ARTICLE

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Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

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

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

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

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

108 independent associated loci

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

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

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

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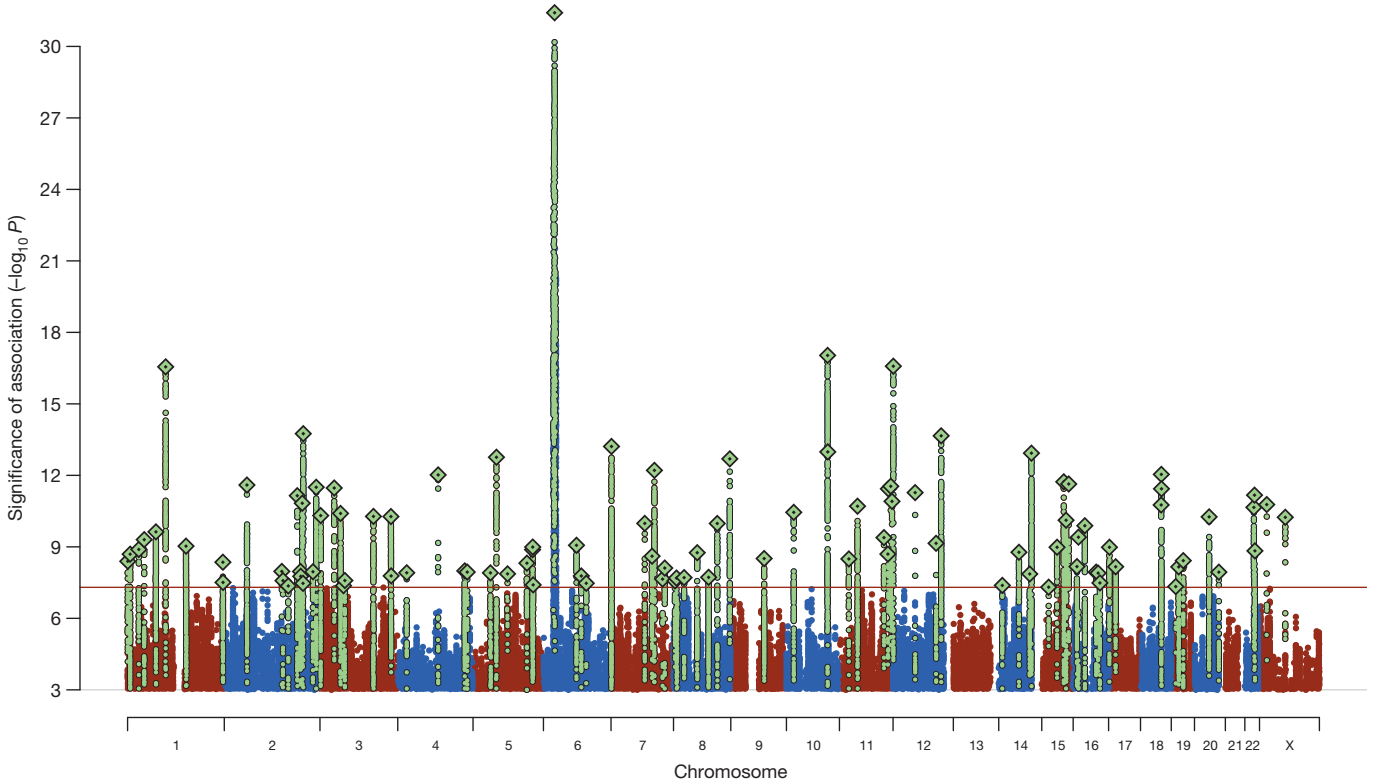

Figure 1 | Manhattan plot showing schizophrenia associations. Manhattan plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). The *x* axis is chromosomal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

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

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

Characterization of associated loci

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

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

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

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

The brain and immunity

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

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

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

Overlap with rare mutations

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

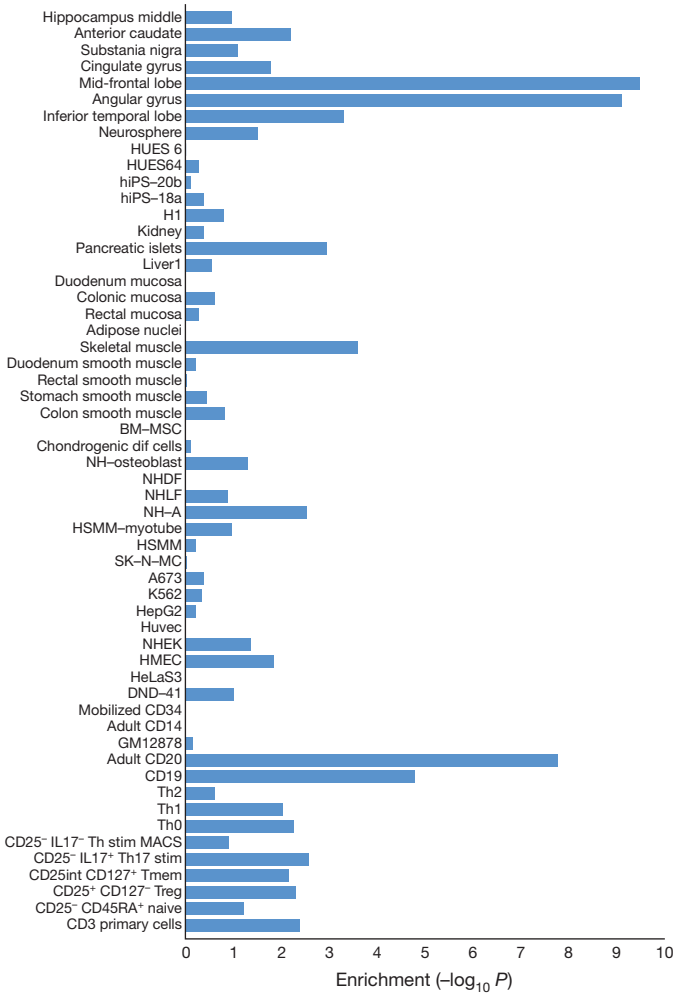

Figure 2 | Enrichment in enhancers of credible SNPs. Cell and tissue type specific enhancers were identified using ChIP-seq data sets (H3K27ac signal) from 56 cell line and tissue samples (y axis). We defined cell and tissue type enhancers as the top 10% of enhancers with the highest ratio of reads in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

