Evaluating Associations between 5-HTTLPR Polymorphism and Alzheimer’s Disease for Korean Patients

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\section*{Introduction}
There has been growing literature that the serotonin (5-hydroxytryptamine, 5-HT) system is important in the regulation of memory and thus might be associated with Alzheimer’s disease (AD) \cite{1, 2}. The 5-HT transporter (5-HTT) is central to the control of brain serotonin neurotransmission by regulating the magnitude and duration of the serotonergic response \cite{3}. There is a bi-allelic polymorphism in the 5-HTT gene linked polymorphic region (5-HTTLPR): the long (\textit{l}) and short (\textit{s}) alleles. The \textit{s} allele reduces the transcriptional activity of the 5-HTT gene promoter resulting in decreased 5-HTT expression \cite{4}, and therefore it can be reasonably hypothesized to be a risk factor for AD. However, studies on the association between the \textit{s} allele and AD have failed to demonstrate consistent results. Some reported a significant association \cite{5-7}, while others found no evidence to support such a generalization \cite{8-10}. The results of the previous studies have shown a particular tendency that studies with Caucasian populations reported positive findings, while most studies with Asians reported negative ones.
The 5-HT system has also been suggested to be responsible for a significant portion of the behavioural aspects of AD. The hypothesis is that the higher transcriptional activity of the l allele may lead to a depletion of extraneuronal 5-HT and might contribute to the risk of behavioural symptoms of AD [11, 12]. Recently, two studies reported that the l allele was significantly associated with psychotic symptoms and aggressive behaviour in AD [13, 14].

The results of a genetic association study could be varied according to the different ethnic backgrounds. Furthermore there has been no previous Korean study in these respects. Therefore the authors aimed: (i) to investigate the association between the 5-HTTLPR polymorphism and AD, and (ii) to investigate the associations between the 5-HTTLPR polymorphism and the delusional and aggressive symptoms of AD in Korean samples.

**Materials and Methods**

**Subjects**
A total of 65 patients with AD aged 65 or over were recruited from the dementia clinic of Inje University Paik Hospital from 2002 to 2003. The diagnosis of AD was determined upon review at a consensus conference and based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, for dementia of the Alzheimer type [15] and the guidelines of the National Institute of Neurological and Communicative Disorders and the Alzheimer’s Disease and Related Disorders Association for probable AD [16].

A cohort of 43 healthy control subjects were chosen from those attending a school for old people at a community center, trying to match them to the patients by age and gender. ‘Healthy’ was defined as follows: a score of 25 or better on the Korean Mini Mental State Examination (MMSE) [17]; no personal or familial history of neuropsychiatric diseases; no definite focal neurological symptoms, and determined to be non-demented by clinical assessment. Descriptive data of the subjects are summarized in table 1. Prior to investigation, the nature and purpose of the study were explained, and written informed consent to participate was obtained from the patient, if possible, and was required from the caregivers. The study was approved by the appropriate research ethics committee.

**Evaluation of Delusional or Aggressive Symptoms**
Patients with AD were evaluated by the Korean version of the Behavioural Pathology in Alzheimer’s Disease Rating Scale (BEHAVE-AD) [18] within 2 days after the initial assessment. Delusional or aggressive patients were defined by the presence of those symptoms measured by the subscales on paranoid and delusional ideation and aggressiveness, respectively, of the BEHAVE-AD.

**5-HTTLPR Genotyping**
Genotyping was performed using previously described methods [19].

**Statistical Analyses**
Comparisons of descriptive data between AD patients and healthy controls were carried out by t tests or χ² tests. Differences in genotypes and allele frequencies between AD patients and healthy controls, and between subgroups with and without delusional or aggressive symptoms, were compared by χ² tests or Fisher’s exact tests. Statistical analyses were carried out using SPSS 10.0 software.

**Results**

**5-HTTLPR Polymorphism and AD**
Data on 5-HTTLPR polymorphism in patients with AD and healthy controls are displayed in table 2. There were no significant differences in 5-HTTLPR genotypes and allele frequencies between patients with AD and healthy controls.

**5-HTTLPR Polymorphism and Delusional or Aggressive Symptoms of AD**
Delusional and aggressive symptoms were present in 43 and 45 patients with AD, respectively. No significant differences were found in age, gender and scores on MMSE according to the presence/absence of these symptoms (all p > 0.3). Data on 5-HTTLPR polymorphism according...
Discussion

The principal findings of the present study were that the 5-HTTLPR polymorphism was neither associated with AD nor with delusional or aggressive symptoms of AD. A striking feature of research on the association between 5-HTTLPR polymorphism and AD was the conflicting findings according to the sampled populations. Studies conducted in England [5], Brazil [6] and Germany [7] reported significant associations, while others from Japan [8], Germany [9] and China [10] found no associations. Two of the 3 studies reporting the negative findings were based on oriental populations, which was in keeping with the result of the present study with Koreans. These results suggested that the association between 5-HTTLPR polymorphism and AD might vary according to the different ethnicities. The s allelic frequency in this study sample (73–75%) was similar to the results of other studies with Asian populations (72–80%) [8, 10], but it was much higher than those from the studies with Caucasian populations (40–50%) [5–7]. If the s allele is a risk factor for AD, the prevalence of AD should be higher in Asian populations. However, epidemiological studies have failed to find results supporting this issue [20]. Another possibility is that phenotypic expression of the 5-HTTLPR polymorphism might be varied according to ethnic differences. Responsiveness to selective serotonin reuptake inhibitors in depressive patients was more powerful in those with the l allele in Caucasians [21], while it was better in those with the s allele in Asians [22].

We found no association between the 5-HTTLPR polymorphism and delusional or aggressive symptoms of AD, which conflicted with the previous 2 studies reporting significant associations [13, 14]. If the l allele is truly associated with delusional or aggressive symptoms of AD, the lower frequency of the l allele in this study sample might obscure the associations between genotypes and those symptoms. Another issue to consider is that of bias. The relatively small sample size of this study could raise the possibility of type II error.

The expression of the 5-HTTLPR polymorphism might show phenotypic variability under the particular conditions such as different ethnicity, having depression and dementia or not. In the future, it would be of interest to study these issues controlling for such conditions.

Table 3. 5-HTTLPR genotypes and allele frequencies according to presence/absence of delusion or aggression in patients with AD

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Delusion</th>
<th></th>
<th>Aggression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>presence</td>
<td>absence</td>
<td>p</td>
<td>presence</td>
</tr>
<tr>
<td>s/s</td>
<td>23 (53%)</td>
<td>12 (55%)</td>
<td>0.997</td>
<td>27 (60%)</td>
</tr>
<tr>
<td>s/l</td>
<td>18 (42%)</td>
<td>9 (41%)</td>
<td>0.888</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>l/l</td>
<td>2 (5%)</td>
<td>1 (4%)</td>
<td>0.888</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allele frequency</th>
<th>Delusion</th>
<th></th>
<th>Aggression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>s</td>
<td>64 (74%)</td>
<td>33 (75%)</td>
<td>0.888</td>
<td>70 (78%)</td>
</tr>
<tr>
<td>l</td>
<td>22 (26%)</td>
<td>11 (25%)</td>
<td>0.888</td>
<td>20 (22%)</td>
</tr>
</tbody>
</table>
References


