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Meta-Analyses of Manganese Superoxide Dismutase Activity, Gene Ala-9Val Polymorphism, and the Risk of Schizophrenia

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Abstract: Schizophrenia is a complex and disabling psychiatric disorder, and tardive dyskinesia (TD) is a severe adverse drug effect occurring in 20% to 40% of schizophrenic patients chronically treated with typical neuroleptics. Previous studies suggested that the manganese superoxide dismutase (MnSOD) activity was associated with the development of schizophrenia. Ala-9Val polymorphism, a functional polymorphism of MnSOD gene, has been reported to be related to the risk of schizophrenia and TD. However, these studies did not lead to consistent results. We performed meta-analyses aiming to assess the association between MnSOD activity and schizophrenia, as well as the association of MnSOD Ala-9Val polymorphism with schizophrenia and TD in schizophrenic patients.

We search for the literature on MnSOD and schizophrenia in English or Chinese published up to May 1, 2015 on PubMed, EMBASE, the Cochrane Databases, Chinese National Knowledge Infrastructure, China Biology Medical and Wanfang databases. Two investigators independently reviewed retrieved literature and evaluated eligibility. Discrepancy was resolved by consensus with a third reviewer. Data were pooled using fixed-effect or random-effect models. The standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for the MnSOD activity. Pooled odds ratio (OR) and 95% CI were calculated for Ala-9Val genotype and allele frequencies.

There were 6, 6, and 10 studies entering 3 parts of meta-analyses, respectively. The MnSOD activity of patients was significantly lower than that of controls (SMD = −0.94; 95% CI: −1.76, −0.12; $P = 0.025$). No significant associations of Ala-9Val genotypes (OR = 1.14; 95% CI: 0.97, 1.33; $P = 0.109$) and alleles (OR = 1.06; 95% CI: 0.94, 1.20; $P = 0.361$) with the risk of schizophrenia were observed. We also did not reveal significant associations of the genotypes (OR = 0.82; 95% CI: 0.66, 1.02; $P = 0.075$) and alleles (OR = 0.90; 95% CI: 0.76, 1.06; $P = 0.215$) with the risk of TD in schizophrenia.

The decreased MnSOD activity may be associated with the risk of chronic schizophrenia in Chinese population, while MnSOD Ala-9Val polymorphism may not play a significant role in the development of schizophrenia and TD. Longitudinal studies with larger sample sizes and different ethnicities are needed to confirm the association of the MnSOD Ala-9Val variants with schizophrenia and TD.

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Abbreviations: AIMS = Abnormal Involuntary Movement Scale, AP = antipsychotics, CCMD = Chinese Classification of Mental Disorders, CI = confidence interval, CPZ = chlorpromazine, DSM = Diagnostic and Statistical Manual, F/M = females/males, HA = hydroxylamine, HSDS = Hillside Simpson Dyskinesia Scale, HWE = Hardy–Weinberg equilibrium, MnSOD = manganese superoxide dismutase, OR = odds ratio, PCR = polymerase chain reaction, SD = standard deviation, SE = standard error, SMD = standardized mean differences, SODs = superoxide dismutases, TD = tardive dyskinesia.

INTRODUCTION

Schizophrenia is a complex and disabling psychiatric disorder characterized by psychopathology, cognition, and neurobiological abnormality abnormalities, with deficits in perception, emotion, and social behavior.[1,2] Although the pathogenesis of schizophrenia is not fully understood, the alteration of the oxidative stress, an imbalance between free radical metabolism and the antioxidant defense system, has been suggested to be associated with the development of schizophrenia.[3]

The superoxide dismutases (SODs) are 1 group of the key antioxidant defense enzymes playing a crucial role in preventing cell oxidative damage from free radicals.[4] Among 3 isoforms of SODs, the manganese superoxide dismutase (MnSOD), the intramitochondrial SOD, is the main antioxidant enzyme playing a critical role in the detoxification of superoxide radicals.[5,6] Although it has been demonstrated that altered total SOD activity existed in schizophrenic patients, the studies on the association between MnSOD activity and schizophrenia were limited and conflicting.[7–12]

The MnSOD gene known as a candidate region for linkage with schizophrenia is located in chromosome 6q25.[13] Among known functional polymorphisms of the MnSOD gene, the Ala-9Val polymorphism in exon 2 is the most widely investigated

