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Association between ErbB4 single nucleotide polymorphisms and susceptibility to schizophrenia

A meta-analysis of case-control studies

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Abstract

Background: Accumulating studies have reported inconsistent association between ErbB4 single nucleotide polymorphisms (SNPs) and predisposition to schizophrenia. To better interpret this issue, here we conducted a meta-analysis using published case-control studies.

Methods: We conducted a systematic search of MEDLINE (Pubmed), Embase (Ovid), Web of Science (Thomson-Reuters) to identify relevant references. The association between ErbB4 SNPs and schizophrenia was assessed by odds ratios (ORs) and 95% confidence intervals (CIs). Between-study heterogeneity was evaluated by *I* squared (I^2) statistics and Cochran's *Q* test. To appraise the stability of results, we employed sensitivity analysis by omitting 1 single study each time. To assess the potential publication bias, we conducted trim and fill analysis.

Results: Seven studies published in English comprising 3162 cases and 4264 controls were included in this meta-analysis. Meta-analyses showed that rs707284 is statistically significantly associated with schizophrenia susceptibility among Asian and Caucasian populations under the allelic model (OR = 0.91, 95% CI: 0.83–0.99, $P = 0.035$). Additionally, a marginal association ($P < 0.1$) was observed between rs707284 and schizophrenia risk among Asian and Caucasian populations under the recessive (OR = 0.85, 95% CI: 0.72–1.01, $P = 0.065$) and homozygous (OR = 0.84, 95% CI: 0.68–1.03, $P = 0.094$) models. In the Asian subgroup, rs707284 was also noted to be marginally associated with schizophrenia under the recessive model (OR = 0.84, 95% CI: 0.70–1.00, $P = 0.053$). However, no statistically significant association was found between rs839523, rs7598440, rs3748962, and rs2371276 and schizophrenia risk.

Conclusion: This meta-analysis suggested that rs707284 may be a potential ErbB4 SNP associated with susceptibility to schizophrenia. Nevertheless, due to the limited sample size in this meta-analysis, more large-scale association studies are still needed to confirm the results.

Abbreviations: CI = confidence interval, GWAS = genome-wide association studies, OR = odds ratios, SNP = single nucleotide polymorphism.

Keywords: ErbB4, schizophrenia, single nucleotide polymorphism, susceptibility

1. Introduction

Increasing evidence supports that not merely are environmental factors implicated in the development of schizophrenia, but also genetic factors are inseparably associated with predisposition to schizophrenia.[1–4] Traditional twin studies[5,6] and population-based family studies[7] have already estimated the heritability for schizophrenia to be over 80% and 60% respectively, revealing genetic traits in the etiology of schizophrenia. Based on high-throughput genotyping technologies, genome-wide association studies (GWAS) remarkably facilitate the identification of genetic variants that are associated with schizophrenia,[8–10] deepening the understanding of genetic architecture of schizophrenia.

Among numerous risk genes for schizophrenia, the gene *erb-b2 receptor tyrosine kinase 4* (*ErbB4*) is located on human chromosome 2 at 2q33.3-q34 and encodes a 180-kDa transmembrane tyrosine kinase (ErbB4), which belongs to the epidermal growth factor receptor (EGFR) family.[11] ErbB4 is the only member in the ErbB family that can bind all 4 neuregulins and some other EGFR ligands,[12] reflecting its multifarious biological functions. *In vivo* loss-of-function studies demonstrated that *ErbB4* homozygous null mice exhibited noticeable aberrations in central nervous system development[13] and heterozygous null mice had detectable behavioral deficits overlapping with a mouse model for schizophrenia.[14,15] Regarding the potential mechanisms for the involvement of ErbB4 in susceptibility to schizophrenia, there have been accumulating studies. ErbB4 signaling was reported to suppress

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long-term potentiation of synaptic transmission and cognitive deficits in schizophrenia may be associated with hyperfunction of ErbB4 signaling and consequent suppression of glutamatergic synaptic plasticity[16] and *N*-methyl-D-aspartic acid receptor response.[17] Another study showed that ErbB4 signaling regulates the development of inhibitory circuits in the cerebral cortex by modulating the connectivity of γ-aminobutyric acid-containing interneurons.[18]

In addition to growing evidence unraveling various mechanisms underlying the ErbB4 involvement in pathogenesis of schizophrenia, multiple association studies have also investigated the genetic role played by *ErbB4* in the etiology of schizophrenia. A GWAS conducted by Shi et al[19] identified rs1851196, an *ErbB4* single nucleotide polymorphism (SNP), as the strongest association signal with schizophrenia in African American samples. Haploview analyses using 3 independent GWAS datasets identified schizophrenia-associated loci in *ERBB4* and validated several haplotypes of *ERBB4* to be associated with the schizophrenia risk.[20] Furthermore, numerous common candidate gene association studies have focused on or implicated the association between *ErbB4* SNPs and schizophrenia across multiethnic populations, including Asian populations (Japanese[21], Chinese[22–24], Koreans,[25] and Indians [26]) and Caucasian populations (Scottish [27], English [28], Irish [28], Ashkenazis,[29] and Americans [30]). Unfortunately, to our knowledge, there is currently no systematic meta-analysis to reconcile the inconsistent findings deriving from these studies. Thereby, to precisely assess the association of *ErbB4* SNPs with schizophrenia liability and deepen our understanding of *ErbB4* as a risk factor for schizophrenia, we performed the first meta-analysis utilizing published case-control studies across multiracial populations under different genetic models.

