INTRODUCTION

Serotonin transporter gene (SLC6A4, solute carrier family 6, member 4) encodes an integral plasma membrane protein that plays a major role in the regulation of serotonin neurotransmission (1). It removes serotonin from the synaptic cleft into the pre-synaptic terminals. It has been widely recognized as the target site of selective serotonin reuptake inhibitor (SSRIs), which have been recognized as both anti-depressant and anti-anxiety drugs. Two common polymorphisms in the promoter region of the serotonin transporter gene, i.e. 5-HTTLPR (polymorphisms in the promoter region of the serotonin transporter gene) have been reported, together with their functional properties. 5-HTTLPR, containing long (“l”) and short (“s”) alleles confirmed by conventional polymerase chain reaction and electrophoresis, were involved in the transcriptional regulation of the serotonin transporter gene (2, 3). The short allele has been suggested to decrease transcriptional activities of serotonin transporter gene, although it is uncertain whether they act in a dominant fashion (4) or a recessive fashion (5-7).

Studies have shown that reliably measured personality dimensions are substantially influenced by genetic factors (8). Among them, anxiety-related traits such as harm avoidance or neuroticism appears to be one of the most fundamental, enduring, and continuously distributed personality dimensions, which are associated with 5-HTTLPR (2, 9, 10). These associations, however, remain controversial, because numerous other studies yielding negative results (11-15). These inconsistencies could be accounted for by various factors including different measures applied, confounding effects of age and gender, and inadequate sample size. Perhaps more important-ly, ethnic differences in allele frequencies and population sub-structure may underlie those inconsistent results.

In the present study, we examined whether association between 5-HTTLPR and harm avoidance of Korean version of the Temperament and Character Inventory (K-TCI) (16) should be replicated in Korean population. Koreans have been considered more ethnically homogenous (17). We also examined other personality traits in K-TCI since other personality dimensions of novelty seeking, reward dependence, and persistence are reported to be independently heritable (18). We confined our sample to one college students, which was presumed to be relatively homogenous population regarding age and sociocultural backgrounds.

MATERIALS AND METHODS

A total of 158 unrelated healthy college students volun-
No Association between 5-HTTLPR and Harm Avoidance

Table 1. TCI Scores grouped by genotype

| Genotype (No./%) | TCI factor scores |
|-----------------|-------------------|
|                 | Harm avoidance    | Novelty seeking | Reward dependence | Persistence |
| "ss" (95/60.1)  | 17.14±7.11        | 20.36±6.15      | 15.40±3.48         | 4.81±2.13   |
| "ls" (54/34.2)  | 16.59±7.71        | 20.28±6.13      | 15.72±4.31         | 4.69±2.36   |
| "ll" (9/5.7)    | 18.78±4.02        | 20.67±7.58      | 15.22±1.99         | 5.22±2.05   |
| p               | 0.71              | 0.93            | 0.23               | 0.55        |
| F               | 0.62              | 0.46            | 0.95               | 0.74        |
| "ss" (95/60.1)  | 17.14±7.11        | 20.36±6.15      | 15.40±3.48         | 4.81±2.13   |
| "ls+ll" (63/39.9) | 16.90±7.31   | 20.33±6.23      | 15.65±4.05         | 4.76±2.31   |
| F               | 1.03              | 0.01            | 0.35               | 0.07        |
| p               | 0.38              | 0.99            | 0.79               | 0.97        |

RESULTS

The genotypes of 5-HTTLPR were distributed according to the Hardy-Weinberg equilibrium (χ²=0.13, p=0.94). Ninety-five subjects (60.1%) were “ss” genotype, and subjects with “sl” and “ll” were 54 (34.2%) and 9 (5.7%), respectively. Neither allele nor genotype frequencies differed according to sex. There were no significant differences in the scores of harm avoidance (F=0.38, p=0.69), novelty seeking (F=0.07, p=0.93), reward dependence (F=0.16, p=0.86) and persistence (F=0.24, p=0.79) using genotype and sex as independent variables (Table 1). When dividing the subjects into 2 groups of “ss” (60.1%) and “sl”+“ll” (39.9%), we could not find associations between the two genotype group and personality traits, either (Table 1).

