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Lack of Association between Polymorphisms of the Dopamine Receptor D4 and Dopamine Transporter Genes and Personality Traits in a Korean Population

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Human personality traits have a considerable genetic component. Cloninger et al. were the first to postulate that certain personality traits, such as novelty seeking, are related to the dopamine neurotransmitter system. In this study, we investigated the associations between dopamine receptor D4 (DRD4) exon III and dopamine transporter (DAT1) polymorphisms and personality traits. The DRD4 and DAT1 gene polymorphisms were genotyped in 214 healthy Korean subjects, whose personality traits were assessed with the Temperament and Character Inventory (TCI). There were no significant differences between scores of TCI temperament dimensions (novelty seeking, harm avoidance, reward dependence, and persistence) and DRD4 gene polymorphism. The DAT1 gene polymorphisms also showed no significant association with any of the temperament subscales of the TCI. These data suggest that DRD4 and DAT1 gene polymorphism may not be associated with personality traits in a Korean population.

Key Words: Dopamine receptor D4, dopamine transporter gene, polymorphism, personality traits, temperament and character inventory, Korean

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.¹ Cloninger² suggested a psychobiological model of the structure and the development of personality that accounts for dimensions of both temperament and character. Temperament is an automatic emotional response which is moderately heritable and stable throughout life. Character is understood as a pattern of self-concepts related to the acceptance of the individual self, acceptance of other people and the acceptance of nature in general. It has been suggested that the character traits are primarily learned while the temperament traits are more biological. According to Cloninger,² among the four dimensions of temperament, 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.

The dopamine receptor D4 (DRD4) belongs to the D2 group of dopamine receptors and is predominantly expressed in a restricted set of dopamine-rich limbic areas that are involved in cognition and emotion. The human DRD4 gene, which is located on chromosome 11p15.5, contains a highly polymorphic sequence of a variable number of tandem repeats (VNTR) spanning 48 base pairs (bp) in exon III. This polymorphism lies in the third cytoplasmic loop of the receptor and has been reported to exert modest effects on both

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ligand binding and receptor-mediated modulation of intracellular cyclic AMP levels.³ Ebstein et al.⁴ reported an association between the seven repeated allele of the 48-bp VNTR in exon III of the DRD4 gene and NS. Simultaneously, Benjamine et al.⁵ reported an association between the same DRD4 polymorphism and the excitement-seeking item measured by the NEO PI-R (Revised NEO Personality Inventory) questionnaire. Some further studies have found a relation between the long DRD4 VNTR allele and a higher NS score,^{6,7} while others have not found such an association.^{8,9}

In addition to DRD4, the dopamine transporter (DAT1) might also be a candidate gene for behavioral traits. DAT1 plays a pivotal role in terminating dopaminergic neurotransmission. Several studies have found an association between DAT1 and attention-deficit hyperactivity disorder (ADHD).¹⁰ A temperament trait hypothesized to be associated with ADHD is NS, which involves behaviors such as impulsivity and excitability. Sabol et al.¹¹ found an association between NS and the DAT1 polymorphism, but other studies found no such association.¹²

Taking these observations into account, the present study examined whether DRD4 and DAT1 variants are related to personality traits in a Korean population.

MATERIALS AND METHODS

Subjects

We recruited 214 unrelated subjects from among the nurses, students, and volunteers at Hallym University Sacred Heart Hospital and Anyang Community Mental Health Center. The subjects comprised 102 men and 112 women, all were Korean, and they were aged 21-35 years. All subjects provided written informed consent to participate in the study after the aim and procedure of the study had been fully explained to them. The study protocols were approved by the ethics committees of Yongdong Severance Hospital. All of the candidate participants underwent a direct interview to exclude those with psychiatric disorders.

Psychometric evaluation

In order to exclude subclinical anxiety and depressive disorders, all of the subjects completed the Korean version of the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI). 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 also excluded. The Korean version of the Temperament and Character Inventory (TCI) was used to assess personality traits.¹³ The TCI is a self-rating instrument of yes/no answers designed to evaluate four personality dimensions of temperament: NS, HA, RD, and Persistence (P); and three character dimensions: Self-Directedness, Cooperativeness, and Self-Transcendence.² Whereas these four temperament factors are thought to be largely heritable and rooted in neurobiology, the three character factors are assumed to be socio-culturally determined and hence less likely to be associated with specific genes.² This study explored the possible association between genetic polymorphisms and the four temperament factors; the three character factors were not taken into consideration.

