Brief Research Communication

A Missense Polymorphism (S205L) of the Low-Affinity Neurotrophin Receptor p75NTR Gene Is Associated With Depressive Disorder and Attempted Suicide

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Several lines of evidence have implicated that neurotrophins play an important role in the pathophysiology of mood disorders. This study examined whether a common missense polymorphism (S205L) of a gene encoding the p75NTR, the low-affinity receptor for neurotrophins, is associated with depressive disorder in a Japanese sample of 164 patients and the same number of controls matched for age and sex. There were significant differences in the genotype distribution and allele frequency between the cases and controls. The minor allele (L205) was significantly decreased in the patients than in the controls (P < 0.05, odds ratio 0.54, 95% CI 0.31–0.94), suggesting that this allele may have a protective effect against the development of major depression. Furthermore, this association was more strongly observed in the patients with a history of attempted suicide than those without such a history. Our results suggest that the S205L polymorphism of the p75NTR gene is involved in the pathogenesis of depressive disorder and suicidal behavior. © 2004 Wiley-Liss, Inc.

KEY WORDS: depression; p75NTR; single nucleotide polymorphism (SNP); suicide; susceptibility

There is growing evidence for the involvement of neurotrophic factors in the pathogenesis of mood disorders and in the mechanism of action of therapeutic agents such as mood stabilizers and antidepressants (reviewed by Duman 2002). Chronic electroconvulsive seizure or antidepressant drug treatments increase mRNA of brain-derived neurotrophic factor (BDNF), a member of neurotrophin family, and its receptor trkB [Hibuyka et al., 1995]. Lithium may also exert its neuroprotective effect through enhancing expression of BDNF and trkB [Hashimoto et al., 2002]. Furthermore, recent studies suggested the possible involvement of a missense polymorphism (V66M) of the BDNF gene giving susceptibility to bipolar disorder [Neves-Pereira et al., 2002; Sklar et al., 2002], although contradictory negative results have also been reported [Nakata et al., 2003]. In this context, the gene encoding the low-affinity receptor for neurotrophin family, p75NTR (alternatively referred to as nerve growth factor receptor (NGFR) or tumor necrosis factor receptor superfamily, member 16 (TNFRSF16)), is a good candidate for association analysis with mood disorders. To our knowledge, however, there is no study examining the possible association between the p75NTR gene and mood disorders. The p75NTR maps to chromosome 17q21-q22 [Huebner et al., 1986] and consisted of six exons and five introns [Sehgal et al., 1988]. We searched for polymorphisms in the p75NTR gene in silico and detected a common single nucleotide substitution (C727T; NCBI SNP ID: rs2072446) [Haga et al., 2002] in exon 4 giving rise to an amino acid change of serine to leucine at codon 205 (S205L) (amino acid numbering is according to NCBI protein data base accession NP_002498). In our search there was no other missense polymorphism that has been well validated in the p75NTR gene. Since this polymorphism may alter functions of the p75NTR; we performed an association analysis between this polymorphism and major depressive disorder.

Subjects were 164 patients (59 males, mean age of 49.5 years (SD 12.7)) with major depressive disorder and 164 healthy controls matched for sex and age (59 males, 47.4 years (SD 9.5)). All the subjects were biologically unrelated Japanese and recruited from the same geographical area (Western part of Tokyo Metropolitan). Diagnosis was made for each patient by a single psychiatrist (TM) according to American Psychiatric Association [1994] criteria on the basis of unstructured interviews and information from medical records. Among the 164 patients, 96 individuals (59%) had recurrent depressive episodes and the remainder had single episode. Eighty subjects (49%) had a history of admission to a psychiatric hospital and 46 (28%) had a history of attempted suicide. The mean age of onset was 42.2 years (SD 12.7). The controls were healthy volunteers recruited from hospital staffs. They were interviewed and those individuals who had current or past history of psychiatric treatment were not included in the study.

The study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). After description of the study, written informed consent was obtained from every subject. The study protocol was approved by institutional ethical committees of Showa University School of Medicine and National Center of Neurology and Psychiatry, Japan.

Venous blood was drawn from the subjects and genomic DNA was extracted from whole blood according to the standard procedures. Genotyping for the S205L polymorphism was performed with polymerase chain reaction (PCR) amplification.
encompassing the polymorphic site with primers of 5'-gtctaaagggagtggggaag-3' (forward) and 5'-tcagteaagtg-cacaccaagtet-3' (reverse). Thermal cycling was performed with an initial denaturing stage at 95 °C for 10 min, 35 cycles of 95 °C for 30 sec, 55 °C for 20 sec, and 72 °C for 30 sec, followed by the final extension at 72 °C for 3 min. The polymorphic site gives rise to a restriction site of enzymes BanII, Bsp1286I, and EcoT38I. In the present study, the 386 base pair (bp) PCR products were cut with BanII into 289 and 97 bp for the S205 allele, but not for the L205 allele. Digested PCR products were visualized by 4% agarose gel electrophoresis with ethidium bromide staining. Genotype data were read blind to the case-control status.

