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Brief report

Manganese superoxide dismutase (MnSOD: Ala–9Val) gene polymorphism may not be associated with schizophrenia and tardive dyskinesia

Chi-Un Pae [a,b,*], Tae-Suk Kim [c], Ashwin A. Patkar [b], Jung-Jin Kim [a], Chang-Uk Lee [a], Soo-Jung Lee [a], Tae-Youn Jun [c], Chul Lee [a], In-Ho Paik [a]

[a] *Department of Psychiatry, Kangnam St. Mary' Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea*
[b] *Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA*
[c] *Department of Psychiatry, St. Mary' Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea*

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Abstract

There has been increasing evidence that the alteration of antioxidant enzymes such as manganese superoxide dismutase (MnSOD) might be implicated in the development of schizophrenia and/or tardive dyskinesia (TD). This study investigated the association of a MnSOD gene (*MnSOD*) polymorphism (Ala–9Val) with schizophrenia as well as its involvement in TD. Patients with schizophrenia ($n=262$) and healthy controls ($n=263$) were enrolled in this study and genotyped by a polymerase chain reaction-based method. The distribution of the *MnSOD* genotypes and alleles was not significantly different between patients and controls. Logistic regression analysis also failed to reveal any association between *MnSOD* genotypes and TD. Taken together, these results suggest that the *MnSOD* polymorphism does not contribute to the development of schizophrenia and/or TD, at least in the Korean population.

Keywords: Schizophrenia; Tardive dyskinesia; Manganese superoxide dismutase; Polymorphism; Korean

1. Introduction

Alteration of the antioxidant system has been suggested to be associated with the pathogenesis of schizophrenia and also the development of tardive dyskinesia (TD) during antipsychotic treatment. Several oxidative stress parameters such as albumin, bilirubin and uric acid and total antioxidant plasma levels were reported to be associated with schizophrenia (Yao et al., 2001; Pae et al., 2004), and suggested to be involved in the intermediate or final common pathogenic processes of its development (Michel et al., 2004). Furthermore, antioxidant enzymes are involved in the generation of superoxide radicals, which are believed to exert a critical role in neurotoxicity (Hori et al., 2000), though not unequivocally (Mahadik and Mukherjee, 1996).

* Corresponding author. Department of Psychiatry, Kangnam St. Mary' Hospital, The Catholic University of Korea College of Medicine, 505 Banpo-Dong, Seocho-Gu, Seoul 137-701, South Korea and Department of Psychiatry and Behavioral Sciences, Duke University, Ben Franklin Blvd., Suite 700, Durham, NC 27704, USA. Tel.: +82 2 590 2780; fax: +82 2 536 8744.
E-mail addresses: pae@catholic.ac.kr, chiun.pae@duke.edu (C.-U. Pae).

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Superoxide radicals could also be associated with the pathophysiology of TD, through modifications of dopamine turnover, excitotoxic damage and loss of GABAergic neurons (Lohr et al., 2003). Recent controlled trials supported the hypothesis of a direct involvement of the failure of the antioxidant system in TD (Lohr and Caligiuri, 1996; Zhang et al., 2004). Another study demonstrated that free radical metabolism and the severity of TD were positively correlated (Zhang et al., 2003a).

Manganese superoxide dismutase (MnSOD) is an interesting intramitochondrial antioxidant enzyme that has a crucial role in the detoxification of superoxide radicals, linked to the prevention of the formation of toxic free radicals in the brain. It has been shown to be involved in the turnover of superoxide radicals (Yao et al., 1998; Zhang et al., 2003a,b; Dakhale et al., 2004; Michel et al., 2004), although some disagreement exists (Parikh et al., 2003; Ranjekar et al., 2003).

The MnSOD gene (*MnSOD*) mapped on chromosome 6q25, previously known as a candidate region for linkage with schizophrenia (Lindholm et al., 2001). Among known functional polymorphisms of *MnSOD*, the Ala–9Val polymorphism was extensively investigated for association with schizophrenia, producing conflicting results in different ethnic groups (Hori et al., 2000; Zhang et al., 2002; Akyol et al., 2005). Therefore, we carried out a case–control association study between the *MnSOD* polymorphism and schizophrenia/TD in the Korean population.

2. Methods

2.1. Subjects

Subjects comprised 262 inpatients with schizophrenia, and 263 voluntary controls. The diagnosis was based on the consensus between two board-certified psychiatrists (C.U.P.; C.U.L.), according to the DSM-IV criteria (American Psychiatric Association, 1994) along with the structured Clinical Interview, DSM-IV Axis I Disorders-Clinician Version (SCID-I-CV, First et al., 1997). The Positive and Negative Syndrome Scale (PANSS) was obtained at the time of hospitalization (Kay et al., 1988). Family history, age of onset and other clinical variables were collected when possible. The evaluation of TD was made by using the TD criteria of Schooler–Kane (Schooler and Kane, 1982) and the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976).

The voluntary controls were recruited from the personnel of The Catholic University of Korea College of Medicine and Kangnam St. Mary's Hospital. They were administered a direct semi-structured interview (by C.U.P.; C.U.L.) to exclude individuals with a current or past history or familial history of psychiatric illnesses.

All subjects were biologically unrelated native Koreans residing in Korea. They all were given information about the study, and written informed consent was obtained. The institutional review board of Kangnam St. Mary's Hospital approved this study.

2.2. Genotyping

The DNA was extracted from whole blood, using the standard method, and *MnSOD* genotyping was performed by a polymerase chain reaction (PCR), under modified conditions, according to a previously reported method (Zhang et al., 2002). Briefly, the genotyping was carried out in a Perkin Elmer 9600 thermocycler (Foster City, CA), using the sense and antisense *MnSOD* primers: 5′-AGC CCA GCC TGC GTA GAC-3′ and 5′-TAC TTC TCC TCG GTG ACG-3′, respectively. After an initial denaturation step at 94 °C for 6 min, the samples were processed through 35 cycles at 95 °C for 30 s, 58 °C for 30 s, and 72 °C for 45 s. A final extension at 72 °C for 10 min was then performed. The PCR product (246 bp) was digested with 5 units of *Bsa*W, and then underwent electrophoresis in a 3.5% agarose gel, with ethidium bromide, giving fragments of 246 bp for the allele (Ala-9) or 164 bp and 82 bp for the allele (Val-9).

2.3. Statistics

Comparisons of the *MnSOD* genotype and allele distribution between patients and controls were performed by Fisher's exact test. Continuous variables were analyzed by the Mann–Whitney test, as the Kolmogorov–Smirnov test showed a skew of the data from normality. Comparison of the *MnSOD* genotype between patients according to presence or absence of TD was performed by Fisher's exact test. A logistic regression analysis was also performed to adjust potential confounding factors for TD using TD as a dependent variable and genotype, duration of antipsychotic treatment, current dose of antipsychotic (in chlorpromazine equivalents), age and sex as independent variables. *P* values less than 0.05 were considered significant. The 95% confidence interval (CI) was provided where appropriate. All statistical tests were performed using SPSS *v*10.0 software (SPSS Inc., Chicago, IL).

The power of our sample to detect differences between variants was calculated, using a two-tailed alpha value of