Association between Obsessive-Compulsive Disorder and Dopamine Transporter Gene Polymorphism

Sang Woo Yoo, M.D.,1 Se Joo Kim, M.D.,2 Chan-Hyung Kim, M.D.2

1YOO & KIM Mental Health Clinic, Seoul, Korea, 2Department of Psychiatry, Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Shinchon-Dong, Seoul, Korea

Abstract

Objective: The definite causes of obsessive-compulsive disorder (OCD) are still unknown. Recently, evidence has been growing that OCD has a specific neurochemical and neuroanatomical basis. The most prevailing biological mechanism of OCD is the serotonin hypothesis. However, in addition to this main hypothesis suggesting serotonin abnormalities, many researchers have proposed that dopamine might also participate in the pathophysiology of OCD. Therefore, the aim of this study was to investigate the association between dopamine transporter (DAT1) polymorphisms and OCD.

Methods: 115 OCD patients and 160 normal controls participated in this study. Genomic DNA was extracted from their blood, and a comparison of the genotypes and allele frequencies of the DAT1 polymorphism between the OCD group and control group was made. The genotypes of DAT1 are classified into 10/10-repeats and non-10/10 repeats.

Results: In this case-control study, there were no statistical differences in the observed genotype distributions or allele frequencies of the DAT1 polymorphism between these two groups. Moreover, there were no significant differences in the total Y-BOCS, CGI-OC, GAF or total HDRS scores between the patients with 10/10-repeat and non-10/10 repeat genotypes. Conclusion: In conclusion, DAT1 polymorphisms do not appear to be associated with the development of OCD, the severity of OC or depressive symptoms, or the general functioning.

Key words: Dopamine transporter, Polymorphism, Obsessive-compulsive disorder.

Introduction

Obsessive-compulsive disorder (OCD) is a relatively common condition, characterized by persistent, unwanted thoughts and ritualistic behavior. The causes of this disorder are still unclear, but there is growing evidence that OCD has some specific neurochemical and neuroanatomical bases. Although the mode of transmission is also unknown, a great deal of evidence from familial, twin, and segregation studies support the existence of a genetic component in the etiology of OCD.1

To date, the most prevailing theory concerning the mechanism of OCD is the serotonin hypothesis.2 However, about 40% of OCD patients do not respond to serotonin reuptake inhibitors (SRIs), and some patients show no convincing functional abnormality related to serotonin.3 Furthermore, the functioning of the serotonin system varies from individual to individ-
ual and is interrelated with other neurotransmitters or neuronal circuits. Therefore, in addition to the main hypothesis suggesting serotonin abnormalities, some authors have proposed that dopamine might also participate in the pathophysiology of OCD. When high concentrations of dopamine-related drugs such as amphetamine and bromocriptine were administered in animal studies, stereotypic behaviors similar to the obsessive behaviors found in OCD patients were observed. The administration of dopamine receptor inhibiting drugs in combination with an SRI resulted in a reduction in the obsessive symptoms in OCD patients who showed resistance to treatment with an SRI alone. There have also been some reports of the emergence of obsessive-compulsive (OC) symptoms during treatment with clozapine, a dopamine receptor D4 (DRD4) antagonist. The above evidence obtained from neuroanatomical and pharmacological data suggests that the dopaminergic neurotransmitter system may also be implicated in mediating OCD.

The dopamine transporter (DAT1) is one of the candidate genes for various behavioral conditions including OCD. DAT1 plays a pivotal role in terminating dopaminergic neurotransmission. However, very few studies of the association between OCD and DAT1 have been conducted. To our knowledge, only two such studies have been reported to date and in both cases the results were negative.

Therefore, the aim of this study was to investigate the association between OCD and DAT1 polymorphisms.

### Methods and Materials

#### Subjects

One hundred and fifteen unrelated patients with OCD were recruited from Hallym University Sacred Heart hospital and Youngdong Severance hospital OCD clinic over a period of 24 months. All of the OCD patients met the DSM-IV criteria for OCD. Those subjects with concomitant major depression (without psychotic features) were included in the study only if their OC symptoms were the most prominent and the onset of OCD antedated the onset of depression. Subjects were excluded if they presented with a movement disorder other than a tic disorder, any psychotic symptoms, mental retardation, alcohol or other substance abuse within the last 6 months, or a history of psychosurgery, encephalitis, or significant head trauma. Of the 115 subjects, 37 were taking medications (mainly SSRIs and low-dose benzodiazepines) and/or were undergoing exposure/response-prevention behavioral therapy. None of the remaining 78 patients had received any treatment for their OCD symptoms, at least within the previous 6 months.

