

**An interaction between the serotonin transporter promoter region
and dopamine transporter polymorphisms contributes to harm avoidance
and reward dependence traits in normal healthy subjects**

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Summary. There is evidence for an association between polymorphisms of serotonin- and dopamine-related genes and temperamental personality traits. Recent findings have shown that interactions between allelic variants of the different genes may contribute to personality traits. We examined the effects of serotonin transporter-linked promoter region (*5-HTTLPR*) and dopamine transporter (*DAT1*) gene polymorphisms for associations with the Temperament and Character Inventory (TCI) temperament subscales in 209 Koreans. We found that the variants of *5-HTTLPR* interacted with the *DAT1* gene polymorphism to influence the HA and RD temperament subscales of TCI. Neither of these two genes affected any subscales of TCI alone.

Controlling for the effects of gender and age, we found significant interactions between *5-HTTLPR* and *DAT1* genes on Harm Avoidance (HA) and Reward Dependence (RD) as measured by the TCI (Hotelling's Trace = 3.0, $P = 0.02$). In the presence of the *DAT1* 10/10 genotype, subjects of group L of

5-HTTLPR had a significantly higher HA score and significantly lower RD score than those of group S ($F = 5.04$, $df = 1$, $p = 0.03$ and $F = 8.35$, $df = 1$, $p = 0.004$, respectively).

These findings suggest that the variants of *5-HTTLPR* interacted with the *DAT1* gene polymorphism to influence the HA and RD temperament subscales of TCI.

Keywords: Serotonin transporter gene, dopamine transporter gene, interaction, harm avoidance, reward dependence.

Introduction

Human personality traits are influenced by both genetic and environmental factors. Twin and family studies have revealed that individual variation of the heritable component may account for 30–60% of the variance in personality traits (Bouchard, 1994; Lander and Schorck, 1994). It has been hypothesized that certain personality traits are correlated with activity in different neuronal systems (Cloninger, 1987). According to Cloninger (1987), Novelty Seeking (NS) – defined as

the tendency to respond actively to novel stimuli – is related to dopaminergic activity. Harm Avoidance (HA) reflects a tendency for an inhibitory response to adverse stimuli leading to avoidance behavior and is related to the serotonergic system. Reward Dependence (RD) is defined as the tendency for a positive response to signals of reward and is hypothetically associated with noradrenergic activity. Persistence (P) was originally derived from the RD subscale, but it is now a separate fourth dimension of the Temperament and Character Inventory (TCI) (Cloninger et al., 1993). These four temperament traits of the TCI are genetically independent (Heath et al., 1994). In accordance with Cloninger's hypothesis, the relationship of particular personality traits to different genes related to the neurotransmitter system have been investigated.

Among these genes, the serotonin transporter gene is one of the most widely investigated in terms of its relationship to certain personality traits. The serotonin transporter 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 base pair nucleotides. Lesch et al. reported that the short variant of the serotonin transporter-linked promoter region (*5-HTTLPR*) polymorphism reduced the transcriptional regulatory efficiency of the promoter. They also observed that this polymorphism was associated with an anxiety-related trait in Caucasian subjects (Lesch et al., 1996). However, subsequent attempts to replicate the association between the *5-HTTLPR* polymorphism and specific personality traits have yielded inconsistent results (Greenberg et al., 2000; Umekage et al., 2003).

In addition to *5-HTTLPR*, the dopamine transporter (*DAT1*) may also influence behavioral traits. *DAT1* plays a pivotal role in terminating dopaminergic neurotransmission (Giros and Caron, 1993). Several studies have found

an association between *DAT1* variable number of tandem repeat (VNTR) and attention-deficit hyperactivity disorder (ADHD) (Cook et al., 1995; Gill et al., 1997; Waldman et al., 1998). One temperament trait hypothesized to be associated with ADHD is NS, which involves behaviors such as impulsivity and excitability (Thapar et al., 1999). Sabol et al. (1999) found an association between NS and the *DAT1* polymorphism, but other studies found no such relationship (Jorm et al., 2000; Samochowiec et al., 2001, 2002).

