Supplementary Information for "Common Variant at 16p11.2 Conferring Risk of Psychosis"

Supplementary Methods

Subjects

Supplementary Table 1 and Supplementary Table 2 present summary information for all psychosis follow-up and autism study groups. For groups not yet described in published studies, ascertainment and diagnosis information is given below. For all study groups, individuals or their legal guardians provided written, informed consent for participation, and approval was obtained from local ethics committees.

Georgia. *Psychosis.* Cases were recruited based on existing databases of patients at the Institute of Psychiatry in Tbilisi, and at out-patient clinics and psychiatric hospitals throughout Georgia. After reviewing the patients' case histories, a trained psychiatrist (NN) conducted interviews with patients and their parents. The SADS-L (in participants over 18 years old) and the Kiddie-SADS-Present and Lifetime (K-SADS-PL) (patients under 18 years old) instruments were employed to aid the interviewing process. Cognitive assessment was performed using WASI. Each case was evaluated together with senior, trained psychiatrist (TS). The final diagnosis was produced using ICD-10 criteria. *Autism.* Patients were recruited after the first assessment of referrals to Mental Health Center of Tbilisi Central Clinical Hospital for Children and from the database of special education schools. Diagnosis was established by a psychiatrist and a Georgian version of the Autism Diagnostic Interview-revised (ADI-R) was performed by an authorized interviewer. Adaptive behavior of children was assessed using the Vineland-II scales and, in cases where it was appropriate, WASI (performance subtests) was used to estimate PIQ. *Controls.* Controls were recruited from undergraduate students at Tbilisi State Medical University, medical professionals and students at other universities. They were included in the study after excluding psychiatric, neurological and substance abuse disorders.

Germany (Homburg/Frankfurt). *Autism.* Caucasian individuals with autism spectrum disorder (ASD) were recruited from an ASD specialty clinic at the Department of Child and Adolescent Psychiatry of the Saarland University Hospital, Germany. Inclusion criteria were as follows: Diagnosis of autism, Asperger Syndrome or atypical autism according to DSM-IV; IQ or developmental quotient >= 35. The Autism Diagnostic Interview-revised (ADI-R) was performed with the parent or primary caregiver, and behavior of children and adolescents was directly observed using the Autism Diagnostic Observation Schedule-generic (ADOS-G). Intelligence testing was performed either by the German version of the Griffith Mental Developmental Scales, the Snijders-Oomen Non-verbal Intelligence test 2½ -7, the German version of the Kaufman-Assessment Battery for Children or the Wechsler Scales for children or adults. The standardized medical history included a thorough pre- and perinatal history, birth parameters, developmental milestones, presence of any medical or neurological disorder including febrile seizures, epilepsy, cerebral palsy, tuberous sclerosis, neurofibromatosis, or any brain anomaly. Additionally, a thorough review of medical records and a standardized medical and neurological exam were performed, and psychotropic/antiepileptic medication status was noted. High resolution karyotyping as well as molecular genetic assessment of fragile-X-Syndrome and chromosome 15q11-13 duplication were obtained for the majority of ASD individuals (95%). Exclusion criteria were as follows: IQ or developmental quotient < 35; birth

weight < 2000g; structural brain anomaly; tuberous sclerosis, neurofibromatosis, cerebral palsy, any other neurological disorder with the exception of a history of febrile or epileptic seizures; microcephaly, dysmorphic features, cleft palate, cardiac anomaly, immune deficiency, chronic medical disorder; non-Caucasian parent; maternal antiepileptic or psychotropic medication during pregnancy. Individuals with a cytogenetic anomaly, fragile-X-Syndrome, chromosome 15q11-13 duplication, Angelman Syndrome, Prader-Willi-Syndrome, Rett Syndrome or any other genetically diagnosed syndrome or disorder were excluded from the study. These strict exclusion criteria were chosen to improve genetic and phenotypic homogeneity of the ASD sample by exclusion of individuals with a known genetic risk factor for ASD or possible phenocopies of the disorder.

Macedonia. *Psychosis.* Recruitment of patients was obtained from the pool of previously-diagnosed patients treated at the University Clinic of Psychiatry (UCP), Department of Biological Psychiatry, Adult department and the Psychiatric Hospital "Skopje", and from new cases referred to the UCP, Department of Child and Adolescent Psychiatry and the Institute of Child and Adolescent Mental Health. The diagnostic criteria that are used are ICD-10 criteria. For the purpose of this project, already diagnosed cases, over 18 years, were assessed by adult psychiatrists with SADS-L. A pair of senior and junior psychiatrists assessed each case, and cognitive assessment was performed by clinical psychologists using WASI. Children under 18 years were assessed by child psychiatrists, using standard clinical procedures in diagnosing childhood-onset psychosis, and the Kiddie-SADS-PL. Cognitive performance was assessed by clinical psychologists with WASI. *Autism.* Cases were recruited from the existing database of patients, as well as after the first assessment of consecutive referrals (UCP, Department of Child and Adolescent Psychiatry and Institute of Mental Health of Children and Adolescents). Assessment was done by child psychiatrists and special educators, using ICD-10 criteria. The Autism Diagnostic Interview - Revised (ADI-R) was translated into Macedonian and was performed by authorized interviewers (child psychiatrists and special educators). For participants in the age range 5-18, the Development and Well-being Assessment (DAWBA) was also used to confirm the diagnosis and to explore possible co-morbidities. *Controls.* Controls were recruited from students at the Medical Faculty, University "Sts Cyril and Methodius" of Skopje; students at the Medical Faculty, University of Tetovo; and personnel at the UCP. Each participant in the control group answered the screening interview, excluding psychiatric and neurological disorders, as well as substance abuse.

