

Association Analysis Between Common Variants of the *TRPM1* Gene and Three Mental Disorders in the Han Chinese Population

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Objective: Our study was designed to determine if the *TRPM1* gene is associated with any of three mental disorders. The project included a cross disorder meta-analysis and association analysis including 141701 cases and 175248 controls.

Materials and Methods: We genotyped eight tag single nucleotide polymorphisms (SNPs) in 1248 unrelated schizophrenia (SCZ) patients, 1056 major depressive disorder patients, 1344 bipolar disorder patients, and 1248 normal controls. We then performed a meta-analysis of 10 GWASs to identify common genetic factors among these three mental disorders. Finally, we performed a meta-analysis of six GWASs to explore the role of rs10162727 in SCZ.

Result: Although two haplotypes of the *TRPM1* gene, rs1035706–rs10162727 and rs10162727–rs3784599, were identified in the control group, as well as all three disease groups, none of the eight tag SNP associations remained significant after correction for multiple tests. In this cross-disorder meta-analysis of the three diseases, none of the tag SNPs were confirmed to be common among the diseases. In addition, in the meta-analysis conducted for the rs10162727 locus in SCZ, there was no significant association (p -value=0.84, odds ratio=1.02 [95% CI=0.87–1.19]).

Conclusion: In the Han Chinese population, no significant evidence was found linking variants of the *TRPM1* gene with any of the mental disorders examined.

Keywords: *TRPM1*, schizophrenia, major depressive disorder, bipolar disorder, association study

Introduction

SCHIZOPHRENIA (SCZ), MAJOR DEPRESSIVE DISORDER (MDD), and bipolar disorder (BPD) are known as complex polygenic psychiatric disorders. SCZ disables brain functions and could produce serious related negative effects on a patient's movement and cognitive function—that is, in their daily life, as well as their social responsi-

bilities. The traits of SCZ are divided into three categories: positive symptoms (hallucinations, delusions); negative symptoms (social withdrawal, reduced affective expression); and cognitive impairments (Karam *et al.*, 2010). MDD is attributed to mental disease, which causes mental and long-term depression as an observational clinical symptom. BPD is characterized by alternating mania and depression.

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The lifetime prevalence of these three diseases in Han Chinese population was estimated at 0.66% (SCZ, 1994, mainland, China), 1.5% (BPD, 2011, Shenzhen, China) (Merikangas *et al.*, 2011), and 3.3% (MDD, 2013, mainland China) (Gu *et al.*, 2013). Although the pathogenic mechanisms of the three psychiatric disorders are still unclear, genetic factors definitely contribute to the pathophysiology of them. In essence, we established a cross-disease meta-analysis for finding the common genetic factors of the three diseases.

Neurotransmission makes an essential impact on neural circuit formation in the central nervous system (CNS). Neurotransmission has been recently clarified as a key modulator of CNS development; however, the roles of individual genes are not yet fully understood. There are types of protein that work as intermicellar transmission, including the transient receptor potential (TRP) superfamily. Currently, the TRP superfamily of ion channels contain more than 30 cationic channels, which are mostly permeable for Ca^{2+} , but some are also for Mg^{2+} (Clapham, 2003). What is more, many TRP-related proteins were expressed in the nervous system (Montell *et al.*, 2002).

The TRP box is located in the C-terminus domain of the TRPM family and no Ankyrin repeats in the N-terminus (Hantute-Ghesquier *et al.*, 2018). According to the latest data obtained, the TRP domain was divided into two segments (Winkler *et al.*, 2017). *TRPM1* was found to be a member of the TRPM subfamily, and its sequence is similar to other members of the TRP family in the cation channels (Montell, 2005). The previous study indicates that *TRPM1* works as a cation permeable protein, and as expressed in ON bipolar cells, it mediates neurotransmission between photoreceptors and ON bipolar cells (Koike *et al.*, 2010).

Essentially, a visual signal is received by photoreceptors in the mammalian retina, and then the information is segregated into ON and OFF pathways (Kozuka *et al.*, 2017). In current studies, Flash electroretinography (fERG) has been used to identify anomalies in the retinal cell function of patients with SCZ and major depression (Hebert *et al.*, 2017; Demmin *et al.*, 2018).

