Article

Common genetic variants shared among five major psychiatric disorders: a large-scale genome-wide combined analysis

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Received Feburary 7, 2019; Accepted Febueary 27, 2019

ABSTRACT

Background: Genetic correlation and pleiotropic effects among psychiatric disorders have been reported. This study aimed to identify specific common genetic variants shared between five adult psychiatric disorders: schizophrenia, bipolar, major depressive disorder, attention deficit-hyperactivity disorder, and autism spectrum disorder.

Methods: A combined p value of about 8 million single nucleotide polymorphisms (SNPs) were calculated in an equivalent sample of 151,672 cases and 284,444 controls of European ancestry from published data based on the latest genome-wide association studies of five major psychiatric disorder using Stouffer's Z-score method. SNPs that achieved genome-wide significance ($P<5x10^{-08}$) were mapped to loci and genomic regions for further investigation; and gene functional annotation and clustering were performed to understand biological process and molecular function of the loci identified. We also examined CNVs and performed expression quantitative trait loci analysis for SNPs by genomic region.

Results: We find that 6,293 SNPs mapped to 336 loci are shared by the three adult psychiatric disorders, 1,108 variants at 73 loci are shared by the childhood disorders, and 713 variants at 47 genes are shared by all five disorders at genome-wide significance ($p<5x10^{-08}$). Of the 2,583 SNPs at the extended major histocompatability complex identified for three adult disorders, none of them were associated with two childhood disorders; and SNPs shared by all five disorders were located in the regions that have been identified as containing copy number variation associated with autism and had largely neurodevelopmental functions.

Conclusion: We show a number of specific SNPs associated with psychiatric disorders of childhood or adult onset, illustrating not only genetic heterogeneity across these disorders but also developmental genes shared by them all. These results provide a manageable list of anchors from which to investigate epigenetic mechanism or gene-gene interaction on the development of neuropsychiatric disorders and for developing a measurement matrix for disease risk that could potentially be used for new taxonomy for precision medicine.

KEYWORDS

Psychiatric disorders; schizophrenia; bipolar disorder; major depressive disorder; attention deficit-hyperactivity disorder; autism spectrum disorder; genome-wide association study; combined analysis.

INTRODUCTION

The genome-wide association study (GWAS) has emerged as a compelling tool for investigating the genetic architecture and the etiology of complex human diseases over the past decade[1]. Many common genetic variants have been associated with complex human disorders through GWAS since the early studies in type 2 diabetes and inflammatory bowel disease[2, 3]. As the application of the GWAS approach has progressed, more and more gen-

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ome-wide genotyped data have been accumulated, which has made it possible to conduct genome-wide meta-analyses of multiple cohorts of GWAS samples[4]. The number of genome-wide association studies that involve a large number of patients and healthy controls are increasing every year. As of 2017, about 40% of recent studies are with a sample size of more than 50,000 individuals [5], and some even with more than 200,000 [6,7]. With samples of such size, investigators expect to identify variants with lower frequency and smaller effect size, by overcoming genetic heterogeneity[8] to attain adequate power to detect a genetic association. More importantly, with the development of genotype imputation and large whole-genome sequencing datasets available, it is feasible to assess the whole genome common variants for association with common complex human disorders without whole genome sequencing of all sample individuals.

The lessons from GWAS include that association of genetic variants with common human disorders is complex and involves a matrix of polygenic and pleiotropic effects. It has become clear that common complex human disorders are affected by multiple variants in a polygenic way [9]; whereas an individual variant may be associated with multiple diseases or traits (i.e., pleiotropic). Preliminary evidence of pleiotropic effects has been found in immune-related disorders, various types of cancers, or neuropsychiatric disorders[10]. For example, genetic varints at 3p21, 10q24, and SNPs within two L-type voltage-gated calcium channel subunits, *CACNA1C* and *CACNB2* have been found to be shared by multiple psychiatric disorders [11]. Coincidentally, genome-wide SNPs association analysis has revealed that psychiatric disorders might share a moderate to high degree of genetic correlation [12]. Identification of the pleiotropic effects of specific genetic variants on common complex human disorders is a potentially important step in building the knowledge network and a measurement matrix for disease risk for developing a new taxonomy of human diseases, which will play a fundamental role in achieving the goals of precision medicine [13, 14].

METHODS

Dataset and analysis. Individual SNP data used in this study were obtained from the published data releases by the Psychiatric Genomic Consortium that contained the largest genome-wide association studies of schizophrenia (SCZ), bipolar disorder (BD) [15], and major depressive disorder (MDD) [7], attention deficit hyperactivity disorder (ADHD) [16], and autism spectrum disorder (ASD) [17]. Detailed information on the sample individuals, original data process and analysis of individual sample cohort has been described previous in the individual studies. Of note, the ADHD sample mainly include a population-based cohort of ADHD cases and controls from Denmark collected by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), and 11 cohorts aggregated by the Psychiatric Genomics Consortium (PGC); the majority of the ASD sample was also from iPSYCH ASD and five family-based samples of European ancestry, which contributed cases and pseudo-controls.

The analysis was performed by calculating the combined p values of individual SNPs across the genome in multiple disorders. The Stouffer's Z-score method (1949), an extension of classical Fisher's combined method (1925) that has been employed in previous GWAS [18], was used to have a two-sided test. The hypothesis would be "multiple psychiatric disorders shared some common genetic variants," and under a null hypothesis, a statistic can be calculated by a combined Z-score, which can be converted into p-value based on the inverse of the standard normal cumulative distribution. The Z-score is defined as $Z=\frac{\sum_{i=1}^{k} Z_i}{\sqrt{k}}$; where k is the number of individual disorders, and the Z_i is the inverse of the standard normal cumulative distribution based on the p value for an individual SNP in the ith disorder.

The analysis was limited to SNPs showing a consistent direction of association at nominal significance ($P< 0.05$) across disorders, to keep internal consistency and reduce heterogeneity, i.e., ruling out SNPs, which is highly significant in one disorder, but not the other or shows opposite allelic directionality across disorders. The combined analysis was performed first for schizophrenia, bipolar and major depressive disorder, i.e., the three adult psychiatric disorders that have been demonstrated a moderate to high genetic correction, then for ADHD and ASD, the two childhood neurodevelopmental disorders, and finally for five disorders combined. A genome-wide significance threshold ($P<5x10^{-08}$) was employed.