2. Materials and methods

2.1. Search strategy

A systematic electronic literature searching of MEDLINE (PubMed), Embase (Ovid), and Web of Science (Thomson-Reuters) was performed to identify relevant references and the date of the latest search was August 16th, 2015. The following search terms in various combination manners were utilized: ("schizophrenia" OR "schizophrenic") AND ("polymorphism" OR "variant" OR "variation") AND ("ErbB4" OR "HER4"). Using this searching strategy, we obtained 55, 99, and 108 citations from Pubmed, Embase, and Web of Science, respectively. After excluding duplicates, 154 citations were retrieved from these 3 electronic databases. Additionally, to consummate the electronic search, we also manually searched reference lists in key studies or reviews to identify extra relevant studies, but no additional studies were retrieved.

2.2. Inclusion criteria

All studies included in our meta-analysis should meet the following criteria: (1) concerning the association between *ErbB4* SNPs and schizophrenia; (2) case-control studies; (3) written in English; (4) containing sufficient data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) or directly providing ORs and 95% CIs; (5) allele and genotype distribution of control population must be in Hardy–Weinberg equilibrium; (6) declaring that well-informed consent was obtained from all participants.

3. Data extraction and quality appraisal

The following data were extracted from each included study: last name of the first author, publication year, country, ethnicity, numbers of schizophrenia patients and controls, diagnosis criteria, gender proportion, age and whether in Hardy–Weinberg equilibrium. The pooled ORs and 95% CIs were calculated, if they were not directly available in original studies. Two investigators independently conducted data extraction and disagreement was addressed through discussion or referred to a third people.

We assessed quality of the included studies in light of a checklist originated from Strengthening the Reporting of Genetic Association (STREGA) studies statement[31] and made some modifications according to the quality checklist described elsewhere.[32]

3.1. Meta-analysis

Between-study heterogeneity was assessed by *I* squared (I^2) statistics and Cochran's *Q* test. The random effects model (the DerSimonian–Laird method) was utilized when high heterogeneity was detected ($I^2 > 50\%$ or $P < 0.1$); otherwise, the fixed effects model (the Mantel–Haenszel method or the Inverse Variance method) was employed to pool the effect sizes. In this meta-analysis, we evaluated the association strength by utilizing ORs and 95% CIs and examined the significance of pooled ORs by the *Z* test. In addition, to detect the influence of 1 single study on heterogeneity and pooled ORs, we conducted sensitivity analysis by removing each study in turn and observing the resultant changes. To assess the potential publication bias, we conducted trim and fill analysis[33] due to a limited number of study cohorts. Difference is considered to be statistically significant if *P* value is less than 0.05 except for specified conditions. All analyses in this study were performed with Stata/SE 11.2 software (StataCorp., TX).

4. Results

4.1. Study selection and characteristics of each included study

The PRISMA flow chart describing literature search process was presented (Fig. 1). Briefly, there were 154 articles retrieved from 3 electronic databases after excluding duplicates. Subsequently, 142 irrelevant records were removed through primary screening of titles and abstracts and 12 full-text studies were then assessed for eligibility. Two studies[30,34] was excluded for not case-control studies, 1 study[26] excluded because SNPs in them did not overlap with SNPs in other studies, and 2 studies[19,28] excluded for insufficient data, though we tried to contacted authors for additional information. At last, 7 case-control studies[21–25,27,29] concerning the association of *ErbB4* and predisposition to schizophrenia were included in our meta-analysis. The excluded records and corresponding reasons were listed in the S1 Text, http://links.lww.com/MD/B578.

Main characteristics of 7 included studies were described in Table 1. In brief, 2 ethnic populations, including Asians and Caucasians, from 5 countries were included in this meta-analysis. Furthermore, *ErbB4* SNPs investigated in 7 studies were listed in Table 2. To assess the quality of each included study, a modified list was also given in Table 3.

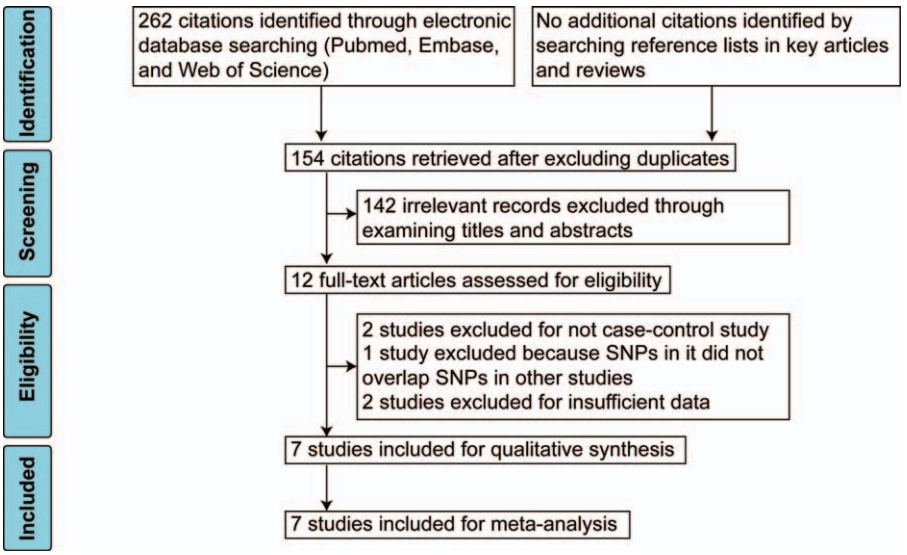

Figure 1. PRISMA flow chart depicting the study selection process.

Table 1

Characteristics of included studies.