SCZ is a common mental illness with a large genetic component (Freedman *et al.*, 2001; Owen *et al.*, 2004). Significant or suggestive evidence linked to SCZ has implicated 18 chromosomal regions (Baron, 2001; Harrison and Owen, 2003). Twelve of these linked chromosomal regions have been replicated—including one or more polymorphisms such as SCZ-associated polymorphisms—and contain biologically believable candidate genes showing altered expression in the disorder (Harrison and Weinberger, 2005). In addition, the 15q13–q14 locus is one of these regions, and its replication results are from the National Institute of Mental Health's (NIMH) SCZ Genetic Initiative (Freedman *et al.*, 2001; Owen *et al.*, 2004).

Notably, the results of a study by Stephens also indicated that *TRPM1* gene, along with *KLF13* and *RYR3*, was associated with SCZ in African Americans—that is, after correcting for multiple comparisons (p -value = 4×10^{-8} , odds ratio = 3.97) (Stephens *et al.*, 2012). Moreover, *TRPM1* was also identified as a candidate gene associated with symptoms of SCZ from genetic and mouse mutant model evidence (Forsingdal *et al.*, 2016).

However, we found two pooling databases that show opposite consequences. In essence, pooling database (drawn from 2010 to 2011) concludes with data from four meta-analyses or genome-wide association studies (GWASs) per-

taining to European ancestry, and then pooling database 2010–2013 concludes with data from five meta-analyses or GWASs in European ancestry as well (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Neale *et al.*, 2010; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Ripke *et al.*, 2013; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). Pooling database 2010–2011 indicates p -value = 0.402 and Odds ratio = 0.884 (rs10162727) while database 2010–2013 indicates p -value = 0.334 and Odds ratio = 1.295 (rs10162727), which means that there is an insignificant association with SCZ (Neale *et al.*, 2010; Ripke *et al.*, 2013). However, we also noticed that, according to Ruderfer *et al.* (2014), GWASs pertaining to bipolar disorder and SCZ patients in the European population indicated that rs10162727 was not associated with SCZ (p -value = 0.5093, Odds ratio = 1.072).

These conflicting results motivate us to further verify in psychiatric disorders in Han Chinese population. In this study, we performed a cross-disorder association analysis of the *TRPM1* gene in unrelated Han Chinese SCZ, MDD, and BPD patients—as well as normal controls—to verify previous findings and possibly discover new potential associations.

Materials and Methods

Subjects

Due to the inheritance factor of mental illness, age of onset in relation to psychiatrics, and also gender, we recruited 4896 unrelated Chinese subjects for our study. Among said subjects, 1248 were unrelated SCZ patients, 1056 were unrelated MDD cases, 1344 were unrelated bipolar disorder cases, and 1248 were normal controls (sample details are shown in Table 1).

All of the cases were interviewed by two independent psychiatrists who, subsequently, made a formal diagnosis that confirmed each subject's classification, which was in accordance with the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). In the control groups, all subjects were not only randomly selected from the general population but also in a manner that ensured that all subjects were without family histories of psychiatric disorders. All participants knew the purpose and potential hazard of the study, and they signed written informed consent forms before their participation.

Single nucleotide polymorphism selection

According to results by Haploview 4.2 software, eight tag SNPs (rs12901022, rs1035706, rs10162727, rs3784599, rs10400821, rs4779503, rs12441329, rs12910440) that

TABLE 1. DETAILED INFORMATION OF THE SAMPLE SET

	Gender		Age (years)	
	Females	Males	Average age	SD
Schizophrenia	403	845	36.44	9.00
MDD	319	737	34.41	12.09
BPD	760	584	34.84	11.44
Normal controls	576	672	30.62	11.35

MDD, major depressive disorder; BPD, bipolar disorder; SD, standard deviation.

emerged were picked across the whole gene, which was accomplished using genotype data—of Han Chinese in Beijing, China (CHB)—from the International HapMap Project (Barrett *et al.*, 2005) and rs10162727, which was defined as having single nucleotide polymorphism (SNP) susceptibility. Linkage disequilibrium r^2 threshold was set as 0.5 with a minor allele frequency that was greater than 0.05 (De Bakker *et al.*, 2005, 2006). Next, a total of eight SNPs were selected for our study, and the locations are indicated in Figure 1.