DISCUSSION

In the present study, we could not find evidence for an association between 5-HTTLPR and harm avoidance measured by K-TCI in healthy Korean subjects. It is contrary to two recent meta-analyses including more than 23 studies which have shown the association between the polymorphism and trait anxiety, despite its weak effects (14, 15). This relationship was not reported in previous two studies using Korean samples (20, 21). Even though the association between 5-HTTLPR and harm avoidance is not confined to one ethnic group (10), majority of studies in East Asian populations did not show the association (20-23), with two possible exceptional studies in Japan (6, 12). This raises the possibility that the reported associations between the 5-HTTLPR and harm avoidance do not exist in East Asian population. We found that allele frequencies in our subjects were similar to those in other East Asian subjects (6, 12, 13, 20, 21), but they were significantly different from those in Caucasian subjects (2, 5, 24). It is well known that allele frequencies distribution has large effects on the power of genetic association studies (25). Together with small
effect size of harm avoidance (14, 15), it is certainly possible that genotype distribution of East Asian samples, especially marked low frequencies of long alleles, could reduce the power of the tests, which might lead to negative results.

There have been many reports suggesting dominance of long allele (5, 19). There are also reports that “ss” genotype acts in recessive fashion in East Asian populations (6, 7, 26). In accordance with these, we divided the subjects into “ss” genotype group and “sl”+“ll” genotype group. There were no significant differences between the two genotype groups and 4 dimensional scores, either.

The ethnicity issue could be addressed in the context of cultural factors. It has been suggested that high frequency of short allele in the Japanese population may be responsible for the interpersonal sensitivity and emotional restraints that is generally regarded as characteristic of Japanese culture (6, 23). The ethnic differences of allele frequencies between Asians and Caucasians might partially explain personality tendencies towards greater or less cautiousness and shyness from a genetic perspective. However, in our sample, we could not find the correlation between the high scores of harm avoidance and short alleles of 5-HTTLPR.

In terms of gender differences, we could speculate that genetic factors have different effects on personality differences between sex (27). However, we could not find previously reported gender differences (5, 11) in this study. In another Korean study exclusively including female subjects, they could not find association between harm avoidance and 5-HTTLPR (28).

Though TCI has been known to reflect the genetic components of personality dimensions including harm avoidance, it also includes non-genetic, environmental components (29). Considering that age, sex and culture could affect on personality traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996; 274: 1527-31.

Little KY, McLaughlin DP, Zhang L, Livermore CS, Dalack GW, McFinton PR, DelProposto ZS, Hill E, Cassin BJ, Watson SJ, Cook EH. Cocaine, ethanol, and genotype effects on human midbrain serotonin transporter binding sites and mRNA levels. Am J Psychiat 1998; 155: 207-13.

Greenberg BD, Toiviver TJ, Huang SJ, Li Q, Bengel D, Murphy DL. Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. Am J Med Genet 1999; 88: 83-7.

Melke J, Landen M, Baghei F, Rosmond R, Holm G, Bjornorp P, Westberg L, Hellstrand M, Eriksson E. Serotonin transporter gene polymorphisms are associated with anxiety-related personality traits in women. Am J Med Genet 2001; 105: 458-63.

Murakami F, Shimomura T, Kotani K, Iwasa S, Nanba E, Adachi K. Anxiety traits associated with a polymorphism in the serotonin transporter gene regulatory region in the Japanese. J Hum Genet 1999; 44: 15-7.

Chen TJ, YU YW, Chen MC, Tsai SJ, Hong CJ. Association analysis for serotonin transporter promoter polymorphism and auditory evoked potentials for major depression. Neuropsychobiology 2002; 46: 57-60.

Jang KL, Hu S, Livesley WJ, Angleitner A, Rieman R, Ando J, Ono Y, Vernon PA, Hamer DH. Covariance structure of neuroticism and agreeableness: a twin and molecular genetic analysis of the role of the serotonin transporter gene. J Pers Soc Psychol 2001; 81: 395-304.

Hamer DH, Greenberg BD, Sabol SZ, Murphy DL. Role of the serotonin transporter gene in temperament and character. J Personal 1999; 13: 312-27.

Osher Y, Hamer D, Benjamin J. Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israeli sibling pairs. Mol Psychiat 2000; 5: 206-9.

Du L, Bakish D, Hrdina PA. Gender differences in association between serotonin transporter gene polymorphism and personality traits. Psychiatr Genet 2000; 10: 159-64.

Katsuragi S, Kunugi H, Sano A, Tsutsumi T, Bogawa K, Nanko S, Akiyoshi J. Association between serotonin transporter gene polymorphism and anxiety-related traits. Biol Psychiat 1999; 45: 368-70.