SNP functional annotation and eQTL analysis. Individual SNPs were mapped to a locus based on the dbSNP and the HapMap data[19], and then the unmapped SNPs by the database were manually verified with the UCSC genome browser (GRCh37/hg19). Functional annotation of associated loci was performed based on the DAVID Bioinformatics Resource 6.8 using Gene Ontology (GO) term [20]. The eQTL analysis was performed on the GTEx dataset developped by the Genotype-Tissue Expression (GTEx) Project; the gene expressions in human tissues were based on the Human Protein Atlas (HPA) RNA-seq (https://www.proteinatlas.org/).

RESULTS

Table 1 presents the number of sample individuals and SNPs included in this study by the individual disorder. Briefly, the schizophrenia and bipolar analysis consisted of 53,555 cases (20,129 BD, 33,426 SCZ) and 54,065 controls with 8,379,106 SNPs; the MDD study comprised 59,851 cases and 113,154 controls with 13,554,492 SNPs; the ADHD study included 20,183 cases and 35,191 controls with 8,047,420 SNPs; and the ASD study included 9,112,386 SNPs in 18,381ASD cases and 22,664 controls. The combined p values were calculated to identify genetic variants shared by multiple disorders (Methods). While the original data in the MDD study included a fair

number of rare variants, we only focused on the common variants (minor allele frequency, MAF>1%).

Table 1. Samples and number of SNPs by individual disorder

Disorder	Sample	No. variants	Cases	Control
Schizophrenia (SCZ)	PGC	8,379,106	33,426	54,065
Bipolar disorder (BD)	PGC	8,958,989	20,129	54,065
Major depressive disorder(MDD)	PGC	13,554,492	59,851	113,154
Attention deficit hyperactivity disorder(ADHD)	Combined	8,047,420	20,183	35,191
	iPSYCH*		14,584	22,492
	PGC-ADHD		5,499	12,599
Autism spectrum disorder (ASD)	Combined	9,112,386	18,381	27,969
	iPSYCH		13,076	22,664
	PGC -ASD		5,305	5,305
Common SNPs in combined five disorders		6,467,684	151,672	284,444

*Cases and controls from Denmark collected by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH); PGC-ASD, Psychiatric Genomic Consortium--Autism spectrum disorders contained five family-based trio samples of European ancestry; PGC-ADHD, Psychiatric Genomic Consortium--Attention deficit and hyperactivity disorder comprised 11 European, North American and Chinese cohorts aggregated by the Psychiatric Genomics Consortium.

Common variants associated with schizophrenia, bipolar and major depressive disorder

We identified 6,293 SNPs shared by three adult-onset disorders at genome-wide significance ($P<5x10^{-08}$). These included 2,583 SNPs in the extended major histocompatability complex (xMHC), which spans a 7.5-Mb region defined by the *SLC17A2* gene at the telomeric end to the *DAXX* gene at the centromeric end of chromosome 6 (Chr6:25,875,084-33,797,216, hg19) and mapped to 421 loci (excluding tRNA genes)according to the gene map of xMHC [21, 22]; and 3,710 SNPs were located in the non-xMHC (Figure 1A). We noted that these SNPs were in strong linkage disequilibrium (LD) and clustered by genomic region. Of the total non-xMHC SNPs, 3,654 SNPs (98.5%) were mapped to 68 genomic regions, defined by which flanking SNPs of any two regions were at least 1-Mb apart. Based on the SNP functional prediction[19], 263 SNPs (8%) were at TFBS, and 109 SNPs (3.3%) were conserved in vertebrates (Table S2).

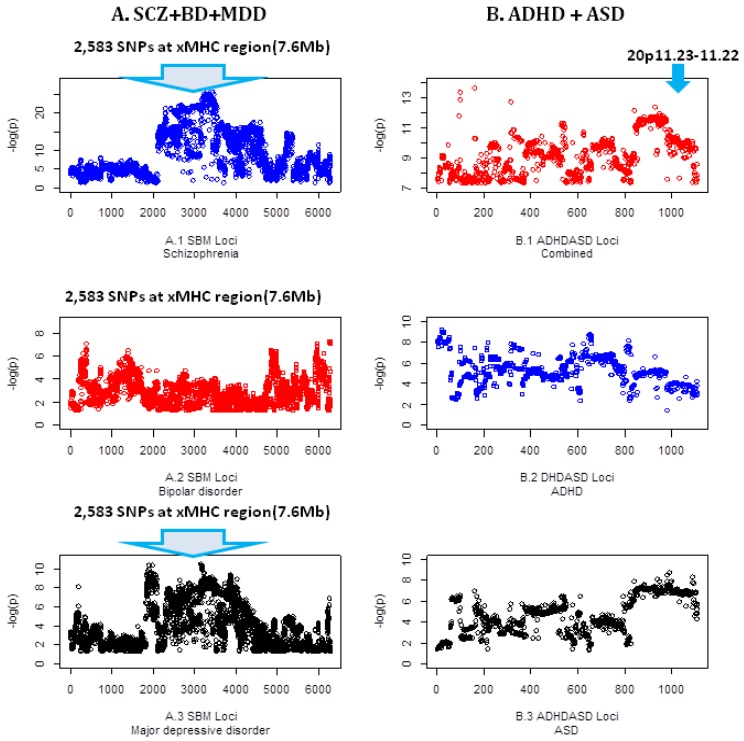

Figure 1. Scatter plots of p values (-log) for SNPs shared by psychiatric disorders. (x-Axis is SNPs in chromosomal order; A.1-A.3, 6,293 SNPs shared by three adult-onset disorders for association with an individual disorder; B.1-B.3, 1,108 SNPs shared by ADHDASD and for associ-ation with ADHD and ASD).

