Meta-analysis of *GABRB2* polymorphisms and the risk of schizophrenia combined with GWAS data of the Han Chinese population and psychiatric genomics consortium

Tian Zhang[1,2,3,4☯], **Jun Li**[1,2,3,4☯], **Hao Yu**[5], **Yongyong Shi**[6,7,8,9,10,11], **Zhiqiang Li**[6,7,8,9], **Linyan Wang**[1,2,3,4], **Ziqi Wang**[1,2,3,4], **Tianlan Lu**[1,2,3,4], **Lifang Wang**[1,2,3,4]*, **Weihua Yue**[1,2,3,4]*, **Dai Zhang**[1,2,3,4,12,13]*

1 Peking University Sixth Hospital, Beijing, China, **2** Peking University Institute of Mental Health, Beijing, China, **3** Key Laboratory of Mental Health, Ministry of Health (Peking University), Beijing, China, **4** National Clinical Research Center for Mental Disorders, (Peking University Sixth Hospital), Beijing, China, **5** Department of Psychiatry, Jining Medical University, Jining, Shandong, China, **6** Affiliated Hospital of Qingdao University and Biomedical Sciences Institute of Qingdao University (Qingdao Branch of SJTU Bio-X Institutes), Qingdao University, Qingdao, China, **7** Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Collaborative Innovation Center for Brain Science, Shanghai Jiao Tong University, Shanghai, China, **8** Institute of Social Cognitive and Behavioral Sciences, Shanghai Jiao Tong University, Shanghai, China, **9** Institute of Neuropsychiatric Science and Systems Biological Medicine, Shanghai Jiao Tong University, Shanghai, China, **10** Department of Psychiatry, First Teaching Hospital of Xinjiang Medical University, Urumqi, China, **11** Changning Mental Health Center, Shanghai, China, **12** Peking-Tsinghua Center for Life Sciences, Peking University, Beijing, China, **13** PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing, China

☯ These authors contributed equally to this work.
* lifangwang@bjmu.edu.cn (LW); dryue@bjmu.edu.cn (WY); daizhang@bjmu.edu.cn (DZ)

Abstract

Schizophrenia (SCZ) is a severe psychiatric disorder with evidence of a strong genetic component in the complex etiologies. Some studies indicated that gamma-aminobutyric acid $(GABA)_A$ receptor β2 subunit gene (*GABRB2*) was associated with SCZ. Other studies reported a negative association. Moreover, the results of two previous meta-analyses of *GABRB2* with SCZ were inconsistent and the sample sizes were limited. Therefore, an updated meta-analysis combined with genome-wide association study (GWAS) data of the Han Chinese population and Psychiatric Genomics Consortium (PGC) was performed. Available case–control and family-based genetic data were extracted from association studies, and the GWAS data were included. The findings showed no association between six single-nucleotide polymorphisms of *GABRB2* (rs6556547, rs1816071, rs1816072, rs194072, rs252944, and rs187269) and SCZ in a total of 51,491 patients and 74,667 controls. The ethnic subgroup analysis revealed no significant association in Asian populations. Since the PGC data of SCZ (SCZ-PGC, 2014) contained 3 studies of Asian populations (1866 patients and 3418 controls), only the data of European samples in SCZ-PGC were used for the meta-analysis of the Caucasian population in the present study. The result still showed no association in the Caucasian population. In conclusion, the present meta-analysis on combined data from GWASs of the Han Chinese population and PGC suggested that *GABRB2* polymorphisms might not be associated with SCZ.

Introduction

Schizophrenia (SCZ) is a complex psychiatric disorder affecting approximately 1% of the global population and manifesting as positive symptoms (delusions and hallucinations), negative symptoms (impaired motivation, unusual speech or behavior, and social withdrawal), and cognitive impairment [1,2]. As SCZ has a high heritability of 70%–85% and a tenfold increase in the risk of siblings of probands, genetic factors are vital in the pathogenesis of SCZ [3,4]. However, the specific role of genetic factors in SCZ remains unclear.

