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Novel Risk Loci Associated With Genetic Risk for Bipolar Disorder Among Han Chinese Individuals

A Genome-Wide Association Study and Meta-analysis

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IMPORTANCE The genetic basis of bipolar disorder (BD) in Han Chinese individuals is not fully understood.

OBJECTIVE To explore the genetic basis of BD in the Han Chinese population.

DESIGN, SETTING, AND PARTICIPANTS A genome-wide association study (GWAS), followed by independent replication, was conducted to identify BD risk loci in Han Chinese individuals. Individuals with BD were diagnosed based on *DSM-IV* criteria and had no history of schizophrenia, mental retardation, or substance dependence; individuals without any personal or family history of mental illnesses, including BD, were included as control participants. In total, discovery samples from 1822 patients and 4650 control participants passed quality control for the GWAS analysis. Replication analyses of samples from 958 patients and 2050 control participants were conducted. Summary statistics from the European Psychiatric Genomics Consortium 2 (PGC2) BD GWAS (20 352 cases and 31 358 controls) were used for the trans-ancestry genetic correlation analysis, polygenetic risk score analysis, and meta-analysis to compare BD genetic risk between Han Chinese and European individuals. The study was performed in February 2020.

MAIN OUTCOMES AND MEASURES Single-nucleotide variations with $P < 5.00 \times 10^{-8}$ were considered to show genome-wide significance of statistical association.

RESULTS The Han Chinese discovery GWAS sample included 1822 cases (mean [SD] age, 35.43 [14.12] years; 838 [46%] male) and 4650 controls (mean [SD] age, 27.48 [5.97] years; 2465 [53%] male), and the replication sample included 958 cases (mean [SD] age, 37.82 [15.54] years; 412 [43%] male) and 2050 controls (mean [SD] age, 27.50 [6.00] years; 1189 [58%] male). A novel BD risk locus in Han Chinese individuals was found near the gene encoding transmembrane protein 108 (*TMEM108*, rs9863544; $P = 2.49 \times 10^{-8}$; odds ratio [OR], 0.650; 95% CI, 0.559-0.756), which is required for dendritic spine development and glutamatergic transmission in the dentate gyrus. Trans-ancestry genetic correlation estimation ($\rho_{ge} = 0.652$, SE = 0.106; $P = 7.30 \times 10^{-10}$) and polygenetic risk score analyses (maximum liability-scaled Nagelkerke pseudo $R^2 = 1.27\%$; $P = 1.30 \times 10^{-19}$) showed evidence of shared BD genetic risk between Han Chinese and European populations, and meta-analysis identified 2 new GWAS risk loci near *VRK2* (rs41335055; $P = 4.98 \times 10^{-9}$; OR, 0.849; 95% CI, 0.804-0.897) and *RHEBL1* (rs7969091; $P = 3.12 \times 10^{-8}$; OR, 0.932; 95% CI, 0.909-0.956).

CONCLUSIONS AND RELEVANCE This GWAS study identified several loci and genes involved in the heritable risk of BD, providing insights into its genetic architecture and biological basis.

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Supplemental content

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Bipolar disorder (BD) is a severe psychiatric illness characterized by recurrent episodes of mania or hypomania and depression.[1,2] The World Health Organization estimated that the lifetime prevalence is 0.6% for bipolar I disorder (BD-I) and 0.4% for bipolar II disorder (BD-II) in 11 countries across the Americas, Europe, and Asia.[3] According to earlier studies, the lifetime prevalence of BD is approximately 5% to 10% in first-degree relatives of patients and approximately 40% to 70% in monozygotic co-twins.[4] Therefore, heritable factors likely contribute to this disorder, and genetic analyses could help to disentangle its mechanisms and to facilitate the discovery of therapeutic targets.[5,6] A recent genome-wide association study (GWAS) estimated that approximately 23% of BD heritability was attributed to common single-nucleotide variations (SNVs) and provided implications for its pathology.[7]

Although GWASs have increased our knowledge of BD in Europeans, genetic heterogeneity between continental populations exists and may result in uncertainty when generalizing these discoveries across different populations. For example, a recent Japanese BD GWAS[8] (including 2964 cases and 61 887 controls) reported on genome-wide risk loci that are either shared among distinct populations or are specific to East Asian individuals.[9,10] Because most of the BD GWASs to date have been performed in European populations, further analyses of the genetic architecture of BD in other populations are needed. A previous Han Chinese BD GWAS[11] (including 1000 cases and 1000 controls) identified no statistically significant loci, probably because of the limited sample size. Therefore, we conducted a BD GWAS in a larger independent sample (1822 cases and 4650 controls) of Han Chinese ancestry, followed by replication in additional Han Chinese individuals (958 cases and 2050 controls), as well as a trans-ancestry meta-analysis combining these results with summary statistics from the European Psychiatric Genomics Consortium 2 (PGC2) BD GWAS[7] (20 352 cases and 31 358 controls).

Key Points

Question What is the genetic architecture of bipolar disorder (BD) in the Han Chinese population?

Findings In this genome-wide association study of 6472 individuals of Han Chinese ancestry (1822 cases and 4650 controls), several novel risk loci for BD were found, and trans-ancestry genetic correlation estimation and polygenic risk score analyses of Han Chinese and European individuals suggested a shared genetic risk of BD.

Meaning Findings of this study highlighted novel genome-wide significant risk loci for BD that can provide insight into the genetic architecture of this disorder.

Methods

Study Design

The study protocol for this GWAS and trans-ancestry meta-analysis was approved by the institutional review board of the Kunming Institute of Zoology, Chinese Academy of Sciences, as well as ethics committees of all participating hospitals and universities (provided in the eMethods in the Supplement). All participants provided written informed consent before any study-related procedures were performed. This study followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline. The study was performed in February 2020.

In total, 6472 Han Chinese individuals (1822 BD cases and 4650 controls) were recruited in mainland China for the discovery GWAS. A unique sample of 958 patients with BD and 2050 control participants of Han Chinese ancestry in mainland China were included for the replication analysis. In both the discovery GWAS and replication stages, patients with BD were diagnosed through the use of an extensive clinical interview and the Structured Clinical Interview for *DSM-IV* Axis I Disorders–Patient Version. The control participants had no BD and no history of any mental illness. Detailed descriptions of the sample are provided in the eMethods in the Supplement.

