No Association of the G1287A Polymorphism in the Norepinephrine Transporter Gene and Susceptibility to Major Depressive Disorder in a Japanese Population

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Norepinephrine transporters in the central nervous system have a major impact on the symptomatology in major depressive disorder (MDD), and genetic polymorphisms of norepinephrine transporter (NET) may have a possibility to be involved in susceptibility to MDD. We investigated the association of the G1287A (rs5569) polymorphism of the NET gene and susceptibility to MDD by comparing 145 major depressive patients with 164 healthy individuals first in a Japanese population. The genotype frequencies in depressed patients and health volunteers of the NET G1287A polymorphism were 52.4% (G/G), 39.3% (G/A) and 8.3% (A/A) in depressed patients, 61.6% (G/G), 29.9% (G/A allele) and 8.5% (A/A) in healthy volunteers, respectively. The allele frequencies in depressed patients and health volunteers of the NET G1287A polymorphism were 72.1% (G allele) and 27.9% (A allele) in depressed patients, 76.5% (G allele) and 23.5% (A allele) in healthy volunteers, respectively. The genotype distribution and allele frequencies were not significantly different between major depressive patients and healthy volunteers. NET G1287A polymorphism appears not to be an important factor in susceptibility to MDD in a Japanese population.

Key words norepinephrine transporter; G1287A polymorphism; susceptibility to depression; PCR-restriction fragment length polymorphism

Norepinephrine (NE) and serotonin have been postulated to play an important role in the pathophysiology and subsequent treatment of depression. There is a considerable amount of evidence to support a pivotal role for norepinephrine in the brain, both as a neurotransmitter and as a modulator of other central nervous system (CNS) neurotransmitters, and CNS norepinephrinergic neurotransmission appears to have a major impact on the symptomatology of major depressive disorder (MDD). The norepinephrine transporter (NET) reaccumulates and recycles released norepinephrine into presynaptic terminals, and blockade of NET has been reported to be concerned with efficacy of tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs). These findings suggest that the NET gene polymorphisms may have a possibility to be involved in susceptibility to MDD as well as in individual difference of antidepressant response. The authors reported that the C/C genotype of the NET T-182C polymorphism was associated with lesser susceptibility to MDD. The NET T-182C polymorphism may be in part related to the pathophysiology of major depressive disorder in a Japanese population.

Another NET gene polymorphism of G1287A (rs5569) in exon 9 has been reported and its implication in several psychiatric disorders has been investigated in Caucasian populations. However, its involvement in susceptibility to MDD has not yet investigated in Oriental populations. In the present study, the authors investigated whether the NET G1287A polymorphism is associated with the susceptibility to MDD first in a Japanese population.

MATERIALS AND METHODS

Subjects This study included 164 healthy volunteers (101 male, 63 female) and 145 patients with major depressive disorder (55 male, 90 female). The mean age (± S.D.) of the major depressive patients was 51.6±12.4 years and that of healthy volunteers was 55.2±16.4 years. Japanese patients who fulfilled the DSM-IV diagnosis of major depressive disorder and who exhibited Montgomery and Asberg Depression Rating Scale (MADRS) scores of ≥21 were included in this study. Patients with other Axis I or Axis II disorders were excluded by careful clinical interview, and those with severe medical disorders were also excluded. Healthy nonrelated subjects were screened with the use of a questionnaire and subjects without any history of psychiatric disorders and previous psychiatric treatment were included in this study. This study was approved by the ethics committee of Akita University School of Medicine, and all patients and healthy volunteers provided a written informed consent.

Method of Genotyping Leukocyte genomic DNA was extracted directly from the blood specimen using a QIAamp blood Mini Kit (QIAGEN, Tokyo, Japan). The NET G1287A polymorphism was determined by PCR restriction fragment length polymorphism (PCR-RFLP) as reported by Jonsson et al. Briefly, samples (20 μl) were of a PCR mixture containing 100 ng of genomic DNA template, 2.0 mM MgCl₂, each 0.5 μmol of forward primer (5’-TTC AGG GAG ACC CTA ATT CC-3’) and reverse primer (5’-TTG ACT TTA TTG AAA TGC GGC-3’), 200 μM of dNTP mixture and 1.25 units of HotStar Taq DNA polymerase (QIAGEN, Tokyo, Japan). Amplification was performed by GeneAmp PCR sys-

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The relationship of G/G genotype and the resistance to MDD may be expected. This may be proved by clinical study using increased number of subjects.

The ethnic difference in NET T-182C polymorphism and the susceptibility to MDD has been reported. The C/C genotype was associated with lesser susceptibility to MDD in Japanese population.6) The T/T genotype was associated with the lesser susceptibility to MDD in Korean population.17) There is no association between any genotype and MDD in Caucasian populations14) and Han Chinese.15) As for NET G1287A polymorphism, the A allele frequency in Japanese healthy volunteers (23.5%) reported in this study was lower than that in previously reported Caucasian (33.1—33.5%),14) and Han Chinese (35.7%) populations.15) Although the large scale study should be done for confirmation, the A allele frequency of NET G1287A polymorphism may account for the ethnic difference in the susceptibility to MDD as well as NET T-182C polymorphism.

Stober et al. reported that the NET G1287A polymorphism was a silent mutation.18) The negative findings of our own and previous studies might be explained by the synonymity of the NET G1287A polymorphism. However, Jonsson et al. reported that this polymorphism was associated with the cerebrospinal fluid (CSF) concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major norepinephrine metabolite.12) They reported that the CSF MHPG concentrations were higher in the G/G genotype than in the G/A and A/A genotypes in healthy volunteers. Hirose et al. reported that the urinary concentration of D-MHPG in depressive patients was 1.3 times higher than that in healthy volunteers.19) We have reported that the A/A genotype is associated with a slower response of milnacipran than G/A genotype in Japanese major depressed patients.20) Kim et al. reported that G/G genotype in this polymorphism is associated with better response to the norepinephrine reuptake inhibitors (NRIs) than to selective serotonin reuptake inhibitors (SSRIs).21) From these observations, NET G1287A polymorphism may also be useful for predicting the response to NET-directed antidepressant.

In conclusion, we did not find the positive correlation between the NET G1287A polymorphism and the susceptibility to MDD in Japanese population. However we got the positive but not significant findings in this study. For re-evaluation of NET G1287A polymorphism as a predictive marker for the susceptibility to MDD in Japanese population and other ethnic groups, we are planning to perform the large-scale study using increased number of subjects.

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