DNA analyses

The subjects donated a blood sample by venipuncture, from which genomic DNA was extracted from blood lymphocytes using a Genomic DNA Extraction kit (Bioneer, Daejeon, Korea). The 40-base pair DAT1 VNTR is located in the 3' untranslated region of the gene, and was genotyped as described by Sano et al.,¹⁴ but with slight modification. The DAT1 site was amplified by a polymerase chain reaction (PCR) using the primers 5'-TGT GGT GTA GGG AAC GGC CTG AG-3' and 5'-CTT CCI GGA GGT CAC GGC TCA AGG-3'. The 48-bp repeat polymorphism (with 2-8 or 10 repeats) in exon III of the DRD4 was also amplified by PCR described by Lichter et al.¹⁵ with oligonucleotide primers 5'-AGG ACC CTC ATG GCC TTG-3' and 5'-GCG ACT ACG TGG TCT ACT CG-3'. PCR reactions contained 100 ng genomic DNA; 10 pmol of each primer; 50 mM KCl; 10 mM Tris-HCl, pH 8.3; 1.5 mM MgCl₂; 0.01% gelatine; 200 uM of dATP, dCTP, and dTTP;

100 μ M of dGTP; 100 μ M of 7-deazaGTP; and 1 unit of Taq polymerase (SolGent, Daejeon, Korea) in a total volume of 25 μ L. The genomic DNA was denatured in 10 μ L sterilized water at 99°C for 5 min prior to the addition of the other components. Cycling conditions were 35 cycles at 95°C for 30 sec, 63°C for 30 sec, and 72°C for 30 sec, followed by 10 min at 72°C in PTC-100 thermal cycler (Bio-Rad Laboratories, Hercules, CA, USA). Amplification products were resolved by 3.5% agarose gel electrophoresis and were visualized by staining with ethium bromide. Fragment sizes were determined by comparison to molecular length standards.

Statistical analysis

To control for the possible effect of age on TCI, the differences in the TCI scores between genotypes were tested after the inclusion of age as a covariate in the analysis of covariance (ANCOVA). Due to the four comparisons (NS, HA, RD, and P) for each polymorphism, significance was stipulated as $p < 0.013$ (i.e., $0.05/4$). Statistical analyses were performed using SPSS (version 11.0) software for Windows.

RESULTS

The age of the subjects was 27.50 ± 6.13 (mean

\pm SD) years. For the DRD4 polymorphism, the most prevalent allele was that with four repeats (88.1%), followed by that with two repeats (9.8%), whereas the five-repeats (1.4%), six-repeats (0.2%), and seven-repeats (0.5%) alleles were extremely rare. In accordance with previous studies involving Asian subjects,^{6,16,17} the genotypes were divided into two groups: (1) those only carrying the short allele (\leq four repeats, $n = 205$), and (2) those with at least one copy of the long allele ($>$ four repeats, $n = 9$).

The genotype frequencies of the DAT1 polymorphism were 14 (6.6%) with genotype 9/10, 192 (89.7%) with 10/10, and 8 (3.7%) with 10/11. The number of subjects with non-10/10 repeats was small. An increased level of DAT1 expression was associated with the number of 10-repeats alleles,¹⁸ and the 10-repeats allele is reported to increase DAT1 gene expression compared with the 7-, 9-, and 11-repeats alleles.¹⁹ Therefore, we classified the genotype of DAT1 into 10/10-repeats and non-10/10-repeats groups.

The mean and SD values of the TCI dimension for the DRD4 and DAT1 gene polymorphisms are listed in Table 1. We found that the scores of HA, NS, RD, and P did not differ significantly between the DRD4 and DAT1 genotypes. Because only one subject had the long-allele genotype of DRD4 and non-10/10 repeats of DAT1, the interaction between the DRD4 and DAT1 genes on personality traits could not be analyzed further.

