# Association between Obsessive-Compulsive Disorder and Dopamine Transporter Gene Polymorphism

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## 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.

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## 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-

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ual and is interrelated with other neurotransmitters or neuronal circuits.[3] Therefore, in addition to the main hypothesis suggesting serotonin abnormalities, some authors have proposed that dopamine might also participate in the pathophysiology of OCD.[4] 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.[4] 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.[5] There have also been some reports of the emergence of obsessive-compulsive (OC) symptoms during treatment with clozapine, a dopamine receptor D4 (DRD4) antagonist.[6] 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.[7] 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.[8,9]

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.[10] 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[11] 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)[12]. Their global functioning was assessed with the Global Assessment of Functioning (GAF) scale.[10]

## 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.[13]

## Statistical analyses

First, the genotype and allele frequencies of the

patients and controls were analyzed by $x^2$ 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.

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

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

* t-test
** $x^2$ test

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

| | OCD patients | Controls | $x^2$ | $p$ |
|---|---|---|---|---|
| **Genotype** | N=115 | N=160 | | |
| 9/10 | 6 (5.2%) | 11 (6.9%) | | |
| 10/10 | 105 (91.3%) | 142 (88.7%) | 0.48 | 0.79 |
| 10/11 | 4 (3.5%) | 7 (4.4%) | | |
| **Genotype** | | | | |
| 10/10 | 105 (91.3%) | 142 (88.7%) | 0.48 | 0.65 |
| Non-10/10 | 10 (8.7%) | 18 (11.3%) | | |
| **Allele** | | | | |
| 9-repeats | 6 (2.6%) | 11 (3.4%) | | |
| 10-repeats | 220 (95.7%) | 302 (94.3%) | 0.46 | 0.80 |
| 11-repeats | 4 (1.7%) | 7 (2.2%) | | |

$x^2$ test

**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

| Factor score | 10/10 genotype N=105 | Non-10/10 genotype N=10 | $t$ | $p$ |
|---|---|---|---|---|
| Total Y-BOCS | 27.21 ±5.69 | 28.17 ±6.74 | 0.39 | 0.70 |
| CGI-OC | 5.37 ±1.20 | 5.33 ±1.03 | -0.07 | 0.95 |
| HDRS | 13.57 ±9.36 | 17.33 ±8.55 | 0.95 | 0.34 |
| GAF | 53.84 ±9.46 | 54.17 ±8.04 | 0.08 | 0.94 |

Student t-test

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

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[18]. Therefore, studies which attempt to identify a single candidate gene in isolation may lack statistical power and reproducibility.[9]

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 protein19), 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.[15] whereas others reported that the gene expression is higher in the 9-repeats allele than in the 10-repeats allele.[17] Martinez et al.[20] 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.[21] 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.[22] The frequency of the 10-repeats allele in this study is similar to those reported in other Korean populations.[23,24,25] 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).[24] Shin et al.[23] 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.[26] did not find any association between DAT1 and ADHD. Among the various anxiety disorders, Oh et al.[27] reported that there was no association between DAT1 VNTR and social phobia. Kim et al.[28] 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


1. Pauls DL, Alsobrook J, Goodman WK, Rasmussen SA, Leckman JF. A family study of obsessive-compulsive disorder. Am J Psychiatry 1995; 152:76-84.

2. Barr LC, Goodman WK, Price LH. The serotonin hypothesis of obsessive compulsive disorder Int Clin Psychopharmacol 1993; 8 (Suppl) 2:79-82.

3. Stein DJ. The neurobiology of obsessive-compulsive disorder. Neuroscientist 1996; 2:300-305.

4. Goodman WK, McDougle CJ, Price LH, Riddle MA, Pauls DL, Leckman JF. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? J Clin Psychiatry 1990; 51 (Suppl):36-43;55-58.

5. Agid O, Lerer B. Risperidone augmentation of paroxetine in a case of severe, treatment-refractory obsessive-compulsive disorder without comorbid psychopathology J Clin Psychiatry 1999; 60:55-56.

6. Baker RW, Chengappa KN, Baird JW, Steingard S, Christ MA, Schooler NR. Emergence of obsessive compulsive symptoms during treatment with clozapine. J Clin Psychiatry 1992; 53:439-442.