First author (publication year)	Country	Ethnicity	Sample size (case/control)	Diagnosis criteria	Gender (M/F)		Age (mean±SD or range, years)		HWE (control)
					Case	Control	Case	Control	
Silberberg (2006)	Israel	Ashkenazi (Caucasian)	59/130	DSM-IV	NA	NA	38.6±9.5	NA	Yes
Benzel (2007)	UK	Aberdeen (Caucasian)	396/1342	OPCRIT	285/111	724/618	44±14	NA	Yes
Shiota (2008)	Japan	Japanese (Asian)	416/520	DSM-IV	225/191	281/239	45±14.7	37.5±11.3	Yes
Lu (2010)	China	Han Chinese (Asian)	227/223	DSM-IV	116/111	95/128	45±8	51.0±10.2	Yes
So (2010)	China (Hong Kong)	Han Chinese (Asian)	489/519	DSM-IV	NA	NA	NA	NA	Yes
Bae (2012)	Korea	Koreans (Asian)	435/390	DSM-IV	247/188	220/170	44.8±9.5	54.6±9.3	Yes
Chen (2012)	China	Han Chinese (Asian)	1140/1140	DSM-IV	635/505	374/766	35.4±7.2	58.7±9.9	Yes

DSM-IV = Diagnostic Statistical Manual of Mental Disorders IV, HWE = Hardy–Weinberg equilibrium, M/F = male/female, NA = not available, OPCRIT = Operational Criteria Checklist for Psychotic Illness and Affective Illness, SD = standard deviation.

Table 2

ErbB4 SNPs studied in each article.

	Silberberg (2006)	Benzel (2007)	Shiota (2008)	Lu (2010)	So (2010)	Bae (2012)	Chen (2012)
rs839523	+	+	+	+	−	+	+
rs707284	+	−	+	−	−	+	+
rs7598440	+	−	+	+	−	+	−
rs3748962	−	+	−	+	−	+	−
rs2371276	−	−	−	−	+	−	+

+: the SNP was involved in the study.
−: the SNP was not investigated in in the study.
SNP = single nucleotide polymorphism.

Table 3

Quality appraisal of included studies.

First author's last name	Year	Study design and main findings	Background and objective	Study setting, participant eligibility criteria and variables	HWE	Genotyping method	Statistical methods	Characteristics of participants, numbers in each allele and genotype, and main results	Discussion of key results, limitations, and implications
Silberberg	2006	+	+	+	+	+	+	±	+
Benzel	2007	+	+	±	+	+	+	±	+
Shiota	2008	+	+	+	+	+	+	+	+
Lu	2010	+	+	+	+	+	+	+	+
So	2010	+	+	±	+	+	+	±	+
Bae	2012	+	+	+	+	+	+	±	+
Chen	2012	+	+	+	+	+	+	+	+

+: detailed description, ±: incomplete description, −: no description.
HWE = Hardy–Weinberg equilibrium.

Table 4

Location and possible function of SNPs in this meta-analysis.

SNP ID	Chromosome	Position	Functional consequence
rs839523	2	211951364	Intron variant
rs707284	2	211974321	Intron variant
rs7598440	2	211928473	Intron variant
rs3748962	2	211387139	Synonymous codon
rs2371276	2	211690360	Intron variant

SNP = single nucleotide polymorphism.

4.2. Location and possible function of SNPs in this meta-analysis

We searched at http://www.ncbi.nlm.nih.gov/snp/ for SNPs in this meta-analysis and tabulated the information comprising locations and possible functions of these SNPs in Table 4.

4.3. Meta-analyses of association between ErbB4 SNPs and susceptibility to schizophrenia under allelic, dominant, recessive, homozygous, and heterozygous models

For rs839523, no statistically significant association was observed between this SNP and schizophrenia predisposition among Asian and Caucasian mixed populations, Asian subgroup or Caucasian subgroup under allelic, dominant, recessive, homozygous, and heterozygous models (Figs. 2–6, Table 5).

For rs707284, a statistically significant association was characterized between this SNP and schizophrenia liability among Asian and Caucasian populations under the allelic model (OR = 0.91, 95% CI: 0.83–0.99, $P = 0.035$; Fig. 2, Table 5). In addition, a marginal association without statistical significance was determined among Asian and Caucasian populations under recessive (OR = 0.85, 95% CI: 0.72–1.01, $P = 0.065$; Fig. 4, Table 5) and homozygous (OR = 0.84, 95% CI: 0.68–1.03, $P = 0.094$; Fig. 5, Table 5) models. However, there is no statistically significant association under dominant and heterozygous models (Figs. 3, 6, Table 5). In Asian subgroup analysis, a marginal association was noted between rs707284 and schizophrenia under the recessive model (OR = 0.84, 95% CI: 0.70–1.00, $P = 0.053$; Table 5). Nevertheless, there is no statistically significant association in Asian populations under allelic, dominant, homozygous, and heterozygous models (Table 5).

For rs7598440, no statistically significant association was determined between this SNP and schizophrenia among Asian and Caucasian mixed populations or Asian subgroup under allelic, dominant, recessive, homozygous, and heterozygous models (Figs. 2–6, Table 5).

For rs3748962, no statistically significant association was found between this SNP and schizophrenia among Asian and

Table 5

Overall analysis of association of ErbB4 SNPs with schizophrenia susceptibility.

