

# Prediction of Response to Paroxetine and Venlafaxine by Serotonin-Related Genes in Obsessive-Compulsive Disorder in a Randomized, Double-Blind Trial

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**Objective:** Serotonin reuptake inhibitors (SRIs) are the most effective pharmacologic treatment currently available for patients with obsessive-compulsive disorder (OCD). Still, up to 40% to 60% of OCD patients do not respond to SRI treatment. The purpose of the present study was to determine whether polymorphisms of the serotonin transporter (5-HTT), 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub> receptor genes affect the efficacy of SRI treatment in OCD.

**Method:** 91 outpatients with OCD according to DSM-IV criteria consented to the study and were randomly assigned in a 12-week, double-blind trial to receive dosages titrated upward to 300 mg/day of venlafaxine or 60 mg/day of paroxetine. Primary efficacy was assessed by the change from baseline on the Yale-Brown Obsessive Compulsive Scale (YBOCS), and response was defined as a  $\geq 25\%$  reduction on the YBOCS. Responders and nonresponders were stratified according to 5-HTT, 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub> genotypes and differentiated in paroxetine- or venlafaxine-treated groups. The study was conducted from August 1998 to July 2002.

**Results:** In the whole group, 64% of responders carried the S/L genotype of the 5-HTTLPR polymorphism ( $\chi^2 = 7.17$ ,  $df = 2$ ,  $p = .028$ ). In the paroxetine-treated patients, the majority of responders carried the G/G genotype of the 5-HT<sub>2A</sub> polymorphism ( $\chi^2 = 8.66$ ,  $df = 2$ ,  $p = .013$ ), whereas in the venlafaxine-treated patients, the majority of responders carried the S/L genotype of the 5-HTTLPR polymorphism ( $\chi^2 = 9.72$ ,  $df = 2$ ,  $p = .008$ ).

**Conclusions:** The results of this study suggest that response in venlafaxine-treated OCD patients is associated with the S/L genotype of the 5-HTTLPR polymorphism and in paroxetine-treated OCD patients with the G/G genotype of the 5-HT<sub>2A</sub> polymorphism.

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Obsessive-compulsive disorder (OCD) is a common and severe, but still underrecognized psychiatric disorder. Although serotonin reuptake inhibitors (SRIs) are the most effective pharmacologic treatment for OCD, up to 40% to 60% of OCD patients do not respond to treatment.<sup>1</sup> Even after a switch to a second SRI treatment, 30% to 40% of OCD patients fail to respond.<sup>2</sup> Clearly, an improved understanding of determinants of response to SRIs would be immensely valuable to develop more efficient treatment strategies in OCD.

Among a number of factors that have been proposed to determine treatment outcome with SRIs, genetic differences among patients may play a significant role.<sup>3</sup> In major depressive disorder, for example, it has been reported repeatedly that the short form (S-allele) of the 44-base pair (bp) deletion/insertion functional polymorphism within the promoter region of the serotonin transporter gene (5-HTTLPR) is associated with impaired efficacy of SRIs.<sup>4</sup> In OCD, 3 studies have investigated the role of the 5-HTTLPR and treatment response. McDougle et al.<sup>5</sup> found an association of the L-allele with poorer response to SRIs, whereas Billet et al.<sup>6</sup> and Di Bella et al.<sup>7</sup> failed to find a relation between response and 5-HTT genotypes. Other receptors that might be involved in the therapeutic efficacy of SRIs are the terminal 5-HT<sub>1B</sub> autoreceptor and the postsynaptic 5-HT<sub>2A</sub> receptor. As of yet, neither polymorphisms of 5-HT<sub>1B</sub> or of 5-HT<sub>2A</sub> receptor genes have been investigated with regard to treatment response of SRIs in OCD.

In this study we tested the hypothesis that variations of the 5-HTT (L-allele of the 5-HTTLPR), 5-HT<sub>1B</sub>, and

5-HT<sub>2A</sub> gene expressions are linked to treatment response with SRIs in OCD. We report the results of 91 patients who participated in a 12-week, double-blind trial with paroxetine and venlafaxine and were assessed for the 44 bp insertion/deletion 5-HTTLPR, the 5-HT<sub>1B</sub> (5-HT<sub>1DB</sub>) G861C, and the 5-HT<sub>2A</sub> 1438G/A polymorphism.