Among the 68 regions at non-xMHC loci, 51 regions did not have an SNP associated with a particular disorder at genome-wide significance; whereas other 17 regions cotained at least one SNPs in each region associated with an individual disorder at genome-wide significance. In the 51 regions that might be novel or specifically shared by the three adult-onset disorders (Table 2), 15 regions contained only a single SNPs; these included chr1: 1636-46390 at *NUF2*, rs7581403 at *MYT1L*, chr2:185676179 at *ZNF804A*, chr2:193934836, rs13078307 at *CNTN4*, rs-7613933 at *WDR49*,chr5:152167615, rs10239423 at *SP4*, rs7905569 at *IFITM8P*, rs4837673 at *DBC1||MIR-147*, rs1828385 at *LOC100120660||LOC751600*, chr18: 26337461, rs72903982 at *KC6*, chr20:43682549 at *STK4*, chr20:48108321 at *RYR2;* and the other 36 regions contained about 80 genes, including *DAMTSL3, ALPK3, ANKS1B, BRAF, COX8A, DCC, ENOX1, FGFR1, GABRA1, GABRG2, GCKR, GRIN2A, KCNB1, KCTD13, NFIX, PCLO, TRIM8,* and *BORCS7*. Meanwhile, SNPs in the other 17 genomic regions, each containing at least one SNP associated with an individual disorder at genome-wide significance, were mapped to 85 genes; and some of which *CACNB2, DRD2*, *CACNA1C, CACNAI1, AS3MT, TSNARE1, KLC1*, and *SOCRS3* have been associated with schizophrenia, and *EP300, VRK2, BAG5*, *APOPT1* have been associated with MDD at genome-wide significance (Table 2) .

Table 2. Genomic regions and loci mapped by the 6,293 SNPs (3,710 at non-xMHC) shared by three adult-onset psychiatric disorders at genome-wide significance.

Locus		Chr	SNP	BP1	BP2	ID	#SNP	Mapped gene loci
1		1	rs200448	6701978	6765079	1	21	*DNAJC11, CAMTA1,*
2		1	rs4949240	30438197	30509225	22	38	*PTPRU||MATN1*
3	**	1	rs2841192	73307627	73856328	60	132	*KRT8P21, LRRC44*
4		1	rs6661796	79186203	79261383	192	43	*IFI44||ADGR4L, ELTD1*
5		1	chr1_16364	163646390		251	1	*NUF2*
6	**	1	rs11587347	239198959	244025999	252	5	*[RGS7, KMO, OPN3, WDR64, EXO1, PLD5], ZNF238*
7		2	rs7581403	2314997	2314997	257	1	*MYT1L*
8		2	chr2_22499	22499207	28290347	258	458	*BRE, C2orf16, GCKR, GPN1, RBKS, SUPT7L, KLHL29, MRPL32, MRPL33, ZNF512*
9	**	2	rs13011472	57961602	58308458	717	10	*VRK2*
10		2	rs56088823	96793024	96905568	727	13	*ASTL, DUSP2, STARD7*
11		2	chr2_18567	185676179		740	1	*ZNF804A*
12		2	chr2_19393	193934836		741	1	*NA*
13		2	chr2_19822	198226403	198940251	742	206	*BOLL, MARS2, PLCL1, RFTN2*
14		2	rs13020196	201071942	201244261	948	56	*ERGIC3, SPATS2L*
15		2	rs2551656	208371637	208531683	1005	84	*CREB1, FAM119A*
16		3	rs13078307	2565355	2565355	1090	1	*CNTN4*
1	**	3	rs6802320	52241835	53475074	1091	523	*ALAS1, DCP1A, DNAH1, GLT8D1,GLYCTK, GNL3, ITIH1, ITIH3, ITIH4, MUSTN1, SFMBT1,*
	**							*TWF2, RFT1, MIR135A1, NEK4, NT5DC2, PBRM1,PHF7, WDR82, SPCS1, STAB1, TLR9, TMEM110*
18		3	rs2176028	80655077	80693369	1613	6	*[ROBO1, GBE1]*
19		3	rs4146338	117493964	117772036	1619	84	*LOC728873||IGSF11*
20		3	rs7613933	167304189	167304189	1703	1	*WDR49*
21		4	rs56089943	48342682	48496368	1704	41	*SLC10A4,TEC||SLAIN2, ZAR1*
22		4	rs1599125	118644885	118753686	1745	82	*NT5C3P1||NDST3*
2	**	5	rs7716818	103684787	104089064	1827	271	*NUDT12||RAB9P1*
24		5	chr5_15216	152167615	152167615	2098	1	*AK123826*
25		5	rs2290732	161324898	161352075	2099	14	*GABRA1, GABRG2*
26	**	6	rs2744301	25323143	25875567	2113	59	*CARMIL1, SCGN, HIST1H2AA, SLC17A1, SLC17A3, HIST1H2APS2, SLC17A4*
27		6	rs36014129	25884519	33797216	2172	2583	*Extended MHC region*
28		6	rs28360639	50783501	50936376	4755	71	*FTHP1, RPS17L4,TFAP2B,TFAP2D*
29		6	rs9360557	73132745	73155701	4826	14	*RIMS1, [KCNQ5]*
30		6	rs12190758	93148341	93176175	4841	4	*[EPHA7]*
31		7	rs10239423	21503450	21503450	4845	1	*SP4*
32		7	rs4291157	24624449	24844736	4846	67	*BLVRA, MRPS24, DFNA5, MPP6, OSBPL3*
33		7	rs2371213	82397302	82482281	4914	35	*PCLO*
34		7	rs10265001	140665521	140777030	4950	43	*BRAF, MRPS33*
35		8	rs6983972	9699144	9728595	4994	5	*MIR597|| MIR124-1*
36		8	chr8_33747	33747954	34021138	4999	5	*DUSP26*
37		8	rs57709857	38290424	38291844	5004	2	*FGFR1*
38		8	rs790569	64621828	64621828	5006	1	*IFITM8P*
39	**	8	rs10098073	143309504	143352779	5007	46	*TSNARE1*
40		9	rs9695226	22759396	22785141	5053	8	*FLJ35282*
41		9	rs4837673	122546769	122546769	5061	1	*DBC1|| MIR147*
42	**	10	rs12777923	18661160	18775255	5062	81	*CACNB2*
43	**	10	rs7893954	104318966	105059896	5143	233	*ARL3, AS3MT, CNNM2, WBP1L, CYP17A1, NT5C2, INA, PCGF6, CXCL12,*
								SFXN2, SUFU, TRIM8, BORCS7
44		10	rs12761679	106512727	106747354	5376	19	*SORCS3*
45		11	rs7946546	63595648	63790521	5395	83	*ATP5LP1,MARK2,MACROD1, RCOR2, NAA40, COX8A, OTUB1*
46	**	11	rs17601612	113317745	113412443	5478	25	*DRD2, TMPRSS5*
47		11	rs402320	131374917	131399805	5504	75	*RREB1*
48	**	12	rs740416	2499892	2514270	5579	8	*CACNA1C*
49		12	rs1319892	99436519	99690240	5587	127	*ANKS1B*
50	**	12	chr12_1236	123639761		5714	1	*SSPN*
51		13	rs9562504	44244876	44351241	5715	11	*ENOX1*
52		14	rs28645341	30174078	30182920	5726	3	*PRKD1*
53		14	rs36341	72390689	72454646	5729	14	*RGS6, SIPA1L1*
54	**	14	rs11160502	99667179	99731731	5743	4	*BCL11B*
55	**	14	chr14_1039	103916280	104319989	5747	247	*BAG5, APOPT1, KLC1, TRMT61A, CKB, XRCC3, PPP1R13B, ZFYVE21*
56		15	rs1828385	36355868			1	*LOC100130660||LOC751603*
57		15	rs2562774	84380096	85393240	5924	65	*ADAMTSL3, ALPK3, ZSCAN2, SEC11A, WDR73, ZNF592,*
58	**	15	rs7168951	91406146	91437388	5989	24	*BLM||FURIN,FES,FURIN*
59		16	rs11648559	9874699	9960879	6013	156	*GRIN2A*
60		16	rs12919683	29943367	30018500	6170	47	*INO80E, DOC2A, KCTD13, TAOK2*
61		18	chr18_2633	26337461		6217	1	*NA*
62		18	rs72903982	39152991		6218	1	*KC6*
63		18	rs7505145	50711776	50870391	6219	30	*DCC*
64		18	rs56096694	52722378	53101598	6249	8	*MAP1LC3P, TCF4*
65		19	rs17706798	13116172	13122612	6257	4	*NFIX*
66		20	chr20_4368	43682549		6261	1	*STK4*
67		20	chr20_4582	45829133		6262	1	*RYR2*
68		20	chr20_4810	48108321	48110279	6263	4	*KCNB1||PTGIS*
69	**	22	rs71799331	39974015	41617897	6267	27	*CACNA11, EP300, L3MBTL2, MCHR1||SLC25A17, MKL1*

