doi:10.1038/nature13595

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Supplementary Methods

Case definitions

As in our previous mega-analysis (PGC1), [1] individuals with schizophrenia or schizoaffective disorder were included as cases since family history studies have shown coaggregation of these two disorders, diagnostic criteria separating them are subjective, and the inter-rater reliability is often low across research groups. [2,3]

To assess the quality of the assessments of our cases, we developed a questionnaire covering the assessment protocol and associated quality control procedures used to establish diagnosis. All participating studies completed this questionnaire. Nine key items were selected for the further evaluation of each study: the use of a structured psychiatric diagnostic interview, systematic training of interviewers in the use of the instrument, systematic quality control of diagnostic accuracy, reliability trials, review of medical record information, use of a "best-estimate" procedure for making a final project diagnosis, use of specific inclusion and exclusion criteria, MDs or PhDs making the final diagnostic determination, and special additional training for the final diagnostician.

A subgroup of PI's (Drs A Corvin, A Fanous, P Gejman, K Kendler, and B Mowry) reviewed and scored each of the studies on this scale. Information on each study and the quality control procedures in place are provided in the case descriptions below and the score for each sample is provided in Supplementary Table 1. We previously empirically validated studies that used fundamentally different ascertainment methods (e.g. hospital discharge register records or patients defined as having treatment-resistant schizophrenia and registered to use the medication Clozapine). [4,5] Consequently, we included all available studies in the reported primary analysis here.

Sample size summary

This paper reports the results of genomic analyses on 38,131 schizophrenia cases and 114,674 controls (152,805 subjects). Individual genotypes from 96.0% of the cases were directly processed and analyzed by the PGC. The subjects were:

- European ancestry cases and controls most of whom were included in a prior mega-analysis, 12,078 cases and 13,271 controls
- New European ancestry case-control subjects, 21,278 cases and 30,453 controls
- Three European ancestry trio samples, 1,396 pedigrees
- Three case-control samples from East Asia, 1,866 cases and 3,418 controls
- Replication samples (European ancestry, case-control), 1,513 cases and 66,236 controls

Details of individual participating studies

We describe below ascertainment and diagnosis of the subjects comprising this report. Supplementary Table 1 provides additional detail including sample sizes and genotyping array. Most studies have been published, and the primary report can usually be found using the PubMed identifiers provided.

The lead PI of each sample warranted that their protocol was approved by their local Ethical Committee. All subjects provided written informed consent (or legal guardian consent and subject assent) with the exception of the CLOZUK sample (see sample details) which obtained anonymous samples via a drug monitoring service under ethical approval and in accordance with the UK Human Tissue Act.

The sections below describe the schizophrenia samples that were part of this report. All of these subjects are independent as confirmed using SNPs directly genotyped in all samples. As the lifetime prevalence of schizophrenia is ~1%, the potential (but minimal) loss of power than comes with the use of (some) control sets that were not screened for schizophrenia is more than offset by our ability to include a larger number of controls. [6] Most studies have been described in detail in the citations provided. The boldfaced first line for each sample is study PI, PubMed ID, country (study name), and the PGC internal tag or study identifier.

European ancestry, case-control design

Adolfsson, R | NP | Umeå, Sweden | scz_umeb_eur

Adolfsson, R | NP | Umeå, Sweden | scz_umes_eur

Cases of European ancestry were ascertained from multiple different studies of schizophrenia (1992-2009). The diagnostic processes were similar between studies, and the final diagnosis is a best-estimate consensus lifetime diagnosis based on multiple sources of information such as clinical evaluation by research psychiatrists, different types of semi-structured interviews made by trained research nurses and research psychiatrists, medical records, course of the disease and data from multiple informants. Diagnosis was made in accordance with the Diagnostic and Statistical Manual of Mental Disorders-Version IV (DSM-IV) or International Classification of Diseases, 10th Revision (ICD-10) criteria. Controls were recruited from the Betula study, an on-going longitudinal, prospective, population-based study from the same geographic area (North Sweden) that is studying aging, health, and cognition in adults. [7] All subjects (cases and controls) participated after giving written informed consent and the regional Ethical Review Board at the University of Umeå approved all original studies and participation in the PGC. GWAS genotyping was performed at Broad Institute.

Andreassen, O | 19571808 | Norway (TOP) | scz_top8_eur

In the TOP study (Tematisk omrade psykoser), cases of European ancestry, born in Norway, were recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to SCID and further ascertainment details have been reported. [8] Healthy control subjects were randomly selected from statistical records of persons from the same catchment area as the patient groups. All participants provided written informed consent and the human subjects protocol was approved by the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency.

Blackwood, D | 19571811 | Edinburgh, UK | scz_edin_eur

Cases and controls were recruited from the southeast of Scotland, and ascertainment has been previously described as part of the International Schizophrenia Consortium studies. [9] All participating subjects gave written, informed consent and the human subjects protocol was approved by the Scotland A Research Ethics Committee. DNA samples were genotyped at the Broad Institute.

Børglum, A | 19571808 | Denmark | scz_aarh_eur

DNA samples for all subjects were collected from blood spots systematically collected by the Danish Newborn Screening Biobank), with case/control status established using the Danish Psychiatric Central Register. Cases were diagnosed clinically according to ICD-10 criteria. Controls were selected to match the cases by birth cohort. The Danish Data Protection Agency and the ethics committees in Denmark approved the human subjects protocol.

Bramon | 23871474 | Seven countries (PEIC, WTCCC2) | scz_pewb_eur

Bramon | 23871474 | Spain (PEIC, WTCCC2) | scz_pewb_eur

The Psychosis Endophenotypes International Consortium (PEIC) was part of WTCCC2. [10] Samples were collected through seven centers in Europe and Australia (the Institute of Psychiatry, King's College London, London; GROUP (consisting of the University of Amsterdam, Amsterdam; the University of Groningen, Groningen; Maastricht University Medical Centre, Maastricht; and the University of Utrecht, Utrecht); the University of Western Australia, Perth; the Universidad de Cantabria, Santander; the University of Edinburgh, Edinburgh; Heidelberg University, Heidelberg and Ludwig-Maximilians-Universität München, Munich). To allow for a DSM-IV diagnosis to be ascertained or ruled out, all participants (including controls and unaffected family members) underwent a structured clinical interview with the Schedule for Affective Disorders and Schizophrenia (SADS), the Structured Clinical Interview for DSM Disorders (SCID), or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). We included cases with schizophrenia and schizoaffective disorder. Participants in all groups were excluded if they had a history of neurological disease or head injury resulting in loss of consciousness.

Buxbaum, J | 20489179 | New York, US & Israel | scz_msaf_eur

Samples contributed by Mount Sinai were derived from three cohorts. In all cohorts, ethical approval was obtained from all participating sites, and all subjects provided informed consent. Two of the cohorts were in a prior paper on copy number variation. [11] One of the cohorts was from the Mount Sinai brain bank, where DNA was extracted from postmortem samples, and another comprised of patients ascertained in Israel. The third cohort included subjects more recently recruited through the Mount Sinai Conte Center.

Corvin, A | 19571811 | Ireland | scz_dubl_eur

The case sample was collected primarily in the Dublin area and the ascertainment procedure has been previously described. [9] The controls were recruited, from the same region through the Irish Blood Transfusion Services. All participants gave written, informed consent and the collections were approved through the Federated Dublin Hospitals and Irish Blood Transfusion Services Research Ethics Committees, respectively. DNA samples were genotyped at the Broad Institute.

Corvin, A; Riley, B | 22883433 | Ireland (WTCCC2) | scz_irwt_eur

The case sample was recruited from the Republic of Ireland and Northern Ireland. All cases had four Irish grandparents and ascertainment details have been reported elsewhere. [12] Ethics approval was obtained from all participating hospitals and centers. Controls were blood donors from the Irish Blood Transfusion Service, whose Ethics Committee approved the human subjects protocol. All participants gave written informed consent. Samples were genotyped at Affymetrix (Santa Clara, California, US) laboratory as part of the WTCCC2 genotyping pipeline.

Ehrenreich, H | 20819981 | Germany (GRAS) | scz_gras

The Gottingen Research Association for Schizophrenia (GRAS) collection included cases recruited across 23 German hospitals. Controls were unscreened blood donors recruited at the Georg-August-University according to national blood donation guidelines. [13] Cases completed a structured clinical interview and were diagnosed with DSM-IV schizophrenia or schizoaffective disorder. The study was approved by the Georg-August-University ethics committee and local internal review boards of the participating centers. All participants gave written informed consent.

Esko, T | 15133739 | Estonia (EGCUT) | scz_egcu_eur

The Estonian cohort comes from the population-based biobank of the Estonian Genome Project of University of Tartu (EGCUT). [14] The project was conducted according to the Estonian Gene

Research Act and all participants provided informed consent (www.biobank.ee). In total, 52,000 individuals aged 18 years or older participated in this cohort (33% men, 67% women). The population distributions of the cohort reflect those of the Estonian population (83% Estonians, 14% Russians and 3% other). General practitioners (GP) and physicians in the hospitals randomly recruited the participants. A Computer-Assisted Personal interview was conducted over 1-2 ours at doctors' offices. Data on demographics, genealogy, educational and occupational history, lifestyle and anthropometric and physiological data were assessed. Schizophrenia was diagnosed prior to the recruitment by a psychiatrist according to ICD-10 criteria and identified from the Estonian Biobank phenotype database. Controls were drawn from a larger pool of genotyped biobank samples by matching on gender, age and genetic ancestry. All the controls were population-based and have not been sampled for any specific disease.

Esko, T; Li, Q; Dominici E | 15133739, 24166486 | J&J and Roche cases, EGCUT controls | scz_jr3a_eur

Esko, T; Li, Q; Domenici E | 15133739, 24166486 | J&J and Roche cases, EGCUT controls | scz_jr3b_eur

Esko, T; Li, Q; Domenici E | 15133739, 24166486 | J&J and Roche cases, EGCUT controls | scz_jri6_eur

Esko, T; Li, Q; Dominici E | 15133739, 24166486 | J&J and Roche cases cases, EGCUT controls | scz_jrsa_eur

Cases were collected by Johnson and Johnson (J&J) and Roche as part of clinical collaborations with hospitals and outpatient centers. Cases were diagnosed according to DSM-IV criteria, with medical record review by a trained psychiatrist. There were reliability trials across centers for the J&J studies. The J& J cases were mostly collected in Eastern Europe, with most coming from Estonian and Russia (>100); intermediate numbers from Austria, the Czech Republic, Latvia, Lithuania, and Spain (50-100); and smaller collections from Bulgaria, Hungary, and Poland (<50). The Roche cases were assessed with a structured psychiatric assessment by trained interviewers. Most of the Eastern European controls were from the Estonian Biobank project (EGCUT) [14] and were ancestrally matched with cases from the J&J sample.

Gejman, P | 19571809 | US, Australia (MGS) | scz_mgs2_eur

European ancestry case samples were collected by the Molecular Genetics of Schizophrenia (MGS) collaboration across multiple sites in the USA and Australia as described in detail elsewhere. [15] Cases gave written informed consent, and IRBs at each collecting site approved the human subjects protocol. A survey company (Knowledge Networks, under MGS guidance) collected the European ancestry control sample and ascertainment is described in detail elsewhere. [16]. DNA samples were genotyped at the Broad Institute.

Gurling, H | 19571811 | London, UK | scz_uclo_eur

All cases and controls were collected by University College London and had both parents from England, Scotland or Wales. All participants gave written informed consent and the U.K. National Health Service multicenter and local research ethics committee approved the human subjects protocol. Further details on ascertainment are available elsewhere. [9] The samples were genotyped at the Broad Institute.

Jönsson, E | 19571808 | Sweden (Hubin) | scz_ersw_eur

Cases were recruited from northwestern Stockholm County and ascertainment has been described previously. [17] Cases gave informed consent and the human subjects protocol was

approved by the ethical committees of the Karolinska Hospital and the Stockholm Regional Ethical Committee. Controls were recruited either among subjects previously participating in biological research at the Karolinska Institute or drawn from a representative register of the population of Stockholm County. All participants provided informed consent.

Kirov, G | Not published | Bulgaria | scz_buls_eur

All cases were recruited from Bulgaria and had a history of hospitalization for treatment of schizophrenia. Controls were recruited from the two largest cities in Bulgaria as previously described. [9] All participants gave written informed consent and the study was approved by local ethics committees at the participating centers.

Knight, J; Collier DA; Nisenbaum L| Not published | Canada (Toronto) -US(Lilly)-US (MIGen)| scz_lktu_eur

Toronto cases were recruited by referral and advertisement. Diagnoses were made according to DSM-III or DSM-IV criteria following interview and medical record review. US cases were recruited from schizophrenia clinical trials in a range of settings as part of a trial with Eli Lilly. Diagnoses were made according to DSM-III or DSM-IV criteria following interview by psychiatrist and medical record review. No controls were sampled as part of the study, and ancestrally-matched controls were chosen from the Myocardial Infarction Genetics Consortium (MIGen, dbGaP ID phs000294.v1.p1) that was genotyped with the same SNP array. [18]

Lencz, T; Darvasi A | 23325106 | Israel | scz_ajsz_eur

Cases and controls were sampled from an Ashkenazi Jewish repository (Hebrew University Genetic Resource, http://hugr.huji.ac.il). Patients were recruited from hospitalized inpatients at 7 medical centers in Israel and were diagnosed with DSM-IV schizophrenia or schizoaffective disorder. Controls were sampled through the Israeli Blood Bank and did not report any chronic disease or regularly prescribed medication at the time of assessment. Full ascertainment details have previously been reported . [19] Local ethics committees and the National Genetic Committee of the Israeli Ministry of Health approved the studies and all participants gave informed, written consent.

Levinson, D | 22885689 | Six countries, WTCCC controls | scz_lacw_eur

Cases collected as part of a larger pedigree-based study [20] were partitioned into two subsamples. Cases with two genotyped parents were analyzed as trios (see PI Levinson, ms.scz_lemu_eur in the Trio section below). Unrelated cases who could not be used as part of a trio were included as a separate case-control analysis, using independent controls, matched by ancestry and genotyping array, from the Wellcome Trust Case Control Consortium. [21] Cases were identified from different clinical settings (e.g. inpatients, outpatients and community facilities) in six countries (Australia, France, Germany, Ireland, UK, and the US). Diagnoses were established using semi-structured interviews, psychiatric records and informant reports. Case subjects were diagnosed with schizophrenia or schizoaffective disorder according to DSM-III-R criteria. All protocols were approved by loci IRBs, and all cases provided written informed consent.

Malhotra, A | 17522711 | New York, US | scz_zhh1_eur

The case and control subjects were recruited in the New York metropolitan area and ascertainment methods have been described previously. [22] All participants gave written, informed consent and the IRB of the North Shore-Long Island Jewish Health System approved the human subjects protocols. DNA was genotyped at Zucker Hillside.

Mowry, B | 21034186 | Australia | scz_asrb_eur

These subjects were part of the Australian Schizophrenia Research Bank. The case sample was recruited in four Australian States (New South Wales, Queensland, Western Australia and Victoria) through hospital inpatient units, community mental health services, outpatient clinics and rehabilitation services, non-government mental illness support organizations, and, in the initial stages, through a large-scale, national, multi-media advertising campaign. This sample is comprised of 509 cases from larger metropolitan centers of Brisbane, Newcastle, Sydney, Melbourne, and Perth. Cases gave written informed consent, and the human subjects protocol was initially approved by the Hunter New England Area Health Research Committee and subsequently approved by relevant Institutional Ethics Committees in Brisbane, Sydney, Melbourne and Perth. Healthy controls were recruited through multi-media advertisements, and other sources. Controls were from the metropolitan centers of Brisbane, Newcastle, Sydney, Melbourne, and Perth. Controls gave written informed consent, and the human subjects protocol was approved by the Hunter New England Area Health Research Committee and Institutional Ethics Committees in Brisbane, Sydney, Melbourne and Perth. The samples were genotyped in two stages at the Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia.

O'Donovan, M: Owen, M | 19571811 | Cardiff, UK | scz_caws_eur

The case sample included European ancestry schizophrenia cases recruited in the British Isles and described previously. [23] All cases gave written informed consent to. The study was approved by the Multicentre Research Ethics Committee in Wales and Local Research Ethics Committees from all participating sites. The control sample used the Wellcome Trust Case-Control Consortium (WTCCC) sample described elsewhere, [21] but included similar numbers of individuals from the 1958 British Birth Cohort and a panel of consenting blood donors (UK Blood Service). Samples were genotyped at Affymetrix service lab (San Francisco, USA).