## MATERIALS AND METHOD

### Study Sample

Ninety-one outpatients gave written informed consent for participation in this study, which had been approved by the University of Utrecht Medical Ethical Review committee (Utrecht, the Netherlands) and was conducted from August 1998 to July 2002. All patients were diagnosed with OCD according to DSM-IV criteria and the Mini-International Neuropsychiatric Interview (MINI),<sup>8</sup> a clinical and structured interview, was used to confirm the diagnosis. Severity of obsessive-compulsive symptoms was rated with the Yale-Brown Obsessive Compulsive Scale (YBOCS),<sup>9</sup> depressive symptoms with the Hamilton Rating Scale for Depression (HAM-D),<sup>10</sup> and anxiety with the Hamilton Rating Scale for Anxiety (HAM-A).<sup>11</sup> Only patients with a score of at least 18 on the YBOCS, or at least 12 if only obsessions or only compulsions were present, were included. Patients with a major depressive disorder or patients with a total score of 15 or more on the 17-item HAM-D on admission were excluded. Information on family history of OCD and other psychiatric disorders was obtained by direct interviews with the patients, and the presence of vocal and/or motor tics was assessed during the clinical interview.

### Study Design

Patients were randomly assigned to receive either paroxetine or venlafaxine XR for 12 weeks in a single-center, double-blind, controlled, and parallel-group study design. The patient groups did not differ significantly in age, sex distribution, age at onset, duration of illness, baseline ratings, comorbid mood or anxiety disorder or any other comorbid DSM Axis I or Axis II disorder, or previous behavioral therapies. Forty percent (36/91) of the sample were treatment naive at time of recruitment, and the remainder were treatment free at baseline for at least 1 month. Paroxetine treatment was initiated at a dose of 15 mg/day and gradually increased to 60 mg/day using a fixed dosing schedule. Venlafaxine treatment was initiated at a dose of 75 mg/day and gradually increased to 300 mg/day. Psychotropic drugs or psychotherapy were not allowed. Primary efficacy was assessed by the change from baseline in obsessive-compulsive symptoms, measured with the YBOCS, and response to treatment was prospectively defined as a  $\geq 25\%$  decrease in YBOCS score. Three of 91 patients dropped out during the study because of lack of motivation or

side effects. A detailed description of the study has been published earlier.<sup>12,13</sup>

### Genotyping

Blood samples were collected from each subject and frozen at  $-80^{\circ}\text{C}$ . DNA was extracted from 10-mL samples of peripheral blood according to standard procedures. The total number of subjects genotyped for the genes in this study was 88. In 7 cases, the genotyping of the 5-HT<sub>1B</sub> polymorphism failed, and in 1 case the genotyping of the 5-HTT polymorphism failed. All subjects were genotyped at the University of Ghent (Belgium) on the basis of a coded identification number. The 5-HTT, 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub> genotyping was performed following a standardized protocol.

### 5-HTT

For the detection of the 44 bp insertion/deletion 5-HTTLPR polymorphism, the oligonucleotide primers 5'-6FAM-GGCGTTGCCGCTCTGAATGC-3' and 5'-AGGGACTGAGCTGGACAAC CAC-3' were used to amplify a 484/528 bp fragment comprising the 5-HTT-linked polymorphic region. The polymerase chain reaction (PCR) was performed according to the following conditions: 94°C for 1 minute, 60°C for 1 minute, 72°C for 1 minute 40 seconds per cycle, for a total of 35 cycles. The PCR products were analyzed by capillary electrophoresis on an Applied Biosystems 3100 Genetic Analyzer (Applied Biosystems Group, Foster City, Calif.)

