

No Association between Serotonin Receptor 2C -759C/T Polymorphism and Weight Change or Treatment Response to Mirtazapine in Korean Depressive Patients

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Objective Activation of one or more serotonin (5-HT) receptors may play a role in mediating the antidepressant effects of serotonergic antidepressants. The serotonin 2C (5HT 2C) receptor is known to be associated with antidepressant action and weight gain. We sought to determine whether the 5-HT_{2C} receptor -759C/T polymorphism was associated with weight gain and treatment response to mirtazapine in major depressive disorder (MDD) patients.

Methods The 5-HT_{2C} receptor -759C/T polymorphism was analyzed in 323 MDD patients. All patients were evaluated using the 21-item Hamilton Depression Rating Scale at the beginning of the study and at 1, 2, 4, and 8 weeks of mirtazapine treatment.

Results There was no significant difference in the 5-HT_{2C} receptor -759C/T genotype distribution between responder and non-responder groups. The 5-HT_{2C} receptor -759C/T polymorphism was not associated with weight change over time after mirtazapine administration.

Conclusion The 5-HT_{2C} receptor -759C/T polymorphism does not appear to be a predictor of treatment response to mirtazapine. This polymorphism was not associated with weight change after 8 weeks of mirtazapine treatment. Further investigation on other polymorphisms of the 5-HT_{2C} gene is required to determine whether the 5-HT_{2C} gene influences treatment response and weight change after mirtazapine administration in patients with major depressive disorder.

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Key Words Serotonin 2C receptor, Major depressive disorder, Mirtazapine, Polymorphism.

INTRODUCTION

The neurobiological mechanisms of responses to antidepressant agents involve alterations in the functions of neurotransmitter systems, especially the serotonergic and noradrenergic systems.^{1,2}

The noradrenergic- and serotonergic-specific antidepressant, mirtazapine, has recently been introduced. It seems that mirtazapine works in a different manner to other SSRIs.³

Weight gain is one of the commonly reported adverse events after mirtazapine administration.^{4,5} The candidate receptor profiles for weight gain in mirtazapine are considered to involve blocking of the function of the serotonin 2C receptor (5-HT_{2C}) and histamine receptor blocking.

The 5-HT_{2C} gene is located on the X chromosome at q24 and contains six exons and five introns, spanning at least 230 kb of DNA.^{6,7} The 5-HT_{2C} receptor has different transcriptional activity according to the 5-HT_{2C} -759C/T polymorphism (rs3813929).⁸

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5-HT_{2C} receptor density and responsiveness is enhanced in experimental models of depression and in humans.^{9,10} The function of 5-HT_{2C} receptors has been suggested to be abnormal in individuals with depression.¹¹ Moreover, the 5-HT_{2C} receptor gene has been a major focus of psychopharmacological research regarding weight gain.^{12,13}

The aim of the present study was to examine whether the 5-HT_{2C} -759C/T polymorphism (rs3813929) was associated with weight change and the treatment response to mirtazapine in Korean patients with major depressive disorder (MDD).

METHODS

Subjects

Between 2005 and 2007, three hundred twenty three in- and outpatients with major depressive disorder were recruited by the Pharmacogenomic Research Center for Psychotropic Drugs at the Department of Psychiatry, Korea University College of Medicine. All potential subjects were examined by trained psychiatrists using the Structured Clinical Interview of the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).¹⁴ All subjects were of the melancholic type. Depression severity was assessed according to the 21-item Hamilton Depression Rating (HAM-D21) scale.¹⁵ Only subjects with a minimum HAM-D score of 18 were enrolled in the study.¹⁶ During the study period, patients self-administered an initial dose of 15-30 mg of mirtazapine (Remeron, Organon), followed by daily doses of 15-60 mg for up to 8 weeks. The daily dose was determined on an individual basis at the discretion of the investigators. Benzodiazepine was allowed as a co-prescribed drug. At baseline, 323 MDD patients were enrolled. Of 323 patients, the number remaining in the study was 249 at week 1, 202 at week 2, and 172 at week

4; 149 patients completed 8 weeks of mirtazapine treatment.