**, loci where SNPs were associated with one of three disorders; #SNP, number of SNPs shared by three adult-onset psychiatric disorder at genome-wide significance in each genomic region; [ ], genes nearby; NA, no gene available within about 1- Mb genomic region; SNP is the first flanking SNPs of individual region; BP1 and BP2 are position of two flanking SNPs of individual gene region.

Functional annotation of the genes in the non-xMHC indicated a few top biological processes, including urate metabolic process, protein phosphorylation, and sodium-dependent phosphate transport. These loci are located at a-

xon, postsynaptic membrane and postsynaptic density, mitochondrion, cell junction, voltage-gated calcium channel complex, and mitochondrial inner membrane; and they have molecular functions of sodium phosphate symporter activity, sodium-dependent phosphate transmembrane transporter activity, protein binding, p53 binding, ephrin receptor binding, and voltage-gated calcium channel activity involved in AV node cell action potential. However, few of these clustering survived the correction for multiple testing (Table S3).

ADHD and ASD shared loci

Our combined analysis of 8,047,420 SNPs in 38,266 cases with ADHD or ASD and 63,160 controls identified 1,108 SNPs shared by the two childhood psychiatric disorders at genome-wide significance (Figure 1B). These SNPs were located at 47 genomic regions, of which flanking SNPs of any two adjacent regions were at least 1-Mb apart. Majority of these 1,108 SNPs (88%) were located at loci 1p34.2, 1p21.3, 4q24, 5q14.3, 5q21.2, 6q13, 7q31.1, 10q25.1, 13q31.1, 16q22.2, 17q21.31, 20p11.23-11.22 (Table 3). All these loci have been reported to contain copy number variants (CNVs) associated with ASD in multiple reports or different study populations, according to the Simons Foundation Autism Research Initiative (SFARI) CNV database (Table S4), The associated genes with these CNVs included *HIVP3, RIMS3, DYPD, PTBP2, TET2, MEF2C, RIMS1,* and *SLC25A39*. In addition, of the total 47 genomic regions identified in this analysis, five regions at 1p21.3, 5q14.3, 16q22.2, 10q25.1,20p11.23-11.22 contained at least one SNP associated with either ADHD or ASD at genome-wide significance. The remain-ing 42 regions that did not have an SNP associated with an individual disorder at GWAS significance may harbor novel loci for ADHD and ASD. The detailed estimates of SNPs with a minimum p-value at each genomic region are in the supplementary data (Table S5). However, we did not find any SNPs shared by ADHD and ASD in the xMHC where a large number of SNPs in strong LD were found shared by the three adult-onset disorders.

Table 3. Genomic regions and loci mapped by the 1,108 SNPs common to ADHD and ASD at genome-wide significance.