O'Donovan, M: Owen, M: Walters, J | 22614287 | UK (CLOZUK) | scz_clm2_eur

O'Donovan, M: Owen, M: Walters, J | 22614287 | UK (CLOZUK) | scz_clo3_eur

CLOZUK cases were taking the antipsychotic clozapine and had received a clinical diagnosis of treatment-resistant schizophrenia. Patients taking clozapine provide blood samples to allow detection of adverse drug-effects. Through collaboration with Novartis (the manufacturer of a proprietary form of clozapine, Clozaril), we acquired blood from people with treatment-resistant schizophrenia according to the clozapine registration forms completed by treating psychiatrists as previously reported. [5] The samples were genotyped at the Broad Institute. The UK Multicentre Research Ethics Committee (MREC) approved the study.

The controls were drawn from the WTCCC2 control samples (~3,000 from the 1958 British Birth Cohort and ~3,000 samples from the UK Blood Service Control Group). An additional 900 controls, held by Cardiff University, were recruited from the UK National Blood Transfusion Service. They were not specifically screened for psychiatric illness. All control samples were from participants who provided informed consent.

Ophoff, R | 19571808 | Netherlands | scz_ucla_eur

The case sample consisted of inpatients and outpatients recruited through psychiatric hospitals and institutions throughout the Netherlands. Cases with DSM-IV schizophrenia were included in the analysis. Further details on ascertainment are provided elsewhere. [17] Controls came from the University Medical Centre Utrecht and were volunteers with no psychiatric history. Ethical approval was provided by local ethics committees and all participants gave written informed consent.

Palotie, A | 19571808 | Finland | scz_fi3m_eur

Palotie, A | Not published | Finnish | scz_fii6_eur

Finnish cases were drawn from a nationwide collection of families with schizophrenia spectrum disorders. [24,25] The control sample was derived from the Finnish Health 2000 survey. [26] All participants provided written informed consent and approval was obtained from the ethics committees at each location.

Pato, C | 19571811 | Portugal | scz_port_eur

Cases and controls lived in Portugal, the Azorean and Madeiran islands, or were the direct (first- or second-generation) Portugese immigrant population in the US, as previously described. [9] Controls were not biologically related to cases. All participants gave written informed consent and the IRB of SUNY Upstate Medical University approved the protocol. The samples were genotyped at the Broad Institute.

Petryshen, T | 24424392| Boston, US (CIDAR) | scz_cims_eur

Cases were recruited from inpatient and outpatient settings in the Boston area by clinician referral, through review of medical records, or through advertisements in local media. Cases were diagnosed with DSM-IV schizophrenia through a structured clinical interview (SCID) by trained interviewers with review of medical records and a best estimate diagnostic procedure including reliability trials across interviewers. A psychiatrist or a PhD-level mental health professional made the final diagnostic determination. Controls were ascertained through local advertisements from the same geographical area. Ethical approval was provided by local ethics committees and all participants gave written informed consent.

Rietschel/Rujescu/Nöthen | 19571808 | Bonn/Mannheim, Germany | scz_boco_eur

These German samples were collected by separate groups within the MooDS Consortium in Mannheim, Bonn, Munich and Jena. For the PGC analyses, the samples were combined by chip and ancestry. In Bonn/Mannheim, cases were ascertained as previously described. [17] Controls were drawn from three population-based epidemiological studies (PopGen), [27] the Cooperative Health Research in the Region of Augsburg (KORA) study, [28] and the Heinz Nixdorf Recall (HNR) study. [29] All participants gave written informed consent and the local ethics committees approved the human subjects protocols. Additional controls were randomly selected from a Munich-based community sample and screened for the presence of anxiety and affective disorders using the Composite International Diagnostic Screener. [30] Only individuals negative for the above mentioned disorders were included in the sample.

Rujescu, D | 19571808 | Munich, Germany | scz_munc_eur

For the Munich sample, cases were ascertained from the Munich area of Germany, as described previously. [17] The controls were unrelated volunteers randomly selected from the general population of Munich. All were screened to exclude a history of psychosis/central neurological disease either personally or in a first-degree relative. All participants gave written informed consent and the local ethics committees approved the human subjects protocols.

St Clair, D | 19571811 | Aberdeen, UK | scz_aber_eur

Ascertainment and inclusion/exclusion criteria for cases and controls have been previously described. [9] All participating subjects were born in the UK (95% Scotland) and gave written informed consent. Both local and multiregional academic ethical committee approved the human subjects protocol. The samples were genotyped at the Broad Institute.

Sullivan, PF | 18347602 | US (CATIE) | scz_cati_eur

Cases were collected as part of the Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE) project and ascertainment was previously described. [31-33] Participants were recruited

from multiple sites in the USA with informed written consent and approval from the IRBs at each CATIE site and the University of North Carolina (Chapel Hill). The control subjects were collected by MGS (described above) and gave online informed consent and were fully anonymized. There was no overlap with controls included in the MGS collaboration sample.

Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz_swe1_eur

Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz_s234_eur

Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz_swe5_eur

Sullivan, PF; Sklar P; Hultman C | 23974872 | Sweden | scz_swe6_eur

Samples from the Swedish Schizophrenia Study were collected in a multi-year project and genotypes in six batches (sw1-6). Reference [4] is the main report for this study but, in order to further progress in the field, sw1-2 were included in reference [9] and sw1-4 in reference. [34] All procedures were approved by ethical committees at the Karolinska Institutet and the University of North Carolina, and all subjects provided written informed consent (or legal guardian consent and subject assent). All samples were genotyped at the Broad Institute.

Cases with schizophrenia were identified via the Swedish Hospital Discharge Register which captures all public and private inpatient hospitalizations. The register is complete from 1987 and is augmented by psychiatric data from 1973-1986. The register contains International Classification of Disease discharge diagnoses made by attending physicians for each hospitalization. Case inclusion criteria included ≥2 hospitalizations with a discharge diagnosis of schizophrenia, both parents born in Scandinavia and age ≥18 years. Case exclusion criteria included hospital register diagnosis of any medical or psychiatric disorder mitigating a confident diagnosis of schizophrenia as determined by expert review. The validity of this case definition of schizophrenia was strongly supported by clinical, epidemiological, genetic epidemiological and genetic evidence (see the Supplementary Note in reference [4]).

Controls were selected at random from Swedish population registers, with the goal of obtaining an appropriate control group and avoiding 'super-normal' controls. Control inclusion criteria included never being hospitalized for schizophrenia or bipolar disorder (given evidence of genetic overlap with schizophrenia), both parents born in Scandinavia and age of ≥18 years.

Walters, J | 21850710 | Cardiff, UK (CogUK) | scz_cou3_eur

Cases were recruited from community mental health teams in Wales and England on the basis of a clinical diagnosis of schizophrenia or schizoaffective disorder (depressed sub-type) as described previously. [35] Diagnosis was confirmed following a SCAN [36] interview and review of case notes followed by consensus diagnosis according to DSM-IV [37] criteria. The samples were genotyped at the Broad Institute. The UK Multicentre Research Ethics Committee (MREC) approved the study and all participants provided valid informed consent.

Weinberger, D | 11381111 | NIMH CBDB | scz_lie2_eur

Weinberger, D | 11381111 | NIMH CBDB | scz_lie5_eur

Subjects were recruited from the Clinical Brain Disorders Branch of the NIMH 'Sibling Study' as previously described. [38] In brief, cases and controls gave informed consent and only participants of European ancestry were included in the current analysis. Cases completed a structured clinical interview and were diagnosed with schizophrenia-spectrum disorders. Samples were genotyped at the NIMH.

Wendland/Schubert | Pfizer | Not Published | Multiple countries | scz_pfla_eur

Pfizer contributed anonymized individual genotypes for cases from seven multi-center randomized, double-blind efficacy and safety clinical trials (A1281063, A1281134, A1281148, A245-102, NRA7500001, NRA7500002, NRA7500003, and NRA7500004) as well as a set of purchased samples (NRA9000099). Trial samples were collected for antipsychotic medications across outpatient and inpatient treatment settings. All participating cases had a diagnosis of schizophrenia and were assessed using a structural clinical interview by trained interviewers, with systematic procedures to quality-control diagnostic accuracy and reliability trials across participating sites in the United States and internationally. Purchased blood samples were obtained from PrecisionMed International by Pharmacia and Upjohn Corporation, and were collected from diagnosed subjects with schizophrenia and schizoaffective disorder. All studies were reviewed by both central and local institutional review boards, depending on the study site, before recruitment of subjects started. Protocol amendments were approved while the study was in progress and before the data were unblinded. The studies were conducted in conformity with the U.S. Food and Drug Administration Code of Federal Regulations (21CFR, Part 50) and the Declaration of Helsinki and its amendments, and were consistent with Good Clinical Practice and the applicable regulatory requirements. Participants provided written informed consent before enrollment. An optional blood sample was collected from clinical trial subjects for pharmacogenetic analysis to investigate potential associations between genetic variant drug response and general characteristics of schizophrenia and related disorders. Sample collection was not required for participation in the original clinical trials. The controls (A9011027) were recruited in a multi-site, cross-sectional, non-treatment prospective trial to collect data, including DNA, from cognitive normal and free of psychiatric diseases elderly subjects in the US. Subjects were specifically recruited to match the gender, age, and ethnicity information from the LEADe [39] and UCSD MCI [40] studies. The study described here is within the scope of patient consent.

Werge, T | 19571808 | Denmark | scz_denm_eur

Cases were ascertained through psychiatric departments and twin pair studies, and were of Danish parentage for at least the prior three generations. The controls were collected at the University of Aarhus, and included 500 medical students, all of Danish parentage for at least three generations. All subjects gave written informed consent and the Danish Data Protection Agency and the ethics committees of Denmark approved the human subjects protocol.

European ancestry, trio design

Kirov, G: Owen M | 22083728| Bulgaria | ms.scz_butr_eur

Families from Bulgaria were recruited if a proband had schizophrenia or schizoaffective disorder, both parents were available, and all members of the trio agreed to participate in the study. Recruitment took place between 1999 and 2004 in several psychiatric hospitals in Bulgaria. Ethical Committee approval was obtained from each of these hospitals. All probands and all parents received an Information Sheet and signed Informed Consent Forms. All participants had attended mainstream schools, which at the time in Bulgaria, excluded people with mental retardation. Probands were either in- or out-patients at the time of the study but each had a history of hospitalization. A team of psychiatrists was trained in using the rating scales and methods of the study. We used the SCAN instrument to perform an interview for psychotic and mood symptoms. This instrument has been translated into Bulgarian and validated by one of its authors (A. Jablensky). Consensus diagnoses were made according to DSM-IV criteria on the basis of an interview and inspection of hospital notes by two clinicians. If consensus was not attained, the patient was re-interviewed by a research interview trained clinician and was excluded if consensus could still not be reached. In addition, approximately 23% of the sample was selected at random and re-interviewed by a research interview trained clinician. Hospital notes were also collected for affected relatives in order to confirm diagnoses.

Levinson, D | 22885689 | Six countries | ms.scz_lemu_eur

Schizophrenia cases were included from the family sample of European-ancestry pedigrees described by Levinson et al. [20] Participants and their families In this trio study, probands were ascertained and recruited from different clinical settings (e.g. inpatients, outpatients and community facilities) in six countries (Australia, France, Germany, Ireland, UK, and the US). [20] (Unrelated individuals were includes as part of a case-control design, see Levinson, D, scz_lacw_eur above.) Diagnoses were established using semi-structured interviews, psychiatric records and informant reports. Case probands were diagnosed with schizophrenia or schizoaffective disorder according to DSM-III-R criteria. The trio-based analysis included families where there was at least one affected proband and two available parents. Each affected sibling in such families was included, with the parents, as an independent trio. All protocols were approved by loci IRBs, and all cases provided written informed consent.

Kirov, G: Owen, M | Not Published | Bulgaria | ms.scz_uktr_eur

All cases and parents were recruited from UK and had a history of hospitalization for treatment of schizophrenia. Diagnosis was confirmed following a SCAN [36] interview and review of case notes followed by consensus diagnosis according to DSM-IV [37] criteria. The samples were genotyped at the Broad Institute. All participants gave written informed consent and the study was approved by local ethics committees at the participating centers. The samples were genotyped at the Broad Institute.

East Asian ancestry, case-control design

Iwata, N | 20832056 | Japan | scz_jpn1_asn

Case and control participants were recruited from the Tokai area of mainland Japan and self-identified as Japanese. Full details on sample ascertainment and ethical approval have been reported previously. [41]

Liu, J | NP | Singapore (STCRP) | scz_tcr1_asn

The Singapore Translational and Clinical Research in Psychosis (STCRP) Study sample consisted of schizophrenia patients and healthy controls of Chinese ancestry. All patients were recruited from the Institute of Mental Health in Singapore from 2005-2008 and were aged 18-83 years. Diagnosis of schizophrenia was made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Research Version, Patient Edition (SCID-I/P) by trained raters. The controls were from the Singapore Prospective Study Program [11] and were randomly sampled from the Singapore population and approximately matched for age and sex to cases.

Sham, P | 24043878 | China | scz_hok2_asn

The case sample include patients with DSM-IV schizophrenia recruited in Hong Kong and Sichuan China described previously. [42] The control group was a convenience sample gathered from several sources - subjects from a GWAS on bone mineral density, [43] the control subjects from a GWAS on hypertension, [44] and on liver cancer. [45], and healthy control subjects recruited from Sichuan and Taiwan. All cases and controls gave written consent to participate. The was approved by the Institutional Review Boards of the University of Hong Kong and the West China Hospital at Sichuan University. Genotyping was performed at deCODE Genetics.

Replication, European ancestry, case-control design

Stefánsson, K | 19571808 | Iceland (SGENE+, deCODE) | NA

Stefánsson, K | 23164818 | Non-Icelandic (SGENE+, deCODE) | NA

This replication sample had two components. The Icelandic sample consisted of cases and controls who were recruited and diagnosed in Iceland as previously described. [17] Diagnoses were assigned according to Research Diagnostic Criteria (RDC) using the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-L). Controls were recruited as a part of various genetic programs at deCODE and were not screened for psychiatric disorders. The non-Icelandic sample included cases and controls from Italy, Georgia, Macedonia, Russia and Serbia; these individuals were recruited and diagnosed as detailed elsewhere. [17,46] All studies were approved by local ethics committees, and all participants provided written, informed consent. Genotyping was carried out at deCODE Genetics.

Quality Control, Imputation and Association Analysis

Quality control, and imputation were performed by the PGC Statistical Analysis Group for each dataset separately. The quality control parameters for retaining SNPs and subjects were: 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 ($P > 10^{-6}$ in controls or $P > 10^{-10}$ in cases). When datasets comprising of only cases were matched to controls, more rigorous quality control was required.

Genotype imputation was performed using the pre-phasing/imputation stepwise approach implemented in IMPUTE2 / SHAPEIT (chunk size of 3 Mb and default parameters).[47,48] The imputation reference set consisted of 2,186 phased haplotypes from the full 1000 Genomes Project dataset (August 2012, 30,069,288 variants, release "v3.macGT1"). Chromosome X imputation was conducted for subjects passing quality control for the autosomal analysis with the additional exclusions of chrX SNPs with missingness ≥ 0.05 or HWE $p < 10^{-6}$ in females. ChrX imputation was performed separately for males and females.

After imputation, we identified SNPs with very high imputation quality (INFO >0.8) and low missingness (<1%) for further quality control. After linkage disequilibrium pruning ($r^2 > 0.02$) and frequency filtering (MAF > 0.05), there were 19,551 autosomal SNPs across all 49 datasets of European ancestry. This SNP set was used for robust relatedness testing and population structure analysis. Relatedness testing was done with PLINK [49] and pairs of subjects with $\hat{\pi} > 0.2$ were identified and one member of each pair removed at random after preferentially retaining cases over controls and trio members over case-control members. Principal component estimation was done with the same collection of autosomal SNPs. We tested the first 20 principal components for phenotype association (using logistic regression with study indicator variables included as covariates) and evaluated their impact on the genome-wide test statistics using λ [50] . Ten principal components were included in all association analyses. The three datasets with East Asian ancestry underwent the same quality control procedures with 40,994 linkage disequilibrium pruned SNPs across the three datasets and inclusion of four principal components.