Subjects with primary or comorbid diagnoses of schizophrenia, schizoaffective disorder, rapid cycling bipolar disorder, dementia, or alcohol or substance dependence, based on DSM-IV criteria, within the previous 6 months were excluded. We also excluded subjects who had a personal or family history of substance abuse/dependence or other major psychiatric disorders prior to the study. Patients taking medications were subjected to a 2-week washout period; patients taking psychotropic medications or other medications that might influence mirtazapine metabolism were subjected to an 8-week washout period. Demographic data were recorded, and patients with serious or unstable medical illnesses were excluded. All subjects were at least 18 years of age.

Responders were defined as subjects who exhibited a decrease of at least 50% in the HAM-D total score after mirtazapine medication.¹⁷ To evaluate specific clusters of depressive symptoms, HAM-D items were grouped according to the following factors, as described by Serretti et al.¹⁸: core (items 1, 2, 7, 8, 10, 13), sleep (items 4, 5, 6), activity (items 7, 8), psychic anxiety (items 9, 10), and somatic anxiety (items 11, 12, 13).

After written informed consent was obtained, venous blood was drawn from each subject. This study was approved by the ethics committee of the Korea University Medical Center.

DNA analysis

DNA was extracted from peripheral blood, and polymerase chain reaction (PCR) was performed using the following primers¹²: sense, 5'-ATC TCC ACC ATG GGG TCT CGC-3' and antisense, 5'-CAA TCT AGC CGC TCC AAA GGC-3'. The amplification mixture contained 3 µL of DNA, 15 µL of 2× GC buffer (TaKaRa, Kyoto, Japan), 4 µL of 2.5 mM dNTP, 1 µL of each primer, 8.4 µL of distilled water, and 0.1 µL of Taq

Table 1. Demographic data and clinical characteristics according to 5-HT_{2C} polymorphism

Female	Genotype			P
	CC	CT	TT	
N	183	56	4	
Age (yr, mean±SD)	50.86±14.60	53.02±12.19	59.25±5.56	0.325
Baseline weight	56.99±8.34	56.66±8.59	63.03±17.58	0.456
Suicide attempt (Y, %)	17 (9.6)	2 (3.7)	0 (0)	0.317
Family history of depression (Y, %)	23 (13.0)	7 (13.5)	0 (0)	0.857
Male	C		T	P
N	75		5	
Age (yr, mean±SD)	49.24±14.17		47.8±16.56	0.828
Baseline weight	67.68±10.33		65.60±4.09	0.692
Suicide attempt (Y, %)	3 (4.2)		0 (0)	0.642
Family history of depression (Y, %)	14 (19.4)		0 (0)	0.276

5-HT: serotonin, C: cytosine, T: thymine, yr: years, Y: present

polymerase (5 U/ μ L; TaKaRa). Samples were amplified using a PCR thermocycler (Takara) for an initial 5 min at 94°C followed by 30 cycles of 30 seconds at 94°C, 25 s at 56°C, and 30 s at 72°C. After a final 7-min extension at 72°C, the reaction was terminated by cooling to 4°C. Amplified DNA was digested with the restriction endonuclease AciI (New England Biolabs, Beverly, MA). The products were electrophoresed on a 3% agarose gel and stained with ethidium bromide; the 128-bp, 92-bp, and 33-bp fragments corresponded to the -759 C allele, and the 161-bp and 92-bp fragments corresponded to the -759 T allele.

Statistical analyses

Hardy-Weinberg equilibrium for the 5-HT 2C -759 C/T polymorphism was tested using a χ^2 test. The genetic association of the SNP was analyzed using multiple logistic regression and linear regression for categorical data and continuous variables, respectively, controlling for age and gender as covariates. Repeated-measures ANOVAs were performed for each weekly HAMD score in LOCF data. Survival analysis was performed by the method of Kaplan and Meier, and comparisons of response and drop-out by log-rank analysis.