Region	ID	Chr	SNP1	BP1	SNP2	BP2	#S	Mapped genes	CNVs	
1	1	1	rs35947542	43,983,679	rs3952787	44,323,244	54	*JMJD2A,PTPRF,ST3GAL3*	1p34.2	
2	55	1	rs61783205	46,317,219	rs77881576	46,587,530	7	*MAST2*	1p34.1	
3	62	1	rs222901	96,508,040	rs11307310	96,998,097	102	*RP11-147C23.1,RP5-898J17.1, PTBP2*	1p21.3	*
4	164	1	rs35518820	99,035,830	rs6662897	99,095,611	6	*LOC729987||SNX7*		
5	170	2	rs76504400	1,722,904	rs76504400	1,722,904	1	*PXDN*		
6	171	2	rs77966298	10,984,514	rs77966298	10,984,514	1	*PDIA6*	2p25.1	
7	172	2	rs6711582	159,327,935	rs1548635	159,529,888	14	*PKP4*	2q24.1	
8	186	2	rs75263467	174,601,275	rs75263467	174,601,275	1	*SP3*		
9	187	3	rs74877867	20,493,116	rs14607701	20,621,759	5	*MITF*		
10	192	3	rs56842404	70,253,808	rs62254854	70,266,538	2	*RP11-231I13.2,LOC100128160||FOXP1*		
11	194	3	rs11488172	82,320,385	rs11488172	82,320,385	1	*GBE1*		
12	195	3	rs11710737	107,464,170	rs7634587	107,516,847	4	*BBX*		
13	199	3	rs9855048	128,163,890	rs9855048	128,163,890	1	*EEFSEC||DNAJB8*		
14	200	3	rs20033201	158,001,670	rs11707386	158,152,073	3	*LOC730057||MAGI1,RSRC1*		
15	203	4	rs71297516	2,768,387	rs6422311	2,781,240	8	*TNIP2||SH3BP2*		
16	211	4	rs14510234	31,147,972	rs20072120	31,151,465	4	*RP11-617I14.1*		
17	215	4	rs228619	103,569,283	rs223504	103,635,183	51	*MANBA*	4q24	
18	266	5	rs71613075	87,514,778	rs2009730	87,933,568	95	*CTC-498M16.4,LINC00461,TMEM161B-AS1*	5q14.3	*
19	361	5	rs2635182	92,255,166	rs34523	92,303,352	6	*CTC-458G6.2*		
20	367	5	rs7716818	103,684,787	rs323509	104,082,179	184	*NUDT12||RAB9P1*	5q21.2	
21	551	5	rs6862136	144,495,743	rs6884441	144,512,659	4	*LOC100132712||ASSP10*		
22	555	6	rs9342783	70,852,493	rs3818327	70,861,135	16	*COL19A1*	6q13	
23	572	7	rs4947694	52,181,844	rs4947694	52,181,844	1	*COBL*		
24	573	7	rs34080086	105,017,329	chr7:10506	105,064,665	2	*SRPK2*		
25	575	7	rs34291892	114,058,731	rs7799269	114,290,491	16	*FOXP2*	7q31.1	
26	591	8	rs34458570	745,496	rs1532744	786,916	6	*ERICH1-AS1*		
27	597	8	rs4739249	21,323,694	rs4739249	21,323,694	1	*LOC100129163||GFRA2,*		
28	598	8	rs11445716	144,749,175	rs11445716	144,749,175	1	*ZNF251*		
29	599	9	rs13440322	31,026,272	rs28495892	31,064,791	9	*LOC100130670||LOC138412*	9p21.1	
30	608	10	rs45595836	16,691,399	rs45595836	16,691,399	1	*RSU1*		
31	609	10	rs12769316	104,152,751	rs12772374	104,156,911	2	*GBF1||NFKB2, NFKB2*		
32	611	10	rs61867293	106,563,924	rs11192280	106,776,925	34	*SORCS3*	10q25.1	*
33	645	11	rs5793730	95,309,155	rs5793730	95,309,155	1	*RP11-338H14.1||FAM76B*		
34	646	12	rs704067	89,726,027	rs60474271	89,776,845	13	*DUSP6,POC1B,RP11-13A1.3*		
35	659	13	rs9544757	78,821,529	rs9530779	78,969,536	130	*EDNRB||POU4F1*	13q13.1	
36	789	14	rs14080258	29,419,892	rs17638843	29,524,041	2	*LOC100128215||PRKD1*		
37	791	14	rs36063234	33,409,812	rs4981170	33,412,996	2	*NPAS3*		
38	793	14	rs11263529	94,838,142	rs28929474	94,844,947	2	*SERPINA1*		
39	795	15	rs11857683	87,769,703	rs8042805	87,779,902	3	*LOC100132083||TMEM83*		
40	798	15	rs11854401	93,929,730	rs8042369	93,957,898	8	*UNQ9370||LOC728292*		
41	806	16	rs17606532	72,333,127	rs12924285	72,653,326	13	*LOC390739, LOC645478,UNQ9370*	16q22.2	*
42	819	17	chr17:4396	43,965,129	rs71375338	44,332,793	5	*MAPT*	17q21.31	
43	824	18	rs4144756	39,305,154	rs4144756	39,305,154	1	*KC6, PIK3C3*		
44	825	19	rs13886705	37,439,641	rs13886705	37,439,641	1	*ZNF569*		
45	826	20	rs6047225	21,054,496	rs6035892	21,549,424	280	*KIZ,RPS15AP1,MRPS11P1,RPL24P2,NKX2-2, PAX1,GSTM3P,XRN2,NKX2*	20p11.23	*
46	1106	20	rs11480060	54,230,218	rs11480060	54,230,218	1	*RPL12P4,CBLN4*		
47	1107	21	rs11775706	36,927,870	rs14491176	37,255,329	2	*RUNX1*		

*, Regions where SNPs were associated with either ADHD or ASD; BP1 and BP2 are position for flanking SNP1 and SNP2.

