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 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.

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
SNP, with the Ala-to-Val substitution possibly leading to the alteration of MnSOD activity in human mitochondria.\textsuperscript{13,14} Studies on the association between Ala-9Val polymorphism and schizophrenia generated inconsistent results in different ethnic groups.\textsuperscript{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.\textsuperscript{19,20} Several studies investigated the genetic association between the MnSOD Ala-9Val variants and TD, but the results were inconsistent.\textsuperscript{10,15,17,21–23} Recently, a meta-analysis performed by Zai et al\textsuperscript{12} 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-analyses 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 Hillside Simpson Dyskinesia Scale (HSDS); data on MnSOD activity or the modified Abnormal Involuntary Movement Scale (AIMS) or the modified Discom Any Involuntary Movement Scale (CAIMS) were presented; and the sample size was at least 100 cases. The exclusion criteria were: the studies were not related to MnSOD activity and 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\textsuperscript{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...
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 $= -0.94; 95\% \text{ CI: } -1.76, -0.12; P = 0.025$) 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 ($>50$ years), gender ratio (female/male $>1$), sample type (serum/plasma), published year (before 2010/after 2010), and duration of illness ($>30$ 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 ($P_{\text{Egger}} = 0.357$ and $P_{\text{Begg}} = 0.851$) (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 $= 1.14; 95\% \text{ CI: } 0.97, 1.33; P = 0.109$) and alleles (OR $= 1.06; 95\% \text{ CI: } 0.94, 1.20; P = 0.361$) 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

![Flow diagram of the studies selection process for the present meta-analysis.](http://links.lww.com/MD/A410)

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

| TABLE 1. Basic Information of Included Studies on Association Between Manganese Superoxide Dismutase Activity and Schizophrenia |
| --- |
| First Author | Published Year | Country | Geographic Location | Age (Mean ± SD) | Gender (F/M) | Duration of Illness (Mean ± SD) | AP Dose (Mean ± SD) | Assay Method | n | Mean SD | n | Mean SD | Quality Score |
| --- |
| Hong | 2000 | China | Asia | 42.0 ± 17.3 | 24/73 | 18.4 ± 6.2 | 4.8 ± 5.1 | HA | 97 | 30.98 ± 4.72 | 100 | 42.34 ± 4.12 | 7 |
| Zhang | 2002 | China | Asia | 55 ± 8.5 | 0/101 | 31.4 ± 7.8 | 3.8 ± 4.8 | HA | 101 | 72.1 ± 27.2 | 50 | 57.8 ± 5.4 | 8 |
| Zhang | 2003 | China | Asia | 49 ± 6.5 | 0/101 | 31.4 ± 7.8 | 3.8 ± 4.8 | HA | 101 | 72.1 ± 27.2 | 50 | 57.8 ± 5.4 | 8 |
| Wu | 2014 | China | Asia | 55 ± 8.5 | 0/101 | 31.4 ± 7.8 | 3.8 ± 4.8 | HA | 101 | 72.1 ± 27.2 | 50 | 57.8 ± 5.4 | 8 |
| Zhang | 2015 | China | Asia | 53 ± 8.7 | 0/101 | 31.4 ± 7.8 | 3.8 ± 4.8 | HA | 101 | 72.1 ± 27.2 | 50 | 57.8 ± 5.4 | 8 |

$\text{AP} = \text{antipsychotics; } \text{CCMD} = \text{Chinese Classification of Mental Disorders; } \text{DSM} = \text{Diagnostic and Statistical Manual; } \text{F/M} = \text{females/males; } \text{HA} = \text{hydroxylamine method; } \text{NA} = \text{no data in the reference; } \text{SD} = \text{standard deviation.}$
**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\(^{\#1}\), yr (Mean ± SD) | Gender\(^{\#1}\), F/M | Genotyping Method | Sample Size, Case/Control | Case Genotypes, n (%) | Control Genotypes, n (%) | Case Alleles | Control Alleles | HWE, P\(^{\#2}\) | Quality Score |
|--------------|----------------|---------|---------------------|-------------------------------|-----------------------|---------------------|--------------------------|----------------------|--------------------------|--------------|----------------|----------------|---------------|
| Hori         | 2000           | Japan   | Asia                | 55.6 ± 9.1                    | 97/95                 | PCR                 | 192/141                  | 42 (21.9)           | 150 (78.1)              | 45 (11.7) | 339 (88.3) | 0.799          | 7             |
| Zhang        | 2002           | China   | Asia                | 55.3 ± 8.5                    | 0/101                 | PCR                 | 101/50                   | 33 (32.7)           | 68 (67.3)               | 33 (16.3) | 169 (83.7) | 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) | 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) | 0.781          | 8             |
| Zhang        | 2007           | Korea   | Asia                | 44.7 ± 9.7                    | 84/178                | PCR                 | 262/265                  | 49 (18.7)           | 213 (81.3)              | 54 (20.5) | 209 (79.5) | 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) | 0.063          | 9             |

\(^{\#1}\) The age and gender of patients.

