Effect of Tryptophan Hydroxylase Gene Polymorphism on Aggression in Major Depressive Disorder and Undifferentiated Somatoform Disorder

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ABSTRACT

Objective: Aggression and anger have been linked with depression, and anger suppression has been linked with somatic symptoms of somatoform disorders. However, the relationship between aggression or anger and genes in patients with depression and somatoform disorders has not been clearly elucidated. The objective of this study was to examine the effect of serotonin-related gene polymorphism on aggression in depressive disorders and somatoform disorders.

Method: A serotonin-related polymorphic marker was assessed by using single nucleotide polymorphism (SNP) genotyping. 106 outpatients with major depressive disorder (MDD), 102 outpatients with undifferentiated somatoform disorder, and 133 healthy subjects were enrolled between October 2005 and May 2008. Diagnoses were made according to the Korean version of the Structured Clinical Interview Schedule for *DSM-IV*. The allele and genotype frequencies of tryptophan hydroxylase-1 (*TPH1*) A218C were compared between groups. The Hamilton Depression Rating Scale and the Aggression Questionnaire were used for psychological assessment.

Results: Each of the 2 disorder groups scored significantly higher on all the Aggression Questionnaire subscales and on the total Aggression Questionnaire score than the healthy subjects ($P < .001$). Patients with MDD had significantly higher frequencies of *TPH1* C allele ($P = .0002$) and CC homozygote ($P = .0003$) than healthy subjects, regardless of sex and age. However, no significant differences were found in *TPH1* C allele and CC homozygote frequencies between the undifferentiated somatoform disorder patients and the healthy subjects. *TPH1* CC homozygote in the MDD group scored significantly higher in terms of verbal aggression ($P = .03$) and total Aggression Questionnaire score ($P = .04$) than A-carrier genotypes, regardless of sex and age. However, no significant differences were found in the scores of all the Aggression Questionnaire subscales and the total Aggression Questionnaire score between *TPH1* CC homozygote and A-carrier genotypes in the undifferentiated somatoform disorder group and the control group, respectively.

Conclusions: Aggression in MDD patients is more susceptible to an excess of *TPH1* CC homozygote than in undifferentiated somatoform disorder patients, though the 2 disorders are high risk groups for aggression. In addition, *TPH1* gene is most likely to have a shared effect on aggression and MDD.

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Major depressive disorder (MDD) is one of the most common mental disorders, with a lifetime prevalence of about 5%–17%.[1,2] Undifferentiated somatoform disorder, a subtype of somatoform disorder, is characterized by 1 or more unexplained physical complaints lasting for at least 6 months but remaining below the threshold for diagnosing somatization disorder.[3] The prevalence of undifferentiated somatoform disorder is known to be quite high, ranging from 10.2% to 30.6%.[4–6]

Serotonin is believed to play an important role in depression, and a number of serotonergic pathway genes have been examined,[7] including the tryptophan hydroxylase-1 (*TPH1*) gene, which is involved in the catalysis of the rate-limiting step for serotonin biosynthesis[8] and regulates levels of serotonin.[9] *TPH1* is regarded as a candidate gene for MDD and is believed to influence response to antidepressants.[10] Recently, genetic variants of the tryptophan hydroxylase-2 (*TPH2*) gene were also reported to be involved in the pathogenesis of MDD.[11] In humans, *TPH1* and *TPH2* are expressed in nearly equal amounts in several brain regions (frontal cortex, thalamus, hippocampus, hypothalamus, and amygdala), but *TPH2* is predominantly expressed in the brain stem, the major locus of the serotonin-producing neurons.[12]

In addition, somatic symptoms of somatoform disorders are thought to be connected to serotonergic neurotransmission because serotonin is known to regulate the functions relevant to one of these disorders, such as pain disorder.[3,13] There is also some evidence suggesting that an abnormality in processing immunoreactive serotonin transporter protein is involved in somatoform disorders.[14]