Outcomes

Genotyping in the discovery stage was performed with either the Illumina Infinium Global Screening Array (GSA) chip or the Illumina Genome-Wide Asian Screening Array (ASA) chip (Beijing Guoke Biotechnology Co, Ltd). Quality control (QC) analyses were performed using the pipeline suggested by Anderson et al.[12] After QC, the autosomal biallelic SNVs on different GWAS platforms underwent genotype imputation using the prephasing imputation stepwise approach in SHAPEIT and IMPUTE2 software programs,[13,14] and the imputation reference set was obtained from phase 3 of the 1000 Genomes Project.[15]

Statistical Analysis

In each GWAS cohort, logistic regression of BD diagnosis on imputed hard-called genotypes (with posterior probability >.95) was performed,[16] during which the associations of the top 20 principal components with BD diagnosis were evaluated, and principal components associated with diagnostic status ($P \leq .05$) were included as covariates to control for population stratification.[17] The statistics in each GWAS cohort were then combined for an inverse variance–weighted meta-analysis using random-effects or fixed-effects models (referred to as the discovery GWAS). Linkage disequilibrium score regression (LDSC) was applied to assess potential population stratification and to estimate SNV heritability.[18,19] Single-nucleotide variations with 2-sided $P < 5.00 \times 10^{-8}$ were considered to show genome-wide significance.

Two expression quantitative trait loci (eQTL) data sets (CommonMind Consortium[20] and BrainSeq Phase 2[21]) of the dorsolateral prefrontal cortex (DLPFC) were obtained for the summary data-based mendelian randomization[22] and transcriptome-wide association (TWAS)[23] analyses. The sample sizes of the RNA sequencing–based eQTL data sets were 467 and 397, respectively.

Given the shared clinical manifestations between different psychiatric disorders and traits,[24,25] we examined the genetic correlations of BD with other psychiatric disorders (eg, schizophrenia[26,27] and depression[28,29]) and traits (cognitive

performance,[30] intelligence,[31] and educational attainment[30]) using LDSC (for analyses within the same population)[18,19] or Popcorn, version 1.0 (Brielin C. Brown [https://github.com/brielin/Popcorn]) (for trans-ancestry analyses)[32] based on the GWAS summary statistics. The proportion of BD variance explained by risk SNVs identified in GWASs of those phenotypes was also estimated using polygenic risk scores (PRSs).[8,33] Fifteen pairs of PRS analyses were conducted in our study; hence, $P < .0033$ was considered statistically significant after multiple correction (approximately 0.05 ÷ 15). Details of these GWAS data sets are provided in the eMethods in the Supplement.

We examined the messenger RNA (mRNA) expression patterns of the risk genes identified by GWAS in human tissues using GTEx and BrainSpan data sets.[34,35] We also used hypergeometric testing in the web-based platform FUMA[36] to examine the tissue expression enrichment of the GWAS risk loci.

Results

GWAS of BD in the Han Chinese Population

We conducted a meta-analysis of 2 BD GWAS Han Chinese cohorts, including 1822 cases (mean [SD] age, 35.43 [14.12] years; 838 [46%] male and 984 [54%] female) and 4650 controls (mean [SD] age, 27.48 [5.97] years; 2465 [53%] male and 2185 [47%] female) (referred to as the discovery GWAS). After systematic QC analysis and imputation using phase 3 of the 1000 Genomes Project,[15] we assessed the associations of 4 499 546 autosomal biallelic SNVs with imputation quality score (INFO) greater than 0.8, minor allele frequency greater than 1%, call rate greater than 95%, and Hardy-Weinberg equilibrium $P > 1.00 \times 10^{-5}$. Population substructures of these samples were examined through a principal components analysis (eFigure 1 in the Supplement). The genomic inflation λ of the discovery GWAS was 1.038, and the λ_{1000} (a scaled value to 1000 cases and 1000 controls) was 1.015. We then conducted LDSC analysis to estimate BD polygenicity in these samples based on precomputed linkage disequilibrium (LD) scores in HapMap3 for East Asian individuals.[18,19] The mean (SE) LDSC intercept was 1.005 (0.008), and the mean (SE) attenuation ratio was 0.077 (0.132), confirming polygenicity of BD in the discovery GWAS and suggesting that only approximately 8% of the observed genomic inflation in test statistics was attributed to population stratification.[18,19] The LDSC estimated that the mean (SE) SNV heritability in the discovery GWAS was 0.220 (0.043) to approximately 0.310 (0.059) on the liability scale, assuming that the population prevalence of BD was 0.5% to approximately 2%.[18,19]