One of the causes of these inconsistent results is gene to gene interaction. Genetic influences which contribute to the expression of complex behavior are presumably affected by the interaction of multiple genes of different sizes. It is likely that the interaction of multiple genes could influence the expression of differences in temperament more than a single gene. However, most previous studies did not consider the effects of gene \times gene interaction on personality traits. Therefore, in this study, we investigated the relationship between *5-HTTLPR* and *DAT1*, especially their interaction in the expression of temperamental personality traits as measured by the TCI.

Material and methods

Subjects

We recruited 230 unrelated subjects from populations of nurses, students and volunteers at two university hospitals and one community mental health center. The subjects included 109 men and 121 women. All of the subjects were Korean and between the ages of 21 and 35 years old. Those with a family history of substance abuse/dependence or major psychiatric disorders, such as schizophrenia or mood disorders, were excluded. All subjects were carefully interviewed by one well-trained psychiatrist prior to the study and were ascertained to be free of major medical and psychiatric problems. All subjects gave written informed 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 Youngdong Severance Hospital and Hallym Sacred Heart Hospital.

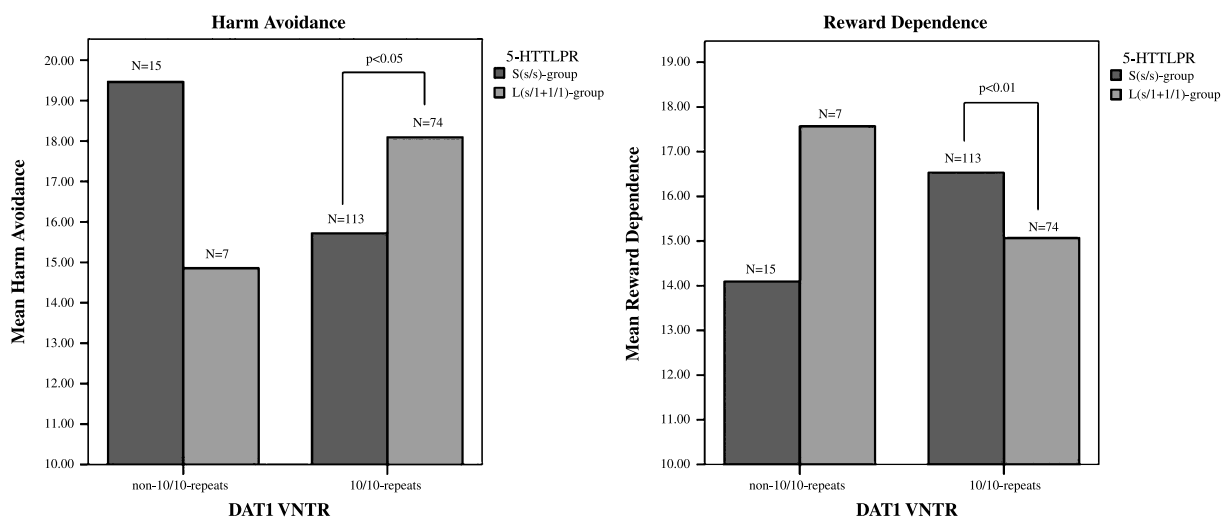


Fig. 1. HA and RD scores for the two polymorphism

Psychometric evaluation

In order to exclude subclinical anxiety or depressive disorders, all subjects completed the Korean version of the Beck Depression Inventory (BDI) (Yook and Kim, 1997) and Beck Anxiety Inventory (BAI) (Han et al., 1986). In accordance with the results of previous studies, those individuals who scored more than 21 points on the BDI or 22 points on the BAI were excluded. The Korean version of the TCI was used to assess personality traits (Sung et al., 2002). The TCI is a self-rating instrument of yes/no answers designed to evaluate the four personality dimensions of temperament – novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P) and the three character dimensions of self-directedness (SD), cooperativeness (C), and self-transcendence (ST) (Cloninger et al., 1993). Whereas the four temperament factors are thought to be largely heritable and rooted in neurobiology, the three character factors are assumed to be socioculturally determined and hence less likely to be associated with specific genes (Cloninger, 1986; Cloninger et al., 1993). For this reason, many other studies (Lee et al., 2003a, b; Melke et al., 2003) also analyzed only four temperament factors. Therefore, this study explored the possible association between gene polymorphism and the four temperament factors; the three character factors were not taken into consideration.

