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Article

Mapping genomic loci implicates genes and synaptic biology in schizophrenia

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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)

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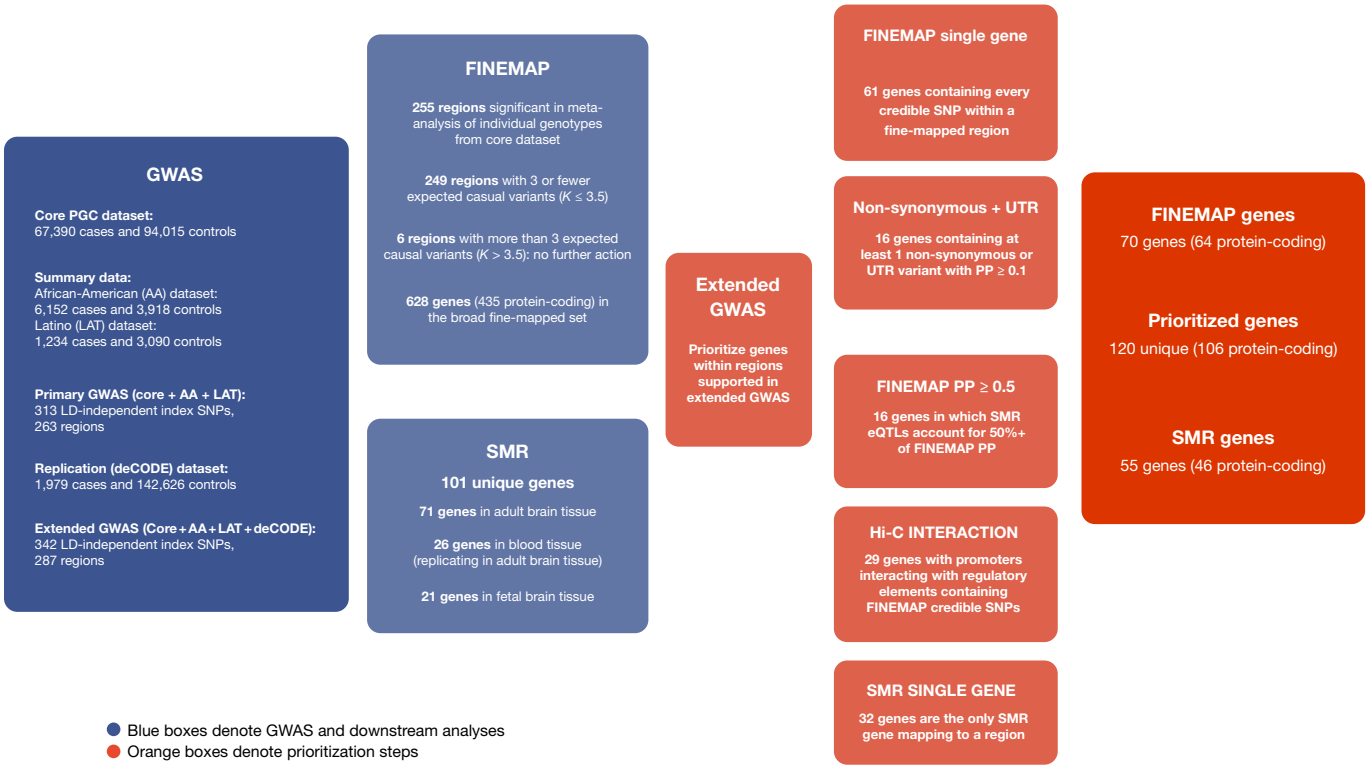


Fig. 1 | Overview of GWAS and gene prioritization. Flow diagram summarizing GWAS, fine-mapping (FINEMAP) and SMR analyses and how these informed gene prioritization.

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.