Genotyping

The genomic DNA was extracted from peripheral blood by QuickGene DNA Whole Blood Kit (Fujifilm, Tokyo, Japan) and according to the manufacturer's agreement. Genotyping was performed using iPLEX chemistry on a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF-MS, named as the MasARRAY system, which is manufactured by Sequenom, San Diego, CA). Polymerase chain reaction (PCR) and extended primers were designed using the online primer design tool Sequenom. Mass spectrum was obtained using Compact Mass Spectrometer and analyzed with MassARRAY Typer 4.0 Software.

Statistical analyses

It was a basic component to ensure that Allele and genotype frequency calculation, pair-wise linkage disequilibrium analysis, Hardy–Weinberg (H-W) equilibrium analysis, and haplotype were all carried out on the SHESisPlus online software platform in single site association study (Shen *et al.*, 2016). H-W equilibrium was received through chi-square test for each group of fitness. Chi-square test independence was used to examine allele and genotype distribution between cases and controls. For haplotype analysis, in all cases and control groups, adjacent tag SNPs with pair-wise linkage disequilibrium D values larger than 0.90 were defined in the same haplotype block.

All statistical analyses were two-tailed tests, and if the p -values were below 0.05, Bonferroni correction (p -value multiplied by the number of testing SNPs) should be set to test the statistical significance of results. Case–control genetic power was calculated on the Genetic Power Calculator (Purcell *et al.*, 2003).

Meta-analysis

We used the keywords “*TRPM1*,” “Schizophrenia,” “Major Depressive Disorder,” and “Bipolar Disorder” to

build a hunting zone in several databases—including PubMed, EMBASE, and Web of Science—to retrieve all pertinent studies or GWAS involving *TRPM1* gene variants. In essence, we found a pooling database from Psychiatric Genomics Consortium (PGC) about SCZ. The collected data were combined with the statistical data from our study to perform a meta-analysis.

The meta-analysis procedures were conducted using Review Manager 5.3 software. Heterogeneity was assessed by the chi square and quantified by I^2 statistics, which ensured that the group of studies was suitable for meta-analysis. An odds ratio (OR) with a 95% confidence interval (CI) indicates the magnitude of the effect. The Z test was used as a means of estimating the p -value of OR. All p -values were reported as two-tailed tests, which would, ultimately, be regarded as significant statistic while determining whether or not the p -value was less than 0.05.

Results

Single site analysis

According to export results from SHESisPlus, all eight SNPs passed H-W equilibrium tests in control groups. The average call rate of all sites in three disease groups and controls was 0.981. Detailed information pertaining to these sites is supplemented in Table 2.

For SCZ, rs10400821 indicated genotypic or allelic association before Bonferroni correction (rs10400821: $P_{\text{allele}}=0.564$, OR [95% CI]=1.178 [0.934–1.485]; $P_{\text{genotype}}=0.022$, adjusted $P_{\text{genotype}}=0.182$). For BPD, rs4779503 was significant before multiple-test corrections (rs4779503: $P_{\text{allele}}=0.256$, OR [95% CI]=1.167 [0.893–1.526]; $P_{\text{genotype}}=0.023$, adjusted $P_{\text{genotype}}=0.187$). For MDD, rs12901022 showed marginal significances in both allelic and genotypic analyses (rs12901022: $P_{\text{allele}}=0.069$, OR [95% CI]=1.162 [0.987–1.366]; $P_{\text{genotype}}=0.067$). However, none of these associations remained after multiple tests and corrections. The results are listed in Table 3.

Pairwise linkage disequilibrium analysis

The pairwise linkage disequilibrium D values among the eight SNPs were calculated in control, as well as all three disease groups (Fig. 2). Relying upon the haplotype analysis criteria illustrated in the former section, the two blocks of *TRPM1* and rs1035706-rs10162727 were identified in a control group, as well as all three disease groups. As such, rs10162727–rs3784599 was identified in a control group and, also, the BPD and SCZ groups.

