Am J Transl Res 2017;9(5):2473-2491
www.ajtr.org /ISSN:1943-8141/AJTR0036268

Original Article

A novel relationship for schizophrenia, bipolar and major depressive disorder Part 5: a hint from chromosome 5 high density association screen

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Received July 20, 2016; Accepted January 31, 2017; Epub May 15, 2017; Published May 30, 2017

Abstract: Familial clustering of schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD) was systematically reported (Aukes, M. F. Genet Med 2012, 14, 338-341) and any two or even three of these disorders could co-exist in some families. In addition, evidence from symptomatology and psychopharmacology also imply that there are intrinsic connections between these three major disorders. A total of 56,569 single nucleotide polymorphism (SNPs) on chromosome 5 were genotyped by Affymetrix Genome-Wide Human SNP array 6.0 on 119 SCZ, 253 BPD (type-I), 177 MDD patients and 1000 controls. Associated SNPs and flanking genes was screen out systematically, and cadherin pathway genes (*CDH6, CDH9, CDH10, CDH12, and CDH18)* belong to outstanding genes. Unexpectedly, nearly all flanking genes of the associated SNPs distinctive for BPD and MDD were replicated in an enlarged cohort of 986 SCZ patients ($P \leq 9.9E-8$). Considering multiple bits of evidence, our chromosome 5 analyses implicated that bipolar and major depressive disorder might be subtypes of schizophrenia rather than two independent disease entities. Also, cadherin pathway genes play important roles in the pathogenesis of the three major mental disorders.

Keywords: Schizophrenia, bipolar disorder, major depressive disorder, diagnosis, gene

Introduction

Schizophrenia (SCZ [MIM 181500]) is a severe mental disorder characterized by a disruption of thought processes that can cause delusions and hallucination. Bipolar disorder (BPD [MIM 125480]) is characterized by alternating episodes of mania (bipolar I) or hypomania (bipolar II) interspersed with periods of depression. Major depressive disorder (MDD [MIM 608516]) is characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. Genetic epidemiology and molecular genetics showoverlaps among the three disorders [1-4].

Genome-wide association study (GWAS), based on linkage disequilibrium, is an examination of many common genetic variants in different individuals to see if any variant is associated with a trait. One trend in the genetic association approach has been towards larger sample sizes for detecting causal SNPs that have smaller odds ratios and lower allele frequency, and another has been towards the use of strict defined phenotypes and homogenous genetic background of the sample population. However, the accurate phenotype delineation may be more important for detecting true genetic associations than increase in sample size [5]. Over the last two decades, linkage and association studies have identified multiple chromosomal regions and candidate genes for SCZ, BPD and MDD [6].

The Affymetrix Genome-wide Human SNP array 6.0 contains more than 906,600 single nucleotide polymorphisms (SNPs), and such dense resolution (approximately 3 KB) make it possible to investigate the association of all human genes to any disease trait. However, such stud-

Table 1. The samples characteristics of three major mental disorder and control in the population of Shandong province of China

Diagnosis (DSM-IV)	Male/female	Average age	Age of onset
Schizophrenia (SCZ119)	1.05 (61/58)	33.98 ± 11.99	27.65 ± 7.79
Bipolar disorder (BPD253)	1.26:1 (141/112)	34.05 ± 14.74	25.90 ± 11.77
Major depressive disorder (MDD177)	0.71:1 (49/68)	44.77 ± 16.96	39.547 ± 17.04
Schizophrenia (SCZ986)	0.99:1 (492/494)	33.80 ± 11.98	26.04 ± 9.72
Control (N1000)	1.32:1 (569/431)	23.08 ± 5.67	

ies usually require large sample sizes and huge cost. Fortunately, DNA pooling constitutes a cost effective alternative in GWAS and could cut dramatically the cost [7, 8].

In this study, we report the results of chromosome 5 of a Genome-wide Association Study (WGAS) by Affymetrix Genome-Wide Human SNP array 6.0 on the three major psychiatric disorders in the population of Shandong province of China, and also discuss the possible relationship between them.

Materials and methods

Subjects

The initial 119 schizophrenia patients (SCZ119) were recruited from the inpatients department of Chang Le Mental Health Center. The average age and age of onset were 33.98 ± 11.99 and 27.65 ± 7.79 respectively, and the male/female ratio was 1.05 (61/58). The 253 bipolar disorder patients (BPD253) were recruited from the inpatient department of Shandong Mental Health Center. The average age and age of onset were 34.05 ± 14.74 and 25.90 ± 11.77 respectively, and the male/female ratio was 1.26:1 (141/112). The 177 major depressive disorder patients (MDD177) were recruited from the inpatient department of Shandong Mental Health Center. The average age and age of onset were 44.77 ± 16.96 and 39.547 ± 17.04 respectively, and the male/female ratio was 0.71:1 (49/68). Another replication cohort of 986 SCZ patients (SCZ986) were mostly recruited from the inpatient department of Shandong Mental Health Center. The average age and age of onset were 33.80 ± 11.98 and 26.04 ± 9.72 respectively, and the male/female ratio was 0.99:1 (492/494). The 1000 normal controls were recruited from Blood Transfusion Center of Shandong Province. The average age was 23.08 ± 5.67 and the male/female ratio was 1.32:1 (569/431). All patients and controls are Han Chinese (**Table 1**).

The diagnoses were made according to The Diagnostic Criteria of Mental Disorders, 4th Edition (DSM-IV) [10] by at least two experienced psychiatrists, on the basis of empirical diagnostic interviews. The 119 SCZ patients were also interviewed by the correspondence author (a consultant psychiatrist). Written consent was obtained from all subjects, and this study was approved by the Ethics Committee of the Institute of Basic Medicine of Shandong Academy of Medical Sciences.

DNA pools construction

Genomic DNA was extracted from peripheral venous blood by a Bio-V automatic DNA extraction machine and Kit (5ak021, CHINA). The concentration was measured twice on a NanoDrop 2000 UV-Vis Spectrophotometer (Thermo Fisher Scientific, USA). Samples showing > 10% difference were measured again, and we used the mean of the three measurements. DNA samples were diluted to 20 ng/ul working concentrations. Five DNA pools were made for the four groups of psychiatric disorder patients and one group of controls by adding up 10 ul of each DNA sample. The first, second, third, fourth and fifth DNA pool were made for the SCZ119, BPD253, MDD177, SCZ986 and N1000 DNA samples respectively.

The Affymetrix genome-wide human SNP array 6.0 genotyping

Genotyping was performed on Affymetrix Genome-Wide Human SNP 6.0 array following the manufacturer's protocol at the CapitalBio Corporation in Beijing. Sample of 1 ug of genomic DNA was equally interleaved on 96-well master plates. Quantity of double stranded DNA was ascertained using Nanodrop 2000.