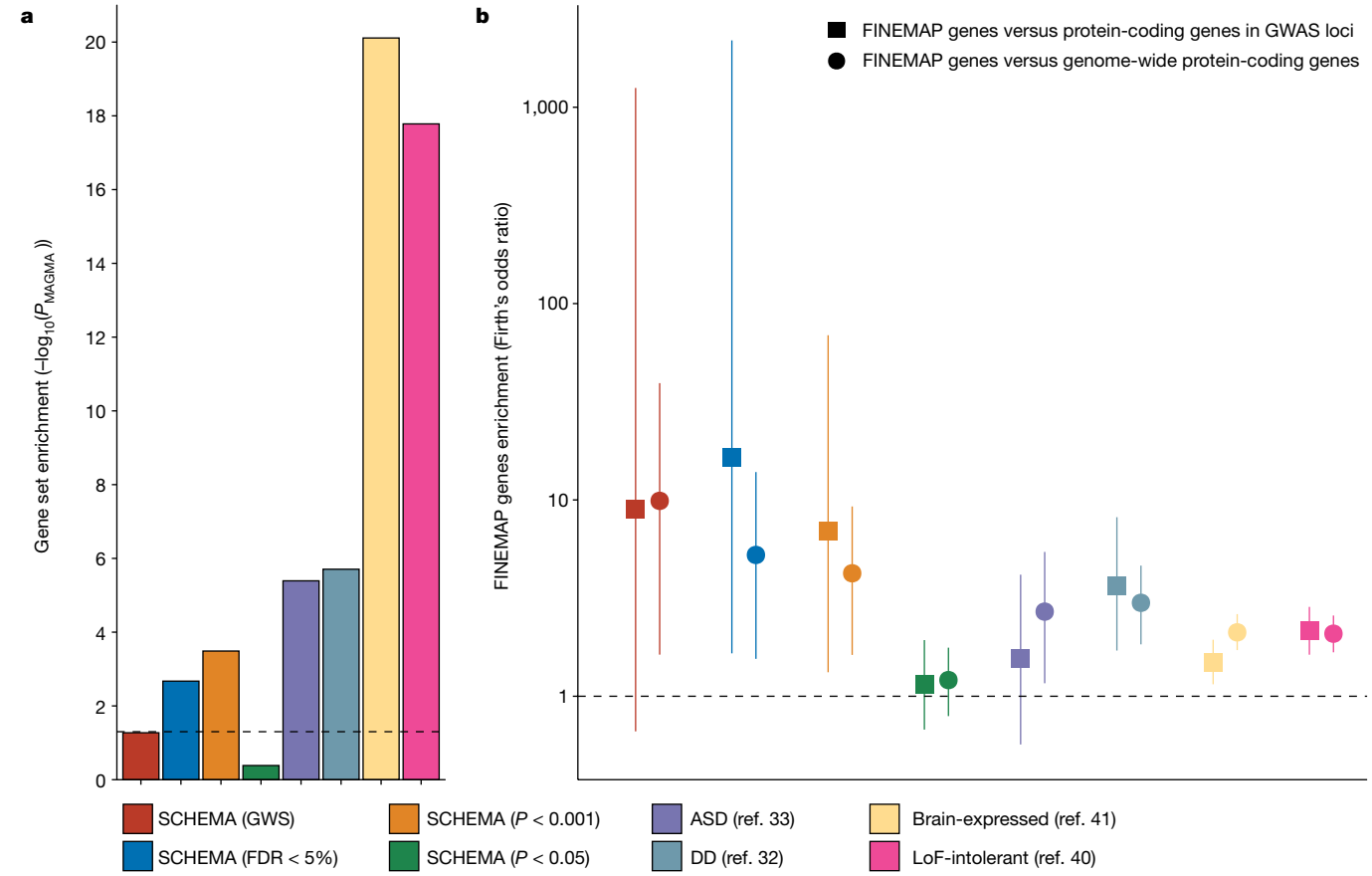


Fig. 2 | Gene set enrichment tests at the genome-wide level and for protein-coding genes that contain FINEMAP credible SNPs. Gene sets tested were retrieved from sequencing studies of schizophrenia[30], ASD[34] and developmental disorders (DD)[33]. Sets representing genes that are intolerant to loss-of 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*

