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Catechol-*O*-methyltransferase Val158Met polymorphism in relation to aggressive schizophrenia in a Korean population

Youl-Ri Kim [a], Jeong Hyun Kim [b], Se Joo Kim [c], Dongeun Lee [d], Sung Kil Min [c,*]

[a] *Department of Neuropsychiatry, Seoul-Paik Hospital, Inje University, Seoul, South Korea*
[b] *Indang Institute of Molecular Biology, Inje University, Seoul, South Korea*
[c] *Department of Psychiatry and Institute of Behavioural Science in Medicine, Yonsei University College of Medicine, Seoul, South Korea*
[d] *Chookryoung Evangelical Hospital, Kyunggi, South Korea*

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Abstract

We examined the association between the Catechol-*O*-methyltransferase (COMT) Val158Met polymorphism and aggressive schizophrenia. The sample included 61 aggressive schizophrenic patients as well as 104 non-aggressive patients from psychiatric hospitals and 415 healthy volunteers in South Korea. In the case–control comparisons, there was no significant association between the aggressive schizophrenic patients and the COMT Val158Met polymorphism. Looking only at the subgroup of aggressive schizophrenic patients, however, we found a dose-dependent relationship between the Met allele and verbal aggression. In this subgroup, the Met carriers showed a higher verbal aggression score than those with the Val/Val homozygote. These findings support the hypothesized moderating role of the COMT gene in the aggressive behaviour in some schizophrenic patients, though they do not support the existence of a direct association between the COMT Val158Met polymorphism and aggressive schizophrenia case status in the Korean population.

1. Introduction

Aggressive behaviour is frequently reported in patients with schizophrenia, where its prevalence is estimated to be 2 to 10 times that of the general population (Hafner and Boker, 1982; Wessely, 1997), and between 18% and 46% of hospitalized schizophrenia patients may manifest overt violence toward others (Craig, 1982; Krakowski et al., 1986). In a previous

* Corresponding author. Department of Psychiatry and Institute of Behavioural Science in Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul, 120-752, South Korea. Tel.: +82 2 2228 1623; fax: +82 2 313 0891.
E-mail address: skmin518@yuhs.ac (S.K. Min).

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study, our group suggested that the aggressive behaviours were not directly related to psychotic symptoms in patients with schizophrenia based on the results obtained using a structured equation model (Song and Min, in press). The causes of aggressive behaviour in schizophrenia are complex and multifactorial, but the data suggest that genetic factors may play a substantial role (Deater-Deckard and Plomin, 1999; Eley et al., 1999).

Dopaminergic and noradrenalinergic systems are known to be necessary for the appropriate expression of aggressive behaviour (Nelson and Trainor, 2007). Catechol-*O*-methyltransferase (COMT) is an enzyme that plays an important role in the metabolism of catecholamine. There is a common Val158Met functional polymorphism where a methionine (Met) substituted for a valine (Val) leads to a four-fold reduction in COMT enzyme activity (Lotta et al., 1995). The results of previous studies on the association between COMT and aggressive behaviour in schizophrenia have been reported to have some inconsistencies (Jones et al., 2001; Koen et al., 2004; Liou et al., 2001; Zammit et al., 2004), whereas some studies found the Met allele to be associated with aggression in schizophrenia (Han et al., 2004; Kotler et al., 1999; Lachman et al., 1998; Strous et al., 2003). Methodological issues, especially association testing, may have contributed to these discrepancies. Four of the previous studies (Lachman et al., 1998; Liou et al., 2001; Koen et al., 2004; Kotler et al., 1999) were case–control phenotype comparison studies conducted using clinical assessment and patient history for primary group stratification, while others measured aggressive behaviour as continuous traits using assessment tools.

In the present study, the first aim was to investigate whether the COMT Val158Met polymorphism was associated with the aggressive schizophrenic patients by using a case–control design. Another related objective was to explore the association between violent behaviour and the COMT Val158-Met allele in aggressive schizophrenic patients by using an assessment tool.

2. Materials and methods

2.1. Study population

The sample included 61 aggressive schizophrenic patients (39 men, 22 women) as well as 104 non-aggressive patients (57 men, 47 women) and 415 healthy volunteers (248 men, 167 women), recruited from the Korean population. The DSM-IV diagnosed schizophrenic patients were recruited to the study between Jan 2004 and Sep 2007 from the inpatients population in Severance hospital, Seoul and the Chookryoung Evangelical Mental Hospital, Kyunggi, South Korea. Patients were selected for the aggressive group according to strict criteria for identifying subjects with both a current and past history of aggressive behaviour. Patients were included in the aggressive group if they had significant episodes of violence resulting in repeated confinement at least twice per week in the 2 weeks prior to study inclusion and a past history of aggressive behaviour defined as a documented history of at least two (and frequently many more) serious assaults against others. Non-aggressive patients had no history of either assaultive or threatening behaviour. All of the patients were assessed within 2 weeks after admission and underwent a psychiatric interview by two independent clinicians based on all available clinical information, including the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) interview, examination of case records and information from relatives and mental health professionals. Forty-eight aggressive patients and 87 non-aggressive patients completed the Modified Overt Aggression Scale (MOAS) (Kay et al., 1988). Fifty-three patients in the aggressive subgroup and 82 patients in the non-aggressive subgroup were taking neuroleptics at the time of the study. When the doses of neuroleptics were converted into chlorpromazine equivalent doses (Davis and Chen, 2004), there was no significant difference in the dose of neuroleptics between the aggressive and non-aggressive patients. A subgroup consisting of 30% of the patients within the schizophrenia sample (13 aggressive patients, 32 non-aggressive patients) also completed the assessment of symptoms using PANSS as part of another ongoing study in our group. There was no significant difference in the age, MOAS or illness variables (onset, duration, hospitalization and dose of neuroleptics) between the patients who completed PANSS and those who did not (data available on request). The exclusion criteria were a history of neurological disorders, substance abuse in the previous 3 months and an estimated IQ of less than 70.

Healthy unrelated Korean volunteers, with a mean age of 24.5 years [S.D. 5.7, range 19–57] were recruited from among the residents of Seoul by advertisement. They had no reported current or past history of psychiatric disorders, including significant violent episodes. The Institutional Review Boards of both Severance Hospital and Chookryoung Evangelical Mental Hospital approved the study and written informed consent was obtained from all participants or their legal guardians after the nature of the study was fully explained to them.

2.2. Modified Overt Aggression Scale

This is an objective rating scale to assess the nature and prevalence of aggression. The MOAS is a revision of Yudofsky et al.'s (1986) method that assesses the same four categories of aggression in psychiatric patients: Verbal Aggression, Physical Aggression against Objects, Physical Aggression against Self, and Physical Aggression against Others. The MOAS was upgraded from the behavioural checklist (nominal scale) of Yudofski et al. to a five-point rating system (ordinal or interval scale) that evaluates increased levels of severity.

2.3. Genotyping

Samples were obtained to establish the COMT Val158Met genotype distribution from all participants. Genotyping was performed blind to the history of aggressive behaviour. DNA was extracted from blood leukocytes by using a commercial DNA extraction kit (ABI, Foster City, CA, USA). Genotyping of the COMT Val158Met variant was carried out with a polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) analysis by using the primers 5′-CTCATCA-CCATCGAGATCAA-3′ and 5′-CCAGGTCTGAAACGGGTCA-3′, as previously described (Rotondo et al., 2002). The PCR products digested with *Nla*III were electrophoresed to distinguish between the Val and Met alleles.