Nakamura M, Ueno S, Sano A, Tanabe H. The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. Mol Psychiat 2000; 5: 32-8.

Schinka JA, Busch RM, Robichaux-Kenze N. A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. Mol Psychiat 2004; 9: 197-202.

Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTL-
PR) and anxiety-related personality traits. Am J Med Genet B Neuropsychiatr Genet 2004; 127: 85-9.
16. Sung SM, Kim JH, Yang E, Abrams KY, Lyoo IK. Reliability and validity of the Korean version of the temperament and character inventory. Compr Psychiatry 2002; 43: 235-43.
17. Benkmann HG, Cho YH, Singh S, Wimmer U, Lee CC, Kim IK, Paik YK, Goedde HW. Red cell enzyme and serum protein polymorphisms in South Korea. Hum Hered 1989; 39: 263-70.
18. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiat 1993; 50: 975-90.
19. Hoefgen B, Schulze TG, Ohlraun S, von Widdern O, Hofels S, Gross M, Heidmann V, Kovalenko S, Eckermann A, Kolsch H, Metten M, Zobel A, Becker T, Nothen MM, Propping P, Heun R, Maier W, Rietschel M, Kim SJ, Kim YS, Choi NK, Hong HJ, Lee HS, Kim CH, Ardlie KG, Kruglyak L, Svrakic DM, Przybeck TR. The power of sample size and homogenous sampling: association between the 5-HTTLPR serotonin transporter polymorphism and major depressive disorder. Biol Psychi 2005; 57: 247-51.
20. Kim SJ, Kim YS, Choi NK, Hong HJ, Lee HS, Kim CH, Ardlie KG, Kruglyak L, Svrakic DM, Przybeck TR, Nilsson LG, Adolfssoin R. Serotonin transporter gene polymorphism and personality traits in a Korean population. Neuropsychobiology 2003; 48: 243-7.
21. Ham BJ, Kim YH, Choi MJ, Cha JH, Choi YK, Lee MS. Serotoninergic genes and personality traits in the Korean population. Neurosci Lett 2004; 354: 2-5.
22. Tsai SJ, Ouyang WC, Hong CJ. Association for serotonin transporter gene variable number tandem repeat polymorphism and schizophrenic disorders. Neuropsychobiology 2002; 45: 131-3.
23. Nakamura T, Muramatsu T, Ono Y, Matushita S, Higuchi S, Mizu-shima H, Yoshimura K, Kanbu S, Asai M. Serotonin transporter gene regulatory region polymorphism and anxiety-related traits in the Japanese. Am J Med Genet 1997; 74: 544-5.
24. Gelernter J, Cubells JF, Kidd JR, Pakstis AJ, Kidd KK. Population studies of polymorphisms of the serotonin transporter protein gene. Am J Med Genet 1999; 88: 61-6.
25. Ardlie KG, Kruglyak L, Svrakic DM, Przybeck TR, Nilsson LG, Adolfssoin R. Patterns of linkage disequilibrium in the human genome. Nat Rev Genet 2002; 3: 299-309.
26. Kim DK, Lim SW, Lee S, Sohn SE, Kim S, Hahn CG, Carroll BJ. Serotonin transporter gene polymorphism and antidepressant response. Neuroreport 2000; 11: 215-9.
27. Barr CS, Newman TK, Lindell S, Shannon C, Chompoux M, Lesch KP, Suomi SJ, Goldman D, Higley JD. Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates. Arch Gen Psychiat 2004; 61: 1146-52.
28. Kim SJ, Choi NK, Han CH, Kim CH. Association between serotonin transporter linked promoter region polymorphism and personality traits-normal female population study. Korean J Psychopharmacol 2004; 15: 206-10.
29. Ando J, Suzuki A, Yamagata S, Kijima N, Maekawa H, Ono Y, Jang KL. Genetic and environmental structure of Cloninger’s temperament and character dimensions. J Personal Disord 2004; 18: 379-93.
30. Brandstrom S, Richter J, Przybeck T. Distributions by age and sex of the dimensions of temperament and character inventory in a cross-cultural perspective among Sweden, Germany, and the USA. Psychol Rep 2001; 89: 747-58.
31. Chotai J, Forsgren T, Nilsson LG, Adolfssoin R. Season of birth variations in the temperament and character inventory of personality in a general population. Neuropsychobiology 2001; 44: 19-26.