### 5-HT<sub>1B</sub>

For detection of the 5-HT<sub>1B</sub> or (5-HT<sub>1DB</sub>) G861C polymorphism, the oligonucleotide primers 5'-GAAACA-GACGCCCAACAGGAC-3' and 5'-CCAGAAACCGCG-AAAGAAGAT-3' were used to amplify a 548 bp region comprising the G861C polymorphism site. The PCR was performed under the following conditions: 90°C for 1 minute, 55°C for 2 minutes, 72°C for 3 minutes per cycle, for a total of 32 cycles. Digestion of 10  $\mu\text{L}$  of PCR product was accomplished by incubation for 4 hours with 10 units of Hinc II restriction enzyme at 37°C. Digestion with Hinc II yields either 2 fragments (452 bp and 96 bp) for the G-allele or 3 fragments (310 bp, 142 bp, and 96 bp) for the C-allele. The fragments resulting from the digestion were resolved on a 1.5% agarose gel and visualized by ethidium bromide staining.

### 5-HT<sub>2A</sub>

For the detection of the 5-HT<sub>2A</sub> 1438G/A polymorphism within the promoter region of the 5-HT<sub>2A</sub> receptor gene, the oligonucleotide primers 5'-6FAM-AAGCTGC-AAGGTAGCAACAGC-3' and 5'-NED-AACCAACTTATTTCTACCAC-3' were used to amplify a 468 bp region comprising the 5HT<sub>2A</sub> 1438G/A polymorphism site. The PCR reaction was performed under the following condi-

**Table 1. Demographic and Clinical Characteristics of Patients With Obsessive-Compulsive Disorder**

Characteristic	Nonresponders (N = 32)	Responders (N = 56)
Gender (male/female), N	14/18	20/36
Age on admission, mean $\pm$ SD, y	31.7 $\pm$ 12.0	34.1 $\pm$ 11.3
Positive family history, N	11	19
Age at onset, mean $\pm$ SD, y	14.7 $\pm$ 9.3	17.2 $\pm$ 7.4
$\leq$ 15 years, N	12	33
$>$ 20 years, N	20	23
YBOCS baseline score, mean $\pm$ SD	26.8 $\pm$ 5.8	25.2 $\pm$ 5.2
YBOCS endpoint score, mean $\pm$ SD	24.8 $\pm$ 5.7	13.2 $\pm$ 5.4
YBOCS score % decrease, mean $\pm$ SD	6.8 $\pm$ 11.0	48.6 $\pm$ 18.0
HAM-D score, mean $\pm$ SD	5.6 $\pm$ 10.7	7.8 $\pm$ 10.8
HAM-A score, mean $\pm$ SD	7.4 $\pm$ 6.7	9.8 $\pm$ 7.5
Paroxetine (N = 40), N	9	31
Venlafaxine (N = 44), N	20	24

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, YBOCS = Yale-Brown Obsessive Compulsive Scale.

tions: 95°C for 1 minute, 47°C for 1 minute, 72°C for 1 minute 20 seconds per cycle, for a total of 40 cycles. Digestion of 10  $\mu$ L of PCR product was accomplished by overnight incubation with 10 units of Msp I restriction enzyme at 37°C. After incubation with Msp I, the 1438A allele remains intact while the 1438G allele is cut into a 223 bp piece (6FAM-labeled) and a 243 bp piece (NED-labeled). The fragments resulting from the digestion were analyzed by capillary electrophoresis on an Applied Biosystems 3100 Genetic Analyzer.

### Data Analysis

The following statistical procedure was pursued. Firstly, the genotypic pattern of distribution and the allele frequencies of the 5-HTT, 5-HT<sub>1B</sub>, and 5-HT<sub>2A</sub> polymorphisms were analyzed in the whole sample (N = 88). Secondly, an analogous analysis was performed in the paroxetine-treated patients (N = 40) and in the venlafaxine-treated patients (N = 44) separately. Medication use and dose were uncertain in 4 patients, who were excluded from the treatment groups. The associations between the distribution of the genotypes and allele frequencies with the responders and nonresponders were assessed by cross-tabulation and  $\chi^2$  analyses. One-way analyses of variance were calculated to determine whether significant differences were present between genotypes in mean decrease of YBOCS scores. Since Bonferroni adjustment is only justified when variables are completely independent, we used the modified Bonferroni adjustment to correct for the level of dependency of variables. Considering a modified Bonferroni adjustment, the p value for statistical significance would be .020 with an  $\alpha$  of .05, 6 tests, 2 degrees of freedom, and a correlation correction factor of 0.5.<sup>14</sup> The data are presented as mean  $\pm$  SD, and performed at 5% level of significance. All statistical analyses were conducted with the SPSS statistical package version 11.5 (SPSS Inc., Chicago, Ill.).

