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# RELATIONSHIP BETWEEN THE SEROTONIN RECEPTOR 1A POLYMORPHISM WITH TREATMENT RESPONSE TO ESCITALOPRAM IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Hun Soo Chang, In-Kwang Choi, Hwa-Young Lee, Yoo-Jung Jeong, Bohye Kim, Min-Soo Lee

## Abstract

*Objective:* Serotonin 1A receptor (HTR1A) is a candidate molecule for influencing the pathophysiology of major depressive disorder (MDD) and clinical responses to antidepressant treatment. Among polymorphisms of the HTR1A gene, *-1019C>G* (rs6295) is reportedly a biologically functional polymorphism associated with response to antidepressant treatment. The aim of this study was to determine the relationship between the *HTR1A-1019C>G* polymorphism and the response to escitalopram in patients with MDD.

*Method:* Eighty Korean patients were examined using the Structured Clinical Interview for DSM-IV Axis I disorders and took escitalopram at a daily dose of 5 to 40 mg. Clinical symptoms were evaluated using the 21-item Hamilton Depression Rating (HAM-D) scale during 8 weeks of treatment. The genotypes were determined using HpyCH4 IV digestion following polymerase chain reaction.

*Results:* The proportion of *G*-allele carriers was 25.0% in responders, which was lower than that in non-responders (53.9%) at 1 week of escitalopram treatment (OR = 0.28, P = 0.030). In allelic analysis, the frequency of the *G* allele was significantly lower in responders at 1 week than in non-responders (12.5% versus 31.7%, respectively; OR = 0.29, P = 0.029). Similarly, the ratio of HAM-D score at 1 week to the baseline score in *C*-allele carriers was 67.6% ± 2.42%, which was significantly lower than the ratio of 75.8% ± 2.74% in patients possessing the *G* allele (P = 0.027).

*Conclusions:* Although this study is preliminary and has several limitations, our results suggest that *HTR1A-1019C>G* may be a genetic marker predicting the response to escitalopram treatment.

**Key words**: serotonin receptor 1A, escitalopram, major depressive disorder, single-nucleotide polymorphism, treatment response

**Declaration of interest:** the authors declare that they have no competing interests

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## Introduction

Patients with major depressive disorder (MDD) show malfunctions in the monoaminergic neurotransmission system, including decreased amounts of monoamine neurotransmitters such as serotonin (5-HT) or norepinephrine (NE) and overexpression of monoamine receptors in synapses (Owens and Nemeroff 1994, Charney 1998, Delgado and Moreno 2000).

Serotonin receptor 1A (HTR1A: MIM *109760) plays important roles in modulation of the neurosignaling and pathophysiology of depression. Binding of serotonin to the HTR1A autoreceptor on dendrites and the cell body of serotonergic neurons inhibits the release of serotonin into the synapse (Verge et al. 1985, Sprouse and Aghajanian 1987, Richer et al. 2002). On the other hand, postsynaptic HTR1A has been thought to be involved in cognition (Borg et al. 2006), anxiety (Heisler et al. 1998, Gross et al. 2002), and depression through hormonal regulation (Van de Kar et al. 1985, Pan and Gilbert 1992, Blier et al. 2002). The differential alternation of the HTR1A level both pre- and post-synapse is involved in regulation of the serotonin neurotransmission system and the pathophysiology of depression. In corticolimbic regions, the level of post-synaptic HTR1A receptors is reduced in depression

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(Sargent et al. 2000, Bhagwagar et al. 2004, Moses-Kolko et al. 2008, Stockmeier et al. 2009). In contrast, somatodendritic HTR1A autoreceptors in the raphe nuclei are increased in depression (Stockmeier et al. 1998, Drevets et al. 2007, Boldrini et al. 2008), which results in downregulation of the activity of the 5-HT system (Hjorth and Auerbach 1994, Hjorth et al. 1996, Richer et al. 2002, Bortolozzi et al. 2004, Liu et al. 2005). The 5-HT1A receptor also plays a role in the neuronal migration, neurite outgrowth, and synapse formation inherent to the neurodevelopmental process (Whitaker-Azmitia et al. 1996).