Of the total 1,108 SNPs shared by ADHD and ASD, 1,095 SNPs were mapped to 63 genes including intergenic regions (Table S6) and 912 SNPs (82.3%) were annotated based on the dbSNP[19]. We noted that five SNPs were

non-synonymous (Table S7); 33 SNPs (3.62%) are located at transcriptional factor binding site (TFBS), mostly at 20q11.23-11.22 involving three loci at *RPL24P||C20orf-19, C20orf9,* and *RPS15AP1||XRN2*(Table S8); 55 SNPs (6.03%) are conserved in vertebrates and mostly located at 5 genomic regions with CNVs (Table S9). These predicted functional SNPs were located at *MAST2, MANBA, SERPINA, C20orf9, FOXP1, TMEM161B-AS1, GBF1||NFKB2, PTBP2, PKP4, NUDT12||RAB9P1, BBX,* and *EDNRB|| POU-F4*. Other SNPs shared by ADHD and ASD were located at loci, including *JMJD2A, PTPRF, ST3GAL3, SNX7, SGOL1 ||VENTXP7, EEFSEC||DNAJB8, MAGI1, RSRC1, TNIP2|| SH-3BP2, KCTD16||PRELID2, COL19A1, FOXP2, C8orf68, GFR-A2, RSU1, FAM76B, PRKD1, NPAS3, TMEM83, MAPT,* and *RPL12P4||CBLN4* (Table 3). All these 63 genes together annotated a few biological processes, cellular component, and molecular functions, but none of these functional annotations and clustering were significant after multiple testing correction (Table S10).

Genetic variants shared by all five disorders

Through a combined analysis of 6,391,075 SNPs available common to all five studies, we identified 713 SNPs at 47 genes in 24 genomic regions (defined as above) shared by all five disorders at genome-wide significance (Figure 2A). We note that no SNPs were associayed with schizophrenia (Figure 2B), Bipolar (Figure 2D) or ASD (Figure 2E); but SNPs *NUDT12||RAB9P* on 5q21.2-21.3 and 10q24-25 have been associated with ADHD (Figure 2C) and MDD (Figure 2E), respectively. SNPs at *NUDT12 ||RAB9P* appear in strong LD in multiple original studies (Figure 2 C, E, F) and SNPs at 10q24-25 were mapped to multiple genes including *BLOC1S2, CHUK, CWF19L1, ERIN1, PKD2L1,* and *SORCS3.* The locus 10q24 has been identified in a previous genome-wide analysis of shared effect by five psychiatric disorders.

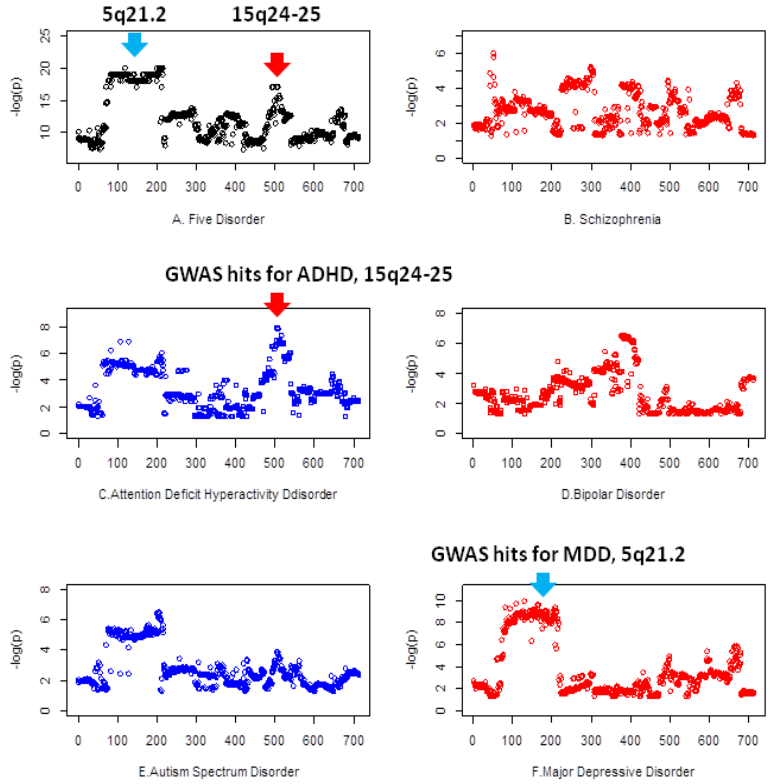

Figure 2. Scatter plots of p values (-log) for 713 SNPs shared by five disorders at genome-wide significance and signals for an individual disorder (X-axis is the SNPs in the chromosomal order). A) Combined signals for SNPs shared by five disorders; B) Signals with schizophrenia; C) Signals association with ADHD, and SNPs at 15q24-25 associated with ADHD at genome-wide significance; D) Signals for bipolar disorder; E) Signals for ASD; F) Signals for MDD, many SNPs at 5q21.2 were associated with MDD.

In the 22 novel genomic regions that did not contain an SNP associated with the particular disorder at genome-wide significance, six SNPs, including rs7945989 at *PKP4*, rs9375138 at *C6orf167*,rs12376855 at *PCSK5*, rs67525-828 at *CIZ1*,rs9804545 at *CWF19L2*,rs3099047 at *CAST-PER2*, were shared by the five disorders (Table 4). Except for *CACNB2* that has been found shared by five disorders, we found additional 40 gene loci in the remaining regions, including *A2BP1, RIMS1, DFNA5, CNTN4, MPP6, PLC1, RFTN2, SLC30A9, PAQR3, ERLIN1, SORCS3, ZNF584,*

and *ZNF132*. The detailed estimates of flanking SNPs at the total 24 regions are in the supplementary (Table S11).

Of the 24 genomic regions that harbored SNPs shared by the five disorders, all had been reported with CNVs associated with ASD (only 15q15.3 known for schizophrenia) and more than half were identified with expression quantitative trait loci (eQTLs) (Table S12). About two-thirds of the CNVs disrupted genes; for example, the CNV at 3p-26.3 were associated with *CNTN6* and *CNTN4*, 6q13 with *RIMS1*, 7p15.3 with *MPP6* and *DFNA5*, 16p13.3 with *A2-BP1,* and 19q13.43 with *ZNF584*. In addition, we identified SNPs in more than 13 genomic regions as eQTLs in human tissues through *cis*-association analysis of the flanking SNPs or alternatives with mRNA expression of the mapped genes. The eQTLs affected gene expression of almost 20 genes, including *ANKRD44, SF3BL, PLCL1, RFTN-2, SLC30A9, PAQR3, NAA11, MPP6, DFNA5, CIZ1, DMM1, C9orf16, BLOC1S2, SORCS3, CWF19L2, STRCP1, ZN584, RPSS,* and *SLC27A5* (Table 4)*.* Additionally, we found that SNP rs3099047 at *CATSPER2* had *cis*-association with about 19 genes in the same region.