7. Giros B, Caron MG. Molecular characterization of the dopamine transporter. Trends Pharmacol Sci 1993; 14:43-49.

8. Frisch A, Michaelovsky E, Rockah R, Amir I, Hermesh H, Laor N, Fuchs C, Zohar J, Lerer B, Buniak SF, Landa S, Poyurovsky M, Shapira B, Weizman R. Association between obsessive-compulsive disorder and polymorphisms of genes encoding components of the serotonergic and dopaminergic pathways. Eur Neuropsychopharmacol 2000; 10:205-209.

9. Hemmings SMJ, Kinnear CJ, Niehaus DJ, Moolman-Smook JC, Lochner C, Knowles JA, Corfield VA, Stein DJ. Investigating the role of dopaminergic and serotonergic candidate genes in obsessive-compulsive disorder. Eur Neuropsychopharmacol 2003; 13:93-98.

10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental disorders. 4th ed. Washington DC, American Psychiatric Press, 1994.

11. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989; 46:1006-1011.

12. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6:278-296.

13. Sano A, Kondoh K, Kakimoto Y, Kondo I. A 40-nucleotide repeat polymorphism in the human dopamine transporter gene. Hum Genet 1993; 91:405-406.

14. Mill J, Asherson P, Browes C, D'Souza U, Craig I. Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. Am J Med Genet 2002; 114:975-979.

15. Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. Pharmacogenomics J 2001; 1:152-156.

16. Vandenbergh DJ, Persico AM, Hawkins AL, Griffin CA, Li X, Jabs EW, Uhl GR. Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics 1992; 14:1104-1106.

17. Miller GM, Madras BK. Polymorphisms in the 3'-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression. Mol Psychiatry 2002; 7:44-55.

18. Souery D, Rivelli SK, Mendlewicz J. Molecular genetic and family studies in affective disorders: state of the art. J Affect Disord 2001; 62:45-55.

19. Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, Lee KS, Linnoila M, Weinberger DR. Genotype influences in vivo dopamine transporter availability in human striatum. Neuropsychopharmacology 2000; 22:133-139.

20. Martinez D, Gelernter J, Abi-Dargham A, van Dyck CH, Kegeles L, Innis RB, Laruelle M. The variable number of tandem repeats polymorphism of the dopamine transporter gene is not associated with significant change in dopamine transporter phenotype in humans. Neuropsychopharmacology 2001; 24:553-560.

21. Jonsson EG, Nothen MM, Gustavsson JP, Neidt H, Bunzel R, Propping P, Sedvall GC. Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationships to monoamine metabolite concentra-

tions in CSF of healthy volunteers. Psychiatry Res 1998; 79:1-9.

22. Kang AM, Palmatier MA, Kidd KK. Global variation of a 40-bp VNTR in the 3'-untranslated region of the dopamine transporter gene (SLC6A3) Biol Psychiatry 1999; 46:151-60.

23. Shin DW, Noh KS, Oh KS, Lee MS. Association between attention deficit hyperactivity disorder and dopamine transporter gene (DAT1) polymorphism in Korea. J Korean Neuropsychiatr Assoc 2002; 41:612-618.

24. Kim JW, Kim BN, Cho SC. The dopamine transporter gene and the impulsivity phenotype in attention deficit hyperactivity disorder: A case-control association study in a Korean sample. J Psychiatr Res 2005 (in press)

25. Choi YJ, Bang SK, Kim JJ, Toh KY, Paik IH. Association of alcohol dependence with the dopamine transporter gene polymorphism. J Korean Neuropsychiatr Assoc 1999; 38:826-833.

26. Kim YS, Leventhal BL, Kim SJ, Kim BN, Cheon KA, Yoo HJ, Kim SJ, Badner J, Cook EH. Family-based association study of DAT1 and DRD4 polymorphism in Korean children with ADHD. Neurosci Lett 2005; 390:176-181.

27. Oh KS, Yoon HK, Lee MS. Polymorphism of dopamine transporter gene (DAT1) in Korean social phobia patients: preliminary study. J Korean Soc Biol Psychiatry 2004; 11: 165-172.

28. Kim DK, Kim EJ, Lim SW, Kim H. Association between the genetic polymorphisms of the biogenic amine transporters and the antidepressant responsiveness in Korean depressed patients. Korean J Psychopharmacol 2003; 14: 274-283.