Because of its importance in serotonergic neurotransmission and in MDD, HTR1A has been a major target of pharmacogenetic studies of antidepressants. Among polymorphisms of the HTR1A gene, the *-1019C>G* single-nucleotide polymorphism (rs6295) reportedly affects the expression and function of HTR1A (Lemonde et al. 2003, Czesak et al. 2006, Le Francois et al. 2008). The GG genotype on *-1019C>G* was reported to be associated with a better response to antidepressants, especially selective serotonin reuptake inhibitors (SSRI), in Asian patients with MDD (Hong et al. 2006, Kato et al. 2009). The *-1019GG* genotype was significantly associated with a better response to transcranial magnetic stimulation (TMS) in an Italian population (Zanardi et al. 2007, Malaguti et al. 2011).

In contrast, no association between *HTR1A-1019C>G* and treatment response was found in several studies of Caucasian populations (Lemonde et al. 2004, Serretti et al. 2004, Levin et al. 2007). Moreover, although they used relatively small samples, Parsey et al. reported that the CC genotype on *-1019C>G* was associated with a better response to various antidepressants and ECT treatment (Parsey et al. 2006). These conflicting reports suggest the need for further examination of the association between *HTR1A-1019C>G* and the treatment response to antidepressants.

The purpose of this study was to determine the relationship between the -1019C>G polymorphism in the HTR1A gene and clinical outcomes of escitalopram treatment in Korean patients with MDD.

## Methods

### *Subjects*

Eighty Korean subjects were recruited from outpatients visiting the Psychiatric Clinic of Korea University Anam Hospital and gave written informed consent to participate in the study. Trained psychiatrists examined all subjects using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) and the Korean version of the Diagnostic Interview for Genetic Studies (K-DIGS). The severity of depression was assessed using the 21-item Hamilton Depression Rating (HAM-D21) scale. Only subjects with a minimum score of 18 on the HAM-D21 were enrolled.

Patients with primary or comorbid diagnoses of schizophrenia, schizoaffective disorder, rapid cycling bipolar disorder, dementia, and alcohol- or substance-dependence based on DSM-IV criteria were excluded from the study. We also excluded patients with a personal or family history of substance abuse/dependence. Patients who were receiving psychotropic medications were subjected to a 2-week washout period. Demographic data, medical history, and laboratory data were documented. Patients with serious or unstable medical illness were also excluded from the study. All subjects were 18 to 65 years of age.

During the treatment period of the study, all subjects took escitalopram (Lexapro®, Lundbeck) at a daily dose of 5 to 40 mg. Psychotropic drugs such as benzodiazepines and mood stabilizers were not permitted. The protocol was approved by the Ethics Committee of the Korea University Medical Center.

Clinical symptoms were evaluated using the HAM-D21 at baseline and after 1, 2, 4, and 8 weeks of treatment. Responders (Rp) were those who showed a ≥50% decrease in their HAM-D21 score compared with that at baseline (Frank et al. 1991).

### *Genotyping of HTR1A-1019C>G*

*HTR1A-1019C>G* genotypes were analyzed using polymerase chain reaction (PCR). The PCR was performed using the sense primer 5'-TGG AAG AAG ACC GAG TGT GTC TAC-3' and antisense primer 5'-TTC TCC CTG GGA GAG TAA GGC TGG-3'. Each amplification mixture contained genomic DNA extracted from peripheral blood of subjects, 2 μl 10× PCR buffer, 4 μl i-GCapture solution, 2 μl 2.5 mM dNTP, 10 pmol of each primer, and 0.3 μl i-Taq™ DNA polymerase (5 U/μl; iNtRon, Korea). PCR mixtures were amplified using PCR Thermal Cycler (TaKaRa, Japan) for an initial denaturation for 2 min at 94°C, followed by 30 cycles of denaturation for 20 sec at 94°C, annealing for 10 sec at 57°C, and extension for 30 sec at 72°C. After a final extension for 5 min at 72°C, the reaction was terminated at 4°C. The amplified DNA was digested at 37°C overnight with the restriction enzyme HpyCH4 IV (New England Biolabs, USA), which cleaves at site -1019C. The product was electrophoresed on 2.5% agarose gels stained with ethidium bromide; the 182-bp fragment corresponded to the *-1019G* allele, and the 158- and 24-bp fragments corresponded to the *-1019C* allele.