Restriction enzyme digestion and PCR amplification using universal primers was performed to generate fragments of between 250-1,100 base pairs in length which were further fragmented to 50-180 BPD and labeled with biotinylated nucleotides. Labeled fragments were hybridized to the microarray, washed stained and scanned using Gene Chip ® Scanner 30007 G. Genotypes were called using Genotyping Console 4.1.

Individually genotyping of rs9383046 and rs16857531 by high resolution melting (HRM) system

In order to comparing the allele frequency from the pooled DNA genotyping of Affymetrix Genome-Wide Human SNP Array 6.0, *rs9383046* (Affymetrix ID, SNP_A-4231440) in *JARID2* gene was selected for individual genotyping in the 119 SCZ patients as *JARID2* was previously detected as a susceptibility gene in this cohort of patients [9]. A pair of primers was designed to amplify an 88 bp segment of DNA that span *rs9383046* (Sense: *ACTGGCTGTGTCTCACTCTT,* AntiSense: *TATTCACGTTCTTTTGCTCTTGGA*). Later, rs16857531 was further individually genotyped in 117 SCZ patients of the same SCZ119 cohort. (Sense: *ACCTAATACAAATTGGTACAGT*, Antisense: *ACTGAAGATAATGCAAGGTT*) Polymerase Chain Reaction (PCR) was carried out in 96 well PCR plate with a total volume of 12.5 ul containing 10 ng of genomic DNA, 1.5 mM MgCl2, 1 × PCR reaction buffer, 0.2 mM of each dNTP, 0.3 uM of each primer, 1.5 uM SYTO⑨9, 0.5 U of Taqpolymerase (Fermentas) and finally, 20 ul of mineral oil was added to prevent evaporation. Two step amplification was performed on Gene Amp 9700 thermocycler (Applied Biosystems) with the following cycling parameters: 94°C for 5 mininitial denaturation, followed by 50 cycles of 94°C 30 sec, 58°C 1 min, then 72°C 7 min for incubation and 4°C hold. High Resolution Melting (HRM) analysis for the allelic discrimination was performed on the 96 LightScanner® System (Idaho, USA) with the analysis software Call-IT®, and the melt was set from 65 to 95°C rising at 0.1°C/s.

Heterozygotes were easily identified by melting peak width and shape. However, the discrimination of two types of homozygous samples for a SNP locus is usually more difficult by simple amplicon melting, because it often has a very similar curve shape. However, homozygous variants could be detected by prior mixing with wild-type DNA [10], or by adding 15% of a known homozygous genotype to unknown samples allows melting curve separation of all three genotypes [11]. We solved this problem by selecting one individual from the far right in Normalized Melting Curves, 1 ul PCR product from this sample was taken and diluted in 1000 ul water, and then 0.2 ul was used as template DNA for the next run of PCR reaction. 10 ul of such PCR product was subsequently distributed into all homozygotes samples (1:1 volume), and HRM was carried out once more. All homozygotes would be differentiated into heterozygote or homozygote clearly in this way. If the genotype of an individual is the same as the genotype of the template DNA added, it would keep no change, otherwise, it would become heterozygous.

Statistical analysis of the Affymetrix genome-wide human SNP array 6.0

To detect significant differences in allele frequency between the patients and controls, Chi-square test was used. Firstly, counts of each allele in both groups were derived from ratio of A to B in each array, where A and B are the probe set intensity values of alleles A and B respectively according to the Affymetrix coding. The intensity of A and B was obtained from the Affymetrix Birdseed v2 algorithm. Secondly, significant differences in allele frequency were tested using a Chi-square test with one degree of freedom by R scripts (www.r-project.org). The genome-wide significance cut off level of the chromosome 5 were set to $P \leq E\text{-}10$, $P \leq E\text{-}20$ and $P \leq E\text{-}15$ for SCZ119, BPD253 and MDD-177 respectively according to the *P*-value plot of the corresponding disorders (Supplementary Figures 1, 2, 3).

Our sample has about 80% power to detect SNP loci with odds ratio (OR) from 2.34 to 3.57 at a significance level of 5%.

Results

The genotyping of 4 groups samples in pooled DNA by Affymetrix 6.0 microarray

A total of 56,569 SNPs on chromosome 5 were analyzed, and a total of 90 SNPs were detected

Table 2. Associated SNPs of chromosome 5 for schizophrenia (SCZ), bipolar disorder (BPD) and major depressive disorder (MDD) from Affymetrix Genome-wide Human SNP Array 6.0 analysis in the population of Shandong province of China