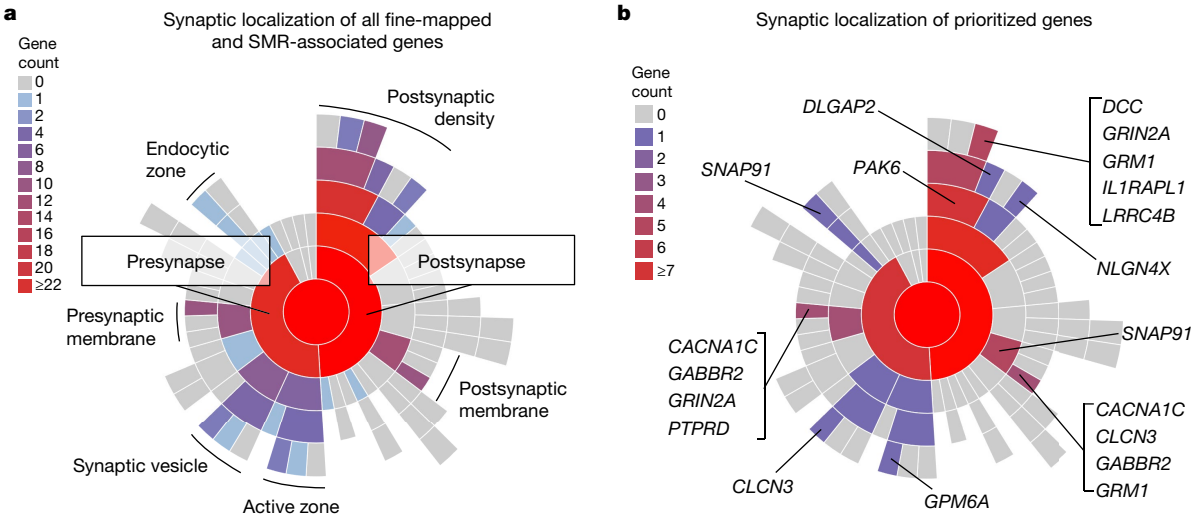


Fig. 3 | Mapping of all fine-mapped and SMR-associated genes, and prioritized genes, to synaptic locations using SynGO. Sunburst plots depict synaptic locations starting with the synapse (centre), pre- and postsynaptic locations in the first ring and child terms (that is, terms that are subsets of the 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