We tested all 52 GWAS datasets separately for association under an additive logistic regression model using PLINK and the derived principal components as covariates[51], and then conducted a meta-analysis of the 52 sets of results using an inverse-weighted fixed effects model.[52] For chrX, gene dosages in males were scored 0 or 2 to account for hemizygosity (dosages in females were scored 0/1/2 as for autosomal markers in both genders).

Many GWAS findings implicate an extended region containing multiple significant SNPs. These are not independent associations but arise because of high LD between associated SNPs. To summarize these associations in terms of the index SNP with the highest association and other SNPs in high linkage disequilibrium with the index SNP, we used the following settings in PLINK:

--clump-p1 1e-4 --clump-p2 1e-4 --clump-r2 0.1 --clump-kb 3000

to retain SNPs with association $P < 0.0001$ and $r^2 < 0.1$ within 3 Mb windows. Due to the strong signal and high linkage disequilibrium in the MHC, only one SNP was kept from the extended MHC region.

We obtained summary association results for SNPs surpassing $P < 1x10^{-6}$ in the discovery meta-analysis from deCODE who provided a small number of individual genotypes for the Eastern Europeans, sufficient to exclude overlapping samples (N=3).

We used sign tests to compare the overall patterns of results between the replication and discovery datasets. We used the clumping settings above to derive a filtered set of SNPs. We then determined the number of SNPs whose logistic regression beta coefficient signs were the same between two independent samples. The significance of the observed proportion from chance (50%) was evaluated using the binomial distribution.

LD Score Regression

The relationship between marker χ^2 association statistics and linkage disequilibrium (LD) as measured by the LD Score. LD Score is the sum of the r^2 values (1000 Genomes Project, European subjects) 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 LD Score rank (plotted in these graphs on an x-axis representing the mean LD Score of the SNPs in each bin). Mean χ^2 denotes the mean test statistic for the markers in each bin. We simulated test statistics under two scenarios: (a) no true association, inflation due to population stratification (λ_{GC}=1.33). For these simulations, we obtained genotypes from two PGC control cohorts from different countries in Europe. To simulate stratified phenotypes, we labeled one cohort as cases and the other cohort as controls, then randomly flipped 30% of case/control labels; and (b) polygenic inheritance (λ_{GC} =1.32), in which we assigned independent and identically distributed per-normalized-genotype effects to a randomly selected subset of variants. Panel (c) present results from the PGC schizophrenia GWAS (λ_{GC} =1.48). Note that this is slightly different from the λ_{GC} in Extended data Figure 1 (1.469) due to a slight difference in the SNPs used to compute the value in the regression. The real data are strikingly similar to the simulated data summarized in (b) but not (a). Our simulations therefore suggest the test statistic inflation in our GWAS essentially reflects polygenic inheritance, not unadjusted population stratification or cryptic relatedness. Precisely, if we regress χ^2–statistics from GWAS against LD Score, the intercept from this regression 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 (compared to a mean χ^2 of 1.613) suggests that ~90% of the observed inflation in the mean χ^2 results from polygenic signal rather than bias.

The results of the simulations are also consistent with theoretical expectations. If test statistic inflation arises as a result of population stratification as in (a), χ^2 –statistics should be uncorrelated with LD Score. This is because the main driver for population stratification, genetic drift, produces allele frequency differences between populations that are independent of LD. In contrast, if inflation is the result of polygenic inheritance, χ^2-statistics should be linearly proportional to LD Score (assuming independent and identically distributed per-normalized-genotype effects), because variants with higher LD Scores have a higher probability of being in LD with a risk-conferring variant, and variants in LD with risk-conferring variants tend to have elevated test statistics.

Estimating the number of true associations behind the trios sign test.

In our analysis of 1,235 parent-proband trios, we found excess transmission of the schizophrenia-associated allele at 69% of 263 LD-independent SNPs with P <1x10^{-6} in the case-control analysis (N.B. these alleles surpassed this threshold before we added either the trios data or the independent data from deCODE to the meta-analysis). This trend test is therefore independent of the results from the primary case-control GWAS). We next estimated the expected proportion of true associations at P <1x10^{-6} in the discovery GWAS required to produce this degree of over-transmission, allowing for the fact that half of the index SNPs are expected to show the same allelic trend in the trios by chance, that some true associations will show opposite trends given the limited number of trio samples, and that the power to show over-transmission is less than would be expected based on the observed odds ratios in the GWAS because of the well known inflation in effect sizes that is expected in an underpowered discovery sample. To estimate the true odds-ratio, we took the genome-wide significant sites in the scan and calculated the average reduction in OR between the scan and the case-control deCODE replication data and applied this as a correction factor to the ORs in the scan. We then calculated the exact probability that a positive trend would be observed in 1235 trios for each locus according to its OR and frequency, and summed these probabilities across all SNPs to determine the expected number of positive trend results across the 263 scan results with scan P <1x10^{-6}. To make the calculation more accurate, the number of trios was modified in each case by the relative information content of the SNP in the trio set/information content of the SNP in the scan. Confidence intervals were calculated using binomial distributions.

Defining Credible Sets of SNPs

From each schizophrenia-associated region (Supplementary Table 3), we identified sets of SNPs that were 99% likely to contain the causal variants.

Denote the case-control data as D (including the variant genotype X and the disease status Y), the model parameters as θ, and whether a variant is associated as M. A variant is associated with schizophrenia if $M = 1$, and $M = 0$ indicates a variant is not associated. Using Bayes' rule, the probability that a variant is associated on the observed data is:

$$\begin{aligned}\Pr(M \mid D) &= \int_{\theta} \Pr(M, \theta \mid D) \\ &= \int_{\theta} \frac{\Pr(M, \theta, D)}{\Pr(D)} \\ &= \int_{\theta} \Pr(D, \theta \mid M) \frac{\Pr(M)}{\Pr(D)}.\end{aligned} \quad (1)$$

Equation (1) can be estimated using the steepest decent approach [53] if the likelihood function only has one global maximum and decays rapidly to zero away from the maximum. All likelihood functions in the exponential family (including the linear, binomial, or multinomial models) meet these criteria. If we assume a flat prior on the model parameter, the integral over the model parameters can be approximated using the maximum likelihood estimator

$$\Pr(M \mid D) \approx \Pr(D \mid M, \hat{\theta}) N^{-|\theta|/2} \frac{\Pr(M)}{\Pr(D)}, \quad (2)$$

in which N is the sample size and $|\theta|$ is the number of parameters. In the linear model, the test statistic, χ^2, is the deviance of the model

$$\chi^2 = -\frac{1}{2}\log\frac{\Pr(D \mid M=0)}{\Pr(D \mid M=1,\hat{\theta})}. \quad (3)$$

The model probability in Equation (2) can then be calculated as a function of the χ^2

$$\Pr(M=1 \mid D) \approx \exp[2\chi^2] \times l_0 \times N^{-|\theta|/2} \times \frac{\Pr(M)}{\Pr(D)}, \quad (4)$$

in which $l_0 = \Pr(D \mid M=0)$. If we assume a flat prior across all variants, the term $l_0 \times N^{-|\theta|/2} \times \Pr(M)/\Pr(D)$ is a constant and the probability for the variant v to be associated with the trait can be calculated as

$$\Pr(M=1 \mid D) \propto P'(v) = \exp[2\chi_v^2] \quad (5)$$

This probability can be normalized across all variants

$$P(v) = P'(v) / \sum_u P'(u). \quad (6)$$

We then define the 99% credible set of variants in as in references [54,55], which is a minimal set of variants, $\mathbf{S} = \{v\}$, such that

$$\sum_{v \in s} \mathrm{P}(v) \geq 99\%. \quad (7)$$

Under the assumptions of a true association (likely true in genome-wide significant regions) and that all possible causal variants have been genotyped (likely true as well for 1000 Genomes Project imputed data), this 99% credible set of variants gives a set that 99% of the time contains the causal variant.

Expression Quantitative Trait Analysis

Ref (GEO ID)	Brain Region	N	Probes	Genotype	SNPs	Case / Control
Myers [56] (GSE8919)	Cortex[a]	193	24,357	Affy 500k	502,627	Controls
Gibbs [57] (GSE15745)	FTCX, TCTX	150	22,184	HapMap550	561,466	Controls
Colantuoni [58] (GSE30272)	DLPFC	112	49,152	HumanHap650	654,330	Controls
Webster [59] (GSE15222)	Cortex[a]	363	24,357	Affy 500k	502,627	AD Cases

Brain eQTL analysis: Brain expression and SNP data were obtained from GEO (http://www.ncbi.nlm.nih.gov/geo/) for datasets based on subjects of European ancestry as above. Brain eQTL data were generated using the covariates reported by each reporting group (these differed between samples, including age, sex, post-mortem interval, brain banks, tissue source, preparation and hybridization batches). In addition we included the first four SNP MDS components to adjust for population stratification. After applying consistent quality control to the genetic and expression data, 550 subjects were used for eQTL association analyses. Imputation was performed as described for the main PGC analysis. Each transcript was evaluated for SNP associations within each study, and then eQTL SNP-transcript associations were mapped to genes and the gene-level association test statistics combined across the studies by meta-analysis. We defined local eQTL SNPs as those within 1 Mb of each transcript. This resulted in

the assessment of 212,709,488 SNP-transcript pairs. FTCX= cortex from frontal lobe, TCTX = cortex from temporal lobe. DLPFC = dorsolateral prefrontal cortex. AD = Alzheimers disease.

We used the "godot" eQTL data from the Netherlands Twin Register and the Netherlands Study of Depression and Anxiety (N=3754 subjects)[60]. This large study is based on RNA extracted from peripheral blood, sampled in the morning after an overnight fast. Genotyping was conducted using Affymetrix 6.0 arrays and gene expression with Affymetrix U219 arrays. Details of extensive quality control and analytic approach are described elsewhere[60]. SNP genotype data were imputed as for the primary GWAS of schizophrenia. We considered SNPs as potential *cis*-eQTLs if they mapped within 1 Mb of a transcript.

Enhancer enrichment analysis

To further characterize the apparent regulatory nature of the schizophrenia associations, we investigated their relationships with cell type specific epigenetic markers of gene regulation. Markers of gene regulation were defined using ChIP-seq datasets produced at the Broad Institute and the University of California at San Diego as part of ENCODE [61] and the NIH Roadmap Epigenome projects (http://www.roadmapepigenomics.org). Based on the histone H3K27ac signal, which identifies active enhancers, [62] we used data from 56 cell line and tissue samples to identify cell-type/tissue specific enhancers which we define as the 10% of enhancers with the highest ratio of reads in that cell/tissue type divided by the total reads. Raw data for these cell/tissue types can be downloaded at http://www.epigenomeatlas.org and further description and implementation of the fine-mapping/enrichment analyses available at http://www.broadinstitute.org/pubs/finemapping/.

We mapped the credible sets of causal variants (see above) at each schizophrenia-associated locus to these enhancer sequences, and compared the overlap observed with tissue specific enhancers relative to all enhancers with that using a background of equal sized sets of 1000 Genomes Project SNPs matched in frequency to those in the schizophrenia study.

The results demonstrate that the set of likely causal candidate SNPs from the schizophrenia genome-wide significant regions highly significantly overlap with enhancer elements active in brain tissue (Figure 2). In addition, there was also significant overlap with enhancers active in immune tissues and cell lines (Figure 2). These persisted after excluding associations mapping to brain enhancers or to the extended MHC locus. These results suggest that the noncoding causal variants in schizophrenia produce their effects by affecting the function of tissue-specific enhancers in brain, as well as immunological tissues.

One limitation of our use of brain tissue in the analyses above is that they contain a mixture of heterogeneous cell types. To try to determine whether the associations are relatively selective for particular cell types, thereby implicating specific brain cell lineages in pathogenesis, we identified the nearest genes (as determined by nearest transcriptional start site) to the most associated SNP at each schizophrenia-associated locus and to equal sized sets of 1000 genomes SNPs, and examined the expression of these genes in purified brain cell subsets obtained from mouse ribotagged lines. [63] These results show that several neuronal but not glial lineages, are enriched for genes adjacent to schizophrenia GWAS hits, (Extended Data Figure 4). These results suggest that neurons are most strongly implicated in schizophrenia, though does not exclude a role for the involvement of other brain cell types.

Other Pathway Analyses

ALIGATOR [64] was performed as described with the modification that genes within 1 Mb of each other that also map to the same pathway only contribute a single hit to that pathway. INRICH was performed as described. [65] For both methods, gene boundaries included 50kb of 5' and 3'

flanking sequence. Minimum and maximum size filters of 10-200 genes were applied to GO because of its large size relative to the other pathway databases and 10-1000 genes to the other pathway collections, giving a total of 9016 pathways (5321 GO, 268 KEGG, 140 PANTHER, 947 Reactome, 214 BioCarta, 1938 MGI and 188 NCI). SNPs were assigned to genes using a 50kb window, and a best-SNP p-value criterion of p<5x10-8 was used to define significant genes for the analyses. The MHC region (chr6: 25-35 Mb) was removed. Both methods were applied to the following gene-sets:

- Gene Ontology (GO), http://www.geneontology.org, downloaded 26/7/2013
- Kyoto Encyclopaedia of Genes and Genomes (KEGG), http://www.genome.jp/kegg, downloaded 4/6/2013
- PANTHER, http://www.pantherdb.org/pathway, accessed on 25/3/2011
- Reactome, http://www.reactome.org/download, downloaded 27/7/2013
- BioCarta, downloaded from the Molecular Signatures Database v4.0 (MsigDB), http://www.broadinstitute.org/gsea/msigdb/index.jsp, accessed on 27/7/2013
- Mouse Genome Informatics (MGI) database, http://www.informatics.jax.org, accessed on 9/8/2013
- NCI pathways, http://pid.nci.nih.gov, accessed on 27/7/2013 from ftp://ftp1.nci.nih.gov/pub/PID.

Risk Profile Scoring (RPS)

To investigate the impact on polygenic RPS prediction of a much larger GWAS than in any other publication, we performed a series of leave-one-out analyses. We first defined 40 target subgroups of the 52 source datasets most of which consisted of only one dataset; although some datasets were combined, each source dataset appeared in at least one subgroup. For details about composition of these entities refer to Supplementary Table 6.

For each of the 40 target subgroups, we performed a meta-analysis of the remaining samples. In order to get a highly informative SNP set with as little statistical noise as possible, we excluded uncommon SNPs (MAF < 10%), low-quality variants (imputation INFO < 0.9), indels, and SNPs in the extended MHC region (chr6:25-34 Mb). We then LD pruned and "clumped" the data, discarding variants within 500 kb of, and in $r^2 \geq 0.1$ with, another (more significant) marker. We performed RPS of our target subgroups as originally described [9] for a range of *P* value thresholds ($5x10^{-8}$, $1x10^{-6}$, $1x10^{-4}$, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1.0), multiplying the logistic regression β (i.e., the natural log of the odds ratio) of each variant by the imputation probability for the risk allele in each individual. The resulting values were summed over each individual, so that each individual had a whole genome RPS for further analysis.

For each leave-one-out experiment five outcome variables calculated from RPS are reported (Supplementary Tables 6, 7, Extended Data Figures 5 and 6) 1) The significance of the case-control score difference was analyzed by standard logistic regression including ancestry based PCs and a study indicator (if more than one target dataset was analyzed) as covariates; and 2) The proportion of variance explained (Nagelkerke's R^2) computed by comparison of a full model (covariates + RPS) score to a reduced model (covariates only). It should be noted that these estimates of R^2 are biased due to recruitment of the case-control studies where the numbers of cases and controls do not reflect the underlying risk of n the population. 3) The proportion of variance on the liability scale explained by RPS. An R^2 was calculated from the difference between full and reduced linear models and was then converted to the liability scale[66] of the population assuming lifetime disease risk of 1%. 4) Area under the receiver operator characteristic curve (R library pROC) in a model with no covariates justified by simulation. 5)

Odds ratio for 10th RPS decile group. Detailed results for all P value thresholds are reported in Supplementary Table 6.

Detailed results for Outcomes 1 - 5 for the MGS polygene analysis (see main text and extended Figure 5A) are reported in Supplementary Table 7.

All leave-one-out analyses yielded effect predictions in the predicted direction (i.e., mean scores in cases greater than in controls) and generated at least one significant result at one of the *P* value thresholds examined after correcting for ten tests. For the larger case-control datasets, significance values as low as $1x10^{-300}$ were observed. The estimate of variance in liability meta-analyzed across leave-one-out experiments was 7.0% (standard error 0.4%), hence a correlation of liability and RPS of 0.26. A formal test of heterogeneity given the estimates and their standard errors was highly significant (Q–statistic 268, 39 df), but reflects in part the different discovery samples as well as heterogeneity between the target samples.