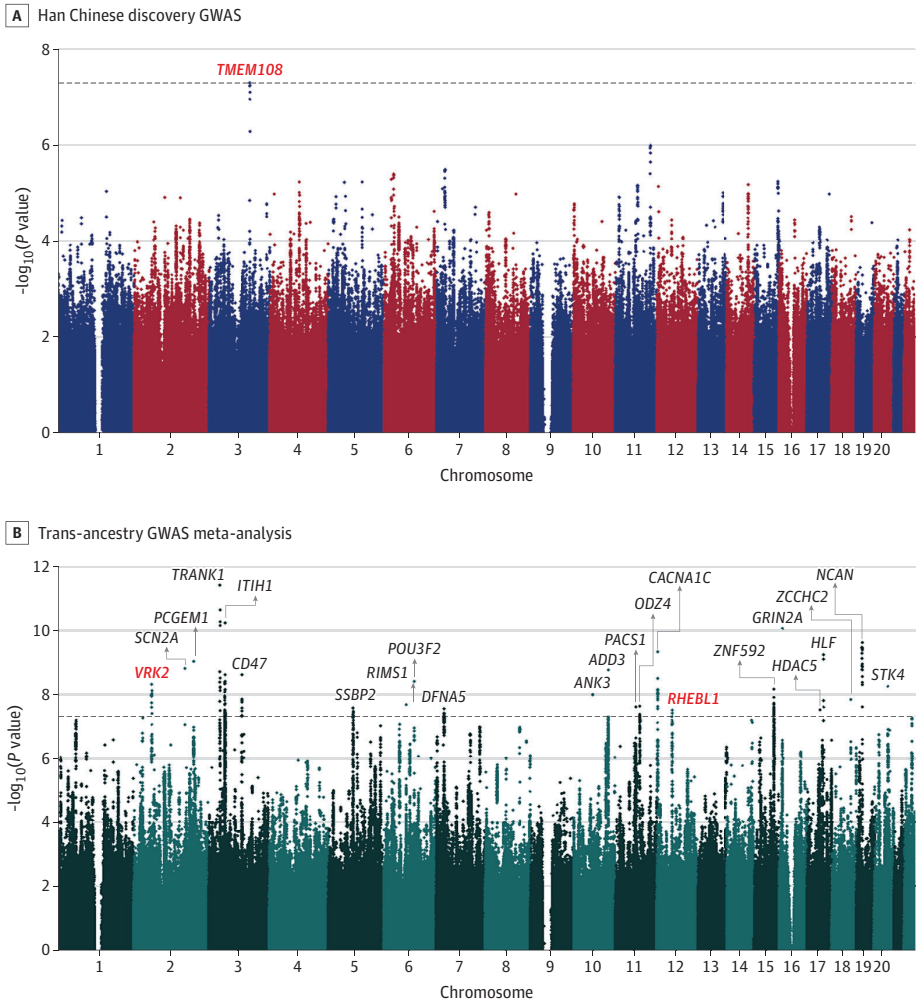
Manhattan and quantile-quantile plots for the Han Chinese discovery GWAS are shown in **Figure 1**A and in eFigure 2 in the Supplement, respectively. The discovery GWAS (1822 cases and 4650 controls) identified a single locus reaching genome-wide significance, which is located at 3q22.1 in the 5′ upstream region of *TMEM108* (OMIM 617361) and the 3′ downstream region of the noncoding RNA *NPHP3-AS1* (Gene ID 348808) (rs9863544; $P = 5.00 \times 10^{-8}$; odds ratio [OR], 0.590; 95% CI, 0.488-0.713) (**Figure 2**A).[15,37] In addition, the discovery GWAS identified 22 SNVs with *P* values lower than the threshold of suggestive significance (ie, $P = 5.00 \times 10^{-6}$) (eTable 1 in the Supplement). These SNVs appeared to represent 4 physically distinct regions after LD pruning at $r^2 = 0.1$ (within 500 kilobase [kb]). To replicate these results, we tested the top 4 SNVs from these distinct regions in an independent sample of Han Chinese individuals, including 958 cases (mean [SD] age, 37.82 [15.54] years; 412 [43%] male and 546 [57%] female) and 2050 controls (mean [SD] age, 27.50 [6.00] years; 1189 [58%] male and 861 [42%] female). We confirmed that rs9863544 also showed nominal significance (defined as $P < .05$) ($P = .04$; OR, 0.771; 95% CI, 0.600-0.991) (**Table 1**). Detailed results obtained in the replication samples are provided in eResults 1, eFigure 3, and eTable 2 in the Supplement.

Meta-analysis of the discovery GWAS and replication samples in Han Chinese individuals demonstrated that rs9863544 had genome-wide significance ($P = 2.49 \times 10^{-8}$; OR, 0.650; 95% CI, 0.559-0.756) (Table 1). We also explored the mRNA expression patterns of the 2 genes (*TMEM108* and *NPHP3-AS1*) near rs9863544 in public RNA sequencing resources. In the GTEx data set,[34] the mRNA of *NPHP3-AS1* was barely detectable in most human organs, including the brain, whereas *TMEM108* was widely expressed in the human brain (eFigure 4 in the Supplement). Further analyses of their temporal expression patterns in human brain in the BrainSpan data set[35] revealed statistically significantly higher levels of *TMEM108* mRNA in prenatal stages, which declined after birth; the mRNA expression of *NPHP3-AS1* remained low in human brain regardless of the developmental stage (eFigure 5 in the Supplement). We also examined whether the genomic loci reaching the threshold of suggestive significance ($P \le 5.00 \times 10^{-6}$) in previous East Asian BD GWASs[8,11] were statistically significant in our Han Chinese sample. We found that rs7221716 ($P = 5.60 \times 10^{-7}$; OR, 1.170; 95% CI, 1.100-1.244 in the prior Japanese BD GWAS[8]) near the *PFAS* (OMIM 602133) gene was nominally significant in our Han Chinese discovery GWAS ($P = .01$; OR, 1.115; 95% CI, 1.023-1.216) and had genome-wide significance in a meta-analysis combining the Han Chinese discovery GWAS and the previous Japanese GWAS ($P = 2.02 \times 10^{-8}$; OR, 1.152; 95% CI, 1.096-1.210) (detailed results are provided in eResults 2 and eTable 3 in the Supplement).

Trans-Ancestry Genetic Correlation and Meta-analysis of BD in Han Chinese and European Populations

The association statistics of SNVs from the Han Chinese discovery GWAS and the European PGC2 BD GWAS,[7] as well as precomputed LD scores for European and East Asian individuals in the 1000 Genomes Project,[15] were obtained to estimate the trans-ancestry genetic correlations of BD between Han Chinese and European individuals using Popcorn, version 1.0. That analysis revealed a statistically significant trans-ancestry genetic effect correlation between the Han Chinese discovery GWAS and the European PGC2 BD GWAS (mean [SE] ρ for genetic effect [ρ_{ge}] = 0.652 [0.106]; $P = 7.30 \times 10^{-10}$), as well as a population genetic impact correlation accounting for the different SNV allele frequencies between populations (mean [SE] ρ for genetic impact [ρ_{gi}] = 0.651 [0.111]; $P = 4.50 \times 10^{-9}$).