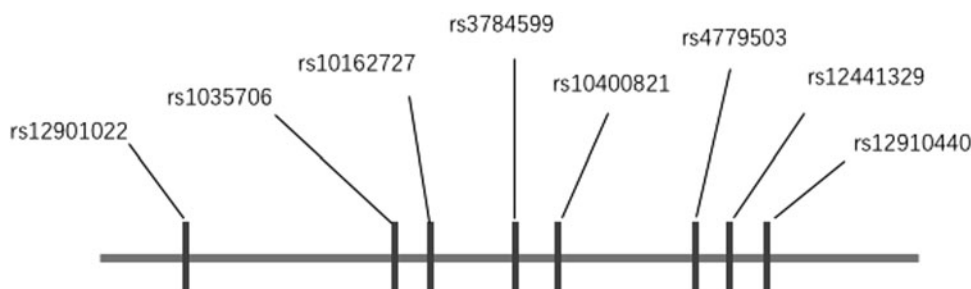


FIG. 1. Locations of the tag SNPs within the *TRPM1* gene and all of that distributed across the whole gene. SNP, single nucleotide polymorphism.

TABLE 2. DETAILED INFORMATION OF THE TESTING SINGLE NUCLEOTIDE POLYMORPHISMS IN THE TRPM1 GENE

SNP ID	Position	Function	Polymorphism	Group	Call rate	H-W p-value
rs12901022	31020540	Intron	C/T	SCZ	0.977	0.5
				MDD	0.99	0.321
				BD	0.989	0.633
				Control		0.768
rs1035706	31050882	Intron	A/G	SCZ	0.977	0.111
				MDD	0.991	0.866
				BD	0.990	0.805
				Control		0.84
rs10162727	31051683	Intron	A/G/T	SCZ	0.975	0.999
				MDD	0.991	0.999
				BD	0.990	0.999
				Control		0.999
rs3784599	31067254	Intron	G/T	SCZ	0.994	0.863
				MDD	0.995	0.827
				BD	0.998	0.691
				Control		0.993
rs10400821	31069401	Intron & UTR 3prime	A/G	SCZ	0.973	0.013
				MDD	0.989	0.218
				BD	0.988	0.971
				Control		0.519
rs4779503	31080131	Intron	A/G/T	SCZ	0.975	0.762
				MDD	0.991	0.126
				BD	0.990	0.19
				Control		0.31
rs12441329	31085370	Intron	C/T	SCZ	0.969	0.615
				MDD	0.973	0.79
				BD	0.950	0.645
				Control		0.656
rs12910440	31088989	Intron	A/C/G/T	SCZ	0.962	0.315
				MDD	0.973	0.769
				BD	0.953	0.995
				Control		0.693

H-W P, H-W equilibrium *p*-value; SCZ, schizophrenia; SNP, single nucleotide polymorphism.

Cross-disorder meta-analysis

In this cross-disorder meta-analysis, we recruited pooling database 2010–2011, pooling database 2010–2013, and five GWAS as collecting databases to build a meta-analysis (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Neale *et al.*, 2010; Ripke *et al.*, 2013; Ruderfer *et al.*, 2014; Stahl *et al.*, 2018; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Wray *et al.*, 2018). We separately analyzed these SNPs for understanding common genetic mechanism. After analyzing, the result shows rs12910440 (*p*-value=0.49, Odds ratio=0.97 [95% CI=0.89–1.06]), rs10162727 (*p*-value=0.41, Odds ratio=0.89 [95% CI=0.68–1.17]), rs10400821 (*p*-value=0.26, Odds ratio=0.81 [95% CI=0.56–1.16]), rs12901022 (*p*-value=0.49, Odds ratio=0.76 [95% CI=0.35–1.65]), rs4779503 (*p*-value=0.44, Odds ratio=0.80 [95% CI=0.45–1.42]), rs3784599 (*p*-value=0.34, Odds ratio=0.77 [95% CI=0.44–1.32]), rs12441329 (*p*-value=0.51, Odds ratio=0.98 [95% CI=0.91–1.05]), and rs1035706 (*p*-value=0.68, Odds ratio=0.99 [95% CI=0.95–1.03]) (Supplementary Figs. S1–S8).