SNP	Allele	Ethnicity	Cohort number	Case/control	Genetic model	OR (95% CI)	*Z* score	*P* (Z)	I2 (%)
rs839523	C>T	Asian/Caucasian	6	2673/3745	T vs C	0.94 (0.83, 1.07)	0.93	0.352	57.2
			5	2277/2403	TT+TC vs CC	0.87 (0.63, 1.19)	0.88	0.378	81.4
			5	2277/2403	TT vs TC+CC	0.95 (0.81, 1.11)	0.64	0.520	0.0
			4	1842/2013	TT vs CC	0.95 (0.78, 1.15)	0.54	0.588	49.3
			4	1842/2013	TC vs CC	0.77 (0.48, 1.24)	1.07	0.283	86.8
		Asian subgroup	4	2218/2273	T vs C	0.98 (0.88, 1.10)	0.33	0.742	36.4
			4	2218/2273	TT+TC vs CC	0.97 (0.86, 1.10)	0.47	0.641	42.1
			4	2218/2273	TT vs TC+CC	0.94 (0.80, 1.11)	0.69	0.491	16.4
			3	1783/1883	TT vs CC	0.99 (0.81, 1.20)	0.13	0.898	31.7
			3	1783/1883	TC vs CC	1.01 (0.79, 1.28)	0.05	0.962	54.8
		Caucasian subgroup	2	455/1472	T vs C	0.72 (0.41, 1.28)	1.11	0.268	81.9
rs707284	C>T	Asian/Caucasian	4	2050/2180	T vs C	0.91 (0.83, 0.99)	2.11	0.035*	38.4
			4	2050/2180	TT+TC vs CC	0.80 (0.59, 1.09)	1.42	0.156	76.4
			4	2050/2180	TT vs TC+CC	0.85 (0.72, 1.01)	1.84	0.065†	0.0
			3	1615/1790	TT vs CC	0.84 (0.68, 1.03)	1.67	0.094†	5.4
			3	1615/1790	TC vs CC	0.67 (0.40, 1.14)	1.47	0.142	87.0
		Asian subgroup	3	1991/2050	T vs C	0.93 (0.85, 1.01)	1.64	0.101	38.4
			3	1991/2050	TT+TC vs CC	0.94 (0.79, 1.02)	0.87	0.385	0.0
			3	1991/2050	TT vs TC+CC	0.84 (0.70, 1.00)	1.93	†	7.5
			2	1556/1660	TT vs CC	0.87 (0.70, 1.08)	1.28	0.199	0.0
			2	1556/1660	TC vs CC	0.96 (0.82, 1.12)	0.50	0.614	0.0
rs7598440	C>T	Asian/Caucasian	4	1137/1263	T vs C	1.08 (0.87, 1.34)	0.70	0.483	67.7
			4	1137/1263	TT+TC vs CC	1.07 (0.89, 1.29)	0.70	0.481	0.0
			4	1137/1263	TT vs TC+CC	1.20 (0.80, 1.82)	0.88	0.379	82.6
			3	702/873	TT vs CC	1.37 (0.61, 3.06)	0.77	0.443	83.8
			3	702/873	TC vs CC	1.00 (0.78, 1.29)	0.04	0.971	0.0
		Asian subgroup	3	1078/1133	T vs C	1.00 (0.88, 1.12)	0.07	0.948	0.0
			3	1078/1133	TT+TC vs CC	1.05 (0.86, 1.27)	0.44	0.658	0.0
			3	1078/1133	TT vs TC+CC	0.93 (0.79, 1.09)	0.91	0.362	0.0
			2	643/743	TT vs CC	0.92 (0.68, 1.24)	0.55	0.579	24.6
			2	643/743	TC vs CC	1.02 (0.79, 1.33)	0.16	0.874	0.0
rs3748962	T>C	Asian/Caucasian	3	1058/1955	C vs T	1.14 (0.86, 1.51)	0.93	0.354	80.1
		Asian	2	662/613	C vs T	1.23 (0.72, 2.10)	0.75	0.454	89.1
			2	662/613	CC+CT vs TT	1.36 (0.77, 2.40)	1.05	0.293	83.3
			2	662/613	CC vs TC+TT	1.11 (0.35, 3.50)	0.18	0.855	86.6
rs2371276	T>C	Asian	2	1629/1659	C vs T	1.21 (0.90, 1.62)	1.29	0.198	72.6

CI= confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

* $P < 0.05$, showing statistically significant association.

† $P < 0.1$, showing marginal association.

