Supplementary Methods and Data

Methods

Subjects

We selected 197 patients with schizophrenia [57.4% males (113 males and 84 females); mean age ± SD, 36.9±12.2 years old] and 324 healthy controls [42.6% males (138 males and 186 females); mean age ± SD, 36.2±12.4 years old] with assessment of at least one schizophrenia-related phenotype, such as neurocognitive function, neuroimaging, and neurophysiological examinations, from an entire cohort of SP (Schizophrenia Project) in Department of Psychiatry, Osaka University Graduate School of Medicine since 2005 for a genome-wide association analysis (1-3). In this Schizophrenia Project, we recruited patients with schizophrenia and their relatives from the Osaka University Hospital and healthy controls through advertisements at Osaka University. Current whole batteries they received are cognitive tests (WAIS: Wechsler Adult Intelligence Scale, JART: a Japanese version of the National Adult Reading Test, WMS-R: Wechsler Memory Scale-Revised, AVLT: Rey Auditory Verbal Learning Test, WCST: Wisconsin Card Sorting Test, CPT: continuous performance test, facial recognition test, etc.), neuroimaging (three-dimensional brain structural imaging, diffusion tensor imaging, resting state fMRI, etc.), neurophysiological tests (PPI: prepulse inhibition, NIRS: near infra-red spectroscopic topography, EEG: electroencephalogram, etc.), personality traits (TCI: Temperament and Character Inventory and SPQ: Schizotypal Personality

Questionnaire), and blood draw for DNA, RNA, plasma and immortalized lymphocytes. All of the selected subjects (197 patients with schizophrenia and 324 healthy controls) were biologically unrelated. There were no first- or second degree relatives and all were of Japanese descent. Subjects were excluded if they had neurological or medical conditions that could potentially affect the central nervous system, e.g., atypical headache, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active cancer, cerebrovascular disease, epilepsy, seizures, substance-related disorders or mental retardation. Each patient with schizophrenia had been diagnosed by at least two trained psychiatrists according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), based on the Structured Clinical Interview for DSM-IV (SCID). Current symptoms of schizophrenia were evaluated using the Positive and Negative Syndrome Scale (PANSS). Psychiatrically, medically and neurologically healthy controls were evaluated using the non-patient version of the SCID to exclude individuals who had received current or past psychiatric services or psychiatric medication.

Written informed consent was obtained from all subjects after the procedures had been fully explained. This study was conducted in accordance with the World Medical Association's Declaration of Helsinki and was approved by the Research Ethics Committee at Osaka University.

Genotyping and quality control (QC)

Genotyping of 197 patients with schizophrenia and 324 healthy controls was performed

using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, CA), according to the manufacturer's protocol. The genotypes were called from the CEL files using Birdseed v2 for the 6.0 chip implemented in the Genotyping Console software (Affymetrix). We then applied the following QC criteria to exclude samples: (1) arrays with low QC (<0.4) by Birdseed v2 (n = 0), (2) samples for which < 95% of genotypes were called (n = 0), and (3) samples in the same family by pi-hat (>0.4, n=0). Using the QC criteria, no sample was excluded. Next, we excluded SNPs (single nucleotide polymorphisms) that: (1) had low call rates (< 0.95), (2) were duplicated, (3) localized to sex chromosomes, (4) deviated from Hardy-Weinberg Equilibrium (HWE) in the controls $P < 0.0001$, or (5) had low minor allele frequencies (MAF < 0.05). After all of these exclusions, 541,657 QC'ed SNPs remained for experimental analysis.

To test for the existence of genetic structure in the data, we performed a principal component analysis (PCA) using EIGENSTRAT 3.0. Ten eigenvectors were calculated. Genotype information from the JPT (Japanese in Tokyo, Japan), CHB (Han Chinese in Beijing, China), CEU (Utah residents with ancestry from northern and western Europe), and YRI (Yoruba in Ibadan, Nigeria) in HapMap phase III was compared with our dataset to check for population stratification (Figure S1).

Assessment of cognitive decline

The premorbid intelligence quotient (IQ) was estimated using the JART (a Japanese version

of the National Adult Reading Test: a reading test consisting of 50 *Kanji* compound words), which was originally developed as an estimated premorbid IQ test for patients with Alzheimer disease (4) and was used for patients with schizophrenia (5-7). The difference score was defined by the subtraction of the estimated premorbid IQ (as measured by the JART) from the present IQ (as measured by the WAIS-R or WAIS-III).

Subjects and statistical method for GWAS

In this study, we used data from 166 patients with schizophrenia and 323 controls who were completed JART and WAIS with QC'ed genotype and sufficient demographic information. Detailed demographic information is shown in Supplementary Table 1. There was no difference in the mean age between the cases and the controls (p>0.3); however, the gender ratio, years of education, estimated premorbid IQ, present IQ, and difference score were significantly different between the two groups. Multiple linear regression analysis was performed to compare the difference score in the major allele homozygous genotypes with that in the minor allele carriers in the patients with schizophrenia, using PLINK 1.07 software. Gender and years of education were used as covariates, because the WAIS and JART scores were already corrected by age. QQ and Manhattan plots are listed in Figures S2 and S3. Multiple linear regression analyses were also used to compare the genotype effects on JART and IQ in the patients with schizophrenia and in the controls.

