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Association of the Serotonin 2A Receptor rs6311 Polymorphism with Diurnal Preference in Koreans

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Objective Evidence for the association between circadian rhythm delay and depression is accumulating. Genetic studies have shown that certain polymorphisms in circadian genes are potential genetic markers of diurnal preference. Along with circadian genes, there is a growing interest in other genetic effects on circadian rhythms. This study evaluated whether the *HTR2A* rs6311 (-1438C/T) polymorphism is associated with diurnal preference in a Korean population.

Methods A total of 510 healthy subjects were included in this study. All subjects were genotyped for the *HTR2A* rs6311 polymorphism and they completed the Korean version of the composite scale of morningness (CSM).

Results The C allele carriers (C/C+C/T) showed significantly higher CSM scores compared to C allele non-carriers (T/T) (t=2.22, p=0.03), suggesting the existence of a morning chronotype tendency in C allele carriers. In other words, the T/T genotype may be associated with the evening chronotype.

Conclusion These results suggest that the *HTR2A* rs6311 polymorphism may be associated with diurnal preference in a healthy Korean population. The absence of the C allele may be responsible for the increasing susceptibility to eveningness in the Korean population. Further studies on *HTR2A* polymorphisms that evaluate their interactions with various candidate genes and differences in phenotypic expression of polymorphisms according to ethnic groups are warranted to fully understand their association with diurnal preference.

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Key Words Diurnal preference, *HTR2A*, Polymorphism, Morningness.

INTRODUCTION

Evidence for the association between circadian misalignment and mood disorders is accumulating.[1-3] It is empirically well known that an irregular sleep-wake cycle in bipolar disorder leads to depression or mania, and sleep-wake cycle abnormalities precede mood changes.[1] A recently published study on circadian misalignment of mood episodes that involved hospitalized bipolar patients revealed that acute manic episodes were associated with circadian dysregulation with a −17 h phase delay, mixed manias were delayed for >6 h, and bipolar depression was associated with 4−5 h phase delays compared to the controls in the study.[2] Circadian rhythmicity, thus, is an important genetic factor that contributes to the bipolar disorder pathogenesis and recurrence.[4] Previous studies indicated that circadian genes also influence bipolar disorder trait markers, such as circadian phase preference for the evening.[4,5]

Diurnal preference, also referred to as chronotype, is an individual's phenotypic trait, which reflects the time of day with the highest activity and performance level. Chronotypes are evaluated using questionnaires, including the composite scale of morning (CSM). The three chronotypes of circadian typology introduced by Adan et al.[6] include the following: morning-type, evening-type, and neither-type. Individuals with the morning-type chronotype have a relatively advanced sleep-wake cycle and perform best early in the day while those with the evening-type chronotype have a relatively delayed sleep-wake cycle and perform best later in the day. Forty percent of the adult population are either morning-type or evening-type, and sociodemographic factors, such as age and sex, are known to influence chronotype across the life span.[6] Diurnal preference is widely studied for its association with psychiatric dis-

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orders, specifically mood disorders, eating disorders, and addictions.[6] The evening-type has been found to have a significant positive association with a number of psychiatric symptoms, such as sleep disturbance and depression, even after controlling for confounding factors including age, sex, education, civil status, physical activity, alcohol consumption, smoking status, and body mass index.[7-9]

This diurnal variation in mental and physical performance is considered to be closely associated with, if not generated by, endogenous circadian rhythms.[10] Circadian rhythms are driven by intracellular molecular mechanisms, which in turn are controlled by the transcriptional-translational feedback of the clock genes located in the suprachiasmatic nucleus of the anterior hypothalamus.[11,12] This transcriptional-translational feedback loop contributes to the generation of a roughly 24-h rhythmic expression pattern of clock genes.[12] The dimerization of the transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle Arnt-like (ARNTL) or neuronal pas domain protein 2 (NPAS2) proteins initiates the expression of clock proteins period (PER) and cryptochrome (CRY).[13] Subsequently, the heterodimerized PER and CRY proteins translocate to the nucleus and inhibit CLOCK-ARNTL or CLOCK-NPAS2 activity, resulting in the negative feedback of their own expression.[10] According to previous studies, polymorphisms of the clock genes are associated with diurnal preference: *CLOCK* 3111C/T single nucleotide polymorphism (SNP) rs1801260,[14,15] *ARNTL*, and *ARNTL2* in mood disorder patients[16,17] and polymorphisms in *PER* homologs (*PER1*, *PER2*, and *PER3*) in the general population.[8,10,14,18-20]