Serbia. *Psychosis.* Cases were recruited from the existing database of patients at the Clinic for Adults and Clinic for Child and Adolescent Psychiatry, Institute of Mental Health, as well as after the first assessment of consecutive referrals at the Clinic for Child and Adolescent Psychiatry, Institute of Mental Health. Assessment was carried out by adult and child psychiatrists using ICD-10 criteria, as well as the SADS-L interview (participants over 18 years old) and the Kiddie-SADS-Present and Lifetime (K-SADS-PL) interview (patients under 18 years old). *Autism*. Cases were recruited from the existing database of patients, as well as after the first assessment of consecutive referrals at the Clinic for Child and Adolescent Psychiatry, Institute of Mental Health. Assessment was done by child psychiatrists using ICD-10 criteria, and by authorized interviewers using the Autism Diagnostic Interview–Revised (ADI-R). For case participants in the age range 5-17, the Development and Well-being Assessment (DAWBA) was also used to confirm the diagnosis and to explore possible comorbidities.

Controls. Controls were recruited from students at the Medical School and the Faculty for Special Education and Rehabilitation, University of Belgrade. Individuals with psychiatric disorders, neurological disorders, or substance abuse were excluded through a screening interview.

Ukraine. *Autism*. Patients were recruited from the database of the Department of Child, Adolescent Psychiatry and Medical-Social Rehabilitation of the Ukrainian Research Institute of Social, Forensic Psychiatry and Drug Abuse**,** a medical center providing psychiatric care for children with development disabilities. The study included children from all regions of Ukraine over the age of 3 years with IQ level at least 50, meeting the ICD-10 diagnostic criteria for F84.0, F84.1 and F84.8. Children who met the criteria for F84.2, F84.3, F84.4 or F84.5 were excluded. Assessments were done by child psychiatrists using the Autism Diagnostic Interview-Revised (ADI-R) and the Wechsler Abbreviated Scale of Intelligence (WASI). *Controls.* Recruitment of the control group was conducted among students of the National Medical University O.O.Bogomolets, and among blood donors at the blood transfusion station in Zhytomyr. Individuals with psychiatric disorders, neurological disorders, or substance abuse were excluded through a screening interview.

WTCCC2. *Psychosis.* Samples were collected through seven centres 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)[1], the Structured Clinical Interview for DSM Disorders (SCID)[2], or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[3]. Of the cases passing quality control, 784 met criteria for schizophrenia, 113 for bipolar disorder with a history of psychotic symptoms, 110 for psychotic disorder not otherwise specified, 97 for schizophreniform disorder, 64 for schizoaffective disorder, 44 for brief psychotic disorder, 20 for delusional disorder and 7 for substance-induced psychosis. Participants in all groups were excluded if they had a history of neurological disease or head injury resulting in loss of consciousness.

Quality control and analysis

Additional psychosis study groups*. Australia, Germany/Bonn 1, Germany/Bonn 2.* Quality control was carried out as described previously[4]. Association analysis was performed using logistic regression, assuming an additive genetic model. To account for potential population stratification, results were adjusted using genomic control (genomic control inflation factors were 1.003, 1.049 and 0.968 for Australia, Germany/Bonn 1 and Germany/Bonn 2, respectively; no adjustment was made for inflation factors that were less than 1). *France.* All samples were passed through the standard quality-control procedures followed at the Centre National de Génotypage (Evry, France) for GWA studies, as described elsewhere[5]. Male samples with more than 0.5% heterozygous markers on the X chromosome and female samples with less than 20% heterozygous markers on that chromosome were removed. In addition, samples with a call rate lower than 0.97 or a low level of identity after having estimated the