SN	Cytoband	Position	dbSNP ID	Allele	Control A/B	Case A/B	P_Chi	OR	95 CI Down	95 CI Up	SCZ 119	BPD 253	MDD 177	Clues from PubMed Central & UCSC	SCZ 986
1	q11.2	53979025	rs6450230	C/T	0.47/0.53	0.25/0.75	2.8E-10	0.38	0.28	0.52	•			▲SNX18: By SYNJ1 to BPD [32], by GRB2, ANXA7 to SCZ [33, 34].	
2						0.24/0.76	7.4E-16	0.35	0.27	0.46			•	▼ESM1: By VEGFA, NT5DC1 to BPD [35], SCZ [36, 37]	•
3		54306959	rs4274944	A/G	0.25/0.75	0.51/0.49	1.4E-28	3.05	2.49	3.73		•			
4	p15.33	3225052	rs13190086	A/G	0.46/0.54	0.24/0.76	9.6E-20	0.36	0.29	0.45		•		▲IRX2: Suicide [38] ▼IRX1: BPD [39].	•
5		3671014	rs2305116	A/G	0.66/0.34	0.45/0.55	1.3E-10	0.41	0.32	0.54	•			▲IRX1: BPD [39] ▼ADAMTS16: Amyotrophic lateral sclerosis [27], Parkinson disease [40], ADHD (UCSC).	•
6	p15.1	17093764	rs11133874	C/T	0.34/0.66	0.55/0.45	3.1E-10	2.37	1.81	3.11	•			▲MYO10: BPD [41] ▼BASP1: SCZ [42]	•
7		17824060	rs1514850	A/T	0.7/0.3	0.5/0.5	1.6E-10	0.42	0.32	0.55	•			▲BASP1: SCZ [42].	
8	p14.3	18505215	rs6870006	A/T	0.59/0.42	0.36/0.64	3.1E-20	0.39	0.32	0.48		•		▼CDH18: BPD, SCZ [43], depression [30], autism [31].	•
9	p14.1	24967897	rs10045680	A/C	0.78/0.22	0.6/0.4	5.0E-10	0.42	0.31	0.55	•			▲CDH10: BPD [44], MDD [45], autism [46].	
10		25365287	rs1508177	C/G	0.55/0.45	0.79/0.21	7.6E-23	3.12	2.47	3.94		•		▼CDH9: BPD [44], suicide [24], autism [46].	•
11		25792519	rs1552007	A/G	0.54/0.46	0.3/0.7	1.2E-21	0.37	0.30	0.45		•			
12		27413954	rs182728	C/G	0.86/0.14	0.68/0.32	2.7E-20	0.35	0.28	0.44		•		▲CDH9: BPD [44], suicide [24], autism [46]. ▼LINC01021	•
13	p13.3	29935240	rs13158751	C/T	0.57/0.43	0.36/0.64	7.6E-10	0.42	0.32	0.56	•			▲LOC101929681	
14		29947791	rs1428323	A/G	0.38/0.62	0.15/0.85	1.8E-22	0.29	0.22	0.37		•		▼CDH6: BPD [44].	•
15	q15	96523079	rs2216709	A/C	0.68/0.32	0.45/0.55	6.2E-21	0.39	0.32	0.48		•		3'UTR//RIOK2: MDD [47]	•
16		96816018	rs11135514	C/G	0.76/0.25	0.56/0.44	3.1E-10	0.42	0.32	0.55	•			▲RIOK2: MDD [47]	•
17	q21.1	97735166	rs10043870	C/T	0.71/0.29	0.92/0.08	4.7E-22	4.56	3.28	6.35		•		▼RGMB: SCZ [48], depression [49].	
18	q21.1	98355309	rs366000	C/T	0.12/0.88	0.31/0.69	7.7E-24	3.17	2.52	4.00		•		▲CHD1: Neuropsychiatric disease [50] ▼LOC102724810	•
19		99466888	rs9686206	C/T	0.82/0.18	0.64/0.36	1.7E-10	0.40	0.30	0.53	•			▲LOC102724855 ▼FAM174A	•
20	q34	166813129	rs1019930	C/T	0.53/0.47	0.31/0.69	2.8E-10	0.40	0.30	0.53	•			⊙TENM2 (ODZ2)	
21		167241717	rs10063203	C/T	0.44/0.56	0.23/0.77	4.2E-10	0.37	0.27	0.51	•				•
22		167023112	rs17068925	A/G	0.52/0.48	0.26/0.74	2.4E-25	0.33	0.26	0.41		•			
23	q33.3	159844996	rs2910164	C/G	0.59/0.41	0.34/0.66	3.0E-25	0.34	0.28	0.42		•		▲MIR3142 ▼ATP10B	•
24	q34	160568845	rs464997	A/G	0.66/0.34	0.44/0.56	2.2E-20	0.40	0.32	0.48		•		▲ATP10B ▼GABRB2: SCZ [51-55] and BPD [56, 57]	•
25		160792501	rs7714930	C/T	0.52/0.48	0.29/0.71	2.9E-11	0.38	0.28	0.51	•			⊙GABRB2: SCZ [51-55] and BPD [56, 57]	•

26	p15.2	11017671	rs2907121	C/T	0.76/0.24	0.57/0.43	4.9E-10	0.42	0.32	0.55	•			▲DAP: SCZ (UCSC) ▼CTNND2: SCZ, MDD [58])	•
27		12113670	rs10462685	C/T	0.61/0.39	0.39/0.61	8.1E-15	0.40	0.32	0.51			•	▲CTNND2: SCZ, MDD [58]	
28		12133257	rs6554670	C/T	0.63/0.37	0.39/0.61	1.1E-17	0.37	0.29	0.47			•	▼CT49	
29		12341591	rs2907085	C/G	0.71/0.29	0.46/0.54	3.3E-19	0.36	0.28	0.45			•		•
30		12379344	rs6420013	A/C	0.46/0.54	0.68/0.32	5.2E-15	2.57	2.02	3.27			•		
31		12383412	rs10073372	A/G	0.66/0.34	0.42/0.58	6.9E-17	0.38	0.30	0.48			•		
32	p14.3	22723935	rs16898146	C/G	0.75/0.25	0.53/0.47	9.8E-17	0.38	0.30	0.48			•	⊙CDH12: SCZ [43], BPD [29], MDD (UCSC).	•
33	p14.2	23485469	rs2973606	C/T	0.79/0.21	0.61/0.39	8.2E-11	0.40	0.30	0.53	•			▲CDH12: SCZ [43], BPD [29], MDD (UCSC). ▼PRDM9: Psychiatric disorder [59]	•
34	q11.2	50978106	rs244552	C/T	0.8/0.2	0.59/0.41	4.4E-13	0.36	0.27	0.48	•			▲ISL1: SCZ, AUT [60]	•
35		52073512	rs6881021	C/T	0.64/0.36	0.86/0.14	7.2E-16	3.44	2.52	4.70			•	▼ITGA1: ADHD [61], Alzheimer's disease [62]	
36	q21.3	109426397	rs2962987	C/T	0.53/0.47	0.29/0.71	1.5E-12	0.35	0.26	0.48	•			▲MAN2A1: BPD [63], MDD [64].	
37						0.27/0.73	6.6E-20	0.32	0.25	0.41			•	▼TMEM232	•
38	q22.2	112011079	rs6882143	C/T	0.46/0.54	0.24/0.76	9.9E-11	0.36	0.27	0.50	•			▲EPB41L4A: Anxiety disorders [65]	
39						0.23/0.77	3.6E-15	0.36	0.28	0.46			•	▼APC: SCZ [66].	•
40	q31.1	133773297	rs328043	C/T	0.67/0.33	0.41/0.59	6.2E-21	0.34	0.27	0.43			•	⊙CDKN2AIPNL: Autism [67]	
41		133843226	rs10070766	C/T	0.55/0.45	0.33/0.67	9.8E-11	0.40	0.30	0.53	•			▲CDKN2AIPNL: Autism [67] ▼PHF15	•
42	p15.31	7017328	rs10512897	C/T	0.89/0.11	0.65/0.35	2.2E-37	0.24	0.19	0.30		•		▲MIR4278 ▼ADCY2: BPD [63, 68], Alzheimer's disease [69]	•
43		7832503	rs7704053	C/T	0.71/0.29	0.46/0.54	3.0E-20	0.35	0.28	0.44			•	⊙ADCY2: BPD [63, 68], Alzheimer's disease [69]	•
44	q13.3	73706852	rs10036596	C/T	0.63/0.37	0.41/0.59	1.2E-15	0.39	0.31	0.50			•	▲ARHGEF28 (RGNEF): Amyotrophic lateral sclerosis [70, 71].	
45		73713942	rs1393085	C/T	0.53/0.47	0.28/0.72	7.5E-23	0.35	0.28	0.44		•		▼ENC1: Amyotrophic lateral sclerosis [72].	•
46						0.3/0.7	1.8E-15	0.38	0.30	0.48			•		
47	q33.2	152389223	rs966088	A/G	0.66/0.34	0.43/0.57	4.1E-20	0.40	0.33	0.49		•		▲NMUR2: BPD [73]	
48		152668371	rs308271	A/T	0.23/0.77	0.42/0.58	7.1E-15	2.51	1.99	3.18			•	▼GRIA1: SCZ [74, 75], BPD [76, 77]	•
49	p15.2	14119552	rs7720709	A/T	0.68/0.32	0.46/0.54	1.9E-11	0.40	0.30	0.52	•			▲DNAH5: SCZ [78]. ▼TRIO: By DISC1 to SCZ (Chen. 2011)	•
50	q11.2	57396427	rs1387638	C/T	0.69/0.31	0.5/0.5	9.8E-10	0.43	0.33	0.57	•			▲ACTBL2: MDD [79].	•
51		57515345	rs6873296	C/T	0.64/0.36	0.43/0.57	3.1E-10	0.42	0.32	0.55	•			▼PLK2: Autism [80].	•
52	q13.3	75940056	rs3797388	C/T	0.78/0.22	0.57/0.43	3.2E-12	0.38	0.29	0.50	•			⊙IQGAP2: Autism [28]	•
53	q22.3	115064623	rs466506	A/T	0.75/0.26	0.55/0.45	6.9E-10	0.42	0.32	0.56	•			▲TMED7 ▼CDO1	•
54	q23.1	116445961	rs6865663	C/T	0.49/0.51	0.24/0.76	3.3E-13	0.32	0.24	0.44	•			▲SEMA6A: Psychosis [81] ▼TNFAIP8	•
55		131464795	rs39897	C/T	0.7/0.3	0.5/0.5	2.0E-10	0.42	0.32	0.55	•			▲CSF2: SCZ [82-84] ▼P4HA2: Depression [49]	•
56	q32	144996311	rs2195938	A/G	0.52/0.48	0.75/0.25	7.8E-11	2.70	1.99	3.66	•			▲YIPF5: Depression [49] ▼SH3RF2: Autism [85]	•
57	q33.3	159458241	rs2546961	C/T	0.58/0.42	0.35/0.65	4.6E-11	0.40	0.30	0.52	•			⊙PWWP2A	•

