

# Serotonin Transporter Gene Polymorphism and Personality Traits in a Korean Population

Se Joo Kim<sup>a</sup> Young Shin Kim<sup>b</sup> Nak Kyung Choi<sup>b</sup> Hyun Joo Hong<sup>b</sup>  
Hong Shick Lee<sup>a</sup> Chan-Hyung Kim<sup>a</sup>

<sup>a</sup>Department of Psychiatry, Yonsei University College of Medicine, Seoul, and <sup>b</sup>Department of Psychiatry, Hallym University College of Medicine, Anyang-Si, Korea

## Key Words

Temperament and Character Inventory · Serotonin transporter gene · Polymorphism · Personality traits · Korean population

## Abstract

Recently, there has been growing enthusiasm for exploring biological approaches to personality, especially in the area of genetic research into the identification of those genes responsible for particular personality traits. The aim of this study was to investigate the association between the serotonin transporter-linked promoter region (5-HTTLPR) polymorphism and personality traits. We recruited 211 unrelated, normal subjects. The Korean version of the Temperament and Character Inventory (TCI) was used to assess certain personality traits. From blood samples taken from the subjects, DNA was isolated using standard techniques and the 5-HTTLPR polymorphism was genotyped by means of polymerase chain reaction and electrophoresis. We classified the subject into the s/s, s/l, and l/l groups according to their genotype. The differences in the temperament factors of the TCI between group S (s/s genotype) and group L (s/l + l/l genotype) were assessed, after the inclusion of gender and age as covariates in the analysis of variance.

After controlling for gender and age, there were no associations between the harm avoidance, novelty seeking, and reward dependence scores and the genotypes. However, the persistence score of group S was significantly higher than that of group L. Our results suggest that the 5-HTTLPR polymorphism may be associated with the persistence score of the TCI in a normal Korean population.

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## Introduction

Individual differences in human behavioral predispositions are relatively enduring [12]. These personality traits are also substantially heritable, and therefore very likely result from the interplay of genetic variations with environmental influences [16]. It has been estimated that approximately 30–60% of the measured variations can be accounted for by genes [3]. Recently, there has been growing enthusiasm for exploring biological approaches to personality, especially in the area of genetic research into the identification of those genes responsible for particular personality traits. Several candidate gene polymorphisms have been reported to be associated with particular personality traits and one of these genes is the serotonin

transporter (5-HTT) polymorphism. The 5-HTT gene has a functional polymorphism in the promoter region. This polymorphism has two common forms, which are distinguished by a long (l) and a short (s) allele according to the insertion or deletion of 44 bp nucleotides. Lesch et al. [25] reported that the short variant of the serotonin transporter-linked promoter region (5-HTTLPR) polymorphism reduced the transcriptional regulatory efficiency of the promoter, and also observed that this polymorphism was associated with an anxiety-related trait in Caucasian subjects. However, subsequent attempts to replicate the association between the 5-HTTLPR polymorphism and specific personality traits have yielded inconsistent results [16, 29].

There are several factors which might have an influence on the results of personality trait studies. First, ethnicity may affect the results. It has been known for some time that the distributions of the 5-HTT alleles vary according to the ethnicity of the subjects involved [14]. The frequencies for the 5-HTTLPR alleles are similar in Asian populations (such as Korean, Japanese, and Chinese) but quite different from those determined for a western population, where a much higher percentage of the l allele was demonstrated [25]. Therefore, genetic studies in the Korean population have a specific advantage over those conducted in other populations. The Korean population is considered ethnically and culturally much more homogeneous than the European, American and African populations. Second, gender and age may also be important factors. Previous studies have shown that gender and age may affect the outcome of questionnaire-based personality assessments [6]. Also, it is well known that the serotonergic system is differentially regulated in males and females, with the mRNA and binding site densities for 5-HTT being regulated by estrogen [26]. Therefore, it is reasonable to control the effects of gender or age in studies on the association between personality traits and a particular gene. Considering these factors, in this article we report the allele frequencies of 5-HTTLPR in a Korean population and their relationship with certain personality traits.

## Materials and Methods

### *Subjects*

We recruited 224 unrelated subjects from among the nurses, students and volunteers at the Hallym University Sacred Heart Hospital and Anyang Community Mental Health Center. There were 115 men and 109 women. All of the subjects were Korean and between 21 and 35 years old. All of them gave their written in-

formed consent to participate in the study, after the procedure had been fully explained to them. The study protocols were approved by the ethics committees of the Hallym University Sacred Heart Hospital. All of the candidate participants underwent a direct interview to exclude psychiatric disorders.

### *Psychometric Evaluation*

In order to exclude subclinical anxiety or depressive disorders, all of the subjects completed the Korean version of the Beck Depression Inventory (BDI) [30] and Beck Anxiety Inventory (BAI) [18]. In accordance with the results of previous studies, those individuals who reported more than 21 points on the BDI or 22 points on the BAI were also excluded. The Korean version of the Temperament and Character Inventory (TCI) was used to assess the personality traits [28]. The TCI is a self-rating instrument of yes/no answers designed to evaluate the 4 personality dimensions of temperament – novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P), and the 3 character dimensions of self-directedness, cooperativeness, and self-transcendence [7]. Whereas the 4 temperament factors are thought to be largely heritable and rooted in neurobiology, the 3 character factors are assumed to be socioculturally determined and hence less likely to be associated with specific genes [7, 9]. This study explores the possible association between the polymorphism and the 4 temperament factors; the 3 character factors were not taken into consideration.