A $p \leq 0.05$ was deemed to indicate statistical significance. All statistical analyses were performed using SPSS (version 10.0;

Table 2. The change of HAMD scores over time according to 5-HT2C polymorphism in female patients with major depressive disorder

Scores	Time	Genotype*			P
		CC	CT	TT	
Total	Baseline	22.80 \pm 4.54	22.03 \pm 4.12	25.50 \pm 6.75	0.065
	1 w	16.60 \pm 5.43	16.86 \pm 5.71	18.50 \pm 3.54	
	2 w	13.78 \pm 5.70	14.19 \pm 6.20	18.00 \pm 4.24	
	4 w	11.57 \pm 5.48	13.27 \pm 6.77	18.00 \pm 4.24	
	8 w	11.22 \pm 5.57	13.54 \pm 7.62	18.00 \pm 4.24	
Core	Baseline	9.31 \pm 2.36	9.11 \pm 2.06	10.25 \pm 1.26	0.286
	1 w	7.08 \pm 2.42	6.97 \pm 2.42	8.00 \pm 2.83	
	2 w	6.16 \pm 2.43	6.24 \pm 2.61	7.50 \pm 3.54	
	4 w	5.37 \pm 2.57	5.76 \pm 2.57	7.50 \pm 3.54	
	8 w	5.30 \pm 2.55	5.84 \pm 3.05	7.50 \pm 3.54	
Sleep	Baseline	3.43 \pm 2.06	3.39 \pm 1.87	5.50 \pm 1.00	0.156
	1 w	2.21 \pm 1.97	2.51 \pm 2.17	5.50 \pm 0.71	
	2 w	1.92 \pm 1.97	1.86 \pm 2.00	4.50 \pm 2.12	
	4 w	1.45 \pm 1.72	1.95 \pm 1.94	4.50 \pm 2.12	
	8 w	1.33 \pm 1.69	2.08 \pm 1.98	4.50 \pm 2.12	
Activity	Baseline	2.88 \pm 1.05	2.70 \pm 1.11	3.00 \pm 0.00	0.253
	1 w	2.26 \pm 1.07	2.11 \pm 1.24	2.00 \pm 1.41	
	2 w	1.97 \pm 1.13	2.00 \pm 1.22	2.00 \pm 1.41	
	4 w	1.62 \pm 1.10	1.81 \pm 1.20	2.00 \pm 1.41	
	8 w	1.63 \pm 1.04	1.76 \pm 1.23	2.00 \pm 1.41	
Psychic anxiety	Baseline	3.14 \pm 1.30	3.29 \pm 0.80	3.00 \pm 1.63	0.548
	1 w	2.46 \pm 1.22	2.70 \pm 1.18	2.50 \pm 0.71	
	2 w	2.03 \pm 1.12	2.22 \pm 1.23	3.00 \pm 0.00	
	4 w	1.89 \pm 1.11	1.89 \pm 1.20	3.00 \pm 0.00	
	8 w	1.78 \pm 1.11	2.11 \pm 1.51	3.00 \pm 0.00	
Somatic anxiety	Baseline	3.74 \pm 1.19	3.48 \pm 1.19	2.50 \pm 1.29	0.658
	1 w	2.90 \pm 1.35	2.84 \pm 1.07	1.50 \pm 0.71	
	2 w	2.49 \pm 1.31	2.57 \pm 1.09	2.00 \pm 0.00	
	4 w	2.24 \pm 1.27	2.46 \pm 1.17	2.00 \pm 0.00	
	8 w	2.16 \pm 1.25	2.24 \pm 1.26	2.00 \pm 0.00	

Repeated measure ANOVA. Mean \pm standard deviation. *genotype of 5-HT2C-759C/T. HAMD: Hamilton Depression Rating, ANOVA: analysis of variance

SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics of study subjects for the 5-HT 2C -759 C/T polymorphism

Table 1 summarizes patient data for mean age, frequency of suicide attempts, and family history of MDD. For both genders, there were no significant differences in clinical characteristics according to the 5-HT 2C -759 C/T polymorphism. The 5-HT 2C -759C/T polymorphism was in Hardy-Weinberg equilibrium in females ($p=0.90$).