58	q35.1	171932932	rs10044047	C/T	0.15/0.85	0.35/0.65	2.2E-14	3.04	2.27	4.07	•		▲SH3PXD2B: Autism [85] ▼NEURL1B: By Notch pathway to SCZ	•
59	q35.3	178369460	rs7704963	A/G	0.4/0.6	0.64/0.36	1.8E-12	2.68	2.03	3.54	•		▲GRM6: SCZ [86] ▼ZNF354C: ADHD [87]	•
60	p15.2	9363216	rs1018956	C/T	0.32/0.68	0.57/0.43	3.6E-24	2.76	2.26	3.37		•	⊙SEMA5A: Autism [88, 89], and BPD [73].	•
61		10204580	rs16884228	A/G	0.63/0.37	0.85/0.15	4.8E-21	3.38	2.60	4.39		•	▲LOC285692 ▼FAM173B	•
62	p13.3	30231420	rs16899990	A/T	0.22/0.79	0.42/0.58	2.3E-21	2.67	2.17	3.28		•	▲LOC391774 ▲CDH6 BPD [44]	•
63	p13.1	40338324	rs1564269	C/G	0.68/0.32	0.42/0.58	2.4E-26	0.35	0.28	0.42		•	▲DAB2: multiple sclerosis [90]. ▼PTGER4: language impairment [91].	•
64	q11.2	52330308	rs10042752	A/C	0.87/0.13	0.68/0.32	5.7E-23	0.33	0.26	0.41		•	⊙ITGA2: Autism [92] and multiple sclerosis [93]	•
65	q12.1	59694833	rs10514895	C/G	0.22/0.78	0.44/0.56	4.0E-23	2.76	2.25	3.39		•	⊙PDE4D: BPD [94]	•
66	q14.2	82767711	rs40028	C/T	0.24/0.76	0.45/0.55	2.8E-20	2.57	2.09	3.14		•	▲XRCC4: BPD [94] ▼VCAN: SCZ [95]	•
67	q14.3	83466967	rs2301103	A/G	0.15/0.85	0.33/0.67	4.0E-20	2.79	2.23	3.48		•	⊙EDIL3: SCZ [96]	•
68		91180986	rs10077502	C/T	0.2/0.8	0.41/0.59	8.5E-22	2.72	2.21	3.35		•	▲ARRDC3 ▼NR2F1: Psychiatric disorders [97]	•
69	q15	96437199	rs11749186	C/T	0.23/0.77	0.47/0.53	5.1E-27	2.98	2.43	3.65		•	▲LNPEP ▼LIX1: SCZ [98]	•
70	q22.2	112743273	rs6594713	A/C	0.63/0.37	0.85/0.15	1.3E-20	3.30	2.54	4.28		•	⊙MCC: BPD [39].	•
71	q23.2	124810390	rs10079405	C/T	0.83/0.17	0.64/0.36	1.1E-21	0.35	0.29	0.44		•	▲ZNF608 ▼GRAMD3	•
72		126099826	rs3935125	C/T	0.5/0.5	0.23/0.77	3.7E-27	0.30	0.24	0.38		•	▲C5orf48 ▼LMNB1: Depression [99]	•
73	q31.2	136642926	rs17781969	A/G	0.62/0.38	0.39/0.61	1.2E-21	0.38	0.31	0.47		•	⊙SPOCK1: Alcoholics [100]	•
74	q31.3	142977804	rs431647	C/T	0.37/0.63	0.15/0.85	2.4E-21	0.29	0.23	0.38		•	⊙NR3C1: SCZ, BPD [101, 102].	•
75	q33.2	154705276	rs260375	A/T	0.36/0.65	0.58/0.42	7.9E-21	2.56	2.10	3.12		•	▲KIF4B ▼SGCD: SCZ [103].	•
76	q35.1	168107618	rs4502845	G/T	0.21/0.79	0.5/0.5	5.8E-38	3.68	3.00	4.52		•	⊙SLIT3: SCZ [104]. MDD [45]	•
77		169411938	rs6860533	C/T	0.25/0.75	0.47/0.53	2.6E-21	2.62	2.14	3.20		•	⊙DOCK2: SCZ [105], autism [28], MDD [45]	•
78	q35.2	172532105	rs2544576	C/T	0.55/0.46	0.79/0.21	1.0E-22	3.07	2.44	3.86		•	▲BNIP1: Alzheimer's Disease [106] ▼STC2	•
79	p13.2	35495406	rs284732	C/T	0.54/0.46	0.31/0.69	1.2E-15	0.38	0.30	0.48		•	▲PRLR: Depression [107] ▼SPEF2: Multiple sclerosis [108]	•
80	p13.1	41746547	rs1895411	C/T	0.42/0.58	0.19/0.81	1.6E-16	0.32	0.24	0.42		•	▲PLCXD3: Autism [109]. ▼OXCT1: BPD [110]	•
81	q12.1	62980772	rs16892091	C/T	0.77/0.23	0.54/0.46	3.8E-19	0.35	0.28	0.44		•	▲IPO11: Alcohol and nicotine co-dependence [111]. ▼HTR1A: MDD [112]	•
82	q14.1	77148783	rs353957	A/G	0.77/0.23	0.53/0.47	5.4E-20	0.34	0.27	0.43		•	▲TBCA: Depression [113].	
83		77332037	rs16874991	A/G	0.41/0.59	0.15/0.85	3.8E-20	0.26	0.19	0.35		•	▼AP3B1: MDD [114].	•
84		80147495	rs3776977	A/G	0.47/0.53	0.71/0.29	6.2E-16	2.69	2.11	3.44		•	⊙MSH3: Neuropsychiatric disorders [115]	•

