



## An association study of catechol-*O*-methyltransferase and monoamine oxidase A polymorphisms and personality traits in Koreans

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### Abstract

Catechol-*O*-methyltransferase (COMT) and monoamine oxidase A (MAOA) are both involved in the degradation of various biogenic amines which have been hypothesized to have a relationship with personality traits. The present study investigated the possible relationships between the genotypes of COMT Val158Met and MAOA-uVNTR polymorphisms and personality traits measured by the Temperament and Character Inventory (TCI). We recruited 286 normal, unrelated Korean subjects (138 males and 148 females). There were no associations between the COMT Val158Met genotypes or the TCI subscales in the male subjects. However, a significant correlation was observed between the COMT genotype and harm avoidance (HA,  $F=6.0$ ,  $p=0.003$ ) in females. Post hoc analyses showed that the subjects with the Met/Met genotype had the lowest mean HA (HA =  $13.8 \pm 5.7$ ,  $p=0.02$ ), Val/Met group had an intermediate mean HA score (HA =  $16.3 \pm 7.0$ ,  $p=0.02$ ), and Val/Val group had the highest mean HA value (HA =  $19.6 \pm 7.0$ ,  $p=0.02$ ). There were no associations between the MAOA-uVNTR and the TCI subscales in either the male or female subjects. These results suggest that genetic variants of the COMT Val158Met gene may play a role in HA in Korean females but not in males.

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Individual differences in human behavioral predispositions are relatively enduring. These personality traits are influenced by both genetic and environmental factors. According to previous studies, approximately 30–60% of the variance in personality traits is due to inherited factors [3]. Several candidate gene polymorphisms have been recently reported to be associated with certain personality traits.

The Temperament and Character Inventory (TCI) is a self-rating instrument that measures four temperament dimensions:

novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P). The TCI is also used to evaluate three character dimensions: self-directedness (SD), cooperativeness (C) and self-transcendence (ST), as defined by Cloninger's psychobiosocial model of personality [6]. According to this theoretical model, NS, HA, and RD are related to dopaminergic, serotonergic, and noradrenergic activity, respectively [5].

Since Catechol-*O*-methyltransferase (COMT) and monoamine oxidase A (MAOA) are involved in the degradation of these monoamines, these enzymes might affect human personality traits measured by the TCI.

Catechol-*O*-methyltransferase is an enzyme involved in the inactivation of catecholamines including adrenaline, noradrenaline, and dopamine. A polymorphism in the human COMT gene (472G>A) results in a valine (Val) to methionine (Met) amino acid substitution (Val158Met) and also reduces the activity of the enzyme to one quarter of that encoded by the Val allele

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[20]. The alleles are codominant, and heterozygotic patients (Val/Met genotype) have intermediate levels of COMT activity in comparison to homozygous individuals [22].

Although the results are heterogeneous, several recent studies indicate a role of COMT Val158Met polymorphism in personality traits. Some researchers have suggested that the Met/Met genotype is related to a higher HA score or even neuroticism [9,10]. Tsai et al. [35] reported an association between the COMT gene and NS and RD. In addition, some studies have demonstrated that COMT Val158Met polymorphism is associated with aggressive personality traits or a self-reported schizotypal score [1].

MAOA is another important enzyme that degrades biogenic amines (noradrenaline, serotonin, and to a lesser degree, dopamine). The polymorphism, which is located 1.2 kb upstream of the MAOA coding sequences, consists of a 30-bp repeated sequence present in 2, 3, 3.5, 4, or 5 repeats (R) and designated MAOA-uVNTR (upstream variable number of tandem repeats). This polymorphism is functional in that 3.5, 4 and 5 R are transcribed 2–3 times more efficiently than those with 3 and 2 R [30]. There have been several studies of an association between the MAOA gene and various human behaviors such as addictive behavior, aggression and impulsive traits [12,32,40]. Although there were several studies which reported negative results [11,14,19], some genetic studies on personality traits demonstrated that this MAOA-uVNTR is associated with HA on the Tridimensional Personality Questionnaire [40], and also with neuroticism [9].