average genome-wide identity-by-state sharing between individuals and analyzed the clustering using a multidimensional scaling plot were excluded. SNPs were removed if they were monomorphic, had a minor allele frequency lower than 0.01, a call rate lower than 0.97, $P < 10^{-3}$ in a comparison of missingness between cases and controls, or deviation from Hardy-Weinberg equilibrium in controls, using a significance threshold of $P < 10^{-3}$. Standard allelic association analysis was carried out, and results were adjusted using genomic control (lamda was 1.05 for the bipolar sample and 1.12 for the combined bipolar disorder/schizophrenia sample).*GAIN/BiGs, Georgia, GSK/Canada, GSK/England, GSK/Scotland, Iceland, Macedonia, NIMH/Pritzker, Norway, Serbia, STEP1, WTCCC*. Exclusion criteria for genome-wide typed samples were: yield less than 98%, a duplicate sample of higher yield already included in the study, sex as determined by X chromosome marker homozygosity inconsistent with reported sex, or evidence of non-European ancestry as determined by running STRUCTURE[6] with the HapMap CEU, YRI and CHB/JPT individuals as reference samples. Centaurus-typed samples were removed if yield was less than 90% or a higher-yield sample was already included in the study. SNPs were removed if yield was less than 95% in cases or controls, or the control Hardy-Weinberg equilibrium (HWE) *P* value was less than 1×10^{-5}. Duplicates and first or second-degree relatives within or across studies were also excluded from the NIMH/Pritzker,GAIN/BiGS, STEP1, GSK/England, GSK/Scotland and WTCCC data sets. The GAIN/BiGs, STEP1 and WTCCC data sets were imputed using IMPUTE2[7] with the June 2011 release of the 1000 genome project as the reference set. For imputed SNPs, dosages were analyzed using SNPTEST[8] , and only results having information > 0.3 were included. *P* values were adjusted using genomic control (inflation factors were 1.12 or less) for the European study groups, and samples from North America were analyzed including the first thirty principal components as covariates in logistic regression. *WTCCC2. G*enotype calling was conducted using the CHIAMO algorithm[9,10], developed at the Wellcome Trust Centre for Human Genetics (WTCHG), Oxford, UK. Sample quality control consisted of removing samples if they were identical to a higher yield sample in the study, had greater than 2% missing data, or had abnormal heterozygosity (absolute value of the inbreeding coefficient F > 0.076). For marker quality control, SNPs were removed if they had more than 5% missing data, four or more Mendelian inheritance errors, departure from Hardy-Weinberg equilibrium ($P < 10^{-6}$), minor allele frequency less than 2%, or poor genotyping as revealed through visual inspection of the cluster plots. In addition, the X chromosome was excluded. The WTCCC2 sample used here also excluded 909 individuals who were duplicates or close (first- or second-degree) relatives of persons included in SGENE-plus, and 51 individuals from the Edinburgh center who may have been included in the ISC study. Association analysis was carried out using UNPHASED[11]. To account for population structure, three principal components were included as covariates. For markers in our set lacking direct typing in the WTCCC2 set, surrogate markers were used. All surrogates had r^2 greater than 0.7with the original marker, based on the HapMap CEU.

Autism. For the genome-wide typed groups, samples with low-yield, evidence of non-European ancestry, a higher-yield duplicate sample already included in the study, or likely incorrect relationship specification were removed. For all groups, the single SNP studied for autism, rs4583255, had yield greater than 0.95, and control HWE *P* value greater than 0.05. For AGRE and AGP, association analysis was carried out using the transmission disequilibrium test (TDT). For the remaining groups, allelic association analysis was carried out, and

genomic control correction was included for genome-wide typed groups. To correct for relatedness in the Netherlands (Staal) samples, chi-square statistics were adjusted by dividing them by a correction factor obtained through gene-drop simulations carried out as described previously[12].

Supplementary Table 1. Psychosis follow-up samples used in this work

a. Primary, from Steinberg *et al*[13] (SZ)

	Schizo-phrenia cases	Bipolar disorder cases	Other psychosis cases	Controls	Unaffected family members	Description	Genotyping platform
Belgium	510 (113)	0	0	341	0	Steinberg *et al*[13]	Centaurus/Illumina HumanHap370
CATIE	391	0	0	404	0	Sullivan *et al*[14]	Affymetrix 500K, 164K
Denmark, Aarhus 1	227	0	0	493	0	Stefansson *et al*[15]	Centaurus
Denmark, Aarhus 2	878	0	0	874	0	Steinberg *et al*[13]	Illumina Human610
Denmark, Copenhagen	1324 (136)	0	0	2350	0	Stefansson *et al*[15]	Centaurus
Finland, excl. Kuusamo	287	0	0	3873	0	Stefansson *et al*[15]	Illumina Human660/HumanHap370
Germany, Bonn	607	0	0	1534	0	Stefansson *et al*[15]	Centaurus
Germany, Munich	303	0	0	1614	0	Stefansson *et al*[15]	Centaurus
Hungary	241	0	0	214	0	Stefansson *et al*[15]	Centaurus
Ireland	1310 (219)	0	0	1023	0	Steinberg *et al*[13]	Affymetrix 6.0
Italy	138	0	0	89	0	Steinberg *et al*[13]	Centaurus
Netherlands 1	693	0	0	3689	0	Stefansson *et al*[15]	Illumina HumanHap370/550
Netherlands 2	176	0	0	603	0	Stefansson *et al*[15]	Centaurus/Illumina HumanHap370
Norway	228 (40)	0	0	293	0	Stefansson *et al*[15]	Centaurus
Russia	597 (28)	0	0	742	0	Stefansson *et al*[15]	Centaurus
Spain, Santiago	282	0	0	598	0	Stefansson *et al*[15]	Sequenom MassArray iPlex
Spain, Valencia	323	0	0	398	0	Stefansson *et al*[15]	Sequenom MassArray iPlex
Sweden	252	0	0	287	0	Stefansson *et al*[15]	Centaurus
United Kingdom	479	0	0	2937	0	O'Donovan *et al*[16]	Affymetrix 500K
Total	9246 (536)	0	0	22356	0		

Shown are numbers of cases and controls following quality control. In parentheses is the number, of the total, of schizoaffective disorder cases.

b. Primary, additional to this work (SZ, BP, other psychosis)