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

Polygenic risk score profiling

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

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

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

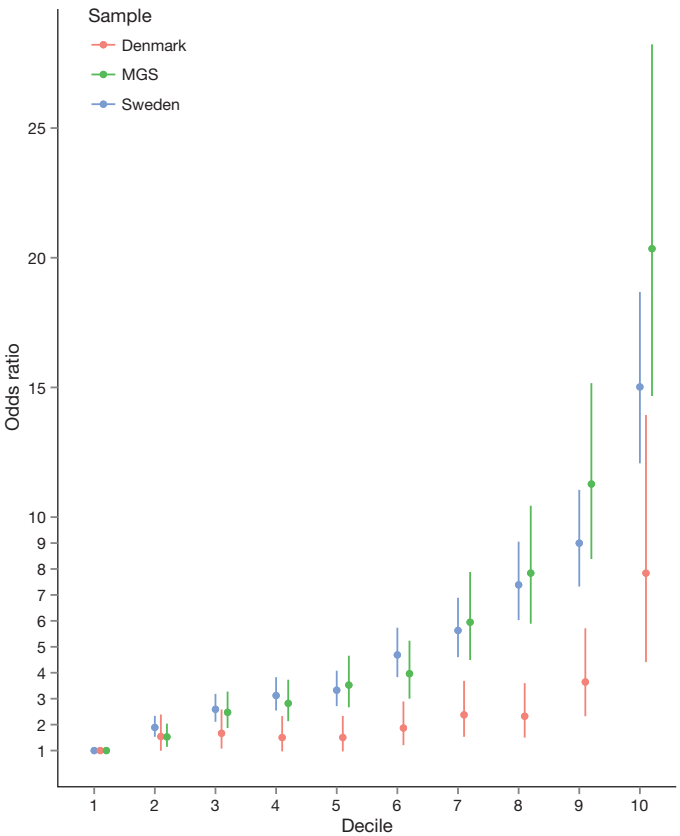

Figure 3 | Odds ratio by risk score profile. Odds ratio for schizophrenia by risk score profile (RPS) decile in the Sweden (Sw1-6), Denmark (Aarhus), and Molecular Genetics of Schizophrenia studies (Supplementary Methods). Risk alleles and weights were derived from 'leave one out' analyses in which those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

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

Discussion

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

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

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

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1. Saha, S., Chant, D. & McGrath, J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch. Gen. Psychiatry* **64,** 1123–1131 (2007).
2. World Health Organization. *The Global Burden of Disease: 2004 Update* (WHO Press, 2008).
3. Knapp, M., Mangalore, R. & Simon, J. The global costs of schizophrenia. *Schizophr. Bull.* **30,** 279–293 (2004).
4. Lieberman, J. A. *et al.* Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Engl. J. Med.* **353,** 1209–1223 (2005).
5. Carlsson, A. & Lindqvist, M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol. Toxicol.* **20,** 140–144 (1963).
6. van Rossum, J. M. The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch. Int. Pharmacodyn. Ther.* **160,** 492–494 (1966).
7. Lichtenstein, P. *et al.* Recurrence risks for schizophrenia in a Swedish national cohort. *Psychol. Med.* **36,** 1417–1425 (2006).
8. Sullivan, P. F., Kendler, K. S. & Neale, M. C. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch. Gen. Psychiatry* **60,** 1187–1192 (2003).
9. Sullivan, P. F., Daly, M. J. & O'Donovan, M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nature Rev. Genet.* **13,** 537–551 (2012).
10. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460,** 748–752 (2009).