\(^{\#2}\) 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\(^{\#1}\), yr (Mean ± SD) | Gender\(^{\#1}\), F/M | Genotyping Method | Sample Size, TD/Non-TD | TD Genotypes, n (%) | Non-TD Genotypes, n (%) | TD Alleles | Non-TD Alleles | HWE, P\(^{\#2}\) | Quality Score |
|--------------|----------------|---------|---------------------|-------------------------------|-----------------------|---------------------|------------------------|----------------------|--------------------------|--------------|----------------|----------------|---------------|
| Hori         | 2000           | Japan   | Asia                | 55.6 ± 9.1                    | 97/95                 | PCR                 | 39/153                 | 3 (7.7)              | 36 (92.3)               | 39 (25.5) | 114 (74.5) | 0.781          | 7             |
| Zhang        | 2002           | China   | Asia                | 55.3 ± 8.5                    | 0/101                 | PCR                 | 42/59                  | 12 (28.6)           | 30 (71.4)               | 21 (35.6) | 38 (64.4) | 0.181          | 8             |
| Zhang        | 2003           | China   | Asia                | 55.6 ± 8.8                    | 0/94                  | PCR                 | 94/52                  | 31 (33.0)           | 63 (67.0)               | 19 (36.5) | 33 (63.5) | 0.781          | 8             |
| Akyol        | 2005           | Turkey  | Europe              | 37.6 ± 10.8                   | 59/94                 | PCR                 | 23/130                 | 14 (60.9)           | 9 (39.1)                | 106 (81.5) | 24 (18.5) | 0.781          | 7             |
| Thelma       | 2007           | India   | Asia                | 32.0 ± 10.9                   | 135/164               | PCR                 | 88/211                 | 67 (76.1)           | 21 (23.8)               | 161 (76.3) | 24 (23.7) | 0.781          | 8             |
| Pae          | 2007           | Korea   | Asia                | 44.4 ± 9.7                    | 84/178                | PCR                 | 44/218                 | 12 (27.3)           | 32 (72.7)               | 37 (17.0) | 181 (83.0) | 0.781          | 6             |
| Kang         | 2008           | Korea   | Asia                | 45.2 ± 9.6                    | 99/110                | PCR                 | 87/126                 | 17 (20.5)           | 66 (79.5)               | 20 (15.9) | 106 (84.1) | 0.781          | 8             |
| Liu          | 2010           | China   | Asia                | 49.5 ± 11.1                   | 170/352               | PCR                 | 174/360                | 45 (25.6)           | 131 (74.4)              | 103 (29.8) | 245 (70.2) | 0.781          | 9             |
| Zai\(^{\#2}\) | 2010           | America | America             | 37.7 ± 10.1                   | 64/129                | PCR                 | 76/114                 | 52 (68.4)           | 24 (31.6)               | 90 (78.9) | 24 (21.1) | 0.781          | 10            |
| Zai\(^{\#2}\) | 2010           | America | America             | 32.5 ± 10.9                   | 9/21                  | PCR                 | 11/18                  | 7 (63.6)            | 4 (36.4)                | 11 (61.1) | 7 (38.9) | 0.781          | 8             |

\(^{\#1}\) The age and gender of patients.

\(^{\#2}\) The quality score was evaluated by the Cochrane’s Newcastle–Ottawa Scale evaluation standard for case–control study.

F/M = females/males; HWE = Hardy–Weinberg equilibrium; PCR = polymerase chain reaction; SD = standard deviation.
dataset to the pooled ORs. The results were consistent in all of the research models except the study by Pae et al\textsuperscript{17} for genotypes and the study by Zhang et al\textsuperscript{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: $P_{\text{Egger}} = 0.104$ and $P_{\text{Begg}} = 0.707$; alleles: $P_{\text{Egger}} = 0.469$ and $P_{\text{Begg}} = 0.707$) (Figure S4, http://links.lww.com/MD/A410).

**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: $P_{\text{Egger}} = 0.904$ and $P_{\text{Begg}} = 0.858$; alleles: $P_{\text{Egger}} = 0.770$ and $P_{\text{Begg}} = 0.721$) (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...
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.

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.

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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