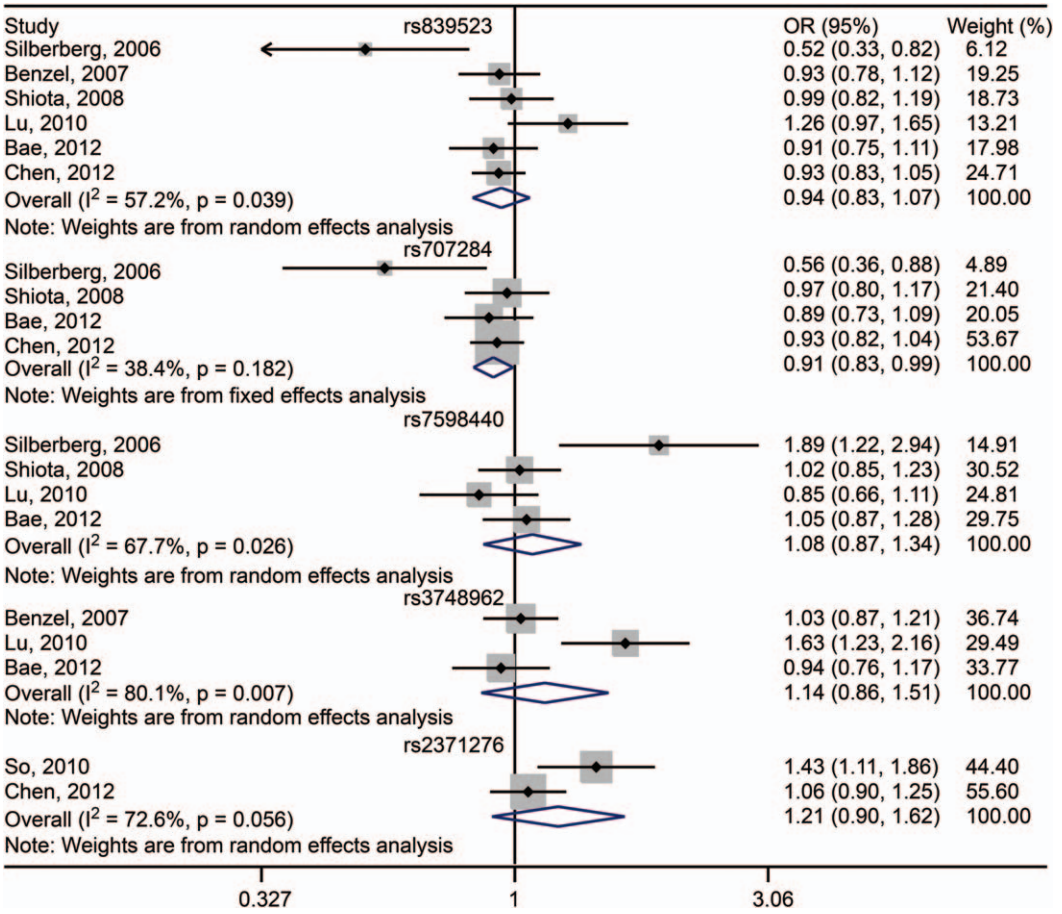

Figure 2. Forest plot displaying the association between *ErbB4* SNPs and susceptibility to schizophrenia under the allelic model.

Caucasian populations under the allelic model (Fig. 2, Table 5). Furthermore, for Asian subgroup analysis, no statistically significant association was observed under allelic, dominant, and recessive genetic models (Table 5).

For rs2371276, no statistically significant association was observed among Asian populations under the allelic model (Fig. 2, Table 5).

To sum up, the overall meta-analyses concerning the association between *ErbB4* SNPs and schizophrenia risk across Asian and Caucasian populations under allelic, dominant, recessive, homozygous, and heterozygous models were tabulated as Table 5.

4.4. Sensitivity analysis

To reflect the influence of 1 single study on the overall effect sizes, we conducted sensitivity analysis towards meta-analyses containing no less than 3 study cohorts by removing 1 study in turn and observing corresponding changes. First, sensitivity analysis showed that the associations between rs839523, rs7598440, or rs3748962 and schizophrenia susceptibility were stable because no sensitive studies were excavated. As for the association between rs707284 and schizophrenia under the allelic model, though 3 sensitive studies were found, a marginal association still existed ($P=0.073$ and 0.085) when Bae's or Chen's study were omitted respectively. As shown in Table 5, a very marginal association was characterized between rs707284 and schizophrenia under the recessive model among the Asian and Caucasian mixed populations ($P=0.065$) or Asian subgroup ($P=0.053$). Sensitivity analysis identified a statistically significant association in the Asian and Caucasian populations ($P=0.033$) or the Asian subgroup ($P=0.025$) when Shiota's study was removed, suggesting that Shiota's study may underrate this analysis. The overall results of sensitivity analysis were tabulated and shown in Table 6.

4.5. Publication bias

To recognize underlying publication bias in our meta-analysis, we only utilized the trim and fill method to analyze meta-analyses comprising at least 4 study cohorts. Results showed that the association between rs839523 or rs7598440 and schizophrenia was stable because statistical significance did not vary after filling missing studies. In addition, a statistically significant association was revealed between rs707284 and schizophrenia under dominant and recessive models after filling the potentially missing studies, suggesting that publication bias may underestimate the association. The overall results of trim and fill analysis were also tabulated and presented in Table 7.

5. Discussion

Increasing evidence has identified *ErbB4* as a susceptibility risk gene for schizophrenia[35] and more antipsychotic therapeutic