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. Abnormalities of specific cortical inhibitory neurons and GABA may contribute to imbalances in excitatory/inhibitory signaling in the brain and hence GABA is crucial in the pathophysiology of SCZ [5]. GABA exerts its inhibitory activity by binding to two types of receptors ($GABA_A$ and $GABA_B$ receptors). $GABA_A$ receptors are ligand-gated Cl^- channels responsible for most of the physiological actions of GABA [6]. The functions of $GABA_A$ receptors are associated with psychiatric diseases, such as SCZ [7–11]. Postmortem studies indicated that a decline in the biosynthesis of cortical GABA led to compensatory upregulation of $GABA_A$ receptors and downregulation of GABAergic cortical function in SCZ [12]. Among $GABA_A$ receptor subunit genes, gene cluster, including *GABRB2*, *GABRA6*, *GABRA1*, and *GABRG2*, attract attention. These genes, which are highly expressed in the brain, are located on chromosome 5q34 [13]. A meta-analysis of genome-wide linkage scans of SCZ identified chromosome 5q23.2–q34 as the second most significant risk locus in the genome [14]. Moreover, a genome-wide association study (GWAS) for SCZ in Japanese population showed association signals on the $GABA_A$ receptor subunit gene cluster on chromosome 5q34 [15].

Among the $GABA_A$ receptor subunit gene cluster on chromosome 5q34, the $GABA_A$ receptor β_2 subunit gene (*GABRB2*) with SCZ has gained interest. GABRB2 regulates the intracellular Ca^{2+} concentration, which is important for the nervous system [16]. Postmortem samples of SCZ indicated alterations in the expression of GABA receptor β_2 subunit protein [17]. Furthermore, abnormal N-glycosylation of GABA receptor β_2 subunit and altered methylation of *GABRB2* were also found in patients with SCZ [18,19].

To date, association studies have been carried out to evaluate the association between *GABRB2* polymorphisms and risk of SCZ. Positive associations between *GABRB2* polymorphisms and SCZ were found in Asian [20–22] and Caucasian populations [21,23]. However, other studies reported no association between *GABRB2* and SCZ in Asian [24,25] or Caucasian population [26]. The results of previous two meta-analyses of *GABRB2* with SCZ were inconsistent [27,28]. Allen *et al.* reported that rs6556547, rs1816071, rs1816072, and rs194072 of *GABRB2* were significantly associated with SCZ in the Caucasian population (about 1863 patients with SCZ and 1631 controls), whereas another study indicated an association of rs1816071 in Caucasian population and rs1816072 in Asian and Caucasian populations with SCZ (about 2240 patients and 2093 controls). Later, other association studies between *GABRB2* and SCZ showed controversial results. Some studies suggested a positive association [29,30], whereas others indicated a negative correlation [31]. Moreover, GWASs were often performed to detect causal or risk-conferring genes for common diseases [32]. The Psychiatric Genomics Consortium (PGC) has reported a few meta-analyses for SCZ [33–35]. However, GWASs on SCZ in non-European populations were limited to small sample sizes. Recently, Yu *et al.* performed a two-stage GWAS on SCZ comprising 4384 patients and 5770 controls, followed by replication in an additional 4339 patients with SCZ and 7043 controls of Chinese Han ancestry [36]. Li *et al.* recruited 7699 SCZ cases and 18,327 controls in Chinese Han and conducted a GWAS for SCZ [37]. Considering the inconsistencies between the previous two

meta-analyses and the limited sample size, the present study performed an updated meta-analysis on the combined GWAS data of the SCZ-PGC and Chinese Han population.

Available case–control and family-based genetic data from association studies and the PGC data of SCZ, as well as GWAS data of Han Chinese ancestry, were extracted in this study. An updated meta-analysis was performed to explore the association of six single-nucleotide polymorphisms (SNP) (rs6556547, rs1816071, rs1816072, rs194072, rs252944, and rs187269) in *GABRB2* and the risk of SCZ.