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SNP, with the Ala-to-Val substitution possibly leading to the alteration of MnSOD activity in human mitochondria.[13,14] Studies on the association between Ala-9Val polymorphism and schizophrenia generated inconsistent results in different ethnic groups.[10,11,15–18]

Tardive dyskinesia (TD) is a severe adverse drug effect occurring in 20% to 40% of schizophrenic patients chronically treated with typical neuroleptics, characterized by the delayed manifestation of involuntary movements.[19,20] Several studies investigated the genetic association between the MnSOD Ala-9Val variants and TD, but the results were inconsistent.[10,15,17,21–25] Recently, a meta-analysis performed by Zai et al[26] did not reveal a significant association of Ala-9Val alleles or genotypes with the risk of TD in schizophrenic patients. However, this study neither included entire references nor found the sources of high heterogeneity.

Therefore, we carried out this meta-analysies to further assess the association between MnSOD Ala-9Val polymorphism and TD in schizophrenic patients, and also to evaluate the association between MnSOD activity, MnSOD Ala-9Val polymorphism, and schizophrenia.

METHODS

Ethical Review

Meta-analysis does not involve ethical review.

Search Strategy

We conducted literature search on MnSOD and schizophrenia in English or Chinese published up to May 1, 2015. PubMed, EMBASE, the Cochrane Databases, Chinese National Knowledge Infrastructure, and China Biology Medical and Wanfang databases were searched by 2 researchers independently. The following terms were used: ''manganese superoxide dismutase OR superoxide dismutase 2 OR SOD2 OR MnSOD'' AND ''schizophrenia OR psychotic disorders OR psychosis.'' We also searched the reference lists of the retrieved articles and reviews for additional articles.

Criteria for Inclusion and Exclusion

Studies were included if they met the following criteria: a case–control study (schizophrenia patients vs healthy controls or patients with TD vs ones without TD) or cohort study was performed; the diagnosis of schizophrenia was conducted according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria or Chinese Classification of Mental Disorders (CCMD); the presence of TD was assessed using the Abnormal Involuntary Movement Scale (AIMS) or the modified Hillside Simpson Dyskinesia Scale (HSDS); data on MnSOD activity of schizophrenia patients and healthy controls, or MnSOD Ala-9Val genotypes and alleles of schizophrenic patients and healthy controls, or MnSOD Ala-9Val genotypes and alleles of schizophrenic patients with TD and without TD were available.

The exclusion criteria were: the studies were not related to MnSOD or schizophrenia; the studies did not provide sufficient information about MnSOD activity or MnSOD Ala-9Val genotype and allele frequencies; the genotypic distributions of MnSOD Ala-9Val gene in healthy controls were inconsistent with Hardy–Weinberg equilibrium (HWE) in the meta-analysis of the association between MnSOD Ala-9Val polymorphism and schizophrenia; the references used overlapping datasets with the included studies.

We used the Newcastle–Ottawa Quality Assessment Scale to assess the quality of studies included in the meta-analysis.

Data Extraction

Data were extracted from the included studies using a standardized data extraction form by 2 reviewers independently, and any discrepancy was discussed and resolved by consensus with a third reviewer. The extracted information included the followings: the first author, the publication year, country, geographic location, the mean age and gender ratio (female/male), diagnostic criteria, specimen, assay method of MnSOD activity, genotyping method, duration of illness (years), sample size, mean, and standard deviation (SD) of MnSOD activity (U/mL) of the case and control groups, Ala-9Val genotype and allele frequencies of cases with TD and without TD as well as the control group.

Outcomes Measures

We performed separate meta-analyses comparing: MnSOD activity between schizophrenic patients and healthy controls; MnSOD Ala-9Val genotype and allele distribution between schizophrenic patients and healthy controls; MnSOD Ala-9Val genotype and allele distribution between schizophrenic patients with TD and without TD.

