Meta-analyses of 10 polymorphisms associated with the risk of schizophrenia

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Abstract. Schizophrenia (SCZ) is a severe complex psychiatric disorder that generates problems for the associated family and society and causes disability with regards to work for patients. The aim of the present study was to assess the contribution of 10 genetic polymorphisms to SCZ susceptibility. Meta-analyses were conducted using the data without a limitation for time or language. A total of 27 studies with 7 genes and 10 polymorphisms were selected for the meta-analyses. Two polymorphisms were found to be significantly associated with SCZ. *SNAP25* rs3746544 was shown to increase the SCZ risk by 18% [P=0.01; odds ratio (OR), 1.18; 95% confidence interval (CI), 1.05-1.34] and *GRIK3* rs6691840 was found to increase the risk by 30% (P=0.008; OR, 1.30; 95% CI, 1.07-1.58). Significant results were found under the dominant (P=0.001; OR, 1.36; 95% CI, 1.13-1.65) and additive (P=0.02; OR, 1.45; 95% CI, 1.06-1.98) model for the *SNAP25* rs3746544 polymorphism and under the additive model for the *GRIK3* rs6691840 polymorphism (P=0.03; OR, 1.73; 95% CI, 1.04-2.85). There were no significant results observed for the other eight polymorphisms, which were *CCKAR* rs1800857, *CHRNA7* rs904952, *CHRNA7* rs6494223, *CHRNA7* rs2337506, *DBH* Ins>Del, *FEZ1* rs559668, *FEZ1* rs597570 and *GCLM* rs2301022. In conclusion, the present meta-analyses indicated that the *SNAP25* rs3746544 and *GRIK3* rs6691840 polymorphisms were risk factors of SCZ, which may provide valuable information for the clinical diagnosis of SCZ.

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Introduction

Schizophrenia (SCZ) is a common severe psychiatric disorder that affects <1% of the population. SCZ patients lose the ability to work or interact socially (1) and require assistance from the government (2). SCZ is a complex disorder. Environment and genetic factors play significant roles in SCZ (3-5). Environmental factors, including redox imbalance (4), inflammation (6) or obstetrical complications (7), have been reported to be associated with SCZ. Family, twin and adoption studies have shown that the genetic components increased the risk of SCZ (8,9). The lifetime risk for twins was >40%, which was much higher compared to 6.5% in first-degree relatives (10) and 1% in the general population (9). Multiple polygenic components have been shown to contribute to the risk of SCZ (11). In addition, epigenetic modification, such as DNA methylation, indicated that aberrant gene methylation may also influence the development of SCZ (12,13).

Dysfunction of the dopaminergic system has been accepted as an associated factor for SCZ (14). *CCKAR* encodes cholecystokinin type A receptor (CCKAR), which is a receptor of CCK. CCK can regulate the release of dopamine and dopamine-related behaviors (15). The activation of CCKAR in caudal nucleus accumbens can stimulate dopamine release, and therefore influence the process of SCZ (16,17). *DBH* encodes an enzyme that can catalyzes the conversion of dopamine to norepinephrine (18,19). The genetic association between *DBH* and SCZ has been shown in a previous study (20). *CHRNA7* is located on chromosome 15q13-q14, which is a susceptible SCZ locus. A low expression of *CHRNA7* was found in postmortem human hippocampus, reticular thalamic nucleus and frontal cortex of SCZ cases (21-23). The association between *CHRNA7* and SCZ has been found in numerous studies (24-26). *FEZ1* encodes fasciculation and elongation protein ζ-1 (FEZ1), which participates in the neurite extension machinery through an interaction with disrupted in schizophrenia 1, a candidate SCZ gene (27-29). A significant association has been demonstrated between *FEZ1* and SCZ (30). A number of