Supplementary Discussion

Selected genes within newly implicated genome-wide significant loci.

Genes within associated loci are highlighted here where we identify them to be of particular interest with respect to current hypotheses of schizophrenia aetiology or treatment. However, we stress that association only implies the existence of one or more risk variant at the associated locus rather than that a specific gene is responsible for the association.

Therapeutic targets (G protein coupled receptor signalling):

***DRD2* (11q23.2).** Dopaminergic neurotransmission is integral to cognition, reward, motivation, learning and memory. The dopamine type 2 receptor subtype is of particular interest in psychiatry because blockade remains a necessary and sufficient condition for antipsychotic activity, despite attempts to develop alternatives.

***GRM3* (7q21.12).** mGluR3 is a metabotropic glutamate receptors predominantly expressed in astrocytes which, along with *GRM2* (mGluR2), has been extensively explored as potential therapeutic target in schizophrenia.

Glutamatergic neurotransmission:

***GRIN2A* (16p13.2).** The NMDA receptor subunit *GRIN2A* (NR2A) is a key mediator of synaptic plasticity. NMDA receptor channel blockers such as ketamine and NMDA autoantibodies mimic some of the symptomatology of schizophrenia in humans. Mutations have been reported in focal epilepsies, ID, autism, and schizophrenia.

***GRIA1* (5q33.2).** Glutamate receptor 1 (GluR1, GluA1) is a subunit of an AMPA (non-NMDA) receptor that mediates fast synaptic transmission. It is involved in activity-dependent synaptic targeting of AMPARs and is critical for dendritic organization of receptors and hippocampal synaptic transmission and plasticity.

***SRR* (17p13.3).** Serine racemase catalyzes L-serine racemization to D-serine, an essential co-agonist and activator of NMDA receptors. Altered D-serine levels have been associated with schizophrenia.

***CLCN3* (4q33).** CLC-3 is a voltage-gated chloride channel localized to glutamatergic synapses in the hippocampus, where it modulates plasticity. Knockout mice also have altered GABAergic function and complete postnatal degeneration of the hippocampus, suggestive of a causal relationship to network connectivity.

Other glutamate relevant genes include ***GRM3*** (see above) and ***SLC38A7*** **(16q21)** encoding SNAT7, an L-glutamine preferring neuronal amino acid transporter that may be important for the reuptake and recycling of glutamate.

Neuronal calcium signalling:

CACNA1I **(22q13.1).** *CACNA1I* is the pore forming alpha subunit of the $Ca_v3.3$ T-type calcium channel. Activation triggers synaptic plasticity and long-term potentiation when co-activated with NR2B-containing NMDA receptors. Several antipsychotics block T-type channels, although efficacy through this blockade has not been demonstrated.

RIMS1 **(6q12-13).** RIMs are multi-domain proteins that tether calcium channels to synaptic active zones, dock and prime synaptic vesicles for release, mediate presynaptic plasticity and facilitate neurotransmitter release.

Prior and other implicated calcium signalling genes include: ***CACNA1C, CACNB2, CAMKK2, NRGN, ATP2A2***. Mutations in *ATP2A2* cause Darier's Disease and co-segregate in some families with bipolar disorder and psychosis.

Synaptic function and plasticity:

KCTD13 **(16p11.2).** Polymerase Delta-Interacting Protein 1 is a substrate-specific adapter of a BCR (BTB-CUL3-RBX1) E3 ubiquitin-protein ligase complex involved in regulation of cytoskeleton structure. It lies within a pathogenic CNV at 16p11.2 associated with neurodevelopmental disorders and brain and body size phenotypes. Zebrafish and mouse studies have implicated the ortholog of KCTD13 as the dosage-sensitive driver gene in this CNV. A previous GWAS study of schizophrenia and bipolar disorder previously implicated this locus.

NLGN4X **(Xp21.33-32).** Neuroligins induce localized formation of functional neurotransmitter release sites in axons, by aggregating neurexins and inducing formation of glutamatergic and GABAergic presynapses. Nlgn4 is present at both excitatory and inhibitory postsynapses, and may modulate the pre-synaptic calcium channel population through its interaction with neurexins. Mutations are associated with autism.

IGSF9B **(11q25).** IgSF9b is a brain-specific adhesion molecule that is strongly expressed in GABAergic interneurons, localized to hippocampal and cortical inhibitory synapses where it is required for their development into interneurons.

CNTN4 **(3p26.3).** Contactins are axon-associated cell adhesion molecules that function in neuronal network formation and plasticity. *CNTN4* is highly expressed in the brain, and deletions and mutations have been associated with ASDs.

MEF2C **(5q14.3).** A transcription factor regulating neurogenesis, excitatory synapse number, dendrite morphogenesis and differentiation of post-synaptic structures. Late embryonic forebrain deletion causes dramatic increase in excitatory synapse number and impairment of hippocampus-dependent learning and memory. Earlier deletion results in abnormal neuronal migration into the neocortex. *MEF2C* haploinsufficiency causes severe intellectual disability.

PTN **(7q33).** Pleiotrophin is a developmentally regulated neurite growth-promoting factor (NEGF) family cytokine/growth factor. It is expressed in an activity-dependent manner in the hippocampus where suppresses long term potentiation.

CNKSR2 **(Xp22.12).** CNK2 is a scaffold/adaptor protein that mediates the MAPK pathway downstream from Ras. Expression is restricted to neuronal tissues where it localizes to dendritic spines and forms a complex with the PSD. It plays a role in assembly of synaptic complexes at the postsynaptic membrane and coupling of signal transduction to membrane/cytoskeletal

remodelling. Loss of function CNKSR2 mutations are a cause of non-syndromic X-Linked intellectual disability.

***PAK6* (15q14).** PAK6 is a highly brain expressed serine/threonine protein kinase associated with neurite outgrowth, filipodia formation and cell survival. PAK6 shows functional redundancy with PAK7 and double knockout mice have specific deficits in learning and memory. A rare inherited duplication at PAK7 has been associated with increased risk of schizophrenia and bipolar disorder.

***SNAP91* (6q14.2).** *SNAP91* (AP180) is enriched in the presynaptic terminal of mammalian neurons where it regulates synaptic vesicle endocytosis through a clathrin-dependent reassembly process. Together with *CALM* it establishes the polarity and controls the growth of axons and dendrites in embryonic hippocampal neurons.

Other neuronal ion channels:

***KCNB1* (20q13.13).** Kv2.1 is a delayed rectifier VGKC in the drosophila shab-related subfamily. It is abundantly expressed in the cortex and hippocampus, where it regulates neuronal excitability, action potential duration, and tonic spiking.

***HCN1* (5p21).** *HCN1* is a potassium channel pore forming subunit and a major contributor to the inward hyperpolarization-activated cation current *(I_h)* current in the brain, which regulates neuronal excitability, rhythmic activity and synaptic plasticity. *HCN1* is widely expressed in brain and is enriched in distal apical dendrites. It is also a pacemaker in cardiac tissue.

***CHRNA3*, *CHRNA5*, and *CHRNB4* (15q25.1).** Nicotinic acetylcholine receptors (nAChRs) form ligand-gated ion channels in certain neurons and also on the presynaptic and postsynaptic sides of the neuromuscular junction. This cluster of nAChR genes has previously been reproducibly associated with nicotine dependence, smoking behaviours, and lung cancer risk.

Neurodevelopment:

***FXR1* (3q26.33).** FXR1P is a member of the family of RNA binding proteins that includes FMRP, mutations in which cause Fragile X syndrome. FXR1P is found in dendritic spines in the mouse hippocampus and targets mRNAs and microRNAs including brain specific miRNA9 and miR-24.

***SATB2* (2q33.1).** A DNA binding protein that binds nuclear matrix attachment regions, regulating transcription and chromatin remodeling. Expression is restricted to post-mitotic, differentiating neurons in the neocortex, where it acts as a determinant for upper-layer projection neuron identity during cortical development. *SATB2* deletion causes 2q32-q33 deletion syndrome and duplication manifests with ASD.

Additional molecules involved in neurodevelopment include: ***PODXL, BCL11B, TLE1, TLE3, FAM5B***

Supplementary Tables

Supplementary Table 1: Description of samples

Note	PI	PMID	Site	QC score	Array	Cases	Controls	Male	Tag
New CC	Adolfsson, R	NP	Umeå, Sweden	9	omni	341	577	0.503	scz_umeb_eur
New CC	Adolfsson, R	NP	Umeå, Sweden	9	omni	193	704	0.475	scz_umes_eur
PGC1+new	Andreassen, O	19571808	Norway (TOP)	9	A6.0	377	403	0.533	scz_top8_eur
PGC1	Blackwood, D	19571811	Edinburgh, UK	8	A6.0	367	284	0.633	scz_edin_eur
New CC	Børglum, A	19571808	Denmark	3	I650	876	871	0.545	scz_aarh_eur
New CC	Bramon	23871474	Seven countries (PEIC, WTCCC2)	6	I1M	574	1812	0.557	scz_pewb_eur
New CC	Bramon	23871474	Spain (PEIC, WTCCC2)	6	I1M	150	236	0.585	scz_pews_eur
New CC	Buxbaum, J	20489179	New York, US & Israel	7	A6.0	325	139	0.614	scz_msaf_eur
PGC1	Corvin, A	19571811	Ireland	9	A6.0	264	839	0.394	scz_dubl_eur
New CC	Corvin, A; Riley, B	22883433	Ireland (WTCCC2)	9	A6.0	1291	1006	0.617	scz_irwt_eur
New CC	Ehrenreich, H	20819981	Germany (GRAS)	9	AXI	1067	1169	0.642	scz_gras
New CC	Esko, T	15133739	Estonia (EGCUT)	2	omni	234	1152	0.268	scz_egcu_eur
New CC	Domenici E Esko, T; Li, Q	15133739, 4166486	J&J, Roche cases, EGCUT controls	2	I317	347	310	0.579	scz_jr3a_eur
New CC	Domenici E Esko, T; Li, Q	15133739,24166486	J&J, Roche cases, EGCUT controls	2	I317	636	636	0.621	scz_jr3b_eur
New CC	Domenici E Esko, T; Li, Q	15133739,24166486	J&J, Roche cases, EGCUT controls	2	I610	256	130	0.461	scz_jri6_eur
New CC	Domenici E Esko, T; Li, Q	15133739,24166486	J&J, Roche cases, EGCUT controls	2	I1M	1154	2310	0.505	scz_jrsa_eur
PGC1	Gejman, P	19571809	US, Australia (MGS)	9	A6.0	2638	2482	0.588	scz_mgs2_eur
PGC1	Gurling, H	19571811	London, UK	8	A6.0	509	485	0.572	scz_uclo_eur
New CC	Jönsson, E	19571808	Sweden (Hubin)	3	omni	265	319	0.618	scz_ersw_eur
New CC	Kirov, G	NP	Bulgaria	8	A6.0	195	608	0.474	scz_buls_eur
New CC	Knight, J/Collier D/ Nisenbaum L	NP	Canada (Toronto) -US(Lilly)-US (MIGen)	5	A6.0	526	1644	0.593	scz_lktu_eur
New CC	Lencz, T/Darvasi A	24253340	Israel	8	I1M	894	1594	0.701	scz_ajsz_eur
New CC	Levinson, D	22885689	Six countries, WTCCC controls	4	I550	157	245	0.918	scz_lacw_eur
PGC1	Malhotra, A	17522711	New York, US	8	A500	190	190	0.577	scz_zhh1_eur
PGC1	Mowry, B	21034186	Australia	9	I650	456	287	0.601	scz_asrb_eur
PGC1	O'Donovan M/Owen M	19571811	Cardiff, UK	9	A500	396	284	0.589	scz_caws_eur
New CC	O'Donovan M/Owen M/Walters J	22614287	UK (CLOZUK)	0	I1M	3426	4085	0.880	scz_clm2_eur
New CC	O'Donovan M/Owen M/Walters J	22614287	UK (CLOZUK)	0	omni	2105	1975	0.629	scz_clo3_eur
PGC1	Ophoff, R	19571808	Netherlands	7	I550	700	607	0.628	scz_ucla_eur
PGC1	Palotie, A	19571808	Finland	9	I317	186	929	0.514	scz_fi3m_eur
New CC	Palotie, A	NP	Finnish	9	I550	360	1082	0.463	scz_fii6_eur
PGC1	Pato, C	19571811	Portugal	9	A6.0	346	215	0.521	scz_port_eur
New CC	Petryshen, T	24424392	Boston, US (CIDAR)	9	omni	67	65	0.757	scz_cims_eur
New CC	Wendland J/ Schubert CR	NP	Pfizer	0	I550	662	1172	0.539	scz_pfla_eur
PGC1+new CC	Rietschel/Rujescu/Nöthen	19571808	Bonn/Mannheim, Germany	9	ILMN*	1773	2161	0.490	scz_boco_eur
PGC1	Rujescu, D	19571808	Munich, Germany	8	I317	421	312	0.569	scz_munc_eur
PGC1	St Clair, D	19571811	Aberdeen, UK	9	A6.0	719	697	0.693	scz_aber_eur
PGC1	Sullivan, PF	18347602	US (CATIE)	7	A500	397	203	0.767	scz_cati_eur

PGC1	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw1)	3	A5.0	215	210	0.527	scz_swe1_eur
PGC1/New CC	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw234)	3	A6.0	1980	2274		scz_s234_eur
New CC	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw5)	3	omni	1764	2581	0.553	scz_swe5_eur
New CC	Sullivan, PF/Sklar P/Hultman C	23974872	Sweden (sw6)	3	omni	975	1145	0.543	scz_swe6_eur
New CC	Walters, J	21850710	Cardiff, UK (CogUK)	9	omni	530	678	0.554	scz_cou3_eur
New CC	Weinberger, D	11381111	NIMH CBDB	5	O25	133	269	0.547	scz_lie2_eur
New CC	Weinberger, D	11381111	NIMH CBDB	5	I550	497	389	0.627	scz_lie5_eur
PGC1	Werge, T	19571808	Denmark	8	I650	471	456	0.583	scz_denm_eur
Total EUR CC						**32,405**	**42,221**		
Trios	Kirov, G/Owen M	22083728	Bulgaria	8	A6.0	649	649	0.502	ms.scz_butr_eur
Trios	Levinson, D	22885689	Six countries	4	I650	516	516	0.556	ms.scz_lemu_eur
Trios	Kirov, G/Owen M	NP	Bulgaria	8	omni	70	70	0.595	ms.scz_uktr_eur
Total Trios						**1,235**	**1,235**		
East Asia	Iwata, N	20832056	Japan	3	A5.0	492	427	0.507	scz_jpn1_asn
East Asia	Liu, J	NP	Singapore (STCRP)	8	I1M	868	938		scz_tcr1_asn
East Asia	Sham, P	24043878	China	6	I550	476	2018	0.398	scz_hok2_asn
Total Asia CC						**1,836**	**3,383**		
Total Discovery						**35,476**	**46,839**		
Replication	Stefánsson, H	19571808	Iceland (SGENE+, deCODE)		ILMN*	628	65,312		N/A
Replication	Stefánsson, H	23164818	Non-Icelandic (SGENE+, deCODE)		ILMN*	885	924		N/A

Abbreviations. PGC1= sample in the discovery phase of the prior PGC schizophrenia mega-analysis[1]. New CC means case-control samples not part of a discovery portion of a prior PGC mega-analysis. PMID = PubMed identifier for the initial report for this study. NP = not published. QC score = based on 9-item questionnaire evaluating assessment protocol and diagnostic QC procedures (see Supplementary Methods on Case Definitions). The Tag column refers to the identifier for this sample in the PGC databases. SNP array in primary GWAS: Affymetrix 5.0 (A5.0) 2 studies, Affymetrix 500K (A500) 3 studies, Affymetrix 6.0 (A6.0) 13 studies, Affymetrix Axiom (AXI) 1 study, Illumina 1M (I1M) 5 studies, Illumina 317K (I317) 4 studies, Illumina 550K (I550) 7 studies, Illumina 610K (I610) 1 study, Illumina 650K (I650) 4 studies, Illumina omni 2.5M (O25) 1 study, and Illumina OmniExpress (omni) 11 studies. ILMN* means multiple different Illumina arrays. For trios, we consider both parents as a single control.