Taking these observations into account, the present study investigated possible relationships between the genotypes of COMT Val158Met and MAOA-uVNTR polymorphisms and the personality traits measured by TCI.

We recruited 286 unrelated subjects (138 men and 148 women) from populations of nurses, students and volunteers at two university hospitals and one community mental health center. All of the subjects were Korean and were between the ages of 21 and 35 years old. All participants completed Korean version of Beck Depression Inventory (BDI) [17] and Beck Anxiety Inventory (BAI) [39], and in accordance with the results of previous studies [17,39], those who scored more than 21 points on the BDI or 22 points on the BAI were excluded. In addition, the study participants were clinically evaluated by a board certified psychiatrist (SJ Kim) prior to the study and were ascertained to be free of major medical and psychiatric illnesses. Those with a past history and family history of substance abuse/dependence or major psychiatric disorders such as schizophrenia or mood disorders were excluded. 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.

The TCI (Korean version, 240 items) is a self-rating instrument of yes or no answers designed to evaluate the four personality dimensions of temperament: novelty seeking, harm avoidance, reward dependence, and persistence. It can also measure the three character dimensions of self-directedness, cooperativeness and self-transcendence [6].

Subjects donated a blood sample through venipuncture, and the DNA was isolated using standard techniques. The functional promoter polymorphism of the COMT Val158Met and the MAOA-uVNTR were genotyped by polymerase chain reaction (PCR) amplification as described by Lachman et al. [20] and Sabol et al. [30], respectively.

In both genders with COMT Val158Met polymorphism, the differences in the TCI subscale scores were compared according to genotypes using one-way ANOVA, followed by the Bonferroni Test for between-group comparisons. With the MAOA-uVNTR, the genotype differences for the TCI subscales were compared using a *t*-test or one-way ANOVA.

Due to the seven comparisons (seven subscales of TCI) for each polymorphism, the significance was stipulated as  $p < 0.0071$  (i.e., 0.05/7). Statistical analyses were performed using SPSS (Version 11.0) software for Windows.

The mean ages of the male and female subjects were  $28.1 \pm 5.1$  years and  $28.6 \pm 6.2$  years, respectively. The distribution of each genotype was consistent with the Hardy–Weinberg Equilibrium. Genotype frequencies in both genes were as follows: COMT Val158Met–Val/Val 150 (52.4%), Val/Met 108 (37.8%), Met/Met 28 (9.8%) and MAOA-uVNTR—in males, 3 R 65 (47.1%) and 4 R 73 (52.9%), and in females, 2/3 R 2 (1.4%), 2/4 R 2 (1.4%), 3/3 R 44 (29.7%), 3/4 R 66 (44.5%), 3/5 R 2 (1.4%), and 4/4 R 32 (21.6%). These were similar to those reported in other Korean and Chinese populations [15,23,40].

The TCI scores according to the COMT Val158Met and MAOA-uVNTR genotypes are presented in Tables 1 and 2. There were no associations between the COMT genotype and the TCI subscales. In females, however, a significant correlation was observed between the COMT genotype and the HA ( $F = 6.0$ ,  $p = 0.003$ ). A post hoc analysis indicated that the Val/Val genotype had a higher HA score than the Val/Met ( $p = 0.02$ ) and the Met/Met genotypes ( $p = 0.02$ ). The Val/Met genotype also had a higher HA score than the Met/Met genotype ( $p = 0.02$ ). In addition, the other subscales of TCI were not associated with COMT Val158Met polymorphisms.