## RESULTS

Demographic variables and outcome measures are presented in Table 1. The patient sample was slightly skewed toward the female population (61%). Fifty-six (64%) of 88 patients were rated as responders, 31 of 40 patients in the paroxetine group and 24 of 44 patients in the venlafaxine group. Four patients were not assigned to a particular treatment group (see Methods section). There were no statistically significant differences between responders and nonresponders as regards gender, age, age at onset, family history, and baseline YBOCS, HAM-A, or HAM-D measures. Though a majority of responders had an early onset of OCD, there was no significant difference between responder rates in the early versus late onset group ( $\chi^2 = 1.7$ ,  $df = 1$ ,  $p = .19$ ).

In the whole sample, a difference in genotype distribution of the 5-HTTLPR polymorphism was found between responders and nonresponders (Table 2). Sixty-four percent of the responders carried the S/L genotype of the 5-HTTLPR polymorphism compared with 18% carrying the S/S genotype and 18% carrying the L/L genotype. The difference just failed to be statistically significant after Bonferroni adjustment ( $\chi^2 = 7.17$ ,  $df = 2$ ,  $p = .028$ ). When the mean YBOCS decrease was stratified by 5-HTTLPR genotype, a superior response was observed in the S/L genotype (37% decrease) versus the S/S genotype (28%) and the L/L genotype (29%), but the analysis of variance failed to reach statistical significance ( $F_{2,84} = 1.2$ ,  $p = .30$ ). Allele frequencies of the 5-HTTLPR polymorphism between responders and nonresponders were not statistically significantly different ( $\chi^2 = 0.05$ ,  $df = 1$ ,  $p = .55$ ), and there were no significant differences between responders and nonresponders in allele or genotype frequencies for the 5-HT<sub>1B</sub> and 5-HT<sub>2A</sub> polymorphisms in the whole sample.

In the paroxetine-treated patients (Table 3), the majority of responders carried the G/G genotype of the 5-HT<sub>2A</sub> polymorphism ( $\chi^2 = 8.66$ ,  $df = 2$ ,  $p = .013$ ). The association of a superior response with the G/G genotype was confirmed in the analysis of variance when the mean YBOCS decrease was broken down according to the genotypes. Patients carrying the G/G genotype of the 5-HT<sub>2A</sub> polymorphism had a mean decrease of 51% on the YBOCS compared with 34% with the A/A genotype and 29% with the A/G genotype ( $F_{2,39} = 4.95$ ,  $p = .012$ ). In general, responders carried predominantly the G-allele compared with nonresponders ( $\chi^2 = 8.43$ ,  $df = 1$ ,  $p = .004$ ) (OR = 4.89, 95% CI = 1.59 to 15.02).

In the venlafaxine-treated patients (Table 4), the majority of responders carried the S/L genotype of the 5-HTTLPR polymorphism ( $\chi^2 = 9.72$ ,  $df = 2$ ,  $p = .008$ ). The analysis of variance showed a difference in favor of the S/L genotype with a mean YBOCS decrease of 38% compared with 24% in patients with the S/S genotype and

**Table 2. Allele Frequencies and Genotype Distribution of the 5-HT<sub>1B</sub>-Receptor, 5-HT<sub>2A</sub>-Receptor, and 5-HT Transporter Polymorphisms in the Whole Sample of Obsessive-Compulsive Disorder Patients (N = 88)**