Supplementary Table 2: 128 genome-wide significant associations for schizophrenia

Rank	Index SNP	A12	Frq_{case}	$Frq_{control}$	Chr	Position	Combined		Discovery		Replication	
							OR (95% CI)	P	OR	P	OR	P
54	rs4648845	TC	0.533	0.527	1	2,372,401-2,402,501	1.072 (1.049-1.097)	8.7e-10	1.071	4.03e-9	1.088	8.85e-2
57	chr1_8424984_D	I2D	0.319	0.301	1	8,411,184-8,638,984	1.071 (1.048-1.095)	1.17e-9	1.071	2.03e-9	1.057	2.96e-1
65	rs1498232	TC	0.311	0.296	1	30,412,551-30,437,271	1.069 (1.046-1.093)	2.86e-9	1.072	1.28e-9	0.999	9.88e-1
50	rs11210892	AG	0.659	0.677	1	44,029,384-44,128,084	0.934 (0.914-0.954)	3.39e-10	0.933	4.97e-10	0.949	3.08e-1
22	rs12129573	AC	0.377	0.358	1	73,766,426-73,991,366	1.078 (1.056-1.101)	2.03e-12	1.072	2.35e-10	1.217	6.25e-5
107	rs76869799	CG	0.959	0.964	1	97,792,625-97,834,525	0.846 (0.798-0.897)	2.64e-8	0.850	1.44e-7	0.779	5.34e-2
2	rs1702294	TC	0.175	0.191	1	98,374,984-98,559,084	0.887 (0.865-0.911)	3.36e-19	0.891	2.79e-17	0.831	1.35e-3
52	rs140505938	TC	0.151	0.164	1	149,998,890-150,242,490	0.914 (0.888-0.940)	4.49e-10	0.913	9.34e-10	0.928	2.53e-1
120	rs6670165	TC	0.196	0.184	1	177,247,821-177,300,821	1.075 (1.047-1.103)	4.45e-8	1.074	1.16e-7	1.090	1.46e-1
121	rs7523273	AG	0.695	0.685	1	207,912,183-208,024,083	1.063 (1.040-1.087)	4.47e-8	1.062	1.61e-7	1.092	8.85e-2
101	rs10803138	AG	0.232	0.238	1	243,503,719-243,612,019	0.933 (0.911-0.956)	2.03e-8	0.932	1.79e-8	0.968	5.56e-1
68	rs77149735	AG	0.0225	0.0191	1	243,555,105-243,555,105	1.317 (1.202-1.444)	3.73e-9	1.329	4.4e-9	1.173	3.66e-1
119	rs14403	TC	0.207	0.222	1	243,639,893-243,664,923	0.934 (0.911-0.957)	4.42e-8	0.935	1.31e-7	0.920	1.53e-1
78	chr1_243881945_I	I2D	0.638	0.619	1	243,690,945-244,002,945	1.068 (1.045-1.092)	6.53e-9	1.066	3.11e-8	1.107	6.17e-2
30	rs11682175	TC	0.52	0.542	2	57,943,593-58,065,893	0.933 (0.914-0.952)	1.47e-11	0.928	2.54e-12	1.018	7.08e-1
117	rs75575209	AT	0.904	0.913	2	58,025,192-58,502,192	0.902 (0.869-0.936)	3.95e-8	0.896	1.01e-8	1.056	5.6e-1
80	rs3768644	AG	0.0967	0.101	2	72,357,335-72,368,185	0.904 (0.874-0.935)	7.39e-9	0.910	1.3e-7	0.765	2.15e-3
62	chr2_146436222_I	I2D	0.176	0.163	2	146,416,922-146,441,832	1.086 (1.057-1.116)	1.81e-9	1.084	1.07e-8	1.128	5.72e-2
95	chr2_149429178_D	I2D	0.955	0.961	2	149,390,778-149,520,178	0.857 (0.813-0.904)	1.59e-8	0.856	2.62e-8	0.880	2.97e-1
124	rs2909457	AG	0.568	0.593	2	162,798,555-162,910,255	0.944 (0.925-0.964)	4.62e-8	0.943	4.38e-8	0.971	5.36e-1
18	rs11693094	TC	0.44	0.458	2	185,601,420-185,785,420	0.929 (0.910-0.948)	1.53e-12	0.929	7.13e-12	0.918	7.64e-2
83	rs59979824	AC	0.322	0.337	2	193,848,340-194,028,340	0.937 (0.916-0.958)	8.41e-9	0.936	1.08e-8	0.959	4.32e-1
33	rs6434928	AG	0.635	0.643	2	198,148,577-198,835,577	0.929 (0.909-0.949)	2.06e-11	0.927	1.48e-11	0.969	5.36e-1
82	rs6704641	AG	0.819	0.805	2	200,161,422-200,309,252	1.081 (1.053-1.110)	8.33e-9	1.079	3.4e-8	1.123	8.1e-2
10	chr2_200825237_I	I2D	0.741	0.754	2	200,715,237-200,848,037	0.909 (0.887-0.932)	5.65e-14	0.906	1.78e-14	1.011	8.7e-1
87	rs11685299	AC	0.313	0.326	2	225,334,096-225,467,796	0.939 (0.919-0.959)	1.12e-8	0.937	1.11e-8	0.974	6.12e-1
23	rs6704768	AG	0.54	0.552	2	233,559,301-233,753,501	0.930 (0.911-0.949)	2.32e-12	0.929	3.15e-12	0.953	3.19e-1
36	rs17194490	TG	0.169	0.156	3	2,532,786-2,561,686	1.101 (1.070-1.132)	2.69e-11	1.102	4.87e-11	1.080	2.31e-1
72	rs4330281	TC	0.479	0.48	3	17,221,366-17,888,266	0.940 (0.921-0.960)	4.64e-9	0.943	5.51e-8	0.890	1.44e-2
12	rs75968099	TC	0.346	0.324	3	36,843,183-36,945,783	1.085 (1.062-1.109)	1.05e-13	1.082	3.39e-12	1.152	5.05e-3
39	rs2535627	TC	0.545	0.529	3	52,541,105-52,903,405	1.071 (1.049-1.092)	4.26e-11	1.073	3.96e-11	1.029	5.41e-1
93	rs832187	TC	0.607	0.615	3	63,792,650-64,004,050	0.941 (0.922-0.961)	1.43e-8	0.941	2.58e-8	0.948	2.82e-1
42	rs7432375	AG	0.421	0.449	3	135,807,405-136,615,405	0.933 (0.914-0.953)	7.26e-11	0.931	5.27e-11	0.973	5.76e-1
28	chr3_180594593_I	I2D	0.196	0.208	3	180,588,843-180,954,593	0.914 (0.890-0.938)	1.3e-11	0.914	5.35e-11	0.904	9.54e-2
106	rs9841616	AT	0.158	0.167	3	181,023,585-181,205,585	0.925 (0.900-0.951)	2.35e-8	0.922	1.65e-8	0.978	7.28e-1
111	rs215411	AT	0.331	0.314	4	23,366,403-23,443,403	1.064 (1.041-1.087)	3.06e-8	1.067	1.22e-8	0.998	9.68e-1
6	rs35518360	AT	0.909	0.922	4	103,146,888-103,198,090	0.857 (0.824-0.891)	7.98e-15	0.865	9.56e-13	0.662	6.61e-5
59	rs10520163	TC	0.493	0.47	4	170,357,552-170,646,052	1.065 (1.043-1.086)	1.47e-9	1.063	1.02e-8	1.100	4.33e-2
84	rs1106568	AG	0.747	0.761	4	176,851,001-176,875,801	0.934 (0.912-0.956)	9.47e-9	0.933	1.15e-8	0.953	3.95e-1
76	rs1501357	TC	0.794	0.802	5	45,291,475-45,393,775	0.926 (0.903-0.950)	5.05e-9	0.926	1.24e-8	0.924	2.09e-1
8	rs4391122	AG	0.505	0.532	5	60,499,143-60,843,543	0.922 (0.904-0.941)	1.1e-14	0.924	1.73e-13	0.889	1.46e-2

71	rs16867576	AG	0.889	0.883	5	88,581,331-88,854,331	1.101 (1.066-1.138)	4.61e-9	1.101	1.36e-8	1.118	1.33e-1
110	rs4388249	TC	0.212	0.213	5	109,030,036-109,209,066	1.076 (1.048-1.104)	3.05e-8	1.075	1.03e-7	1.098	1.26e-1
86	rs10043984	TC	0.266	0.252	5	137,598,121-137,750,021	1.069 (1.045-1.094)	1.09e-8	1.069	2.18e-8	1.069	2.36e-1
73	rs3849046	TC	0.542	0.523	5	137,838,092-137,948,092	1.063 (1.042-1.085)	4.67e-9	1.065	4.83e-9	1.031	5.22e-1
128	chr5_140143664_I	I12D	0.486	0.475	5	140,023,664-140,222,664	1.058 (1.036-1.079)	4.85e-8	1.055	3.6e-7	1.114	2.5e-2
79	rs79212538	TG	0.0512	0.046	5	151,941,104-152,495,104	1.155 (1.100-1.213)	7e-9	1.152	3.84e-8	1.214	5.77e-2
44	rs111294930	AG	0.788	0.782	5	152,097,521-152,323,121	1.094 (1.064-1.124)	1.06e-10	1.091	1.31e-9	1.147	1.92e-2
45	rs2973155	TC	0.353	0.373	5	152,505,619-152,711,619	0.933 (0.913-0.953)	1.11e-10	0.935	1.02e-9	0.892	2.55e-2
100	rs12522290	CG	0.84	0.83	5	152,795,306-152,797,656	1.084 (1.054-1.115)	1.99e-8	1.086	2.23e-8	1.051	4.6e-1
112	rs11740474	AT	0.601	0.621	5	153,671,057-153,688,217	0.942 (0.922-0.962)	3.15e-8	0.941	3.94e-8	0.964	4.51e-1
1	rs115329265	AG	0.864	0.85	6	28,303,247-28,712,247	1.205 (1.168-1.244)	3.48e-31	1.213	3.86e-32	1.037	6.44e-1
108	rs1339227	TC	0.347	0.368	6	73,132,701-73,171,901	0.942 (0.922-0.962)	2.69e-8	0.942	6.86e-8	0.936	1.78e-1
53	chr6_84280274_D	I2D	0.524	0.505	6	84,279,922-84,407,274	1.068 (1.046-1.091)	8.15e-10	1.070	8.57e-10	1.040	4.6e-1
60	rs117074560	TC	0.0418	0.0476	6	96,459,651-96,459,651	0.849 (0.805-0.896)	1.64e-9	0.855	1.66e-8	0.730	1.61e-2
7	chr7_2025096_I	DI3	0.405	0.423	7	1,896,096-2,190,096	0.922 (0.903-0.941)	8.2e-15	0.923	6.12e-14	0.911	5.76e-2
109	chr7_24747494_D	DI3	0.104	0.0959	7	24,619,494-24,832,094	1.101 (1.064-1.139)	2.85e-8	1.095	3.59e-7	1.198	1.15e-2
48	rs12704290	AG	0.111	0.123	7	86,403,226-86,459,326	0.904 (0.876-0.933)	3.33e-10	0.899	1.04e-10	1.007	9.28e-1
56	rs6466055	AC	0.35	0.332	7	104,598,064-105,063,064	1.068 (1.046-1.091)	1.13e-9	1.068	2.46e-9	1.065	2.01e-1
115	rs211829	TC	0.641	0.628	7	110,034,393-110,106,693	1.061 (1.039-1.083)	3.71e-8	1.057	5.47e-7	1.154	4.33e-3
16	rs13240464	TC	0.667	0.647	7	110,843,815-111,205,915	1.083 (1.060-1.106)	3.03e-13	1.084	6.16e-13	1.065	2.19e-1
118	rs7801375	AG	0.146	0.152	7	131,539,263-131,567,263	0.924 (0.898-0.951)	4.42e-8	0.920	2.26e-8	0.998	9.73e-1
66	rs3735025	TC	0.657	0.642	7	137,039,644-137,085,244	1.066 (1.043-1.089)	3.28e-9	1.066	7.75e-9	1.065	2.24e-1
85	rs10503253	AC	0.223	0.219	8	4,177,794-4,192,544	1.073 (1.048-1.100)	1.06e-8	1.073	2.69e-8	1.075	2.11e-1
102	rs73229090	AC	0.107	0.116	8	27,412,627-27,453,627	0.908 (0.877-0.939)	2.1e-8	0.905	1.95e-8	0.958	5.91e-1
77	rs6984242	AG	0.586	0.6	8	60,475,469-60,954,469	0.941 (0.922-0.961)	5.97e-9	0.938	1.76e-9	1.015	7.66e-1
88	rs7819570	TG	0.187	0.174	8	89,340,626-89,753,626	1.079 (1.051-1.108)	1.22e-8	1.080	1.9e-8	1.059	3.46e-1
35	rs36068923	AG	0.787	0.803	8	111,460,061-111,630,761	0.919 (0.896-0.942)	2.61e-11	0.919	1.05e-10	0.908	9.79e-2
5	rs4129585	AC	0.447	0.424	8	143,309,503-143,330,533	1.087 (1.065-1.109)	1.74e-15	1.082	2.03e-13	1.194	2.12e-4
67	rs11139497	AT	0.346	0.337	9	84,630,941-84,813,641	1.069 (1.045-1.093)	3.61e-9	1.070	3.09e-9	1.031	5.76e-1
20	rs7893279	TG	0.899	0.889	10	18,681,005-18,770,105	1.125 (1.088-1.162)	1.97e-12	1.120	3.56e-11	1.231	7.32e-3
27	rs7907645	TG	0.9	0.888	10	104,423,800-104,423,800	1.143 (1.099-1.188)	1.27e-11	1.141	5.82e-11	1.185	8.59e-2
3	rs11191419	AT	0.337	0.36	10	104,585,135-104,956,335	0.906 (0.886-0.926)	6.2e-19	0.907	9.24e-18	0.891	2.23e-2
105	rs55833108	TG	0.208	0.196	10	104,587,583-105,165,583	1.075 (1.048-1.103)	2.23e-8	1.078	1.42e-8	1.015	8.02e-1
13	chr10_104957618_I	I2D	0.0654	0.0756	10	104,957,618-104,957,618	0.843 (0.806-0.882)	1.06e-13	0.842	1.04e-13	0.911	5.45e-1
64	rs11027857	AG	0.515	0.499	11	24,367,320-24,412,990	1.064 (1.042-1.085)	2.55e-9	1.065	3.21e-9	1.043	3.74e-1
26	chr11_46350213_D	I2D	0.835	0.85	11	46,342,943-46,751,213	0.906 (0.881-0.932)	1.26e-11	0.905	1.97e-11	0.934	3.06e-1
63	rs9420	AG	0.327	0.311	11	57,386,294-57,682,294	1.068 (1.045-1.092)	2.24e-9	1.063	6.65e-8	1.187	9.36e-4
114	rs12421382	TC	0.318	0.334	11	109,285,471-109,610,071	0.941 (0.921-0.962)	3.7e-8	0.943	1.72e-7	0.911	6.57e-2
37	rs2514218	TC	0.31	0.314	11	113,317,794-113,423,994	0.927 (0.907-0.948)	2.75e-11	0.930	4.09e-10	0.875	8.19e-3
81	rs77502336	CG	0.337	0.322	11	123,394,636-123,395,986	1.066 (1.043-1.090)	7.54e-9	1.071	2.01e-9	0.982	7.22e-1
24	rs55661361	AG	0.319	0.335	11	124,610,007-124,620,147	0.926 (0.906-0.946)	2.8e-12	0.925	3.68e-12	0.950	3.31e-1
17	rs10791097	TG	0.479	0.46	11	130,714,610-130,749,330	1.076 (1.055-1.098)	1.09e-12	1.077	2.88e-12	1.071	1.49e-1
38	rs75059851	AG	0.812	0.797	11	133,808,069-133,852,969	1.091 (1.063-1.119)	3.87e-11	1.096	1.23e-11	0.995	9.33e-1
4	rs2007044	AG	0.602	0.624	12	2,321,860-2,413,760	0.912 (0.894-0.931)	3.22e-18	0.912	2.63e-17	0.910	5.07e-2