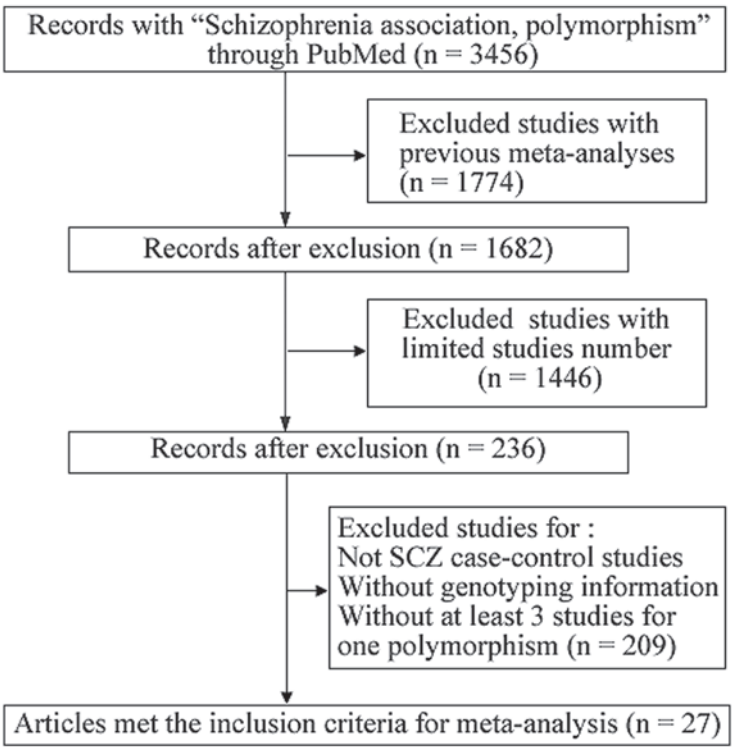

Figure 1. Flowchart of selection process in the meta-analyses. SCZ, schizophrenia.

studies have indicated that oxidative stress is a risk factor for SCZ (31-33). Glutathione (GSH) is one of the key redox regulators that can protect the nervous tissue from reactive oxygen species (34). *GCLM* encodes glutamate-cysteine ligase modifier (GCLM), which is a key enzyme of the GSH pathway that may be associated with SCZ (35). Glutamate receptors may be involved in the pathophysiology of SCZ (36). *GRIK3* encodes a protein that is a member of the glutamate receptors. A higher expression of *GRIK3* has been found in SCZ cases compared to controls (37). *SNAP25* encodes a protein that is implicated in the docking priming and fusion of the vesicles, which has been shown to be associated with SCZ (38,39).

Association studies between the genetic polymorphisms of the aforementioned 7 genes and SCZ have been performed in different populations (Table I). The discrepancies in the association studies of these genetic loci may be due to the different ethnic background and insufficient power. Meta-analysis can enhance the power by combining data from different individual studies and can draw a more comprehensive conclusion than a single association study. The aim of the present meta-analysis was to assess the associations between the 7 genes and the SCZ risk.

Materials and methods

Systemic search. A systemic search was performed using the PubMed database. The following keywords were used to identify the available studies: Schizophrenia, polymorphism and association. The studies included in the meta-analysis met certain criteria: i) The study was an original human case-control study on the association between gene polymorphisms and SCZ; ii) the study had sufficient information to obtain the odds ratios (ORs) and 95% confidence intervals (CIs); iii) genotype distribution of each polymorphism in the controls met the Hardy-Weinberg equilibrium (HWE); iv) each polymorphism contained more than three datasets from the studies; and v) there was no previous meta-analysis on the association between the selected polymorphism and SCZ. The following information was carefully extracted or calculated from each selected study: Gene name, polymorphism, first author's name, year of publication, country, ethnicity, the numbers of cases and controls, HWE for controls, results of the association in certain polymorphism with SCZ and the power of individuals.

Statistical analysis. The Arlequin program was used to test HWE (40). The power of each study was calculated by the Power and Sample Size Calculation program. The statistical heterogeneity across the studies included in the meta-analysis was assessed by Cochran's Q statistic and I^2 test (41) to decide the type of analysis. The fixed-effects model was used for the analysis with an $I^2<50\%$, whereas the random-effects model was used for the analysis with an $I^2>50\%$. In addition to the allelic analysis model, the meta-analyses were also performed under the dominant, recessive and additive models. The statistical analyses of the meta-analyses were performed by Review Manager 5 (42). Funnel plots were generated to observe the potential publication bias.