85	q14.3	88938720	rs7712641	C/T	0.75/0.25	0.55/0.45	5.6E-15	0.40	0.32	0.51	•	▲MEF2C: Depression [49]	
86		88960367	rs7705144	C/T	0.82/0.18	0.6/0.4	1.7E-20	0.33	0.26	0.42	•	▼CETN3: Autism [116], Alzheimer's disease [106]	•
87		89045686	rs6870812	C/G	0.5/0.5	0.27/0.73	1.5E-15	0.37	0.29	0.47	•		
88	q31.1	133136328	rs258060	C/T	0.6/0.41	0.37/0.63	2.3E-15	0.39	0.31	0.50	•	▲FSTL4: Anger [117] ▼C5orf15: ADHD (UCSC); VDAC1: BPD [118]	•
89	q31.3	142554980	rs2028268	C/T	0.53/0.48	0.29/0.71	1.5E-15	0.38	0.29	0.48	•	⊙ARHGAP26: SCZ, BPD [119]; by RHOA [120, 121] and CDC42 [122, 123] to MDD	•
90	q35.2	173224859	rs3849725	C/G	0.34/0.66	0.13/0.87	4.7E-15	0.29	0.21	0.40	•	▲BOD1: SCZ [124]. ▼CPEB4: Anxiety [125].	•

Footnotes: ●associated SNP, ▲upstream of the associated SNP, ▼downstream of the associated SNP, ⊙Intronic SNP; ADHD: attention deficit disorder with hyperactivity.

Table 3. The replication of chromosome 5 SCZ associated SNPs in the enlarged cohort of 986 SCZ patients by Affymetrix Genome-wide Human SNP Array 6.0

	Cytoband	Position	dbSNP RS ID	Allele	Control A/B	Case A/B	P_Chi	OR	95 CI Down	95 CI Up
1	p15.33	3671014	rs2305116	A/G	0.66/0.34	0.6/0.4	1.6E-04	0.78	0.68	0.89
2	p15.2	11017671	rs2907121	C/T	0.76/0.24	0.68/0.32	1.0E-07	0.68	0.59	0.79
3	p15.2	14119552	rs7720709	A/T	0.68/0.32	0.52/0.48	7.0E-27	0.49	0.43	0.56
4	p15.1	17093764	rs11133874	C/T	0.34/0.66	0.45/0.55	4.2E-11	1.54	1.36	1.75
5	p15.1	17824060	rs1514850	A/T	0.7/0.3	0.53/0.47	1.4E-27	0.49	0.43	0.55
6	p14.2	23485469	rs2973606	C/T	0.79/0.21	0.73/0.27	2.2E-06	0.70	0.60	0.81
7	p14.1	24967897	rs10045680	A/C	0.78/0.22	0.69/0.31	3.9E-11	0.62	0.54	0.71
8	p13.3	29935240	rs13158751	C/T	0.57/0.43	0.41/0.59	2.9E-24	0.52	0.46	0.59
9	q11.2	50978106	rs244552	C/T	0.8/0.2	0.74/0.26	1.5E-05	0.72	0.62	0.83
10	q11.2	53979025	rs6450230	C/T	0.47/0.53	0.35/0.65	6.7E-14	0.61	0.54	0.70
11	q11.2	57396427	rs1387638	C/T	0.69/0.31	0.72/0.28	7.3E-02	1.14	0.99	1.30
12	q11.2	57515345	rs6873296	C/T	0.64/0.36	0.6/0.4	6.7E-03	0.84	0.74	0.95
13	q13.3	75940056	rs3797388	C/T	0.78/0.22	0.7/0.3	8.5E-08	0.68	0.59	0.78
14	q15	96816018	rs11135514	C/G	0.76/0.25	0.72/0.28	6.3E-03	0.82	0.71	0.94
15	q21.1	99466888	rs9686206	C/T	0.82/0.18	0.73/0.27	2.1E-11	0.60	0.51	0.69
16	q21.3	109426397	rs2962987	C/T	0.53/0.47	0.38/0.62	1.8E-20	0.55	0.48	0.62
17	q22.2	112011079	rs6882143	C/T	0.46/0.54	0.42/0.58	4.2E-02	0.88	0.77	0.99
18	q22.3	115064623	rs466506	A/T	0.75/0.26	0.62/0.38	5.7E-17	0.56	0.49	0.64
19	q23.1	116445961	rs6865663	C/T	0.49/0.51	0.48/0.52	6.9E-01	0.97	0.86	1.10
20	q31.1	131464795	rs39897	C/T	0.7/0.3	0.56/0.44	5.0E-19	0.55	0.48	0.63
21	q31.1	133843226	rs10070766	C/T	0.55/0.45	0.49/0.51	1.9E-04	0.79	0.69	0.89
22	q32	144996311	rs2195938	A/G	0.52/0.48	0.62/0.38	2.1E-10	1.51	1.33	1.71
23	q33.3	159458241	rs2546961	C/T	0.58/0.42	0.45/0.55	9.7E-17	0.59	0.52	0.67
24	q34	160792501	rs7714930	C/T	0.52/0.48	0.44/0.56	3.5E-07	0.72	0.64	0.82
25	q34	166813129	rs1019930	C/T	0.53/0.47	0.43/0.57	9.7E-10	0.68	0.60	0.77
26	q34	167241717	rs10063203	C/T	0.44/0.56	0.33/0.67	9.3E-13	0.62	0.55	0.71
27	q35.1	171932932	rs10044047	C/T	0.15/0.85	0.22/0.78	3.9E-07	1.53	1.30	1.80
28	q35.3	178369460	rs7704963	A/G	0.4/0.6	0.54/0.46	1.2E-18	1.76	1.55	2.00

to be associated with SCZ119, BPD253 and MDD177 patients. All information and clues of the associated genes related to neuropsychiatric diseases are retrieved from PubMed Central and UCSC. The results of statistical analysis and the replication of SCZ, BPD and MDD association in an enlarged cohort of SCZ are listed (**Table 2**).