DNA analyses

Subjects donated a blood sample by venipuncture, and DNA was isolated using standard techniques. The functional promoter polymorphism of the sero-

tonin transporter gene was genotyped by polymerase chain reaction (PCR) amplification, as described by Helis et al. (1996). The *DAT1* VNTR is located in the 3' untranslated region of the gene and was genotyped using the method described by Sano et al. (1993).

Statistical analysis

To test the effects of the *5-HTTLPR* and *DAT1* polymorphism and their interaction on TCI subscales, we performed multivariate analysis of variance (MANOVA) after inclusion of age and gender as covariates. In these analyses, the genotypes of *5-HTTLPR* and *DAT1* were the independent factors, and the mean scores on the TCI subscale were dependent variables. Subsequent tests were carried out using ANOVA with age and gender as covariates. Although the number of subjects with *DAT1* non-10/10 genotype was relatively small ($n=22$, 15 of the S group and 7 of the L group), we performed ANOVA instead of non parametric test, since the Kolmogorov-Smirnov test showed the HA or RD scores did not skew from normal distribution ($Z=0.85$, $p=0.46$ in HA and $Z=1.14$, $p=0.15$ in RD) (Fig. 1).

Statistical analyses were performed using SPSS (Version 11.0) software for Windows.

Results

Twenty-one of the 230 recruited subjects were excluded because of high BDI or BAI scores. Therefore, a total of 209 normal subjects (101 men and 108 women) participated in this study. The mean age (standard devia-

tion, SD) of the male subjects was 27.12 years (SD 5.37) and the mean age of female subjects was 27.69 years (SD 6.38). The mean values for the temperament dimensions for males and females were as follows: in males – NS 18.77 (SD 5.95), HA 16.27 (SD 7.40), RD 15.18 (SD 4.11), and P 4.22 (SD 1.84) and in females – NS 17.66 (SD 5.38), HA 17.14 (SD 6.97), RD 16.55 (SD 3.21), and P 3.89 (SD 1.76).

We classified the subjects into the s/s, s/l, and l/l groups according to their genotypes and observed that the *5-HTTLPR* genotype frequencies were as follows: 128 were s/s (61.2%), 74 were s/l (35.4%) and 7 were l/l (3.3%). The frequencies for the *5-HTTLPR* genotype 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 (Lesch et al., 1996) has been reported. In addition, the number of subjects with the l/l genotype in our sample was small. In further contrast to the Caucasian population in which [³H]5-

HT uptake of the l/l genotype is higher than that of the s/l or s/s (Lesch et al., 1996), the Korean population s/s genotype is known to be associated with a greater V_{max} value of [³H]5-HT uptake in platelets, compared to the s/l or l/l promoter variants (Kim et al., 2003). Recently, several researchers have suggested that the s allele of *5-HTTLPR* is recessive (Bellivier et al., 1998; Collier et al., 1996). Therefore, for our analysis, we combined the s/l and l/l genotypes together into group L and compared these with the s/s genotype (group S), in accordance with previous studies (Ham et al., 2004; Kim et al., 2003, 2005a).