Subject and statistical methods for replication study

Replication study has been performed using a part of the CBDB/NIMH (Clinical Brain Disorders Branch, National Institute of Mental Health) data (8). These data were composed of multiple cognitive batteries with genotyping data by Illumina HumanHap550K/610Quad Bead Chips (San Diego, California) in 339 people with DSM IV schizophrenia. The difference score was calculated by the subtraction of the estimated premorbid IQ (as measured by the Wide range achievement test) from the estimated present IQ (as measured by the WAIS). The association analysis between difference score and three SNPs for replication was performed using PLINK statistical software (v1.07), assuming an additive genetic model and controlling for age, sex, and ancestry (four MDS axes). P values are one tailed, and statistical significance was defined as $p<0.05$.

Data

Analysis for confounding factors

When the genotype groups in the top 10 SNPs of cognitive decline were compared in the patients with schizophrenia, we found no differences across the demographic variables, except for age and duration of illness (in rs1555702 and rs17069667) and the chlorpromazine equivalent of the daily antipsychotic dose (in rs17005024 and rs11946008) ($0.01<$ all $p<0.05$). To examine whether our findings were influenced by possible confounding variables such as age, gender, education level,

illness duration, and antipsychotic dose, we additionally performed analyses using 5 covariates and 4 covariates models (5 covariates model: age, gender, education level, illness duration, and antipsychotic dose; 4 covariates model: gender, education level, illness duration, and antipsychotic dose). P-values and β for the genotype association by adjusting using 5 or 4 covariates were slightly reduced but remained significant, despite reduced power for these analyses (Supplemental table 3).

Analysis of controls

In 323 comparison subjects (mean estimated premorbid IQ: 107.3±8.1, full scale IQ: 109.0±12.2 and difference score: 1.7±9.8), no effect of the 10 SNPs was observed on either estimated premorbid IQ or full scale IQ, except for a weak association between rs7157599 and full scale IQ (p=0.033). We did not analyzed the association between 10 SNPs and difference score (subtraction score of estimated premorbid IQ from present IQ) in comparison subjects, as comparison subjects were not in disease process.

Replication study

We tried to replicate top 10 SNPs for cognitive decline in patients with schizophrenia using the CBDB/NIMH sample. We could perform replication analysis only three out of ten SNPs because of differences in allele frequencies and genotyping platform (this study: Affymetrix Genome-Wide Human SNP Array 6.0, CBDB/NIMH: Illumina HumanHap550K/610Quad Bead Chips). However,

there was a directionally consistent, trend association of genotype for a proxy SNP of the top SNP (rs3783332: a proxy of rs7157599, r^2=0.63, one tailed p=0.03). No statistically significant association was observed between other two SNPs and difference score (rs1219704 and rs9586776, p>0.5). These data indicated suggestive evidence for association between difference score in schizophrenia and rs7157599.

References

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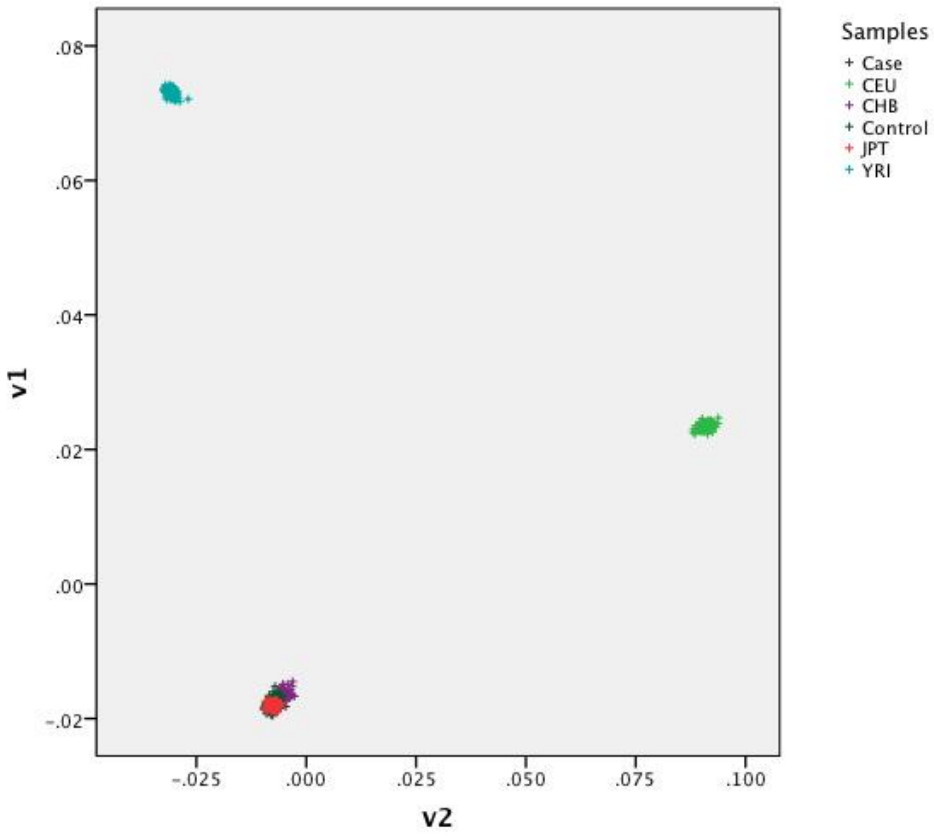