Meta-analysis for rs10162727 in SCZ

We recruited pooling database 2010–2011 and pooling database 2010–2013 from PGC and, also, a GWAS about SCZ in which experimented SNPs overlapped with ours in the meta-analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Neale *et al.*, 2010; Ripke *et al.*, 2013; Ruderfer *et al.*, 2014; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). After further consideration of studies performed in Han Chinese population, it was determined that rs10162727 was suitable for the meta-analysis. Merging all data, we suggest that there is no significant association between rs10162727 and SCZ (*p*-value=0.84, Odds ratio=1.02 [95% CI=0.87–1.19]). The result of meta-analysis supports our results in this study of the Han Chinese population (Fig. 3).

Discussion

Currently, the pathogenesis of these three psychiatric diseases is still unclear. Family-based association studies also show comorbidity among BPD and MDD (Smoller and Finn, 2003), as well as SCZ and BPD (Valles *et al.*, 2000). These three diseases have general characteristic symptoms, shared genetic etiology, and increased numbers of variants and gene

TABLE 3. SINGLE SITE ASSOCIATION RESULTS OF THE EIGHT LOCUS IN SCHIZOPHRENIA, MAJOR DEPRESSIVE DISORDER, BIPOLAR DISORDER CASES, AND NORMAL CONTROLS

SNP ID	Group	Allele frequency		OR	95%CI	Allelic p-value	Bonferroni p-value	Genotype frequency				Genotypic p-value	Bonferroni p-value
		T	C					T/T	T/C	C/C	T/T		
rs12901022	SCZ	2109 (0.875)	299 (0.124)	1.007	0.849-1.194	0.933	0.983	928 (0.77)	253 (0.21)	23 (0.019)		0.414	
	MDD	2293 (0.859)	375 (0.14)	1.162	0.987-1.366	0.069	0.278	992 (0.743)	309 (0.231)	33 (0.024)		0.067	
	BD	1826 (0.878)	252 (0.121)	0.98	0.82-1.171	0.829	0.903	799 (0.769)	228 (0.219)	12 (0.011)		0.948	
	Control	2160 (0.876)	304 (0.123)					944 (0.766)	272 (0.22)	16 (0.012)			
rs1035706	SCZ	2352 (0.979)	50 (0.02)	0.824	0.565-1.202	0.316	0.535	1153 (0.96)	46 (0.038)	2 (0.001)		0.13	
	MDD	2612 (0.978)	58 (0.021)	0.861	0.599-1.237	0.42	0.84	1277 (0.956)	58 (0.043)			0.75	
	BD	2015 (0.969)	63 (0.03)	1.213	0.85-1.731	0.285	0.554	976 (0.939)	63 (0.06)			0.278	
	Control	2406 (0.974)	62 (0.025)					1172 (0.949)	62 (0.05)	0 (0)			
rs10162727	SCZ	2395 (0.999)	1 (4.17e-04)	1.03	0.064-16.478	0.983	0.983	1197 (0.999)	1 (8.35e-04)			0.983	