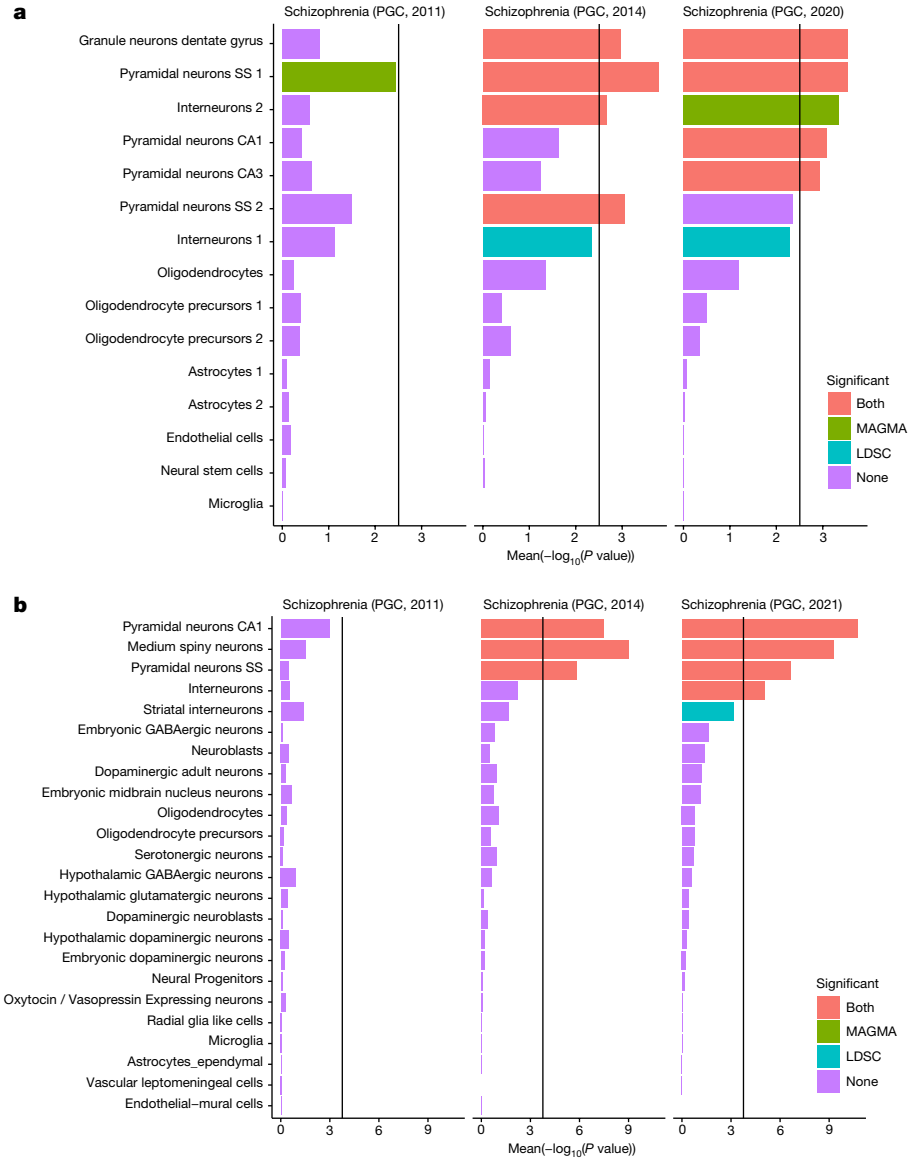


Fig. 4 | Associations between schizophrenia and cell types from multiple brain regions in human and mouse. a, **b**, The mean of the evidence ($-\log_{10}$ *P* value) obtained from two methods (MAGMA and LDSC) for testing GWAS data for enrichment of associations in genes with high expression in cell 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.

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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/.

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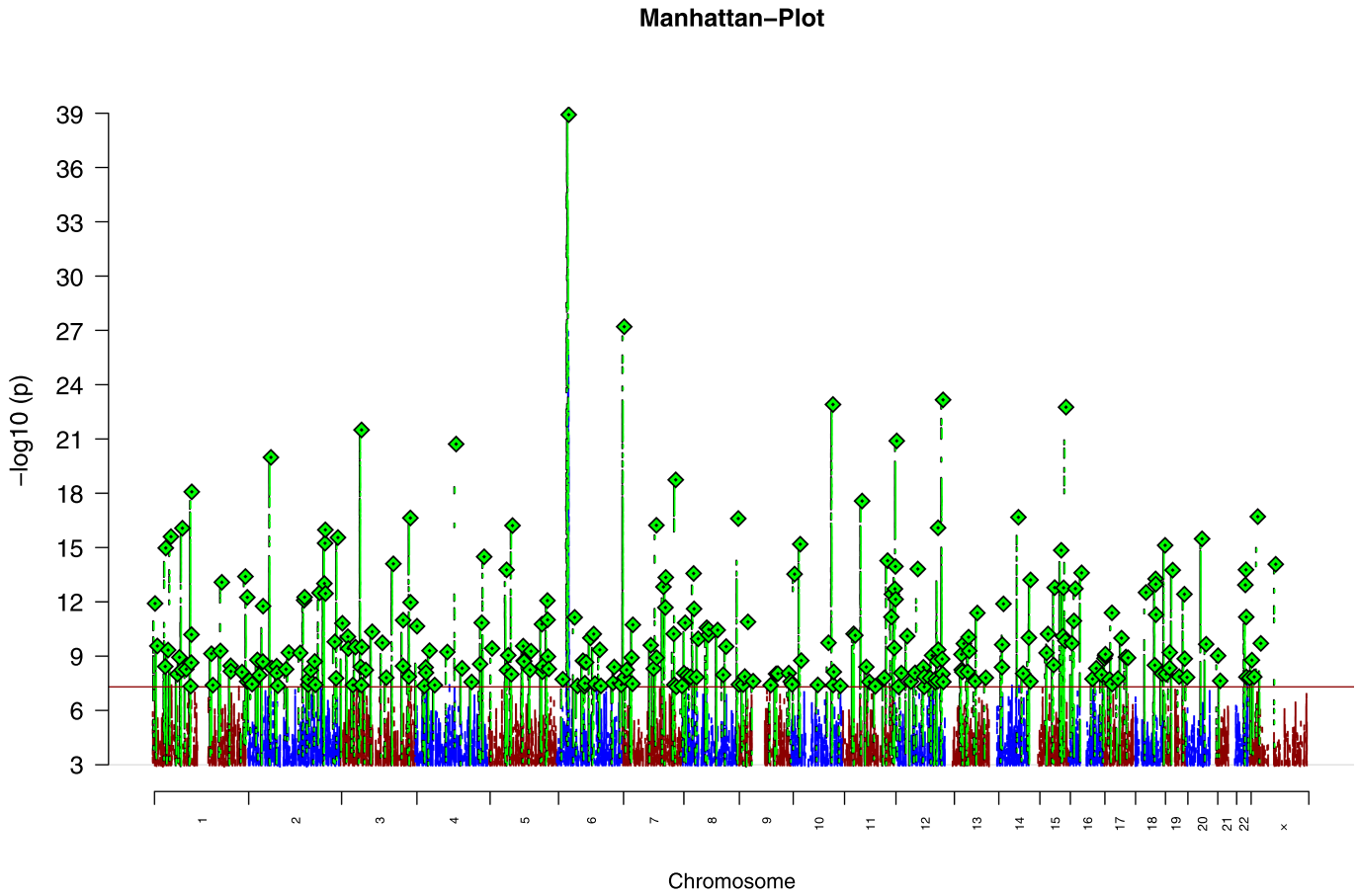
Additional information