Figure 1. Manhattan Plots

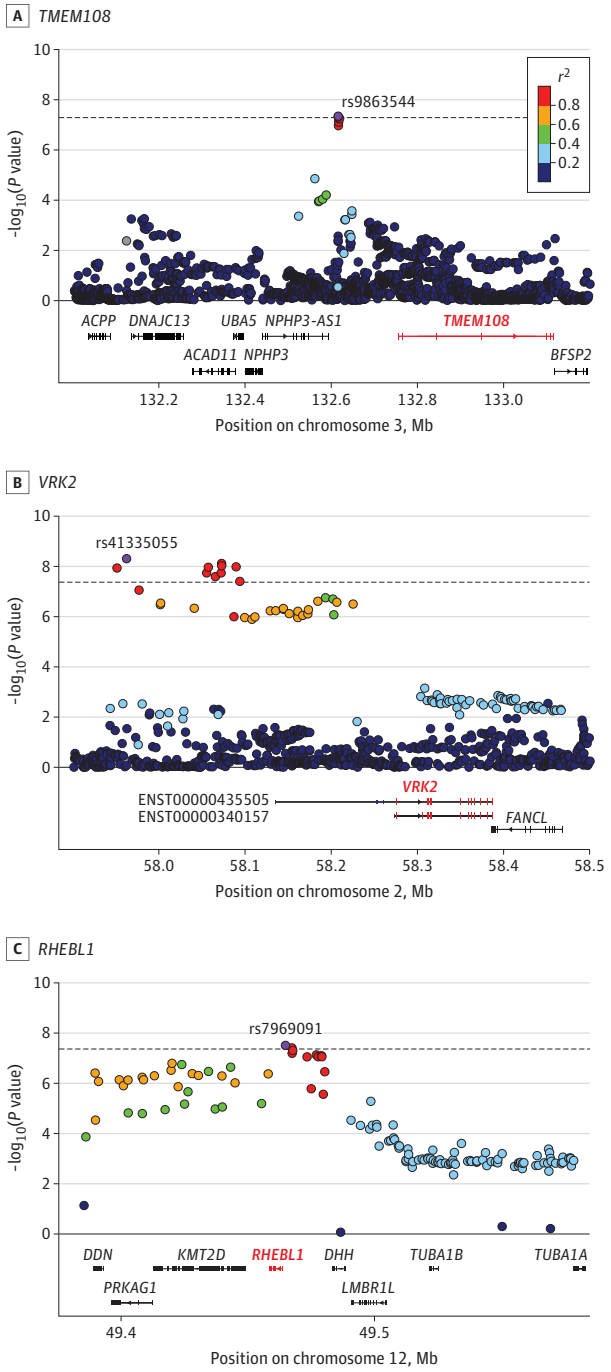


The dashed line represents the threshold for genome-wide significance ($P < 5.00 \times 10^{-8}$), and the gene names marked in red are novel risk genes identified by this study. GWAS indicates genome-wide association study.

We then conducted a trans-ancestry meta-analysis of our discovery GWAS and the European PGC2 BD GWAS. A total of 3 742 365 autosomal biallelic SNVs with INFO greater than 0.8 and minor allele frequency greater than 1% in both Han Chinese and European individuals were included in the trans-ancestry meta-analysis. Of these SNVs, 46 441 SNVs (approximately 1.2% of the total SNVs) showed pronounced heterogeneity (I^2 >75%) and were thus meta-analyzed using a random-effects model; the other 3 695 924 SNVs were meta-analyzed using a fixed-effects model given their nonsignificant heterogeneity (I^2 ≤75%). The genomic inflation λ of the trans-ancestry meta-analysis was 1.355, and the λ_{1000} was 1.013. The mean (SE) LDSC intercept (based on precomputed LD scores for European populations) was 1.023 (0.011), and the mean (SE) attenuation ratio was 0.054 (0.025), indicating polygenicity rather than population stratification.[18,19] The mean (SE) LDSC SNV heritability estimate for BD was 0.160 (0.008) to approximately 0.220 (0.011) on the liability scale, assuming that the population prevalence of BD was 0.5% to approximately 2%.[18,19]

Manhattan and quantile-quantile plots for the trans-ancestry meta-analysis are shown in Figure 1B and eFigure 6 in the Supplement, respectively. A total of 191 SNVs reached the genome-wide significance threshold ($P \leq 5.00 \times 10^{-8}$) (eTable 4 in the Supplement). We then combined the SNVs with r^2 <0.1 within 500 kb based on European LD panels and noted that they mapped to 23 physically distinct genomic regions (Figure 1B). The top SNVs in each of these GWAS loci are listed in **Table 2**. Further detailed characterization of these 23 GWAS loci suggested that 21 of them had genome-wide significance in either the GWAS stage or the GWAS plus replication stages of the European PGC2 BD GWAS. The trans-ancestry meta-analysis herein identified 2 novel loci (*VRK2* [OMIM 602169] and *RHEBL1* [OMIM 618956]) that were not genome-wide significant in the European PGC2 BD GWAS. Specifically, the European PGC2 BD GWAS SNVs reaching the threshold of suggestive significance in the 5′ upstream region of the *VRK2* gene showed nominal significance in our Han Chinese discovery GWAS and showed genome-wide significance in the trans-ancestry meta-analysis (eg, rs41335055; $P = 9.85 \times 10^{-8}$; OR,

Figure 2. Regional Association Plots



Regional association plots are shown for the top loci in the Han Chinese bipolar disorder (BD) discovery genome-wide association study (GWAS) and the novel loci in the trans-ancestry meta-analysis of BD. All regional association plots were generated using LocusZoom.[37] The linkage disequilibrium information is from phase 3 of the 1000 Genomes Project.[15] The dashed line represents the threshold for genome-wide significance ($P < 5.00 \times 10^{-8}$). Mb indicates megabase.