Material and methods

Identification and selection of studies

Electronic databases, such as Essential Science Indicators, PubMed, Embase, and China National Knowledge Infrastructure were searched for all relevant reports (the last search update was on December 31, 2017) using the search following terms: "*GABRB2*" OR "GABA (A) receptor subunit beta2 gene" AND "schizophrenia". The search was limited to peer-reviewed, published studies. Studies in English language only were considered. As a complementary measure, references of correlative studies were retrieved to search for other eligible studies. The inclusion criteria were as follows: (1) studies involving the associations between *GABRB2* and SCZ (2) those using a case–control or family-based design and (3) those providing complete data on allele frequencies or genotype frequencies of patients and controls. The exclusion criteria were as follows: (1) review studies, animal studies, simply commentaries, case reports, or unpublished reports (2) studies not reporting the complete data and (3) duplicate publications.

Meta-analysis sample

Nine eligible candidate association studies were finally adopted with a sample size of 3434 patients and 3232 controls as well as 499 trios. These studies comprised seven case–control studies, one family-based study, and one study with both case–control and family-based designs. Based on the ancestry, four Asian association studies and four Caucasian association studies, as well as one study performed on both Asian and Caucasian population, were included. Moreover, data from the SCZ-PGC GWAS (SCZ-PGC, 2014) and two GWASs for SCZ in the Han Chinese population were used for the meta-analysis. The data of the PGC GWAS (SCZ-PGC, 2014) were downloaded from the PGC website (http://www.med.unc.edu/pgc; SCZ2). The current SCZ-PGC GWAS consisted of 49 case-control samples (46 of European and 3 of East Asian ancestry, involving 34,241 patients and 45,604 controls) and 3 family-based samples of European ancestry (1235 parent affected-offspring trios). The sample of PGC included 35,476 patients and 46,839 controls. The 2 SCZ GWASs of Chinese Han population comprised 4384 patients and 5770 controls, and 7699 patients and 18,327 controls, respectively. In this meta-analysis, the total samples included 51,491 patients and 74,667 controls.

Data extraction

Two independent researchers extracted the following information in each study: journal, name of the first author, year of publication, ethnicity, design of the study, diagnostic criteria for SCZ, sample size of patients and controls or family trios, and genotype data or transmission/disequilibrium test (TDT) data. If the data were incomplete, the study authors were requested to provide the missing data.

Statistical methods

The meta-analysis was performed using the Stata version 14.0 software (Stat Corp., TX, USA). In case–control studies, if allele frequencies or genotype data were incomplete, they were calculated from the existing corresponding information. The allelic data were used to calculate the natural logarithms of odds ratios [Ln (ORs)] and standard errors (SEs). For family-based studies, the Ln (ORs) and SEs of each study were calculated based on the TDT data [38,39]. For the meta-analysis samples, the data of Ln (ORs) and SEs were directly extracted from the GWAS results. The pooled *P* values, ORs, and 95% confidence intervals (CIs) were calculated to investigate the association between the risk of SCZ and *GABRB2* polymorphisms between two population subgroups (Asian and Caucasian). The heterogeneity between studies was tested using the Q-statistic (cutoff: $P < 0.1$), and its magnitude was evaluated using the I^2 statistic. The fixed-effects or random-effects models were used according to the heterogeneities ($I^2 < 50\%$, fixed-effects models; $I^2 > 50\%$, random-effects models). Subgroup analysis was conducted by ethnicity (Asian and Caucasian).

Meta-regression was used to investigate the effects of the sample size, study design, and year of publication. The *P* value of meta-regression less than 0.05 was considered to have a significant effect. A sensitivity analysis was also applied to evaluate the effect of each study on the combined ORs by omitting each study in each turn. Publication bias was assessed using funnel plots and Egger's test. A *P* value less than 0.05 in the Egger's test indicated significance.