Genotype distributions and allele frequencies of the S205L polymorphism among the patients and controls are shown in Table I. The genotype distributions for the two groups were both in Hardy–Weinberg equilibrium (data not shown). Since there were only two individuals homozygous for the minor allele (L205), individuals homozygous for this allele and those heterozygous were combined when we compared the genotype distribution between the patients and controls. There was a significant difference in the frequency of individuals carrying the L205 allele between the cases and controls ($\chi^2 = 4.2$, df = 1, $P < 0.05$, odds ratio 0.54, 95% CI 0.30–0.98). When allele frequencies were compared, the L205 allele was significantly reduced in the patients than in the controls ($\chi^2 = 4.8$, df = 1, $P < 0.05$, odds ratio 0.54, 95% CI 0.31–0.94).

Then we examined whether the polymorphism is related to suicide behavior. When the patients were dichotomized into two groups by the presence or absence of a history of attempted suicide, the frequency of the L205 allele was further decreased in individuals with a history of attempted suicide, compared to those without such a history (Table I). When the allele frequency was compared between patients with a history of attempted suicide (N = 46) and controls, the difference was almost significant ($\chi^2 = 3.9$, df = 1, $P < 0.05$, odds ratio 0.36, 95% CI 0.12–1.03). However, there was no significant difference in the allele frequency between the non-suicidal patients (N = 118) and controls ($\chi^2 = 2.6$, df = 1, $P = 0.11$, odds ratio 0.61, 95% CI 0.33–1.11). This disappearance of a significant difference in the allele frequency in spite of the larger number of subjects in the non-suicidal group, compared to the suicidal group, indicates a possibility that the effect of the S205L polymorphism of the p75NTR gene is more pronounced in depressive disorder with suicidal behavior. The observed frequency for the minor allele (L205) in our control group, indicates a possibility that the effect of the S205L polymorphism is related to suicide behavior. Alternatively, the major allele (S205) may provide clues to production of new treatment of depression and possibly, suicidal behavior. Additionally, the major allele (S205) may have a risk-increasing effect on the development of such psychiatric conditions. However, there remains a possibility that other polymorphisms, which are in linkage disequilibrium to the S205L polymorphism, are truly responsible for protective effect or giving susceptibility.

The p75NTR gene encodes a 427 amino acid protein containing a 28 amino acid signal peptide, an extracellular domain containing four 40 amino acid repeats with six cysteine residues at conserved positions followed by a serine/threonine-rich region, a single transmembrane domain, and a 155 amino acid cytoplasmic domain [Johnson et al., 1986]. The p75NTR binds all members of the neurotrophin family (nerve growth factor, BDNF, neurotrophin-3, and neurotrophin 4/5) in mammals [Rodriguez-Tebar et al., 1993]. Although main function of the p75NTR was thought to modulate the affinity and activity of tyrosine kinases (trKA, trkB, and trkC) that promote neuronal survival [Chao and Hempstead, 1995], the p75NTR has also been shown to play an important role in inducing apoptotic cell death mediated by a “death domain” in the cytoplasmic region, a domain common to other members of TNF receptor superfamily [Rabizadeh et al., 1993]. The S205L missense polymorphism changes one of the serine residues in the serine/threonine-rich region to a leucine residue. Although physiological roles of the serine/threonine-rich region are still unclear, this region possesses extensive O-linked glycosylation, suggesting a potential role in ligand binding and signaling [Chapman et al., 1996]. Furthermore, the p75NTR is heavily phosphorylated on serine residues by a protein kinase that has not been definitely identified [Grob et al., 1985; Taniuchi et al., 1986]. Thus it is likely that the S205L polymorphism, which substitutes serine residue (polo amino acid) with leucine (non-polar), alters the functions of p75NTR.

A limitation in the present study might be that the obtained evidence for an association was weak (P-values of 0.05 level). Replication studies in larger sample sizes are clearly required. If our results are replicated in other samples, experiments elucidating the possible effects of the S205L amino acid substitution on the p75NTR protein function may serve to advance our understanding of the molecular mechanism of depression and may provide clues to production of new treatment of depression and suicide behavior.

**REFERENCES**


