

# Prediction of Antidepressant Response to Milnacipran by Norepinephrine Transporter Gene Polymorphisms

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**Objective:** With a multitude of antidepressants available, predictors of response to different classes of antidepressants are of considerable interest. The purpose of the present study was to determine whether norepinephrine transporter gene (NET) and serotonin transporter gene (5-HTT) polymorphisms are associated with the antidepressant response to milnacipran, a dual serotonin/norepinephrine reuptake inhibitor.

**Method:** Ninety-six Japanese patients with major depressive disorder were treated with milnacipran, 50–100 mg/day, for 6 weeks. Severity of depression was assessed with the Montgomery-Åsberg Depression Rating Scale. Assessments were carried out at baseline and at

1, 2, 4, and 6 weeks of treatment. The method of polymerase chain reaction was used to determine allelic variants.

**Results:** Eighty patients completed the study. The presence of the T allele of the NET T-182C polymorphism was associated with a superior antidepressant response, whereas the A/A genotype of the NET G1287A polymorphism was associated with a slower onset of therapeutic response. In contrast, no influence of 5-HTT polymorphisms on the antidepressant response to milnacipran was detected.

**Conclusions:** The results suggest that NET but not 5-HTT polymorphisms in part determine the antidepressant response to milnacipran.

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The selective serotonin reuptake inhibitors (SSRIs) were first introduced in the United States in 1988 and remain the antidepressants of first choice. Because the serotonin transporter (5-HTT) is believed to be the primary therapeutic target of SSRIs, genetic polymorphisms of the 5-HTT have been investigated in relationship to the antidepressant response to SSRIs. Smeraldi et al. (1) reported that the presence of the L allele of the 5-HTT gene-linked polymorphic region (5-HTTLPR) conferred a superior therapeutic response to fluvoxamine. Several subsequent studies in Europe and the United States revealed similar results (2–4). In contrast, in a Korean study, Kim et al. (5) reported that the S/S homozygous allele pairs were more frequently associated with a therapeutic response to fluoxetine or paroxetine than other allele combinations. Concordant with this result is our finding that the S allele occurs more frequently in fluvoxamine-responsive Japanese patients than in nonresponsive patients (6). It is unclear what mechanism may underlie ethnic differences in antidepressant response. Several other serotonergic system genetic polymorphisms have also been scrutinized in relationship to the antidepressant response to SSRIs (7–11), but a consistent pattern of results has not emerged.

Recently, dual serotonin/norepinephrine reuptake inhibitors (SNRIs) have emerged as particularly effective antidepressants. Unfortunately, there are few validated predictors of antidepressant response, except for past and family history of response (12). Prediction of antidepressant

response to SNRIs would represent an important advance in the field. Our previous study (13) revealed that there is no significant relationship between plasma concentrations of milnacipran, an SNRI, and the antidepressant response.

To our knowledge, there have been no reports published to date on the relationship between genetic polymorphisms and antidepressant response to SNRIs. Because SNRIs act not only on the 5-HTT but also on the norepinephrine transporter (NET), the effects of polymorphisms of both transporters are of interest. In the current study, we examined the effect of NET and 5-HTT polymorphisms on the antidepressant response to milnacipran. In addition, we also investigated a genetic polymorphism of the 5-HT<sub>2A</sub> receptor.

## Method

### Subjects and Treatment

Ninety-six Japanese patients who fulfilled DSM-IV criteria for a diagnosis of major depressive disorder and whose scores on the Montgomery-Åsberg Depression Rating Scale (14) were 21 or higher were included in this study. Patients with other axis I disorders (including dementia, substance abuse, dysthymia, panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder) and those with axis II disorders determined by clinical interview were excluded. Patients with a past history of childhood disorders were also excluded, as were patients with severe non-psychiatric medical disorders.

**TABLE 1. Clinical Characteristics of the 80 Patients Who Did or Did Not Respond to 6 Weeks of Treatment With Milnacipran**

Characteristic	Responders (N=50)		Nonresponders (N=30)		Analysis $\chi^2$ (df=1) p	
	N	%	N	%		
Sex					0.53	0.47
Male	19	38	9	30		
Female	31	62	21	70		
Melancholia					$1.16 \times 10^{-30}$	0.99
Yes	15	30	9	30		
No	35	70	21	70		
	Mean	SD	Mean	SD	t (df=78)	p
Age (years)	51.1	12.2	51.8	12.2	-0.27	0.79
Number of previous episodes	0.48	1.6	0.23	0.57	1.00	0.32

The patients were 20–69 years of age and had been free of psychotropic drugs for at least 14 days before entry into the study. After complete description of the study to the subjects, written informed consent was obtained.