In addition to the core circadian clock genes, other genes have been investigated for their association with diurnal preference. One candidate for such an investigation could be the 5HT2A receptor (HTR2A). The *HTR2A* gene, located on chromosome 13q14-q21,[21] is composed of three exons and two introns).[22] Human HTR2A binding is altered in patients with suicidal and aggressive behaviors, major depression, and schizophrenia.[23] Specifically, the association between *HTR2A* promoter region polymorphism (*HTR2A* -1438C/T) and seasonal affective disorder has been investigated; previous studies have reported inconsistent findings.[24,25] According to Lee et al.,[26] *HTR2A* -1438A/G SNP was found to be associated with seasonality in Korean college students. The *HTR2A* gene contains a polymorphism (102C/T), and this polymorphism is in absolute linkage disequilibrium with a polymorphism (-1438C/T) in the promoter region of the gene.[27] The 102C/T polymorphism of the *HTR2A* gene was also found to be associated with the seasonal pattern in major depression.[27] The relationship between the -1438C/T polymorphism of the *HTR2A* gene and seasonality, with circadian misalignment as one hypothesis of its pathophysiology,[28] makes this polymorphism a reasonable candidate for investigating the association with diurnal preference.

In this study, we examined the association between diurnal preference and a polymorphism, *HTR2A* rs6311 (-1438C/T) SNP, in healthy Korean adults. We also assessed the effects of genotype and allele carrier status on the mean total and three subscale (morningness, morning alertness, and activity planning) scores of CSM. We hypothesized that the *HTR2A* 1438T allele is associated with lower mean total and subscale scores of CSM.

METHODS

Subjects

A total of 510 healthy Korean adults aged 18−35 years were recruited through an online advertisement. An experienced psychiatrist confirmed that none of the participants had lifetime or current psychiatric disorders based on the results of the Mini-International Neuropsychiatric Interview. Study participants also did not have any major medical problems; those with a family history of substance abuse or major psychiatric disorders (e.g., schizophrenia or major mood disorders) were excluded. All 510 subjects (male/female ratio=303/207; mean age, 23.41 years; range, 18−35 years) completed the Korean version of the Composite Scale of Morningness (CSM). All participants provided informed consent prior to enrollment in the study. The study protocols were approved by the Ethics Committee of Korea University (IEC No. 1067), and the study was conducted according to the Declaration of Helsinki. Other findings involving these study subjects have been previously reported.[10,29-32]

Assessment of diurnal preference

Diurnal preference was evaluated using the CSM, which was developed by Smith et al.[33] in 1989. The CSM consists of 13 items, which are further classified into three subscales: morningness (items 1, 3, 6, 8, 10, and 11), activity planning (items 2, 7, 9, 13), and morning alertness (items 4, 5, and 12) (9). Of the 13 items, three items were scored on a five-point scale (ranging from 1 to 5) and the remaining 10 items were scored on a four-point scale (ranging from 1 to 4). The total CSM score ranges from 13 to 55; a higher score indicates a morning preference and vice versa. The CSM is not only psychometrically as accurate as the Horne and Ostberg's morningness-eveningness questionnaire but also shorter in length.[33,34] All participants were asked to complete the Korean version of CSM.[35] The validity of the Korean version of CSM was established by Yoon et al.[35]

Genotyping

Genomic DNA was extracted from leukocytes using the

QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). Genotyping was performed using high-resolution melting curve analysis.[36] Polymerase chain reaction (PCR) was performed in a 20-μL reaction mixture and a 96-well CFX96 Real-Time PCR System (BioRad Laboratories, Hercules, CA, USA). The reaction mixture consisted of 2 μL genomic DNA (template), 200 mM of primer *HTR2A*[rs6311], forward primer (5'-TTA GGC TGA AGG GTG AAG A-3'), reverse primer (5'-CAC TCT GGA CAC AAA CAC T-3'), SsoFast EvaGreen Supermix (1×final concentration; BioRad Laboratories, Inc.), and sterile H_2O. The amplification protocol starts with an initial denaturation step at 98°C for 3 min, followed by 39 cycles of denaturation at 98°C for 10 s and 58°C for 20 s. After an initial step at 95°C for 10 s and 65°C for 10 s, melting curves were generated from 65°C to 95°C, in increments of 0.2°C at each cycle. Melting profiles were analyzed using Precision Melt Analysis software (BioRad Laboratories, Hercules, CA, USA).