One hundred and sixty unrelated control individuals were recruited from among the nurses, students and volunteers at Hallym University Sacred Heart hospital and Anyang community mental health center. The control individuals had no history of anxiety, mood or psychotic disorder. All of the subjects were of Korean descent based on their native language and reported descent. The protocol was approved by the ethics committees of Hallym University Sacred Heart hospital and Youngdong Severance hospital, and all of the subjects gave their written, informed consent. The obsessive-compulsive (OC) symptoms and severity were evaluated and scored by the Y-BOCS and Clinical Global Impression-OCD (CGI-OCD) scales. The severity of the depressive symptoms in the OCD patients was scored by the Hamilton Depression Rating Scale (HDRS). Their global functioning was assessed with the Global Assessment of Functioning (GAF) scale.

#### Genotyping

Peripheral blood was collected and genomic DNA was extracted by a standard procedure. The DAT1 VNTR is located in the 3’ untranslated region of the gene, and was genotyped as described by Sano et al.

#### Statistical analyses

First, the genotype and allele frequencies of the
patients and controls were analyzed by \( \chi^2 \) statistics.
Second, the comparisons of the total Y-BOCS, CGI-OCD, GAF and HDRS scores according to the DAT1 polymorphisms were performed using the t-test.

**Results**

There were no differences in the age or gender distributions between the OCD and control groups (Table 1). The number of subjects with non-10/10 repeats was small. An increased level of DAT1 expression was reported to be associated with the number of 10-repeats alleles,\(^{14}\) and the 10-repeats allele was reported to increase DAT1 gene expression compared with the 7-, 9-, and 11-repeats alleles.\(^{15}\) Therefore, we also classified the genotype of DAT1 into the 10/10-repeats and non-10/10-repeats groups.

There were no statistical differences in the observed genotype distributions or allele frequencies of the DAT1 polymorphism between these two groups (Table 2).

There were no significant differences in the total Y-BOCS, CGI-OC, GAF, or total HDRS scores between the patients with 10/10-repeats and non-10/10-repeats genotypes (Table 3).

**Discussion**

The present study represents a further investigation into the role of polymorphisms of the DAT1 genes in OCD. We did not find any association between DAT1 gene polymorphisms and OCD.

The DAT1 gene is located in chromosome 5p15.3 and has 40bp VNTR(with 3~11 repeats) on the 3’-untranslated region.\(^{16}\) There is some possibility that these VNTR influence the gene expression and the level of DAT1 protein in the brain.\(^{17}\)

To our knowledge, only a few studies have been conducted on the association between DAT1 and OCD. Frisch et al.\(^8\) reported that there was no association between the DAT1 gene and OCD in a Jewish population. Hemmings et al.\(^9\) did not find any difference in the distribution of DAT1 VNTR between the OCD and control groups either. The results of this and the above two studies suggest that variations in the DAT1 gene

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**TABLE 1.** Demographic characteristics of obsessive-compulsive disorder patients and controls

<table>
<thead>
<tr>
<th></th>
<th>OCD patients (N=115)</th>
<th>Controls (N=160)</th>
<th>( t/x^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>31.81 ± 10.71</td>
<td>32.51 ± 6.70</td>
<td>-0.67</td>
<td>0.51*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>79 (68.7%)</td>
<td>100 (62.5%)</td>
<td>1.13</td>
<td>0.31**</td>
</tr>
<tr>
<td>Female</td>
<td>36 (31.3%)</td>
<td>60 (37.5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* t-test  
** \( x^2 \) test

**TABLE 2.** Genotype frequency of DAT1 gene polymorphism in obsessive-compulsive disorder patients and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OCD patients (N=115)</th>
<th>Controls (N=160)</th>
<th>( x^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/10</td>
<td>6 (5.2%)</td>
<td>11 (6.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/10</td>
<td>105 (91.3%)</td>
<td>142 (88.7%)</td>
<td>0.48</td>
<td>0.79</td>
</tr>
<tr>
<td>10/11</td>
<td>4 (3.5%)</td>
<td>7 (4.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OCD patients</th>
<th>Controls</th>
<th>( x^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/10</td>
<td>105 (91.3%)</td>
<td>142 (88.7%)</td>
<td>0.48</td>
<td>0.65</td>
</tr>
<tr>
<td>Non-10/10</td>
<td>10 (8.7%)</td>
<td>18 (11.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allele</th>
<th>OCD patients</th>
<th>Controls</th>
<th>( x^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-repeats</td>
<td>6 (2.6%)</td>
<td>11 (3.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-repeats</td>
<td>220 (95.7%)</td>
<td>302 (94.3%)</td>
<td>0.46</td>
<td>0.80</td>
</tr>
<tr>
<td>11-repeats</td>
<td>4 (1.7%)</td>
<td>7 (2.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3.** Comparisons of obsessive-compulsive, depressive symptoms and global function between obsessive-compulsive disorder patients with 10/10 and non-10/10 genotype of DAT1 polymorphism