The individual genotyping of rs9383046 and rs16857531

The pooled DNA genotyping of the 119 SCZ patients for rs9383046 by Affymetrix Human Genome wide Array 6.0 were G = 154 (0.65), A = 84 (0.35), and the individual DNA genotyping of the 119 SCZ patients for rs9383046 by High Resolution Melting Analysis method were G = 157 (0.66), A = 81 (0.34). The difference of the allele frequency obtained from these two method was only 1%.

The pooled DNA genotyping of the 119 SCZ patients for rs16857531 by Affymetrix Human Genome wide Array 6.0 were C = 69 (0.29), T = 169 (0.71), and the individual DNA genotyping of the 117 SCZ patients from the 119 SCZ cohort for rs16857531 by High Resolution Melting Analysis method were C = 67 (0.29), T = 167 (0.71). No difference of the allele frequency was observed from these two method.

The validation of 119 SCZ associated SNPs in an enlarged sample of 986 SCZ patients

Twenty-eight SNPs associated with the 119 SCZ patients were evaluated in an enlarged sample of 986 SCZ patients with the same

diagnosis criteria and genotyping protocol (**Table 3**). Twenty SNPs reached the threshold of P ≤ 2.2E-6 (71.4%). The 986 SZ patients (SZ986) were mostly recruited from the inpatient department of Shandong Mental Health Center including SCZ119 patients. The average age was 33.80 ± 11.98, and the male/female ratio was 0.99:1 (492/494).

The association of cadherin genes in an enlarged cohort of 986 SCZ patients

See (**Table 4**, Supplementary Table 1).

The validation of the all associated genes in the enlarge cohort of SCZ986 patients

Associated genes identified in SCZ119, BPD-253 and MDD177 (**Table 2**) were all replicated in an enlarged cohort of 986 SCZ patients (Supplementary Table 1).

Discussion

Schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD) are major three devastating mental diseases, each with distinctive and overlapping epidemiological, symptomatological and genetic components [12]. However, SCZ have a very large spectrum of symptoms which covers all symptoms of BPD and MDD. According to the diagnosis system of mental disorder, these three major mental disorder are classified as different disease entities, however, such classification might be problematic.

Kraepelin (1909) termed dementia praecox mainly based on the course and prognosis of the illness [13], and he also identified subtypes of SCZ (hebephrenic, catatonic, and paranoid) (OMIM: 181500). However, subtypes are not etiologically distinct syndromes, as subtypes are not 'breed true' within families [14].

Bleuler (1908) publicly introduced the term and concept schizophrenia, and his idea was more fully developed in 1911 for the "Group of Schizophrenias" [13].

Hallmayer (2005) believed that the inherent heterogeneity originally recognized has been obfuscated in modern diagnostic classifications, which are designed to meet the needs of patient management, not fundamental research, and which may not target phenotypes anchored in the biology of the illness [15].

Despite the availability of official guidelines, such as the DSM-IV and ICD-10, the controversial about the relationship of SCZ to BPD and MDD could not be avoided, as some puzzling phenomena need explanation, for example, (1) high rates of depression in mothers of SCZ patients were observed [16]. (2) Probands with SCZ had relative risks (RR) for having a sibling with SCZ (RR = 3.77) and with BPD (RR = 1.79); Probands affected with BPD have an RR of 6.51 for having a sibling with BPD and of 1.71 for having a sibling with SCZ; Probands affected with MDD also have increased risk for having a sibling with SCZ (RR = 2.04), which was similar to the risk for having a sibling with MDD (RR = 1.91) or BPD (RR = 2.06) [3]. (5) Schizoaffective patients possess both symptoms of SCZ and affective disorder. (6) some BPD and MDD patients possess delusion and/or hallucination [17]. (7) Lithium carbonate are efficacy in treating both of BPD and MDD. (8) Many newer atypical antipsychotic agents approved for the treatment of SCZ are also proving useful for BPD [18].

According to Ming Taizu Record, the population of Shandong province in the 14th century was reduced dramatically due to continuous war, natural disasters (flood, plague, and grasshoppers) and most of the villages were devastated. In contrary, no war or natural disasters took place in Shan Xi province at that time. The two provinces are separated by 1000 kilometers distance and high mountains, serving as a natural barrier. To balance the population distribution in China, the Emperor Yuanzhang Zhu initiated two massive immigration waves from Shan Xi to Shandong province from 1388 to 1389 in order to re-populate that region. It appears that the present-day populations of Shandong province are mostly offspring expanded from different groups of limited number of ancestors 600 years ago. Therefore, we expect a high degree of homogeneity in the genetic structure of this population. It is probably the key factors to ensuring the successful discovery of the underlined relationship of the three mental disorders.

In this study, almost all genes associated with BPD and MDD were overlapped by the genes

Table 4. The analysis of *CDH6, CDH9, CDH10, CDH12 and CDH18* associated SNPs in 986 schizophrenia (SCZ986) from Affymetrix Genome-wide Human SNP Array 6.0