0.854; 95% CI, 0.806-0.905 in the European PGC2 BD GWAS; $P = .01$; OR, 0.808; 95% CI, 0.683-0.956 in the Han Chinese discovery GWAS; and $P = 4.98 \times 10^{-9}$; OR, 0.849; 95% CI, 0.804-0.897 in the trans-ancestry meta-analysis (Figure 2B). Simi-

Table 1. Summary of the Association Results of the Top SNVs in 4 Independent Loci Identified by the Han Chinese Discovery GWAS

Nearest gene	OMIM accession No.	Chromosome	Position	SNV	A1/A2	Fre_A1	Han Chinese discovery GWAS			Han Chinese replication sample		Han Chinese meta-analysis			
							INFO[a]	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	Q statistic	I^2 statistic, %
TMEM108[b]	617361	3	132612664	rs9863544	T/C	0.058	0.988/0.964	0.590 (0.488-0.713)	5.00E−08	0.771 (0.600-0.991)	.04	0.650 (0.559-0.756)	2.49E−08	0.250	27.80
C6orf15	611401	6	31080919	rs2233964	G/A	0.269	0.999/0.999	0.809 (0.739-0.885)	4.03E−06	0.973 (0.805-1.176)	.78	0.836 (0.770-0.907)	1.75E−05	0.230	32.04
SNX10	614780	7	26427543	rs6461936	G/A	0.116	0.939/0.957	0.735 (0.646-0.837)	3.20E−06	1.077 (0.899-1.291)	.42	0.837 (0.643-1.090)	.19	0.002	83.99
DRD2	126450	11	113318007	rs4245147	C/T	0.161	0.974/1.000	0.756 (0.676-0.846)	1.04E−06	0.860 (0.735-1.006)	.06	0.789 (0.720-0.865)	3.98E−07	0.315	13.53

Abbreviations: A1, effect allele corresponding to OR; A2, non-effect allele; Fre_A1, frequency of effect allele in our Han Chinese discovery GWAS sample; GWAS, genome-wide association study; INFO, imputation quality score; OR, odds ratio; SNV, single-nucleotide variation.

[a] INFO in Global Screening Array GWAS/Asian Screening Array GWAS.

[b] The gene locus reached genome-wide significance.

Table 2. Summary of the Association Results of the Top Genome-Wide Significant SNVs in 23 Independent GWAS Loci Identified by the Trans-Ancestry Meta-analysis

						Trans-ancestry GWAS meta-analysis				European PGC2 BD GWAS			European PGC2 BD GWAS replication sample		Han Chinese discovery GWAS		
Nearest gene	OMIM accession No.	Chromosome	Position	SNV	A1/A2	OR (95% CI)	*P* value	*Q* statistic	I^2 statistic, %	INFO	OR (95% CI)	*P* value	OR (95% CI)	*P* value	INFO[a]	OR (95% CI)	*P* value
VRK2	602169	2	57961229	rs41335055	*T/C*	0.849 (0.804-0.897)	4.98E−09	0.400	0	0.973	0.854 (0.806-0.905)	9.85E−08	NA	NA	0.961/0.940	0.808 (0.683-0.956)	.01
SCN2A	182390	2	166152389	rs17183814	*A/G*	0.883 (0.848-0.919)	1.57E−09	0.627	0	0.944	0.869 (0.825-0.916)	1.49E−07	0.892 (0.826-0.963)	.003	1.000/1.000	0.932 (0.830-1.046)	.23
PCGEM1	605443	2	194465711	2:194465711:D:I	*I/D*	0.935 (0.915-0.955)	9.36E−10	0.623	0	0.978	0.926 (0.901-0.951)	2.34E−08	0.946 (0.909-0.984)	.006	0.980/0.960	0.969 (0.894-1.050)	.44
TRANK1	Gene ID 9881	3	36856030	rs9834970	*T/C*	0.928 (0.909-0.948)	3.85E−12	0.012	72.71	0.989	0.904 (0.881-0.928)	5.53E−14	0.979 (0.941-1.019)	.30	1.000/1.000	0.954 (0.879-1.035)	.26
ITIH1	147270	3	52814256	rs2302417	*A/T*	0.932 (0.913-0.952)	5.86E−11	0.471	0	0.972	0.924 (0.900-0.949)	4.93E−09	0.941 (0.905-0.979)	.002	0.991/0.994	0.962 (0.889-1.041)	.33
CD47	601028	3	107793709	rs3804640	*A/G*	1.068 (1.045-1.091)	2.48E−09	0.366	5.51	0.993	1.075 (1.047-1.104)	9.27E−08	1.044 (1.004-1.086)	.03	0.998/0.993	1.150 (1.026-1.289)	.02
SSBP2	607389	5	80796368	rs10035291	*T/C*	1.068 (1.044-1.093)	2.67E−08	0.476	0	0.950	1.081 (1.050-1.113)	1.15E−07	1.047 (1.003-1.093)	.04	0.975/0.974	1.034 (0.934-1.145)	.52
RIMS1	606629	6	72519394	6:72519394:D:I	*D/I*	1.063 (1.041-1.086)	2.14E−08	0.902	0	0.968	1.066 (1.038-1.095)	3.13E−06	1.062 (1.020-1.105)	.003	0.978/0.970	1.044 (0.963-1.132)	.30
POU3F2	600494	6	98591622	rs2388334	*A/G*	0.939 (0.920-0.959)	3.88E−09	0.730	0	1.000	0.931 (0.907-0.956)	8.62E−08	0.950 (0.914-0.988)	.01	0.999/0.998	0.967 (0.892-1.048)	.42
DFNA5	600994	7	24647222	rs12672003	*A/G*	0.893 (0.858-0.929)	2.83E−08	0.535	0	1.010	0.890 (0.854-0.927)	2.87E−08	NA	NA	0.992/0.986	0.948 (0.790-1.138)	.57
ANK3	600465	10	62125856	rs10994318	*C/G*	1.134 (1.086-1.184)	1.03E−08	0.445	0	1.000	1.151 (1.090-1.216)	4.49E−07	1.130 (1.039-1.228)	.004	0.993/0.948	1.054 (0.931-1.193)	.41
ADD3	601568	10	111745562	10:111745562:D:I	*I/D*	1.089 (1.059-1.120)	1.74E−09	0.598	0	0.928	1.105 (1.066-1.145)	4.95E−08	1.059 (1.004-1.117)	.03	0.976/0.986	1.084 (1.000-1.175)	.05
PACS1	607492	11	65945186	rs10896090	*A/G*	1.079 (1.051-1.108)	2.45E−08	0.532	0	0.991	1.094 (1.058-1.132)	2.08E−07	1.062 (1.010-1.116)	.02	0.991/0.989	1.033 (0.944-1.130)	.48
ODZ4	610084	11	79153080	rs968369	*T/G*	1.124 (1.079-1.171)	2.36E−08	0.652	0	0.970	1.128 (1.081-1.177)	2.74E−08	NA	NA	0.978/0.949	1.072 (0.901-1.276)	.43
CACNA1C	114205	12	2387099	rs10744560	*T/C*	1.075 (1.051-1.100)	4.70E−10	0.501	0	1.000	1.087 (1.057-1.117)	2.92E−09	1.052 (1.009-1.097)	.02	0.990/0.982	1.007 (0.852-1.191)	.94
RHEBL1	618956	12	49464449	rs7969091	*A/G*	0.932 (0.909-0.956)	3.12E−08	0.908	0	0.987	0.933 (0.909-0.958)	3.25E−07	NA	NA	0.994/0.996	0.918 (0.848-0.993)	.03
ZNF592	613624	15	85125838	rs12902052	*A/T*	1.088 (1.057-1.120)	7.07E−09	0.789	0	0.966	1.087 (1.055-1.119)	2.75E−08	NA	NA	0.920/0.963	1.098 (0.977-1.233)	.12
GRIN2A	138253	16	9926966	rs11647445	*T/G*	0.928 (0.907-0.949)	8.74E−11	0.973	0	0.970	0.928 (0.903-0.954)	1.22E−07	0.926 (0.889-0.964)	.0002	0.993/0.993	0.949 (0.821-1.097)	.48
HDAC5	605315	17	42201041	rs112114764	*T/G*	0.937 (0.916-0.959)	3.10E−08	0.853	0	0.962	0.932 (0.906-0.959)	1.68E−06	0.939 (0.899-0.980)	.004	0.988/0.992	0.975 (0.886-1.073)	.61
HLF	142385	17	53367300	rs884303	*A/G*	0.921 (0.897-0.945)	5.78E−10	0.405	0	0.986	0.923 (0.898-0.948)	5.87E−09	NA	NA	0.964/1.000	0.896 (0.813-0.987)	.03
ZCCHC2	Gene ID 54877	18	60243876	rs11557713	*A/G*	1.069 (1.045-1.094)	1.49E−08	0.534	0	0.972	1.074 (1.043-1.105)	1.23E−06	1.059 (1.015-1.105)	.008	0.962/0.965	1.064 (0.971-1.166)	.19
NCAN	Gene ID 1463	19	19358207	rs111444407	*T/C*	1.097 (1.065-1.130)	5.26E−10	0.067	58.18	0.993	1.124 (1.084-1.165)	2.40E−10	1.040 (0.986-1.097)	.15	0.993/0.987	1.087 (0.963-1.227)	.18
STK4	604965	20	43750410	rs6130764	*T/C*	1.067 (1.044-1.091)	5.63E−09	0.550	0	0.982	1.070 (1.042-1.099)	5.78E−07	1.051 (1.010-1.093)	.01	0.983/0.975	1.131 (1.009-1.268)	.03