	Schizo-phrenia cases	Bipolar disorder cases	Other psychosis cases	Controls	Unaffected family members	Description	Genotyping platform
Australia	0	330	0	1811	0	Sklar *et al*[17]	Illumina Human610/660
France	173	473	0	1806	0	Sklar *et al*[17]	Illumina HumanHap300/550, Human610
GAIN/BiGs	0	528 (26)	0	843	0	Smith *et al*[18]	Affymetrix 6.0
Georgia	197	2	0	203	0	this work	Illumina Human610
Germany, Bonn	0	682	0	934	0	Cichon *et al*[4]	Illumina HumanHap550
Germany, Bonn 2	0	488	0	861	0	Sklar *et al*[17]	Illumina HumanHap300/550, Human610/650/Omni1
GSK/Canada	0	288	0	200	0	Scott *et al*[19]	Illumina HumanHap550
GSK/England	0	183	0	450	0	Scott *et al*[19]	Illumina HumanHap550
GSK/Scotland	0	77	0	184	0	Scott *et al*[19]	Illumina HumanHap550
Iceland	0	544	0	23750	0	Vassos *et al*[20]	Illumina HumanHap300, HumanCNV370
Macedonia	152	7	0	137	0	this work	Illumina Human610
NIMH/Pritzker	0	651	0	602	0	Scott *et al*[19]	Illumina HumanHap550
Norway	0	282	50	0	0	Djurovic *et al*[21]	Centaurus
Russia 2	241 (14)	17	0	253	0	Stefansson *et al*[15]	Illumina Human610
Serbia	49 (10)	13	17	100	0	this work	Illumina Human610
STEP1	0	939	0	672	0	Sklar *et al*[22]	Affymetrix 500K
WTCCC	0	1868 (280)	0	11373*	0	WTCCC[9]	Affymetrix 500K
WTCCC2	723 (54)	97	266	1981	808	this work	Affymetrix 6.0
Total	1535 (78)	7469 (306)	333	46160	808		

Shown are numbers of cases and controls following quality control. In parentheses is the number, of the total, of schizoaffective, bipolar type disorder cases (in the bipolar disorder cases column) or of schizoaffective disorder cases (in the schizophrenia cases column). Other psychosis includes psychotic disorders (*N* = 206), delusional disorder (*N* = 31) and schizofreniform disorder (*N* = 96). *controls from the Crohn's disease, rheumatoid arthritis and type 1 diabetes projects were excluded for SNPs in the MHC region

c. Secondary, from Steinberg *et al*[13] (SZ)

	Schizo-phrenia cases	Bipolar disorder cases	Other psychosis cases	Controls	Unaffected family members	Description	Genotyping platform
GRAS	1014	0	0	1144	0	Steinberg *et al*[13]	Roche LightCycler480

Shown are numbers of cases and controls following quality control.

Supplementary Table 2. Autism spectrum disorder (ASD) samples from various study centers

	Cases			Controls	Unaffected Family Members	Sample Description	Genotyping platform
	Autism Spectrum	Autism	Multiplex Autism Spectrum				
AGP	1110	632	NA	-	2285	Anney *et al*[23]	Illumina Human1M
AGRE	1307	1237	1239	-	1921	Wang *et al*[24]	Illumina Human610
England (MGAS)	90	35	7	755	-	Curran *et al*[25]	Taqman
Finland	155	119	59	796	-	Kilpinen *et al*[26], Teslovich *et al*[27]	Illumina HumanHap300/550, HumanHapCNV370, Human610
Georgia	109	109	NA	203*	-	this work	Illumina Human610
Germany (Homburg/Frankfurt)	150	89	0	367*	-	this work, Stefansson *et al*[15]	Centaurus/Illumina HumanHap550
Iceland	403	127	46	13033	-	Curran *et al*[25]	Illumina HumanHap300, HumanCNV370, Human610/660/1M/Omni1
Netherlands (Poot)	70	NA	14	134	-	van Daalen *et al*[28]	Illumina HumanHap300
Netherlands (Staal)	191	112	128	629*	-	Curran *et al*[25], Stefansson *et al*[15]	Centaurus/Illumina HumanCNV370
Serbia	92	69	NA	100*	-	this work	Illumina Human610
Ukraine	96	79	NA	86	-	this work	Illumina Human610
Total	3773	2608	1493	16103	4206		

Only European-ancestry samples were included. Samples that were part of both AGP and AGRE were used only once. Autism was distinguished from autism spectrum disorder (ASD) based on the ADI-R except in Finland, Georgia, Serbia and Ukraine, where autism was defined based on ICD-10 F84.0 diagnosis. In Finland, hospital F84.0 diagnosis has been shown to be highly correlated with ADI-R diagnosis[29]. The samples from Germany (Homburg/Frankfurt) included here were not part of AGP, but were also used in Curran *et al*[25], and in Freitag *et al*[30]. Multiplex ASD cases had a sibling diagnosed with ASD. NA, not available. *Controls

were also included in the psychosis study

Supplementary Table 3. Association results in the previous schizophrenia meta-analysis (SGENE-plus+ISC+MGS), the psychosis follow-up set, and the combined (discovery+follow-up) data set