99	rs2239063	AC	0.729	0.714	12	2,474,631-2,523,731	1.067 (1.043-1.091)	1.93e-8	1.071	5.39e-9	0.972	6.17e-1
116	rs679087	AC	0.324	0.337	12	29,905,265-29,940,365	0.941 (0.921-0.962)	3.91e-8	0.941	7.06e-8	0.951	3.17e-1
103	rs324017	AC	0.293	0.309	12	57,428,314-57,490,104	0.938 (0.917-0.959)	2.13e-8	0.941	2.13e-7	0.877	1.52e-2
21	rs12826178	TG	0.0627	0.0708	12	57,569,471-57,682,971	0.846 (0.808-0.887)	2.02e-12	0.846	5.3e-12	0.862	1.71e-1
123	rs4240748	CG	0.358	0.366	12	92,243,186-92,258,286	0.943 (0.923-0.963)	4.59e-8	0.943	1.03e-7	0.941	2.16e-1
127	rs10860964	TC	0.65	0.646	12	103,559,855-103,616,655	1.060 (1.038-1.083)	4.84e-8	1.061	9.92e-8	1.056	2.71e-1
58	rs4766428	TC	0.481	0.474	12	110,723,245-110,723,245	1.068 (1.045-1.091)	1.4e-9	1.071	7.09e-10	1.009	8.62e-1
9	rs2851447	CG	0.723	0.741	12	123,448,113-123,909,113	0.915 (0.894-0.936)	1.86e-14	0.913	2.19e-14	0.953	3.67e-1
92	rs2068012	TC	0.76	0.771	14	30,189,985-30,190,316	0.933 (0.910-0.955)	1.41e-8	0.933	4.14e-8	0.919	1.32e-1
75	rs2332700	CG	0.262	0.249	14	72,417,326-72,450,526	1.073 (1.048-1.098)	4.86e-9	1.076	1.69e-9	0.988	8.38e-1
74	rs2693698	AG	0.412	0.418	14	99,707,919-99,719,219	0.939 (0.919-0.959)	4.8e-9	0.939	1.38e-8	0.933	1.51e-1
14	rs12887734	TG	0.299	0.287	14	103,996,234-104,184,834	1.088 (1.064-1.113)	1.36e-13	1.091	1.17e-13	1.033	5.3e-1
69	rs56205728	AG	0.291	0.274	15	40,566,759-40,602,237	1.074 (1.048-1.099)	4.18e-9	1.070	4.92e-8	1.142	1.25e-2
49	rs12903146	AG	0.544	0.52	15	61,831,663-61,909,663	1.067 (1.046-1.089)	3.38e-10	1.067	1.04e-9	1.078	1.47e-1
97	rs12148337	TC	0.478	0.465	15	70,573,672-70,628,872	1.060 (1.038-1.081)	1.79e-8	1.059	5.33e-8	1.068	1.73e-1
15	rs8042374	AG	0.75	0.725	15	78,803,032-78,926,732	1.093 (1.067-1.119)	2.44e-13	1.091	1.87e-12	1.117	4.57e-2
126	rs190065944	AG	0.274	0.26	15	78,859,610-78,859,610	1.078 (1.049-1.107)	4.71e-8	1.078	7.22e-8	1.074	4.22e-1
31	rs950169	TC	0.247	0.257	15	84,661,161-85,153,461	0.923 (0.902-0.945)	1.62e-11	0.924	7.62e-11	0.906	6.64e-2
11	rs4702	AG	0.547	0.562	15	91,416,560-91,429,040	0.922 (0.902-0.942)	8.3e-14	0.925	2.3e-12	0.872	4.3e-3
90	rs9922678	AG	0.299	0.281	16	9,875,519-9,970,219	1.067 (1.043-1.091)	1.28e-8	1.070	6.72e-9	1.005	9.31e-1
55	rs7405404	TC	0.238	0.223	16	13,728,459-13,761,359	1.077 (1.052-1.103)	1.01e-9	1.081	3.93e-10	0.999	9.81e-1
40	rs12691307	AG	0.524	0.51	16	29,924,377-30,144,877	1.073 (1.051-1.096)	4.55e-11	1.073	1.3e-10	1.074	1.41e-1
98	rs12325245	AT	0.849	0.859	16	58,669,293-58,682,833	0.920 (0.893-0.947)	1.87e-8	0.916	1.15e-8	0.984	8.11e-1
94	rs8044995	AG	0.173	0.162	16	67,709,340-68,311,340	1.081 (1.052-1.111)	1.51e-8	1.081	3.27e-8	1.090	1.95e-1
47	rs4523957	TG	0.642	0.627	17	2,095,899-2,220,799	1.071 (1.049-1.094)	2.86e-10	1.071	1.04e-9	1.084	1.05e-1
96	rs8082590	AG	0.611	0.614	17	17,722,402-18,030,202	0.939 (0.918-0.960)	1.77e-8	0.936	6.84e-9	1.003	9.49e-1
43	chr18_52749216_D	I2D	0.589	0.567	18	52,747,686-52,752,696	1.071 (1.049-1.093)	8.03e-11	1.075	1.75e-11	0.988	8.1e-1
91	rs78322266	TG	0.0345	0.0292	18	52,987,176-53,172,676	1.188 (1.120-1.261)	1.32e-8	1.194	1.1e-8	1.070	6.53e-1
25	rs9636107	AG	0.49	0.503	18	53,195,247-53,200,117	0.930 (0.911-0.949)	3.34e-12	0.927	9.09e-13	0.997	9.47e-1
32	rs72934570	TC	0.0701	0.0797	18	53,453,389-53,585,689	0.873 (0.839-0.909)	1.97e-11	0.865	3.67e-12	1.018	8.37e-1
89	rs715170	TC	0.261	0.275	18	53,769,014-53,804,154	0.935 (0.914-0.957)	1.27e-8	0.936	3.47e-8	0.926	1.59e-1
51	rs2905426	TG	0.611	0.628	19	19,374,022-19,658,022	0.934 (0.914-0.954)	3.63e-10	0.937	6.92e-9	0.866	4.23e-3
70	rs2053079	AG	0.755	0.769	19	30,981,643-31,039,023	0.931 (0.909-0.954)	4.49e-9	0.929	3.79e-9	0.977	6.93e-1
125	rs56873913	TG	0.775	0.766	19	50,067,499-50,135,399	1.071 (1.045-1.098)	4.69e-8	1.069	2.19e-7	1.108	7.2e-2
29	rs6065094	AG	0.307	0.322	20	37,361,494-37,485,994	0.928 (0.908-0.948)	1.46e-11	0.928	5.52e-11	0.922	1.15e-1
122	rs7267348	TC	0.741	0.754	20	48,114,136-48,131,649	0.937 (0.916-0.959)	4.56e-8	0.938	1.18e-7	0.931	1.84e-1
41	chr22_39987017_D	I2D	0.591	0.594	22	39,975,317-40,016,817	0.930 (0.911-0.951)	4.73e-11	0.928	2.2e-11	0.997	9.6e-1
34	rs9607782	AT	0.25	0.232	22	41,408,556-41,675,156	1.087 (1.060-1.113)	2.07e-11	1.091	6.76e-12	1.005	9.29e-1
113	rs1023500	TC	0.817	0.81	22	42,315,744-42,361,344	1.076 (1.048-1.104)	3.43e-8	1.076	5.04e-8	1.058	3.73e-1
61	rs6002655	TC	0.456	0.443	22	42,375,814-42,689,414	1.066 (1.044-1.088)	1.71e-9	1.068	1.48e-9	1.028	5.68e-1
104	rs12845396	AT	0.739	0.753	X	5,916,533-6,032,733	0.947 (0.930-0.966)	2.21e-8	0.950	3.14e-7	0.890	7.46e-3
19	rs1378559	TC	0.848	0.831	X	21,193,266-21,570,266	1.090 (1.064-1.116)	1.61e-12	1.088	1.68e-11	1.131	2.88e-2
46	rs5937157	TG	0.738	0.759	X	68,377,126-68,379,036	0.938 (0.919-0.956)	1.98e-10	0.934	5.74e-11	1.007	8.69e-1

Shown are LD-independent genome-wide significant SNP associations for schizophrenia from the final analysis (sorted by genomic position according to UCSC hg19/NCBI Build 37). Markers are ranked from 1-128 in order of significance. Insertion/deletion variants are given in the form "chrA_B_C" where A=chromosome, B=position, and C=insertion (I) or deletion (D). Column A12 has the SNP alleles, with the first allele (a1) the reference allele for the frequency and odds ratio columns. Frq=frequency of allele 1. Chr and Position denote the associated region surrounding the index SNP containing 1 or more SNPs in LD (r^2>0.6) with the index SNP. OR=odds ratio for allele 1, CI=95% confidence interval for OR.

Statistically independent associations in some instances implicate regions that sometimes overlap. To conservatively define loci as physically independent genomic regions, we annealed associated regions that were not separated by at least 250 kb, and obtained 108 distinct loci. The loci that were annealed are shaded in colour.

Given the extensive LD in the extended MHC region of chromosome 6 (chr6: 26-34 Mb), we represent this by a single region (rank 1). Two associations on chromosome 1 (ranks 2 and 107) implicated the same protein-coding gene (*DPYD*) and on the grounds of parsimony, these were merged.

Supplementary Table 3: Bioinformatic summary data for 108 genome-wide significant loci

Rank	*P*-value	Position (hg19)	SCZ	Protein coding genes	OMIM	NHGRI GWAS catalog	KO phenotype
1	3.48e-31	chr6:28303247-28712247	Y	*Locus too broad*		SCZ pmid=19571808/19571809/ 19571811	
2	3.362e-19	chr1:97792625-98559084	Y	*DPYD MIR137 (micro-RNA)*	DPYD 5-fluorouracil toxicity; DPYD Dihydropyrimidine dehydrogenase deficiency	ASD-ADHD-BIP-MDD-SCZ p=2E-11 pmid=23453885; SCZ p=2E-11 pmid=21926974	
3	6.198e-19	chr10:104423800-105165583	Y	*ARL3 AS3MT C10orf32 CNNM2 CYP17A1 INA NT5C2 PCGF6 PDCD11 SFXN2 TAF5 TRIM8 USMG5 WBP1L*	CNNM2 Hypomagnesemia 6, renal; CYP17A1 17,20-lyase deficiency, isolated; CYP17A1 17-alpha-hydroxylase/17,20-lyase deficiency	ASD-ADHD-BIP-MDD-SCZ p=2E-9 pmid=23453885; Blood pressure p=4E-17 pmid=21572416; Coronary heart disease p=1E-9 pmid=21378990; Intracranial aneurysm p=1E-9 pmid=20364137; SCZ p=2E-9 pmid=22688191; Systolic blood pressure p=7E-26 pmid=21909115	Arl3 nervous; Cyp17a1 behavioral neurological; Ina nervous
4	3.217e-18	chr12:2321860-2523731	Y	*CACNA1C*	CACNA1C Brugada syndrome 3; CACNA1C Timothy syndrome	SCZ: pmid=22614287; ASD-ADHD-BIP-MDD-SCZ p=5E-9 pmid=23453885; Bipolar disorder p=2E-8 pmid=21926972; Bipolar disorder and major depressive disorder (combined) p=3E-8 pmid=20351715; Red blood cell traits p=3E-9 pmid=23222517	Cacna1c behavioral neurological nervous
5	1.737e-15	chr8:143309503-143330533	Y	*TSNARE1*		SCZ pmid = 23974872	
6	7.98e-15	chr4:103146888-103198090	N	*SLC39A8*		Blood pressure p=1E-10 pmid=21909110; Body mass index p=2E-13 pmid=20935630; Diastolic blood pressure p=2E-17 pmid=21909115; HDL cholesterol p=7E-11 pmid=20686565; Systolic blood pressure p=3E-14 pmid=21909115	
7	8.2e-15	chr7:1896096-2190096	Y	*MAD1L1*	MAD1L1 Lymphoma, somatic; MAD1L1 Prostate cancer, somatic	SCZ p=2E-9 pmid=22688191	
8	1.099e-14	chr5:60499143-60843543	Y	*ZSWIM6*		SCZ p=4E-8 pmid=22688191	
9	1.859e-14	chr12:123448113-123909113	Y	*ABCB9 ARL6IP4 C12orf65 CDK2AP1 MPHOSPH9 OGFOD2 PITPNM2 RILPL2 SBNO1 SETD8*	C12orf65 Combined oxidative phosphorylation deficiency 7; C12orf65 Spastic paraplegia 55, autosomal recessive	SCZ pmid = 23974872; HDL cholesterol p=8E-9 pmid=20686565; Head circumference (infant) p=8E-9 pmid=22504419; Height p=4E-15 pmid=20881960	
10	5.652e-14	chr2:200715237-200848037	Y	*AC073043.2 C2orf47 C2orf69 TYW5*		SCZ pmid = 23974872	
11	8.296e-14	chr15:91416560-91429040	N	*FES FURIN MAN2A2*			Fes nervous; Furin nervous
12	1.053e-13	chr3:36843183-36945783	N	*TRANK1*		Bipolar disorder p=1E-12 pmid=22182935	
13	1.363e-13	chr14:103996234-104184834	N	*AL049840.1 APOPT1 BAG5 CKB KLC1 PPP1R13B TRMT61A XRCC3 ZFYVE21*	XRCC3 Breast cancer, susceptibility to; XRCC3 Melanoma, cutaneous malignant, 6		Ckb behavioral neurological nervous; Klc1 behavioral neurological nervous
14	2.439e-13	chr15:78803032-78926732	N	*AC027228.1 AGPHD1 CHRNA3 CHRNA5 CHRNB4 IREB2 PSMA4*	CHRNA3 Lung cancer susceptibility 2; CHRNA5 Lung cancer susceptibility 2; CHRNA5 Nicotine dependence, susceptibility to	Airflow obstruction p=3E-9 pmid=22837378; Chronic obstructive pulmonary disease p=1E-10 pmid=19300482; Lung adenocarcinoma p=2E-51 pmid=19836008; Lung cancer p=3E-26 pmid=19654303; Nicotine dependence p=6E-20 pmid=18385739; Response to tocilizumab in rheumatoid arthritis	Chrna3 behavioral neurological nervous; Chrna5 behavioral neurological nervous; Chrnb4 behavioral neurological nervous; Ireb2 behavioral neurological nervous