Aggression and anger have long been linked with depression.[15–19] It has been also reported that anger suppression is associated with somatic symptoms of somatoform disorders.[18,20,21] In particular, impulsive aggression is highly comorbid with other mental disorders, including depression. Serotonergic hypofunction has been implicated as a possible source of comorbidity in individuals with depression and accompanying impulsive aggression.[22] In humans, 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid correlates inversely with various aggressive behaviors as demonstrated in healthy and psychiatric samples throughout one's life span. The majority of findings suggest that lowered 5-HIAA is related to vulnerability to aggressive behavior.[23,24]

It has been reported that impulsive aggression is associated with the *TPH1* LL genotype in men in a small sample of subjects with personality disorders.[25] In addition, Mann et al[26] reported that, among inpatients with major depression,

the less common A218C U allele was more frequently seen in persons who had a history of attempted suicide. Manuck and colleagues[27] have shown that individual differences in aggressive disposition are associated with the *TPH1* A218C single nucleotide polymorphism (SNP) in a nonpatient sample of community-derived volunteers.

Taken together, it is possible that MDD and somatoform disorders are related to both aggression or anger and serotonin-related gene polymorphisms. Therefore, we hypothesized that aggression or anger in MDD and undifferentiated somatoform disorder might be associated with serotonin-related gene polymorphisms. In this study, we examined *TPH1* A218C gene polymorphism in patients with MDD and undifferentiated somatoform disorder and in healthy control subjects to test this hypothesis.

Clinical Points

- Levels of aggression in patients with major depressive disorder (MDD) may be differentiated by a genetic method.
- Genetic examination in patients with MDD may lead to better assessment, treatment, and prevention of aggression.
- Clinicians can use these findings as the rationale for continuous psychopharmacologic treatment in potentially aggressive patients with MDD.

METHOD

Participants

The study was reviewed and approved by the institutional review board of Yonsei University College of Medicine at Severance Hospital, Seoul, Korea. The purpose and procedures of the study were explained to all potential subjects, who were of the same geographic and ethnic origins, and informed consent was obtained from those who decided to participate. Depression levels were assessed by 2 experienced psychiatrists (K.B.K. and C.H.K.) using the Hamilton Depression Rating Scale (HDRS).[28]

One hundred thirty-three healthy subjects (53 men, 80 women) were recruited from among volunteers for hospital guide service and hospital employees, such as secretaries, janitors, clerical workers, nurse's aides, nurses, medical residents, and medical students. The mean ± SD age of the healthy subjects was 32.2 ± 7.6 years, with a range of 25 to 53 years. The subjects were selected after completing a self-report questionnaire and having an interview to confirm the absence of physical and psychiatric disorders and family history of psychiatric disorders. None of the volunteers reported being treated for or having symptoms of physical or psychiatric disorders or having a family history of psychiatric disorders in the self-report questionnaire.

In addition, unrelated Korean outpatients who had been diagnosed with MDD and undifferentiated somatoform disorder from the Department of Psychiatry at Severance Hospital (Seoul, Korea) were enrolled in this study. Patients were consecutively selected and interviewed. All patients with MDD exhibited suicidal ideation but had no episodes of suicidal attempt. A semistructured interview was conducted, and diagnoses were made by 2 experienced psychiatrists using the Korean version[29,30] of the Structured Clinical Interview Schedule for *DSM-IV*[31] upon the first visit to the outpatient department. History of suicidal behavior and medication was ascertained by the psychiatrists through a direct interview with patients and their family members. Among the patients who completed the procedure, we selected those who had not received medication. Therefore, most of the subjects were unmedicated, but some patients who were within a few days of starting medication were included in this study. They received antidepressants (selective serotonin reuptake inhibitors [SSRIs]) such as fluoxetine or paroxetine. However, those who showed change in emotional and behavioral symptoms after initiation of the medication were excluded.