Results

Meta-analysis and associations. As shown in Fig. 1, a search in the online PudMed database was performed. A total of 3,456 studies were retrieved by using the aforementioned keywords. Among them, 1,774 studies were removed that had a previous meta-analysis, and 1,446 studies with a limited

Table I. Characteristics of the case-control studies in the current meta-analyses.

Gene	Polymorphism	Authors	Year	Country	Ethnicity	Cases/controls	HWE	Result	Power	(Refs.)
CCK	rs1800857	Zheng *et al*	2012	China	Asians	508/519	NA	S	0.416	(50)
		Minato *et al*	2007	Japan	Asians	290/290	Yes	NS	0.321	(51)
		Sanjuan *et al*	2004	Spain	Europeans	105/93	Yes	NS	0.103	(52)
		Tachikawa *et al*	2001	Japan	Asians	87/100	Yes	NS	0.138	(53)
CHRNA7	rs904952	Bakanidze *et al*	2013	German	Europeans	224/224	Yes	S	0.275	(54)
		Bakanidze *et al*	2013	Georgian	Europeans	50/51	Yes	S	0.099	(54)
		Cabranes *et al*	2013	Spain	Europeans	152/95	Yes	NS	0.166	(55)
		Ancin *et al*	2010	Spain	Europeans	508/793	Yes	NS	0.618	(56)
		Iwata *et al*	2007	China	Asians	188/188	Yes	NS	0.363	(57)
	rs6494223	Cabranes *et al*	2013	Spain	Europeans	153/95	Yes	NS	0.161	(55)
		Joo *et al*	2010	Korea	Asians	254/349	NA	S	0.426	(58)
		Ancin *et al*	2010	Spain	Europeans	510/793	Yes	NS	0.613	(56)
	rs2337506	Bakanidze *et al*	2013	German	Europeans	224/222	Yes	NS	0.189	(54)
		Joo *et al*	2010	Korea	Asians	254/349	NA	NS	0.365	(58)
		Iwata *et al*	2007	China	Asians	188/186	Yes	NS	0.206	(57)
DBH	Ins>Del	Hui *et al*	2013	China	Asians	195/304	Yes	NS	0.280	(59)
		Zhou *et al*	2013	China	Asians	747/625	Yes	S	0.655	(60)
		Yamamoto *et al*	2003	Canada	Europeans	106/120	Yes	NS	0.162	(61)
FEZ1	rs559668	Koga *et al*	2007	Japan	Asians	1,913/1,911	Yes	NS	0.688	(62)
		Hodgkinson *et al*	2007	USA	Europeans	159/173	Yes	NS	0.193	(63)
		Yamada *et al*	2004	Japan	Asians	356/359	Yes	NS	0.164	(30)
	rs597570	Koga *et al*	2007	Japan	Asians	1,913/1,911	Yes	NS	0.697	(62)
		Hodgkinson *et al*	2007	USA	Europeans	159/170	Yes	NS	0.172	(63)
		Yamada *et al*	2004	Japan	Asians	360/359	Yes	NS	0.166	(30)
SNAP25	rs3746544	Lochman *et al*	2013	Czech	Europeans	183/193	Yes	S	0.212	(47)
		Carroll *et al*	2009	British Isles	Europeans	650/712	Yes	S	0.615	(48)
		Kawashima *et al*	2008	Japan	Asians	372/367	NA	S	0.340	(49)
GRIK3	rs6691840	Kilic *et al*	2010	Turkey	Europeans	256/242	Yes	S	0.240	(64)
		Ahmad *et al*	2009	India	Asians	100/100	Yes	NS	0.138	(65)
		Lai *et al*	2005	Taiwan	Asians	160/160	Yes	NS	0.086	(66)
		Begni *et al*	2002	Italy	Europeans	99/116	Yes	S	0.136	(67)
GCLM	rs2301022	Hanzawa *et al*	2011	Japan	Asians	358/359	Yes	NS	0.769	(68)
		Ma *et al*	2010	China	Asians	427/415	NA	S	0.334	(69)
		Kishi *et al*	2008	Japan	Asians	742/817	Yes	NS	0.344	(70)
		Matsuzawa *et al*	2009	Japan	Asians	214/220	Yes	NS	0.623	(71)