Results

Study characteristics

The literature search and article screening procedure are shown in Fig 1. Applying the article screening strategy, 28 published articles that might meet the inclusion criteria were identified. After reading full-text studies, 16 studies were excluded, including 2 review studies, 2 animal studies, 3 studies that had overlap samples with other studies, 1 study with no complete data, 7 studies that did not explore the polymorphisms, and 1 study that did not investigate the polymorphisms included in the present meta-analysis. Therefore, the present meta-analysis included data from 12 publications that consisted data from case–control designed studies (3434 patients and 3232 controls), family-based designed studies (499 trios), and 3 GWAS data (SCZ-PGC 2014, 35,476 patients and 46,839 controls; Yu *et al.* 2017, 4383 patients and 5770 controls; Li *et al.* 2017, 7699 patients and 18,327 controls). The observed genotype distribution in the controls was consistent with Hardy–Weinberg equilibrium. The detailed characteristics of each study are described in Table 1.

Meta-analysis

The SNPs were selected according to the following criteria: (1) SNPs in *GABRB2* included in most of the related association studies and (2) previously reported positive SNPs in *GABRB2* related to SCZ. Therefore, six SNPs of *GABRB2* (rs6556547, rs1816071, rs1816072, rs194072, rs252944, and rs187269) were selected to perform the present meta-analysis with SCZ. Before combining with GWAS data, all six SNPs in *GABRB2* showed no significant association with SCZ (rs6556547: OR = 1.02 95% CI = 0.88–1.18 *P* = 0.837, rs1816071: OR = 0.97 95% CI = 0.89–1.07 *P* = 0.553, rs1816072: OR = 1.02 95% CI = 0.90–1.16 *P* = 0.731, rs194072: OR = 1.03 95% CI = 0.91–1.16 *P* = 0.673, rs252944: OR = 1.01 95% CI = 0.90–1.15 *P* = 0.829, rs187269: OR = 1.08 95% CI = 0.90–1.29 *P* = 0.398; S1 Table and S1 Fig). Considering the difference in ethnicity, the data for Asian and Caucasian populations were analyzed separately. One SNP rs1816072 (C/T) was significantly associated with SCZ in Asian (OR = 1.18; 95% CI,
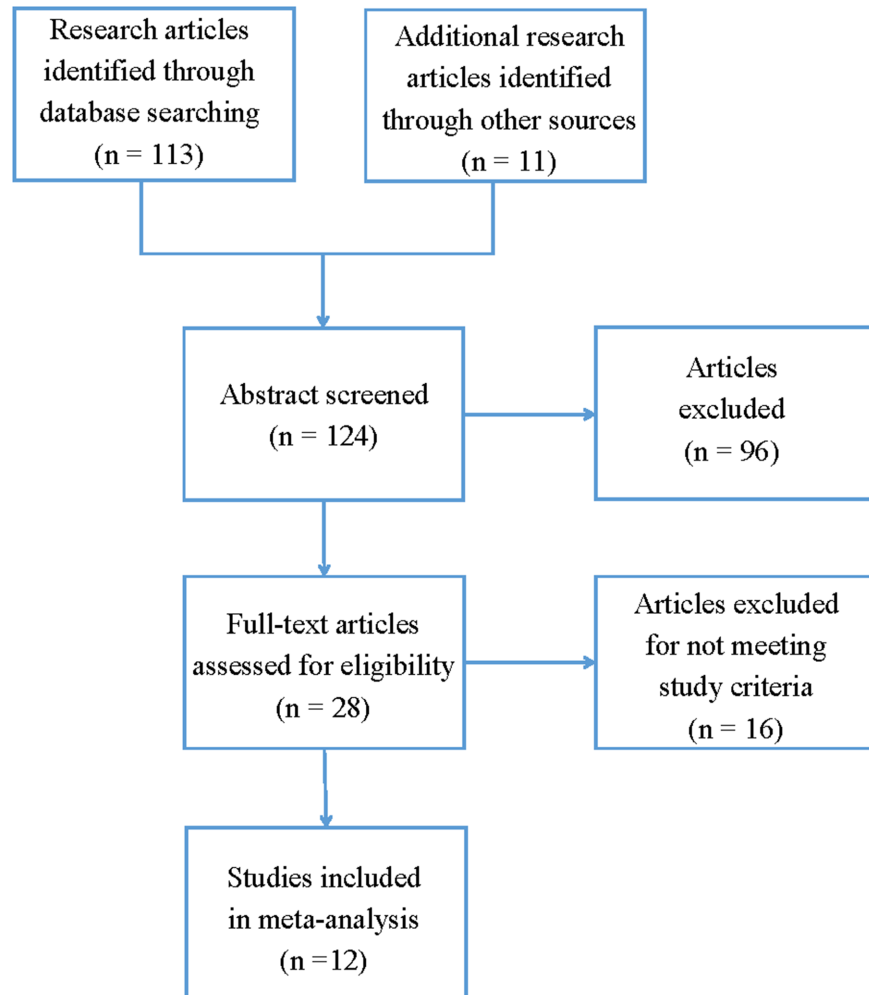
Fig 1. Overview of the literature search and article screening procedure.