Figure S1. Principal component analysis: Scatter plot of eigenvectors 1 and 2.

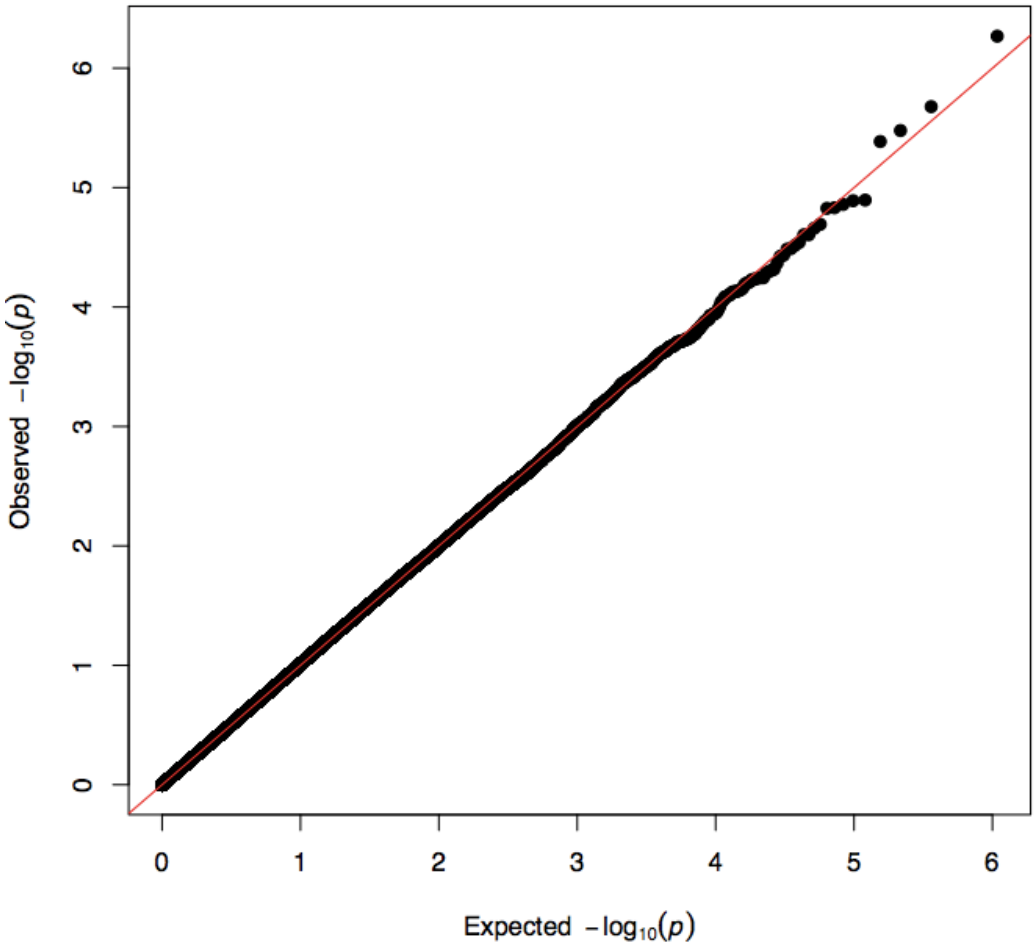

Figure S2. QQ plot in multiple linear regression analysis of cognitive decline in patients with schizophrenia.