Statistical Analysis

The meta-analysis on the association between the MnSOD activity and schizophrenia was carried out by pooled standardized mean differences (SMD) with 95% confidence interval (95% CI). The meta-analyses on the association of the MnSOD Ala-9Val polymorphism with schizophrenia and TD were performed using recessive genetic model (Ala/Ala and Ala/Val vs Val/Val) and allele frequency (Ala vs Val), and the pooled odds ratio (OR) and 95% CI were calculated. Heterogeneity among studies was estimated using the Cochran Q and I^2 statistic. For the Q statistic, $P < 0.10$ indicates statistically significant heterogeneity. For the I^2 statistic, $I^2 > 50\%$ indicates a large heterogeneity. A fixed-effect model with Mantel–Haenszel method was used if Q statistic ($P < 0.10$) or $I^2 < 50\%$. Otherwise, a random-effect model was used. In case of heterogeneity, meta-regression analysis or subgroup analysis was conducted. Sensitivity analysis was performed to strengthen the result of the meta-analysis. Publication bias was assessed using the Begg's and Egger's tests. All data analyses were performed using Stata 12.0 (Stata Corp LP, College Station, TX).

RESULTS

Basic Information of the Included Studies

The process of identifying eligible articles was summarized in Figure 1. The meta-analysis of the association between MnSOD activity and schizophrenia included 6 studies involving 1541 (61.1%) schizophrenic patients and 981 (38.9%) healthy controls which were all Chinese subjects (Table 1). For the meta-analysis of the association between Ala-9Val polymorphism and schizophrenia, 6 studies were included and most of them were from Asia (66.7%, 4/6), with a total of 1976 (56.5%) patients and 1520 (43.5%) controls (Table 2). Table 3 showed the information of 10 included studies for the meta-analysis of the association between Ala-9Val polymorphism and TD in schizophrenic patients. Totally, there were 676 (32.1%) patients with TD and 1427(67.9%) ones without TD. Most of the studies

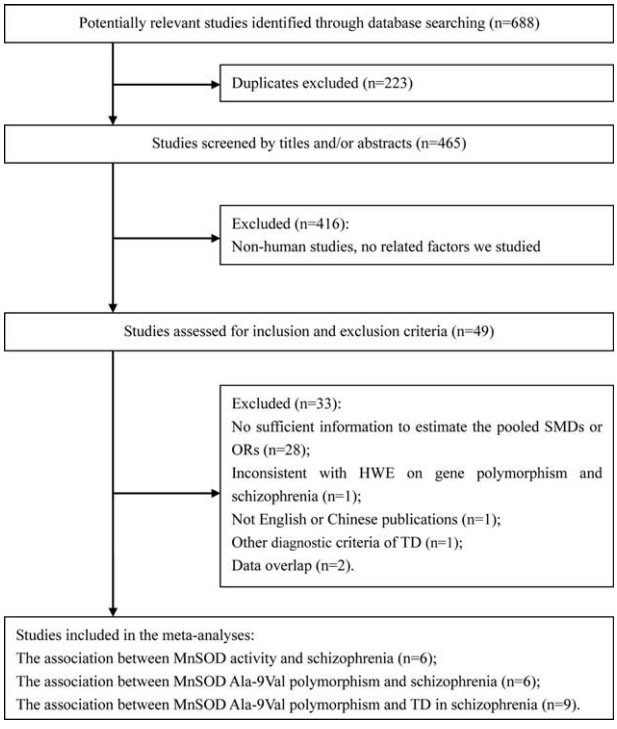

FIGURE 1. Flow diagram of the studies selection process for the present meta-analysis.

were from Asia (70.0%, 7/10). All studies received a score of ≥6, indicating good qualities.

The MnSOD Activity and Schizophrenia Risk

The random-effect model showed that the MnSOD activity of patients was significantly lower than that of controls (SMD = −0.94; 95% CI: −1.76, −0.12; $P = 0.025$) with significant heterogeneity among studies ($I^2 = 98.4\%$, $P < 0.001$) (Figure 2).

We performed subgroup analysis to analyze the sources of heterogeneity (Figure S1, http://links.lww.com/MD/A410). Five factors were used for subgroup analysis, including mean age of the case group (≤50/>50 years), gender ratio (female/male = 0/>1), sample type (serum/plasma), published year (before 2010/after 2010), and duration of illness (≤30/>30 years) (Figure S1, http://links.lww.com/MD/A410). However, the heterogeneity still kept high (>90%) in all the subgroups. No evidence of publication bias were observed in the included studies ($P_{Egger} = 0.357$ and $P_{Begg} = 0.851$) (Figure S2, http://links.lww.com/MD/A410).