Medical workups as needed were performed on all patients to rule out any medical diseases at either the Department of Psychiatry or other departments. Patients with physical diseases or abnormal laboratory findings were excluded from the study to avoid including subjects with secondary depression. Patients who developed additional medical or psychiatric diagnoses (Axis I and Axis II disorders) during the course of the study were also excluded. The final sample included 106 patients with MDD (28 men, 78 women) and 102 patients with undifferentiated somatoform disorder (47 men, 55 women). The mean ± SD age of patients with MDD was 39.0 ± 12.1 years, with a range of 20 to 59 years. The mean ± SD age of patients with undifferentiated somatoform disorder was 41.9 ± 11.0 years, with a range of 20 to 59 years. Study participants were enrolled between October 2005 and May 2008.

Psychometric Measures

The psychometric measures included the Hamilton Depression Rating Scale (HDRS)[28] and the Korean version[32] of the Aggression Questionnaire.[33] The Aggression Questionnaire is a 27-item self-rating instrument developed for assessing the severity of aggression that includes the 4 subscales physical aggression, verbal aggression, anger, and hostility. In this study, it was rated on a 5-point scale ranging from 0 (never) to 4 (very much).

SNPs Genotyping

Genomic DNA was extracted from peripheral blood by using a Puregene DNA purification kit (Gentra, Minneapolis, Minnesota). Tryptophan hydroxylase-1 A218C polymorphisms were genotyped by using a TaqMan fluorogenic 5′ nuclease assay (Applied Biosystems, Foster City, California). A polymerase chain reaction (PCR) was conducted with 5 μL containing 10 ng of genomic DNA, 2.5 μL of TaqMan Universal PCR Master Mix, and 0.13 μL of 40× assay mix (Applied Biosystems, Foster City, California). Thermal cycle

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conditions were as follows: 50° C for 2 minutes to activate the uracil-*N*-glycosylase and to prevent carryover contamination, 95° C for 10 minutes to activate the DNA polymerase, followed by 45 cycles at 95° C for 15 seconds and 60° C for 1 minute. All PCRs were performed using 384-well plates in a Dual 384-Well GeneAmp PCR System 9700 (Applied Biosystems, Foster City, California), and allelic discrimination analysis was performed with an ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems, Foster City, California).

Table 1. Demographic Data and Mean HDRS Scores

Variable	MDD (n = 106)	Undifferentiated Somatoform Disorder (n = 102)	Healthy Controls (n = 133)	Statistic	*df*	*P*
Sex, n (%)						
Male	28 (26.4)	47 (46.1)	53 (39.8)			
Female	78 (73.6)[a]	55 (53.9)	80 (60.2)	$\chi^2 = 9.07$	2	.01
Age, mean ± SD, y	39.0 ± 12.1[b]	41.9 ± 11.0[c]	32.2 ± 7.6	$F = 20.92$	2,338	< .0001
HDRS score, mean ± SD	22.7 ± 7.9[b]	20.8 ± 6.8[c]	3.5 ± 2.0	$F = 384.78$	2,334	< .0001

[a]Female sex: MDD > control ($\chi^2_1 = 4.75$, $P = .03$), undifferentiated somatoform disorder ($\chi^2_1 = 8.72$, $P = .003$).
[b]MDD > control (post hoc Scheffe test $P < .0001$).
[c]Undifferentiated somatoform disorder > control (post hoc Scheffe test $P < .0001$).
Abbreviations: HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder.

Table 2. Mean ± SD Scores for Aggression Questionnaire in Patients With MDD, Patients With Undifferentiated Somatoform Disorder, and Healthy Control Subjects

Aggression Questionnaire	MDD (n = 106)	Undifferentiated Somatoform Disorder (n = 102)	Healthy Controls (n = 133)	*F*	*df*	*P*
Physical aggression	7.7 ± 5.9[a,b]	6.0 ± 4.5[c]	4.5 ± 2.7	14.85	2,333	< .0001
Verbal aggression	4.9 ± 3.6[a]	4.9 ± 3.3[c]	3.5 ± 2.5	7.54	2,337	.0006
Anger	9.0 ± 4.4[a,b]	7.6 ± 3.7[c]	4.3 ± 2.7	55.37	2,336	< .0001
Hostility	9.5 ± 6.4[a,b]	6.6 ± 5.7[c]	3.1 ± 2.9	47.09	2,336	< .0001
Total score	31.1 ± 16.4[a,b]	25.2 ± 14.8[c]	15.4 ± 8.0	43.17	2,329	< .0001

[a]MDD > Control (post hoc Scheffe test $P < .005$).
[b]MDD > undifferentiated somatoform disorder (post hoc Scheffe test $P < .05$).
[c]Undifferentiated somatoform disorder > control (post hoc Scheffe test $P < .05$).
Abbreviation: MDD = major depressive disorder.