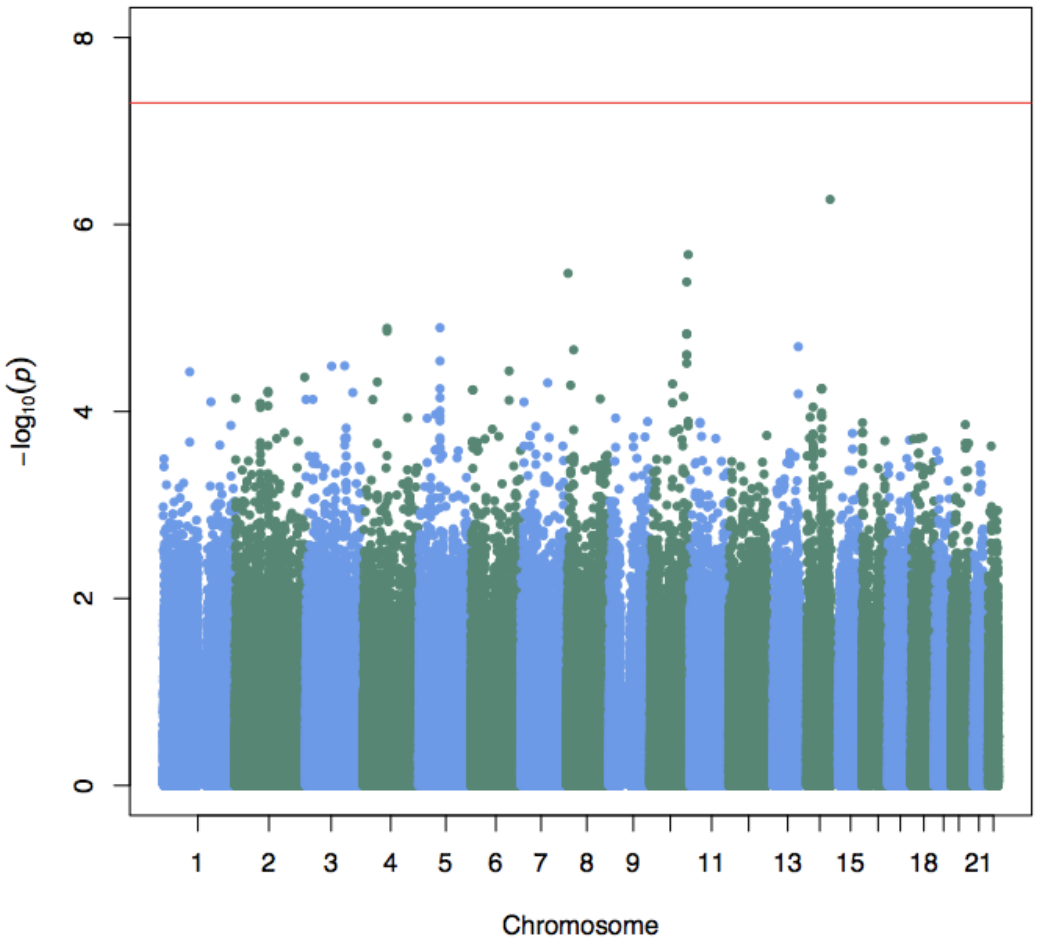

Figure S3. Manhattan plot in multiple linear regression analysis of cognitive decline in patients with schizophrenia. The red line indicates a P value of 5xE-08.

Table S1. Demographic information for subjects

Variables	Patients with schizophrenia (n=166)	Comparison subujects (n=323)	p value
Age (years)	37.0 ± 12.1	36.2 ± 12.3	3.66E-01
Gender (male/female)	(97/69)	(138/185)	9.93E-04
Education (years)	13.9 ± 2.4	15.0 ± 2.3	1.01E-05
Age at onset (years)	24.2 ± 9.5		
Duration of illuness (years)	12.7 ± 10.1	-	
CPZeq. (mg/day)	588.3 ± 539.0		
PANSS total	79.1 ± 21.0	-	
Positive symptoms	18.9 ± 5.9	-	
Negative symptoms	19.4 ± 6.4	-	
General psychopathology scale	40.8 ± 10.9		
JART	101.2 ± 10.0	107.3 ± 8.1	3.65E-11
WAIS	85.1 ± 16.8	109.0 ± 12.2	2.47E-41
Difference score	-16.1 ± 13.1	1.7± 9.8	1.71E-39