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1.01–1.39; $P = 0.043$) and Caucasian populations (OR = 0.88; 95% CI, 0.78–0.99; $P = 0.038$), but not in the overall population (S1C Fig).

Furthermore, three GWAS data were added for meta-analysis. No association was detected in the Asian population (rs6556547: OR = 1.00 95% CI = 0.95–1.04 $P = 0.913$, rs1816071: OR = 1.03 95% CI = 0.99–1.07 $P = 0.1,93$, rs1816072: OR = 1.05 95% CI = 0.98–1.12 $P = 0.141$, rs194072: OR = 1.01 95% CI = 0.97–1.06 $P = 0.684$, rs252944: OR = 1.01 95% CI = 0.96–1.05 $P = 0.746$, rs187269: OR = 1.06 95% CI = 0.94–1.20 $P = 0.321$; Table 2 and Fig 2). The PGC data of SCZ (SCZ-PGC, 2014) predominantly focused on people of European descent. However, it contained 3 studies of Asian population, approximately only 3.5% people of Asian descent (1866 patients and 3418 controls). Only the data of European samples of SCZ-PGC were used for the present meta-analysis in the Caucasian population to decrease the ethnic heterogeneity. The results showed no significant association between *GABRB2* and SCZ (rs6556547: OR = 1.00 95% CI = 0.96–1.04 $P = 0.968$, rs1816071: OR = 1.00 95% CI = 0.98–1.02 $P = 0.817$, rs1816072: OR = 1.00 95% CI = 0.98–1.02 $P = 0.717$, rs194072: OR = 0.99 95% CI = 0.96–1.02 $P = 0.464$, rs252944: OR = 1.01 95% CI = 0.98–1.04 $P = 0.485$, rs187269: OR = 1.00 95% CI = 0.98–1.02 $P = 0.903$; Table 2 and Fig 2). Then, the SCZ-PGC data were

Table 1. Descriptive characteristics of selected studies in meta-analysis.

No.	Author	Year	Sample Size (Case/Control, trios)	Ancestry	Criteria
1	Ikeda *et al.*	2005	288/288	Asian, Japanese	DSM-IV
2	Petryshen *et al.*	2005	321/242	Caucasians, Portuguese	DSM-IV
			111 trios	Caucasians, Portuguese	DSM-IV
			238 trios	Caucasians, German	DSM-IV
3	Zhao *et al.*	2006	31/31	Caucasians, US population	DSM-IV
4	Lo *et al.*	2007	304/207	Asian, Japanese	DSM-IV
			301/190	Caucasians, German	DSM-IV
5	Zhao *et al.*	2007	292/286	Asian, Chinese Han	DSM-III-R
6	Jamra *et al.*	2007	367/360	Caucasians, German	DSM-IV
7	Pun *et al.*	2011	150 trios	Caucasians, US population	DSM-IV
8	Tsang *et al.*	2013	115/117	Asian, Chinese Han	DSM-IV
9	SCZ-PGC	2014	35476/46839	Caucasians and Asian	/
10	Yu *et al.*	2017	4383/5770	Asian, Chinese Han	DSM-IV
11	Balan *et al.*	2017	1415/1511	Asian, Japanese	DSM-IV
12	Li *et al.*	2017	7699/18327	Asian, Chinese Han	DSM-IV

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders.

applied in the analysis of overall populations (51,491 patients and 74,667 controls). The results were still negative (rs6556547: OR = 1.00 95% CI = 0.97–1.03 *P* = 0.964, rs1816071: OR = 1.00 95% CI = 0.99–1.02 *P* = 0.655, rs1816072: OR = 1.00 95% CI = 0.99–1.02 *P* = 0.756, rs194072:

Table 2. Meta-analytic results of SNPs in *GABRB2* and schizophrenia in different ethnic subgroups combined with GWAS data.