Statistical Analyses

We performed χ^2 test and analysis of variance to compare demographic variables and levels of depression and aggression between MDD, undifferentiated somatoform disorder, and healthy control groups. Hardy-Weinberg equilibrium for genotyping results was tested both in the patients and in healthy subjects by using the χ^2 test. Comparisons of allele and genotype frequencies between the 2 groups were also made by using the χ^2 test or Fisher exact test. The Bonferroni correction was applied to data for multiple tests. Odds ratios (ORs) for MDD by allele or genotype frequencies with $P < .05$ were determined by logistic regression, controlling for sex and age. A *t* test was used to compare levels of aggression and depression between subjects with the homozygous and carrier genotypes. Multiple regression analysis was computed to control for the effect of confounding variables, with the dependent variable being the total or subscale score of the Aggression Questionnaire and the independent variables being those demographic variables, such as sex and age, and homozygous versus carrier genotype.

RESULTS

Demographic Data and the Levels of Depression and Aggression

There were significantly more female subjects in the MDD group than in the healthy control and undifferentiated somatoform disorder groups. The patients with MDD and undifferentiated somatoform disorder were significantly older than the healthy control subjects. However, no significant differences were found in age between the 2 disorder groups (Table 1).

Patients with MDD and undifferentiated somatoform disorder scored significantly higher on the HDRS, all the Aggression Questionnaire subscales, and the total Aggression Questionnaire score than the healthy subjects. In addition, patients with MDD scored significantly higher on the physical aggression, anger, and hostility subscales and on the total Aggression Questionnaire score than patients with undifferentiated somatoform disorder (Tables 1 and 2).

Relationship Between Levels of Depression and Aggression in MDD and Undifferentiated Somatoform Disorder Groups

In patients with MDD, HDRS scores correlated significantly with scores on the anger ($r = 0.32$, $P = .001$) and hostility subscales ($r = 0.35$, $P = .0003$) and with total Aggression Questionnaire score ($r = 0.31$, $P = .002$). However, HDRS scores did not correlate significantly with scores of the physical aggression ($r = 0.12$, $P = .25$) and verbal aggression subscales ($r = 0.12$, $P = .23$) of the Aggression Questionnaire in the MDD patients.

In patients with undifferentiated somatoform disorder, HDRS scores correlated significantly with scores on the verbal aggression ($r = 0.21$, $P = .03$) and anger subscales ($r = 0.31$, $P = .002$) and with total Aggression Questionnaire score ($r = 0.22$, $P = .03$). However, the HDRS scores did not correlate significantly with scores on the physical aggression ($r = 0.09$, $P = .36$) and hostility subscales ($r = 0.17$, $P = .10$) of the Aggression Questionnaire in the undifferentiated somatoform disorder patients.

Allele Frequency of *TPH* Gene Polymorphism in Patients With MDD and Patients With Undifferentiated Somatoform Disorder Compared With Healthy Subjects

The MDD group had a significantly higher frequency of the *TPH1* C allele than the control group ($\chi^2 = 6.56$, $P = .01$)

Table 3. Allele and Genotype Frequencies of Tryptophan Hydroxylase-1 (*TPH1*) Gene Polymorphism in Patients With MDD, Patients With Undifferentiated Somatoform Disorder, and Healthy Control Subjects