HWE, Hardy-Weinberg equilibrium; NA, not applicable; S, significant; NS, not significant.

number of studies on the same gene were subsequently excluded. Another 209 studies were excluded as they did not meet the included criteria. In total, 27 studies of 10 polymorphisms for 7 genes were involved in the meta-analyses. All the genotype distributions in the involved studies met HWE (Table I).

No significant heterogeneity was observed between SCZ and rs1800857 of *CCKAR* (I^2=31%), rs904952 (I^2=6%) and rs2337506 (I^2=0%) of *CHRNA7*, rs559668 (I^2=0%) and rs597570 (I^2=0%) of *FEZ1*, rs3746544 of *SNAP25* (I^2=0%), rs6691840 of *GRIK3* (I^2=16%), rs2301022 of *GCLM* (I^2=53%). Significant heterogeneity was found in the meta-analyses for rs6494223 of *CHRNA7* (I^2=84%) and *DBH* Ins>Del (I^2=61%) with SCZ. No publication bias was found in all the meta-analyses due to the symmetrical shape of the funnel plots (Fig. 3).

The meta-analyses demonstrated a significant association between rs6691840 of *GRIK3* and SCZ at the allelic level (P=0.008; OR, 1.30; 95% CI, 1.07-1.58; Table II and Fig. 2) and additive model (P=0.03; OR, 1.73; 95% CI, 1.04-2.85; Table II; Fig. 2). A significant association was also found in rs3746544 of *SNAP25* in the allelic analysis (P=0.01; OR, 1.18;