The genotype frequencies of *DAT1* polymorphism were 14 (6.7%) with genotype 9/10, 187 (89.5%) with genotype 10/10, and 8 (3.8%) with genotype 10/11. Whereas the frequencies for the *DAT1*10-repeats allele in our sample (94.7%) was distinguishably higher than those in Western populations (71.7–72.9%) (Jorm et al., 2001; Mitchell et al., 2000; Samochowiec et al., 2001), this result is consistent with previous findings reported in the Korean population (Kim

Table 1. Descriptive statistics for TCI temperament subscales grouped by *5-HTTLPR* and *DAT1* polymorphisms

	<i>5-HTTLPR</i>	<i>DAT1</i>	Mean ± SD	n
Novelty seeking	S-group	10/10-repeats	18.5 ± 5.7	113
		Non-10/10-repeats	15.5 ± 3.5	15
	L-group	10/10-repeats	17.9 ± 5.5	74
		Non-10/10-repeats	19.9 ± 4.9	7
Harm avoidance	S-group	10/10-repeats	15.7 ± 6.5	113
		Non-10/10-repeats	19.5 ± 6.4	15
	L-group	10/10-repeats	18.1 ± 8.3	74
		Non-10/10-repeats	14.9 ± 6.6	7
Reward dependence	S-group	10/10-repeats	16.5 ± 3.4	113
		Non-10/10-repeats	14.1 ± 5.0	15
	L-group	10/10-repeats	15.1 ± 3.9	74
		Non-10/10-repeats	17.6 ± 1.9	7
Persistence	S-group	10/10-repeats	4.2 ± 1.8	113
		Non-10/10-repeats	4.3 ± 2.1	15
	L-group	10/10-repeats	3.7 ± 1.8	74
		Non-10/10-repeats	3.4 ± 1.8	7

5-HTTLPR serotonin transporter-linked promoter region, *DAT1* dopamine transporter 1. S-group: s/s genotype of *5-HTTLPR*, L-group: s/l + l/l genotypes of *5-HTTLPR*

Table 2. Multivariate Analysis of Variance (MANOVA) of personality traits

	Novelty seeking			Harm avoidance			Reward dependence			Persistence		
	F	df	p	F	df	p	F	df	p	F	df	p
Main effects												
<i>5-HTTLPR</i>	2.03	1	0.16	0.68	1	0.41	0.68	1	0.41	2.01	1	0.16
<i>DATI</i>	0.12	1	0.73	0.01	1	0.93	0.01	1	0.94	0.12	1	0.90
Interaction												
<i>5-HTTLPR</i> × <i>DATI</i>	3.12	1	0.08	4.94	1	0.03*	6.68	1	0.01*	0.09	1	0.77

Gender and age as covariates; * $p < 0.05$

et al., 2005b). The number of subjects with non-10/10 repeats was small. An increased level of *DATI* expression is associated with the number of 10-repeats alleles (Mill et al., 2002), and the 10-repeats allele is reported to increase *DATI* gene expression, relative to the 7-, 9-, and 11-repeats alleles (Fuke et al., 2001). Therefore, we classified the genotype of *DATI* into 10/10-repeats and non-10/10-repeats groups.

While controlling for effects of gender and age, we did not find any significant multivariate main effects of *5-HTTLPR* and *DATI* gene polymorphism on any temperament subscale of the TCI. However, there was a significant multivariate *5-HTTLPR* × *DATI* interaction effect ($F = 3.02$, $df = 4$, $p = 0.02$). Univariate analyses showed that the multivariate effect on TCI originated from the significant effect of *5-HTTLPR* × *DATI* interaction on HA and RD scores ($F = 4.94$, $df = 1$, $p = 0.03$ and $F = 6.68$, $df = 1$, $p = 0.01$ for the S- vs. L- and the 10/10- vs. non-10/10 repeats groupings, respectively). The respective effect sizes (eta squared) were 0.024 and 0.032 (Table 2).

Within subjects with the *DATI* 10/10 genotype, those belonging to the L group of *5-HTTLPR* had significantly higher HA scores than those of the S group ($F = 5.04$, $df = 1$, $p = 0.03$). This is not the case for subjects with the *DATI* non-10/10 genotype: there was no difference in HA score between subjects in groups L and S ($F = 2.30$, $df = 1$,

$p = 0.14$). Within subjects with the *DATI* 10/10, those belonging to the S group of *5-HTTLPR* had significantly higher RD scores than those of the L group ($F = 8.35$, $df = 1$, $p = 0.004$). In contrast, this is not the case for subjects with the *DATI* non-10/10 genotype: there was no difference in RD score between subjects in groups L and S ($F = 1.77$, $df = 1$, $p = 0.20$) (Fig. 1).