<table>
<thead>
<tr>
<th>Factor score</th>
<th>10/10 genotype (N=105)</th>
<th>Non-10/10 genotype (N=10)</th>
<th>( t )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Y-BOCS</td>
<td>27.21 ± 5.69</td>
<td>28.17 ± 6.74</td>
<td>0.39</td>
<td>0.70</td>
</tr>
<tr>
<td>CGI-OC</td>
<td>5.37 ± 1.20</td>
<td>5.33 ± 1.03</td>
<td>-0.07</td>
<td>0.95</td>
</tr>
<tr>
<td>HDRS</td>
<td>13.57 ± 9.36</td>
<td>17.33 ± 8.55</td>
<td>0.95</td>
<td>0.34</td>
</tr>
<tr>
<td>GAF</td>
<td>53.84 ± 9.46</td>
<td>54.17 ± 8.04</td>
<td>0.08</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Student t-test
are not involved in the pathogenesis of OCD.

However, in the interpretation of this result, we should keep in mind the following considerations. First, the statistical power of the present study may be compromised by the relatively small sample size. Therefore, only genes that have a major to moderate effect on the pathogenesis of OCD are susceptible to be identified in this study, and the existence of minor effects of DAT1 VNTR polymorphisms cannot be excluded. Second, a major obstacle to identifying genes that have minor effects on the pathogenesis of OCD is the heterogeneity. Therefore, different genes might play a role in the pathogenesis of OCD in different subgroups of patients. Third, it is also speculated that multiple genes may operate in unison with one another, such that the synergic effect of a particular combination of alleles on the vulnerability to OCD might be much stronger than that of the individual genes. Therefore, studies which attempt to identify a single candidate gene in isolation may lack statistical power and reproducibility.

We could not find any differences in the total Y-BOCS, CGI-OCD, HDRS or GAF scores between the patients with 10/10-repeats and non-10/10-repeats. This suggests that DAT1 VNTR polymorphisms have no effect on the severity of OCD, depressive symptoms or general functioning. However, these clinical variables represent state factors rather than traits, and some of our OCD patients previously underwent some kind of treatment. Therefore, caution should be exercised in interpreting our results and, in order to confirm their importance, independent replications utilizing a larger number of drug-naive samples are warranted.

We do not know the exact causes of the inconsistent results obtained in this and previous studies of the DAT1 gene and OCD. Although there is preliminary evidence which suggests that the DAT1 VNTR polymorphism affects the translation of the DAT1 protein, the results have varied between studies. Some researchers found higher DAT1 gene expression in the 10-repeats allele than in the 7-, 9-, and 11-repeats alleles, whereas others reported that the gene expression is higher in the 9-repeats allele than in the 10-repeats allele. Martinez et al. reported that the VNTR polymorphism of the DAT1 gene is not significantly associated with changes in the DAT1 phenotype in humans. Furthermore, Jonsson et al. did not find any association between DAT1 polymorphisms and a major dopamine metabolite, homovanillic acid, in the cerebrospinal fluid. It appears that the distribution of the DAT1 VNTR polymorphism is associated with ethnicity. The frequency of the 10-repeats allele in this study is similar to those reported in other Korean populations. The frequency of the 10-repeats allele is higher in Asian populations (as in the present study; 0.86~0.94) than in Caucasian and Black populations (0.59~0.79). These two factors may at least partially explain the inconsistencies in the results of previous studies.

Although OCD was not included, there have been several Korean studies of the association between DAT1 VNTR and ADHD or other psychiatric disorders. Kim et al. reported that the frequencies of the 9-repeat allele and 9/10 genotype were significantly higher in the ADHD probands and parents of probands than in those of the normal control group. They also suggested the possibility of there being an association between the DAT1 9-repeat allele and the impulsivity phenotype of attention deficit and hyperactivity disorder (ADHD). Shin et al. also reported that those patients with ADHD were more likely to have the 9/10 genotype and 9-repeat allele than the control group. However, Kim et al. did not find any association between DAT1 and ADHD. Among the various anxiety disorders, Oh et al. reported that there was no association between DAT1 VNTR and social phobia. Kim et al. did not find any association between DAT1 VNTR and depression.

In conclusion, we found no association between the DAT1 VNTR polymorphism and OCD. However, it would be premature to rule out the existence of any association between DAT1 and OCD and a more defi-
nite conclusion requires the elucidation of the effects of allelic variations on DAT1 on DAT1 function or expression.

References