### *Statistical analysis*

The Hardy−Weinberg equilibrium for the *HTR1A-1019C>G* polymorphism was tested using a $\chi^2$ test. The genetic association of the SNP was analyzed using multiple logistic regression and generalized linear model (GLM) type III for categorical data and continuous variables, respectively, controlling for age and sex as covariates. A *P*-value of ≤0.05 was regarded as statistically significant. The power to detect associations given the sample size was analyzed using G·Power ver. 3.1 (Buchner et al. 1996). All statistical analyses were performed using SPSS version 10.0 (SPSS, Inc., Chicago, IL, USA).

## Results

### *Clinical characteristics of study subjects and Hardy−Weinberg equilibrium for the HTR1A-1019C>G polymorphism*

Chi-square tests applied to the three genotype frequencies revealed Hardy−Weinberg equilibrium ($\chi^2$ = 0.033, *P* = 0.856). **Table 1** summarizes the patient data in terms of mean age, age at onset, gender, previous history of depression, experience of stressful life events, frequency of suicide attempts, family history of MDD or other psychotic diseases, and baseline HAM-D-21 scores. None of these parameters differed significantly among the three genotypes. Additionally, baseline HAM-D21 scores did not differ according to *HTR1A-1019C>G* genotypes or alleles.

**Table 1**. *Demographic characteristics in the major depressive disorder intention-to-treat (ITT) group*

| | *HTR1A-1019C>G* | | | *P*-value |
|---|---|---|---|---|
| | *CC* | *CG* | *GG* | |
| N | 41 | 33 | 6 | 0.856* |
| Age (yr, mean ± SE) | 46.56 ± 2.48 | 46.42 ± 2.49 | 49.17 ± 7.35 | 0.920 |
| Onset age (yr, mean ± SE) | 40.20 ± 2.65 | 39.97 ± 2.84 | 43.67 ± 6.91 | 0.879 |
| Sex (male, %) | 5 (12.2%) | 5 (15.2%) | 0 (0.0%) | 0.585 |
| Previous history of depression (present, %) | 32 (78.0%) | 25 (75.8%) | 4 (66.7%) | 0.826 |
| Suicide attempt (present, %) | 3 (7.3%) | 2 (6.1%) | 1 (16.7%) | 0.662 |
| Stressful life event (present, %) | 15 (36.6%) | 19 (57.6%) | 4 (66.7%) | 0.123 |
| Family history of depression (present, %) | 5 (12.2%) | 3 (9.1%) | 1 (16.7%) | 0.832 |
| Family history of other psychotic disease (present, %) | 2 (4.9%) | 5 (15.2%) | 1 (16.7%) | 0.292 |
| Baseline HAM-D21 score (mean ± SE) | 22.90 ± 0.66 | 21.94 ± 0.68 | 24.00 ± 2.11 | 0.425 |

* P-values for Hardy-Weinberg Equilibrium (chi-square test, *d.f.* = 1).

**Table 2**. *Association analysis of HTR1A-1019C>G with the response to escitalopram treatment in major depressive disorder patients*