The Association Between MnSOD Ala-9Val Polymorphism and Schizophrenia Risk

The genotypic as well as allelic analysis using the fixed-effect model, did not show significant associations of Ala-9Val genotypes (OR = 1.14; 95% CI: 0.97, 1.33; $P = 0.109$) and alleles (OR = 1.06; 95% CI: 0.94, 1.20; $P = 0.361$) with the risk of schizophrenia (Figure 3). There were no evidence for heterogeneity among the studies for both genotypes ($I^2 = 0.0\%$, $P = 0.696$) and alleles ($I^2 = 0.0\%$, $P = 0.579$).

In the sensitivity analyses, each included study was removed one by one to determine the effect of an individual

TABLE 1. Basic Information of Included Studies on Association Between Manganese Superoxide Dismutase Activity and Schizophrenia

First Author	Published Year	Country	Geographic Location	Age*, yr (Mean ± SD)	Gender*, F/M	Duration of Illness, yr (Mean ± SD)	Patient Type	Duration of Treatment, yr (Mean ± SD)	AP Dose†, mg/d (Mean ± SD)	Diagnostic Criteria	Sample	Assay Method	Cases			Controls			Quality Score‡
													n	Mean	SD	n	Mean	SD	
Hong	2000	China	Asia	42.0 ± 17.3	24/73	18.4 ± 6.2	Chronic	6.1 ± 2.4	NA	CCMD-2	Serum	HA	97	30.98	4.72	100	42.34	4.12	7
Zhang	2002	China	Asia	55.3 ± 8.5	0/101	31.4 ± 7.8	Chronic	30.5 ± 8.5	343 ± 130	DSM-IV	Plasma	HA	101	72.1	27.2	50	57.8	5.4	8
Zhang	2013	China	Asia	50.2 ± 8.5	0/185	26.3 ± 8.1	Chronic	4.3 ± 4.4	480 ± 475	DSM-IV	Plasma	HA	185	18.8	1.0	132	21.2	1.2	8
Wu	2014	China	Asia	55.40 ± 5.70	0/83	30.0 ± 7.6	Chronic	4.8 ± 5.1	477 ± 613	DSM-IV	Plasma	HA	83	18.8	12.3	58	25.7	13.0	9
Zhang	2014	China	Asia	48.1 ± 9.6	152/771	24.6 ± 9.8	Chronic	NA	446 ± 413	DSM-IV	Plasma	HA	923	16.9	13.4	566	21.1	14.2	9
Wu	2015	China	Asia	53.8 ± 7.3	0/152	28.8 ± 8.7	Chronic	3.8 ± 4.2	527 ± 547	DSM-IV	Plasma	HA	152	17.2	10.7	75	24.5	12.1	9

AP = antipsychotics; CCMD = Chinese Classification of Mental Disorders; DSM = Diagnostic and Statistical Manual; F/M = females/males; HA = hydroxylamine method; NA = no data in the reference; SD = standard deviation.

* The age and gender of patients.

† The daily antipsychotics dose was converted to mean chlorpromazine equivalents.

‡ The quality score was evaluated by the Cochrane's Newcastle–Ottawa Scale evaluation standard for case–control study.

TABLE 2. Basic Information of Included Studies on the Association Between Manganese Superoxide Dismutase Ala-9Val Polymorphism and Schizophrenia