Milnacipran was administered twice daily (after dinner and at bedtime in the same dose) for 6 weeks. The initial total dose was 50 mg/day, and after 1 week it was increased to 100 mg/day. Patients with insomnia were prescribed brotizolam, 0.25 or 0.5 mg, a benzodiazepine sedative hypnotic, at bedtime. No other psychotropic drugs were permitted during the study. Of 96 enrolled patients, 10 did not complete the study—five patients because of side effects, one patient because of severe insomnia, and four patients without explanation. Of the 86 patients who completed the 6-week study, six patients were excluded from the current analysis because plasma samples revealed very low milnacipran concentrations, indicative of poor compliance.

Patients who completed the study included 52 women and 28 men, 49 outpatients and 31 inpatients, 25–69 years of age (mean age=51.4, SD=12.2). The clinical characteristics of the patients are shown in Table 1. The number of previous depressive episodes among these patients was very low. Indeed, 64 (80%) of the 80 patients were experiencing their first episode. None of the patients had childhood-onset depression.

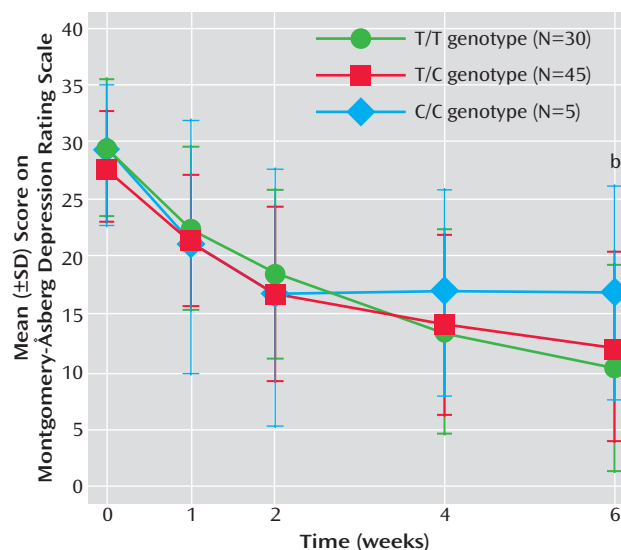
### Data Collection

Depression symptom severity was assessed with the use of the Montgomery-Åsberg Depression Rating Scale. Assessments were conducted at baseline and at 1, 2, 4, and 6 weeks after initiation of antidepressant treatment. A single rater conducted each of the ratings for each patient. A clinical response was defined as a 50% or greater decrease in the baseline Montgomery-Åsberg Depression Rating Scale score. Clinical remission was defined as a final Montgomery-Åsberg Depression Rating Scale score less than 10. Collection of blood samples was performed 12 hours after drug administration at bedtime, 4 weeks after initiation of milnacipran treatment.

### Genotyping

**NET polymorphisms.** T-182C polymorphism in the promoter region (NET T-182C) was determined by a modification of the method of Zill et al. (15). G1287A polymorphism in exon 9 (NET G1287A) was determined by the method of Jönsson et al. (16).

**5-HTT polymorphisms.** 5-HTTLPR, a variable number of tandem repeats in the second intron of the 5-HTT gene (5-HTTVNTR), and a G-1438A polymorphism in the promoter region of the 5-HT<sub>2A</sub> receptor gene (5-HT<sub>2A</sub> G-1438A) were determined by using

**FIGURE 1. Montgomery-Åsberg Depression Rating Scale Scores During 6 Weeks of Treatment With Milnacipran in Three NET T-182C Genotype Groups<sup>a</sup>**

<sup>a</sup> Each point represents the mean score plus or minus standard deviation. Differences among groups examined with repeated-measures analysis of variance.

<sup>b</sup> No significant differences among the genotype groups.

the method of polymerase chain reaction. The method is described in detail in previous publications (6, 9, 10).

### Quantification of Plasma Milnacipran Concentration

Plasma concentrations of milnacipran were measured by using high performance liquid chromatography. Details of the method have been described previously (13). Milnacipran was measured in duplicate samples; the mean of the two samples is presented.

Genotyping and measurement of plasma milnacipran concentrations were performed by laboratory personnel blind to the identity and clinical response of the patients. Moreover, the clinicians were unaware of the genotyping results and plasma milnacipran concentrations of each patient.