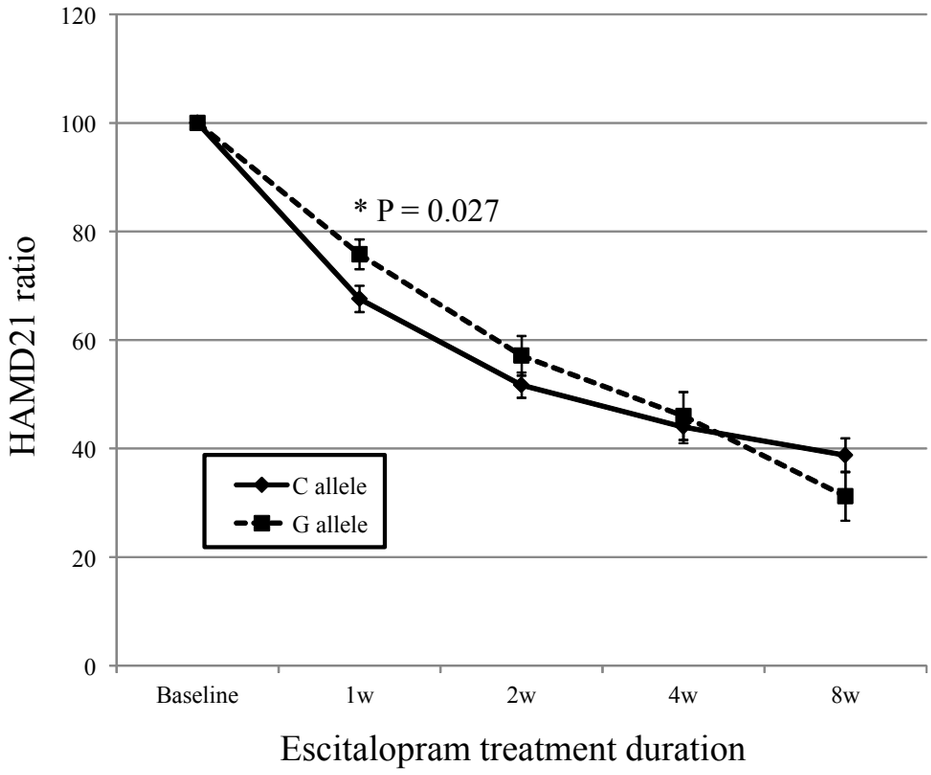
| Duration | Response status | Genotype | | | | *P* | OR [95%CI] | Allele | | | *P* | OR [95%CI] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CC | CG | GG | Total | | | C | G | Total | | |
| 1 w | Non-responders | 29 (46.0%) | 28 (44.4%) | 6 (9.5%) | 63 (100%) | 0.030 | 0.28 [0.09–0.88] | 86 (68.3%) | 40 (31.7%) | 126 (100%) | 0.029 | 0.29 [0.09–0.88] |
| | Responders | 12 (75.0%) | 4 (25.0%) | 0 (0.0%) | 16 (100%) | | | 28 (87.5%) | 4 (12.5%) | 32 (100%) | | |
| 2 w | Non-responders | 17 (44.7%) | 17 (44.7%) | 4 (10.5%) | 38 (100%) | 0.339 | 0.69 [0.32–1.49] | 51 (67.1%) | 25 (32.9%) | 76 (100%) | 0.102 | 0.18 [0.02–1.41] |
| | Responders | 17 (58.6%) | 10 (34.5%) | 2 (6.9%) | 29 (100%) | | | 44 (75.9%) | 14 (24.1%) | 58 (100%) | | |
| 4 w | Non-responders | 12 (50.0%) | 9 (37.5%) | 3 (12.5%) | 24 (100%) | 0.754 | 0.87 [0.38–2.03] | 33 (68.8%) | 15 (31.3%) | 48 (100%) | 0.320 | 0.67 [0.30–1.48] |
| | Responders | 19 (47.5%) | 18 (45.0%) | 3 (7.5%) | 40 (100%) | | | 56 (70.0%) | 24 (30.0%) | 80 (100%) | | |
| 8 w | Non-responders | 10 (66.7%) | 5 (33.3%) | 0 (0.0%) | 15 (100%) | 0.148 | 2.42 [0.73–8.03] | 25 (83.3%) | 5 (16.7%) | 30 (100%) | 0.634 | 0.79 [0.31–2.06] |
| | Responders | 19 (48.7%) | 15 (38.5%) | 5 (12.8%) | 39 (100%) | | | 53 (67.9%) | 25 (32.1%) | 78 (100%) | | |

### *Association between HTR1A-1019C>G and escitalopram treatment response in patients with MDD*

We evaluated the relationship between the *HTR1A-1019C>G* polymorphism and escitalopram treatment response. As shown in **table 2**, *HTR1A-1019C>G* was associated with the treatment response at 1 week of escitalopram treatment. The proportion of *G*-allele carriers was 25.0% in responders, which was lower than

that in non-responders (53.9%) at the corresponding time points (OR = 0.28, *P* = 0.030). In allelic analysis, the frequency of the *G* allele was significantly lower in responders at 1 week compared with that in non-responders (12.5% versus 31.7%, respectively; OR = 0.29, P = 0.029) (**table 2**). This observation of the allelic association was confirmed in the analysis for the percent decline in HAM-D21 scores by escitalopram treatment (**figure 1**). At 1 week of escitalopram treatment, the percentile ratio of HAM-D21 scores to the baseline score in *C*-allele carriers was 67.6% ± 2.42%, which was significantly lower than the 75.8% ± 2.74% ratio found in patients possessing the *G* allele (P = 0.027).