CPZeq.; chlorpromazine equivalent of antipsychotics

Table S2 TOP200 SNPs for cognitive decline in schizophrenia

				MAF				
SNP	chr	bp	tested allele (minor allele)	cases	comparison subjects	beta	P	GENE(+/-20KB)
rs7157599	14	100625902	C	0.2805	0.2445	9.919	5.39E-07	DEGS2
rs1555702	10	130622498	C	0.4024	0.3796	10.03	2.1E-06	
rs17069667	8	4092133	C	0.3827	0.3668	9.425	3.33E-06	CSMD1
rs1219705	10	125585034	G	0.3373	0.338	-9.257	4.11E-06	CPXM2
rs17555780	5	73423525	G	0.1867	0.2043	-9.069	1.27E-05	
rs17005024	4	81945383	G	0.09639	0.1173	11.17	1.29E-05	BMP3
rs11946008	4	81925707	A	0.1159	0.1211	10.48	1.38E-05	
rs7900253	10	125599464	G	0.3343	0.3333	-8.721	1.47E-05	CPXM2
rs6599627	10	125609811	C	0.3445	0.339	-8.776	1.49E-05	CPXM2
rs9586776	13	105909261	T	0.1364	0.1382	-9.778	2.03E-05	
rs4639518	8	23256092	G	0.311	0.2802	8.459	2.19E-05	LOXL2
rs2176488	10	125601148	C	0.3384	0.3375	-8.535	2.48E-05	CPXM2
rs7920094	10	125608590	C	0.3478	0.3465	-8.538	2.48E-05	CPXM2
rs290725	5	73461072	T	0.4576	0.483	-9.205	2.88E-05	
rs1219704	10	125585163	G	0.3553	0.3462	-8.686	3.05E-05	CPXM2
rs6800143	3	133844946	A	0.441	0.473	9.424	3.24E-05	
rs1384771	3	88872504	A	0.3705	0.3812	8.513	3.28E-05	
rs9492683	6	130967588	G	0.4729	0.446	9.125	3.69E-05	
rs17501381	1	92003919	C	0.1114	0.07121	-10.11	3.77E-05	CDC7
rs9751676	2	238906315	C	0.2048	0.2176	8.543	0.000043	UBE2F
rs13114836	4	48495577	G	0.06098	0.06406	-12.66	4.83E-05	ZAR1
rs3735650	7	92988398	T	0.3098	0.2461	-8.15	4.93E-05	CCDC132
rs11001281	10	76831010	G	0.4299	0.4112	9.071	5.06E-05	DUPD1
rs1044011	8	12941709	C	0.4789	0.425	8.83	5.24E-05	DLC1
rs221899	14	71605268	G	0.3584	0.3858	-8.276	5.69E-05	
rs2810098	14	71433911	G	0.3584	0.3843	-8.276	5.69E-05	PCNX
rs10045219	5	73391725	T	0.2061	0.2283	-8.47	5.7E-05	
rs2810073	14	71383848	C	0.3667	0.3921	-8.319	5.77E-05	PCNX
rs1001289	6	5910305	T	0.04518	0.06019	-14.47	5.87E-05	
rs10155695	6	5904791	C	0.04518	0.06019	-14.47	5.87E-05	
rs6736093	2	112655242	G	0.1012	0.1047	-10.28	6.08E-05	MERTK

rs2175263	3	161841018	A	0.4604	0.4668	9.056	6.27E-05	
rs17779482	2	112665677	T	0.1054	0.1146	-9.983	6.31E-05	MERTK
rs9558521	13	105925554	C	0.1386	0.1375	-9.087	6.48E-05	
rs290481	10	114923825	C	0.3223	0.392	-8.005	6.94E-05	TCF7L2
rs4704110	5	73437503	C	0.1898	0.213	-8.323	7.13E-05	
rs10192365	2	1231315	G	0.3645	0.339	8.114	7.26E-05	SNTG2
rs6983475	8	115039038	G	0.2922	0.3009	-7.951	7.34E-05	
rs2683540	3	24221947	T	0.2805	0.2868	8.066	7.41E-05	THRB
rs3773383	3	416943	G	0.4909	0.4657	-9.651	7.44E-05	CHL1
rs10033556	4	32962030	A	0.4337	0.4658	8.716	7.46E-05	
rs1532986	6	130962874	T	0.4846	0.4585	8.978	7.58E-05	
rs12049436	1	165032101	T	0.4543	0.4969	8.712	7.89E-05	
rs4620184	7	11282387	C	0.3273	0.3204	-8	7.93E-05	
rs11001286	10	76834982	C	0.4398	0.4195	8.901	8.1E-05	DUPD1
rs2164878	2	86153855	T	0.3645	0.3457	8.005	8.23E-05	
rs6547647	2	86155271	T	0.3645	0.3457	8.005	8.23E-05	
rs4848979	2	112816236	T	0.103	0.1242	-9.945	0.000087	TMEM87B
rs17678541	14	41773741	C	0.2485	0.216	-7.989	8.95E-05	
rs7576135	2	86160562	T	0.3616	0.35	8.157	9.07E-05	
rs2120729	5	73442438	G	0.488	0.5	-8.951	9.82E-05	
rs8007026	14	71464384	G	0.3576	0.3854	-8.102	0.000103	PCNX
rs6450476	5	57771087	A	0.1717	0.1543	8.285	0.000108	LOC100289379
rs2158997	14	71497794	G	0.3606	0.3793	-7.974	0.000112	PCNX
rs2926721	5	73450088	G	0.4819	0.4938	-8.777	0.000112	
rs2189807	14	71363031	A	0.375	0.3765	-8.066	0.000114	PCNX
rs6571396	14	31681227	T	0.3086	0.3537	-7.883	0.000115	HECTD1
rs17690873	4	152418466	A	0.1304	0.1242	-9.178	0.000117	FAM160A1
rs1414243	9	21748433	G	0.3788	0.3172	-7.977	0.000118	
rs7717683	5	29249544	G	0.103	0.1331	-9.619	0.000118	
rs392079	5	73441848	G	0.4699	0.4892	-8.548	0.000126	
rs11016498	10	130622295	G	0.2888	0.3006	7.972	0.000127	
rs7046961	9	131849036	T	0.1487	0.1491	-9.16	0.000128	DOLPP1
rs12804535	11	35955713	T	0.3018	0.3266	7.828	0.00013	LDLRAD3
rs12926827	16	2488693	T	0.1536	0.1373	8.469	0.000132	CCNF
rs11033335	11	35957322	T	0.3042	0.3272	7.724	0.000134	LDLRAD3
rs663890	20	48405168	G	0.3735	0.3688	-7.922	0.000138	
rs6687540	1	233893329	C	0.494	0.4696	9.367	0.000141	
rs942525	10	130624838	C	0.2866	0.2919	7.809	0.000142	