The frequency of the 2 and 5 R alleles of MAOA-uVNTR was rare in this study. Therefore, the individuals who carried them (no males and only two females had the 2 R allele and two females had the 5 R allele) were excluded in the statistical analysis of MAOA-uVNTR. Since the MAOA gene is X-linked, males had only one allele while females had two. Therefore, in the present study, men and women were analyzed separately. The alleles were grouped as 3 R and 4 R in the males for statistical analyses, and in women the genotypes were grouped as 3/3 genotypes and 3/4 plus 4/4 genotypes. This was because the transcription efficiency of MAOA was shown to be two to three-fold higher for the longer alleles (3.5, 4, and 5) than for the shorter alleles (3 and the rare 2 R alleles) [7,30]. There were not any associations between the MAOA-uVNTR genotype and the TCI subscales in both male and female subjects.

The major finding of this study is that the COMT Val158Met polymorphism may be associated with the HA personality traits, at least in female subjects. This finding was consistent with previous studies that reported some associations between COMT Val158Met polymorphism and anxiety-related personality traits

Table 1  
TCI scores for subject groups stratified according to the COMT Val158Met genotypes in Korean males and females

Personality dimension	Men				Women			
	Genotype			<i>p</i>	Genotype			<i>p</i>
	Val/Val <i>N</i> = 74	Val/Met <i>N</i> = 48	Met/Met <i>N</i> = 16		Val/Val <i>N</i> = 76	Val/Met <i>N</i> = 60	Met/Met <i>N</i> = 12	
HA	17.0 ± 5.8	16.2 ± 8.5	14.3 ± 7.6	0.36	19.6 ± 7.0	16.3 ± 7.0	13.8 ± 5.7	0.003
NS	19.1 ± 6.3	17.0 ± 5.5	19.7 ± 5.2	0.10	17.3 ± 5.4	18.0 ± 5.5	18.3 ± 5.0	0.72
RD	14.9 ± 4.3	14.6 ± 4.3	15.9 ± 4.9	0.58	17.0 ± 3.1	16.3 ± 3.1	16.6 ± 2.9	0.43
P	3.8 ± 1.8	4.5 ± 1.9	5.1 ± 1.6	0.02	3.5 ± 1.6	4.0 ± 2.0	4.6 ± 1.3	0.07
SD	25.6 ± 8.1	26.8 ± 6.3	28.8 ± 7.2	0.25	25.6 ± 7.8	27.2 ± 8.2	30.1 ± 5.3	0.13
C	29.2 ± 6.6	30.6 ± 5.6	32.6 ± 4.9	0.11	32.1 ± 4.7	31.8 ± 5.5	32.3 ± 3.4	0.89
ST	10.6 ± 5.8	12.3 ± 6.5	11.6 ± 5.3	0.30	9.0 ± 4.3	9.7 ± 5.2	8.4 ± 3.6	0.55

HA: harm avoidance; NS: novelty seeking; RD: reward dependence; P: persistence; SD: self-directedness; C: cooperativeness; ST: self-transcendence.

such as HA [10], neuroticism [34] and some anxiety disorders [37].

In contrast to our results, Henderson et al. did not find any associations between the COMT gene and the personality traits measured by the Eysenck Personality Questionnaire-Revised (EPQ-R). Tsai et al. [35] reported that COMT Val158Met polymorphism was significantly associated with NS and RD but not with HA. Reuter et al. [29] also found that COMT Val158Met polymorphism was related to both extraversion and NS, although they did not consider the neuroticism of NEO-PI and the HA shown on TCI. Benjamin et al. [2] reported that an interaction between COMT and 5-HTTLPR contributes to the determination of the RD2 of TPQ. In addition, Smolka et al. [33] did not find any difference in HA score according to the COMT Val158Met genotype. These discrepancies might be due to common problems seen in association studies such as differences in ethnicity, assessment scales, or sample sizes. In addition to these, another important factor that we must take into consideration is the effect of gender on the association between COMT Val158Met and personality traits. However, most of the studies that reported different results than ours did not analyze their data separately according to gender.