**Figure 1**. *The comparison of % decline of HAM-D21 score by escitalopram treatment at indicated period between HTR1A-1019C>G allele (C vs G). The numbers presented above the time point indicated P values, which were obtained by type III generalize linear model (GLM) age and sex as covariates*




### *Association between HTR1A-1019C>G and remission status by escitalopram treatment*

Because an association between the *HTR1A-1019C>G* polymorphism and the response to escitalopram treatment was observed, we also evaluated the relationship between the polymorphism and remission status by the escitalopram treatment response. As shown in **table 3**, however, *HTR1A-1019C>G* genotypes did not show a significant association with remission during the study period from 1 to 8 weeks. Similarly, the frequencies of the *C* and *G* alleles were comparable in remitters and non-remitters during the study period.

## Discussion

In this study, we evaluated the pharmacogenetic association between *HTR1A-1019C>G* (rs6295) and treatment response to escitalopram in a Korean population. We selected this polymorphism for the study due to its frequency and function. To date, 145 SNPs in the region of the human HTR1A gene have been submitted to dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP). Among them, rs6294 and rs6295 have minor allele frequencies of >0.05, and rs6294 is a non-functional synonymous polymorphism located at codon 98. On the other hand, rs6295, which is located on the 5' flanking region of HTR1A, has been known to affect the expression of HTR1A. The region around rs6295 provides a binding site for transcription factors such as Deaf-1 and Hes5. Deaf-1 acts as a transcriptional repressor for somatodendritic HTR1A in the raphe. In contrast, it upregulates HTR1A transcription in neurons expressing postsynaptic HTR1A (Czesak et al. 2006). The presence of the G allele on rs6295 may alter the binding site, causing overexpression of the HTR1A autoreceptor in the raphe. In fact, the GG genotype has been associated with increased raphe 5-HT1A autoreceptor expression, which may cause reduced serotonergic neurotransmission in the projection areas (Lemonde et al. 2003, Le Francois et al. 2008).

We found that *HTR1A-1019C>G* was associated with treatment response and decrease in HAM-D21 scores at 1 week of escitalopram treatment; the patients possessing the CC genotype showed a better treatment response. A similar association was observed in allelic analysis. Kato et al. pointed out a mis-definition of alleles in the *HTR1A-1019C>G* SNP in several pharmacogenetic studies (Kato et al. 2009). The mis-genotyping may result from the complementary nature of each allele (C and G), from

**Table 3**. *Association analysis of HTR1A-1019C>G with remission status by escitalopram treatment in major depressive disorder patients*