rs1986783	7	52158542	A	0.3926	0.371	8.016	0.000145	
rs13101018	3	138861711	C	0.4848	0.4844	8.463	0.000151	BPESC1
rs17109189	14	71709355	A	0.2781	0.3074	-7.951	0.000153	C14orf56
rs1572208	6	73171594	C	0.4398	0.4707	-8.433	0.000155	
rs2784920	10	98913628	G	0.3163	0.3627	-7.592	0.000155	SLIT1
rs4278162	8	23169455	G	0.2485	0.2966	7.688	0.000157	LOXL2
rs11002475	10	80031020	C	0.09748	0.08805	9.772	0.000166	LOC100132987
rs4497687	16	2446021	G	0.1265	0.1289	8.91	0.000168	
rs6600203	16	2445480	T	0.1265	0.1265	8.91	0.000168	
rs11894600	2	168784354	A	0.3129	0.3083	7.648	0.000169	
rs379468	15	70150451	T	0.09091	0.09722	-10.48	0.000171	C15orf50
rs1779516	14	41753964	G	0.4187	0.4408	-7.846	0.000174	
rs1431032	14	41788077	A	0.2438	0.2186	-7.801	0.000176	
rs8181764	12	131062900	C	0.4849	0.4861	8.523	0.00018	
rs1622804	14	41752589	A	0.4099	0.4446	-7.869	0.000181	
rs12532023	7	32394878	C	0.1235	0.1435	8.962	0.000182	
rs7791060	7	32397269	G	0.1235	0.1435	8.962	0.000182	
rs10501252	11	41258331	T	0.3303	0.3047	7.62	0.000185	
rs9354118	6	95147902	C	0.4121	0.4479	7.883	0.000185	
rs10984840	9	122868788	G	0.4604	0.4567	8.82	0.000187	
rs10735544	9	82971428	T	0.3705	0.3657	7.769	0.000187	
rs7626152	3	138675066	C	0.09036	0.1065	9.916	0.000189	C3orf72
rs12971263	18	38768209	C	0.4568	0.4026	-8.49	0.00019	
rs12155122	7	98483072	T	0.1024	0.1146	-9.75	0.00019	TRRAP
rs2926720	5	73450695	G	0.4713	0.4825	-8.411	0.000192	
rs2093075	14	29031632	C	0.4581	0.4561	8.629	0.000193	
rs1131262	3	133941320	C	0.4548	0.4722	8.285	0.000193	RYK
rs17257677	11	90364187	G	0.04658	0.0538	-13.38	0.000194	
rs6429923	2	142578483	C	0.2139	0.1904	-7.848	0.000194	LRP1B
rs7228535	18	24807371	T	0.3606	0.284	-7.749	0.000195	
rs17108804	14	71441524	C	0.3415	0.3416	-7.606	0.000195	PCNX
rs10807383	6	47882808	A	0.1863	0.2105	7.997	0.000197	PTCHD4
rs2348394	3	138716500	A	0.08537	0.07919	10.2	0.000197	PRR23A
rs7505079	18	6666417	G	0.2724	0.2746	7.659	0.000197	
rs17122872	10	109358096	C	0.3282	0.3261	-7.694	0.000199	
rs2279055	17	74309561	G	0.08282	0.07837	10.2	0.000202	PRPSAP1
rs12517914	5	73432001	A	0.2048	0.2238	-7.699	0.000204	
rs821232	16	79570138	A	0.2229	0.2484	7.638	0.000207	