						p=4E-8 pmid=22491018; Smoking behavior p=3E-73 pmid=20418890	
15	3.034e-13	chr7:110843815-111205915	N	*IMMP2L*			
16	1.088e-12	chr11:130714610-130749330	Y	*SNX19*		SCZ pmid = 23974872	
17	1.53e-12	chr2:185601420-185785420	Y	*ZNF804A*		SCZ pmid = 20368704	
18	1.606e-12	chrX:21193266-21570266	N	*CNKSR2*			
19	1.971e-12	chr10:18681005-18770105	Y	*CACNB2*	CACNB2 Brugada syndrome 4	SCZ pmid = 23974872; Blood pressure p=2E-16 pmid=21909110; Diastolic blood pressure p=1E-8 pmid=19430479	Cacnb2 nervous
20	2.015e-12	chr12:57428314-57682971	N	*LRP1 MYO1A NAB2 NDUFA4L2 NXPH4 R3HDM2 SHMT2 STAC3 STAT6 TAC3 TMEM194A*	MYO1A Deafness, autosomal dominant 48; TAC3 Hypogonadotropic hypogonadism 10 with or without anosmia	Abdominal aortic aneurysm p=5E-10 pmid=22055160; IgE levels p=2E-12 pmid=22075330; Migraine p=4E-9 pmid=21666692; Pulmonary function p=1E-8 pmid=21946350	Nab2 behavioral neurological nervous
21	2.025e-12	chr1:73766426-73991366	Y	*LRRIQ3 **		SCZ pmid = 23974872	
22	2.315e-12	chr2:233559301-233753501	Y	*C2orf82 EFHD1 GIGYF2 KCNJ13 NGEF*	GIGYF2 Parkinson disease 11; KCNJ13 Leber congenital amaurosis 16; KCNJ13 Snowflake vitreoretinal degeneration	SCZ pmid = 23974872	Gigyf2 behavioral neurological nervous; Ngef nervous
23	2.804e-12	chr11:124610007-124620147	Y	*ESAM MSANTD2 NRGN VSIG2*		SCZ pmid=19571808	Nrgn behavioral neurological nervous
24	3.337e-12	chr18:52747686-53200117	Y	*TCF4*	TCF4 Diabetes mellitus, type 2, susceptibility to; TCF4 Pitt-Hopkins syndrome	ASD-ADHD-BIP-MDD-SCZ p=3E-10 pmid=23453885; SCZ p=3E-10 pmid=23571483	Tcf4 nervous
25	1.259e-11	chr11:46342943-46751213	Y	*AMBRA1 ARHGAP1 ATG13 CHRM4 CKAP5 CREB3L1 DGKZ F2 HARBI1 MDK ZNF408*	F2 Dysprothrombinemia; F2 Hypoprothrombinemia; F2 Pregnancy loss, recurrent, susceptibility to, 2; F2 Stroke, ischemic, susceptibility to; F2 Thrombophilia due to thrombin defect; MDK Mesomelic dysplasia, Kantaputra type	SCZ pmid=21747397; Bone mineral density p=5E-18 pmid=22504420; Bone mineral density (hip) p=4E-9 pmid=19801982; HDL cholesterol p=3E-18 pmid=20686565	Ambra1 nervous; Arhgap1 nervous; Chrm4 behavioral neurological nervous; F2 nervous; Mdk behavioral neurological nervous
26	1.301e-11	chr3:180588843-181205585	N	*CCDC39 DNAJC19 FXR1*	CCDC39 Ciliary dyskinesia, primary, 14; DNAJC19 3-methylglutaconic aciduria, type V		Fxr1 behavioral neurological
27	1.462e-11	chr20:37361494-37485994	N	*ACTR5 PPP1R16B SLC32A1*			Slc32a1 behavioral neurological nervous
28	1.473e-11	chr2:57943593-58502192	Y	*FANCL VRK2*	FANCL Fanconi anemia, complementation group L	SCZ pmid= 21791550	
29	1.618e-11	chr15:84661161-85153461	N	*ADAMTSL3 GOLGA6L4 ZSCAN2*			
30	1.971e-11	chr18:53453389-53804154	N	*TCF4 **			
31	2.064e-11	chr2:198148577-198835577	N	*ANKRD44 BOLL COQ10B HSPD1 HSPE1 MARS2 PLCL1 RFTN2 SF3B1*	HSPD1 Leukodystrophy, hypomyelinating, 4; HSPD1 Spastic paraplegia 13, autosomal dominant; SF3B1 Myelodysplastic syndrome, somatic	Intracranial aneurysm p=4E-8 pmid=18997786	Plcl1 behavioral neurological nervous
32	2.069e-11	chr22:41408556-41675156	N	*CHADL EP300 L3MBTL2 RANGAP1*	EP300 Colorectal cancer, somatic; EP300 Rubinstein-Taybi syndrome 2	Crohn's disease p=3E-8 pmid=22936669	Ep300 nervous
33	2.607e-11	chr8:111460061-111630761	N	*KCNV1 **			
34	2.692e-11	chr3:2532786-2561686	N	*CNTN4*			Cntn4 nervous
35	2.749e-11	chr11:113317794-113423994	N	*DRD2*	DRD2 Dystonia, myoclonic		Drd2 behavioral neurological nervous
36	3.874e-11	chr11:133808069-133852969	N	*IGSF9B*			
37	4.264e-11	chr3:52541105-52903405	Y	*GLT8D1 GNL3 ITIH1 ITIH3*	ITIH4 Hypercholesterolemia,	SCZ pmid=22614287; Adiponectin	

				ITIH4 MUSTN1 NEK4 NISCH NT5DC2 PBRM1 SMIM4 SPCS1 STAB1 TMEM110 TMEM110-MUSTN1	susceptibility to	levels p=1E-13 pmid=22479202; ASD-ADHD-BIP-MDD-SCZ p=3E-12 pmid=23453885; Immune response to smallpox (secreted IL-2) p=2E-9 pmid=22610502; Major mood disorders p=2E-9 pmid=20081856; Osteoarthritis p=5E-9 pmid=22763110	
38	4.548e-11	chr16:29924377-30144877	N	*ALDOA ASPHD1 C16orf92 DOC2A FAM57B GDPD3 HIRIP3 INO80E KCTD13 MAPK3 PPP4C SEZ6L2 TAOK2 TBX6 TMEM219 YPEL3*	ALDOA Glycogen storage disease XII	Pubertal anthropometrics p=9E-11 pmid=23449627	Doc2a behavioral neurological nervous; Mapk3 behavioral neurological nervous; Sez6l2 behavioral neurological nervous; Tbx6 nervous
39	4.725e-11	chr22:39975317-40016817	N	*CACNA1I*			
40	7.264e-11	chr3:135807405-136615405	N	*MSL2 NCK1 PCCB PPP2R3A SLC35G2 STAG1*	PCCB Propionicacidemia	Fibrinogen p=6E-10 pmid=20031576; Height p=4E-9 pmid=20881960; Triglycerides p=3E-8 pmid=20686565	Nck1 behavioral neurological nervous
41	1.055e-10	chr5:151941104-152797656	Y	*GRIA1* *		SCZ pmid = 23974872	
42	1.982e-10	chrX:68377126-68379036	N	*PJA1*			
43	2.862e-10	chr17:2095899-2220799	N	*SGSM2 SMG6 SRR TSR1*		Aortic root size p=2E-11 pmid=19584346; Coronary heart disease p=9E-10 pmid=21378990; Esophageal cancer (squamous cell) p=2E-11 pmid=22960999; Type 2 diabetes p=3E-9 pmid=20174558	Srr behavioral neurological nervous
44	3.332e-10	chr7:86403226-86459326	N	*GRM3*			Grm3 behavioral neurological
45	3.384e-10	chr15:61831663-61909663	N	*VPS14C* *			
46	3.394e-10	chr1:44029384-44128084	N	*KDM4A PTPRF*			Ptprf behavioral neurological nervous
47	3.634e-10	chr19:19374022-19658022	Y	*CILP2 GATAD2A HAPLN4 MAU2 NCAN NDUFA13 PBX4 SUGP1 TM6SF2 TSSK6*	NDUFA13 Thyroid carcinoma, Hurthle cell	SCZ pmid = 23974872; Cholesterol, total p=3E-38 pmid=20686565; LDL cholesterol p=7E-22 pmid=20686565; Triglycerides p=2E-29 pmid=20686565	Gatad2a nervous; Ncan nervous
48	4.487e-10	chr1:149998890-150242490	N	*ANP32E APH1A C1orf51 C1orf54 CA14 OTUD7B PLEKHO1 VPS45*			Anp32e behavioral neurological; Aph1a nervous
49	8.147e-10	chr6:84279922-84407274	N	*SNAP91*			
50	8.701e-10	chr1:2372401-2402501	N	*PLCH2*		Non-obstructive azoospermia p=6E-12 pmid=22197933	
51	1.009e-9	chr16:13728459-13761359	N	*ERCC4* *			
52	1.127e-9	chr7:104598064-105063064	N	*MLL5 PUS7 SRPK2*			
53	1.166e-9	chr1:8411184-8638984	N	*RERE SLC45A1*	RERE Leukemia, acute myeloid, with eosinophilia	Vitiligo p=7E-15 pmid=20410501	Rere nervous
54	1.398e-9	chr12:110723245-110723245	N	*ATP2A2*	ATP2A2 Acrokeratosis verruciformis; ATP2A2 Darier disease		Atp2a2 behavioral neurological
55	1.465e-9	chr4:170357552-170646052	N	*C4orf27 CLCN3 NEK1*	NEK1 Short rib-polydactyly syndrome, type IIA		Clcn3 behavioral neurological nervous; Nek1 nervous
56	1.644e-9	chr6:96459651-96459651	N	*FUT9*			
57	1.709e-9	chr22:42315744-42689414	N	*CENPM CYP2D6 FAM109B NAGA NDUFA6 SEPT3 SHISA8 SMDT1 SREBF2 TCF20 TNFRSF13C WBP2NL*	CYP2D6 Codeine sensitivity; CYP2D6 Debrisoquine sensitivity; NAGA Kanzaki disease; NAGA Schindler disease, type I; NAGA Schindler disease, type III; TNFRSF13C Immunodeficiency, common variable, 4		Sept3 nervous
58	1.814e-9	chr2:146416922-146441832	N				

59	2.243e-9	chr11:57386294-57682294	N	*BTBD18 C11orf31 CLP1 CTNND1 MED19 SERPING1 TMX2 YPEL4 ZDHHC5*	SERPING1 Angioedema, hereditary, types I and II; SERPING1 Complement component 4, partial deficiency of		Ctnnd1 nervous
60	2.554e-9	chr11:24367320-24412990	N	*LUZP2 **			
61	2.86e-9	chr1:30412551-30437271	N				
62	3.278e-9	chr7:137039644-137085244	N	*DGKI PTN*			Ptn behavioral neurological nervous
63	3.613e-9	chr9:84630941-84813641	N	*TLE1*			
64	3.73e-9	chr1:243503719-244002945	Y	*AKT3 SDCCAG8*	AKT3 Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; SDCCAG8 Senior-Loken syndrome 7	SCZ pmid=22614287	Akt3 behavioral neurological nervous
65	4.178e-9	chr15:40566759-40602237	N	*ANKRD63 PAK6 PLCB2*	PLCB2 Platelet PLC beta-2 deficiency		Pak6 behavioral neurological nervous
66	4.489e-9	chr19:30981643-31039023	N	*ZNF536*		Myopia (pathological) p=3E-12 pmid=23049088	
67	4.606e-9	chr5:88581331-88854331	N	*MEF2C **			
68	4.642e-9	chr3:17221366-17888266	N	*TBC1D5*			
69	4.666e-9	chr5:137598121-137948092	N	*CDC25C CTNNA1 EGR1 ETF1 FAM53C GFRA3 HSPA9 KDM3B REEP2*			Ctnna1 nervous; Egr1 behavioral neurological nervous; Gfra3 nervous
70	4.801e-9	chr14:99707919-99719219	N	*BCL11B*			Bcl11b behavioral neurological
71	4.863e-9	chr14:72417326-72450526	N	*AC005477.1 RGS6*			
72	5.046e-9	chr5:45291475-45393775	N	*HCN1*			Hcn1 behavioral neurological nervous
73	5.97e-9	chr8:60475469-60954469	N	*CA8 **			
74	7.388e-9	chr2:72357335-72368185	N	*CYP26B1*	CYP26B1 Craniosynostosis with radiohumeral fusions and other skeletal and craniofacial anomalies		
75	7.539e-9	chr11:123394636-123395986	N	*GRAMD1B*			
76	8.333e-9	chr2:200161422-200309252	N	*SATB2*	SATB2 Cleft palate and mental retardation		
77	8.408e-9	chr2:193848340-194028340	Y	*PCGEM1 **		SCZ pmid = 21926974	
78	9.469e-9	chr4:176851001-176875801	N	*GPM6A*			
79	1.058e-8	chr8:4177794-4192544	Y	*CSMD1*		SCZ=pmid 21926974; ASD-ADHD-BIP-MDD-SCZ p=4E-8 pmid=23453885; SCZ p=2E-8 pmid=21926974	
80	1.115e-8	chr2:225334096-225467796	N	*CUL3*	CUL3 Pseudohypoaldosteronism, type IIE		
81	1.215e-8	chr8:89340626-89753626	Y	*MMP16*		SCZ pmid = 21926974	
82	1.28e-8	chr16:9875519-9970219	N	*GRIN2A*	GRIN2A Epilepsy with neurodevelopmental defects		Grin2a behavioral neurological nervous
83	1.411e-8	chr14:30189985-30190316	N	*PRKD1*			
84	1.432e-8	chr3:63792650-64004050	N	*ATXN7 C3orf49 PSMD6 THOC7*	ATXN7 Spinocerebellar ataxia 7		Atxn7 behavioral neurological nervous
85	1.513e-8	chr16:67709340-68311340	N	*ACD C16orf86 CENPT CTRL DDX28 DPEP2 DPEP3 DUS2L EDC4 ENKD1 ESRP2 GFOD2 LCAT NFATC3 NRN1L NUTF2 PARD6A PLA2G15 PSKH1 PSMB10 RANBP10 SLC12A4 SLC7A6 SLC7A6OS THAP11 TSNAXIP1*	LCAT Fish-eye disease; LCAT Norum disease	HDL cholesterol p=8E-33 pmid=20686565; Metabolic syndrome p=2E-10 pmid=22399527	Nfatc3 behavioral neurological nervous
86	1.585e-8	chr2:149390778-149520178	N	*EPC2*			

87	1.769e-8	chr17:17722402-18030202	N	*ATPAF2 DRG2 GID4 LRRC48 MYO15A RAI1 SREBF1 TOM1L2*	ATPAF2 Mitochondrial complex V (ATP synthase) deficiency, nuclear type 1; MYO15A Deafness, autosomal recessive 3; RAI1 Smith-Magenis syndrome		Myo15 behavioral neurological nervous; Rai1 behavioral neurological nervous; Tom1l2 behavioral neurological nervous
88	1.787e-8	chr15:70573672-70628872	N	*TLE3* *			
89	1.873e-8	chr16:58669293-58682833	N	*CNOT1 SLC38A7*			
90	2.096e-8	chr8:27412627-27453627	N	*CLU EPHX2*	EPHX2 Hypercholesterolemia, familial, due to LDLR defect, modifier of; GULOP Scurvy		Clu nervous; Gulo behavioral neurological nervous
91	2.205e-8	chrX:5916533-6032733	N	*NLGN4X*	NLGN4X Asperger syndrome susceptibility, X-linked 2; NLGN4X Autism susceptibility, X-linked 2; NLGN4X Mental retardation, X-linked		
92	2.688e-8	chr6:73132701-73171901	N	*RIMS1*	RIMS1 Cone-rod dystrophy 7		Rims1 behavioral neurological nervous
93	2.853e-8	chr7:24619494-24832094	N	*DFNA5 MPP6 OSBPL3*	DFNA5 Deafness, autosomal dominant 5		Dfna5 nervous
94	3.053e-8	chr5:109030036-109209066	N	*MAN2A1*			
95	3.056e-8	chr4:23366403-23443403	N	*MIR548AJ2* *			
96	3.145e-8	chr5:153671057-153688217	N	*GALNT10*			
97	3.695e-8	chr11:109285471-109610071	N	*C11orf87*			
98	3.713e-8	chr7:110034393-110106693	N	*IMMP2L* *			
99	3.906e-8	chr12:29905265-29940365	N	*TMTC1*			
100	4.417e-8	chr7:131539263-131567263	N	*PODXL* *			
101	4.448e-8	chr1:177247821-177300821	N	*FAM5B*			
102	4.468e-8	chr1:207912183-208024083	N	*C1orf132 CD46 CR1L*	CD46 Hemolytic uremic syndrome, atypical, susceptibility to, 2		
103	4.559e-8	chr20:48114136-48131649	N	*KCNB1 PTGIS*	PTGIS Hypertension, essential		
104	4.591e-8	chr12:92243186-92258286	N	*C12orf79* *			
105	4.615e-8	chr2:162798555-162910255	N	*DPP4 SLC4A10*			Slc4a10 behavioral neurological nervous
106	4.686e-8	chr19:50067499-50135399	N	*NOSIP PRR12 PRRG2 RCN3 RRAS SCAF1*			
107	4.843e-8	chr12:103559855-103616655	N	*C12orf42*			
108	4.849e-8	chr5:140023664-140222664	N	*AC005609.1 CD14 DND1 HARS HARS2 IK NDUFA2 PCDHA1 PCDHA10 PCDHA2 PCDHA3 PCDHA4 PCDHA5 PCDHA6 PCDHA7 PCDHA8 PCDHA9 TMCO6 WDR55 ZMAT2*	HARS Usher syndrome type 3B; HARS2 Perrault syndrome 2; NDUFA2 Leigh syndrome due to mitochondrial complex I deficiency		

Bioinformatics integration for 108 genome-wide significant regions from Extended Data Table 2 after annealing (ranked by final association *P*-value). Column 2 shows the minimum regional *P*-value. Column 3 is the UCSC hg19/NCBI build 37 position. Column 4 (SCZ) notes whether this genomic region has previously been associated (at genome-wide significance) with schizophrenia (NHGRI GWAS catalog, a recent review, and the most recent GWAS [4,67,68]). Our study does not support 5 loci previously reported to be significant ($P>5x10^{-8}$) with combined discovery and replication sample sizes of 10,000 cases and 10,000 controls (or combined sample of 20,000 subjects). These include rs10489202 (chr1:167903079) and rs16887244 (chr8:38031345) from a study of Han Chinese (PMID: 22037555) although in that study, it should be noted that the locus on chromosome 1 was not significant in the full analysis in that study when European samples were included. The other three loci rs2373000 (chr2:37592628), rs12991836 (chr2:145141541), and rs6878284 (chr5:101769726) come from a large European study (PMID: 23974872). Column

5 notes intersections with protein-coding genes based on GENCODE gene models (v17, file=gencode.v17.annotation.gtf filtered for feature_type=”gene”, gene_type="protein_coding" and gene_status="KNOWN").[69] Boundaries of each gene are expanded by 20 kb on each side prior to intersection to capture putative regulatory elements. Where the region does not contain a gene (e.g., locus 30), we list the nearest gene within 500 kb (indicated by *). Column 6 (OMIM) shows entries in the Online Mendelian Inheritance in Man (http://www.omim.org, downloaded July 2013).[70] Column 7 shows intersections with the NHGRI GWAS catalog (http://www.genome.gov/gwastudies, downloaded July 2013)[67] filtered for SNPs with $P < 5x10^{-8}$ and retaining SNP-phenotype entry with the smallest *P*-value. Shown are the trait, *P*-value, and PubMed identifier. Column 8 provides phenotype information for genes where mouse knock-outs were reported to have behavioral, neurological, or nervous system phenotypes (http://www.informatics.jax.org).[71,72]

Abbreviations: ASD=autism spectrum disorder, ADHD=attention deficit hyperactivity disorder, BIP=bipolar disorder, MDD=major depressive disorder, SCZ=schizophrenia. Hyphens between phenotypes (column 7) denote composite phenotype generated by combining disorders.