| Duration | Remission status | Genotype | | | | *P* | OR [95%CI] | Allele | | | *P* | OR [95%CI] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CC | CG | GG | Total | | | C | G | Total | | |
| 1 w | Non-remission | 35 (48.6%) | 31 (43.1%) | 6 (8.3%) | 72 (100%) | 0.108 | 0.18 [0.02–1.46] | 101 (70.1%) | 43 (29.9%) | 144 (100%) | 0.754 | 0.87 [0.38–2.03] |
| | Remission | 6 (85.7%) | 1 (14.3%) | 0 (0.0%) | 7 (100%) | | | 13 (92.9%) | 1 (7.1%) | 14 (100%) | | |
| 2 w | Non-remission | 27 (50.9%) | 20 (37.7%) | 6 (11.3%) | 53 (100%) | 0.644 | 0.80 [0.32–2.04] | 74 (69.8%) | 32 (30.2%) | 106 (100%) | 0.305 | 0.65 [0.29–1.48] |
| | Remission | 7 (50.0%) | 7 (50.0%) | 0 (0.0%) | 14 (100%) | | | 21 (75.0%) | 7 (25.0%) | 28 (100%) | | |
| 4 w | Non-remission | 18 (46.2%) | 16 (41%) | 5 (12.8%) | 39 (100%) | 0.313 | 0.66 [0.29–1.49] | 52 (66.7%) | 26 (33.3%) | 78 (100%) | 0.134 | 2.41 [0.76–7.62] |
| | Remission | 13 (52.0%) | 11 (44.0%) | 1 (4.0%) | 25 (100%) | | | 37 (74.0%) | 13 (26.0%) | 50 (100%) | | |
| 8 w | Non-remission | 18 (62.1%) | 8 (27.6%) | 3 (10.3%) | 29 (100%) | 0.430 | 1.41 [0.60–3.28] | 44 (75.9%) | 14 (24.1%) | 58 (100%) | 0.409 | 1.44 [0.60–3.45] |
| | Remission | 11 (44.0%) | 12 (4.08%) | 2 (8.0%) | 25 (100%) | | | 34 (68.0%) | 16 (32.0%) | 50 (100%) | | |

the fact that the reference genome sequence is presented as a complement strand of the actual HTR1A gene, and/or from its relatively high minor allele frequency in Caucasians. After allele correction according to Kato et al., depressed patients possessing the GG genotype showed a better response to fluoxetine than did C-allele carriers, especially among Asians (Hong et al. 2006, Yu et al. 2006, Kato et al. 2009). In contrast, the C allele was associated with a better treatment response to various antidepressants in Caucasian subjects with MDD (Parsey et al. 2006). Our results are inconsistent with previous reports involving Asian populations; however, our results agree with the observations of Parsey et al.

In the present study, the association was limited at 1 week, and no significant association was observed after 2 weeks. A possible explanation for the limited association may be that the independent effect of HTR1A polymorphism on the escitalopram treatment response is small, and interaction with polymorphisms on other genes may be useful for predicting antidepressant treatment responses. In fact, Anttila et al. reported that the combination of the *HTR1A-1019GG* and *GA+AA* genotypes for *BDNF+196G>A* (rs6265) was associated with an increased risk of treatment-resistant depression, although *HTR1A-1019C>G* alone is not associated with the risk of depression in Caucasian subjects (Anttila et al. 2007). Additionally, Arias et al. (2005) proposed an epistatic effect of *HTR1A-1019C>G* on treatment response in MDD when combining polymorphisms on serotonin transporters (MIM#:*182138). Furthermore, Spanish patients with MDD who were ss homozygotes for 5-HTTLPR and GG homozygotes for *HTR1A-1019C>G* were less likely to achieve remission after citalopram treatment than were subjects possessing other genotypes (Arias et al. 2005). The effect of *HTR1A-1019C>G* on treatment outcome is also associated with the gender of subjects (Yu et al. 2006). These results suggest that HTR1A polymorphism may be involved cooperatively with other genetic polymorphisms and biological factors in the pathogenesis of MDD and treatment response to antidepressants.

This study has several limitations. We enrolled a small number of patients with MDD. This may have lowered the statistical power of the analyses; this study is preliminary, and the power for presented results was <80%. Thus, our observation may become more obvious if a larger population is analyzed. Additionally, we evaluated only a single SNP on the HTR1A gene. Although *HTR1A-1019C>G* is the only known functional SNP with enough allele frequency for effective analysis, whole-gene screening and association studies for other variations of the HTR1A gene may be necessary to identify markers associated with the response to antidepressants in various populations. We also cannot exclude the presence of a population stratification bias (Gorwood 1999). However, because the Korean population is characterized by a relatively high degree of genetic homogeneity (Kim 2003), we consider that such a stratification bias is unlikely in our sample.

Although this study is a preliminary and has several limitations, to our knowledge, it is the first report on the association between *HTR1A-1019C>G* polymorphism and clinical outcomes of escitalopram treatment in patients with MDD. Our results suggest that this polymorphism affects the therapeutic action of escitalopram in MDD and that *HTR1A-1019C>G* may be a genetic marker for the response to escitalopram treatment.

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