### Statistical Analysis

Differences in patient characteristics were analyzed with the use of the unpaired t test or chi-square test where appropriate. Differences in the time course of Montgomery-Åsberg Depression Rating Scale scores were examined with the use of repeated-measures analysis of variance (ANOVA). Genotype distribution and allele frequencies were analyzed with the use of the chi-square test. Plasma concentrations of milnacipran were analyzed with the use of one-way factorial ANOVA in each genotype group; an unpaired t test was then used to analyze differences between groups who were or were not responsive to milnacipran. Power analysis was performed with the use of G-Power (17). All tests were two-tailed; alpha was set at 0.05.

## Results

### NET Polymorphisms and Antidepressant Effect

**NET T-182C polymorphism.** Figure 1 shows the Montgomery-Åsberg Depression Rating Scale scores over time in relation to the NET T-182C polymorphism. The Montgomery-Åsberg Depression Rating Scale score of the C/C genotype group was nonsignificantly higher than that of the T/C

**TABLE 2. Genotype Distribution and Allele Frequencies in 50 Patients Who Did and 30 Patients Who Did Not Respond to 6 Weeks of Treatment With Milnacipran**

Genotype and Patient Group	Genotype Distribution						Allele Frequency			
	N	%	N	%	N	%	N	%	N	%
NET T-182C <sup>a</sup>	T/T		T/C		C/C		T		C	
Responders	23	46.0	26	52.0	1	2.0	72	72.0	28	28.0
Nonresponders	7	23.3	19	63.3	4	13.3	33	55.0	27	45.0
NET G1287A <sup>b</sup>	G/G		G/A		A/A		G		A	
Responders	26	52.0	18	36.0	6	12.0	70	70.0	30	30.0
Nonresponders	12	40.0	17	56.7	1	3.3	41	68.3	19	31.7
5-HTTLPR <sup>c</sup>	S/S		S/L		L/L <sup>d</sup>		S		L	
Responders	34	68.0	15	30.0	1	2.0	83	83.0	17	17.0
Nonresponders	16	53.3	13	43.3	1	3.3	45	75.0	15	25.0
5-HTTVNTR <sup>e</sup>	10/10 <sup>d</sup>		10/12		12/12		10		12	
Responders	2	4.0	6	12.0	42	84.0	10	10.0	90	90.0
Nonresponders	0	0.0	7	23.3	23	76.7	7	11.7	53	88.3
5-HT <sub>2A</sub> G-1438A <sup>f</sup>	G/G		G/A		A/A		G		A	
Responders	12	24.0	27	54.0	11	22.0	51	51.0	49	49.0
Nonresponders	8	26.7	9	30.0	13	43.3	25	41.7	35	58.3

<sup>a</sup> Significant difference between responders and nonresponders for genotype distribution ( $\chi^2=6.85$ ,  $df=2$ ,  $p=0.03$ ) and allele frequency ( $\chi^2=4.80$ ,  $df=1$ ,  $p=0.03$ ).

<sup>b</sup> No significant difference between responders and nonresponders ( $\chi^2=4.01$ ,  $df=2$ ,  $p=0.13$ , for genotype distribution and  $\chi^2=0.05$ ,  $df=1$ ,  $p=0.82$ , for allele frequency).

<sup>c</sup> No significant difference between responders and nonresponders ( $\chi^2=1.60$ ,  $df=1$ ,  $p=0.21$ , for genotype distribution and  $\chi^2=1.50$ ,  $df=1$ ,  $p=0.22$ , for allele frequency).

<sup>d</sup> Excluded from the analysis because of the small number of patients ( $N=2$ ).

<sup>e</sup> No significant difference between responders and nonresponders ( $\chi^2=1.56$ ,  $df=1$ ,  $p=0.21$  for genotype distribution, and  $\chi^2=0.11$ ,  $df=1$ ,  $p=0.74$  for allele frequency).

<sup>f</sup> No significant difference between responders and nonresponders ( $\chi^2=5.30$ ,  $df=2$ ,  $p=0.07$  for genotype distribution, and  $\chi^2=1.31$ ,  $df=1$ ,  $p=0.25$  for allele frequency).