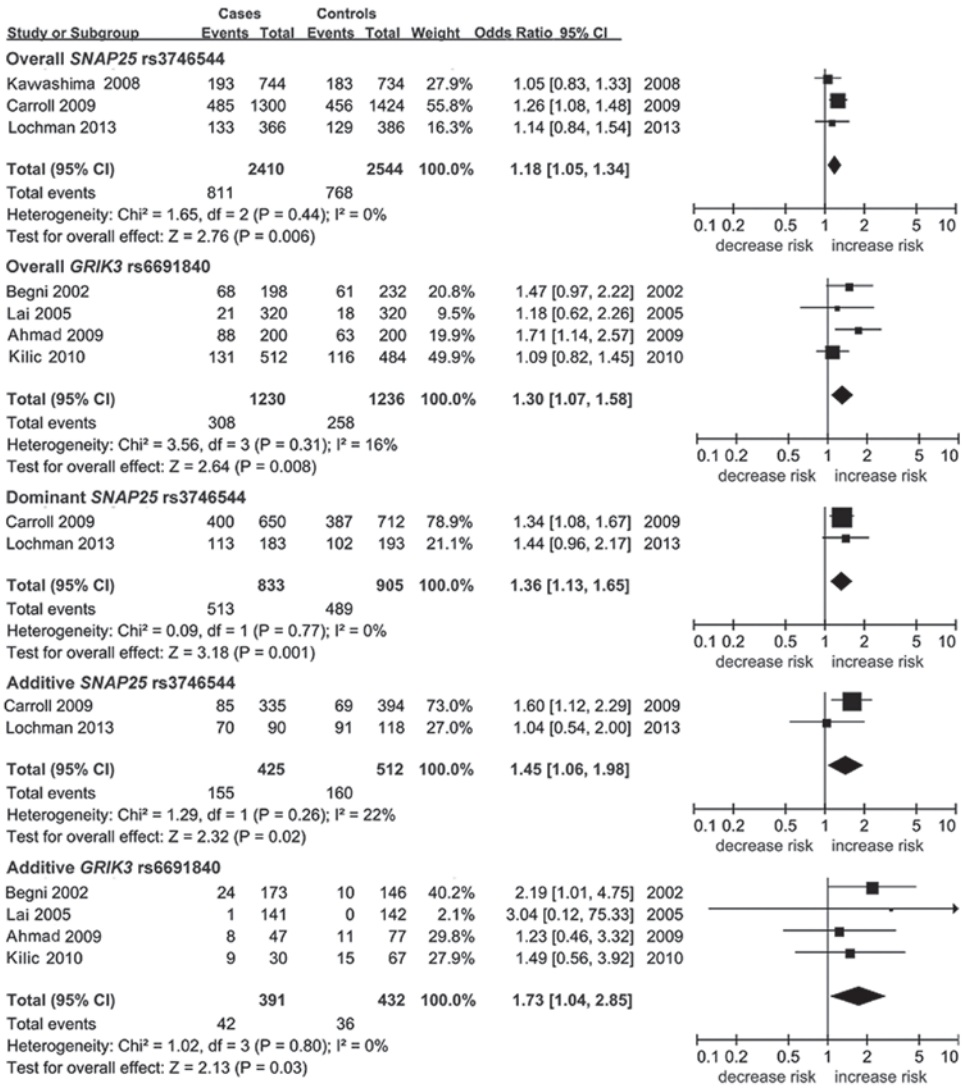

Figure 2. Forest plots of *SNAP25* rs3746544 and *GRIK3* rs6691840 polymorphisms with schizophrenia. CI, confidence interval.

95% CI, 1.05-1.34; Table II and Fig. 2), and under the dominant (P=0.001; OR, 1.36; 95% CI, 1.13-1.65; Table II; Fig. 2) and additive models (P=0.02; OR, 1.45; 95% CI, 1.06-1.98; Table II; Fig. 2). No significant association was demonstrated in the meta-analyses of the other polymorphisms (P>0.05; Table II).

Power analyses. All the power analyses in the meta-analyses were tested under a moderate risk of SCZ (OR, 1.2) (Tables I and II). The results showed that the power of the meta-analyses was much higher compared to the previous studies (Tables I and II). The power of the majority of the meta-analyses was sufficient (Power>0.730; Table II), except for the meta-analysis of rs6691840 (Power=0.471).

Discussion

The present meta-analyses performed a systemic overview of the association between gene polymorphisms and SCZ. A total of 7 selected genes (*CCKAR*, *CHRNA7*, *DBH*, *FEZ1*, *SNAP25*, *GRIK3* and *GCLM*) and 10 polymorphisms (rs1800857, rs904952 rs6494223, rs2337506, *DBH* Ins>Del, rs559668, rs597570, rs3746544, rs6691840 and rs2301022) were used to identify the association between the genetic factors and SCZ. rs6691840 was demonstrated to be a risk factor for SCZ on the allelic level. rs3746544 was found to increase the SCZ risk by 18% on the allelic level, 34% under the dominant model and 45% under the additive model. The meta-analyses could not identify the significant associations between the remaining polymorphisms and SCZ (Table II). To the best of our knowledge, this is the first meta-analyses for all the 10 polymorphisms.

Glutamate receptors in the frontal cortex play a significant role in the memory system that may be associated with SCZ (43). *GRIK3* encodes a key subtype of glutamate receptors that is expressed with a higher level in SCZ cases compared to controls (37). The *GRIK3* rs6691840 polymorphism can affect the primary structure of human ionotropic glutamate by changing serine to alanine (Ala) at position 310 in extracellular N-terminus (44,45). Previous case-control studies showed that rs6691840-Ala may increase the risk of SCZ in Turkish, Italian and Indian populations. By contrast, there was no association between rs6691840 and SCZ in the Chinese population. The present meta-analysis of *GRIK3* rs6691840 combined the data from the four studies and demonstrated that rs6691840-Ala