There are three particular points of interest in our results. In contrast with two previous studies [10,34] that found an association between either a high HA or neuroticism and Met/Met, we found that the Val allele was associated with higher HA scores. We do not know the exact reason why the COMT Val158Met genotypes act reversely on HA in Koreans, but it is thought to

be partially due to ethnicity. The reported allele frequencies of G = 0.64–0.82 and A = 0.18–0.36 for Asian populations differ markedly from those for Caucasians, which are G = 0.48–0.60 and A = 0.40–0.52 [28]. We found very similar allele frequencies between Koreans and those reported for other Asian populations. There is another possibility to explain our results: contrary to previous two studies, COMT Met/Met genotype and decreased enzyme activity may actually have no associations to HA. Although not related to HA, there are reports that not Met allele, but Val allele are associated with anxiety. These studies, in part, are consistent with our results. McGrath et al. [26] found that the COMT Val/Val genotype was associated with an increased risk of phobic anxiety when assessed by the Crown-Crisp Experimental Index, which measures personality traits and symptoms of phobic anxiety. Domschke et al. [8] also reported that the COMT Val allele was significantly in excess in female patients with panic disorder, even though this is not a personality trait. Hamilton et al. [16] found significant linkage disequilibrium between the COMT Val allele and panic disorders. These findings are somewhat consistent with our results. However, a recent study on the Korean population [37] showed that the frequency of the Met/Met allele was significantly higher in those with panic disorder, so there could have been sample stratification in our study. This bias is less likely to have developed in our study because our participants were collected from only one geographic area and Koreans were assumed to be free from ethnic stratification [21]. Our results must be treated with caution and the importance of our results confirmed, because the

Table 2  
TCI scores for subject groups stratified according to the MAOA-uVNTR allele and genotypes in Korean males and females

Personality dimension	Men			Women			
	Allele		<i>p</i>	Genotype			<i>p</i>
	3 R <i>N</i> = 65	4 R <i>N</i> = 73		3/3 R <i>N</i> = 44	3/4 R <i>N</i> = 66	4/4 R <i>N</i> = 32	
HA	16.2 ± 7.0	16.5 ± 7.1	0.81	16.8 ± 7.5	19.1 ± 7.2	16.9 ± 7.5	0.21
NS	19.0 ± 5.8	18.0 ± 6.2	0.31	18.6 ± 5.5	16.7 ± 5.2	18.4 ± 5.6	0.15
RD	14.7 ± 4.5	15.1 ± 4.1	0.54	16.6 ± 3.0	16.5 ± 3.0	17.0 ± 3.5	0.73
P	4.1 ± 1.7	4.3 ± 1.9	0.48	3.9 ± 2.5	3.7 ± 1.8	3.9 ± 1.6	0.70
SD	26.2 ± 6.9	26.6 ± 7.8	0.72	28.5 ± 7.0	25.4 ± 8.2	26.6 ± 8.8	0.15
C	30.2 ± 5.3	29.9 ± 6.9	0.79	33.3 ± 3.8	31.3 ± 5.7	31.5 ± 5.0	0.12
ST	11.0 ± 5.3	11.5 ± 6.6	0.61	9.6 ± 5.0	8.9 ± 4.6	10.0 ± 4.1	0.51

HA: harm avoidance; NS: novelty seeking; RD: reward dependence; P: persistence; SD: self-directedness; C: cooperativeness; ST: self-transcendence.

number of female subjects with COMT Met/Met was only 12. Therefore, independent replications utilizing larger sample sizes should be carried out.

One effect of Val158 Met on HA was confined only to females in our study. Enoch et al. [10] and more recently, Stein et al. [34] also reported the association between COMT Val158Met and anxiety-related personality traits in women alone. Furthermore, several other studies which found associations between COMT and panic disorder were specific to women [8,37]. Animal studies have also shown that homozygous COMT-deficient female (but not male) mice demonstrate greater anxiety-like behavior [13]. Women have significantly lower COMT activity than do men [4], perhaps due to the fact that estrogen can inhibit COMT gene transcription [38]. For these reasons, Olsson et al. [27] suggested that an increased vulnerability to anxiety in females might only be realized through the combined effects of Val158Met polymorphism and the down-regulation of COMT expression mediated by cyclic effects of estrogen.