( $F=0.80$ ,  $df=4$ ,  $192$ ,  $p=0.53$ ) and T/T ( $F=2.14$ ,  $df=4$ ,  $132$ ,  $p=0.08$ ) genotype groups at 4 and 6 weeks. There was also no difference between the T/T and T/C genotype groups ( $F=1.63$ ,  $df=4$ ,  $292$ ,  $p=0.17$ ). Mean plasma concentrations of milnacipran were 84.9 ng/ml (SD=46.9), 92.5 ng/ml (SD=33.0), and 102.1 ng/ml (SD=36.8) for the T/T, T/C, and C/C genotype groups, respectively, and there was no significant difference among them ( $F=0.58$ ,  $df=2$ ,  $77$ ,  $p=0.56$ ).

Table 2 shows the genotype distribution and allele frequencies in milnacipran responders and nonresponders. There was a significant difference in the genotype distribution and allele frequencies between responders and nonresponders (Table 2). When remitters and nonresponders were compared, there was no significant difference in the genotype distribution ( $\chi^2=5.58$ ,  $df=2$ ,  $p=0.06$ ) but there was a significant difference in allele frequencies ( $\chi^2=3.91$ ,  $df=1$ ,  $p<0.05$ ) (data not shown). These results indicate that the presence of the T allele is associated with a superior therapeutic response to milnacipran.

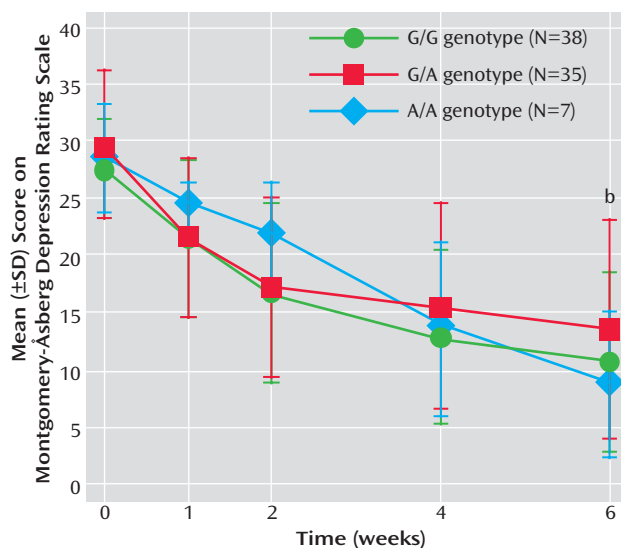
**NET G1287A polymorphism.** Figure 2 shows the Montgomery-Åsberg Depression Rating Scale scores over time in relation to the NET G1287A polymorphism. There was a significant difference between the G/A and A/A genotype groups: the A/A genotype exhibited a slower response. There were no significant differences among the genotype groups other than the one between those with the A/A and G/A genotypes. Mean plasma concentrations of milnacipran were 87.7 ng/ml (SD=31.2), 87.9 ng/ml (SD=43.0), and 115.8 ng/ml (SD=49.9) in G/G, G/A, and A/A genotype groups, respectively, and there was no significant difference among them ( $F=1.69$ ,  $df=2$ ,  $77$ ,  $p=0.19$ ). Table 2 shows

the genotype distribution and allele frequencies in the milnacipran responders and nonresponders. There was no significant difference in the genotype distribution and allele frequencies between responders and nonresponders (Table 2). When remitters and nonresponders were compared, no significant differences in the genotype distribution ( $\chi^2=3.43$ ,  $df=2$ ,  $p=0.18$ ) or allele frequencies ( $\chi^2=0.03$ ,  $df=1$ ,  $p=0.85$ ) were observed (data not shown). These results suggest that the A/A genotype is associated with a slower onset of antidepressant action but that the NET G1287A genetic polymorphism is not associated with the final therapeutic response.

### 5-HTTLPR Polymorphism and Antidepressant Effect

The individuals with the L/L genotype were included only in the allele-frequency analysis because there were only two patients in this group. Figure 3 shows the scores on the Montgomery-Åsberg Depression Rating Scale over time in relation to the 5-HTTLPR polymorphism. There was no significant difference in the time-course of Montgomery-Åsberg Depression Rating Scale scores between the S/S and S/L genotype groups ( $F=1.76$ ,  $df=4$ ,  $304$ ,  $p=0.14$ ). Mean plasma concentrations of milnacipran were 89.4 ng/ml (SD=40.3) and 93.1 ng/ml (SD=37.8) in the S/S and S/L genotype groups, respectively, and there was no significant difference between them ( $t=-0.40$ ,  $df=76$ ,  $p=0.69$ ). Table 2 shows the genotype distribution and allele frequencies in the patients who were or were not responsive to milnacipran. No significant differences in the genotype distribution and allele frequencies were noted (Table

**FIGURE 2.** Montgomery-Åsberg Depression Rating Scale Scores During 6 Weeks of Treatment With Milnacipran in Three NET G1287A Genotype Groups<sup>a</sup>



<sup>a</sup> Each point represents the mean score plus or minus standard deviation. Differences among groups examined with repeated-measures analysis of variance.