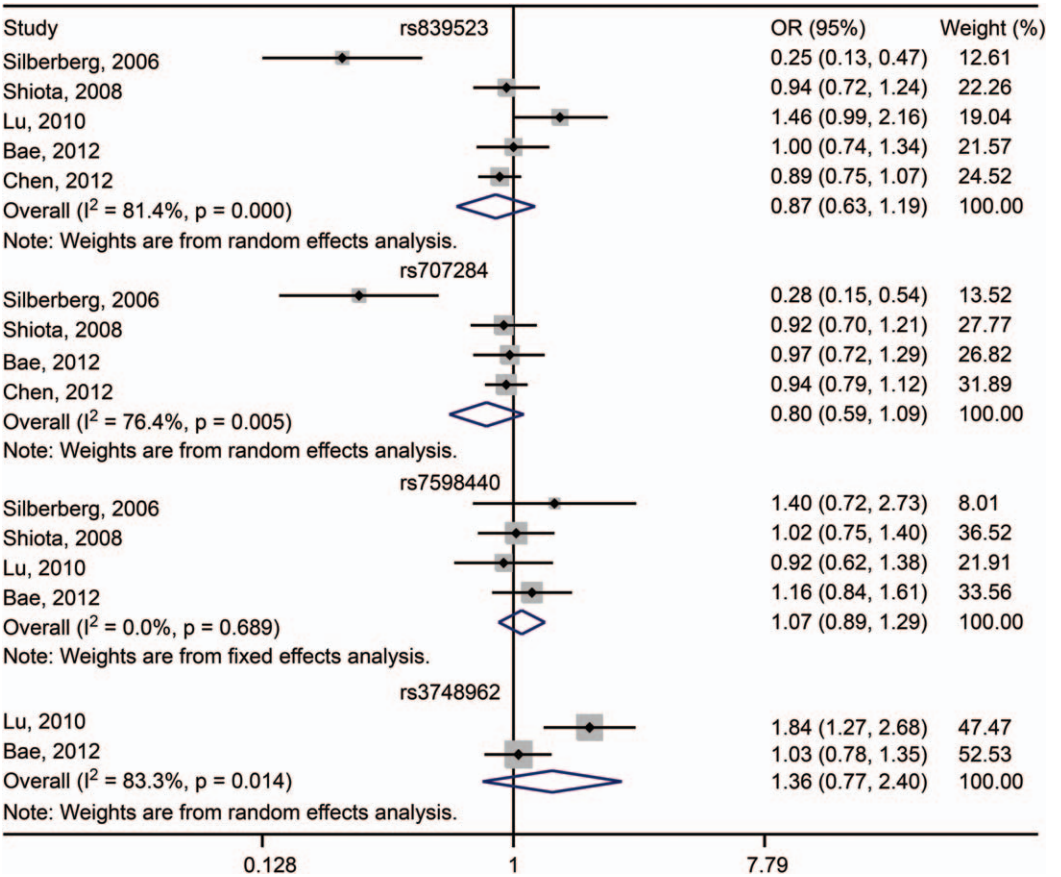

Figure 3. Forest plot manifesting the association between *ErbB4* SNPs and susceptibility to schizophrenia under the dominant model.

strategies have been targeted at the ErbB4 signaling pathway.[36,37] A GWAS[19] has already identified schizophrenia-associated ErbB4 SNPs in African American populations. In addition, reusing GWAS data regarding schizophrenia, Agim et al[20] have identified and validated several haplotypes of *ErbB4* to be related with schizophrenia risk. Besides high-throughput GWAS, numerous common genetic association studies have also revealed genetic role of *ErbB4* in the etiology of schizophrenia, though the results of these studies are inconsistent and inconvenient to be interpreted. To our knowledge to date, no systematic meta-analyses integrate published case-control studies to analyze the association of *ErbB4* SNPs with susceptibility to schizophrenia, so we conducted this first meta-analysis to accurately assess the relationship between ErbB4 and schizophrenia under allelic, dominant, recessive, homozygous, and heterozygous genetic models.

For meta-analyses of association between rs839523 and schizophrenia under allelic, dominant and heterozygous genetic models, we observed substantial between-study heterogeneities. Subgroup analysis stratified by ethnicity found that heterogeneities in Asian subgroup decreased significantly (allelic model: I^2 from 57.2% to 36.4%; dominant model: I^2 from 81.4% to 42.1%; heterozygous model: I^2 from 86.8% to 54.8%), though there is still a substantial heterogeneity in Caucasian subgroup under the allelic model. It is highly possible that ethnicity is the main cause for heterogeneity. As for the high heterogeneity in the Caucasian subgroup, it is probable that limited study cohorts (only 2 studies) and sample size (455 cases and 1472 controls) reduce the test power of meta-analysis. Sensitivity analysis (Table 6) and trim and fill analysis (Table 7) collectively suggested the results are stable.

Regarding the association of rs707284 with schizophrenia under the allelic model, a statistically significant association ($P = 0.035$) was observed. Though sensitivity analysis revealed that this result was influenced by 3 studies, a scrutiny still found a marginal association ($P = 0.073$ and 0.085) when Bae's or Chen's study was omitted, respectively. When meta-analysis was under the recessive model, a highly marginal association was observed in the Asian and Caucasian populations ($P = 0.065$) and Asian subgroup ($P = 0.053$). Sensitivity analysis discovered a statistically significant association in the Asian and Caucasian populations ($P = 0.033$) and Asian subgroup ($P = 0.025$) when Shiota's study was omitted, suggesting that Shiota's study may underestimate this analysis. In addition, new meta-analysis after filling 1 possibly missing study detected by the trim and fill method revealed a statistically significant association ($P = 0.042$, Table 6). Given these analyses, it is improper to arbitrarily disregard these marginal though statistically insignificant associations.

As for association of rs7598440 with schizophrenia, large heterogeneities among Asian and Caucasian populations were noted under allelic, recessive and homozygous models. Subgroup analysis showed that heterogeneities was decreased significantly in the Asian subgroup (allelic model: I^2 from 67.7% to 0.0%; recessive model: I^2 from 82.6% to 0.0%; homozygous model: I^2 from 83.8% to 24.6%), suggesting that ethnicity may be the main