					SGENE-plus+ISC+MGS (7,946 cases; 19,036 controls)		Psychosis follow-up set (18,583 cases; 68,516 controls; 808 family members)		SGENE-plus+ISC+MGS + psychosis follow-up set (26,529 cases; 87,552 controls; 808 family members)		
Chr	Mb	SNP	Al	Freq	OR	*P* value	OR	*P* value	OR	*P* value	Close Genes
11	124.1	rs12807809	T	0.83	1.16	2.3×10^{-6}	1.10	9.4×10^{-7}	1.11	3.5×10^{-11}	*SPA17, NRGN*
16	29.9	rs4583255	T	0.56	1.10	2.5×10^{-5}	1.07	9.2×10^{-7}	1.08	2.0×10^{-10}	*TAOK2*
6	28.4	rs13211507	T	0.92	1.22	5.2×10^{-6}	1.13	2.3×10^{-6}	1.15	2.2×10^{-10}	*PGBD1*
6	27.4	rs6932590	T	0.78	1.15	5.6×10^{-7}	1.06	0.00018	1.08	9.0×10^{-9}	*PRSS16, FKSG83*
6	27.2	rs6913660	C	0.85	1.19	4.6×10^{-8}	1.06	0.00067	1.09	1.6×10^{-8}	*-, HIST1H2BJ*
1	53.5	rs5174	G	0.57	1.09	8.2×10^{-5}	1.05	0.00012	1.06	9.4×10^{-8}	*LRP8*
6	32.3	rs3131296	G	0.87	1.18	9.8×10^{-6}	1.08	0.00030	1.10	1.1×10^{-7}	*NOTCH4*
6	73.2	rs2789588	T	0.68	1.10	4.7×10^{-5}	1.05	0.00028	1.07	2.1×10^{-7}	*RIMS1, KCNQ5*
18	50.9	rs4309482	A	0.58	1.10	7.1×10^{-5}	1.05	0.00032	1.06	3.0×10^{-7}	*CCDC68, TCF4*
11	112.9	rs6589386	C	0.61	1.10	1.3×10^{-5}	1.05	0.00095	1.06	3.6×10^{-7}	*DRD2, TMPRSS5*
2	58.1	rs2312147	C	0.61	1.11	3.7×10^{-6}	1.04	0.0017	1.06	3.9×10^{-7}	*-, VRK2*
2	144.9	rs12991836	C	0.37	1.11	3.8×10^{-5}	1.05	0.0013	1.06	1.1×10^{-6}	*GTDC1, ZEB2*
3	162.9	rs2063836	T	0.61	1.10	4.7×10^{-5}	1.04	0.0017	1.06	1.8×10^{-6}	-
18	51.3	rs9960767	C	0.056	1.27	1.8×10^{-6}	1.08	0.0079	1.13	2.2×10^{-6}	*TCF4*
5	76.2	rs2460508	G	0.45	1.10	9.2×10^{-5}	1.05	0.0013	1.06	2.4×10^{-6}	*S100Z*
10	104.7	rs1046778	T	0.67	1.11	4.5×10^{-5}	1.04	0.0031	1.06	3.9×10^{-6}	*AS3MT*
9	120.4	rs1572299	A	0.49	1.12	3.1×10^{-6}	1.04	0.0080	1.06	4.5×10^{-6}	-
5	101.9	rs1502844	C	0.30	1.11	3.8×10^{-6}	1.04	0.013	1.06	6.2×10^{-6}	*SLCO6A1, -*
6	43.3	rs2273709	A	0.81	1.13	4.1×10^{-5}	1.05	0.0061	1.07	8.2×10^{-6}	*PARC*
8	89.3	rs6994019	T	0.25	1.12	1.0×10^{-5}	1.04	0.012	1.06	1.0×10^{-5}	*MMP16*
9	26.9	rs7863476	A	0.19	1.16	6.3×10^{-7}	1.03	0.047	1.06	2.5×10^{-5}	*PLAA*
3	182.2	rs1010471	G	0.65	1.12	3.2×10^{-6}	1.03	0.052	1.05	5.3×10^{-5}	*FXR1*
16	4.5	rs3747600	A	0.28	1.12	3.2×10^{-6}	1.02	0.097	1.05	0.00014	*C16orf5*
11	30.3	rs1765142	A	0.64	1.12	1.4×10^{-5}	1.03	0.060	1.05	0.00015	*C11orf46, MPPED2*
12	1.5	rs3741976	G	0.36	1.10	8.8×10^{-5}	1.03	0.050	1.05	0.00021	*ERC1*
5	113.5	rs1487222	A	0.41	1.11	7.3×10^{-6}	1.02	0.18	1.04	0.00054	-

11	55.3	rs11230864	T	0.37	1.10	3.9×10^{-5}	1.02	0.17	1.04	0.0011	*OR4C6, OR5D13*
					SGENE-plus+ISC+MGS (7,946 cases; 19,036 controls)		Psychosis follow-up set (18,583 cases; 68,516 controls; 808 family members)		SGENE-plus+ISC+MGS + psychosis follow-up set (26,529 cases; 87,552 controls; 808 family members)		
Chr	Mb	SNP	Al	Freq	OR	*P* value	OR	*P* value	OR	*P* value	Close Genes
7	110.9	rs38752	T	0.62	1.11	4.6×10^{-5}	1.02	0.17	1.04	0.0012	*IMMP2L*
5	11.9	rs4466166	T	0.012	1.57	3.9×10^{-5}	1.09	0.17	1.19	0.0014	*CTNND2*
4	72.3	rs2579309	A	0.054	1.22	2.5×10^{-5}	1.03	0.25	1.08	0.0019	*SLC4A4*
6	31.2	rs3815087	T	0.19	1.12	6.7×10^{-5}	1.02	0.21	1.05	0.0020	*PSORS1C1*
X	6.0	rs6639583	T	0.24	1.12	8.6×10^{-5}	1.04	0.12	1.06	0.0020	*NLGN4X*
22	46.9	rs131137	A	0.57	1.11	9.3×10^{-5}	1.02	0.17	1.04	0.0025	-
6	32.4	rs2076537	C	0.59	1.14	5.5×10^{-5}	1.02	0.17	1.04	0.0039	*C6orf10*
22	18.3	rs7289747	C	0.063	1.22	9.6×10^{-6}	1.02	0.55	1.07	0.0058	*TXNRD2*
3	175.2	rs13078193	G	0.24	1.12	2.2×10^{-5}	1.01	0.50	1.04	0.0076	*NLGN1*
6	64.3	rs1744163	C	0.90	1.19	6.9×10^{-5}	1.01	0.56	1.05	0.015	*PTP4A1*
22	26.1	rs5752534	C	0.73	1.11	5.6×10^{-5}	1.00	0.85	1.03	0.051	-
12	74.3	rs1383098	C	0.21	1.11	9.7×10^{-5}	0.98	0.22	1.01	0.33	*KRR1,* -

