts of the same ancestry as the test samples. Circles denote core PGC samples. Triangles denote African American and Latino samples processed external to PGC by the providing author.



Extended Data Fig. 3 | Association between 37 human tissues and schizophrenia. The mean of the evidence (-$\log_{10}P$) obtained from two methods (MAGMA, LDSC) for testing GWAS data for enrichment of association in genes with high expression in each tissue as determined from bulk RNA-seq[14]. The bar colour indicates whether gene expression in the tissue is significantly associated with both methods, one method or none. The black vertical line represents the significance threshold corrected for the total number of tissues tested in this experiment. We also analysed previous waves of PGC schizophrenia GWAS[11,15] for comparison.

Extended Data Table 1 | List of prioritized genes

Index SNP	Ensembl ID	Symbol ID	gene_biotype	FINEMAP priority gene	SMR priority gene	Rare priority gene
rs12712510	ENSG00000231200	AC068490.2	lincRNA	•		
rs6504163	ENSG00000159640	ACE	protein_coding		•	
rs7575796	ENSG00000115073	ACTR1B	protein_coding	•		
rs61833239	ENSG00000117020	AKT3	protein_coding		•	
rs6546857	ENSG00000163016	ALMS1P	pseudogene		•	
rs9925915	ENSG00000174939	ASPHD1	protein_coding		•	
rs12285419	ENSG00000175224	ATG13	protein_coding		•	
rs4766428	ENSG00000174437	ATP2A2	protein_coding	•		
rs1540840	ENSG00000127152	BCL11B	protein_coding	•		•
rs2304205	ENSG00000126453	BCL2L12	protein_coding	•		
rs3808581	ENSG00000104765	BNIP3L	protein_coding	•		
rs2649999	ENSG00000157895	C12orf43	protein_coding	•		
rs10774034	ENSG00000151067	CACNA1C	protein_coding	•		•
rs2944821	ENSG00000183166	CALN1	protein_coding	•		
rs6839635	ENSG00000145354	CISD2	protein_coding		•	
rs61405217	ENSG00000109572	CLCN3	protein_coding		•	
rs17194490	ENSG00000144619	CNTN4	protein_coding	•		
rs10127983	ENSG00000143578	CREB3L4	protein_coding		•	
rs2532240	ENSG00000120088	CRHR1	protein_coding		•	
8:4180090_T_A	ENSG00000183117	CSMD1	protein_coding	•		
rs715170	ENSG00000206129	CTD-2008L17.2	lincRNA	•		
rs113113059	ENSG00000112659	CUL9	protein_coding	•	•	
rs10957321	ENSG00000172817	CYP7B1	protein_coding		•	
rs61828917	ENSG00000117593	DARS2	protein_coding		•	
rs4632195	ENSG00000187323	DCC	protein_coding	•		
rs4678552	ENSG00000163673	DCLK3	protein_coding		•	
rs7816998	ENSG00000085788	DDHD2	protein_coding		•	
rs2600490	ENSG00000198010	DLGAP2	protein_coding	•		
rs8048039	ENSG00000103423	DNAJA3	protein_coding		•	
rs72728416	ENSG00000188641	DPYD	protein_coding	•		
rs8175378	ENSG00000170571	EMB	protein_coding		•	
rs999494	ENSG00000135638	EMX1	protein_coding	•		
rs11619756	ENSG00000120658	ENOX1	protein_coding	•		
rs959071	ENSG00000262319	ENSG00000262319	antisense		•	
rs4073003	ENSG00000072134	EPN2	protein_coding	•		
rs6925079	ENSG00000188107	EYS	protein_coding	•		
rs815609	ENSG00000055147	FAM114A2	protein_coding		•	
rs4766428	ENSG00000204856	FAM216A	protein_coding		•	
rs1006945	ENSG00000101447	FAM83D	protein_coding		•	
rs58120505	ENSG00000122687	FTSJ2	protein_coding		•	
rs4702	ENSG00000140564	FURIN	protein_coding	•	•	
rs10985811	ENSG00000136928	GABBR2	protein_coding	•		
rs1858999	ENSG00000167491	GATAD2A	protein_coding		•	
rs12498839	ENSG00000150625	GPM6A	protein_coding	•		
rs12188094	ENSG00000164199	GPR98	protein_coding	•		
rs77502336	ENSG00000023171	GRAMD1B	protein_coding	•		
rs9926049	ENSG00000183454	GRIN2A	protein_coding	•		•
rs2206956	ENSG00000152822	GRM1	protein_coding	•		
rs11210892	ENSG00000178922	HYI	protein_coding		•	
rs1378559	ENSG00000169306	IL1RAPL1	protein_coding	•		
rs38752	ENSG00000184903	IMMP2L	protein_coding	•		