	MDD	2669 (0.999)	1 (3.75e-04)	0.924	0.057-14.786	0.955	0.968	1334 (0.999)	1 (7.49e-04)			0.955	
	BD	2077 (0.999)	1 (4.81 e-04)	1.187	0.074-19.002	0.903	0.903	1038 (0.999)	1 (9.62e-04)			0.903	
	Control	2467 (0.999)	1 (4.05e-04)					1233 (0.999)	1 (8.10e-04)				
rs3784599	SCZ	2102 (0.851)	368 (0.148)	1.047	0.894-1.226	0.564	0.752	892 (0.722)	318 (0.257)	25 (0.02)		0.807	
	MDD	2238 (0.838)	432 (0.161)	1.154	0.991-1.344	0.063	0.278	941 (0.704)	356 (0.266)	38 (0.028)		0.162	
	BD	1732 (0.848)	310 (0.151)	1.07	0.908-1.262	0.415	0.554	731 (0.715)	270 (0.264)	20 (0.019)		0.61	
	Control	2130 (0.856)	356 (0.143)					912 (0.733)	306 (0.246)	25 (0.02)			
rs10400821	SCZ	2227 (0.931)	163 (0.068)	1.178	0.934-1.485	0.164	0.535	1044 (0.873)	139 (0.116)	12 (0.01)		0.022	0.182
	MDD	2507 (0.941)	155 (0.058)	1.154	0.991-1.344	0.063	0.968	1184 (0.889)	139 (0.104)	8 (0.006)		0.159	
	BD	1939 (0.934)	137 (0.065)	1.137	0.893-1.448	0.296	0.554	906 (0.872)	127 (0.122)	5 (0.004)		0.315	
	Control	2318 (0.941)	144 (0.058)					1089 (0.884)	140 (0.113)	2 (0.001)			
rs4779503	SCZ	2271 (0.947)	125 (0.052)	1.136	0.876-1.474	0.334	0.535	1075 (0.897)	121 (0.101)	2 (0.001)		0.204	
	MDD	2563 (0.959)	107 (0.04)	0.862	0.658-1.128	0.28	0.747	1233 (0.923)	97 (0.072)	5 (0.003)		0.542	
	BD	1963 (0.946)	111 (0.053)	1.167	0.893-1.448	0.256	0.554	926 (0.892)	111 (0.107)	0 (0)		0.023	0.187
	Control	2354 (0.953)	114 (0.046)					1125 (0.911)	104 (0.084)	5 (0.004)			
rs12441329	SCZ	2089 (0.847)	375 (0.152)	0.924	0.791-1.079	0.321	0.535	890 (0.722)	309 (0.25)	33 (0.026)		0.247	
	MDD	2228 (0.832)	448 (0.167)	1.035	0.892-1.202	0.644	0.968	931 (0.695)	366 (0.273)	41 (0.03)		0.468	
	BD	1735 (0.85)	305 (0.149)	0.905	0.768-1.066	0.233	0.554	734 (0.719)	267 (0.261)	19 (0.018)		0.479	
	Control	1983 (0.837)	385 (0.162)					826 (0.697)	331 (0.279)	27 (0.022)			
rs12910440	SCZ	2039 (0.842)	381 (0.157)	0.898	0.771-1.046	0.169	0.535	866 (0.715)	307 (0.253)	37 (0.03)		0.098	
	MDD	2203 (0.826)	463 (0.173)	1.01	0.873-1.169	0.885	0.968	914 (0.685)	375 (0.281)	44 (0.033)		0.528	
	BD	1705 (0.838)	329 (0.161)	0.928	0.791-1.087	0.356	0.554	715 (0.703)	275 (0.27)	27 (0.026)		0.528	
	Control	1967 (0.827)	409 (0.172)					810 (0.681)	347 (0.292)	31 (0.026)			