Table 1. TCI Personality Scores for Subject Groups According to the DRD4 and DAT1 Genotypes

Genotype	N	NS	HA	RD	P
DRD4					
S genotype	205	17.98 \pm 7.18	16.82 \pm 7.18	15.95 \pm 3.77	4.07 \pm 1.83
L genotype	9	20.00 \pm 8.85	12.33 \pm 8.14	14.78 \pm 4.47	4.11 \pm 1.36
<i>p</i> value		0.31	0.06	0.36	0.94
DAT1					
Non-10/10	22	16.90 \pm 4.42	17.90 \pm 6.67	15.16 \pm 4.55	4.04 \pm 1.99
10/10	192	18.18 \pm 5.81	16.70 \pm 7.37	15.97 \pm 3.64	4.01 \pm 1.81
<i>p</i> value		0.35	0.46	0.35	0.95

Data are mean \pm SD values.

NS, Novelty seeking; HA, Harm avoidance; RD, Reward dependence; P, Persistence; L, long allele; S, short allele; TCI, Temperament and Character Inventory; DRD4, Dopamine Receptor D4 gene; DAT1, Dopamine Transporter gene 1.

DISCUSSION

The present study represents a further investigation into the role of polymorphisms of the DRD4 and DAT1 genes in the modulation of personality traits, especially NS. We did not find any association between the DRD4 gene polymorphism and personality traits of TCI. There is controversy over the association between the long allele of the polymorphic exon III repeat sequence of DRD4 and personality traits, especially NS. Cloninger² initially postulated an association between the personality dimension of NS and the dopaminergic system localized in the limbic system, and a relationship between DRD4 and NS has received some support from previous studies;^{6,16,20} however, other studies have found no significant association.²¹

There are several possible explanations for the conflicting results from studies that have investigated the associations between the DRD4 gene and personality traits. The studies have used samples that differ substantially in terms of gender and age, both of which might affect personality traits. Ethnicity is another important factor. The distributions of the alleles of the DRD4 gene varied greatly between populations, and the genetic basis for the same personality trait might also differ between populations. In fact, the distribution of the allele of the DRD4 in this study (4 repeats 88% and 7 repeats 0%) is different from those of the Caucasians (4 repeats 68% and 7 repeats 18%)²² or the Swedes (4 repeats 66% and 7 repeats 18%) but similar to those of the Asian population such as the Japanese (4 repeats 84% and 7 repeats 0%)¹⁶ or other Koreans (4 repeats 82% and 7 repeats 1%)⁷ Considering this perspective, it will be worthy to review the studies of the Asian population who have similar genotype distributions to Koreans. To date, one Korean study has found an association between NS and the DRD4 long allele in female subjects but not in male subjects.⁷ We have also performed separate analyses in men and women (data not shown), but found no associations between the DRD4 genotype and any dimensions of TCI in either male or female subjects. The subjects in the previous study were younger (age 13.87 ± 0.30 years) than those in the present study, and the NS per-

sonality dimension is likely to diminish with age.^{7,23} The subjects of the previous study who were adolescents applied. Although the subjects of that study were adolescents, they applied the adult TCI rather than the junior version. The adult TCI has not been validated for adolescents, and the language used therein might not be suitable for evaluating adolescents.²⁴ These factors might explain the discrepancies between their results and those of the present study. Another Korean study by Lee et al.²⁵ also found no direct association between NS and DRD4 48-bp VNTR. Several other studies investigating the association between the DRD4 gene and personality traits have been conducted with Japanese and Chinese populations, whose frequencies of DRD4 48-bp VNTRs are similar to that of Koreans.^{6,16,17} Among these studies, two Japanese studies found an association between the long allele of the DRD4 48-bp VNTR and NS in female subjects.^{6,16} One of these studies, however, only involved 69 female subjects, which might be a small number to draw definite conclusions.⁶ The subjects of the other study were younger (age 18.7 ± 1.0 years) than those in our study,¹⁶ and as mentioned above, NS scores are negatively correlated with age.²³ Moreover, other Japanese and Chinese studies did not find any associations between the DRD4 gene and personality traits.¹⁷

In this study, we also did not find any association between DAT1 gene polymorphism and personality traits of the TCI. Sabol et al.¹¹ found that a low NS score was associated with the nine-repeats allele of the DAT1, and Van Gestel et al.²⁶ reported that genotype 10/10 of DAT1 was more frequently associated with high NS scores in females but not in males. However, most other studies have not found such an association.¹² We do not know the exact causes of these inconsistent results. Although there is preliminary evidence that the DAT1 VNTR polymorphism affects translation of the DAT1 protein,²⁷ the results have varied between studies. Some researchers found higher DAT1 gene expression in the 10-repeats allele than in the 7-, 9-, and 11-repeats alleles,¹⁹ whereas others have reported that gene expression is higher in the 9-repeats allele than in the 10-repeats allele.²⁸ Moreover, Martinez et al.²⁹ reported that the