rs3814883	ENSG00000169592	INO80E	protein_coding		•	
rs2304205	ENSG00000126456	IRF3	protein_coding	•		
rs2532240	ENSG00000120071	KANSL1	protein_coding		•	•
rs10243922	ENSG00000122778	KIAA1549	protein_coding	•		
rs17731	ENSG00000067082	KLF6	protein_coding	•		
rs459391	ENSG00000224924	LINC00320	lincRNA	•	•	
rs9545047	ENSG00000227676	LINC01068	lincRNA		•	
rs28454198	ENSG00000249307	LINC01088	antisense	•		
rs2387414	ENSG00000131409	LRRC4B	protein_coding	•		
rs59498392	ENSG00000175324	LSM1	protein_coding		•	
rs58120505	ENSG00000002822	MAD1L1	protein_coding	•		
rs35164357	ENSG00000112893	MAN2A1	protein_coding	•		
rs9925915	ENSG00000102882	MAPK3	protein_coding		•	
rs2532240	ENSG00000186868	MAPT	protein_coding		•	
rs143116451	ENSG00000175727	MLXIP	protein_coding		•	
rs2914983	ENSG00000115540	MOB4	protein_coding		•	
rs4793888	ENSG00000153944	MSI2	protein_coding	•		
rs11263770	ENSG00000141140	MYO19	protein_coding		•	
rs324017	ENSG00000166886	NAB2	protein_coding	•		
rs9545047	ENSG00000102471	NDFIP2	protein_coding		•	
rs2119242	ENSG00000078114	NEBL	protein_coding	•		
rs1121296	ENSG00000172260	NEGR1	protein_coding	•		
rs5943629	ENSG00000146938	NLGN4X	protein_coding	•		
rs9975024	ENSG00000180530	NRIP1	protein_coding	•		
rs11972718	ENSG00000122584	NXPH1	protein_coding	•		
rs1939514	ENSG00000183715	OPCML	protein_coding	•		
rs56205728	ENSG00000137843	PAK6	protein_coding	•		
rs7432375	ENSG00000114054	PCCB	protein_coding		•	
rs10069930	ENSG00000204969	PCDHA2	protein_coding		•	
rs246024	ENSG00000204962	PCDHA8	protein_coding		•	
rs35734242	ENSG00000185619	PCGF3	protein_coding	•		
rs58950470	ENSG00000197136	PCNXL3	protein_coding	•		
rs6588168	ENSG00000184588	PDE4B	protein_coding	•		
rs2929278	ENSG00000167004	PDIA3	protein_coding		•	
rs34539323	ENSG00000181191	PJA1	protein_coding	•		
rs6873880	ENSG00000149527	PLCH2	protein_coding	•		
rs3813567	ENSG00000041357	PSMA4	protein_coding		•	
rs2890914	ENSG00000153707	PTPRD	protein_coding	•		
rs61937595	ENSG00000179912	R3HDM2	protein_coding	•		
rs11121172	ENSG00000142599	RERE	protein_coding		•	•
rs11227250	ENSG00000172922	RNASEH2C	protein_coding		•	
rs13107325	ENSG00000246560	RP11-10L12.4	antisense		•	
rs6479487	ENSG00000227603	RP11-165J3.6	antisense		•	
rs505061	ENSG00000234840	RP11-399D6.2	lincRNA	•		
rs1198588	ENSG00000259946	RP11-490G2.2	lincRNA		•	
rs35351411	ENSG00000259616	RP11-507B12.2	lincRNA	•		
rs10035564	ENSG00000272335	RP11-53O19.3	lincRNA		•	
rs1915019	ENSG00000253553	RP11-586K2.1	antisense		•	
rs10873538	ENSG00000256500	RP11-73M18.2	protein_coding		•	
rs154433	ENSG00000103037	SETD6	protein_coding		•	
rs2914983	ENSG00000115524	SF3B1	protein_coding		•	
rs12652777	ENSG00000170624	SGCD	protein_coding	•		
rs13107325	ENSG00000138821	SLC39A8	protein_coding	•		•
rs2909457	ENSG00000144290	SLC4A10	protein_coding	•		
rs6839635	ENSG00000164037	SLC9B1	protein_coding		•	
rs2022265	ENSG00000065609	SNAP91	protein_coding	•	•	
rs7811417	ENSG00000105866	SP4	protein_coding	•		•
rs3810450	ENSG00000161277	THAP8	protein_coding	•		
rs704364	ENSG00000163634	THOC7	protein_coding		•	
rs7312697	ENSG00000133687	TMTC1	protein_coding	•		
rs1924377	ENSG00000133107	TRPC4	protein_coding	•		
rs13262595	ENSG00000171045	TSNARE1	protein_coding	•		
rs10861176	ENSG00000198431	TXNRD1	protein_coding	•		
rs10238960	ENSG00000185274	WBSCR17	protein_coding	•		
rs2929278	ENSG00000092470	WDR76	protein_coding		•	
rs3764002	ENSG00000075035	WSCD2	protein_coding	•		
rs11693094	ENSG00000170396	ZNF804A	protein_coding	•		
rs72986630	ENSG00000197933	ZNF823	protein_coding	•	•	
rs758749	ENSG00000127903	ZNF835	protein_coding	•		