Abbreviations: A1, effect allele corresponding to OR; A2, non-effect allele; BD, bipolar disorder; GWAS, genome-wide association study; INFO, imputation quality score; NA, not applicable; OR, odds ratio; PGC2, Psychiatric Genomics Consortium 2; SNV, single-nucleotide variation.

[a] INFO in Global Screening Array GWAS/Asian Screening Array GWAS.

larly, the European PGC2 BD GWAS SNVs reaching the threshold of statistical significance in the *RHEBL1* gene showed nominal significance in our Han Chinese discovery GWAS and showed genome-wide significance in the trans-ancestry meta-analysis (eg, rs7969091; $P = 3.25 \times 10^{-7}$; OR, 0.933; 95% CI, 0.909-0.958 in the European PGC2 BD GWAS; $P = .03$; OR, 0.918; 95% CI, 0.848-0.993 in the Han Chinese discovery GWAS; and $P = 3.12 \times 10^{-8}$; OR, 0.932; 95% CI, 0.909-0.956 in the trans-ancestry meta-analysis) (Figure 2C). Herein, we refer to the novel risk loci by the names of their closest genes, without suggesting that a causal association between these genes and BD; the previously implicated loci are still referred to by the European PGC2 BD GWAS names.

In addition, we examined the 30 GWAS loci identified in the European PGC2 BD GWAS in our trans-ancestry meta-analysis (eTable 5 in the Supplement). We found that 18 of them had genome-wide significance, including the previously known loci at *CACNA1C* [OMIM 114205], *TRANK1* [Gene ID 9881], *ITIH1* [OMIM 147270], *ANK3* [OMIM 600465], *NCAN* [Gene ID 1463], *SCN2A* [OMIM 182390], and *POU3F2* [OMIM 600494]. The top SNVs or the high LD SNVs in another 8 loci (*PLEKHO1*, *ADCY2*, *RPS6KA2*, *SRPK2*, *MRPS33*, *FADS2*, *SHANK2*, and *STARD9*) identified in the European PGC2 BD GWAS were not genotyped or imputed in our discovery GWAS sample, so these loci were not included in the trans-ancestry meta-analysis. The other 4 loci (*LMAN2L*, *FSTL5*, *THSD7A*, and *PC*) from the European PGC2 BD GWAS were not statistically significant in the trans-ancestry meta-analysis because their allelic effect directions in the Han Chinese discovery GWAS were the opposite of those in the European PGC2 BD GWAS.

Tissue Expression Enrichment, Biological Processes, and In Silico Functional Analyses

To prioritize potential BD risk genes, we integrated the GWAS summary statistics of the trans-ancestry meta-analysis with the DLPFC eQTL data from both the CommonMind Consortium[20] and the BrainSeq Phase 2[21] data sets through summary data-based mendelian randomization[22] and TWAS[23] analyses. Summary data-based mendelian randomization identified a single gene (*NEK4* [OMIM 601959]) that had a statistically significant association with BD after multiple testing correction ($P \le 1.00 \times 10^{-5}$) in both DLPFC eQTL data sets, without evidence of heterogeneity between GWAS and eQTL association signals (eTable 6 in the Supplement). Transcriptome-wide association identified 3 genes (*NEK4* [OMIM 601959], *GLT8D1* [OMIM 618399], and *MCM3AP* [OMIM 603294]) that had statistically significant associations with BD after multiple correction in both DLPFC eQTL data sets ($P \le 2.50 \times 10^{-5}$) (eTable 7 in the Supplement).