11. Ripke, S. *et al.* Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nature Genet.* **45,** 1150–1159 (2013).
12. Ikeda, M. *et al.* Genome-wide association study of schizophrenia in a Japanese population. *Biol. Psychiatry* **69,** 472–478 (2011).
13. Hamshere, M. L. *et al.* Genome-wide significant associations in schizophrenia to *ITIH3/4*, *CACNA1C* and *SDCCAG8*, and extensive replication of associations reported by the Schizophrenia PGC. *Mol. Psychiatry* **18,** 708–712 (2013).
14. O'Donovan, M. C. *et al.* Identification of novel schizophrenia loci by genome-wide association and follow-up. *Nature Genet.* **40,** 1053–1055 (2008).
15. Rietschel, M. *et al.* Association between genetic variation in a region on chromosome 11 and schizophrenia in large samples from Europe. *Mol. Psychiatry* **17,** 906–917 (2012).
16. Schizophrenia Psychiatric Genome-Wide Association Study Consortium. Genome-wide association study identifies five new schizophrenia loci. *Nature Genet.* **43,** 969–976 (2011).
17. Irish Schizophrenia Genomics Consortium & Wellcome Trust Case Control Consortium. Genome-wide association study implicates HLA-C*01:02 as a risk factor at the major histocompatibility complex locus in schizophrenia. *Biol. Psychiatry* **72,** 620–628 (2012).
18. Shi, J. *et al.* Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* **460,** 753–757 (2009).
19. Shi, Y. *et al.* Common variants on 8p12 and 1q24.2 confer risk of schizophrenia. *Nature Genet.* **43,** 1224–1227 (2011).
20. Stefansson, H. *et al.* Common variants conferring risk of schizophrenia. *Nature* **460,** 744–747 (2009).
21. Steinberg, S. *et al.* Common variants at *VRK2* and *TCF4* conferring risk of schizophrenia. *Hum. Mol. Genet.* **20,** 4076–4081 (2011).
22. Yue, W. H. *et al.* Genome-wide association study identifies a susceptibility locus for schizophrenia in Han Chinese at 11p11.2. *Nature Genet.* **43,** 1228–1231 (2011).
23. Lencz, T. *et al.* Genome-wide association study implicates *NDST3* in schizophrenia and bipolar disorder. *Nature Commun.* **4,** 2739 (2013).
24. Psychiatric GWAS Consortium. A framework for interpreting genomewide association studies of psychiatric disorders. *Mol. Psychiatry* **14,** 10–17 (2009).
25. The 1000 Genomes Project Consortium. A map of human genome variation from population-scale sequencing. *Nature* **467,** 1061–1073 (2010).
26. Begum, F., Ghosh, D., Tseng, G. C. & Feingold, E. Comprehensive literature review and statistical considerations for GWAS meta-analysis. *Nucleic Acids Res.* **40,** 3777–3784 (2012).
27. Lango Allen, H. *et al.* Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* **467,** 832–838 (2010).
28. Jostins, L. *et al.* Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* **491,** 119–124 (2012).
29. Yang, J. *et al.* Genomic inflation factors under polygenic inheritance. *Eur. J. Hum. Genet.* **19,** 807–812 (2011).
30. Bulik-Sullivan, B. K. *et al.* LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Preprint at http://dx.doi.org/10.1101/002931 (2014).
31. Ferreira, M. A. *et al.* Collaborative genome-wide association supports a role for *ANK3* and *CACNA1C* in bipolar disorder. *Nature Genet.* **40,** 1056–1058 (2008).
32. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* **381,** 1371–1379 (2013).
33. Purcell, S. M. *et al.* A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* **506,** 185–190 (2014).
34. Fromer, M. *et al. De novo* mutations in schizophrenia implicate synaptic networks. *Nature* **506,** 179–184 (2014).
35. 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).
36. Wellcome Trust Case Control Consortium Bayesian refinement of association signals for 14 loci in 3 common diseases. *Nature Genet.* **44,** 1294–1301 (2012).
37. Nicolae, D. L. *et al.* Trait-associated SNPs are more likely to be eQTLs: annotation to enhance discovery from GWAS. *PLoS Genet.* **6,** e1000888 (2010).
38. Maurano, M. T. *et al.* Systematic localization of common disease-associated variation in regulatory DNA. *Science* **337,** 1190–1195 (2012).
39. Richards, A. L. *et al.* Schizophrenia susceptibility alleles are enriched for alleles that affect gene expression in adult human brain. *Mol. Psychiatry* **17,** 193–201 (2012).
40. Wright, F. A. *et al.* Heritability and genomics of gene expression in peripheral blood. *Nature Genet.* **46,** 430–437 (2014).
41. Doyle, J. P. *et al.* Application of a translational profiling approach for the comparative analysis of CNS cell types. *Cell* **135,** 749–762 (2008).
42. Tkachev, D. *et al.* Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* **362,** 798–805 (2003).
43. Benros, M. E., Mortensen, P. B. & Eaton, W. W. Autoimmune diseases and infections as risk factors for schizophrenia. *Ann. NY Acad. Sci.* **1262,** 56–66 (2012).
44. Holmans, P. *et al.* Gene ontology analysis of GWA study data sets provides insights into the biology of bipolar disorder. *Am. J. Hum. Genet.* **85,** 13–24 (2009).
45. Lee, P. H., O'Dushlaine, C., Thomas, B. & Purcell, S. InRich: interval-based enrichment analysis for genome-wide association studies. *Bioinformatics* **28,** 1797–1799 (2012).
46. 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).
47. Gottesman, I. I. & Gould, T. D. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* **160,** 636–645 (2003).
48. Insel, T. *et al.* Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* **167,** 748–751 (2010).