First Author	Published Year	Country	Geographic Location	Age*, yr (Mean ± SD)	Gender*, F/M	Genotyping Method	Sample Size, Case/Control	Case Genotypes, n (%)		Control Genotypes, n (%)		Case Alleles		Control Alleles		HWE, P†	Quality Score‡
								Ala/Ala and Ala/Val	Val/Val	Ala/Ala and Ala/Val	Val/Val	Ala	Val	Ala	Val		
Hori	2000	Japan	Asia	55.6 ± 9.1	97/95	PCR	192/141	42 (21.9)	150 (78.1)	29 (20.6)	112 (79.4)	45 (11.7)	339 (88.3)	31 (11.0)	251 (89.0)	0.799	7
Zhang	2002	China	Asia	55.3 ± 8.5	0/101	PCR	101/50	33 (32.7)	68 (67.3)	17 (34.0)	33 (66.0)	33 (16.3)	169 (83.7)	17 (17.0)	83 (83.0)	0.148	8
Ventriglia	2006	Italy	Europe	42.4 ± 12.1	81/131	PCR	212/257	166 (78.3)	46 (21.7)	193 (75.1)	64 (24.9)	212 (50.0)	212 (50.0)	247 (48.1)	267 (51.9)	0.181	7
Hitzeroth	2007	South Africa	Africa	34.1 ± 10.7	52/206	PCR	286/243	194 (67.8)	92 (32.2)	163 (67.1)	80 (32.9)	235 (41.1)	337 (58.9)	209 (43.0)	277 (57.0)	0.781	8
Pae	2007	Korea	Asia	44.7 ± 9.7	84/178	PCR	262/263	49 (18.7)	213 (81.3)	54 (20.5)	209 (79.5)	49 (9.4)	475 (90.6)	54 (10.3)	472 (89.7)	0.063	8
Zhang	2014	China	Asia	48.1 ± 9.6	152/771	PCR	923/566	249 (27.0)	674 (73.0)	125 (22.1)	441 (77.9)	254 (13.8)	1592 (86.2)	129 (11.4)	1003 (88.6)	0.163	9

F/M = females/males; HWE = Hardy–Weinberg equilibrium; PCR = polymerase chain reaction; SD = standard deviation.
* The age and gender of patients.
† The *P* value in the control group.
‡ The quality score was evaluated by the Cochrane's Newcastle–Ottawa Scale evaluation standard for case–control study.

TABLE 3. Basic Information of Included Studies on the Association Between Manganese Superoxide Dismutase Ala-9Val Polymorphism and TD in Schizophrenic Patients

First Author	Published Year	Country	Geographic Location	Age*, yr (Mean ± SD)	Gender*, F/M	Sample Size, TD/Non-TD	TD Genotypes, n (%)		Non-TD Genotypes, n (%)		TD Alleles, n (%)		Non-TD Alleles, n (%)		Quality Score†
							Ala/Ala and Ala/Val	Val/Val	Ala/Ala and Ala/Val	Val/Val	Ala	Val	Ala	Val	
Hori	2000	Japan	Asia	55.6 ± 9.1	97/95	39/153	3 (7.7)	36 (92.3)	39 (25.5)	114 (74.5)	3 (3.8)	75 (96.2)	42 (13.7)	264 (86.3)	7
Zhang	2002	China	Asia	55.3 ± 8.5	0/101	42/59	12 (28.6)	30 (71.4)	21 (35.6)	38 (64.4)	12 (14.3)	72 (85.7)	21 (17.8)	97 (82.2)	8
Zhang	2003	China	Asia	55.6 ± 8.8	0/94	94/52	31 (33.0)	63 (67.0)	19 (36.5)	33 (63.5)	31 (16.5)	157 (83.5)	19 (18.3)	85 (81.7)	8
Akyol	2005	Turkey	Europe	37.6 ± 10.8	59/94	23/130	14 (60.9)	9 (39.1)	106 (81.5)	24 (18.5)	16 (34.8)	30 (65.2)	118 (45.4)	142 (54.6)	7
Thelma	2007	India	Asia	32.0 ± 10.9	135/164	88/211	67 (76.1)	21 (23.8)	161 (76.3)	50 (23.7)	93 (52.8)	83 (47.2)	228 (54.0)	194 (46.0)	6
Pae	2007	Korea	Asia	44.7 ± 9.7	84/178	44/218	12 (27.3)	32 (72.7)	37 (17.0)	181 (83.0)	12 (13.6)	76 (86.4)	37 (8.5)	399 (91.5)	8
Kang	2008	Korea	Asia	45.2 ± 9.6	99/110	83/126	17 (20.5)	66 (79.5)	20 (15.9)	106 (84.1)	20 (12.0)	146 (88.0)	21 (8.3)	231 (91.7)	8
Liu	2010	China	Asia	49.5 ± 11.1	170/352	176/346	45 (25.6)	131 (74.4)	103 (29.8)	243 (70.2)	47 (13.4)	305 (86.6)	103 (14.9)	589 (85.1)	9
Zai‡	2010	America	America	37.7 ± 10.1	64/129	76/114	52 (68.4)	24 (31.6)	90 (78.9)	24 (21.1)	73 (48.0)	79 (52.0)	120 (52.6)	108 (47.4)	8
Zai‡	2010	America	America	32.5 ± 10.9	9/21	11/18	7 (63.6)	4 (36.4)	11 (61.1)	7 (38.9)	9 (40.9)	13 (59.1)	13 (36.1)	23 (63.9)	8

F/M = Females/Males; SD = standard deviation; TD = tardive dyskinesia.
* The age and gender of patients.
† The quality score was evaluated by the Cochrane's Newcastle–Ottawa Scale evaluation standard for case–control study.
‡ The study by Zai et al included 2 samples, 1 was Caucasian and the other was African American which were all from America.