Mb, megabases based on NCBI Build 36; Al, allele; Freq, average control frequency in the SGENE-plus genome-wide typed data; Close genes, the gene a SNP is located in or, if the SNP is not located in a gene, the closest genes within 200 kb to either side.

Supplementary Table 4. Association of rs4583255[T] with psychosis by study group

Study Group	Pheno-type	*N*		Freq	OR (95% CI)	*P* value
		Cases	Controls			
SGENE-plus						
England	SZ	93	88	0.489	1.27 (0.84, 1.92)	0.26
Finland, excl Kuusamo	SZ	59	147	0.565	1.34 (0.86, 2.10)	0.19
Finland, Kuusamo	SZ	123	50	0.610	1.67 (1.00, 2.80)	0.049
Germany, Bonn	SZ	482	367	0.571	1.16 (0.95, 1.42)	0.15
Germany, Munich	SZ	565	604	0.533	1.36 (1.15, 1.61)	0.00036
Iceland	SZ	589	11483	0.556	1.07 (0.94, 1.22)	0.30
Italy	SZ	84	89	0.618	0.96 (0.62, 1.48)	0.84
Scotland	SZ	658	661	0.532	1.02 (0.87, 1.20)	0.79
2009 Collaboration						
ISC[1]	SZ	NA	NA	NA	1.05 (0.97, 1.13)	0.26
MGS[2]	SZ	NA	NA	NA	1.11 (1.02, 1.19)	0.011
Primary Follow-up						
Australia	BP	330	1811	0.538	0.89 (0.76, 1.05)	0.16
Belgium	SZ	506	340	0.571	1.06 (0.87, 1.29)	0.56
CATIE[3]	SZ	390	399	0.561	0.97 (0.78, 1.21)	0.79
Denmark, Aarhus 1	SZ	222	489	0.556	0.91 (0.73, 1.14)	0.43
Denmark, Aarhus 2	SZ	871	872	0.571	0.99 (0.87, 1.14)	0.92
Denmark, Copenhagen	SZ	1305	2330	0.553	1.09 (0.99, 1.20)	0.093
Finland, excl. Kuusamo	SZ	287	3873	0.590	1.03 (0.86, 1.24)	0.72
France	BP/SZ	NA	NA	0.579	1.16 (1.01, 1.33)	0.037
GAIN/BiGs[2]	BP	528	843	0.547	1.16 (0.98, 1.37)	0.084
GSK/Canada	BP	288	200	0.550	1.06 (0.79, 1.41)	0.70
GSK/England	BP	183	450	0.549	1.21 (0.94, 1.55)	0.13
GSK/Scotland	BP	77	184	0.519	1.03 (0.71, 1.50)	0.89
Georgia	BP/SZ	199	203	0.559	1.11 (0.84, 1.47)	0.45
Germany, Bonn	SZ	604	1507	0.549	1.13 (0.98, 1.29)	0.086
Germany, Bonn	BP	NA	NA	0.566	1.04 (0.90, 1.20)	0.62
Germany, Bonn 2	BP	488	861	0.559	1.19 (1.01, 1.40)	0.041
Germany, Munich	SZ	294	1587	0.566	0.97 (0.82, 1.16)	0.78
Hungary	SZ	235	207	0.585	1.13 (0.87, 1.49)	0.36
Iceland	BP	544	23740	0.553	1.09 (0.96, 1.24)	0.17
Ireland[2]	SZ	1310	1023	0.509	1.11 (0.98, 1.25)	0.10
Italy	SZ	134	89	0.596	1.11 (0.75, 1.63)	0.61
Macedonia	BP/SZ	159	136	0.603	1.25 (0.89, 1.74)	0.20
NIMH/Pritzker	BP	651	602	0.554	0.97 (0.82, 1.14)	0.70
Netherlands 1	SZ	693	3687	0.548	0.96 (0.86, 1.09)	0.55
Netherlands 2	SZ	174	603	0.555	0.97 (0.76, 1.23)	0.77
Norway	BP/SZ	550	279	0.566	1.11 (0.90, 1.36)	0.34
Russia	SZ	580	734	0.559	1.08 (0.92, 1.26)	0.33
Russia 2	BP/SZ	258	253	0.543	1.14 (0.89, 1.46)	0.30
STEP1[2]	BP	935	672	0.556	1.08 (0.93, 1.25)	0.32
Serbia	BP/SZ	78	100	0.635	1.33 (0.85, 2.08)	0.21
Spain, Santiago	SZ	282	596	0.598	1.23 (1.00, 1.52)	0.048
Spain, Valencia	SZ	323	398	0.579	1.04 (0.85, 1.29)	0.68
Sweden	SZ	243	282	0.553	1.16 (0.90, 1.48)	0.25
United Kingdom[2]	SZ	479	2937	NA	1.05 (0.91, 1.21)	0.49
WTCCC[2]	BP	1868	11373	0.548	1.08 (1.00, 1.16)	0.057
WTCCC2[3]	BP/SZ	NA	NA	0.548	1.10 (0.98, 1.23)	0.10
Secondary Follow up						
GRAS	SZ	992	1141	0.553	1.10 (0.97, 1.24)	0.14