### *DNA Analyses*

The subjects donated a blood sample by venipuncture, and DNA was isolated using standard techniques. The functional promoter polymorphism was genotyped by polymerase chain reaction amplification as described by Heils et al. [20]. The polymerase chain reaction products were separated on 3% agarose gels supplemented with ethidium bromide to allow identification of the long (528 bp) and the short (484 bp) variants.

### *Statistical Analysis*

To control the possible effects of gender and age on the TCI, the differences in the TCI scores between genotypes were assessed after including gender and age as covariates in the analysis of variance. In the analyses, the genotype was the independent factor, and the score in the main temperamental scales of the TCI were dependent variables. Correction for multiple testing was done by the Bonferroni method. With the 4 comparisons (NS, HA, RD, and P) for each polymorphism, significance was stipulated as  $p < 0.013$  ( $0.05/4$ ). Statistical analyses were performed using SPSS (version 11.0) software for Windows.

## Results

Thirteen of the 224 recruited subjects were excluded because of high BDI or BAI scores. Therefore, a total of 211 normal subjects (106 men and 105 women) participated in this study. The mean age [standard deviation (SD)] of the male subjects was 26.35 (SD 4.27) and of the female subjects it was 26.66 (SD 4.47). The mean values for the temperament dimensions of males and females

were as follows: in males – NS 17.75 (SD 5.46), HA 16.32 (SD 7.57), RD 15.21 (SD 4.14), and P 4.26 (SD 1.89); in females – NS 18.61 (SD 5.94), HA 17.36 (SD 6.98), RD 16.58 (SD 3.28), and P 3.88 (SD 1.75).

We classified the subjects into the s/s, s/l, and l/l groups according to their genotypes. The frequencies for the 5-HTTLPR genotypes in our sample were quite different from those determined for a western population, where a higher percentage (32.3%) of the l/l genotype and a relatively lower percentage (18.8%) of the s/s genotype is observed [25]. In our sample, the number of subjects with the l/l genotype was small (n = 9, only 4.3%). Also, in contrast to the Caucasian population in which [<sup>3</sup>H]5-HT uptake of the l/l genotype was much higher than that of the s/l or s/s genotypes [25], in the Korean population the s/s genotype is known to be associated with a greater V<sub>max</sub> value of [<sup>3</sup>H]5-HT uptake in platelets compared with the s/l or l/l promoter variants [23]. A recent pharmacogenetic study of depressed patients has revealed that carriage of the l allele of the 5-HTTLPR polymorphism is associated with better response to fluvoxamine treatment in comparison to carriage of the s/s homozygote genotype. In addition, recent studies have demonstrated that homozygosity for the s variant of the 5-HTTLPR is significantly more frequent for mood disorder patients than controls [1, 10]. These findings suggest that the s allele is recessive. So we combined the s/l and l/l genotypes together into group L, and compared these with the s/s genotype (group S) for our analysis.

The observed 5-HTTLPR genotype frequencies were 130 s/s (61.6%), 72 s/l (34.1%), and 9 l/l (4.3%) and their distribution was in accordance with the Hardy-Weinberg equilibrium ( $\chi^2 = 0.06$ ,  $p = 0.81$ ; table 1). After controlling for gender and age, there were no associations between the HA, NS, or RD scores and the genotypes. However, the P score of group S was significantly higher than that of group L ( $p = 0.012$ ; table 2).

## Discussion

The aim of this study using a nonclinical population sample was to assess the impact of an inherited, lifelong alteration in the 5-HTT expression on the normal spectrum of individual differences. This study has several advantages over other similar studies. First, the homogeneity of the subjects is a critical issue in genetic studies and the Korean population is considered ethnically and culturally much more homogenous than other populations due to its distinct language and culture. Second, in addition

**Table 1.** Frequencies of genotypes for 5-HTTLPR

	s/s (S type)	s/l	l/l	s/l + l/l (L type)
Number	130	72	9	81
Percentage	61.6	34.1	4.3	38.4

**Table 2.** The mean age and temperament scores of male and female subjects

	Male (n = 106)	Female (n = 105)	p value
Age, years	26.35 ± 4.27	26.66 ± 4.47	0.607
Temperament			
Novelty seeking	18.61 ± 5.94	17.75 ± 5.46	0.277
Harm avoidance	16.32 ± 7.57	17.36 ± 6.98	0.299
Reward dependence	15.21 ± 4.14	16.58 ± 3.28	0.008
Persistence	4.26 ± 1.89	3.88 ± 1.75	0.124

to the direct interview, we also used two self-rating scales to exclude those subjects with potential anxiety disorders or depressive disorders that could be associated with 5-HTT polymorphism. Third, to reduce the confounding effects of gender or age, we attempted to control the effect of gender and age on the TCI in the statistical analysis.