Further, we noted that 387 of 713 SNPs shared by five disorders were discovered neither in the analysis of three adult disorders or ADHDASD. However, they were involved in the majority of the genomic regions where the shared 713 SNPs are located (Table S13). We also noted that 146 SNPs were shared by both the three adult-onset disorders and ADHDASD (Figure S1), and they were located at a 400-kb intergenic region *NUDT12||RAB9P1* on 5-q21.2 and *SORCS3* on 10q24-25. The *SORCS3* encodes a type-I receptor transmembrane protein, a member of the vacuolar protein sorting 10 (VSP10) receptor family, and had a biased expression in the human brain tissues of the Human Protein Atlas dataset.

DISCUSSIONS

We conducted a genome-wide association combined analysis of five major psychiatric disorders with an identification of 336 loci shared by three adult psychiatric disorders, 63 loci by ADHD and ASD, and 47 independent loci in 24 genomic regions associated with the combined all five disorders. The more loci shared among three adult disorders were consistent with a recent study that the overlapping gene expression pattern in human brains that SCZ, BD, and MDD have a moderate to high level of transcriptome correlation, but a low correlation with ASD, indicated[23]. Our study reveal a different genetic architecture, in particular the xMHC region, but some shared common variants between the childhood and adult-onset psychitric disorders.

In the present study, we found a substantial heterogeneity of genetic variants shared by three adult-onset psychiatric disorders and two childhood disorders. The analysis of a large number of SNPs across the genome indicated that the xMHC SNPs shared by three adulthood disorders had stronger associations with SCZ and MDD than bipolar disorder, but the two childhood disorders did not share them. In addition, three adulthood psychiatric disor-ders shared a number of non-xMHC loci including *DR-D2, GRIN2A, GABRA1, GABRG2, KCNB1,* and *CACNAI1*, in particular *CACNA1C, TSNARE1, KLC1*, *MYTIL* that have been found differentially methylated in the human prefrontal cortex between schizophrenia and controls[24], suggesting that these variants may be associated with the risk of the adulthood psychiatric disorders through an epigenetic mechanism. However, none of these genes were found overlapped with that mapped by the SNPs shared by the two childhood disorders. Further, among SNPs at 63 loci shared by ADHD and ASD, only two loci at *NUDT12||RAB9P1* and *SORCS3* were common to the three adult psychiatric disorders. Given that, 80% of SNPs shared by two childhood disorders are located at genomic regions with CNVs known for ASD; it may support that CNVs contribute to the genetic causes of two childhood disorders significantly, at least for ASD[25]. However, this study was not aimed to focus on CNVs or rare mutations, which have been implicated for the biology of autism spectrum disorder[26].

Despite the noted heterogeneity for the loci between adult-onset and childhood disorders, new novel or specific loci were identified for five disorders, and they indicate that neurodevelopmental genes may play a role in the development of a spectrum of major psychiatric disorders. *First*, all of the loci shared by the five disorders were located at genomic regions with CNVs reported for ASD. Previous studies have found that both microdeletions and microduplications greater than 100-kilobases disrupt genes in the neurodevelopmental pathway in schizophrenia[27]. Several genes identified are worthy of mention here. *A2BP1* has been identified as the top candidate gene in one of two network modules revealed through transcriptome analysis of differentially expressed genes between autism and controls in post-mortem human brains [28]. Disruption of *CNTN4* has been shown to result in developmental delay and contributing to the 3p deletion syndrome [29]. *CATSPER2* encodes a protein in the family of cation channel proteins that localize to the flagellum of spermatozoa; defects at this locus cause male infertility, and further a single SNP rs3099047 at *CATSPER2* was shown as a significant *cis*-association with nearly 20 genes in the GTEx dataset. *Moreover*, we noted that 102 SNPs in a 5-Mb region on 10q24.31-25.1 were mapped to multiple genes and they were eQTLs for *BLOC1S2* and *SORCS3* in multiple human tissues; and 2-3 Mb *de novo* deletions within this region have been detected in individuals with mental retardation and multiple congenital anomalies [30]. All these findings support that the genetic variants shared by the five disorders play a role in neurodevelopment and may through this general mechanism contribute to risk for all psychiatric disorders.

Further, the loci shared by five disorders may have implications for common neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). Of the loci shared by five psychiatric disorders, genetic variants at *SOCRS3* and *CACNB2* have been assoc-

Table 4. Genomic regions and loci annotated by 713 SNPs common to five disorders at genome-wide significance ($P<5x10^{-08}$).