	Cytoband	Position	dbSNP RS ID	Allele	Control A/B	Case A/B	P_Chi	P_Fexact	OR	95 CI Down	95 CI Up	*P*-value	Associated Gene
1	p14.3	19531083	rs2131581	A/G	0.32/0.68	0.22/0.78	3.7E-12	2.7E-12	0.60	0.52	0.70	3.57E-12	*CDH18 (intron)*
2	p14.3	19561848	rs3811865	C/G	0.38/0.63	0.48/0.52	2.5E-11	2.0E-11	1.54	1.36	1.75	2.16E-11	
3	p14.3	19574351	rs1015104	A/T	0.16/0.84	0.34/0.66	5.3E-40	8.3E-41	2.76	2.37	3.21	9.96E-39	
4	p14.3	19662006	rs1402435	C/T	0.38/0.62	0.51/0.49	5.2E-17	4.2E-17	1.72	1.51	1.95	4.91E-17	
5	p14.3	19690355	rs9292710	A/G	0.86/0.14	0.79/0.21	6.2E-08	5.2E-08	0.63	0.53	0.75	5.71E-08	
6	p14.3	19690713	rs10059843	A/G	0.72/0.28	0.59/0.41	1.9E-18	1.6E-18	0.55	0.48	0.63	1.00E+00	
7	p14.3	19714521	rs4866039	G/T	0.78/0.22	0.69/0.31	3.1E-12	2.7E-12	0.60	0.52	0.69	3.01E-12	
8	p14.3	19720791	rs4543271	A/C	0.17/0.83	0.25/0.75	3.9E-09	3.1E-09	1.60	1.37	1.87	3.59E-09	
9	p14.3	19757247	rs12187552	A/G	0.11/0.89	0.18/0.82	6.1E-10	5.1E-10	1.76	1.47	2.10	6.37E-10	*CDH18 (CDS)*
10	p14.3	19841846	rs10520864	A/T	0.14/0.86	0.2/0.8	6.5E-08	5.3E-08	1.59	1.35	1.89	6.04E-08	CDH18 (intron)
11	p14.3	19874904	rs989316	A/G	0.14/0.86	0.22/0.78	4.5E-10	3.7E-10	1.69	1.43	1.99	4.42E-10	CDH18 (5UTR)
1	p14.2	24615728	rs1505880	C/T	0.51/0.49	0.6/0.4	6.6E-09	5.9E-09	1.45	1.28	1.65	5.74E-09	*CDH10 (intron)*
2	p14.2	24662355	rs7380367	C/T	0.39/0.61	0.29/0.71	1.9E-12	1.4E-12	0.62	0.54	0.71	1.72E-12	
1	p14.1	26939948	rs16896364	C/T	0.48/0.53	0.58/0.42	1.3E-11	1.2E-11	1.54	1.36	1.75	1.18E-11	*CDH9 (intron)*
2	p14.1	26993953	rs6874768	A/G	0.81/0.19	0.73/0.27	1.1E-08	1.1E-08	0.65	0.56	0.75	1.04E-08	
3	p14.1	26997600	rs13174843	A/G	0.11/0.89	0.06/0.94	1.0E-07	8.2E-08	0.53	0.42	0.67	1.10E-07	
4	p14.1	27048651	rs3811924	A/G	0.64/0.36	0.73/0.27	1.7E-09	1.5E-09	1.51	1.32	1.73	1.52E-09	
1	p13.3	31294830	rs17475603	C/G	0.58/0.42	0.66/0.34	3.2E-08	2.7E-08	1.44	1.27	1.64	2.79E-08	*CDH6 (intron)*
2	p13.3	31310248	rs12654539	A/C	0.67/0.33	0.59/0.41	9.0E-08	8.3E-08	0.70	0.62	0.80	7.89E-08	
3	p13.3	31317556	rs13187907	A/G	0.58/0.42	0.66/0.34	1.0E-07	8.4E-08	1.42	1.25	1.62	8.80E-08	
4	p13.3	31323163	rs17398305	G/T	0.48/0.52	0.62/0.38	1.7E-18	1.2E-18	1.76	1.55	2.00	1.66E-18	
5	p13.3	31331825	rs33991743	A/C	0.51/0.49	0.6/0.4	2.1E-08	1.9E-08	1.43	1.27	1.63	1.85E-08	
6	p13.3	31336572	rs2330698	C/T	0.85/0.15	0.76/0.24	1.3E-11	1.2E-11	0.57	0.49	0.67	1.41E-11	
7	p13.3	31357569	rs639386	C/T	0.36/0.64	0.25/0.75	1.8E-15	1.2E-15	0.57	0.50	0.66	1.78E-15	
1	q31.3	141306360	rs758460	C/T	0.18/0.82	0.25/0.75	1.6E-08	1.4E-08	1.56	1.34	1.81	1.43E-08	*PCDH12 (intron)*

for SCZ. Furthermore, such a phenomenon was not only on chromosome 5, but on other chromosome as well [19]. Considering convergent evidence, we propose that both of BPD and MDD should be subtype of SCZ. Another phenomena we also observed in this study is that most of the genes for the three disorders have been reported to be associated with some other neuropsychiatric disease before (**Table 2**).

Outstanding susceptibility genes in this population

Cadherins are Ca^{2+} dependent transmembrane glycoproteins and crucial for cell-cell adhesion in vertebrates and invertebrates. Classification of this superfamily due to their phylogenetic relationship is currently restricted to three major groups subfamilies: classical, desmosomal and protocadherins [20]. Convergent evidence indicatesthat cadherins play an importance role in the morphogenesis of the CNS and in the development of complex psychiatric disorders [21]. Five members of cadherin genes were identified in this study including *CDH6, CDH9, CDH10, CDH12 and CDH18* (**Table 2**).

(1) *CDH6* (**Table 2**, 13, 14, 62 & Supplementary Table 1, 4,380-4,427) gene is strongly expressed in the fetal brain, as well as parietal and occipital lobe of the brain. This gene was reported to be associated with BPD [22]. Two SNPs *(rs13158751, rs1428323)* were detected to be associated with SCZ and BPD respectively in this study. Furthermore, six SNPs (*rs17475603, rs12654539, rs17398305, rs33991743, rs23-30698, rs639386*) were identified in the enlarged cohort of 986 SCZ patients.

(2) *CDH9* (**Table 2**, 12 & Supplementary Table 1, 4,063-4,379) is strongly expressed in the fetal brain and parietal lobe of the brain. This gene was reported to be associated with antidepressants [23], BPD [22], suicide [24], and autism [25]. One downstream SNP (*rs1004-5680*) and three upstream SNPs (*rs1508177, rs1552007, rs182728*) were found to be associated with SCZ and BPD respectively in this study (**Table 2**, 9-12). Also, a cluster of intronic SNPs (*rs16896364, rs1007586, rs7725061, rs6874768, rs3811924*) were replicated in the enlarged cohort of 986 SCZ patients.

(3) *CDH10* (**Table 2**, 9-11 & Supplementary Table 1, 3,945-4,062) is predominantly expressed in brain and is putatively involved in synaptic adhesions, axon outgrowth and guidance. This gene was reported to be associated with BPD [22], MDD [26], autism [25] and amyotrophic lateral sclerosis (ALS) [27]. Four downstream SNPs (*rs10045680, rs1508177, rs15-52007, rs182728*) were detected to be associated with SCZ and BPD in this study. Furthermore, two intronic SNPs *(rs1505880, rs-7380367)* were replicated in the enlarged cohort of 986 SCZ patients.

(4) *CDH12* (**Table 2**, 32, 33 & Supplementary Table 1, 3,657-3,901) appears to be expressed specifically in the brain. Also, it's temporal pattern of expression would be consistent with a role during a critical period of neuronal development, perhaps specifically during synaptogenesis. This gene was reported to be associated with SCZ [28], BPD [29] and MDD (UCSC). One intronic SNP (*rs16898146*) and a downstream SNP (*rs2973606*) were identified to be associated with MDD and SCZ respectively in this study (**Table 2**, 32, 33). Furthermore, two intronic SNPs (*rs758460, rs735068*) were replicated in the enlarged cohort of 986 SCZ patients.

(5) *CDH18* (**Table 2**, 7, 8 & Supplementary Table 1, 3,128-3,656) is expressed specifically in the central nervous system and involved in synaptic adhesion, axon outgrowth and guidance. This gene was reported to be associated with BPD, SCZ [28], depression [30] and autism [31]. In this study, two upstream SNPs *(rs15-14850, rs6870006)* were detected to be associated with SCZ and BPD respectively. Moreover, one SNP (rs989316) in 5'UTR, one SNP in CDS (*rs12187552*) and nine intronic SNPs (*rs2131581, rs3811865, rs1015104, rs1402-435, rs9292710, rs10059843, rs4866039, rs4543271, rs10520864)* were replicated in the enlarged cohort of 986 SCZ patients.