Variable	Healthy Controls, n (%)	MDD, n (%)	Undifferentiated Somatoform Disorder, n (%)	Healthy Controls vs MDD			Healthy Controls vs Undifferentiated Somatoform Disorder			MDD vs Undifferentiated Somatoform Disorder		
				χ^2	*df*	*P*	χ^2	*df*	*P*	χ^2	*df*	*P*
TPH1												
A	147 (55.7)	93 (43.9)	92 (45.1)	6.56	1	.01[a]	5.16	1	.02	0.06	1	.80
C	117 (44.3)	119 (56.1)	112 (54.9)									
TPH1												
AA	38 (28.8)	20 (18.9)	19 (18.6)	7.23	2	.03	5.58	2	.06	0.22	2	.90
AC	71 (53.8)	53 (50.0)	54 (52.9)									
CC	23 (17.4)	33 (31.1)	29 (28.5)									
TPH1												
CC	23 (17.4)	33 (31.1)	29 (28.4)	6.14	1	.01[b]	4.03	1	.04	0.18	1	.67
AC + AA	109 (82.6)	73 (68.9)	73 (71.6)									

[a]Logistic regression analysis controlling for sex and age: OR = 2.30; 95% CI, 1.48–3.58; *P* = .0002.
[b]Logistic regression analysis controlling for sex and age: OR = 3.84; 95% CI, 1.85–7.97; *P* = .0003.
Abbreviation: MDD = major depressive disorder.

(Table 3), and the difference remained significant after Bonferroni correction (3 tests, *P* = .03). We then compared the ORs for MDD between the 2 groups by using logistic regression to determine the effects of C allele on the risk of MDD. Because female gender and older age were significantly associated with MDD in this study, ORs were adjusted for these 2 variables. As a result, *TPH1* C allele had 2.3-fold higher odds of MDD than the A allele after controlling for sex and age (OR = 2.30; 95% CI, 1.48 – 3.58; *P* = .0002) (Table 3).

The undifferentiated somatoform disorder group had a significantly higher frequency of the *TPH1* C allele than the control group, but the difference was not significant after Bonferroni correction (3 tests, *P* = .02; *P* = .06) (Table 3). No significant difference was found in allele frequency of the *TPH1* polymorphism between the MDD group and the undifferentiated somatoform disorder group (Table 3).

Genotype Frequency of *TPH* Gene Polymorphism in Patients With MDD and Patients With Undifferentiated Somatoform Disorder Compared With Healthy Subjects

All SNPs were found to be in Hardy-Weinberg equilibrium in the MDD patients (*TPH1*: $\chi^2 = 0.02$, *P* = .88), the undifferentiated somatoform disorder patients (*TPH1*: $\chi^2 = 0.49$, *P* = .49), and control samples (*TPH1*: $\chi^2 = 1.07$, *P* = .30). One sample (106 MDD patients and 133 controls) provided a power of 69% at $\alpha = .05$ to detect a difference between 0.31 and 0.17 in *TPH1* CC homozygote frequency, while another sample (102 undifferentiated somatoform disorder patients and 133 controls) provided a power of 51% at $\alpha = .05$ to detect a difference between 0.29 and 0.17 in *TPH1* CC frequency.

The MDD group had a significantly higher frequency of the *TPH1* CC homozygote than the control group ($\chi^2 = 6.14$, *P* = .01) (Table 3), and the difference remained significant after Bonferroni correction (3 tests, *P* = .03). The results of logistic regression analysis also showed that subjects with *TPH1* CC homozygote had 3.8-fold higher odds of MDD than the A-carrier genotype after controlling for sex and age (OR = 3.84; 95% CI, 1.85 – 7.97; *P* = .0003). The undifferentiated somatoform disorder group had a significantly higher frequency of the *TPH1* CC homozygote than the control group ($\chi^2 = 4.03$, *P* = .04), but the difference was not significant after Bonferroni correction (3 tests, *P* = .12) (Table 3). No significant difference was found in genotype frequency of the *TPH1* polymorphism between the MDD and the undifferentiated somatoform disorder groups (Table 3).