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Supplementary Notes

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Acknowledgements

Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org) hosted by SURFsara and financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam. The GRAS data collection was supported by the Max Planck Society, the Max-Planck-Förderstiftung, and the DFG Center for Nanoscale Microscopy & Molecular Physiology of the Brain (CNMPB), Göttingen, Germany. The Boston CIDAR subject and data collection was supported by the National Institute of Mental Health (1P50MH080272, RWM; U01MH081928, LJS; 1R01MH092380, TLP) and the Massachusetts General Hospital Executive Committee on Research (TLP). ISC – Portugal: CNP and MTP are or have been supported by grants from the NIMH (MH085548, MH085542, MH071681, MH061884, MH58693, and MH52618) and the NCRR (RR026075). CNP, MTP, and AHF are or have been supported by grants from the Department of Veterans Affairs Merit Review Program. The Danish Aarhus study was supported by grants from The Lundbeck Foundation, The Danish Strategic Research Council, Aarhus University, and The Stanley Research Foundation. Work in Cardiff was supported by MRC Centre (G0800509) and MRC Programme (G0801418) Grants, the European Community's Seventh Framework Programme (HEALTH-F2-2010-241909 (Project EU-GEI)), the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 279227, a fellowship to JW from the MRC/Welsh Assembly Government and the Margaret Temple Award from the British Medical Association. We thank Novartis for their input in obtaining CLOZUK samples, and staff at The Doctor's Laboratory (Lisa Levett/ Andrew Levett) for help with sample acquisition and data linkage and in Cardiff (Kiran Mantripragada/Lucinda Hopkins) for sample management. CLOZUK and some other samples were genotyped at the Broad Institute (which has a separate acknowledgment) or by the WTCCC and WTCCC2 (WT (083948/Z/07/Z). We acknowledge use of the British 1958 Birth Cohort DNA (MRC: G0000934) and the Wellcome Trust (068545/Z/0/ and 076113/C/04/Z), the UK Blood Services Common Controls (UKBS-CC collection), funded by the WT (076113/C/04/Z) and by NIHR programme grant to NHSBT (RP-PG-0310-1002). Virginia Commonwealth University: BPR and KSK thank all the faculty of the Virginia Institute for Psychiatric and Behavioral Genetics for invaluable insights and discussions over many years. BSM, SAB, BTW, BW, KSK and BPR were supported by National Institute of Mental Health grant R01 MH083094 to BPR. Sample collection was supported by previous funding of National Institute of Mental Health grant R01 MH041953 to KSK and BPR. Genotyping was supported by National Institute of Mental Health grant R01 MH083094 to BPR, National Institute of Mental Health grant R01 MH068881 to BPR and Wellcome Trust Case Control Consortium 2 grant

WTCCC-084710. We thank Novartis for their input in obtaining CLOZUK samples, and staff at The Doctor's Laboratory (Lisa Levett/ Andrew Levett) for help with sample acquisition and data linkage and in Cardiff (Kiran Mantripragada/Lucinda Hopkins) for sample management. Our work was supported by: Medical Research Council (MRC) Centre (G0800509; G0801418), the European Community's Seventh Framework Programme (HEALTH-F2-2010-241909 (Project EU-GEI)), the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 279227, a fellowship to JW from the MRC/Welsh Assembly Government and the Margaret Temple Award from the British Medical Association. CLOZUK and some other samples were genotyped at the Broad Institute (which has a separate acknowledgment) or by the WTCCC and WTCCC2 (WT (083948/Z/07/Z). We acknowledge use of the British 1958 Birth Cohort DNA (MRC: G0000934) and the Wellcome Trust (068545/Z/0/ and 076113/C/04/Z), the UK Blood Services Common Controls (UKBS-CC collection), funded by the WT (076113/C/04/Z) and by NIHR programme grant to NHSBT (RP-PG-0310-1002). The recruitment of families in Bulgaria was funded by the Janssen Research Foundation, Beerse, Belgium. We are grateful to the study volunteers for participating in the Janssen research studies and to the clinicians and support staff for enabling patient recruitment and blood sample collection. Informed consent was obtained from all participants or their parents or guardians. We thank the staff in the Neuroscience Biomarkers Genomic Lab led by Reyna Favis at Janssen for sample processing and the staff at Illumina for genotyping Janssen DNA samples. We also thank Anthony Santos, Nicole Bottrel, Monique-Andree Franc, William Cafferty of Janssen Research & Development) for operational support. Funding from the Netherlands Organization for Health Research and Development (ZonMw), within the Mental Health program (to GROUP consortium for collecting patients and clinical data). High-Density Genome-Wide Association Study Of Schizophrenia In Large Dutch Sample (R01 MH078075 NIH/National Institute Of Mental Health PI: Roel A. Ophoff). The Danish Council for Strategic Research (Journ.nr. 09-067048); The Danish National Advanced Technology Foundation (Journ.nr. 001-2009-2); The Lundbeck Foundation (Journ.nr. R24-A3243); EU 7th Framework Programme (PsychGene; Grant agreement nr. 218251); EU 7th Framework Programme (PsychDPC; Grant agreement nr. 286213). The Wellcome Trust supported this study as part of the Wellcome Trust Case Control Consortium 2 project. E. Bramon holds a MRC New Investigator Award and a MRC Centenary Award. The TOP Study was supported by the Research Council of Norway (#213837, # 217776, # 223273), South-East Norway Health Authority (# 2013-123) and K.G. Jebsen Foundation. This work was supported by the Donald and Barbara Zucker Foundation, the North Shore – Long Island Jewish Health System Foundation, and grants from the Stanley Foundation (AKM), the National Alliance for Research on Schizophrenia and Depression (AKM), and the NIH (MH065580 to TL; MH001760 to AKM). SynSys, EU FP7-242167, Sigrid Juselius Foundation, The Academy of Finland, grant number: 251704, Sohlberg Foundation. The Swedish Research Council [grant numbers 2006-4472, 2009-5269, 2009-3413] and the County Councils of Västerbotten and Norrbotten, Sweden supported the collection of the scz_umeb_eur and scz_umes_eur samples. The Betula Study, from which the Umea controls were recruited, is supported by grants from the Swedish Research Council [grant numbers 345-2003-3883, 315-2004-6977] and the Bank of Sweden Tercentenary Foundation, the Swedish Council for Planning and Coordination of Research, the Swedish Council for Research in the Humanities and Social Sciences and the Swedish Council for Social Research. The GRAS (Göttingen Research Association for Schizophrenia) data collection has been supported by the Max Planck Society, the Max Planck Förderstiftung, and the DFG (CNMPB). We thank all GRAS patients for participating in the study, and all the many colleagues who have contributed over the past 10 years to the GRAS data collection. We acknowledge support from the North Shore – LIJ Health System Foundation and NIH grants RC2 MH089964 and R01 MH084098. We acknowledge support from NIMH K01 MH085812 (PI Keller) and NIMH R01 MH100141 (PI Keller). EGCUT work was supported by the Targeted Financing from the Estonian Ministry of Science and

Education [SF0180142s08]; the US National Institute of Health [R01DK075787]; the Development Fund of the University of Tartu (grant SP1GVARENG); the European Regional Development Fund to the Centre of Excellence in Genomics (EXCEGEN; grant 3.2.0304.11-0312); and through FP7 grant 313010. Milan Macek was supported by CZ.2.16/3.1.00/24022OPPK, NT/13770–4and 00064203 FN Motol. For the scz_tcr1_asn dataset funding from the National Medical Research Council (Grant: NMRC/TCR/003/2008) and the Biomedical Research Council, A*STAR is acknowledged. Genotyping of the Swedish Hubin sample was performed by the SNP&SEQ Technology Platform in Uppsala, which is supported by Uppsala University, Uppsala University Hospital, Science for Life Laboratory - Uppsala and the Swedish Research Council (Contracts 80576801 and 70374401). The Swedish Hubin sample was supported by Swedish Research Council (IA, EGJ) and the regional agreement on medical training and clinical research between Stockholm County Council and the Karolinska Insititutet (EGJ). B.J.M., V.J.C., R.J.S., S.V.C., F.A.H., A.V.J., C.M.L., P.T.M., C.P., and U.S. were supported by the Australian Schizophrenia Research Bank, which is supported by an Enabling Grant from the National Health and Medical Research Council (Australia) [No. 386500], the Pratt Foundation, Ramsay Health Care, the Viertel Charitable Foundation and the Schizophrenia Research Institute and the NSW Department of Health. C.P. is supported by a Senior Principal Research Fellowship from the National Health and Medical Research Council (Australia). We acknowledge the help of: Johanna Badcock, Linda Bradbury, Jason Bridge, David Chandler, Janell Collins-Langworthy, Trish Collinson, Milan Dragovic, Cheryl Filippich, David Hawkes, Danielle Lowe , Kathryn McCabe, Tamara MacDonald, Barry Maher, Bharti Morar Marc Seal, Heather Smith, Melissa Tooney, Paul Tooney, and Melinda Ziino. The Danish Aarhus study was supported by grants from The Lundbeck Foundation, The Danish Strategic Research Council, Aarhus University, and The Stanley Research Foundation. The Perth sample collection was funded by Australian National Health and Medical Research Council project grants and the Australian Schizophrenia Research Bank. The Bonn/Mannheim sample was genotyped within a study that was supported by the German Federal Ministry of Education and Research (BMBF) through the Integrated Genome Research Network (IG) MooDS (Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia; grant 01GS08144 to M.M.N. and S.C., grant 01GS08147 to M.R.), under the auspices of the National Genome Research Network plus (NGFNplus), and through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme.(GSK control sample; Müller-Myhsok). This work has been funded by the Bavarian Ministry of Commerce and by the Federal Ministry of Education and Research in the framework of the National Genome Research Network, Förderkennzeichen 01GS0481 and the Bavarian Ministry of Commerce. M.M.N. is a member of the DFG-funded Excellence-Cluster ImmunoSensation. M.M.N. also received support from the Alfried Krupp von Bohlen und Halbach-Stiftung. M.R. was also supported by the 7th Framework Programme of the European Union (ADAMS project, HEALTH-F4-2009-242257; CRESTAR project, HEALTH-2011-1.1-2) grant 279227. Roche: Thanks are expressed to Olivia Spleiss for great support in genetic data generation, Daniel Umbricht and Delphine Lagarde for their valuable support in clinical and genetic data sharing, and Anirvan Ghosh for continuous encouragement. Authors also wish to thank all investigators and patients who participated in the Roche clinical studies. Jo Knight holds the Joanne Murphy Professor in Behavioural Science. We thank Maria Tampakeras for her work on the samples. The Stanley Center for Psychiatric Research at the Broad Institute acknowledges funding from the Stanley Medical Research Institute. Swedish schizophrenia study (PI CMM, PFS, PS, SM): We are deeply grateful for the participation of all subjects contributing to this research and to the collection team that worked to recruit them: E. Flordal-Thelander, A.-B. Holmgren, M. Hallin, M. Lundin, A.-K. Sundberg, C. Pettersson, R. Satgunanthan-Dawoud, S. Hassellund, M. Rådstrom, B. Ohlander, L. Nyrén and I. Kizling. Funding support for the Sweden Schizophrenia Study (PIs Hultman, Sullivan, and Sklar) was

provided by the NIMH (R01 MH077139 to P.F.S. and R01 MH095034 to P.S.), the Stanley Center for Psychiatric Research, the Sylvan Herman Foundation, the Friedman Brain Institute at the Mount Sinai School of Medicine, the Karolinska Institutet, Karolinska University Hospital, the Swedish Research Council, the Swedish County Council, the Söderström Königska Foundation. We acknowledge use of DNA from The UK Blood Services collection of Common Controls (UKBS collection), funded by the Wellcome Trust grant 076113/CI04/Z, by the Juvenile Diabetes Research Foundation grant WT0618S8, and by the National Institute of Health Research of England. The collection was established as part of the Wellcome Trust Case-Control Consortium. We thank the study participants, and the research staff at the study sites. This study was supported by NIMH grant R01MH062276 (to DF Levinson, C Laurent, M Owen and D Wildenauer), grant R01MH068922 (to PV Gejman), grant R01MH068921 (to AE Pulver) and grant R01MH068881 (to B Riley). The authors are grateful to the many family members who participated in the studies that recruited these samples, to the many clinicians who assisted in their recruitment. In addition to the support acknowledged for the Multicenter Genetics Studies of Schizophrenia and Molecular Genetics of Schizophrenia studies, Dr. DF Levinson received additional support from the Walter E. Nichols, M.D., Professorship in the School of Medicine, the Eleanor Nichols Endowment, the Walter F. & Rachael L. Nichols Endowment and the William and Mary McIvor Endowment, Stanford University. This study was supported by NIH R01 grants (MH67257 to N.G.B., MH59588 to B.J.M., MH59571 to P.V.G., MH59565 to R.F., MH59587 to F.A., MH60870 to W.F.B., MH59566 to D.W.B., MH59586 to J.M.S., MH61675 to D.F.L., MH60879 to C.R.C., and MH81800 to P.V.G.), NIH U01 grants (MH46276 to C.R.C., MH46289 to C. Kaufmann, MH46318 to M.T. Tsuang, MH79469 to P.V.G., and MH79470 to D.F.L.), the Genetic Association Information Network (GAIN), and by The Paul Michael Donovan Charitable Foundation. Genotyping was carried out by the Center for Genotyping and Analysis at the Broad Institute of Harvard and MIT (S. Gabriel and D. B. Mirel), which is supported by grant U54 RR020278 from the National Center for Research Resources. Genotyping of half of the EA sample and almost all the AA sample was carried out with support from GAIN. The GAIN quality control team (G.R. Abecasis and J. Paschall) made important contributions to the project. We thank S. Purcell for assistance with PLINK. We (DRW, RS) thank the staff of the Lieber Institute and the Clinical Brain Disorders Branch of the IRP, NIMH for their assistance in data collection and management. We thank Ningping Feng and Bhaskar Kolachana for Illumina genotyping and for managing DNA stocks. The work was supported by the Lieber Institute and by direct NIMH IRP funding of the Weinberger Lab. Pfizer is very grateful to the study volunteers for participating in our research studies. We thank our numerous clinicians and support staff for enabling patient recruitment, blood sample collection, and biospecimen administration. Informed consent was obtained from all participants, their parents or guardians. Eli Lilly is grateful to the participants of clinical trials and research studies who gave consent for participation in this study. We are also grateful to Philip J Ebert and Jeffrey S Arnold for facilitating our participation in this project. We acknowledge the Irish contribution to the International Schizophrenia Consortium (ISC) study, the WTCCC2 SCZ study & WTCCC2 controls from the 1958BC and UKNBS, the Science Foundation Ireland (08/IN.1/B1916). We acknowledge use of the Trinity Biobank sample from the Irish Blood Transfusion Service & the Trinity Centre for High Performance Computing. Funding for this study was provided by the Wellcome Trust Case Control Consortium 2 project (085475/B/08/Z and 085475/Z/08/Z), the Wellcome Trust (072894/Z/03/Z, 090532/Z/09/Z and 075491/Z/04/B), NIMH grants (MH 41953 and MH083094) and British 1958 Birth Cohort DNA collection funded by the Medical Research Council (grant G0000934) and the Wellcome Trust (grant 068545/Z/02) and of the UK National Blood Service controls funded by the Wellcome Trust. We acknowledge Hong Kong Research Grants Council project grants GRF 774707M, 777511M, 776412M and 776513M.