Polymorphism	N	Allele Frequency		p Value	Genotype, N (%)			p Value
		C	G		C/C	C/G	G/G	
5-HT <sub>1B</sub>								
Nonresponders	30	0.23	0.74	.273	1 (3.3)	12 (40.0)	17 (56.7)	.510
Responders	51	0.31	0.69		4 (7.8)	24 (47.1)	23 (45.1)	
5-HT <sub>2A</sub>								
Nonresponders	32	0.48	0.52	.418	5 (15.6)	21 (65.6)	6 (18.8)	.144
Responders	56	0.42	0.58		11 (19.6)	25 (44.6)	20 (35.7)	
5-HTT								
Nonresponders	32	0.55	0.45	.551	12 (37.5)	11 (34.4)	9 (28.1)	.028
Responders	55	0.50	0.50		10 (18.2)	35 (63.6)	10 (18.2)	

**Table 3. Allele Frequencies and Genotype Distribution of the 5-HT<sub>1B</sub>-Receptor, 5-HT<sub>2A</sub>-Receptor, and 5-HT Transporter Polymorphisms in the Paroxetine-Treated Group (N = 40)**

Polymorphism	N	Allele Frequency		p Value	Genotype, N (%)			p Value
		C	G		C/C	C/G	G/G	
5-HT <sub>1B</sub>								
Nonresponders	8	0.19	0.81	.513	0 (0.0)	3 (37.5)	5 (62.5)	.625
Responders	28	0.27	0.73		3 (10.7)	9 (32.1)	16 (57.1)	
5-HT <sub>2A</sub>								
Nonresponders	9	0.67	0.33	.004	3 (33.3)	6 (66.7)	0 (0.0)	.013
Responders	31	0.29	0.71		4 (12.9)	10 (32.3)	17 (54.8)	
5-HTT								
Nonresponders	9	0.56	0.44	.772	3 (33.3)	4 (44.4)	2 (22.2)	.787
Responders	30	0.52	0.48		7 (23.3)	17 (56.7)	6 (20.0)	

**Table 4. Allele Frequencies and Genotype Distribution of the 5-HT<sub>1B</sub>-Receptor, 5-HT<sub>2A</sub>-Receptor, and 5-HT Transporter Polymorphisms in the Venlafaxine-Treated Group (N = 44)**

Polymorphism	N	Allele Frequency		p Value	Genotype, N (%)			p Value
		C	G		C/C	C/G	G/G	
5-HT <sub>1B</sub>								
Nonresponders	19	0.24	0.76	.214	1 (5.3)	7 (36.8)	11 (57.9)	.221
Responders	22	0.36	0.64		1 (4.5)	14 (63.6)	7 (31.8)	
5-HT <sub>2A</sub>								
Nonresponders	20	0.40	0.60	.087	2 (10.0)	12 (60.0)	6 (30.0)	.165
Responders	24	0.58	0.42		7 (29.2)	14 (58.3)	3 (12.5)	
5-HTT								
Nonresponders	20	0.55	0.45	.393	8 (40.0)	6 (30.0)	6 (30.0)	.008
Responders	24	0.46	0.54		2 (8.3)	18 (75.0)	4 (16.7)	

15% in patients with the L/L genotype, who had the worst outcome, but failed to be statistically significant after correction ( $F_{2,43} = 3.27$ ,  $p = .04$ ).

Since the number of responders appeared to be correlated to the G/G genotype of the 5-HT<sub>2A</sub> polymorphism in the paroxetine-treated patients, and to the S/L genotype of the 5-HTTLPR polymorphism in the venlafaxine-treated patients, we analyzed, thereupon, responder rates in patients who had either one of the genotypes in the full sample. More than 81% of the responders (45/55) carried either the G/G genotype of the 5-HT<sub>2A</sub> polymorphism or the S/L genotype of the 5-HTTLPR polymorphism ( $\chi^2 = 8.1$ ,  $df = 1$ ,  $p = .004$ ). Nine patients carried both the G/G genotype of the 5-HT<sub>2A</sub> polymorphism and the S/L genotype of the 5-HTTLPR polymorphism. All of them were responders with a mean YBOCS decrease of 49% ( $\chi^2 = 16.0$ ,  $df = 8$ ,  $p = .01$ ).