Other susceptibility genes in this population (see **Table 2**).

Conclusions

Firstly, susceptibility geneson chromosome 5 for the three major psychiatric disorders were comprehensively revealed; Secondarily, cadherin pathway genes (*CDH6, CDH9, CDH10,*

CDH12, CDH18) are important susceptibility genes for the three mental disorders in this population; Thirdly, bipolar and major depressive disorders might be subtypes of schizophrenia rather than two independent disease entities; Fourthly, vast majority of flanking genes of the associated SNPs were reported for neuropsychiatric disorder before.

Acknowledgements

We would like to thanks for all of the patients, controls and others participated in this study. Study supported bygrants from theNatural Science Foundation of Shandong Province (Grant No. ZR2013HM078, Z2008C11, Z2004C10), Shandong Province Science and Technology Development Plan (Grant No. 2011GSF11821), National High-tech R&D Program of China (863 Program Grant No. 2002AA223021), The National Natural Science Foundation of China (Grant No. 30770780, 30440042), Ministry of Human Resources and Social Security of China (Grant No. 2009.416), Department of Science & Technology of Shandong Province (Grant No. 2008GG27C01011-8), National Bureau of Foreign Experts Affairs (Grant No. CG2006370002), Shandong Bureau of Foreign Experts Affairs (Grant No. L200637-00407, Shandong Academy of Medical Sciences Grant No. 2012-25, 2009-15, The Innovation Project of Shandong Academy of Medical Sciences). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Written consent was obtained from all subjects, or legally authorized representative consented on the behalf of participants. This study was approved by the Ethics Committee of the Institute of Basic Medicine of Shandong Academy of Medical Sciences.

Disclosure of conflict of interest

None.

Authors' contribution

Xing Chen completed the major part of the research work; Feng, Long completed the some of the research work; Bin Cai carried out the statistical analysis of the genome-wide association study (GWAS) by affymetrix genome-wide human SNP array 6.0; Xiaohong Chen carried out the genotyping of the genome-wide association study (GWAS) by affymetrix genome-wide human SNP array 6.0; Gang Chen designed the study, interviewed the 119 SCZ patients, collected some of the blood samples, checked all medical records, validated the diagnosis of all patients, analyzed the data and wrote the manuscript.

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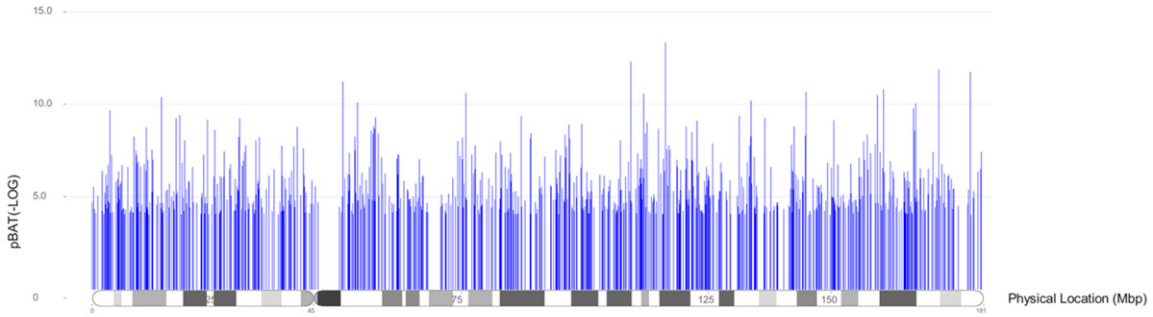
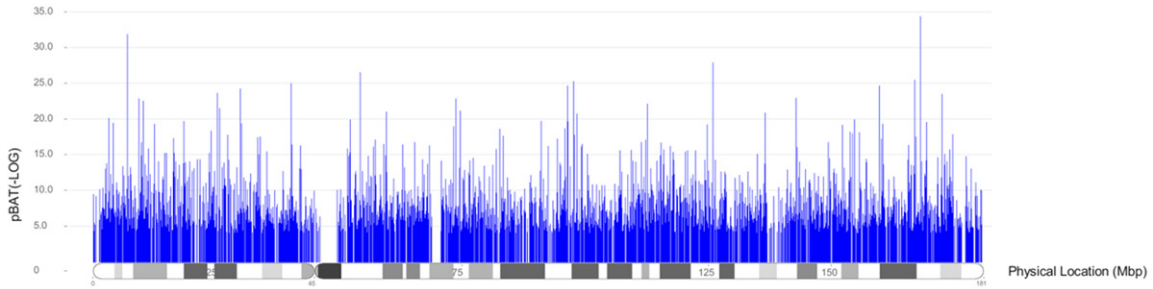
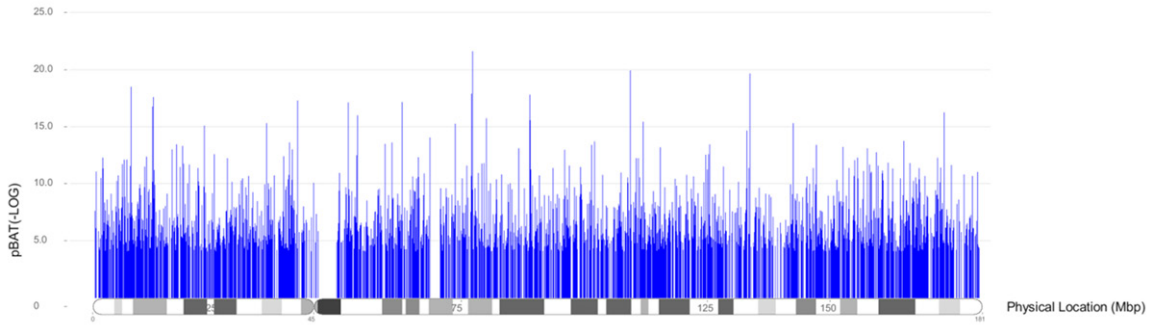


Supplementary Figure 1. The *P*-value plot of single nucleotide polymorphisms (SNPs) on Chromosome 5 from the analysis of 119 schizophrenia (SCZ) patients and 1000 controls in a Genome-wide Association Study by Affymetrix Genome-Wide Human SNP array 6.0 in the population of Shandong province of China.



Supplementary Figure 2. The *P*-value plot of single nucleotide polymorphisms (SNPs) on Chromosome 5 from the analysis of 253 bipolar disorder (BPD) patients and 1000 controls in a Genome-wide Association Study by Affymetrix Genome-Wide Human SNP array 6.0 in the population of Shandong province of China.



Supplementary Figure 3. The *P*-value plot of single nucleotide polymorphisms (SNPs) on Chromosome 5 from the analysis of 177 major depressive disorder (MDD) patients and 1000 controls in a Genome-wide Association Study by Affymetrix Genome-Wide Human SNP array 6.0 in the population of Shandong province of China.