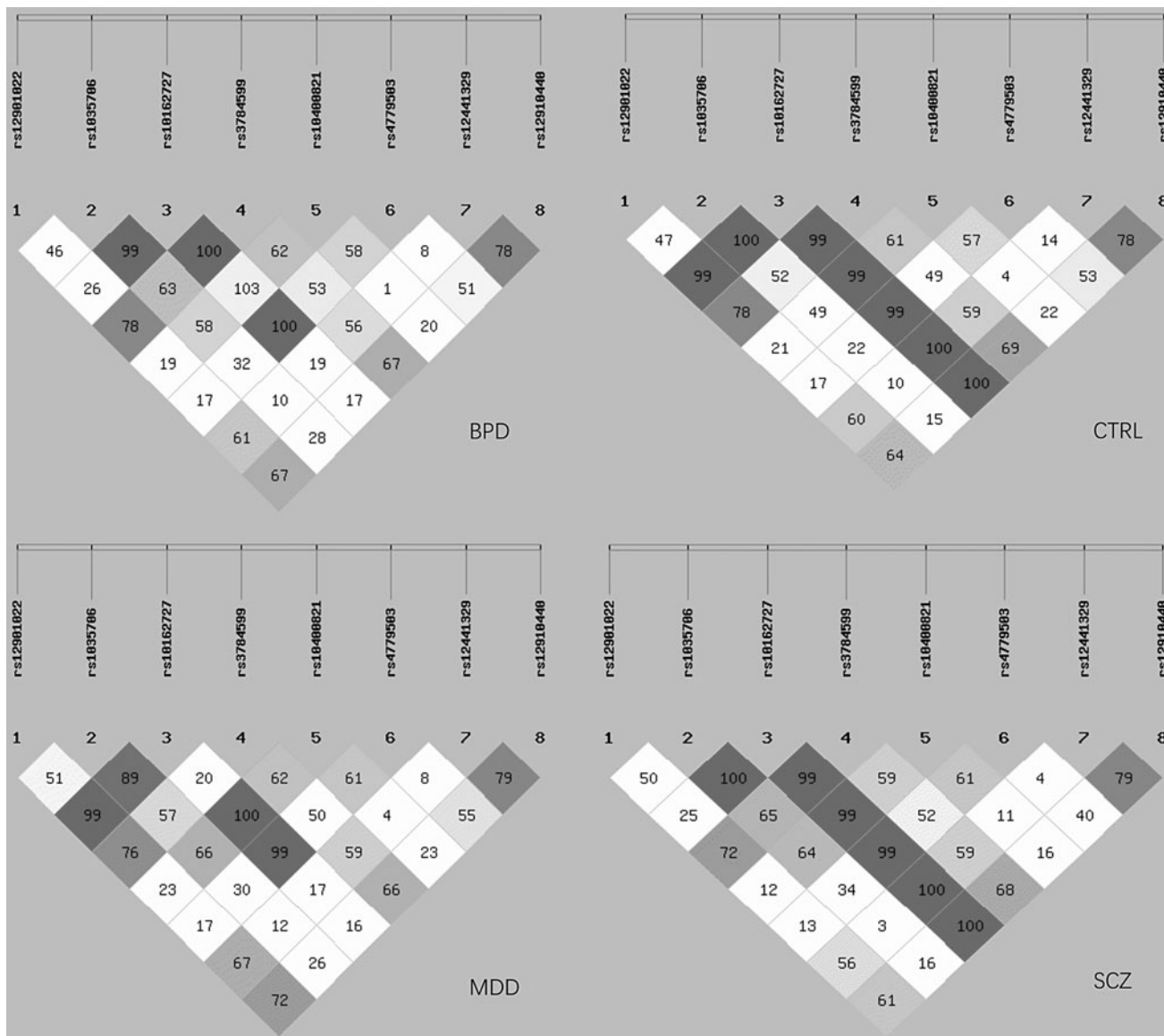


FIG. 2. Linkage disequilibrium among the eight SNPs in CTRL, SCZ, MDD, and BPD groups. The pairwise D' values are presented in the matrices. *Dark gray* implicates relatively strong linkage disequilibrium, and vice versa. CTRL, control; MDD, major depressive disorder; BPD, bipolar disorder; SCZ, schizophrenia.

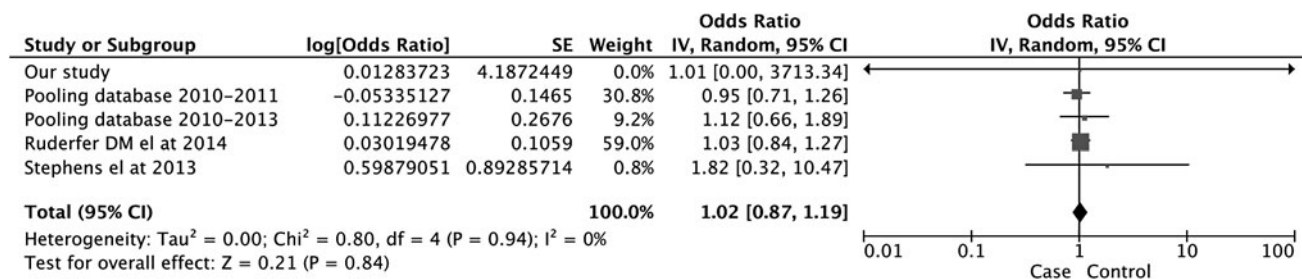


FIG. 3. Forest plot of the association between rs10162727 and schizophrenia in a random effects model. The *point* represents the OR, and *horizontal lines* indicate 95% CI for each study. The *diamond* illustrates that summary OR and 95% CI by random effect calculations.

regions, such as: rs1344706 in the *ZNF804A* gene (Williams *et al.*, 2011); rs1006737 in the *CACNA1C* gene also confers risk of recurrent MDD and SCZ (Green *et al.*, 2010); and intron 42 of the *MYO18B* gene and intron 1 of the *NPAS3* gene (Huang *et al.*, 2010). Meanwhile, a previous cross-disorder GWAS revealed that common genetic factors can be shared among SCZ, MDD, and BPD (Ruderfer *et al.*, 2014).