Reg	ID	Chr	SNP1	BP1	SNP2	BP2	#SNP	Annotated genes or loci	eQTL*	CNVs	
1	1	1	rs904307	30473551	rs1874784	30507893	41	*PTPRU||MATN1*		1p35.2	
2	42	1	rs28374258	190949551	rs12139300	191010445	2	*FAM5C||RGS18*		1q31.2	
3	44	2	rs79452989	159452935		159452935	1	*PKP4*		2q24.1	
4	45	2	rs711810	176888760	rs6755092	176906255	5	*KIAA1715||EVX2*	*AC009336.24*	2q31.1	
5	50	2	rs13404366	198522632	rs2033570	198952637	4	*PLCL1,RFTN2*	*ANKRD44, SF3B1, PLCL1, RFTN2*	2q33.1	
6	54	3	rs6778940	2571220	rs75345673	2576606	4	*CNTN4*		3p26.3	
7	58	4	rs1454607	33643360	rs1454608	33643627	2	*RP11-79E3.2*		4p15.1	
8	60	4	rs6846961	42176060	rs11930133	42184374	3	*BEND4, SLC30A9*	*SLC30A9, BEND4*	4p13	
9	63	4	rs13108290	80198876	rs17441732	80221215	8	*LINC01088,PAQR3||ARD1B*	*LINC01008, PAQR3, NAA11(ARD1B)*	4q21.21	
10	71	5	rs7716818	103684787	rs325528	104048590	146	*NUDT12||RAB9P1*	*RP11-6N13.1*	5q21.2	
11	217	6	rs16880300	50384635	rs6930867	50936376	80	*DEFB112, TFAP2D ,FTHP1, FPS17L4, TFAP2B*		6p12.3	
12	297	6	rs9360557	73132745	rs9351918	73149101	9	*RIMS1||LOC643067*		6q13	
13	306	6	rs9375138	98518518		98518518	1	*C6orf167||LOC100129158*		6q16.1	
14	307	7	rs2529055	24590331	rs12154649	24832129	114	*CTRB1,DFNA5,OSBPL3, MPP6, NPY*	*MPP6, DFNA5*	7p15.3	
15	421	9	rs12376855	78591275		78591275	1	*PCSK5*		9q21.13	
16	422	9	rs67525828	130953511		130953511	1	*CIZ1*	*CIZ1, DNM1, C9orf16, LCN2, CERCAM*	9q34.11	
17	423	10	rs58703423	18540122	rs7091833	18660333	22	*CACNB2*	*RP11-499P20.2*	10p12.33	
18	445	10	rs12769818	1019155629	rs13854010	107329835	102	*BLOC1S2,CHUK,CWF19L1, ERLIN1, PKD2L1, SORCS3*	*BLOC1S2, SORCS3, PKDZI1*	10q24.31-q25.1	**
19	547	11	rs9804545	107278817		107278817	1	*CWF19L2*	*CWF19L2*	11q22.3	
20	548	15	rs3099047	43926033		43926033	1	*CATSPER2*	*AC011330.5, ADAL, CATSPER2, CATSPER2P1, CCNDBP1, CKMT1A, ELL3, LCMT2, PDIA3, RNU6-554P, SERF2, STRC,STRCP1,TGM5,TGM7,TP53BP1,WDR76,ZSCAN29*	15q15.3	
21	549	16	rs61547418	6345040	rs12448420	6346613	14	*A2BP1*		16q13.3	
22	563	18	rs4890712	38903507	rs72893943	39318793	89	*KC6||NPM1P1,MIR924||KC6*	*RP11-142I20.1*	18q12.3	
23	652	18	rs7505145	50711776	rs8091083	50870391	28	*DCC*	*DCC*	18q21.2	
24	680	19	rs73060258	58902954	rs12981875	58935130	34	*FLJ39005, ZNF584, ZNF132*	*ZFN584, ZNF132, RPS5, SLC27A5, AC016629.3, CHMP2A, CTD-2619J13.14, ZNF324, ZNF446, ZNF497*	19q13.43	

#SNP, the number of SNPs shared by five psychiatric disorders in the genomic region;
*, eQTLs were tested mostly for the flanking SNPs or alternative SNPs in the loci at each region;
**, of this region, 2-3-Mb size of de novo deletions have been detected with mental retardation and multiple congenital anomalies (MCA) in multiple populations;
Highlighted, SNPs associated with the individual disorder at genome-wide significance;
SNP1 and SNP2 are flanking SNPs for individual region; and BP1 and BP2 are corresponding position (hg19).

iated with Alzheimer's disease, and both genes had a biased expression in normal brain tissues of the Human Protein Atlas RNA-Seq data. Knockdown of *SORCS3* in cell culture leads to an increase in amyloid precursor protein (APP) processing, and APP may be as a mediator of the synapse pathology in the AD [31]. Common genetic variants at *CACNB2* have been associated with AD or through a within-locus SNP by SNP interaction [32]. In addition, we identified five SNPs at microtubule-associated protein tau (MAPT) that were shared by ADHD and ASD. Common genetic variants at *MAPT* have been associated with the risk of the late-onset AD, and also of PD in an early large family-based study [33], and shared by AD and PD[34]. Mutations in MAPT have also been detected in the early-onset AD and MAPT-related disorders, a group of neurological disorders including frontotemporal dementia with parkinsonism-17 (FTDP-17), progressive supranuclear palsy (PSP), cortico-basal degeneratetion (CBD), and mild late-onset parkinsonism, dementia with epilepsy**.**

Finally, it is worth highlighting that our study identified multiple shared genes *CACNA1C, TSNARE1, KLC1*, and *MYTIL* for three adult disorders that have been found differentially methylated in the human prefrontal cortex between schizophrenia and controls in a recent study [24]. Findings of genetic loci would provide a clue about what kind of environment would have caused the high methylation at individual genes associated with psychiatric disorders or a biological basis for conducting gene-environment interaction analyses. While the collection of environmental data is essential for a complete study of the etiology for common human disorders in the future, the effect that environmental factors exert on humans has to be through the human genome. It would be a great challenge to measure environmental factors across lifespan compared to measure the variants across the whole genome. What is more, most of the lifestyle and behavioral factors are not exogenous, and genetic variants might influence them. In addition to the further neurobiological study, our study provides a manageable list of anchors from which to investigate epigenetic mechanism or gene-gene interaction on the development of neuropsychiatric disorders.

In summary, we identify a sizeable number of genetic variants shared by three psychiatric disorders diagnosed during adulthood, by two childhood disorders, and by all five disorders. These variants indicate genetic heterogeneity but also point to the genetic etiology of neurodevelopment in five major psychiatric disorders or other neurological disorders. Our study provides new insights into genetic etiology and may have important implications for precision neuropsychiatry or medicine.

SUPPLEMENTARY MATERIALS

Published as e-cintent at the journal's website. (https://www.gcatresearch.com).
Figure S1 and Table S1-S13

CONFILCTS OF INTERESTS

The authors declare no conflict of interest regarding the publication of this paper.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Natural Science Foundation of China (No. 81525007 and No.81730036, KX), the China Scholarship Council (LX), direct funding of Lieber Institute for Brain Development (DRW), the Haiju Scholarship through Peking University Beijing Huilongguan Hospital and Global Clinical and Tranlaslational Research Institute (FZ). We also thanks the Psychiatric Genetics Consotium, which makes the data available.

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How to cite this article:
Xia, L, Xia, K, Weinberger, DR, Zhang F. Common genetic variants shared among major psychiatric disorders: A genome-wide combined analysis. Glob Clin Transl Res. 2019; 1(1):21-30