List of genes meeting prioritization criteria summarized in Fig. 1. Index SNP: index-associated SNP for the locus from the GWAS. Ensembl ID: Ensembl gene identifier. Symbol ID: HGNC gene symbol. Gene Biotype: as classified by Ensembl. FINEMAP and SMR priority genes: genes meeting the prioritization criteria described in the text. Rare priority genes: genes implicated by rare coding variants in schizophrenia, ASD or developmental disorder. Full details regarding the prioritization criteria for each gene are provided in Supplementary Tables 11–18.

nature research

Corresponding author(s): Schizophrenia Working Group Psychiatric Genomics Consortium

Last updated by author(s): October 21, 2021

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used to collect the data in this study.
Data analysis	Genotype QC, imputation, association analysis, meta-analysis and risk scoring framework: RICOPILI (https://github.com/Ripkelab/ricopili/wiki) RICOPILI: QC, frequency estimation, association analysis and risk scoring: PLINK1.9 (https://www.cog-genomics.org/plink2/) Principal Components Analysis: Eigenstrat (https://github.com/DReichLab/EIG/tree/master/EIGENSTRAT) Genotype phasing: EAGLE (https://github.com/poruloh/Eagle), SHAPEIT https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html Genotype imputation: IMPUTE (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html) QC and heritability: LDSC (https://github.com/bulik/ldsc) Meta-analysis: METAL (https://github.com/statgen/METAL) Downstream analysis: Set-based association analysis: MAGMA (https://ctg.cncr.nl/software/magma) Fine mapping: FINEMAP(http://christianbenner.com/#sss) Gene ontology annotation: BioMart R package (https://bioconductor.org/packages/release/bioc/html/biomaRt.html) Mendelian randomization and pleiotropy: SMR + HEIDI (https://cnsgenomics.com/software/smr/) Conditional analysis: GCTA-COJO (https://cnsgenomics.com/software/gcta/index.html#Overview) Transcriptome imputation: FUSION (http://gusevlab.org/projects/fusion/) Transcriptome imputation and epigenetics: EpiXcan (https://zhangw17.u.hpc.mssm.edu/epixcan/about.php)