Freq, control frequency [1]rs4283241 (HapMap CEU r^2=1.0) [2]imputed [3]rs11150577 (HapMap CEU r^2=1.0)

Supplementary Table 5. Comparison of association results in schizophrenia and bipolar disorder follow-up samples

			Schizophrenia (10,671 cases; 23,900 controls)		Bipolar Disorder (7,333 cases; 43,779 controls)	
Mb	SNP	AI	OR (95% CI)	*P*	OR (95% CI)	*P*
2p15.1, *VRK2*						
58.1	rs2312147	C	1.07 (1.03, 1.11)	0.00023	1.03 (0.99, 1.07)	0.16
6p21.3-6p22.1, MHC						
27.2	rs6913660	C	1.11 (1.06, 1.17)	2.3×10^{-5}	1.03 (0.98, 1.09)	0.25
27.4	rs6932590	T	1.10 (1.05, 1.14)	2.5×10^{-5}	1.02 (0.98, 1.08)	0.33
28.4	rs13211507	T	1.22 (1.14, 1.31)	5.2×10^{-9}	1.05 (0.98, 1.13)	0.17
32.3	rs3131296	G	1.15 (1.08, 1.21)	1.4×10^{-6}	1.02 (0.96, 1.09)	0.46
11q24.2, *NRGN*						
124.1	rs12807809	T	1.09 (1.04, 1.15)	0.00034	1.09 (1.03, 1.16)	0.0023
16p11.2, *TAOK2*						
29.9	rs4583255	T	1.06 (1.02, 1.10)	0.0011	1.08 (1.03, 1.12)	0.00026
18p21.2, *TCF4*						
50.9	rs4309482	A	1.08 (1.04, 1.12)	1.7×10^{-5}	1.00 (0.96, 1.05)	0.89
51.3	rs9960767	C	1.14 (1.06, 1.23)	0.00057	1.03 (0.94, 1.13)	0.57

For schizophrenia, follow-up study groups from Belgium, CATIE, Denmark/Aarhus 1, Denmark/Aarhus 2, Denmark/Copenhagen, Finland/excluding Kuusamo, Georgia (schizophrenia cases only), Germany/Bonn, Germany/Munich, GRAS, Hungary, Ireland, Italy, Macedonia (schizophrenia cases only), Netherlands 1, Netherlands 2, Russia, Russia 2 (schizophrenia cases only) , Serbia (schizophrenia cases only), Spain/Santiago, Spain/Valencia, Sweden, and the United Kingdom were used. For bipolar disorder, follow-up study groups from Australia, France (bipolar cases only), GAIN/BiGs, Germany/Bonn, Germany/Bonn 2, GSK/Canada, GSK/England, GSK/Scotland, Iceland, NIMH/Pritzker, Norway, STEP and WTCCC were incorporated. No control samples were included in both analyses.

Supplementary Table 6. Association of rs4583255[T] with autism by study group

a. Family-based samples

	Autism Spectrum				Autism				Multiplex Autism Spectrum			
	T	U	OR (95% CI)	*P*	T	U	OR (95%CI)	*P*	T	U	OR (95%CI)	*P*
AGP	530	555	0.96 (0.85, 1.08)	0.45	300	317	0.95 (0.81, 1.11)	0.49	NA	NA	NA	NA
AGRE	548	506	1.08 (0.96, 1.22)	0.20	530	490	1.08 (0.96, 1.22)	0.21	517	476	1.09 (0.96, 1.23)	0.19

T, transmitted T alleles; U, transmitted T alleles; NA, not available

b. Case-control samples

		Autism Spectrum		Autism		Multiplex Autism Spectrum	
	Freq	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
England (MGAS)	0.532	1.39 (1.01, 1.91)	0.04	1.80 (1.10, 2.96)	0.02	NA	NA
Finland	NA	0.99 (0.75, 1.31)	0.94	0.97 (0.72, 1.30)	0.84	1.15 (0.70, 1.89)	0.58
Georgia	0.559	0.97 (0.69, 1.34)	0.84	0.97 (0.69, 1.34)	0.84	NA	NA
Germany (Homburg/Frankfurt)	0.571	0.88 (0.67, 1.15)	0.34	0.91 (0.65, 1.27)	0.57	NA	NA
Iceland	0.553	0.99 (0.86, 1.15)	0.92	1.06 (0.82, 1.37)	0.66	1.15 (0.72, 1.85)	0.56
Netherlands (Poot)	0.545	0.97 (0.64, 1.46)	0.88	NA	NA	0.96 (0.44, 2.10)	0.93
Netherlands (Staal)	0.552	0.88 (0.64, 1.21)	0.43	0.89 (0.62, 1.29)	0.55	0.87 (0.57, 1.32)	0.51
Serbia	0.635	0.96 (0.63, 1.45)	0.84	0.98 (0.63, 1.54)	0.93	NA	NA
Ukraine	0.576	0.83 (0.55, 1.26)	0.39	0.86 (0.55, 1.32)	0.48	NA	NA