VNTR polymorphism of the DAT1 is not associated with a significant change in the DAT1 phenotype in humans. Jonsson et al.³⁰ also did not find an association between DAT1 polymorphism and a major dopamine metabolite, homovanillic acid, in cerebrospinal fluid. It appears that the distribution of the DAT1 VNTR polymorphism is associated with ethnicity.³¹ The frequency of the 10-repeats allele is higher in Asian populations (as in the present study; 0.86-0.94) than in Caucasian and Black populations (0.59-0.79). These two factors may at least partially explain the inconsistencies in the results of previous studies. Although we found no association between the DAT1 VNTR polymorphism and NS, it would be inappropriate to conclude that DAT1 is not related to NS. A more definite conclusion requires elucidation of the effects of allelic variation at DAT1 on DAT1 function or expression.

Our study has some limitations. First, the population studied was small, which may have resulted in our failure to find any significant associations due to the resultant limitations of statistical power. Moreover, the long allele of DRD4 and non-10/10 genotype of DAT1 was extremely rare in our study population, and this low frequency might reduce the probability of detecting any potential associations. Second, we could not analyze the interaction between DRD4 and DAT1 on personality traits and did not consider epistatic effects. However, one study recently found a significant interaction between the DRD4 and DAT1 genes in NS.²⁶ Lastly, we considered only the effects of genetic factors on personality traits, whereas there is evidence that personality is affected by interaction of genes and environments.³² Therefore, further studies should investigate the interplay between genes and environments from both biological and psychosocial points of view.

In conclusion, we did not find any associations between the DRD4 and DAT1 genes and personality traits. However, our findings need to be replicated in larger independent samples, and the combined effects of polymorphic variants of genes on personality traits needs to be investigated.

REFERENCES

1. Bouchard TJ Jr. Genes, environment, and personality. *Science* 1994;264:1700-1.
2. Cloninger CR. A systematic method for clinical description and classification of personality variants. *Arch Gen Psychiatry* 1987;44:573-88.
3. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *J Neurochem* 1995;65:1157-65.
4. Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blanie D, et al. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nat Genet* 1996;12:78-80.
5. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nat Genet* 1996;12:81-4.
6. Tomitaka M, Tomitaka S, Otuka Y, Kim K, Matuki H, Sakamoto K, et al. Association between novelty seeking and dopamine receptor D4 (DRD4) exon III polymorphism in Japanese subjects. *Am J Med Genet* 1999;88:469-71.
7. Lee HJ, Lee HS, Kim YK, Kim L, Lee MS, Jung IK, et al. D2 and D4 dopamine receptor gene polymorphisms and personality traits in a young Korean population. *Am J Med Genet B Neuropsychiatr Genet* 2003;121:44-9.
8. Jonsson EG, Nothen MM, Gustavsson JP, Neidt H, Brene S, Tylec A, et al. Lack of evidence for allelic association between personality traits and the dopamine D4 receptor gene polymorphisms. *Am J Psychiatry* 1997;154:697-9.
9. Mitsuyasu H, Hirata N, Sakai Y, Shibata H, Takeda Y, Ninomiya H, et al. Association analysis of polymorphisms in the upstream region of the human dopamine D4 receptor gene (DRD4) with schizophrenia and personality traits. *J Hum Genet* 2001;46:26-31.
10. Gill M, Daly G, Heron S, Hawi Z, Fitzgerald M. Confirmation of association between attention deficit hyperactivity disorder and a dopamine transporter polymorphism. *Mol Psychiatry* 1997;2:311-3.
11. Sabol SZ, Nelson ML, Fisher C, Gunzerath L, Brody CL, Hu S, et al. A genetic association for cigarette smoking behavior. *Health Psychol* 1999;18:7-13.
12. Jorm AF, Henderson AS, Jacomb PA, Christensen H, Korten AE, Rodgers B, et al. Association of smoking and personality with a polymorphism of the dopamine transporter gene: results from a community survey. *Am J Med Genet* 2000;96:331-4.
13. 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.
14. Sano A, Kondoh K, Kakimoto Y, Kondo I. A 40-nucleotide repeat polymorphism in the human dopamine