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

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

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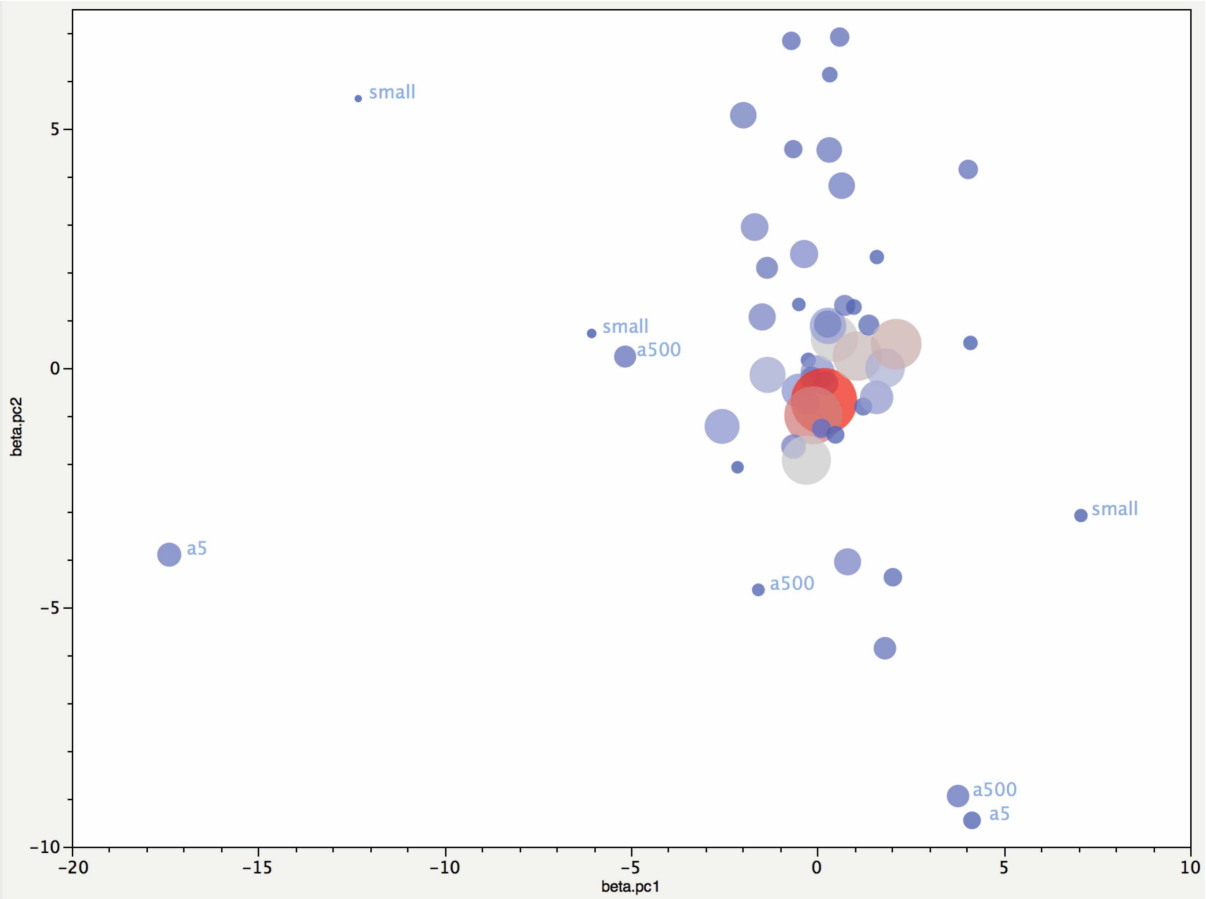
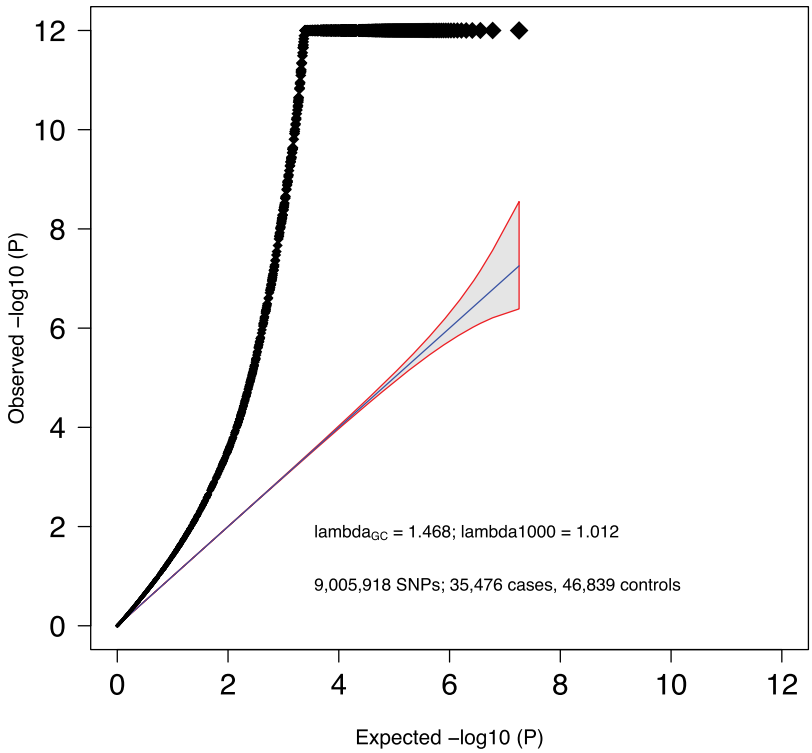
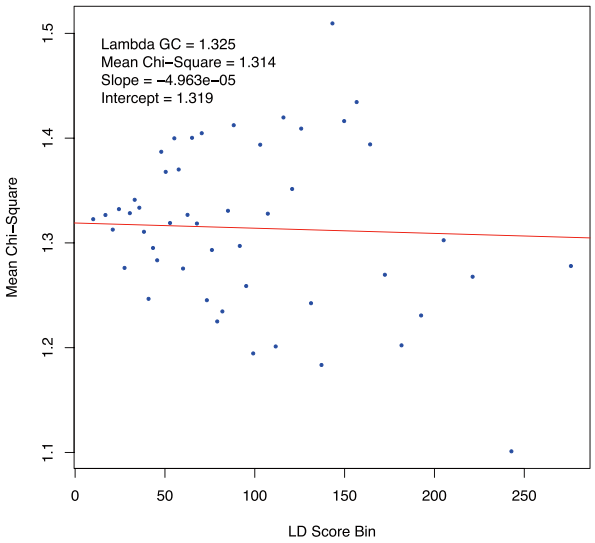


Extended Data Figure 1 | Homogeneity of effects across studies. Plot of the first two principal components (PCs) from principal components analysis (PCA) of the logistic regression β coefficients for autosomal genome-wide significant associations. The input data were the β coefficients from 52 samples for 112 independent SNP associations (excluding 3 chrX SNPs and 13 SNPs with missing values in Asian samples). PCAs were weighted by the number of cases. Each circle shows the location of a study on PC1 and PC2. Circle size and colour are proportional to the number of cases in each sample (larger and darker red circles correspond to more cases). Most samples cluster. Outliers had either small numbers of cases ('small') or were genotyped on older arrays. Abbreviations: a500 (Affymetrix 500K); a5 (Affymetrix 5.0). Studies that did not use conventional research interviews are in the central cluster (CLOZUK, Sweden, and Denmark-Aarhus studies, see Supplementary Methods for sample descriptions).



Extended Data Figure 2 | Quantile-quantile plot. Quantile-quantile plot of the discovery genome-wide association meta-analysis of 49 case control samples (34,241 cases and 45,604 controls) and 3 family based association studies (1,235 parent affected-offspring trios). Expected $-\log_{10}$ *P* values are those expected under the null hypothesis. Observed are the GWAS association results derived by logistic regression (2-tailed) as in Fig. 1. For clarity, we avoided expansion of the *y* axis by setting the smallest association *P* values to 10^{-12}. The shaded area surrounded by a red line indicates the 95% confidence interval under the null. λ_{GC} is the observed median χ^2 test statistic divided by the median expected χ^2 test statistic under the null hypothesis.

a



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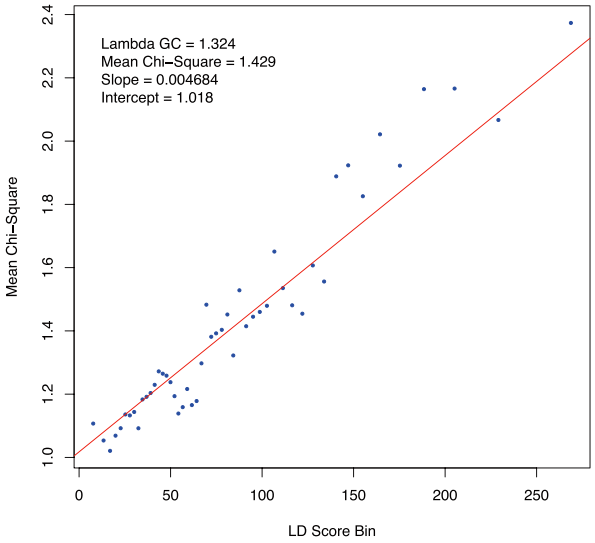