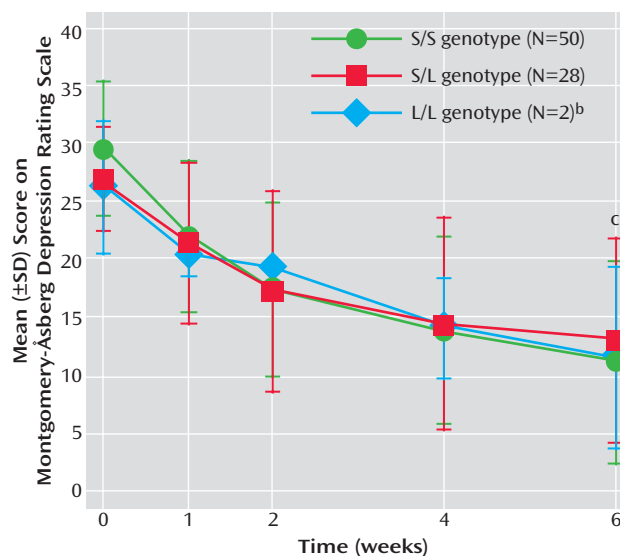
<sup>b</sup> Significant difference between G/A and A/A groups ( $F=2.56$ ,  $df=4$ ,  $160$ ,  $p=0.04$ ).

2). When remitters and nonresponders were compared, no significant differences in the genotype distribution ( $\chi^2=2.66$ ,  $df=1$ ,  $p=0.10$ ) and allele frequencies ( $\chi^2=2.23$ ,  $df=1$ ,  $p=0.14$ ) were observed (data not shown). These results suggest that the 5-HTTLPR polymorphism is not associated with the time-course and final therapeutic response to milnacipran.

#### Other Serotonergic Polymorphisms and the Antidepressant Response to Milnacipran

The 10/10 genotype individuals of the 5-HTTVNTR polymorphism were included only in the allele frequency analysis because there were only two patients in this group. There was no significant difference in the time-course of Montgomery-Åsberg Depression Rating Scale scores in each genotype group in the analysis of 5-HTTVNTR and 5-HT<sub>2A</sub> G-1438A polymorphisms (data not shown). Plasma concentrations of milnacipran were not significantly different in each genotype group in the analysis of each genetic polymorphism (data not shown). There was also no significant difference in the genotype distribution or allele frequencies between responders and nonresponders in each genetic polymorphism (Table 2). When remitters and nonresponders were compared, no significant differences in the genotype distribution (5-HTTVNTR:  $\chi^2=1.76$ ,  $df=1$ ,  $p=0.18$ ; 5-HT<sub>2A</sub> G-1438A:  $\chi^2=4.13$ ,  $df=2$ ,  $p=0.13$ ) or allele frequencies (5-HTTVNTR:  $\chi^2=1.61$ ,  $df=1$ ,  $p=0.21$ ; 5-HT<sub>2A</sub> G-1438A:  $\chi^2=1.28$ ,  $df=1$ ,  $p=0.26$ ) were observed (data not shown).

**FIGURE 3.** Montgomery-Åsberg Depression Rating Scale Scores During 6 Weeks of Treatment With Milnacipran in Three 5-HTTLPR Genotype Groups<sup>a</sup>



<sup>a</sup> Each point represents the mean score plus or minus standard deviation. Differences among groups examined with repeated-measures analysis of variance.

<sup>b</sup> Excluded from the analysis because of the small number of patients ( $N=2$ ).

<sup>c</sup> No significant difference between S/S and S/L groups.

#### Milnacipran Plasma Levels and Antidepressant Effect

The plasma milnacipran concentration of responders (mean=89.0 ng/ml, SD=34.9) and nonresponders (mean=92.3 ng/ml, SD=45.1) did not differ ( $t=0.37$ ,  $df=78$ ,  $p=0.72$ ). The plasma concentration of remitters (mean=91.8 ng/ml, SD=36.0) and nonresponders also did not differ ( $t=-0.06$ ,  $df=71$ ,  $p=0.95$ ).