Hypergeometric testing using the web-based platform FUMA[36] was performed to examine tissue expression enrichment (in 54 subdivided types of tissues in the GTEx data set[34]) of the risk loci in our trans-ancestry meta-analysis. Although the cerebellum had the strongest enrichment of these genes ($P = 1.78 \times 10^{-12}$; false discovery rate [FDR], 5.31×10^{-11}) (eFigure 7 in the Supplement), they were also statistically significantly enriched in multiple other brain tissues, such as the frontal cortex, anterior cingulate cortex, nucleus accumbens, hippocampus, amygdala, and caudate (FDR, $\le 1.00 \times 10^{-5}$). We then performed an enrichment analysis using Multimarker Analysis of Genomic Annotation (MAGMA)[38] to examine biological processes and pathways underlying BD genetic risk identified in the trans-ancestry meta-analysis. One pathway (regulation of insulin secretion) was statistically significantly enriched for genes with BD associations after multiple correction ($P = 4.83 \times 10^{-6}$; FDR, 0.035) (eTable 8 in the Supplement).

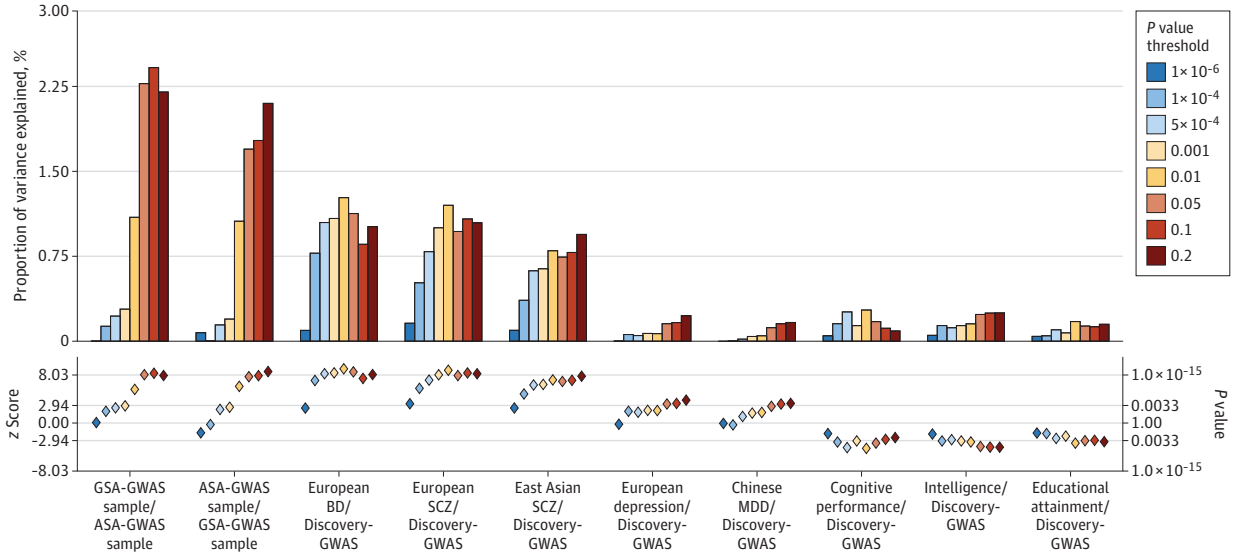
PRS Analysis of BD Across Han Chinese and European Populations

We analyzed the polygenic architecture of BD by performing PRS analysis. The GAS GWAS sample was first used as the training data set to examine whether BD cases had a higher PRS than controls in the ASA GWAS sample. This procedure was then repeated with the training and target data sets swapped. Both the training and target data sets could be used to predict the risk of BD, and the maximum measures of the explained variance (ie, liability-scaled Nagelkerke pseudo R^2) were approximately 2.42% when using GSA GWAS to predict ASA GWAS and approximately 2.10% when using ASA GWAS to predict GSA GWAS ($P < 1.00 \times 10^{-15}$) (**Figure 3**). Assuming that the population prevalence of BD was 0.01, the liability-scaled Nagelkerke pseudo R^2 was calculated to estimate the variance of the disorder explained by the SNPs (eMethods in the Supplement). We also examined the polygenic risk of BD across Han Chinese and European populations using the European PGC2 BD GWAS as the training data set and our total discovery GWAS samples as the target data set. That analysis revealed that individuals with BD had a statistically significantly higher PRS than control participants in the target data set of samples from Han Chinese individuals (maximum liability-scaled Nagelkerke pseudo $R^2 = 1.27\%$; $P = 1.30 \times 10^{-19}$) (Figure 3).

Shared Genetic Risk of BD and Other Psychiatric Disorders or Traits

We conducted LDSC analysis[18,19] to ascertain whether there was a genetic correlation between the Han Chinese BD discovery GWAS and the East Asian schizophrenia GWAS,[26] as well as the Han Chinese depression GWAS[28] (eTable 9 in the Supplement). That analysis revealed statistically significant genetic correlations between BD and schizophrenia (mean [SE] r for genetic [r_g] = 0.535 [0.090]; LDSC $P = 3.31 \times 10^{-9}$) and between BD and depression (mean [SE] $r_g = 0.392$ [0.153]; LDSC $P = .0110$). In both Han Chinese and European populations, we also found statistically significant trans-ancestry genetic effect correlations and population genetic impact correlations between BD in Han Chinese individuals and other psychiatric disorders and relevant traits in European individuals (eTable 9 in the Supplement), including schizophrenia (mean [SE] $\rho_{ge} = 0.503$ [0.074]; $P = 1.25 \times 10^{-11}$; mean [SE] $\rho_{gi} = 0.486$ [0.078]; $P = 5.15 \times 10^{-10}$),[27] cognitive performance (mean [SE] $\rho_{ge} = -0.284$ [0.057]; $P = 5.53 \times 10^{-7}$; mean [SE] $\rho_{gi} = -0.291$ [0.058]; $P = 4.78 \times 10^{-7}$),[30] intelligence (mean [SE] $\rho_{ge} = -0.257$ [0.054]; $P = 2.17 \times 10^{-6}$; mean [SE] $\rho_{gi} = -0.262$ [0.055]; $P = 1.85 \times 10^{-6}$),[31] and educational attainment (mean [SE] $\rho_{ge} = -0.178$ [0.051]; $P = 4.31 \times 10^{-4}$; mean [SE] $\rho_{gi} = -0.182$