Comparison of the Aggression and Depression Levels Between Homozygous and Carrier Genotypes of *TPH* Gene Polymorphism

TPH1 CC homozygote in the MDD group scored significantly higher on the verbal aggression and anger subscales and total Aggression Questionnaire score than A-carrier genotypes (Table 4), and this difference remained significant after multiple regression analysis (verbal aggression, *P* = .03; total, *P* = .04), except in the anger subscale, regardless of sex and age (Table 5). However, no significant differences were found in the scores of all the Aggression Questionnaire subscales and the total Aggression Questionnaire score between *TPH1* CC homozygote and A-carrier genotypes in each of the undifferentiated somatoform disorder patients and healthy subjects (Table 4). In addition, there was no significant difference in mean ± SD HDRS scores between *TPH1* CC homozygote and A-carrier genotypes in the MDD patients (23.4 ± 7.4 vs 22.4 ± 8.2; $t_{103} = 0.60$, *P* = .55) nor in the undifferentiated somatoform disorder patients (20.7 ± 7.0 vs 20.9 ± 6.3; $t_{99} = -0.08$, *P* = .93).

DISCUSSION

This study found that both patients with MDD and patients with undifferentiated somatoform disorder scored significantly higher on all the Aggression Questionnaire subscales and on the total Aggression Questionnaire score than the healthy subjects, revealing that MDD and undifferentiated somatoform disorder are high risk groups for aggression. Moreover, patients with MDD showed higher levels of aggression than patients with undifferentiated somatoform disorder, as evidenced in the subscale scores of physical aggression, anger, and hostility as well as the total Aggression Questionnaire score. Therefore, MDD patients are likely to be more aggressive than undifferentiated somatoform disorder patients.

In addition, patients with MDD had significantly higher frequencies of *TPH1* C allele than healthy subjects,

Table 4. Mean ± SD Scores for Aggression Questionnaire in Homozygous and Carrier Genotypes of Tryptophan Hydroxylase-1 in Patients With MDD, Patients With Undifferentiated Somatoform Disorder, and Healthy Control Subjects

	MDD					Undifferentiated Somatoform Disorder					Healthy Controls				
Aggression Questionnaire	AC + AA (n = 73)	CC (n = 33)	*t*	*df*	*P*	AC + AA (n = 72)	CC (n = 29)	*t*	*df*	*P*	AC + AA (n = 109)	CC (n = 23)	*t*	*df*	*P*
Physical aggression	6.9 ± 5.4	9.3 ± 6.7	−1.85	100	.07	5.9 ± 4.4	6.3 ± 4.9	−0.43	99	.67	4.7 ± 2.8	3.8 ± 2.3	1.40	130	.16
Verbal aggression	3.6 ± 3.1	4.6 ± 4.4	−2.24	47	.03	4.7 ± 3.3	5.2 ± 3.1	−0.69	99	.49	3.6 ± 2.5	3.3 ± 2.5	0.38	130	.70
Anger	8.3 ± 4.0	10.6 ± 4.7	−2.59	104	.01	7.3 ± 3.6	8.3 ± 4.0	−1.19	98	.24	4.3 ± 2.8	4.0 ± 1.9	0.63	45	.53
Hostility	8.7 ± 5.5	11.2 ± 7.6	−1.70	48	.10	6.4 ± 5.6	7.1 ± 6.0	−0.53	99	.60	3.2 ± 3.0	2.7 ± 2.2	0.80	130	.43
Total score	28.3 ± 13.4	37.3 ± 20.5	−2.26	44	.03	24.5 ± 14.5	27.0 ± 15.4	−0.76	96	.45	15.8 ± 8.4	13.8 ± 5.7	1.34	45	.19

Abbreviation: MDD = major depressive disorder.

Table 5. Multiple Regression Analysis of Levels of Aggression on the Aggression Questionnaire as Dependent Variable and Tryptophan Hydroxylase-1 (*TPH1*) Genotype as a Predictor in the Major Depressive Disorder Group (n = 106)