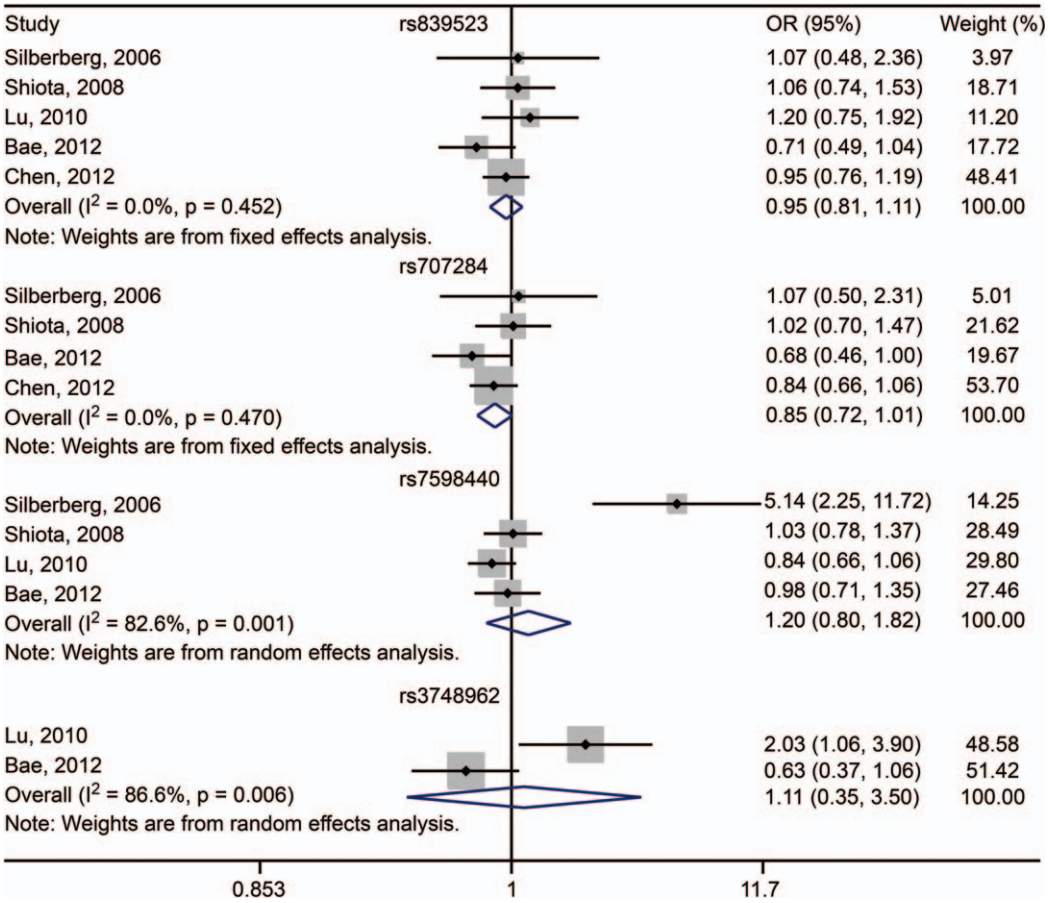

Figure 4. Forest plot illustrating the association between *ErbB4* SNPs and susceptibility to schizophrenia under the recessive model.

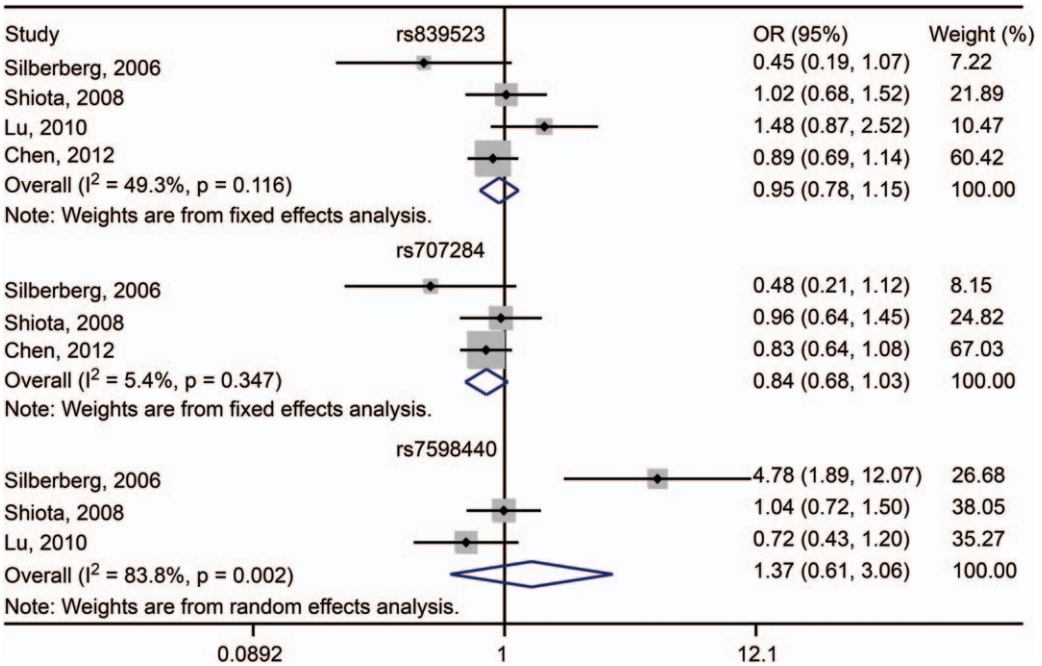

Figure 5. Forest plot showing the association between *ErbB4* SNPs and susceptibility to schizophrenia under the homozygous model.