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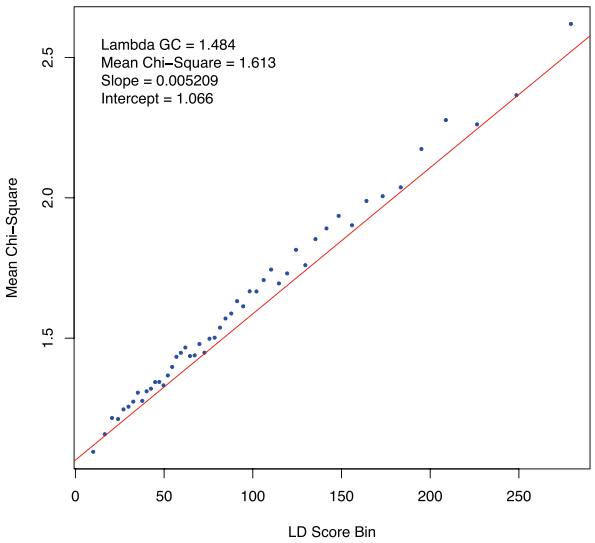
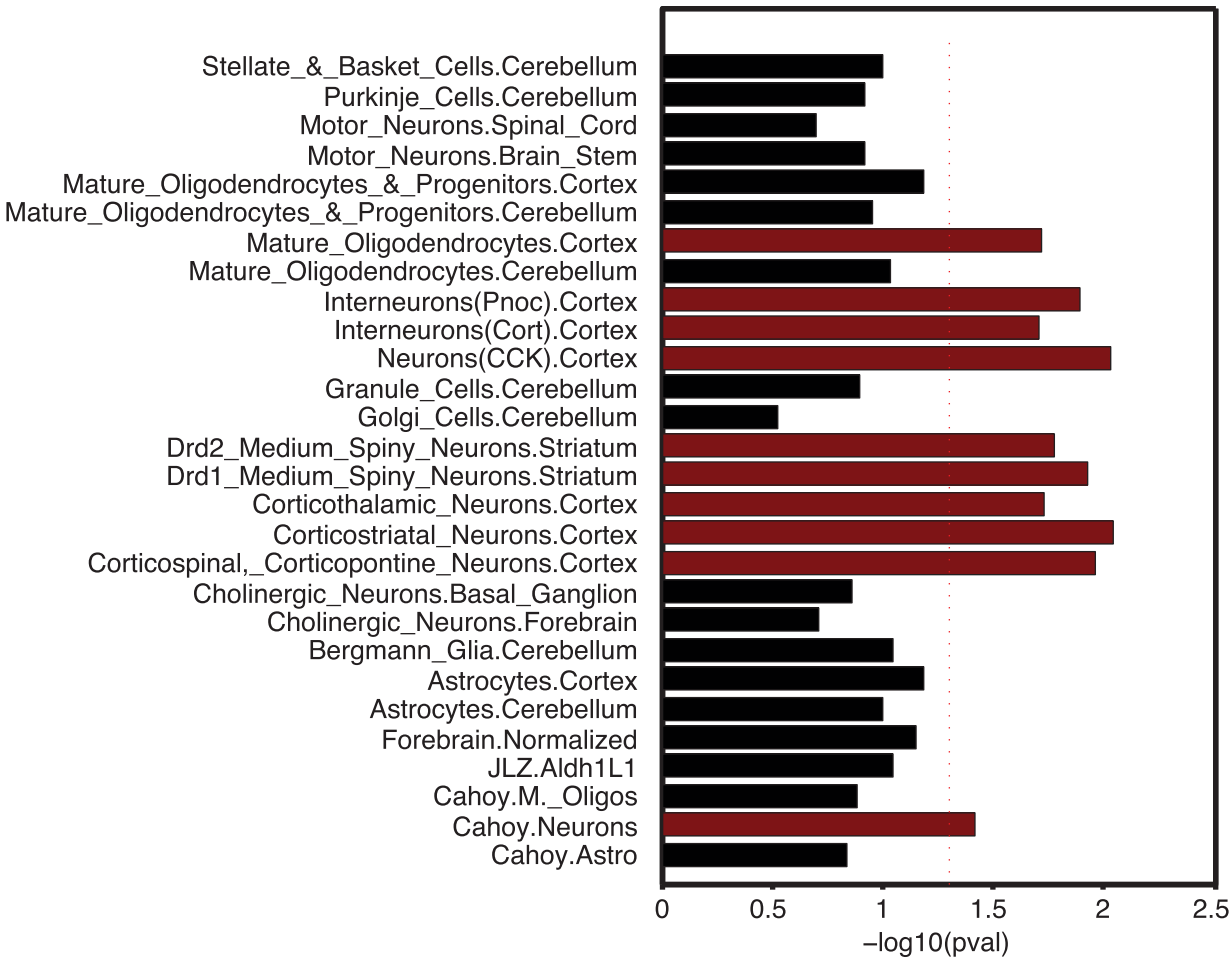
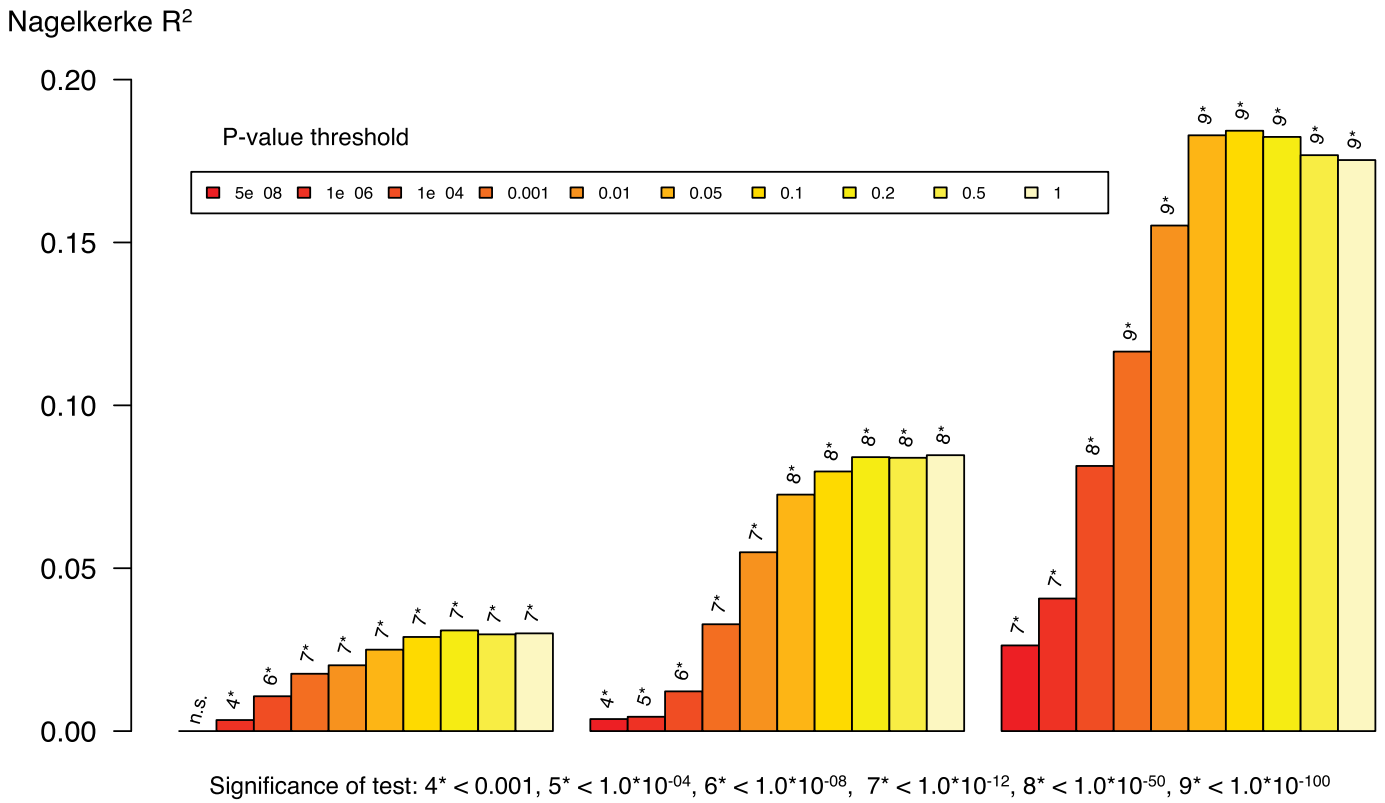