SNP	Population	OR	CI (95%)	Z	P	Heterogeneity		
						Q	P	I-squared
rs6556547	Asian	1.00	0.95–1.04	0.11	0.913	5.59	0.232	28.5%
	Caucasian	1.00	0.96–1.04	0.04	0.968	11.58	0.072	48.20%
	overall	1.00	0.97–1.03	0.04	0.964	17.18	0.103	36.0%
rs1816071	Asian	1.03	0.99–1.07	1.30	0.193	2.14	0.544	0.0%
	Caucasian	1.00	0.98–1.02	0.23	0.817	10.01	0.188	30.10%
	overall	1.00	0.99–1.02	0.45	0.655	13.69	0.250	19.7%
rs1816072	Asian	1.05	0.98–1.12	1.47	0.141	10.67	0.058	53.1%
	Caucasian	1.00	0.98–1.02	0.36	0.717	10.82	0.094	44.60%
	overall	1.00	0.99–1.02	0.31	0.756	22.78	0.030	47.30%
rs194072	Asian	1.01	0.97–1.06	0.41	0.684	5.44	0.142	44.9%
	Caucasian	0.99	0.96–1.02	0.73	0.464	8.21	0.314	14.80%
	overall	1.00	0.97–1.02	0.37	0.708	14.22	0.221	22.7%
rs252944	Asian	1.01	0.96–1.05	0.32	0.746	3.72	0.294	19.3%
	Caucasian	1.01	0.98–1.04	0.70	0.485	8.87	0.262	21.10%
	overall	1.01	0.99–1.04	0.76	0.448	12.60	0.320	12.70%
rs187269	Asian	1.06	0.94–1.20	0.99	0.321	12.24	0.007	75.5%
	Caucasian	1.00	0.98–1.02	0.12	0.903	6.58	0.362	8.80%
	overall	1.00	0.98–1.02	0.14	0.887	19.10	0.039	47.6%