- transporter gene. *Hum Genet* 1993;91:405-6.
15. Lichter JB, Barr CL, Kennedy JL, Van Tol HH, Kidd KK, Livak KJ. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Hum Mol Genet* 1993;2:767-73.
 16. Ono Y, Manki H, Yoshimura K, Muramatsu T, Mizushima H, Higuchi S, et al. Association between dopamine D4 receptor (D4DR) exon III polymorphism and novelty seeking in Japanese subjects. *Am J Med Genet* 1997;74:501-3.
 17. Tsai SJ, Hong CJ, Yu YW, Chen TJ. Association study of catechol-O-methyltransferase gene and dopamine D4 receptor gene polymorphisms and personality traits in healthy young chinese females. *Neuropsychobiology* 2004;50:153-6.
 18. Mill J, Asherson P, Browes C, D'Souza U, Craig I. Expression of the dopamine transporter gene is regulated by the 3' UTR VNTR: Evidence from brain and lymphocytes using quantitative RT-PCR. *Am J Med Genet* 2002;114:975-9.
 19. Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. *Pharmacogenomics J* 2001;1:152-6.
 20. Ebstein RP, Nemanov L, Klotz I, Gritsenko I, Belmaker RH. Additional evidence for an association between the dopamine D4 receptor (D4DR) exon III repeat polymorphism and the human personality trait of Novelty Seeking. *Mol Psychiatry* 1997;2:472-7.
 21. Jonsson EG, Nothen MM, Gustavsson JP, Neidt H, Forslund K, Mattila-Evendén M, et al. Lack of association between dopamine D4 receptor gene and personality traits. *Psychol Med* 1998;28:985-9.
 22. Szekeley A, Ronai Z, Nemoda Z, Kolmann G, Gervai J, Sasvari-Szekeley M. Human personality dimensions of persistence and harm avoidance associated with DRD4 and 5-HTTLPR polymorphisms. *Am J Med Genet B Neuropsychiatr Genet* 2004;126:106-10.
 23. Ebstein RP, Belmaker RH. Saga of an adventure gene: novelty seeking, substance abuse and the dopamine D4 receptor (D4DR) exon III repeat polymorphism. *Mol Psychiatry* 1997;2:381-4.
 24. Lyoo IK, Han CH, Lee SJ, Yune SK, Ha JH, Chung SJ, et al. The reliability and validity of the junior temperament and character inventory. *Compr Psychiatry* 2004; 45:121-8.
 25. Lee HJ, Lee HS, Kim YK, Kim SH, Kim L, Lee MS, et al. Allelic variants interaction of dopamine receptor D4 polymorphism correlate with personality traits in young Korean female population. *Am J Med Genet B Neuropsychiatr Genet* 2003;118:76-80.
 26. Van Gestel S, Forsgren T, Claes S, Del-Favero J, Van Duijn CM, Sluijs S, et al. Epistatic effect of genes from the dopamine and serotonin systems on the temperament traits of novelty seeking and harm avoidance. *Mol Psychiatry* 2002;7:448-50.
 27. Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, et al. Genotype influences *in vivo* dopamine transporter availability in human striatum. *Neuropsychopharmacology* 2000;22:133-9.
 28. Miller GM, Madras BK. Polymorphisms in the 3'-untranslated region of human and monkey dopamine transporter genes affect reporter gene expression. *Mol Psychiatry* 2002;7:44-55.
 29. Martinez D, Gelernter J, Abi-Dargham A, van Dyck CH, Kegeles L, Innis RB, et al. The variable number of tandem repeats polymorphism of the dopamine transporter gene is not associated with significant change in dopamine transporter phenotype in humans. *Neuropsychopharmacology* 2001;24:553-60.
 30. Jonsson EG, Nothen MM, Gustavsson JP, Neidt H, Bunzel R, Propping P, et al. Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationships to monoamine metabolite concentrations in CSF of healthy volunteers. *Psychiatry Res* 1998;79:1-9.
 31. Kang AM, Palmatier MA, Kidd KK. Global variation of a 40-bp VNTR in the 3'-untranslated region of the dopamine transporter gene (SLC6A3). *Biol Psychiatry* 1999;46:151-60.
 32. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301:386-9.