Discussion

The main finding of the present investigation is that an interaction between two functional polymorphisms, *5-HTTLPR* and *DATI* VNTR, contributes to the HA and RD scores of TCI in Korean population. Some previous studies reported direct associations between *5-HTTLPR* (Katsuragi et al., 1999; Kim et al., 2005a; Lesch et al., 1996; Murakami et al., 1999; Osher et al., 2000) or *DATI* (Sabol et al., 1999) and personality traits. All of these studies considered only single gene effect of *5-HTTLPR* or *DATI* VNTR on personality traits rather than their interaction effects. Also, most of these studies were different from ours in terms of sample size, ethnicity, the questionnaires used, and methods used for statistical analyses. In addition, in present study, because there were significant interaction effects of these genes on TCI temperament scales, our results could not be directly compared with previous studies which showed direct associations.

However, we observed an indirect effect of *5-HTTLPR* on HA and RD which was apparently mediated by an interaction between *5-HTTLPR* and *DAT1* VNTR. The present study showed that the L-group of *5-HTTLPR* scores higher on HA and lower on RD measurements when the *DAT1* 10/10 genotype is present. As mentioned above, in Koreans, it is likely that the s/s genotype is associated with a greater 5-HT uptake than either the s/1 or 1/1 promoter variants (Kim et al., 2003), and in Japanese who have the similar genotype distributions of *DAT1* as Koreans (Shinohara et al., 2004), the 10-repeats allele is reported to increase *DAT1* gene expression (Fuke et al., 2001). Although, one might expect that high reuptake activity of serotonin or dopamine transporter results in low serotonin or dopamine levels, the opposite is also conceivable. The activity of the transporter may be increased due to an adaptation to high substrate level. Moreover, other factors like (neurotransmitter) synthesis or catabolic enzyme activity also contributes to the serotonergic or dopaminergic activity. Therefore, it is not possible to infer total serotonergic or dopaminergic activity from genotypes of *5-HTTLPR* or *DAT1* VNTR.

As showed in Fig. 1, although the differences of HA or RD between genotypes of *5-HTTLPR* did not reach statistical significance in the presence of non-10/10 *DAT1* VNTR, the *5-HTTLPR* genotypes acted reversely on HA or RD according to the presence or absent of *DAT1* 10/10 VNTR genotype. The effect size of the differences of HA (partial eta squared = 0.12) or RD (partial eta squared = 0.18) were high (Stevens, 1996). These means that the reason why we couldn't find statistical differences might be small sample sizes (non-10/10 repeats group, $n=22$) rather than effect sizes. Therefore, although the obtained level of significance do not allow us to arrive at clear conclusions, there is a possibility that the presence (or absence) of the 10/10 *DAT1* VNTR may

reverse the impacts of the S versus L genotype of *5-HTTLPR*. Additionally, it would imply a really large impact of the interaction between *5-HTTLPR* and *DAT1* VNTR on TCI. However, to draw more clear conclusions, further studies regarding this mechanism should be made.

We emphasize that our results should be interpreted cautiously because of following reasons. First, in our study, only a small number of individuals ($n=7$) have both the less common *5-HTTLPR* and *DAT1* VNTR genotypes, suggesting that a larger cohort must be employed in order to substantiate the role played by multiple polymorphisms in the determination of behavioral traits. Second, there are substantial differences in the genotype distribution of the *5-HTTLPR* and *DAT1* VNTR between Korean and Western populations. Therefore, the replication studies regarding the interaction between the serotonergic and dopaminergic system should also be conducted in different ethnic groups with different allele-frequencies.