Statistical analysis

The presence of Hardy-Weinberg equilibrium was tested using the chi-square (χ^2) test for goodness of fit. Analysis of covariance (ANCOVA) with sex as a covariate was performed to examine the effects of genotypes on the mean total CSM score and mean scores of the three CSM subscales (morningness, activity planning, and morning alertness). The Student's t-test was used to determine the effects of allele carrier status on the mean total CSM and its subscale scores. A two-tailed, alpha =0.05 test was chosen for the analysis. All statistical analyses were performed using SPSS version 22.0 for Windows (IBM, Corp., Armonk, NY, USA).

RESULTS

Of the 510 subjects included in this study, 303 (59.4%) were male and 207 (40.6%) were female, with an age range of 18 to 35 years (mean±SD, 23.1±2.8 years). The total CSM scores ranged from 14 to 51, with a mean score of 32.1±6.4. Table 1 shows the mean total CSM scores and mean scores of the three subscales that were classified based on the *HTR2A* -1438C/T polymorphisms. The genotypic distributions of the *HTR2A* -1438C/T polymorphisms followed Hardy-Weinberg equilibrium and were not significantly different (χ^2=2.7, p=0.1). In addition to genotype comparison, the study subjects were compared according to their allele carrier status. No significant differences were observed in the mean total CSM scores and mean scores of the three subscales among the genotypes of the *HTR2A* rs6311 (-1438C/T) polymorphism (F=2.48, p=0.08 for total CSM; F=2.26, p=0.10 for morningness; F=2.03, p=0.13 for morning alertness; and F=1.80, p=0.17 for activity planning). Although there were no statistically significant results, a general propensity was noted in the results. The T/T genotype in this study was found to be associated with lower mean total and subscale scores of CSM than C/C and C/T genotypes. There was no significant difference in the mean scores of the two subscales based on the C allele carrier status (t=1.52, p=0.13 for morning alertness and t=1.91, p=0.06 for activity planning). However, C allele non-carriers had significantly lower mean scores for total CSM (t=2.22, p=0.03) and the morningness subscale (t=2.10, p=0.04) than C allele carriers. The mean total CSM score for the three genotypes (F=2.48, p=0.08) and the mean score for the activity planning subscale for the C allele carriers and C allele non-carriers (t=1.91, p=0.06) were marginally significant.

Table 1. Composite scale for morningness scores in subject groups according to the *HTR2A* rs6311 (-1438C/T) polymorphism

	CSM score			
	Morningness	Morning alertness	Activity planning	Total
Genotypes				
C/C (N=149)	15.75±3.42	7.37±1.82	9.17±2.27	32.30±6.51
C/T (N=236)	15.67±3.44	7.62±1.69	9.32±2.20	32.61±6.40
T/T (N=125)	14.97±3.31	7.25±1.76	8.83±2.07	31.05±6.06
F	2.26	2.03	1.80	2.48
p-value	0.10	0.13	0.17	0.08
Allele carriers				
C carriers (N=385)	15.70±3.43	7.52±1.74	9.26±2.22	32.50±6.44
C non-carriers (N=125)	14.97±3.31	7.25±1.76	8.83±2.07	31.05±6.06
t	2.10	1.52	1.91	2.22
p-value	0.04*	0.13	0.06	0.03*

*p<0.05. CSM: composite scale for morningness

DISCUSSION

This study investigated the association between *HTR2A* -1438C/T polymorphisms and diurnal preference. We found that C allele non-carriers (T/T genotype) had significantly lower mean scores for the total CSM and morningness subscale than C allele carriers (C/C + C/T genotypes). Although the mean total and three CSM subscale scores were not significantly associated with *HTR2A* -1438C/T genotypes, the T/T genotype had lower scores than the C/C and C/T genotypes. In addition, the mean total CSM score of the three genotypes and the mean score of activity planning subscale for C allele carriers and C allele non-carriers showed marginal significance.