Our data also showed a clear genotype-dose dependent association. Lotta et al. [22] have reported that the activity of the COMT variant containing Met is one fourth that of the Val allele. The alleles are codominant, as it has been demonstrated that individuals bearing a Val/Met genotype have an intermediate level of COMT activity relative to their homozygous counterparts. In our study, the female subjects with the Met/Met genotype had the lowest mean HA ( $HA = 13.8 \pm 5.7$ ), the Val/Met group had an intermediate mean HA ( $HA = 16.3 \pm 7.0$ ), and the Val/Val group had the highest mean HA ( $HA = 19.6 \pm 7.0$ ). All differences between the groups were statistically significant. There was evidence of a dose–response relationship of COMT Val158Met polymorphism and various conditions. Olsson et al. [27] found a dose relationship between additional copies of the Met allele and persistent episodic anxiety. Smolka et al. [33] also reported that brain reactivity measured by fMRI to unpleasant stimuli was significantly positively correlated with the number of Met alleles in the limbic system. In addition, some studies have shown that homozygotes for the Met allele perform better than homozygotes for the Val allele in executive function tests, with heterozygotes producing an intermediate score [18,36].

In MAO-A polymorphism, there were no significant differences in the mean scores of TCI subscales between alleles (3 and 4 R). This result is in accordance with many other studies [11,14,31] that could not find any association between COMT genotypes and personality traits measured by TCI, TPQ or NEO-PI. Although some studies found a positive association between MAOA-uVNTR and impulsivity [24] and aggression [25], it is not possible to directly compare their results with ours because the questionnaires they used for personality evaluations were quite different from ours.

According to our knowledge to date, there were only two studies that reported positive associations between MAOA-uVNTR and some personality traits measured by TCI, TPQ, or NEO-PI. One study by Eley et al. [9,10] found a trend of association between a high activity allele on the MAOA-uVNTR ( $\geq 3.5$  R) and a high neuroticism score on the NEO-FFI. However, their findings were based on an extreme design and the use of peer ratings instead of self-report questionnaires. Another study by

Yu et al. [40] reported that 4/4 repeats of MAOA-uVNTR tend to have a high HA of TPQ in Chinese females. This study did not consider multiple testing, however, and their results were not statistically significant after correcting for multiple testing.

Although the data are not presented here, we also performed an epistatic analysis. A multivariate two-way ANOVA showed no significant interaction of COMT  $\times$  MAOA on the TCI subscales in either male or female subjects (in males, Hotelling's Trace  $F = 1.7$ ,  $p = 0.07$  and in females, Hotelling's Trace  $F = 0.14$ ,  $p = 0.92$ ).

Our study has some limitations. First, our failure to find other significant associations may be a reflection of our small sample size and the 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 the power (0.80) to detect a small effect size ( $f^2 = 0.194$ ). In addition, we only considered the effects of genetic factors on personality traits, but these traits may be influenced by an interaction of both genetic and environmental factors. Lastly, the subjects in this study were between 21 and 35 years of age. Also, we did not select the subjects according to the statistical population of Korea in respects to the education level, sex, as well as age. And our exclusion of subjects with psychiatric illness was based on a non-standardized interview. This level of exclusion may not completely exclude mentally ill group of patients, and might not represent the result obtained from the general mentally healthy Korean population. These limitations in our study imply that our results might be applied only to a subgroup of young and probably not mentally ill Koreans.

In summary, the present study showed a possible association between COMT Val158Met polymorphism and HA in the Korean female population. To confirm our findings, further studies are needed with a larger number of subjects in different populations, and environmental factors need to be controlled for.

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