Although they did not involve *DAT1* VNTR, several previous studies have suggested an interaction between *5-HTTLPR* and dopamine-related genes, such as dopamine receptor D4 (*DRD4*) polymorphisms, on personality traits. Szekely et al. found a significant interaction between the *DRD4* exon III VNTR and *5-HTTLPR* polymorphisms on HA. The 7-repeat allele raised HA scores, but only in the presence of the s/s *5-HTTLPR* genotype (Szekely et al., 2004). Benjamine et al. observed an indirect effect of *5-HTTLPR* and HA, apparently mediated by an interaction between *5-HTTLPR* and the *DRD4* exon III VNTR. Auerbach et al. (1999) also reported that in 2 month-old infants, the s/s *5-HTTLPR* polymorphism significantly raised the Negative Emotionality and Distress to Limitation score, temperament traits akin to adult HA, especially in the absence of the long allele of the *DRD4*. *DAT1* as well as the *DRD4* gene also play major roles in the regulation of dopamine

neurotransmission. Therefore, it must be possible that *DAT1* gene interaction with 5-*HTTLPR* polymorphism affects certain personality traits, such as HA or RD.

To our knowledge, there have been no previous reports of an interaction effect between 5-*HTTLPR* and *DAT1* gene polymorphisms on personality traits. Although epistatic effects were not considered, some researchers have found associations between 5-*HTTLPR* or *DAT1* and RD. Samochowiec et al. (2001) found that individuals carrying the 9/9 repeats *DAT1* genotype had lower RD4 scores (dependence vs. independence) than 10/10 individuals. Samochowiec et al. (2004) also found that individuals carrying the 'short' variant of 5-*HTTLPR* had lower values on the RD dimension and the RD4 subdimension than individuals not carrying the 'short' variant. Although it was not an epistatic effect of 5-*HTTLPR* × *DAT1* on RD, there was preliminary evidence for an interaction between the *DRD4* gene and the 5-HT_{2C} receptor gene, with a marked effect on the trait of reward dependence in Israeli samples (Ebstein et al., 1997). Kuhn et al. also found a significant interaction between *DRD4* and 5-HT_{2C} receptor polymorphisms on RD (Kuhn et al., 1999). These findings support our results in terms of a possible interactive effect of serotonergic and dopaminergic genes on the RD score of TCI.

Growing evidence shows that genetic polymorphisms of dopaminergic and serotonergic neurotransmission can strongly interact at the molecular level (Kapur and Remington, 1996; Prisco et al., 1994). Recently, some researchers showed that there are epistatic effects of serotonin (*SERT*) × dopamine transporter (*DAT*) genes on serotonin levels and certain behaviors in animals (Murphy et al., 2003; Sora et al., 2001). Sora et al. (2001) reported that *SERT* × *DAT* combined knockout mice produce some interesting differences beyond those previously observed in *SERT* or *DAT* single mutant mice. The *SERT* +/− × *DAT*

−/− mice had 1/3 lower serotonin levels than *SERT* +/− with the *DAT* +/+ allele. In their study, there were also epistatic effects of *SERT* × *DAT* genes on cocaine-conditioned place preference behavior, which is closed related to RD (Sora et al., 2001).

There are some limitations to our study. First, since occupation might have an influence on the development of personality, subjects with similar occupational backgrounds could have some advantages in genetic studies of personality. In our study, more than half of the subjects were nurses and medical students. However, this also means that our subjects may not sufficiently represent the larger Korean population. Second, our failure to find other significant associations may be a reflection of a 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 and 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 ($f = 0.194$). In addition, in our study we considered only the effects of genetic factors on personality traits. However, personality traits may be influenced by an interaction of genetic and environmental factors. Grabe et al. reported that 5-*HTTLPR* genotypes were associated with mental vulnerability to social stressors and chronic disease (Grabe et al., 2005).

In conclusion, we found significant interactions between 5-*HTTLPR* and *DAT1* polymorphisms on HA and RD personality traits. Our findings need to be replicated in larger independent samples and in other clinical populations.

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