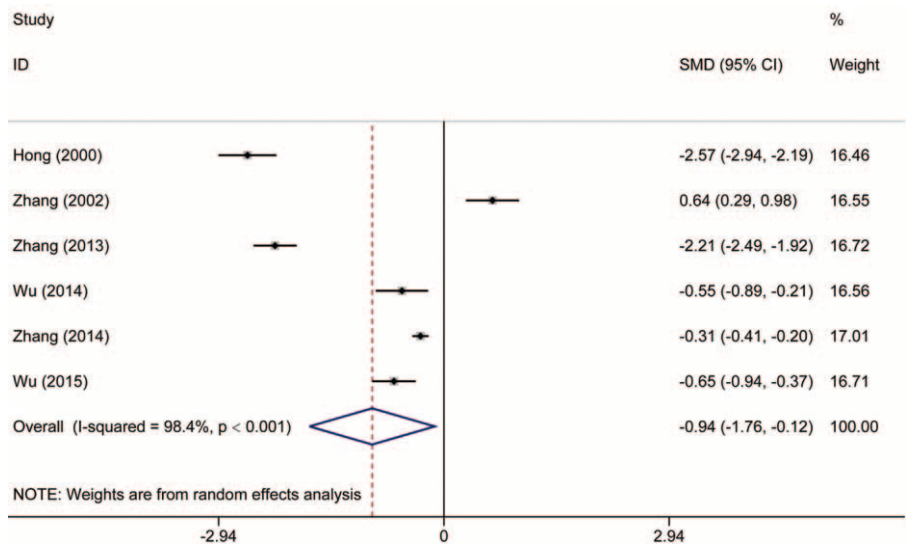

FIGURE 2. Forest plot of the studies on the association between manganese superoxide dismutase activity and schizophrenia by meta-analysis with the random-effect analysis. SMD = standardized mean differences.

dataset to the pooled ORs. The results were consistent in all of the research models except the study by Pae et al[17] for genotypes and the study by Zhang et al[11] for alleles (Figure S3, http://links.lww.com/MD/A410). No publication biases were observed for the associations between Ala-9Val genotypes, alleles, and schizophrenia (genotypes: $P_{Egger} = 0.104$ and $P_{Begg} = 0.707$; alleles: $P_{Egger} = 0.469$ and $P_{Begg} = 0.707$) (Figure S4, http://links.lww.com/MD/A410).

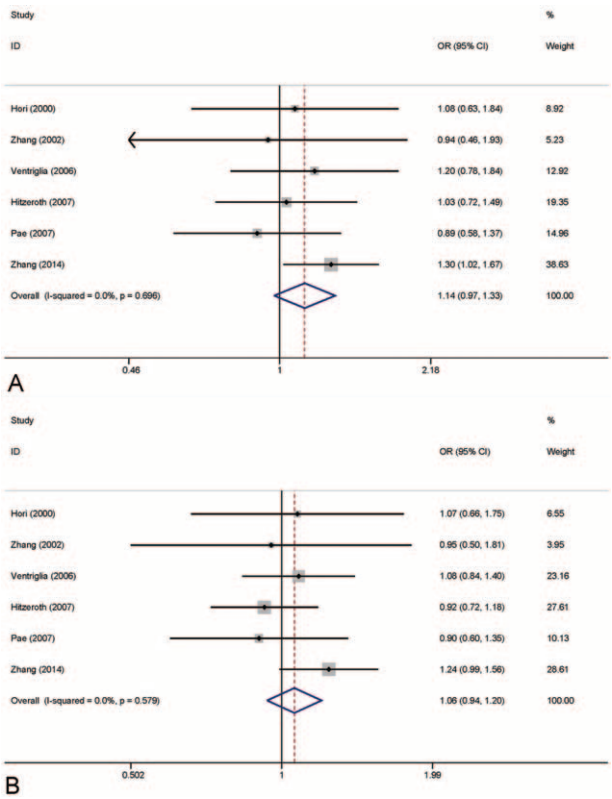

FIGURE 3. Forest plot of the studies on the association between manganese superoxide dismutase Ala-9Val polymorphism and schizophrenia by meta-analysis with the fixed-effect analysis. (A) Ala-9Val genotypes and (B) Ala-9Val alleles. OR = odds ratio.