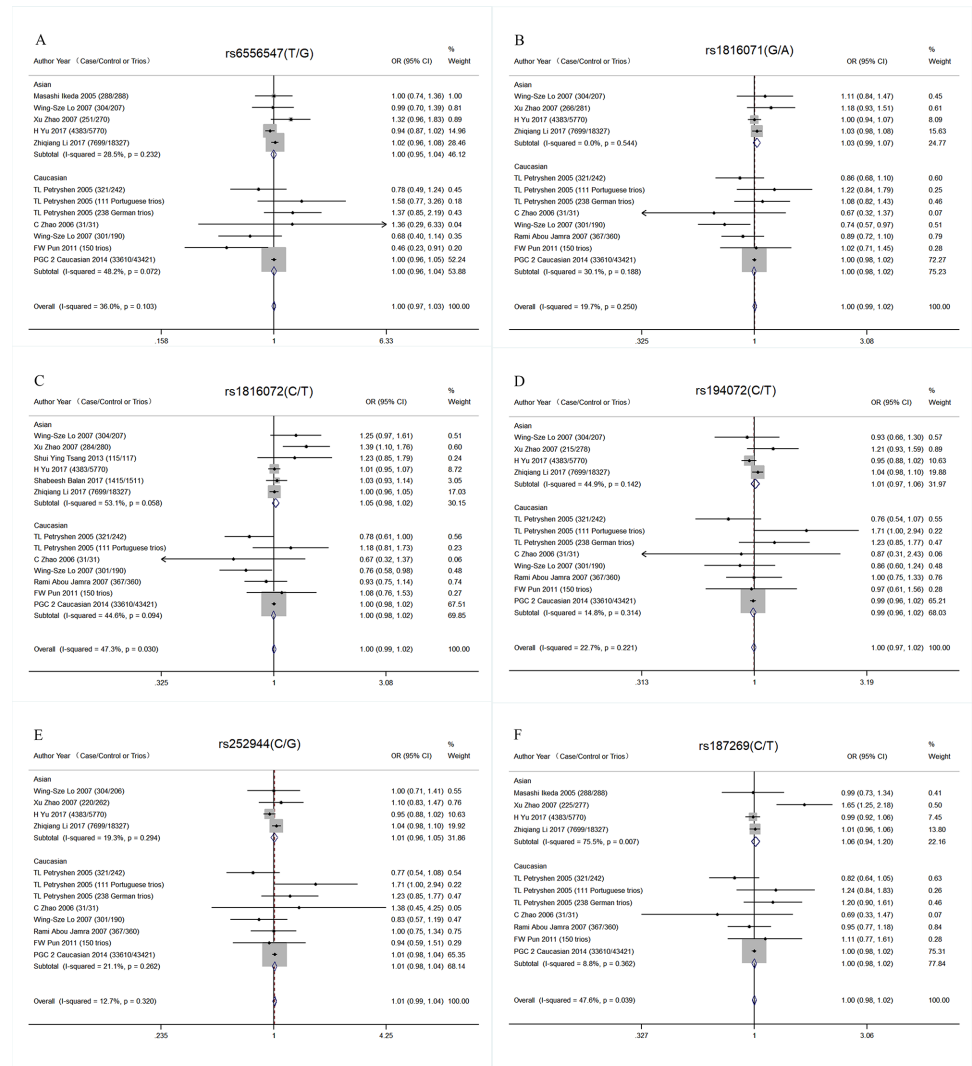Abbreviations: OR, odds ratio; CI, confidence intervals.

Fig 2. Forest plot of SNPs in *GABRB2* in different ethnic subgroups combined with GWAS schizophrenia data.
(A) Meta-analysis of *GABRB2* rs6556547. (B) Meta-analysis of *GABRB2* rs1816071. (C) Meta-analysis of *GABRB2* rs1816072. (D) Meta-analysis of *GABRB2* rs194072. (E) Meta-analysis of *GABRB2* rs252944. (F) Meta-analysis of *GABRB2* rs187269.

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OR = 1.00 95% CI = 0.97–1.02 *P* = 0.708, rs252944: OR = 1.01 95% CI = 0.99–1.04 *P* = 0.448, rs187269: OR = 1.00 95% CI = 0.98–1.02 *P* = 0.887; S2 Table).

Meta-regression

Meta-regression was used to investigate the effects of the possible modifiers. It revealed no significant moderation by year of publication, sample size, or study design (S3 Table).

Sensitivity analysis

Sensitivity analysis was performed to examine the influence set by the individual study on the pooled ORs by deleting each study once in every genetic model. Consistently, the pooled estimate did not meet the statistical significance (S3 Fig).

Publication bias

The funnel plot and Egger's test were used to evaluate the publication bias between studies. The funnel plots for all six SNPs were symmetrical (S2 Fig). As a statistical method to test funnel plot symmetry, the Egger's test did not detect significant publication bias in any SNP (rs6556547, $P = 0.839$; rs1816071, $P = 0.693$; rs1816072, $P = 0.771$; rs194072, $P = 0.681$; rs252944, $P = 0.866$; rs187269, $P = 0.452$).

Discussion

The present meta-analysis study included a large sample size (51,491 patients and 74,667 controls) to investigate the potential association of 6 SNPs of *GABRB2* (rs6556547, rs1816071, rs1816072, rs194072, rs252944, and rs187269) with the occurrence of SCZ. The findings revealed no association. The ethnic subgroup analysis also showed no association in Asian and Caucasian populations.