However, it is possible that similar genetic overlap relating to *TRPM1* happens in major psychiatric illnesses of the Han Chinese population, especially in SCZ, MDD, and BPD. It is notable that SCZ, MDD, and BPD share many clinical symptoms and sign change. Due to the complicated pathogenesis of mental diseases, one of the obstacles in psychiatric exploration that is too difficult to dynamically analyze is the state of human brain.

Several retina dysfunctions have been observed in psychiatric patients through the fERG, and it is suggested that retinal activity may reflect uncommon neurochemistry in brain disorders (Lavoie *et al.*, 2014). Forsingdal built a 15q13.3 homozygous knockout mouse model effect using seven genes—*FANI*, *MTMR10*, *TRPM1*, *miR-211*, *KLF13*, *OTUD7A*, and *CHRNA7*—and the study suggests that the cognitive disabilities of *Df* (h15q13)^{-/-} mice were related to SCZ (Forsingdal *et al.*, 2016). Thus, this could be the reason for why cognitive disabilities may cause visual impairments—that is, because the *TRPM1* gene has been linked to deficits in visual light response (Morgans *et al.*, 2009; Koike *et al.*, 2010; Hughes *et al.*, 2012; Kozuka *et al.*, 2017).

Previously, it was reported that *TRPM1* showed a significant association with SCZ in African Americans (105 cases and 45 controls) (Stephens *et al.*, 2012), but we also found opposite results in some GWASs that considered multiple races (Ruderfer *et al.*, 2014) (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Stahl *et al.*, 2018; Wray *et al.*, 2018). Because of the conflicting conclusions between these different studies, we searched an imputed dataset of a Zhiqiang *et al.* (2017) study that was published in 2017 to find out whether or not *TRPM1* was associated with these three diseases. However, the results suggest insignificant association between SCZ and *TRPM1*, and these tag SNPs were not found in the imputed database.

It is well known that the three diseases have similar clinical signs. What is more, recent genetic and epidemiological studies have demonstrated substantial overlap between these three disorders (Cross-Disorder Group of the Psychiatric Genomics C, 2013). Meta-analysis can improve the efficiency of research and further discover the relationship between the three diseases. Only then can we combine patients with SCZ or BPD or MDD for cross-disorder genetic research analysis. In this cross-disorder meta-analysis of the diseases, all tag SNPs fail to confirm that there are cross-disorder common genetic factors. In addition, in meta-analysis for rs10162727 in SCZ, we still suggested that there was no significant association between rs10162727 and SCZ (p -value = 0.84, Odds ratio = 1.02 [95% CI = 0.87–1.19]).

All of the SNPs failed to prove statistically significant associations with SCZ, MDDs, and bipolar disorders by the negative result of the meta-analysis. This means *TRPM1* did not play a role in the three psychiatric diseases within Han Chinese population. Alas, research on disease is infinite, so more research is expected to contribute to the exploration of disease occurrence and development.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This work was supported by the National Key R&D Program of China (2017YFC0908105), National Key R&D Program of China (2019YFA0905400), Shanghai Municipal Science and Technology Major Project (2017SHZDZX01), the Natural Science Foundation of China (U1804284, 81421061, 81701321, 31571012, 81501154), the Program of Shanghai Subject Chief Scientist (15XD1502200), the National Program for Support of Top-Notch Young Professionals, Shanghai Key Laboratory of Psychotic Disorders (13dz2260500), the National Program for Support of Top-Notch Young Professionals to Y.S., Shanghai Hospital Development Center (SHDC12016115), Shanghai Municipal Commission of Science and Technology (17JC1402900, 17490712200, 18DZ2260200) and Shanghai Municipal Health Commission (ZK2015B01, 201540114), and Scientific Research and Development Fund of Shanghai Jiao Tong University (19X150010012).

Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Figure S4
Supplementary Figure S5
Supplementary Figure S6
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Supplementary Figure S8

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