The Association Between MnSOD Ala-9Val Polymorphism and TD in Schizophrenia Patients

The random-effect model did not show the significant association between Ala-9Val genotypes and the risk of TD in schizophrenia (OR = 0.82; 95% CI: 0.66, 1.02; $P = 0.075$) with a heterogeneity of $I^2 = 39.5\%$ ($P = 0.095$) among studies (Figure 4A). There was no significant association between Ala-9Val alleles and TD (OR = 0.90; 95% CI: 0.76, 1.06; $P = 0.215$) with no heterogeneity among studies ($I^2 = 23.6\%$, $P = 0.226$) by the fixed-effect model (Figure 4B).

Meta-regression was performed further to explore the possible sources of the heterogeneity for genotypes results. We put 4 factors into the meta-regression model. As shown in Table 4, none of these factors had any significant influence on the genotypes results ($P > 0.05$). We further conducted subgroup analysis, observing a light decrease of heterogeneity in the subgroups of geographic location (Figure S5B, http://links.lww.com/MD/A410).

The sensitivity analysis indicated stability and reliability of results for the associations of MnSOD Ala-9Val genotypes and alleles with TD (Figure S6, http://links.lww.com/MD/A410). No publication biases were observed for the pooled ORs (genotypes: $P_{Egger} = 0.904$ and $P_{Begg} = 0.858$; alleles: $P_{Egger} = 0.770$ and $P_{Begg} = 0.721$) (Figure S7, http://links.lww.com/MD/A410).

DISCUSSION

In our meta-analyses, the significant association was observed between MnSOD activity and chronic schizophrenia in Chinese population. However, no statistically significant associations were observed between MnSOD Ala-9Val polymorphism and schizophrenia as well as TD.

It has been reported that the SOD activity was decreased in chronic schizophrenic patients while increased in first-episode

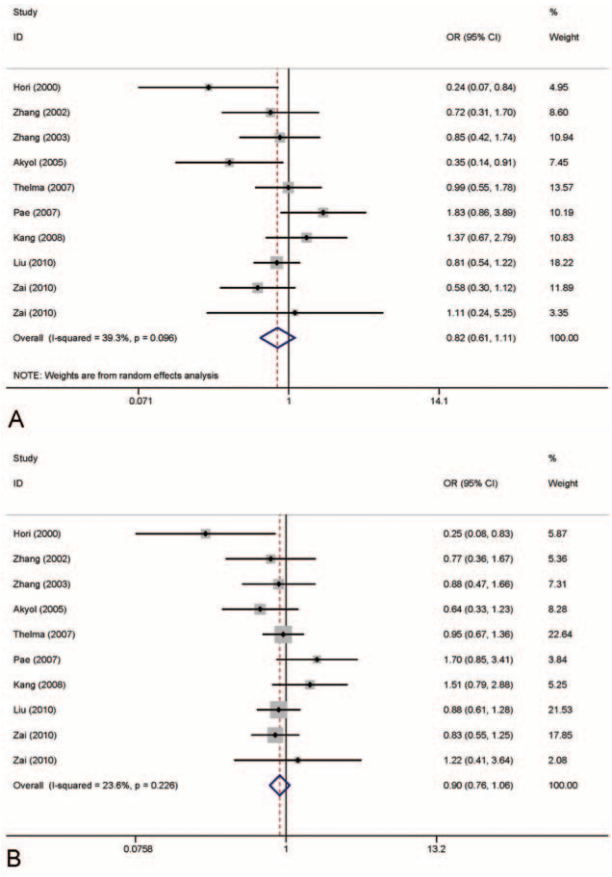

FIGURE 4. Forest plot of the studies on the association between manganese superoxide dismutase Ala-9Val polymorphism and tardive dyskinesia in schizophrenia patients by meta-analysis. (A) Ala-9Val genotypes by the random-effect analysis and (B) Ala-9Val alleles by the fixed-effect analysis. OR = odds ratio.