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

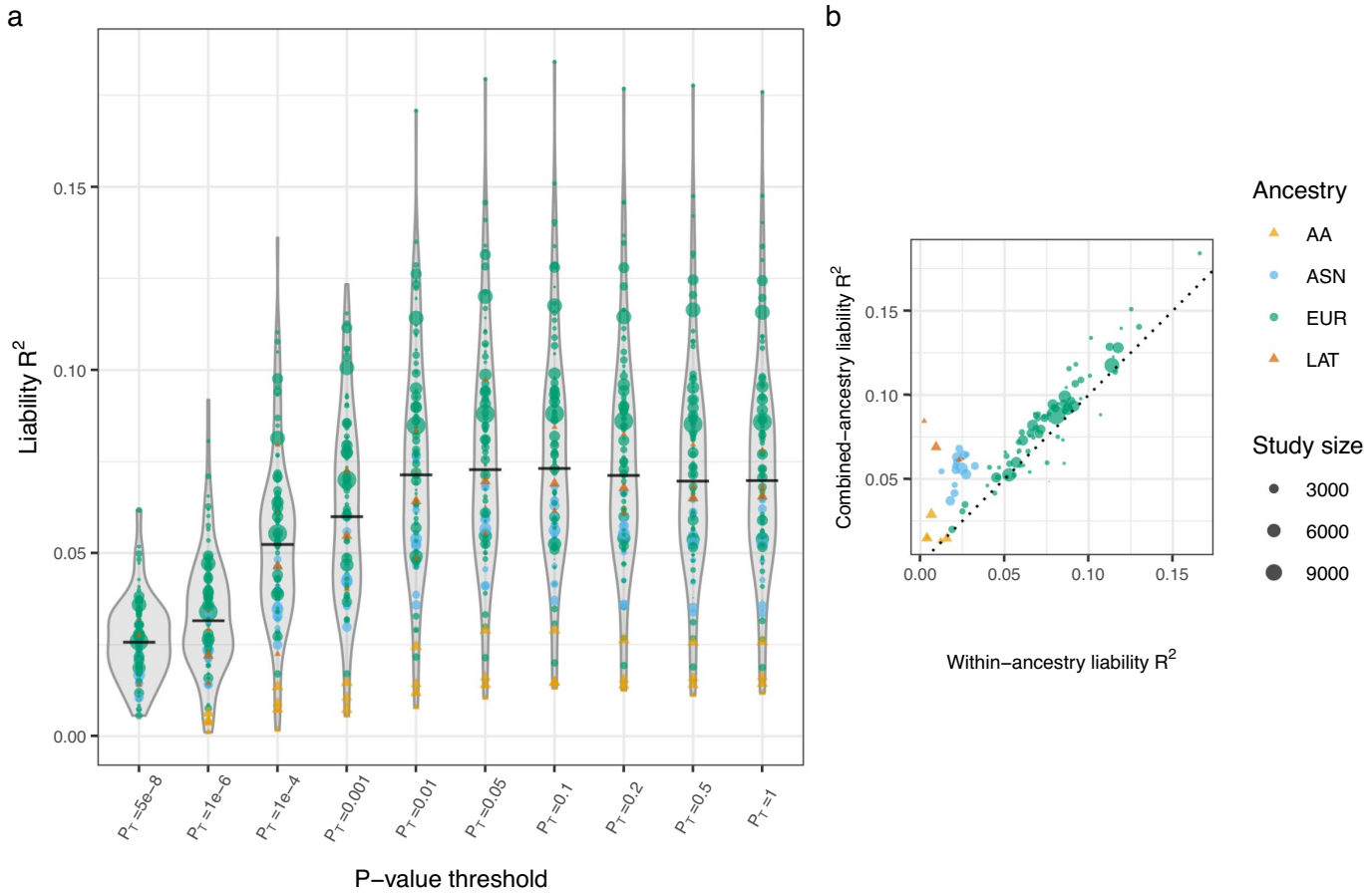
Correspondence and requests for materials should be addressed to Stephan Ripke, James T. R. Walters or Michael C. O'Donovan.