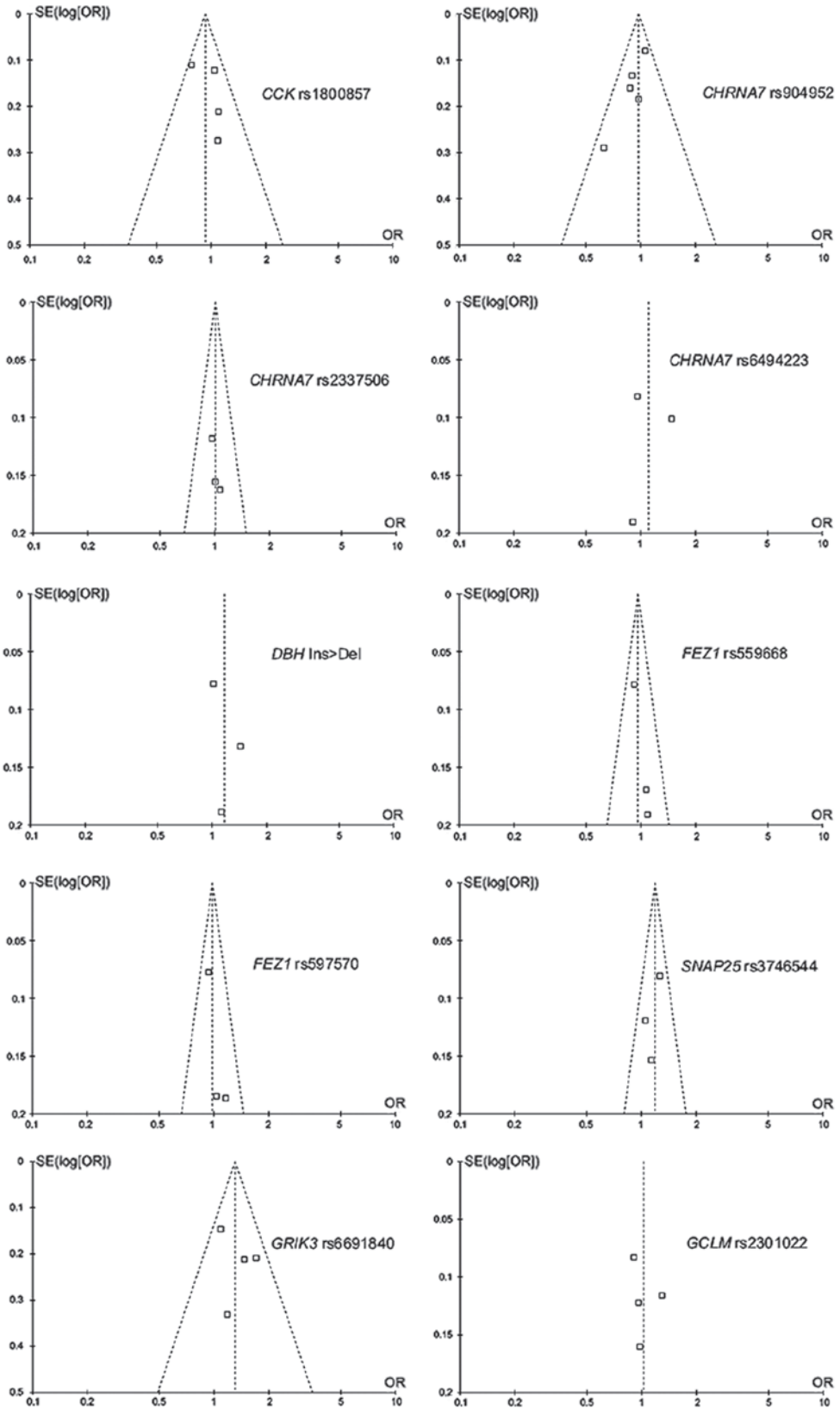

Figure 3. Funnel plots of 10 relative polymorphisms with schizophrenia. SE, standard error; OR, odds ratio.

increased the SCZ risk by 30% (P=0.008). There was no ethnic difference evaluated in rs6691840 [fixation index (Fst), 0.053; HapMap-CEU, 0.757; HapMap-HCB, 0.952; HapMap-GIH, 0.784] and low heterogeneity was also observed (allelic level, I^2=16%; additive model, I^2=0%). Notably, the power of the meta-analysis was relatively small (Power=0.471), indicating that larger scale replication studies are required to confirm the strong association in the present meta-analysis.