#### Power

This study had a power of 0.11 to detect a small effect, 0.67 to detect a medium effect, and 0.99 to detect a large effect in the genotype distribution ( $N=80$ ). For the allele frequency analysis ( $N=160$ ), this study had a power of 0.24 to detect a small effect, 0.97 to detect a medium effect, and 0.99 to detect a large effect. In this power analysis, effect size conventions were determined according to the method of Buchner et al. (17) as follows: small effect size=0.10, medium effect size=0.30, large effect size=0.50 ( $\alpha=0.05$ ).

#### Discussion

The present study revealed that NET but not 5-HTT polymorphisms affected the antidepressant response to milnacipran, an SNRI. The presence of the T allele of the NET T-182C polymorphism was associated with a greater therapeutic response, and the presence of the A/A genotype of the NET G1287A polymorphism was associated with a slower onset of therapeutic response.

Several investigators have studied the relationship between NET genetic polymorphisms and susceptibility to psychiatric disorders, including major depression, bipolar disorder, schizophrenia, and alcohol dependence (15, 18–20), without observing major findings. However, our findings in the present study suggest that it is possible to predict the antidepressant response to an SNRI with the use of NET polymorphisms. It is unclear why the 5-HTTLPR polymorphism does not predict the antidepressant response to milnacipran. As noted, controversy exists in this area concerning SSRI response.

The NET G1287A polymorphism was reported to be a silent mutation (21). However, Jönsson et al. (16) reported that this polymorphism was associated with the CSF concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), a major norepinephrine metabolite. They reported that CSF MHPG concentrations were higher in the G/G genotype than in the G/A and A/A genotypes. The NET G1287A polymorphism may be in linkage disequilibrium with an as-yet unidentified functional polymorphism. Higher concentrations of MHPG have been postulated to be attributable to more active reuptake of norepinephrine. Because patients with the A/A genotype have less active reuptake of norepinephrine, the effect of reuptake inhibition might occur more slowly.

The NET T-182C polymorphism was first reported by Zill et al. (15), and its functional consequences remain obscure. Such functional information would aid in interpretation of the findings obtained in this study. Further studies are needed to analyze its potential effects on NET expression.

Collier et al. (22) reported that the transcriptional activity of the L allele of the 5-HTTLPR polymorphism was more than twice as high as that of the S allele in transformed lymphoblast cell lines. However, using positron emission tomography, Shioe et al. (23) recently reported that 5-HTT binding in vivo was not significantly different among the 5-HTTLPR genotypes. Lovejoy et al. (24) reported that individual repeat elements within the 5-HTTVNTR domain differed in their enhancer activity in an embryonic stem cell model. These elements may be active in response to specific stimuli, but their functional effect in vivo has not been reported. Turecki et al. (25) reported that the 5-HT<sub>2A</sub> G-1438A polymorphism affected 5-HT<sub>2A</sub> receptor binding in postmortem brain samples, but Bray et al. (26) reported that the 5-HT<sub>2A</sub> G-1438A variant did not exert a significant effect on 5-HT<sub>2A</sub> receptor mRNA expression in postmortem brain tissue. We noted no consistent effect of serotonergic genetic polymorphisms in this study.

One major limitation of this study is the relatively small number of subjects and the fact that the endpoint treatment differences were relatively small. A second limitation is the short duration of treatment. The washout period in this study was 2 weeks. Most of the patients in this study were experiencing their first episode of depression and were medication-free before entry into the study. Several

patients had previously been treated with SSRIs, but the only available SSRIs in Japan are fluvoxamine and paroxetine. Fluoxetine, a very long half-life SSRI, is not available in Japan.

Patients with comorbid axis I or axis II disorders were excluded to ensure a relatively homogeneous sample. The relatively high rate of substance abuse in the United States (8.3% of the population 12 years old or older was reported to have used any illicit drug during the past month [27]) may suggest that it is unusual that we could select patients with no comorbid substance abuse. However, in Japan, only 0.1% of the population 15 years old or older had used illicit substances during the past year (28). The low prevalence rate of substance abuse in Japan renders it relatively easy to select patients with major depressive disorder who do not have substance abuse.

The results of this study should be confirmed outside of Japan, because ethnic differences have been reported in studies seeking to determine the influence of the 5-HTTLPR polymorphism on the antidepressant response to SSRIs (29).

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