Freq, control frequency; NA, not available

Supplementary Table 7. Association of rs4583255[T] with gene expression in adult brain

	Webster *et al (N = 362)*		Gibbs *et al (N = 145)*		Colantuoni *et al (N = 58)*		Combined *(N = 565)*	
Gene	Effect (95% CI)	*P*	Effect (95% CI)	*P*	Effect (95% CI)	*P*	Effect (95% CI)	*P*
KCTD13	0.17 (0.02, 0.31)	0.029	0.05 (-0.08, 0.18)	0.43	-0.02 (-0.17, 0.14)	0.84	0.07 (-0.01, 0.15)	0.11
MAPK3	0.07 (-0.07, 0.22)	0.33	0.16 (0.04, 0.29)	0.010	0.04 (-0.22, 0.30)	0.76	0.12 (0.03, 0.21)	0.011
MVP	-0.07 (-0.21, 0.08)	0.38	0.13 (-0.02, 0.27)	0.093	NA	NA	0.03 (-0.07, 0.13)	0.56

Only European-ancestry samples were included in the analysis.

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References

1. Endicott, J. & Spitzer, R.L. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* **35**, 837-44 (1978).
2. Williams, J.B. et al. The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. *Arch Gen Psychiatry* **49**, 630-6 (1992).
3. Wing, J.K. et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry* **47**, 589-93 (1990).
4. Cichon, S. et al. Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. *Am J Hum Genet* **88**, 372-81.
5. Heath, S.C. et al. Investigation of the fine structure of European populations with applications to disease association studies. *Eur J Hum Genet* **16**, 1413-29 (2008).
6. Pritchard, J.K., Stephens, M. & Donnelly, P. Inference of population structure using multilocus genotype data. *Genetics* **155**, 945-59 (2000).
7. Howie, B.N., Donnelly, P. & Marchini, J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* **5**, e1000529 (2009).
8. Marchini, J. & Howie, B. Genotype imputation for genome-wide association studies. *Nat Rev Genet* **11**, 499-511.
9. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661-78 (2007).
10. Marchini, J., Howie, B., Myers, S., McVean, G. & Donnelly, P. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet* **39**, 906-13 (2007).
11. Dudbridge, F. Likelihood-based association analysis for nuclear families and unrelated subjects with missing genotype data. *Hum Hered* **66**, 87-98 (2008).
12. Grant, S.F. et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* **38**, 320-3 (2006).
13. Steinberg, S. et al. Common variants at VRK2 and TCF4 conferring risk of schizophrenia. *Hum Mol Genet* **20**, 4076-81.
14. Sullivan, P.F. et al. Genomewide association for schizophrenia in the CATIE study: results of stage 1. *Mol Psychiatry* **13**, 570-84 (2008).
15. Stefansson, H. et al. Common variants conferring risk of schizophrenia. *Nature* **460**, 744-7 (2009).
16. O'Donovan, M.C. et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet* **40**, 1053-5 (2008).
17. Sklar, P. et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* **43**, 977-83.
18. Smith, E.N. et al. Genome-wide association study of bipolar disorder in European American and African American individuals. *Mol Psychiatry* **14**, 755-63 (2009).
19. Scott, L.J. et al. Genome-wide association and meta-analysis of bipolar disorder in individuals of European ancestry. *Proc Natl Acad Sci U S A* **106**, 7501-6 (2009).
20. Vassos, E. et al. Replication Study and Meta-Analysis in European Samples Supports Association of the 3p21.1 Locus with Bipolar Disorder. *Biol Psychiatry*.
21. Djurovic, S. et al. A genome-wide association study of bipolar disorder in Norwegian individuals, followed by replication in Icelandic sample. *J Affect Disord*.
22. Sklar, P. et al. Whole-genome association study of bipolar disorder. *Mol Psychiatry* **13**, 558-69 (2008).
23. Anney, R. et al. A genome-wide scan for common alleles affecting risk for autism. *Hum Mol Genet* **19**, 4072-82.
24. Wang, K. et al. Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature* **459**, 528-33 (2009).
25. Curran, S. et al. No association between a common single nucleotide polymorphism, rs4141463, in the MACROD2 gene and autism spectrum disorder. *Am J Med Genet B Neuropsychiatr Genet* **156B**, 633-9.
26. Kilpinen, H. et al. Association of DISC1 with autism and Asperger syndrome. *Mol Psychiatry* **13**, 187-96 (2008).
27. Teslovich, T.M. et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707-13.

28. van Daalen, E. et al. Social Responsiveness Scale-aided analysis of the clinical impact of copy number variations in autism. *Neurogenetics* **12**, 315-23.
29. Lampi, K.M. et al. Brief report: validity of Finnish registry-based diagnoses of autism with the ADI-R. *Acta Paediatr* **99**, 1425-8.
30. Freitag, C.M. et al. Adenosine A(2A) receptor gene (ADORA2A) variants may increase autistic symptoms and anxiety in autism spectrum disorder. *Eur Child Adolesc Psychiatry* **19**, 67-74.