Association between the 5-HT 2C -759 C/T polymorphism and HAMD21 score in MDD patients

In histograms, the HAMD score seemed normally distributed. First, we evaluated the relationship between the 5-HT 2C -759 C/T polymorphism and baseline HAMD-21 scores in the Korean MDD patients. As shown in Table 2, baseline HAMD-21 scores did not differ according to the 5-HT 2C -759 C/T genotypes or alleles. In female patients with MDD, there was no significant difference in total HAMD score among three genotypes over the 8-week treatment adjusted to baseline HAMD score. There was no significant difference in HAMD subscale score according to allele in repeated measures ANO-

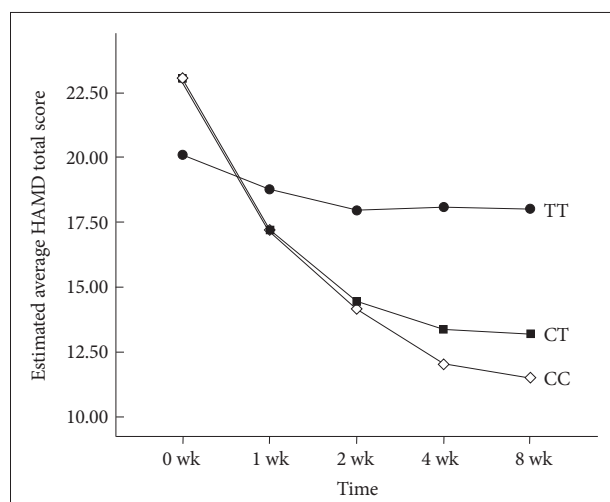


Figure 1. HAMD change over 8 weeks according to the 5-HT 2C gene -759 C/T allele in female depressive patients. HAMD: Hamilton Rating Scale for Depression.

VA (Table 2). There was no significant difference in response and drop-out according to genotypes using survival analysis ($p=0.35$).

No significant difference in HAMD change over 8 weeks was found between the two alleles in females (Figure 1). No significant association was found between the 5-HT 2C -759 C/T polymorphism and HAMD score in males.

We used logistic regression to evaluate the relationship between the 5-HT 2C -759 C/T polymorphism and clinical outcome at 8 weeks after initiation of mirtazapine treatment. The 5-HT 2C -759 C/T genotypes and allele distributions were not significantly different between responders and non-responders in a codominant genetic model at 8 weeks (Table 3). In a dominant or recessive genetic model, 5-HT 2C -759 C/T genotypes and allele distributions were not different between responders and non-responders (data not shown). The 5-HT 2C -759 C/T genotypes and allele distributions were not significantly different between remitters and non-remitters in codominant, dominant, and recessive genetic models at 8 weeks (data not shown).

Association between the 5-HT 2C -759 C/T polymorphism and weight gain after mirtazapine treatment in MDD patients

No significant difference in weight at baseline was observ-

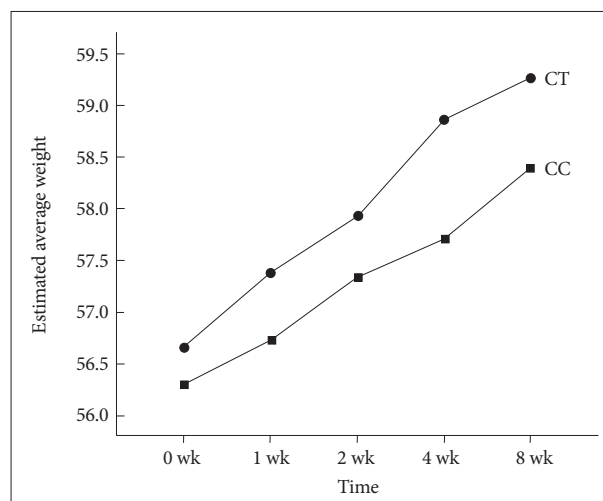


Figure 2. Weight change over 8 weeks according to the 5-HT 2C gene -759 C/T allele in female depressive patients.

Table 3. The effect of 5-HT 2C polymorphism on the treatment response to mirtazapine at 8 weeks in female patients with major depressive disorder (codominant model)

	Genotype			P	Allele		
	C/C	C/T	T/T		C	T	P
Responder (%)	75 (81.5)	19 (18.5)	0 (0)	0.319*	167 (90.8)	17 (9.2)	0.277†
Non-responder (%)	114 (76.6)	20 (21.3)	2 (2.1)		164 (87.2)	24 (12.8)	

*OR: 0.8 (confidence interval 0.38-1.69), †OR: 0.84 (confidence interval 0.38-1.87). OR: odds ratio

ed among the three genotypes. When we evaluated the weight gain at 1, 2, 4, and 8 weeks adjusted to baseline weight using repeated measures ANOVA, no significant association between weight change and 5-HT 2C -759 C/T allele was found in females (Figure 2). No significant association was found between the 5-HT 2C -759 C/T polymorphism and weight change in males.