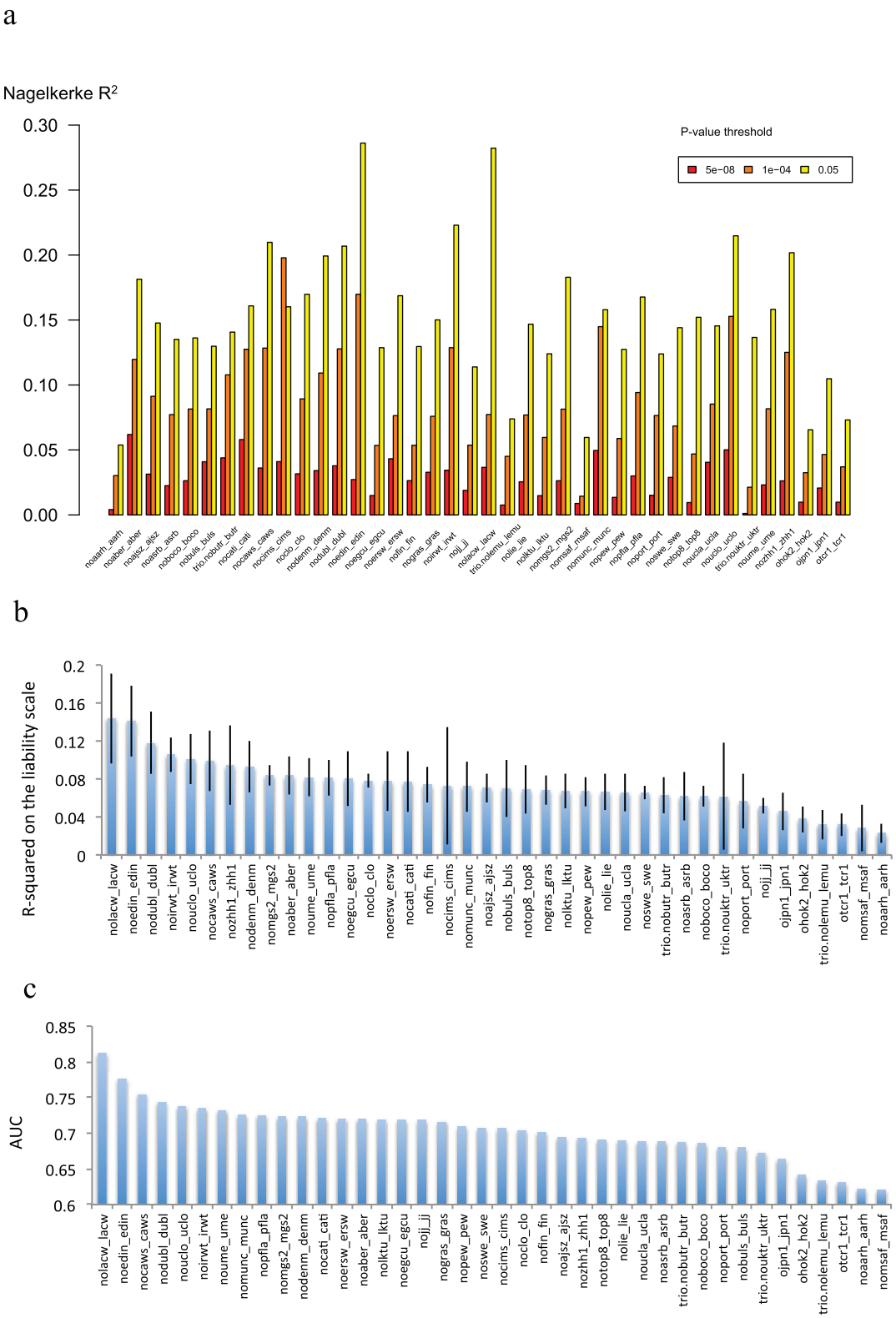
Extended Data Figure 3 | Linkage disequilibrium score regression consistent with polygenic inheritance. The relationship between marker χ^2 association statistics and linkage disequilibrium (LD) as measured by the linkage disequilibrium score. Linkage disequilibrium score is the sum of the r^2 values between a variant and all other known variants within a 1 cM window, and quantifies the amount of genetic variation tagged by that variant. Variants were grouped into 50 equal-sized bins based on linkage disequilibrium score rank. Linkage disequilibrium score bin and mean χ^2 denotes mean linkage disequilibrium score and test statistic for markers each bin. **a**, **b**, We simulated (Supplementary Methods) test statistics under two scenarios: **a**, no true association, inflation due to population stratification; and **b**, polygenic inheritance ($\lambda = 1.32$), in which we assigned independent and identically distributed per-normalized-genotype effects to a randomly selected subset of variants. **c**, Results from the PGC schizophrenia GWAS ($\lambda = 1.48$). The real data are strikingly similar to the simulated data summarized in **b** but not **a**. The intercept estimates the inflation in the mean χ^2 that results from confounding biases, such as cryptic relatedness or population stratification. Thus, the intercept of 1.066 for the schizophrenia GWAS suggests that ~90% of the inflation in the mean χ^2 results from polygenic signal. The results of the simulations are also consistent with theoretical expectation (see Supplementary Methods). λ is the median χ^2 test statistic from the simulations (**a, b**) or the observed data (**c**) divided by the median expected χ^2 test statistic under the null hypothesis.