In this study, we could not find any significant association between the 5-HTTLPR polymorphism and the HA score. Although some previous studies [25] reported an association between the 5-HTTLPR polymorphism and anxiety-related traits, such as HA of the TCI or neuroticism of the NEO-PI-R (Revised NEO Personality Inventory), others [29] found no such association. Two of the 5 studies which have been conducted with Japanese study populations, who have similar frequencies of 5-HTTLPR genotypes compared to Koreans, reported some associations between the 5-HTTLPR polymorphism and anxiety-related personality traits [21, 27]. However, because these 2 studies did not consider the effects of gender and age on the temperament and character traits, their results could not be directly compared with our own. Only 1 study by Umekage et al. [29] separated the subjects by gender and this study reported no association between the 5-HTTLPR polymorphism and neuroticism.

In the present study, those subjects with the s/s genotype had higher P scores of the TCI than those subjects with the l/s plus l/l genotype. The P score is a measure of

perseverance despite frustration and fatigue, and such individuals are defined as being industrious, hard-working, ambitious, and perfectionist [9]. Benjamin et al. [2] reported that the short allele of the 5-HTT raises the persistence scores of the Tridimensional Personality Questionnaire in individuals homozygous for the COMT polymorphism. Also, Comings et al. [11] found that three serotonin genes, i.e. 5-HTT, 5-HT2A, and tryptophan hydroxylase, were associated with the P scores of the TCI and Cloninger [8] suggested that serotonin genes might be associated with the P scores of the TCI. It is well known that serotonin reuptake inhibitor has unique effects on the treatment of obsessive-compulsive disorder, which might be considered an extreme form of the persistence trait. Because the frequencies of the s/s genotype in Asian populations are quite different from western populations, we did not know exactly whether the s/s genotype is likely to have the same impact on personality or depression in Asian subjects as it might have in Caucasians. However, there are several evidences that the s/s genotype may alter the functioning of the 5-HT system in Asian populations. As mentioned above, Kim et al. [23] reported that in Korean populations, the s/s genotype is known to be associated with a greater  $V_{max}$  value of [ $^3H$ ]5-HT uptake in platelets compared with the s/l or l/l promoter variants. In addition, Chen et al. [5] reported that in the Chinese populations, similar to l/l homozygotes, a greater  $P_2$  latency of auditory evoked potentials was determined for the s/l heterozygotes in comparison to the s/s homozygotes, suggesting that the l allele may be dominant in terms of the effect of  $P_2$  latency. The  $P_2$  component of auditory evoked potentials is considered to reflect cerebral functions which are mediated by serotonin [19]. Several studies also reported that the s/s genotype is related to the response to selective serotonin reuptake inhibitors in depressed Korean patients [22, 24]. Murakami et al. [27] reported that in Japanese populations, the subjects with the s/s genotype have a greater score of anxiety-related personality traits than those with the l/s plus l/l genotype. Considering these findings, the 5-HTTLPR s/s genotype coupled with an altered 5-HT function may contribute to personality traits, such as P in our study. However, the P dimension of the TCI is the least reliable of the measures, depends on only 8 questions and has a poor factor structure [9]. Therefore, our results must be treated with caution and to confirm the importance of our results, independent replications utilizing larger sample sizes should be performed.

To date, there has only been 1 study of the Korean population which investigated the relationships between

5-HTT polymorphism and personality traits [17]. In contrast to our results, in this study, no associations were found between 5-HTTLPR and any of the subscales of the TCI. However, this study did not consider the effects of gender on the TCI and despite the subjects involved having a relatively broad age range (mean age  $31.94 \pm 9.05$ ), it did not consider the effects of age. These factors might explain the discrepancies between the results of this study and our own.

There are some limitations in our study. First, since occupation might have an influence on the development of personality, subjects with similar occupational background could have some advantages in genetic studies of personality. In our study, more than half of the subjects were nurses and medical students. However, it also means that they may not be sufficiently representative of the larger Korean population. Second, recent studies in personality genetics are now revealing the role of multiple gene effects in the determination of a complex phenotype of personality [13]. However, in our study, we investigated the associations between only a single polymorphism and personality traits. Therefore, we could not consider the epistatic (or interactive) effects of several other genes on personality traits. Third, our failure to find other significant associations may be a reflection of the small sample size and resultant limitations in statistical power. The power of our sample to detect differences between genotypes was calculated using a two-tailed alpha value of 0.05. With these parameters, considering the genotype frequencies in our sample, the power analysis showed that our sample size had a power (0.80) to detect a small effect size ( $f = 0.195$ ). And last, in our study, we considered only the effects of genetic factors on personality traits. However, personality traits might be influenced by interaction of genetic and environmental factors. Caspi et al. [4] reported that a functional polymorphism in 5-HTTLPR could moderate the influence of stressful life events on depression. Grabe et al. [15] also reported that 5-HTTLPR genotypes were associated with mental vulnerability to social stressors and chronic disease.

In conclusion, we found some associations between the 5-HTTLPR polymorphism and the personality dimension P in a normal population. However, our findings need to be replicated in larger independent samples and in other clinical populations.

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