Figure 3. Polygenic Risk Score Analysis



Nagelkerke pseudo R^2 on the liability scale was used to present the proportion of variance explained on the y-axis. Positive *z* scores represent positive prediction of case-control status in our discovery samples using the training genome-wide association study (GWAS) summary statistics. For these polygenic risk scores, maximum liability-scaled Nagelkerke pseudo R^2 values (*P* values) are as follows for each of the 10 variables, respectively, on the x-axis: 2.42% (9.03×10^{-17}), 2.10% (7.84×10^{-18}), 1.27% (1.30×10^{-19}), 1.20% (1.16×10^{-18}), 0.94% (5.16×10^{-15}), 0.22% (1.30×10^{-4}), 0.17% (1.02×10^{-3}), 0.28% (2.26×10^{-5}), 0.25% (5.33×10^{-5}), and 0.17% (7.67×10^{-4}). ASA indicates Asian Screening Array; BD; bipolar disorder; GSA, Global Screening Array; MDD, major depressive disorder; and SCZ, schizophrenia.

[0.050]; $P = 2.40 \times 10^{-4}$).[30] The estimation of shared polygenic risk using PRS analysis yielded consistent results, and details are shown in Figure 3 (eResults 3, eDiscussion, and eFigure 8 in the Supplement).

Discussion

This Han Chinese BD GWAS revealed genome-wide significant association between the *TMEM108* locus and BD. Intriguingly, *tmem108*-deficient neurons in mice have fewer and smaller spines, reduced neurogenesis, and decreased excitatory postsynaptic currents,[39] and *tmem108*-deficient mice have impaired sensorimotor gating and cognitive function.[40] Therefore, *TMEM108*-correlated physiological processes likely contribute to BD pathogenesis. However, the Han Chinese genome-wide significant SNV rs9863544 and its surrounding variations did not show evidence of association with BD in Europeans ($P = .23$; OR, 1.016; 95% CI, 0.990-1.043) (eFigure 9 in the Supplement),[7] suggesting that it may be a Chinese-specific BD risk locus. The *T* allele frequency of rs9863544 is 0.057 in Han Chinese and 0.439 in Europeans according to the 1000 Genomes Project,[15] and LD structural differences in this locus between the 2 populations are also evident (ie, SNVs around rs9863544 exhibit stronger LD in Han Chinese than in Europeans) (eFigure 10 in the Supplement). Therefore, differences in both allele frequencies and LD structures implicate potential genetic heterogeneity of this locus between continental populations, which likely resulted from their different population histories and specific environmental adaptations.[41]

In the trans-ancestry meta-analysis, we identified novel risk loci (eg, *VRK2* and *RHEBL1*) that did not reach genome-wide significance in the European PGC2 BD GWAS. Indeed, studies[42,43] have reported preliminary evidence that *VRK2* may alter neuronal proliferation and migration, as well as microglia-mediated synapse elimination. Common variations near *VRK2* have also shown genome-wide significant associations with schizophrenia[26,27,43-45] and depression,[29] supporting the putative involvement of *VRK2* in multiple psychiatric disorders.[46] Another novel *RHEBL1* locus in the present trans-ancestry meta-analysis, although it did not show genome-wide significance in the European PGC2 BD GWAS, was previously implicated in a smaller BD GWAS of Europeans.[47] Despite the unclear function of *RHEBL1*, this gene encodes a brain-enriched G-protein activator of the mechanistic target of rapamycin (mTOR) pathway and thus likely participates in neurodevelopmental and neurodegenerative disorders.[48,49]

In the post-GWAS analysis based on the trans-ancestry meta-analysis results, we identified 3 genes (*NEK4*, *GLT8D1*, and *MCM3AP*) having statistically significant brain eQTL associations with genetic risk using at least one approach. It has been previously shown that *NEK4* and *GLT8D1* can alter dendritic spine development and synaptic transmission,[50,51] which is in line with the pathological hypothesis of BD.[52-54] However, the function of *MCM3AP* in the brain and in BD pathogenesis is less clear. Further investigations of these genes in BD-relevant physiological and behavioral abnormalities using animal models are necessary. Although some previously identified BD risk genes (eg, *CACNA1C*, *ANK3*, *NCAN*, *SCN2A*, and

POU3F2) were not highlighted in the present post-GWAS analysis, these genes are still worth investigating because their associations with BD genetic risk and pathophysiology have been confirmed from multiple perspectives.[5] The involvement of *CACNA1C* and *ANK3* in BD has been extensively described in studies using the approaches of functional genomics, transcriptomics, and physiology.[55-65] Similarly, *ncan* knockout (*ncan*$^{-/-}$) mice exhibited mania-like behavioral abnormalities but normalized after lithium administration,[66] *SCN2A* encodes the sodium voltage-gated channel alpha subunit 2 that changes neurophysiology and cognitive processes,[67,68] and the protein encoded by *POU3F2* alters the differentiation and proliferation of neural progenitor cells.[69]

Limitations

This study has some limitations. First, the post-GWAS analyses were primarily conducted using European-based eQTL data or European LD reference panels, which would impact the prioritization of risk genes and variants given the genetic heterogeneity between Han Chinese and European individuals. Further analyses in Han Chinese individuals using such resources are necessary. Second, the control participants in the present study were recruited based on their self-reported health status rather than screening by professionals. Therefore, potential "contamination" of the controls by individuals having undiagnosed psychiatric disorders may need to be addressed.[70] However, the consequences of such contamination, if any, are likely minimal because the lifetime prevalence of BD is only approximately 1% in the general population.[3]

Conclusions

This study describes several novel risk loci for BD and a shared genetic basis for BD across Han Chinese and European populations. Further investigations are warranted to illuminate the underlying pathological mechanisms.

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