Heritability and polygenicity estimation: GCTB-SBayesS (https://cnsgenomics.com/software/gctb/#Overview)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Genome-wide summary statistics from the discovery meta-analysis, and ancestry specific meta-analyses will be made available upon publication at the following site: https://www.med.unc.edu/pgc/results-and-downloads/.
See "Supplementary Cohort Descriptions" for information for participating cohorts.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The discovery sample consisted of 74,776 samples with Schizophrenia and 101,023 controls, aggregated from 99 distinct cohorts. While this sample size is hypothesized to be insufficient to explain the full extent of genetic liability to Schizophrenia, it is the largest study of its kind to date.
Data exclusions	We excluded individual samples and genetic markers using the standard RICOPILI pipeline (Lam. et. al. 2019).This consisted of, 1) Excluding variants with call rate below 95%; 2) Excluding subjects with call rate below 98%; 3) Excluding monomorphic variants; 4) Excluding subjects with inbred coefficient above 0.2 and below -0.2; 5) Excluding subjects with mismatch in reported gender and chromosome X computed gender; 6) Excluding variants with missing rate differences greater than 2% between cases and controls; 7) Subsequent to step 6, exclude variants with call rate below 98%; and 8) Exclude variants in violation of Hardy-Weinberg equilibrium ($P < 10\text{-}6$ for controls or $P < 10\text{-}10$ for cases). Using imputed data to estimate identity-by-descent, we were able to identify duplicate samples within and between cohorts. Samples with pi-hat > 0.2 were extracted, followed by Fisher-Yates shuffle on all samples. When deciding which samples to retain, trio were preferred, followed by cases, and thereafter a random sample for each related pair was removed. To identify population outliers, we computed Principal Components within each cohort and inspected PCA plots for the top four PCs manually, identifying outliers and removing them These exclusions follow standard guidelines for genome-wide association studies.
Replication	We replicated results from the discovery meta-analysis of 89 cohorts using summary statistics provided by deCODE Genetics (1,979 cases and 142,627 controls of European ancestry).
Randomization	This is an observational, genetic-epidemiological study, and as such no randomization was performed. Based on the principles of mendelian inheritance, it is hypothesized that such study designs are protected against typical forms of confounding. See section "Mendelian Randomization" in the methods texts. One known confounder in genome-wide association studies is population structure, which we adjust for by computing Principal Components (PCs) within each cohort, and adding the top four PCs — plus any in the top twenty that are marginally associated with disease-status — as covariates in the marker-level logistic regression. This is a standard form of adjustment for GWAS study designs.
Blinding	No disease-status-blinding was used in recruitment or analysis. In principle, samples were recruited blind with respect to their genotype, and we do not expect to observe bias in the association between genotype and disease-status.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	This study aggregates data from 100 different cohorts, for a total of 75,703 cases and 242,251 controls and a replication sample. Of these, 76 in the discovery sample were drawn from populations of European descent (53,386 cases, 77,258 controls), and 14 in populations of East Asian descent (14,004 cases, 16,757 controls). Additionally, of the 100 cohorts, 4 European cohorts (1,369 trios) and 2 East Asian cohorts consisted of parent-proband trios (1,009 trios).
Recruitment	See "Supplementary Cohort Descriptions" for descriptions of recruitment strategies for participating cohorts. Additionally, see "Supplementary Note" section "Potential Heterogeneity due to Ascertainment" for evidence that differing ascertainment did not lead to heterogeneity in results.
Ethics oversight	The study protocols were approved by the institutional review board at each center involved with recruitment. Informed consent and permission to share the data were obtained from all subjects, in compliance with the guidelines specified by the recruiting center's institutional review board. Genotyping of samples recruited in mainland China were processed and analysed by Chinese groups on Chinese local servers, to comply with the Human Genetic Resources Administrative Regulations. Only summary statistics, with no individual-level data, were included in the final study from samples recruited from mainland China. See "Supplementary Cohort Descriptions" for descriptions of ethics approval protocols for participating cohorts.

Note that full information on the approval of the study protocol must also be provided in the manuscript.