schizophrenic patients.[27] However, studies on the association between MnSOD activity and schizophrenia were limited, most of which indicated that MnSOD activity of schizophrenia patients was lower than that of controls. To our knowledge, this is the first study to conduct a meta-analysis focusing on MnSOD activity in schizophrenia. We found that MnSOD activity was significantly decreased in Chinese population with chronic schizophrenia, which was consistent with the result of the total SOD activity. MnSOD is a main antioxidant enzyme scavenging the greatest number of superoxide anions produced by mitochondrial energy metabolism,[5] and also plays a significant role in neurodevelopment.[28] Lower MnSOD activity in schizophrenic patients may reflect an imbalance between free radical production and antioxidant levels in schizophrenia. However, these included studies all focused on Chinese patients of chronic type, so further researches on other populations of different ethnicities and first-episode patients were needed to evaluate the association between MnSOD activity and schizophrenia. Apart from some factors we considered in this study, the high heterogeneity among the included studies may be due to some other factors such as the type and daily dose of antipsychotics, duration of treatment, the subtypes of patients recruited, and so forth.

TABLE 4. Meta-Regression Analysis of the Potential Factors Affecting the Heterogeneity

Factor	Coefficient	SE	95% CI	*t*	*P*
Year	−0.14	0.86	−2.35, 2.07	−0.16	0.876
Geographic location	0.12	0.78	−1.88, 2.12	0.15	0.885
Age	0.04	1.25	−3.17, 3.25	0.03	0.977
Gender ratio	−0.15	0.39	−1.15, 0.84	−0.4	0.705
Constant	0.76	1.05	−1.95, 3.47	0.72	0.503

CI = confidence interval; *P* = *P* value; SE = standard error; *t* = *t* value.

The MnSOD gene contains a functional polymorphism Ala-9Val in the mitochondrial targeting sequence, of which the Val allele induces a conformational change in the mitochondrial targeting sequence and misdirects intracellular trafficking of the protein.[6,29] The presence of this allele may result in decreased capacity of detoxification of the harmful superoxide radicals. Most of previous studies suggested that the MnSOD Ala-9Val polymorphism might not directly contribute to the risk of schizophrenia and TD. However, the study by Zhang et al[11] showed a protective effect for the Val/Val genotype on schizophrenia in Chinese population, while Hori et al[15] and Akyol et al[22] found that Ala allele played a role in protecting against susceptibility to TD in Japanese schizophrenic patients. Our meta-analyses did not reveal significant associations of the alleles or genotypes with schizophrenia and TD in schizophrenia, which is consistent with the study by Zai et al.[26] It is likely due to the complex interaction between multiple genetic and environmental factors, and insufficient sample size which failed to detect small genetic effect sizes.

It is noteworthy that the Val/Val genotype and Val allele frequencies were higher in most Asian populations compared to those in other ethnicities, and the general heterogeneity among the studies on genotypes and TD association witnessed a light decline in the subgroups from different geographic locations, although meta-regression did not indicate a significant influence of the geographic location on our results. Therefore, replications in different ethnicities are needed since the genetic vulnerability may have effects on the development of schizophrenia or TD in different ethnic populations.

There are some limitations in our study. The references included in our study may not be comprehensive, since we failed to obtain the articles apart from English and Chinese publications. We only acquired the data of MnSOD activity in Chinese population since studies about other populations all focused on the activity of total SOD. Therefore, the extrapolation of the association between the MnSOD activity and schizophrenia to other populations may be limited. The high heterogeneity among the studies for MnSOD activity was not resolved due to lack of details of some other factors such as antipsychotics type.

In summary, our meta-analyses indicated that the decreased MnSOD activity may be associated with the risk of chronic schizophrenia in Chinese population, while the MnSOD Ala-9Val polymorphism may not play a significant role in the development of schizophrenia and TD. Longitudinal studies with larger sample sizes and different ethnicities are needed, and interaction between multiple genetic and environmental factors should be considered to confirm the association of the MnSOD Ala-9Val variants with schizophrenia and TD.

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