Meta-analysis is an effective method to reanalyze multiple independent studies revolving around the same issue and obtain a general conclusion. The results of the present meta-analysis were inconsistent with those of two previous meta-analyses on *GABRB2* and SCZ. A possible reason might be the larger sample size used in the present study. Sampling error can be decreased by increasing the sample size of the study. The sample size of the previous two meta-analyses studies was limited. In the present meta-analysis, a total of 51,491 patients and 74,667 controls were included. Therefore, the sampling error was greatly reduced, making the assertion of the study more convincing. The weights carried by PGC samples in this meta-analysis were large. Moreover, the large sample size in GWAS might increase the statistical power to detect common SNP with a minor effect on the pathogenesis of SCZ.

Furthermore, the risk allele of rs1816072 with SCZ was different in Asian (C allele) and Caucasian (T allele) populations in the present study. These results were also detected in a previously published meta-analysis. Moreover, the minor allele frequency of rs6556547 was 0.178 in the East Asian population and 0.054 in the European population. It is suggested that subjects with different ethnicity exhibit genetic heterogeneity. Considering the ethnic heterogeneity, subgroup analyses were performed in Asian and Caucasian populations separately. In the present study, after combining data from GWASs in the Chinese Han population and PGC, the results of the subgroup analysis by ethnicity showed no association between *GABRB2* and SCZ.

The present meta-analysis still had a few limitations. First, the limited number of studies investigating the *GABRB2* SNPs implied the possibility of type II error [40]. Second, the different designs of the studies included in the meta-analysis might have influenced the association results, although the meta-regression analysis revealed no significant moderation by study design.

In conclusion, the present updated meta-analysis combined with GWAS Data of Han Chinese population and PGC suggested that *GABRB2* polymorphisms might not be associated with SCZ.

Supporting information

S1 Fig. Forest plot for meta-analysis on data of candidate gene association studies between *GABRB2* and schizophrenia. (A) Meta-analysis of rs6556547. (B) Meta-analysis of rs1816071. (C) Meta-analysis of rs1816072. (D) Meta-analysis of rs194072. (E) Meta-analysis of rs252944. (F) Meta-analysis of rs187269.
(DOCX)

S2 Fig. Funnel plot for odds ratio of allele frequency comparison of SNPs in *GABRB2* combined with GWAS schizophrenia data. (A) Funnel plot of rs6556547. (B) Funnel plot of rs1816071. (C) Funnel plot of rs1816072. (D) Funnel plot of rs194072. (E) Funnel plot of rs252944. (F) Funnel plot of rs187269.
(DOCX)

S3 Fig. Sensitivity analysis for SNPs in *GABRB2* combined with GWAS schizophrenia data. (A) rs6556547. (B) rs1816071. (C) rs1816072. (D) rs194072. (E) rs252944. (F) rs187269.
(DOCX)

S1 Table. Meta-analysis on candidate gene association studies between *GABRB2* and schizophrenia in different ethnic subgroups without GWAS data.
(DOCX)

S2 Table. Meta-analytic results of *GABRB2* and schizophrenia in all populations combined with GWAS data.
(DOCX)

S3 Table. *P* value of Meta-regression results of different covariates.
(DOCX)

S4 Table. Summary of extracted data from the candidate gene association studies selected for the meta-analysis.
(XLSX)

S1 File. PRISMA checklist.
(DOC)

S2 File. PRISMA flow diagram.
(DOC)

S3 File. Meta-analysis-on-genetic-association-studies-form.
(DOCX)

S4 File. The list of excluded articles and the reasons for exclusion of each article.
(DOCX)

Acknowledgments

Author Contributions

Data curation: Tian Zhang, Jun Li, Hao Yu, Yongyong Shi, Zhiqiang Li, Weihua Yue.

Formal analysis: Tian Zhang, Jun Li.

Funding acquisition: Weihua Yue, Dai Zhang.

Investigation: Tian Zhang, Jun Li.

Methodology: Tian Zhang, Jun Li.

Supervision: Lifang Wang, Dai Zhang.

Writing – original draft: Tian Zhang.

Writing – review & editing: Tian Zhang, Linyan Wang, Ziqi Wang, Tianlan Lu, Lifang Wang, Weihua Yue.

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