Table II. Meta-analyses of 10 relative polymorphisms with schizophrenia.

Genetic model	Polymorphism	Cases/controls	S	OR (95% CI)	P-value	I^2 (%)	Power
Overall	*CCKAR* rs1800857	990/1,002	4	0.93 (0.80-1.07)	0.29	31	0.736
	CHRNA7 rs904952	1122/1351	5	0.97 (0.87-1.09)	0.63	6	0.891
	CHRNA7 rs6494223	916/2055	3	1.10 (0.80-1.53)	0.56	84	0.881
	CHRNA7 rs2337506	665/1304	3	1.00 (0.86-1.18)	0.95	0	0.737
	DBH Ins>Del	1048/1049	3	1.16 (0.92-1.46)	0.20	61	0.832
	FEZ1 rs559668	2428/2443	3	0.96 (0.84-1.09)	0.54	0	0.827
	FEZ1 rs597570	2432/2440	3	0.98 (0.86-1.11)	0.73	0	0.819
	SNAP25 rs3746544	1205/1272	3	1.18 (1.05-1.34)	0.006[a]	0	0.850
	GRIK3 rs6691840	615/618	4	1.30 (1.07-1.58)	0.008[a]	16	0.471
	GCLM rs2301022	1741/1811	4	1.02 (0.86-1.20)	0.83	53	0.921
Dominant	*CCKAR* rs1800857	482/483	3	1.03 (0.79-1.33)	0.85	0	0.514
	CHRNA7 rs904952	1122/1351	5	1.07 (0.89-1.28)	0.50	0	0.800
	CHRNA7 rs6494223	663/888	2	0.90 (0.73-1.11)	0.33	0	0.664
	CHRNA7 rs2337506	412/408	2	1.17 (0.81-1.68)	0.40	0	0.362
	DBH Ins>Del	1048/1049	3	1.24 (0.87-1.77)	0.23	63	0.798
	FEZ1 rs559668	2428/2443	3	0.94 (0.81-1.08)	0.38	0	0.960
	FEZ1 rs597570	2432/2440	3	0.94 (0.81-1.09)	0.40	0	0.958
	SNAP25 rs3746544	833/905	2	1.36 (1.13-1.65)	0.001[a]	0	0.759
	GRIK3 rs6691840	615/618	4	1.68 (0.86-3.28)	0.13	84	0.593
	GCLM rs2301022	1314/1396	3	0.91(0.79-1.07)	0.25	0	0.917
Recessive	*CCKAR* rs1800857	482/483	3	1.20 (0.82-1.78)	0.35	0	0.260
	CHRNA7 rs904952	1122/1351	5	0.71 (0.46-1.11)	0.13	68	0.795
	CHRNA7 rs6494223	663/888	2	1.00 (0.75-1.33)	0.99	0	0.459
	CHRNA7 rs2337506	412/408	2	0.95 (0.68-1.34)	0.78	0	0.426
	DBH Ins>Del	1048/1049	3	1.11 (0.89-1.38)	0.36	0	0.645
	FEZ1 rs559668	2428/2443	3	1.13 (0.73-1.75)	0.57	47	0.260
	FEZ1 rs597570	2432/2440	3	1.40 (0.89-2.21)	0.15	39	0.188
	SNAP25 rs3746544	833/905	2	1.09 (0.60-1.98)	0.78	66	0.403
	GRIK3 rs6691840	615/618	4	1.14 (0.50-2.59)	0.75	57	0.197
	GCLM rs2301022	1314/1396	3	0.92 (0.67-1.26)	0.60	0	0.407
Additive	*CCKAR* rs1800857	297/288	3	1.17 (0.77-1.77)	0.47	0	0.242
	CHRNA7 rs904952	537/700	5	0.91 (0.72-1.16)	0.44	45	0.612
	CHRNA7 rs6494223	341/442	2	0.94 (0.68-1.28)	0.68	0	0.387
	CHRNA7 rs2337506	241/251	2	1.18 (0.67-2.11)	0.56	0	0.291
	DBH Ins>Del	543/567	3	1.20 (0.94-1.54)	0.15	48	0.537
	FEZ1 rs559668	2010/1990	3	1.15(0.74-1.87)	0.54	45	0.222
	FEZ1 rs597570	2016/1985	3	1.38 (0.87-2.18)	0.17	39	0.188
	SNAP25 rs3746544	425/512	2	1.45 (1.06-1.98)	0.02[a]	22	0.457
	GRIK3 rs6691840	391/432	4	1.73 (1.04-2.85)	0.03[a]	0	0.186
	GCLM rs2301022	840/869	3	0.89 (0.65-1.22)	0.47	0	0.394