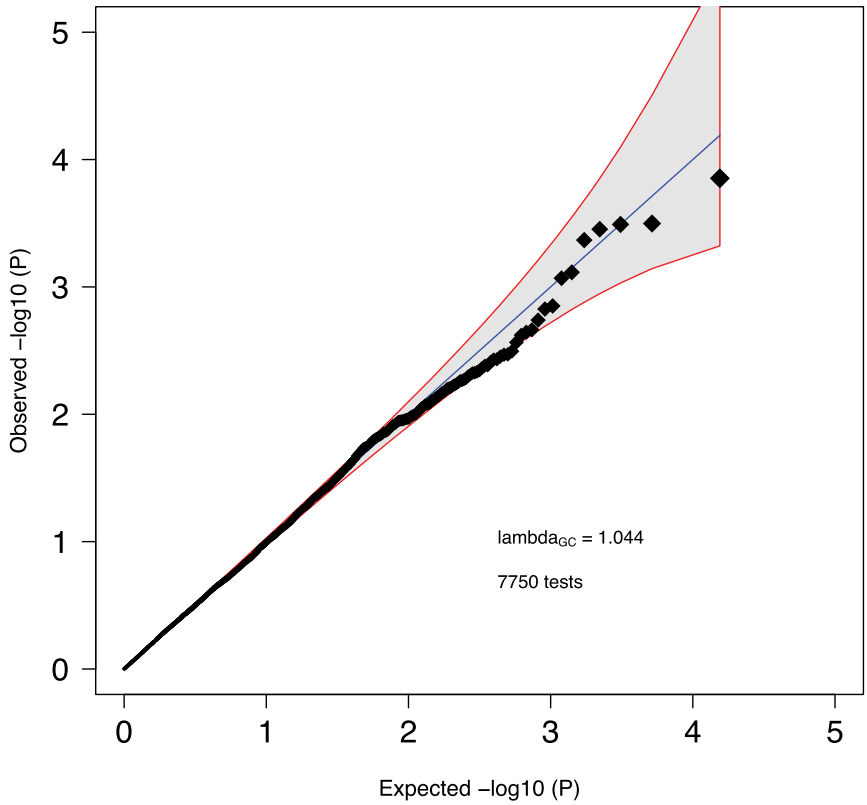
Extended Data Figure 4 | Enrichment of associations in tissues and cells. Genes whose transcriptional start is nearest to the most associated SNP at each schizophrenia-associated locus were tested for enriched expression in purified brain cell subsets obtained from mouse ribotagged lines[41] using enrichment analysis described in the Supplementary Methods. The red dotted line indicates $P = 0.05$.



Extended Data Figure 5 | MGS risk profile score analysis. Polygenic risk profile score (RPS) analyses using the MGS[18] sample as target, and deriving risk alleles from three published schizophrenia data sets (*x* axis): ISC (2,615 cases and 3,338 controls)[10], PGC1 (excluding MGS, 9,320 cases and 10,228 controls)[16], and the current meta-analysis (excluding MGS) with 32,838 cases and 44,357 controls. Samples sizes differ slightly from the original publications due to different analytical procedures. This shows the increasing RPS prediction with increasing training data set size reflecting improved precision of estimates of the SNP effect sizes. The proportion of variance explained (*y* axis; Nagelkerke's R^2) was computed by comparison of a full model (covariates + RPS) score to a reduced model (covariates only). Ten different *P* value thresholds (P_T) for selecting risk alleles are denoted by the colour of each bar (legend above plot). For significance testing, see the bottom legend which denotes the *P* value for the test that R^2 is different from zero. All numerical data and methods used to generate these plots are available in Supplementary Table 6 and Supplementary Methods.