Predictor	Dependent Variable	R^2	*F*	*P*	β	SE	*P*
	Verbal Aggression	0.10	3.57	.02			
Sex					0.63	0.81	.44
Age					−0.04	0.02	.13
TPH1 AC + AA vs CC					1.65	0.76	.03
	Anger	0.13	5.06	.003			
Sex					−0.96	0.96	.32
Age					−0.09	0.03	.006
TPH1 AC + AA vs CC					1.70	0.89	.06
	Total score	0.20	8.03	< .0001			
Sex					1.29	3.47	.71
Age					−0.42	0.11	.0003
TPH1 AC + AA vs CC					6.55	3.26	.04

regardless of sex and age. The frequency of the *TPH1* CC homozygote was significantly higher in the patients than in the healthy subjects, and this result remained significant after Bonferroni correction. This kind of grouping, involving homozygotes and other pooled genotypes, had already been used in many previous studies[27,34–37] for statistical analysis. Logistic regression analysis also revealed that the *TPH1* CC homozygote had 3.8-fold higher odds of MDD than the A-carrier genotypes after controlling for sex and age. In contrast, no significant differences were found in *TPH1* C allele and CC homozygote frequencies between patients with undifferentiated somatoform disorder and healthy subjects, nor between MDD and undifferentiated somatoform disorder patients. These findings suggest that either the *TPH1* C allele or the *TPH1* CC homozygote is associated with susceptibility to MDD but not to undifferentiated somatoform disorder.

Some research has already suggested that MDD is associated with dysfunction of the *TPH1* genes.[38] In particular, it was reported that suicide attempts among patients with MDD were associated with an excess of *TPH* A218 allele.[26,39,40] These findings contrast directly with our finding that showed an association between an excess of *TPH1* C allele and MDD. This difference may be due to the use of samples with different ethnic backgrounds; the former studies included Caucasian subjects, while our sample included only unrelated Korean subjects from the same geographic and ethnic origin. In addition, the former study included patients who had attempted suicide, whereas all the patients with MDD in our study had exhibited suicidal ideation but had no history of suicidal attempt. However, other studies have found no association between MDD and *TPH1* gene polymorphism.[41–43]

Our study found that *TPH1* CC homozygote in patients with MDD showed significantly higher levels of verbal aggression and total Aggression Questionnaire score than A-carrier genotypes, regardless of sex and age. The severity of depression is likely to be linked to levels of some aggression, such as anger and hostility, but not to levels of other forms of aggression, such as verbal and physical. However, it was interesting to find that there was no significant difference in depression levels, such as HDRS score, between the *TPH1* CC homozygote and A carriers in patients with MDD. Therefore, these findings indicate that *TPH1* CC homozygote is likely to be associated with higher levels of aggression rather than with higher levels of depression in MDD patients. Another study[36] reported that the frequency of impulsive-aggressive behavior may be associated with the *TPH* 218C allele in impulsive inpatients. However, our study found no significant differences in levels of aggression, including all Aggression Questionnaire subscales and total Aggression Questionnaire score, between *TPH1* CC homozygote and A-carrier genotypes in the undifferentiated somatoform disorder group and the control group. In contrast, Manuck and colleagues[27] have shown that individual differences in aggressive disposition are associated with the A218C SNP in nonpatients. Therefore, our findings suggest that aggression in MDD patients is more susceptible to an excess of *TPH1* CC homozygote than in undifferentiated somatoform disorder patients, though both disorders are high risk groups for aggression. In particular, higher levels of aggression in MDD patients compared with undifferentiated somatoform disorder patients might be associated with susceptibility to *TPH1* CC homozygote.

One limitation of this study was the choice of a control group unmatched by sex and age. In addition, the small sample size might have affected the ability to detect the main effect of *TPH1* gene polymorphism and led to type 2 error. Therefore, some results of this study should be interpreted with caution, although they were found to be negative, and future studies need to include a larger sample of subjects because the medically recruited sample is not representative of the population.

Taken together, aggression in MDD patients is more susceptible to an excess of *TPH1* CC homozygote than in

undifferentiated somatoform disorder patients, though the 2 disorders are high risk groups for aggression. In addition, *TPH1* gene is likely to have a shared effect on aggression and MDD. Therefore, these findings suggest that the levels of aggression in patients with MDD may be differentiated by a genetic method, which may lead to better assessment, treatment, and prevention of aggression. Future studies need to include a larger sample of subjects and polymorphisms of more serotonin-related gene variants.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others).

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