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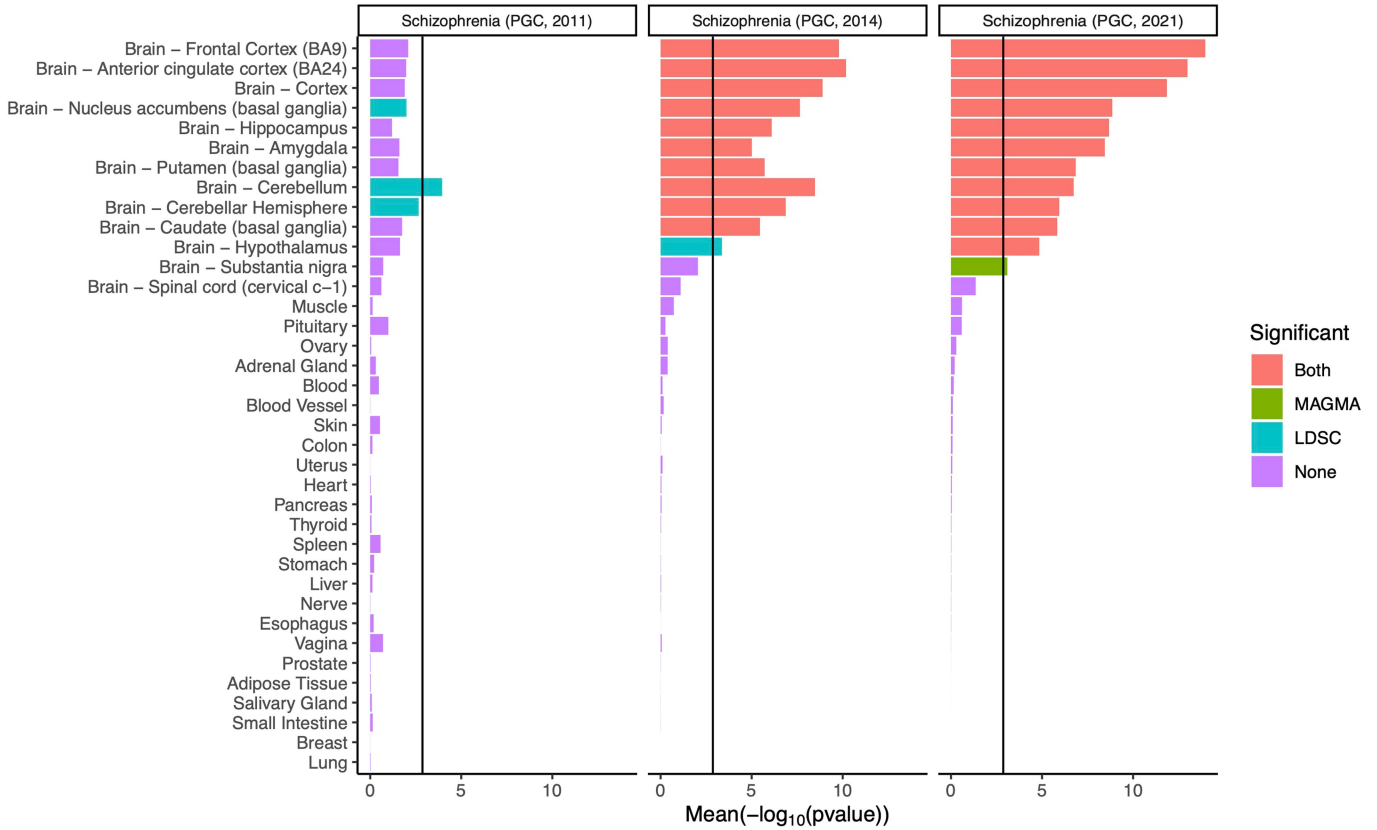
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Extended Data Fig. 1 | Primary GWAS Manhattan plot. The *x* axis indicates chromosomal position and the *y* axis is the significance of association ($-\log_{10}(P)$). The red line represents genome-wide significance level (5×10^{-8}). SNPs in green 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.

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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)

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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.

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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.