## DISCUSSION

The main finding of this study is that OCD patients with the S/L genotype of the 5-HTTLPR polymorphism have a more favorable response following venlafaxine treatment, while response to paroxetine mainly was associated with the G/G genotype of the 5-HT<sub>2A</sub> polymorphism. The small group of patients (N = 9) who carried both the S/L genotype of the 5-HTTLPR polymorphism and the G/G genotype of the 5-HT<sub>2A</sub> polymorphism all responded to treatment.

Three previous studies have investigated the role of the 5-HTTLPR and treatment response in OCD. McDougle et al.<sup>5</sup> found in a sample of 33 patients a trend for an association of the L-allele with poorer response to SRIs (clomipramine, fluvoxamine, fluoxetine, sertraline, and paroxetine). Billet et al.<sup>6</sup> examined retrospectively 72

patients after a 10-week trial with SRIs and found no association, and Di Bella et al.<sup>7</sup> failed to find a relation between response and 5-HTTLPR genotypes in a sample of 99 patients following a standardized fluvoxamine treatment of 12 weeks. Our results do not suggest a better outcome with SRIs in carriers of the L/L genotype of the 5-HTTLPR, which is in flat contradiction with the majority of reports in mood disorders in which the presence of the L variant of the 5-HTTLPR has been related to a more favorable and faster response with SRIs.<sup>4</sup> On the other hand, in Asian populations, an association in the opposite direction was found, with a better response for carriers of the S allele. In sum, our findings disagree with Billet et al.<sup>6</sup> and Di Bella et al.<sup>7</sup> and the majority of the studies in MDD patients.

Contradictory results among OCD studies might be explained by differences in pharmacologic properties of SRIs. Though SRIs generally are regarded as having a more or less selective affinity for the 5-HTT, they also exhibit affinity for the norepinephrine transporter (NET) and dopamine transporter (DAT). SRIs differ substantially in pharmacodynamic properties as regards the reuptake inhibition of the transporters. Paroxetine, for example, is the most potent and citalopram the most selective compound at the 5-HTT, whereas sertraline has relatively high affinity for the DAT, and venlafaxine for the NAT.<sup>15</sup> Though highly speculative, one could argue that subtle differences in 5-HTT, NET, and DAT affinity between SRIs may account for different effects in relation to genotype. Discrepancies between OCD and MDD studies may be due to pathophysiologic and neurobiological dissimilarities between OCD and MDD. It has been suggested that SRIs exert their beneficial effects with their typical delay of 6 to 8 weeks in OCD by down-regulating 5-HT<sub>1B</sub> receptors in the orbito-frontal, whereas in MDD a faster response is observed probably due to 5-HT autoreceptor desensitization in other brain areas such as the hippocampus and hypothalamus.<sup>16</sup> This supposition is appealing, but still needs to be confirmed.

It is unclear exactly why the S/L genotype of the 5-HTTLPR would confer a favorable potential for a better response with SRIs in OCD. One might comprehend the connection of the L/L genotype with a superior response since it has been related to higher 5-HTT densities and hence an increased efficacy of SRIs. On the other hand, the L/L genotype of the 5-HTTLPR has been associated to placebo response as well, thereby questioning the rationale of the direct link between the 5-HTTLPR and therapeutic efficacy of SSRIs.<sup>4</sup> Furthermore, it still needs to be clarified whether or not the 5-HTTLPR determines the number of 5-HTT in the human brain in vivo.<sup>17,18</sup> Some studies have reported that L/L homozygous individuals had higher 5-HTT availability compared with S/L or S/S homozygous individuals in the raphe area, but others failed to find an association in the dien-

cephalon, brainstem, and the thalamus.<sup>19–22</sup> Equally, post-mortem studies did not detect any significant influence of 5-HTTLPR on 5-HTT density in the hippocampus or frontal cortex.<sup>23,24</sup> Thus it would be premature to relate superior response of the S/L genotype carriers in OCD to lower 5-HTT densities since it still remains to be elucidated whether the 5-HTTLPR genotypes relate to 5-HTT function and hence different psychopharmacologic mechanisms of SRIs.