rs3770535	2	216838699	T	0.4667	0.4612	-8.259	0.000207	MREG
rs12213320	6	5919702	G	0.04848	0.06386	-13.04	0.000208	
rs17501512	1	92012481	C	0.1084	0.07099	-9.234	0.000213	
rs10155777	6	5902668	G	0.04819	0.06481	-12.99	0.000213	
rs11243038	6	5897768	C	0.04819	0.06481	-12.99	0.000213	
rs7744130	6	5903994	A	0.04819	0.06481	-12.99	0.000213	
rs7769375	6	5904322	G	0.04819	0.06481	-12.99	0.000213	
rs2679722	2	86135154	A	0.3515	0.3474	7.602	0.000215	ST3GAL5
rs9368292	6	21279204	G	0.4819	0.4645	8.346	0.000215	
rs9466024	6	21286834	A	0.4819	0.4583	8.346	0.000215	
rs4297943	20	48423756	G	0.3675	0.3627	-7.659	0.000219	SLC9A8
rs6129028	20	59635795	G	0.2952	0.3179	-7.462	0.000219	LOC100506470
rs1565217	4	48479718	T	0.06928	0.08514	-11	0.00022	SLC10A4
rs8011741	14	41817982	G	0.25	0.2238	-7.526	0.000223	
rs12140768	1	195836268	C	0.3913	0.385	-7.999	0.000229	
rs9856298	3	133957265	A	0.4634	0.4777	8.29	0.00023	RYK
rs11684476	2	112793981	C	0.1	0.1265	-9.303	0.000231	MERTK
rs7083193	10	112175889	T	0.3212	0.309	7.511	0.000234	
rs10950343	7	11285339	T	0.4187	0.435	-7.783	0.000234	
rs13222586	7	145185358	T	0.1235	0.125	8.816	0.000234	
rs134748	22	26543287	T	0.3241	0.3738	7.57	0.000234	
rs12531858	7	32340099	A	0.2139	0.2616	7.651	0.000235	PDE1C
rs1333940	9	82971893	A	0.3697	0.3723	7.602	0.000238	
rs1684675	14	42584436	C	0.1327	0.1359	8.414	0.000241	
rs2165409	9	21748962	A	0.3616	0.3306	-7.715	0.000241	
rs4703622	5	73430161	G	0.2089	0.2414	-7.754	0.000242	
rs7593080	2	86145787	T	0.3645	0.3565	7.529	0.000242	
rs1136062	16	2502641	T	0.1402	0.1269	8.422	0.000245	CCNF
rs12193326	6	5898375	G	0.04878	0.06719	-12.81	0.000245	
rs1546920	20	50200782	T	0.4548	0.4012	-7.993	0.000247	ATP9A
rs6096487	20	50201217	A	0.4548	0.406	-7.993	0.000247	ATP9A
rs10058853	5	73433080	T	0.1914	0.2242	-7.787	0.000251	
rs6572138	14	42671745	C	0.1799	0.1656	7.834	0.000251	
rs2916179	15	70596974	G	0.2424	0.2654	-7.548	0.000252	
rs9379687	6	24721787	A	0.4669	0.4735	8.195	0.000257	C6orf62
rs26977	5	57658416	T	0.09639	0.1056	9.578	0.000258	
rs375523	5	57686575	A	0.09639	0.1049	9.578	0.000258	
rs9295020	6	170043646	A	0.04839	0.07632	12.97	0.000261	WDR27

rs17779700	5	136572793	G	0.07927	0.1013	10.22	0.000264	SPOCK1
rs9348464	6	21282089	G	0.4788	0.4675	8.181	0.000265	
rs12460407	19	8181037	C	0.4127	0.4444	7.702	0.000266	FBN3
rs8060813	16	2499011	T	0.1472	0.134	8.255	0.000268	CCNF
rs1782156	14	41752669	A	0.4281	0.4519	-7.835	0.000273	
rs2777732	13	76884327	A	0.4121	0.3994	7.831	0.000276	
rs1000448	14	71707633	A	0.2771	0.3166	-7.461	0.000277	C14orf56
rs11660384	18	24801301	T	0.3614	0.284	-7.548	0.00028	
rs17712675	18	24806736	C	0.3614	0.2824	-7.548	0.00028	
rs10237629	7	52139899	T	0.3916	0.3727	7.609	0.000286	
rs13017143	2	86466549	C	0.09337	0.108	9.395	0.000288	REEP1
rs7736398	5	82309128	C	0.09091	0.07562	-9.978	0.000292	
rs4909788	8	139424363	C	0.3765	0.3545	7.594	0.000293	FAM135B
rs2868128	4	81943068	C	0.1166	0.1672	8.742	0.000297	BMP3
rs11623006	14	22851141	A	0.1807	0.1984	-7.841	0.000299	TRA@
rs17793886	14	22806220	C	0.1807	0.1975	-7.841	0.000299	TRAV41
rs2574706	3	11615207	C	0.3343	0.3688	7.456	0.0003	VGLL4
rs11915859	3	138867882	A	0.4848	0.4782	8.096	0.0003	
rs10146319	14	42605529	A	0.1364	0.1378	8.192	0.000301	
rs6557672	8	23286234	G	0.2455	0.2299	7.433	0.000302	ENTPD4
rs17028885	3	32155048	T	0.4849	0.4707	-8.273	0.000303	GPD1L
rs9561694	13	95453071	C	0.4758	0.4907	-7.961	0.000303	
rs2285505	7	92987445	C	0.297	0.2469	-7.304	0.000307	CCDC132
rs1395804	8	132510680	T	0.2169	0.1863	7.418	0.000308	
rs13178251	5	132495185	A	0.3182	0.3704	7.304	0.000313	
rs1684696	14	42547019	A	0.1515	0.1426	7.968	0.000314	
rs4286013	13	76857474	G	0.4146	0.3898	7.704	0.000316	
rs2282199	9	94909375	A	0.1957	0.205	7.902	0.000316	
rs1120577	17	64866456	A	0.1867	0.1944	-7.762	0.000318	CACNG5
rs725144	5	73397114	A	0.1585	0.205	-7.893	0.000319	
rs7822769	8	23304456	C	0.3012	0.2709	7.257	0.000321	ENTPD4
rs7843529	8	23289536	G	0.3012	0.2731	7.257	0.000321	ENTPD4
rs6424073	1	3285628	G	0.4323	0.4231	-8.315	0.000321	PRDM16
rs16921893	10	21961864	G	0.2932	0.2848	-7.322	0.000324	MLLT10
rs7815294	8	10419303	A	0.05723	0.09752	11.52	0.000326	
rs6548209	2	1228487	G	0.3614	0.3452	7.35	0.000329	SNTG2
rs6481156	10	57098859	T	0.378	0.3044	7.424	0.000329	
rs7258240	19	15772414	G	0.4758	0.483	7.918	0.000331	CYP4F3