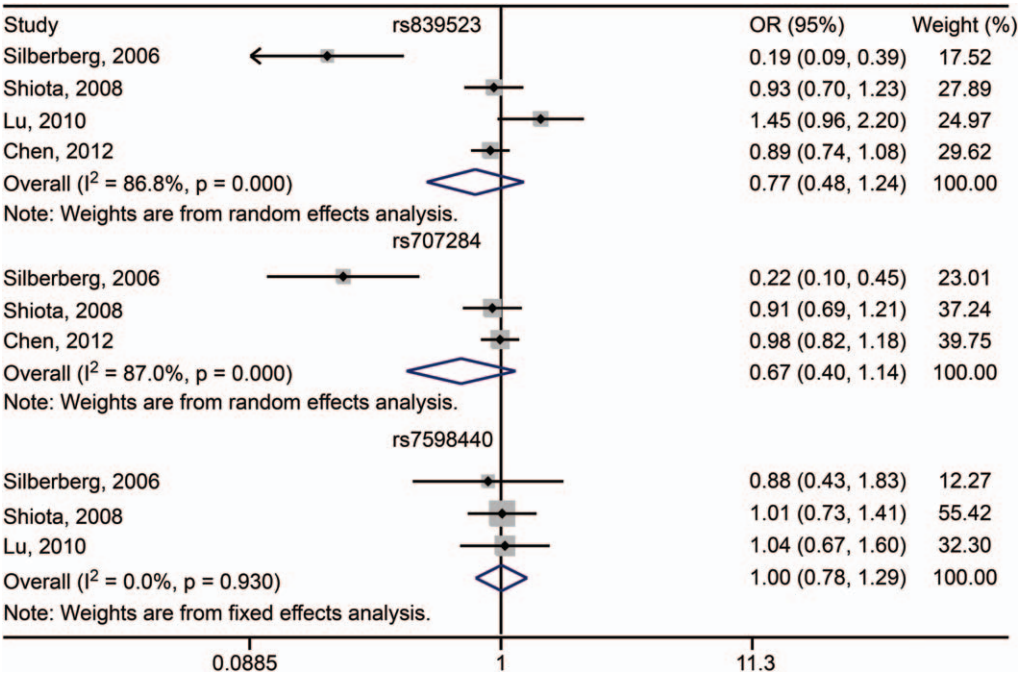

Figure 6. Forest plot exhibiting the association between *ErbB4* SNPs and susceptibility to schizophrenia under the heterozygous model.

Table 6

Sensitivity analysis of meta-analyses.

SNP	Ethnicity	Genetic model	Sensitive study	OR (95% CI)	*P* (*Z*)
rs839523	Asian/Caucasian	T vs C	None		
		TT+TC vs CC	None		
		TT vs TC+CC	None		
		TT vs CC	None		
		TC vs CC	None		
	Asian subgroup	T vs C	None		
		TT+TC vs CC	None		
		TT vs TC+CC	None		
		TT vs CC	None		
		TC vs CC	None		
rs707284	Asian/Caucasian	T vs C	Silberberg, 2006	0.93 (0.85, 1.01)	0.101
			Bae, 2012	0.91 (0.83, 1.01)	0.073
			Chen, 2012	0.89 (0.78, 1.02)	0.085
		TT+TC vs CC	None		
		TT vs TC+CC	Shiota, 2008	0.81 (0.67, 0.98)	0.033
		TT vs CC	None		
		TC vs CC	None		
	Asian subgroup	T vs C	None		
		TT+TC vs CC	None		
		TT vs TC+CC	Shiota, 2008	0.79 (0.65, 0.97)	0.025
rs7598440	Asian/Caucasian	T vs C	None		
		TT+TC vs CC	None		
		TT vs TC+CC	None		
		TT vs CC	None		
		TC vs CC	None		
	Asian subgroup	T vs C	None		
		TT+TC vs CC	None		
		TT vs TC+CC	None		
rs3748962	Asian/Caucasian	C vs T	None		

The OR (95% CI) and *P* (*Z*) in this table are calculated when omitting the sensitive study.
CI= confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

Table 7

Publication bias estimation of meta-analyses which contain no less than 4 study cohorts using the trim and fill method.

SNP	Ethnicity	Genetic model	Number of potentially missing studies	New *P* value after filling missing studies	Whether the result is stable
rs839523	Asian/Caucasian	T vs C	0		
		TT+TC vs CC	1	0.113	Yes
		TT vs TC+CC	2	0.241	Yes
		TT vs CC	0		
		TC vs CC	1	0.075	Yes
	Asian subgroup	T vs C	0		
		TT+TC vs CC	2	0.328	Yes
		TT vs TC+CC	1	0.258	Yes
rs707284	Asian/Caucasian	T vs C	0		
		TT+TC vs CC	1	0.041	No
		TT vs TC+CC	1	0.042	No
rs7598440	Asian/Caucasian	T vs C	0		
		TT+TC vs CC	1	0.631	Yes
		TT vs TC+CC	0		

SNP = single nucleotide polymorphism.

reason for high heterogeneities. Sensitivity and trim and fill analysis together showed that the association between rs7598440 and schizophrenia was stable (Tables 6, 7).

Concerning association of rs3748962 and rs2371276 with schizophrenia, large heterogeneities were observed and subgroup analysis did not reduce between-study heterogeneities. It is possible that some other factors, such as geographic factors, age, gender, lifestyle diversity, sampling difference and different disease courses, complicatedly influence heterogeneity.

This meta-analysis may have the following strengths. First, to our knowledge, this is the first meta-analysis combining the already-published case-control studies in English to precisely analyze the association of *ErbB4* SNPs with liability for schizophrenia. Next, we have systematically evaluated the quality of included study according mainly to Strengthening the Reporting of Genetic Association (STREGA) studies statement. Third, to comprehensively assess the potential association between *ErbB4* SNPs and schizophrenia, we have applied multiple genetic models, including allelic, dominant, recessive, homozygous, and heterozygous models. Fourth, we have conducted sensitivity analysis by excluding 1 individual study in turn and publication bias analysis with trim and fill analysis. What is more important, to better interpret results in this meta-analysis, we performed a detailed discussion taking into consideration results from sensitivity analysis and trim and fill analysis.

It is admitted that this meta-analysis has several limitations. First, we excluded 2 studies[19,28] for insufficient data though we have tried to contact the authors. Thereby, the number of study datasets and participants included into this meta-analysis was reduced particularly in Caucasian populations, because only 2 studies on Caucasian populations were finally included into this meta-analysis. In addition, the sample size of case-control studies included is still limited and therefore results should be interpreted with caution. Second, though our results suggested that ethnicity may be 1 factor causing high heterogeneities in our meta-analysis, there should be other complex factors influencing heterogeneities, which we were unable to determine.

In conclusion, our meta-analysis identified a statistically significant association between *ErbB4* SNP rs707284 and susceptibility to schizophrenia among Asian and Caucasian populations under allelic model and marginal associations under recessive and homozygous models. In addition, in Asian subgroup analysis, rs707284 was marginally associated with schizophrenia under the recessive model. However, owing to the limited sample size in our meta-analysis, more large-scale well-designed studies are still needed to further confirm and uncover *ErbB4* SNPs significantly associated with schizophrenia risk.

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