Extended Data Figure 6 | Risk profile score analysis. We defined 40 target subgroups of the primary GWAS data set and performed 40 leave-one-out GWAS analyses (see Supplementary Methods and Supplementary Table 7) from which we derived risk alleles for RPS analysis (*x* axis) for each target subgroup. **a**, The proportion of variance explained (*y* axis; Nagelkerke's R^2) was computed for each target by comparison of a full model (covariates + RPS) score to a reduced model (covariates only). For clarity, 3 different *P* value thresholds (P_T) are presented denoted by the colour of each bar (legend above plot) as for Extended Data Fig. 5, but for clarity we restrict to fewer *P* value thresholds (P_T of 5×10^{-8}, 1×10^{-4} and 0.05) and removed the significance values. **b**, The proportion of variance on the liability scale from risk scores calculated at the P_T 0.05 with 95% CI bar assuming baseline population disease risk of 1%. **c**, Area under the receiver operating curve (AUC). All numerical data and methods used to generate these plots are available in Supplementary Table 7 and Supplementary Methods.



Extended Data Figure 7 | Pairwise epistasis analysis of significant SNPs. Quantile-quantile plot for all pair-wise ($n = 7{,}750$) combinations of the 125 independent autosomal genome-wide significant SNPs tested for non-additive effects on risk using case-control data sets of European ancestry (32,405 cases and 42,221 controls). We included as covariates the principal components from the main analysis as well as a study indicator. The interaction model is described by:

$$Y = \beta_0 + \hat{a}_1 X_1 + \hat{a}_2 X_2 + \hat{a}_3 * X_1^* X_2 + \hat{a}_4 X_4 + \hat{a}_5 X_5$$

X_1 and X_2 are genotypes at the two loci, $X_1^* X_2$ is the interaction between the two genotypes modelled in a multiplicative fashion, X_4 is the vector of principal components, X_5 is the vector of study indicator variables. Each â is the regression coefficient in the generalized linear model using logistic regression. The overall distribution of P values did not deviate from the null and the smallest P value (4.28×10^{-4}) did not surpass the Bonferroni correction threshold ($P = 0.05/7750 = 6.45 \times 10^{-6}$). The line $x = y$ indicates the expected null distribution with the grey area bounded by red lines indicating the expected 95% confidence interval for the null.

Extended Data Table 1 | ALIGATOR and INRICH

SET	ALIGATOR	INRICH
Postsynaptic sets		
ARC	NA	1
NMDAR	NA	0.458
Curated pre- and postsynaptic sets		
Cell adhesion and trans-synaptic signalling	0.902	0.44
Structural plasticity	NA	NA
Excitability	NA	NA
FMRP sets		
FMRP	**0.0066**	**5 X 10^{-5}**
MIR137 sets		
Targetscan v5 with PCT > 0.9	**0.0371**	**0.0103**
Targetscan v6.2	0.059	**0.0024**
Calcium signalling sets		
CACN* channel subunits	**0.0338**	**0.022**

Gene sets that have been reported to be enriched for schizophrenia associations and or rare mutations were tested for enrichment for genome-wide significant associations using ALIGATOR[44] and INRICH[45]. Specifically, we tested the glutamatergic postsynaptic proteins comprising activity-regulated cytoskeleton-associated protein (ARC) and *N*-methyl-D-aspartate receptor (NMDAR) complexes[33–35], other curated synaptic gene-sets[14,49], targets of fragile X mental retardation protein (FMRP)[33–35], calcium channels[11,33], and TargetScan predicted MIR137 sets[11,16]. The MIR137 TargetScan sets contain computationally predicted conserved miRNA target sites in 3′ UTRs of human genes[50]. The current version is v6, but the version used in the prior PGC SCZ report[16] was based on v5 (filtered for a probability of conserved targeting > 0.9). We report the results of both analyses for consistency with previous work. The association at the extended MHC complex was not included given the extensive linkage disequilibrium at this region spans large numbers of genes. NA means that the pathway in question contained fewer than 2 significant genes (for ALIGATOR) or regions (INRICH).

49. Lips, E. S. *et al.* Functional gene group analysis identifies synaptic gene groups as risk factor for schizophrenia. *Mol. Psychiatry* **17,** 996–1006 (2012).

50. Lewis, B. P., Burge, C. B. & Bartel, D. P. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* **120,** 15–20 (2005).

Extended Data Table 2 | *de novo* overlap

Disease group	NS (N)	*P*	# NS in PGC2 loci	Observed (stat)	Expected (stat)	Genes
SCZ	702	**0.0061**	25	10.97	5.27	CACNA1I(x2) *CCDC39* CD14(x2) CR1L CUL3 DPEP2 *DPYD*(x2) EP300 *ESAM* GRIN2A *LRP1* NCAN PDCD11 PTPRF RIMS1 SBNO1 SGSM2 SLC7A6 STAG1 TMEM219 *ZDHHC5* ZNF536
ID	141	**0.00002**	11	6.87	1.05	GRIA1 GRIN2A(x2) LRP1 NEK1 NGEF SATB2 SREBF2 STAG1 TCF4(x2)
ASD	789	**0.035**	19	9.99	5.93	*APH1A* CNOT1 CSMD1 *CUL3* CYP17A1 CYP26B1 EPHX2 LRP1 MAPK3 MEF2C MPP6 MYO15A NISCH PBRM1 PRKD1 *RIMS1* TSNARE1 WDR55 ZNF804A
Controls	434	0.15	16	4.88	3.28	ANKRD44 C11orf87 CCDC39 CDK2AP1 CHRM4 DPEP2 EP300 LRP1 LRRC48 MAN2A1 MYO1A OSBPL3 RAI1 SF3B1 SREBF2 TLE3

Test of overlap between genes mapping to schizophrenia-associated loci in the present study and genes affected by non-synonymous (NS) *de novo* mutations. Enrichment was calculated using the dnenrich permutation framework as described[34]. Genes within the GWS loci (Supplementary Table 3) were weighted by 1/*N*, where *N* is the number of coding genes within each associated locus. The observed test statistic (stat) is the sum of weights of genes impacted by *de novo* mutations. The expected test statistics are calculated by averaging over 50,000 permuted *de novo* mutation sets. Genes within schizophrenia-associated loci affected by *de novo* mutations are listed (multiple hits listed in parentheses). Cohorts: SCZ, schizophrenia; ID, intellectual disability; ASD, autism spectrum disorder. All mutations analysed annotated according to a unified system (see Supplementary Tables 1 and 2 of ref. 34). Genes with loss-of-function *de novo* mutations are underlined and in italics.