To the best of our knowledge, this is the first study to investigate the association between *HTR2A* polymorphisms, including the -1438C/T polymorphism, and diurnal preference. Previous studies on *HTR2A* polymorphisms have focused mainly on the relationship between gene polymorphisms and various psychiatric disorders, including mood and eating disorders, impulsivity and suicidal behavior, and addiction. Seasonality, with seasonal affective disorder at the extreme on the continuum, was found to be associated with the *HTR2A* -1438A allele,[24] which is consistent with the result of a study conducted in healthy Korean young adults.[26] Since eveningness is known to be associated with seasonal affective disorder,[37-39] the finding of the present study that T/T genotype and C allele non-carriers showed lower CSM scores with a propensity towards eveningness, is consistent with those of previous studies. This association between eveningness and seasonality could be explained by the possible common underlying mechanism of circadian rhythm, which in turn leads to the clinical implication that chronotherapeutics, primarily light therapy, could also have meaningful effects as an intervention modality for pathologies related to eveningess.[40] Furthermore, it could be postulated that -1438 C/T polymorphism is associated with neuropsychiatric disorder through circadian disruption.

Nonetheless, in one study conducted to investigate the association between *HTR2A* 102C/T polymorphism and depression with seasonal patterns, it was found that the seasonal pattern was 7.57 times more frequent in 102C allele carriers than in 102T homozygous carriers.[27] Furthermore, the C allele of the *HTR2A* 102C/T polymorphism was shown to be associated with neuropsychiatric diseases, even though this finding is controversial.[41] The 102C/T polymorphism of the *HTR2A* gene does not result in changes in the amino acid sequence of the receptor protein. However, it is in absolute linkage disequilibrium with a polymorphism (-1438A/G) in the promoter region of the gene. Therefore, the -1438A allele is most likely accompanied by the 102T allele while the -1438G allele is most likely accompanied by the 102C allele. This inconsistency with the results of the present study could be explained by the possible ethnic differences in the expression of *HTR2A* gene polymorphisms[42] and the underestimated effect of the polymorphisms on diurnal preference due to the underlying complex mechanism with a number of internal and external factors. Thus, further studies on how the phenotypic expression of *HTR2A* polymorphisms may be different in ethnic groups and how it affects the association between *HTR2A* gene polymorphisms and diurnal preference are needed.

The current study has several limitations. First, population stratification bias cannot be excluded. However, the Korean population is known to have a relatively high degree of genetic homogeneity;[43] thus, it would be reasonable to assume that population stratification bias in our study participants is unlikely. In addition, the study sample represents a very homogenous population because it comprised healthy young adults with the same ethnicity. Second, the sample size may not be large enough to fully assess the effect of the *HTR2A* -1438C/T polymorphism on diurnal preference. Although our sample size (n=510) was not smaller than those of previous gene studies on diurnal preference, it may not have caught all the effects of the polymorphism, if it worked only as one component of a complex network. Third, the possible effects of occupations on diurnal preference need to be considered. It would have been more informative if specific occupations, such as those that involve shiftwork, were taken into consideration in the analysis. However, most of the participants were college students.

In conclusion, *HTR2A* -1438C/T polymorphism may be associated with diurnal preference in the Korean population. The propensity of the T/T genotype and C allele non-carriers to have lower mean total and CSM subscale scores was noted; the absence of the C allele may be responsible for the increase in the susceptibility of healthy Koreans to eveningness. Due to the limited research on *HTR2A* gene polymorphisms and diurnal preference, future studies to investigate various candidate genes in different ethnic groups are needed to improve our understanding of genetic influence on the phenotypic expression of circadian rhythmicity in the form of diurnal preference. Further research would be also clinically meaningful because pharmacological interventions acting on serotonin receptors may help regulate diurnal preference, especially eveningness, which is widely associated with numerous psychiatric disorders.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Heon-Jeong Lee. Data curation: Ju Yeon Seo, Sehyun Jeon. Formal analysis: Ji Won Yeom, Heon-Jeong Lee. Funding acquisition: Heon-Jeong Lee. Investigation: Ji Won Yeom, Seunghwa Jeong. Methodology: Ji Won Yeom, Seunghwa Jeong, Sehyun Jeon. Project administration: Ju Yeon Seo, Heon-Jeong Lee. Resources: Heon-Jeong Lee. Software: Ji Won Yeom, Seunghwa Jeong, Sehyun Jeon. Supervision: Heon-Jeong Lee. Validation: Heon-Jeong Lee. Visualization: Ji Won Yeom. Writing—original draft: Ji Won Yeom. Writing—review & editing: Heon-Jeong Lee.

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