[a]P≤0.05. S, number of studies; OR, odds ratio; CI, confidence interval.

Soluble N-ethylmaleimide-sensitive factor attachments receptor (SNARE) is involved with the pathophysiology of SCZ, as it is associated with the neurotransmitter exocytotic machinery (46). *SNAP25* encodes a protein that is a key part of the SNARE complex. SNAP25 can deliver neurotransmitter-containing vesicles to the inner plasma membrane. Human and animal studies indicate that SNAP25 is a risk factor for mental illness, such as SCZ (38,39). For the *SNAP25* rs3746544 polymorphism, there have been two previous studies with positive results (47,48) in Europeans (Czechs and British populations) and one negative result (49) in Asians (Japanese). The present meta-analysis of rs3746544 found a strong association with SCZ on the allelic level (P=0.006), and under the dominant (P=0.001) and additive models (P=0.02). The power was sufficient for the allelic level (Power=0.850) and dominant model (Power=0.759), and no significant heterogeneity

was found on the allelic levels and under the dominant model (I^2=0%). Due to the limited study number, more studies are required to confirm the positive findings in other ethnic populations, including Asian and African populations.

The present meta-analyses did not find a significant association of other polymorphisms with SCZ (P>0.05; Table II). A low heterogeneity and ethnic difference were found in the meta-analyses for rs904952 of *CHRNA7* (I^2=6%, Fst=0.06), rs559668 (I^2=0%, Fst=0.0054) and rs597570 (I^2=0%, Fst=0.0059) of *FEZ1*. This indicated the stability of the meta-analyses. Additionally, although a high heterogeneity was found for the rs6494223 of *CHRNA7* (I^2=84%) and rs2301022 of *GCLM* (I^2=53%) with SCZ, a low ethnic difference was observed (rs6494223, Fst=0.018; rs2301022, Fst=0.010). No significant heterogeneity was found in the two single-nucleotide polymorphisms (rs1800857, I^2=31%; rs2337506, I^2=0%) and no publication bias was found according to the symmetrical shapes in the funnel plots.

There are certain limitations of the study that require clarification. Firstly, the amount of studies was limited. Thus, a subgroup analyses by ethnicity could not be performed, and further studies in different ethnic background are required. Secondly, publication bias may exist, as the studies with a negative result are harder to publish than those with a positive result. Thirdly, there are numerous polymorphisms for each gene (*CCKAR*, n=1,049; *CHRNA7*, n=11,139; *DBH*, n=4,673; *FEZ1*, n=4,133; *SNAP25*, n=11,694; *GRIK3*, n=18,554; and *GCLM*, n=2,348). The meta-analyses only focused on 10 polymorphisms among those 7 genes, which may not fully represent the function of the genes. Future studies with more polymorphisms are required. Fourthly, SCZ is a complex disorder that a number of factors may participate in. Different statuses of SCZ patients, such as redox imbalance and inflammation, may influence the result. More genes with a larger number of polymorphisms should be considered, although 7 genes were analyzed that participate in several mechanisms, including the dopamine system, neurite extension machinery, oxidative stress and the GSH pathway.

In conclusion, the present meta-analyses indicated that the *SNAP25* rs374654 and *GRIK3* rs6691840 polymorphisms are risk factors for SCZ. Future studies with larger scale sample sizes and different ethnicities are required to confirm the present findings.

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