rs13235812	7	147556653	A	0.2349	0.2562	7.284	0.000335	CNTNAP2
rs3853291	11	44369477	A	0.3232	0.2966	-7.135	0.000336	
rs6705604	2	45216585	A	0.2861	0.2747	7.29	0.000338	SIX2
rs10963750	9	18769138	A	0.3735	0.3459	-7.345	0.000341	ADAMTSL1
rs689183	11	110012143	G	0.07831	0.07256	10.19	0.000341	ZC3H12C
rs10845067	12	10356973	C	0.1273	0.1475	8.384	0.000342	GABARAPL1
rs13023154	2	86516984	A	0.09394	0.1068	9.278	0.000346	REEP1
rs517543	18	75367624	C	0.1566	0.1615	-8.11	0.000347	
rs2366958	2	86169989	C	0.1024	0.125	9.022	0.000347	
rs780886	12	116200160	G	0.1909	0.1807	-7.624	0.000349	
rs11603377	11	21999145	G	0.06627	0.06075	10.98	0.000351	
rs7444137	5	29313927	C	0.1296	0.172	-8.398	0.000352	
rs17837241	13	66613187	A	0.06442	0.075	11.16	0.000352	
rs6993786	8	23309914	G	0.2455	0.2284	7.347	0.000353	ENTPD4
rs10440955	7	11282369	T	0.3795	0.3793	-7.438	0.000354	
rs11129165	3	24813614	T	0.3	0.2588	7.277	0.000359	
rs8052046	16	2484783	A	0.1506	0.1311	7.991	0.000361	CCNF

MAF: minor allele frequency

Table S3: Top 10 SNPs for cognitive decline in schizophrenia with different analytical models

rs number	Closest gene	dominant model		additive model		5 covariates model		4 covariates model	
		β	p value	β	p value	β	p value	β	p value
rs7157599	DEGS2	-9.92	5.39E-07	-8.056	2.76E-06	-9.119	1.11E-06	-9.114	1.01E-06
rs1555702	MKI67	-10.03	2.10E-06	-6.119	2.70E-05	-8.330	6.28E-05	-8.307	6.17E-05
rs17069667	CSMD1	-9.43	3.33E-06	-4.228	3.56E-03	-8.332	2.32E-05	-8.333	2.19E-05
rs1219705	CPXM2	9.26	4.11E-06	4.727	1.28E-03	8.263	1.57E-05	8.250	1.47E-05
rs17555780	RGNEF	9.07	1.27E-05	8.522	1.31E-05	8.276	2.37E-05	8.278	2.22E-05
rs17005024	BMP3	-11.17	1.29E-05	-11.13	4.44E-06	-8.711	5.36E-04	-8.673	5.19E-04
rs11946008	BMP3	-10.48	1.38E-05	-10.52	4.72E-06	-8.121	5.46E-04	-8.073	5.44E-04
rs7900253	CPXM2	8.72	1.47E-05	4.131	4.43E-03	7.792	4.51E-05	7.790	4.23E-05
rs6599627	CPXM2	8.78	1.49E-05	3.946	5.83E-03	7.883	4.28E-05	7.860	4.14E-05
rs9586776	DAOA	9.78	2.03E-05	9.124	1.82E-05	8.869	6.24E-05	8.862	5.89E-05

Dominant model: Multiple linear regression analysis was performed to compare the difference score in the major allele homozygous genotypes with that in the minor allele carriers in the patients with schizophrenia. Additive model: Multiple linear regression analysis was performed to compare the difference score among subjects with major allele homozygous (0), heterozygous (1), the minor allele homozygous (2) in the patients with schizophrenia. Dominant and additive models: covariate with gender and education year; 5 covariates model: covariate with age, gender, years of education, duration of illness, and antipsychotic dose in dominant model; 4 covariates model: covariate with gender, years of education, duration of illness, and antipsychotic dose in dominant model.