Except for Tot et al.,<sup>25</sup> who failed to find an association between the -1438G/A and T102C polymorphism of the 5-HT<sub>2A</sub> receptor in 52 patients following a 12-week trial with fluvoxamine, fluoxetine, or sertraline, no further study has investigated the 5-HT<sub>2A</sub> receptor gene with regard to treatment response in OCD.<sup>25</sup> This is surprising since sensitization of the 5-HT<sub>2A</sub> receptor has been hypothesized to be a common mechanism of SRI treatment.<sup>26,27</sup> For example, Meyer et al.<sup>28</sup> have reported increased densities of the 5-HT<sub>2A</sub> receptor after paroxetine treatment. Massou et al.,<sup>29</sup> on the other hand, have found the opposite. A recent study<sup>30</sup> in 54 Japanese patients with MDD failed to find a major role for the -1438G/A promoter polymorphism in therapeutic response to fluvoxamine, and similarly, Choi et al.<sup>31</sup> found no significant association between the 5-HT<sub>2A</sub> G-1438A genotype and treatment response. Thus far, it is unclear whether the -1438A/G promoter polymorphism results in functional effects.<sup>32</sup> Spurlock et al.<sup>33</sup> found no effect of the -1438A/G promoter polymorphism on basal or cAMP-induced and protein kinase C-induced gene transcription in HeLa cells and found no difference in lymphocyte 5-HT<sub>2A</sub> receptor mRNA expression between 1438A/A and G/G homozygotes. Turecki et al.,<sup>34</sup> in a small postmortem study, reported higher prefrontal 5-HT<sub>2A</sub> receptor binding in subjects with the -1438A allele, but Bray et al.<sup>35</sup> failed to find a significant effect on 5-HT<sub>2A</sub> receptor mRNA expression in postmortem brain tissue.

It is puzzling why response in paroxetine-treated patients is related to the 5-HT<sub>2A</sub> receptor genotype and response in venlafaxine-treated patients to the 5-HTTLPR. It has been reported that chronic treatment with paroxetine produces a significant desensitization in postsynaptic 5-HT<sub>2A</sub> receptor function.<sup>28,36</sup> On the other hand, the 5-HTT and 5-HT<sub>2A</sub> receptor are intimately linked; for example, the constitutive lack of the 5-HTT alters the density of the 5-HT<sub>2A</sub> receptor in a brain region-specific manner, with an increase in the hypothalamus and decrease in the striatum.<sup>27,37</sup> Thus, the apparent specific association of paroxetine and venlafaxine might be a spurious finding as a result of a type 2 error due to the small sample sizes. Further investigation in larger samples might clarify this issue.

It is of note that the data generated from this study must be interpreted with caution. First, our sample sizes were small and therefore urge for consistent replication in

future studies and larger clinical trials. Second, though there is no definite association between demographic and clinical variables and treatment response in OCD, potentially confounding effects should be considered such as differences between early- and late-onset OCD in responders versus nonresponders. Third, our results with regard to the 5-HTTLPR should be reconsidered since a recent study<sup>38</sup> has pointed to an important additional origin of variability in the 5-HTTLPR. As the 5-HTTLPR is functionally triallelic, patients carrying the S/L genotype of the 5-HTTLPR polymorphism might include Lg alleles.<sup>38</sup>

In summary, this study suggests a better outcome in OCD after treatment with venlafaxine for patients carrying the S/L genotype of the 5-HTTLPR polymorphism, whereas response to paroxetine was associated with the G/G genotype of the 5-HT<sub>2A</sub> polymorphism. The small group of patients who carried both the S/L genotype of the 5-HTTLPR polymorphism and the G/G genotype of the 5-HT<sub>2A</sub> polymorphism all responded to treatment. Our results indicate that 5-HT<sub>2A</sub> and 5-HTTLPR polymorphisms may be markers for treatment outcome in OCD.

*Drug names:* citalopram (Celexa and others), clomipramine (Anafranil and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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