DISCUSSION

The aim of this study was to examine whether the 5-HT 2C receptor -759 C/T polymorphism was associated with weight change or treatment response after mirtazapine administration in MDD patients. We demonstrated that weight change after mirtazapine administration was not significantly different among the three 5-HT 2C -759 C/T genotypes. Several pharmacogenetic studies have examined antipsychotic agent-induced weight gain (e.g., clozapine,^{19,20} risperidone,²¹ and olanzapine²²). It has been reported that 759T had protective effects against obesity and diabetes¹² and showed higher transcriptional activity than 759C.⁸ However, some results are inconsistent.^{23,24} A possible reason for non-significance in the present study is as follows. It is known that weight gain is mainly attributed to the antihistaminic activity of mirtazapine, including 5-HT 2C receptor blocking.⁴ In a rat study, antagonists for specific receptors were shown to increase food intake (e.g., with 5-HT 2C antagonists²⁵ and the histamine H1 receptor²⁶). Thus, polymorphisms on the histaminergic receptor may influence weight gain.

We demonstrated that treatment responses to mirtazapine were not significantly different among the three 5-HT 2C 759 C/T genotypes. Agents that bind to 5-HT_{2C} receptors with a high affinity, such as m-chlorophenylpiperazine, induce dysphoric effects in some depressive illnesses.²⁷ Conversely, electrophysiological and biochemical data demonstrate that 5-HT 2C receptor antagonists enhance mesocorticolimbic DA function.²⁸ Thus, 5-HT_{2C} (and -2A) receptor antagonists (e.g., ketanserin and ritanserin) are clinically efficacious antidepressants.^{29,30} Consistent with this result, it was reported that there was no significant association between 5-HT 2C receptor 759 C/T polymorphism and treatment response or weight change during treatment with mirtazapine.³¹

Regarding the potential influence of the 5-HT 2C polymorphism on the psychopathology of major depressive disorder, 5-HT 2C polymorphism was not associated with symptomatology in the present study. Regarding activity associated with the dopamine system, a significant difference in activity subscale scores of the HAM-D was found among the three genotypes of the 5-HT 2C receptor 759 C/T polymorphism. Consistent with the present study, no association was found between 5HT

2C and psychopathology, as defined by the four symptomatologic factors used in phenotype definition (mania, depression, delusion, disorganization), even when bipolar subjects were analyzed separately.³²

This study has some limitations. First, although a single gene may affect responses to antidepressants, any single gene likely plays a relatively minor role in a complex process. Moreover, it was recently suggested that weight gain in response to certain drugs is also associated with another polymorphism of the promoter of the 5-HT_{2C} gene, the -697G/C polymorphism.³³ Thus, further studies are required to investigate the cumulative effect of interactions with other genes. Second, we did not analyze plasma mirtazapine levels, although we made efforts (tablet count checks and detailed interviews by psychiatrists and research nurses) to exclude patients with poor or no drug compliance. Because mirtazapine is mainly metabolized by a P450 enzyme, performing CYP2D6 genotyping would improve the accuracy of the present results. Third, patients did not take regular doses of mirtazapine. This created another confounding factor that might have influenced both response to treatment and weight gain. Fourth, since HAM-D score is based on patients' answers, the possibility that the response could be misclassified should also be added to the limitations of the present study.

Notwithstanding these limitations, this study is a first step in examining the potential association between 5-HT 2C gene polymorphisms and mirtazapine effects in Korean depressive patients. Few studies have examined the association between the 5HT 2C receptor 759 C/T polymorphism and weight gain in mirtazapine treatment. Finally, identification of other polymorphisms related to 5-HT 2C activity would be useful in clarifying the role of the 5-HT 2C gene in response to mirtazapine administration.

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