The Relation of Serotonin-Related Gene and *COMT* Gene Polymorphisms With Criminal Behavior in Schizophrenic Disorder

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ABSTRACT

Objective: It has been suggested that patients with schizophrenia might be involved in criminal behavior, such as homicidal and violent behavior. However, the relationship between criminal behavior and genes in patients with schizophrenia has not been clearly elucidated. The objective of this study was to examine the relation between criminal behavior and serotonin-related gene or catechol-*O*-methyltransferase (*COMT*) gene polymorphisms in patients with schizophrenia.

Method: Serotonin-related and *COMT* polymorphic markers were assessed by using single nucleotide polymorphism (SNP) genotyping. Ninety-nine crime-related inpatients with schizophrenia (57 homicidal and 42 nonhomicidal violent) and 133 healthy subjects were enrolled between October 2005 and May 2008. Diagnoses were made according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria. The genotype frequencies of tryptophan hydroxylase-1 (*TPH1*) A218C and *COMT* V158M were compared between groups.

Results: The *TPH1* CC genotype had 2.7-fold higher odds of crime-related schizophrenia compared with A-carrier genotype after the analysis was controlled for sex and age (OR, 2.69; 95% CI, 1.22 – 5.91; $P = .01$). In addition, the *TPH1* CC genotype had 3.4-fold higher odds of homicidal schizophrenia compared with A-carrier genotype after the analysis was controlled for sex and age (OR, 3.38; 95% CI, 1.40 – 8.18; $P = .007$). However, no significant differences were found in the frequencies of genotype of *COMT* polymorphism between criminal schizophrenics and healthy subjects, nor were any significant differences found between nonhomicidal schizophrenics and healthy subjects.

Conclusions: These results indicate that the *TPH1* CC recessive genotype is likely to be a genetic risk factor for criminal behavior, especially homicidal behavior in patients with schizophrenia. However, *COMT* gene polymorphisms were not associated with criminal behavior in schizophrenic patients.

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Schizophrenia has been reported to be associated with an increased risk of violent crime including homicide.[1–4] Low levels of serotonin have frequently been suggested as a causative factor for impulsive, violent, and dangerous behavior in animals and humans.[5–8] Since both aggression-related traits and serotonergic activity are partially heritable, variations in genes of the serotonergic system might account for variations in aggression-related behavior.[9]

The genes encoding the main enzymes of serotonin metabolism in the brain (tryptophan hydroxylase-1 [*TPH1*]) and the serotonin 1A (5-hydroxytriptamine [5-HT_{1A}]) receptor are known to be members of a set of genes modulating aggressive behavior.[10] The tryptophan hydroxylase (*TPH*) gene is involved in catalysis of the rate-limiting step for serotonin biosynthesis[11] and regulates levels of serotonin.[12] Therefore, variations in the *TPH* gene could contribute to the predisposition to low serotonergic neurotransmission.[9] In humans, *TPH1* and tryptophan hydroxylase-2 (*TPH2*) are expressed in nearly equal amounts in several brain regions (frontal cortex, thalamus, hippocampus, hypothalamus, and amygdala), but particularly *TPH2* is predominantly expressed in the brain stem, the major locus of the serotonin-producing neurons.[13] In recent studies, a genetic variation in *TPH1* has been associated with aggression and anger-related traits in volunteers.[9,14] Other studies found an association with the 218C polymorphism in personality-disordered patients[15] and nonpsychotic nonorganic inpatients.[16] For the 5-HT receptor, the 5-HT_{2A}-1438GG genotype was found to be lower in the criminal group than in the control group.[17]

In addition, alterations in catecholamines have been implicated in aggressive behavior.[18–20] Catechol-*O*-methyltransferase (*COMT*) inactivates catecholamines, such as dopamine, norepinephrine, and epinephrine,[21] and therefore could be a factor in regulating aggressive behavior. A subgroup of patients who were extremely violent was also found to be homozygous for 158Met.[22] Kotler et al[23] reported a significant excess of the low activity *COMT* homozygote in a homicidal schizophrenia group compared with controls. It was also reported that the *COMT* gene was associated with the severity of aggression in schizophrenia.[24,25] However, other studies[26,27] failed to detect an association between *COMT* and aggression in schizophrenia.

In this study, *TPH2* rs1352251 SNP was selected among *TPH2* SNPs because it was found to be predominant in impulsive suicidal attempters compared with healthy controls in Finnish whites.[28] *TPH1* A218C was located on intron 6 of the *TPH1* gene, whereas *TPH2* rs1352251 was located on intron 8 of the *TPH2* gene. Therefore, the objective of this study was to examine the relation between the criminal behavior and serotonin-related gene or *COMT* gene polymorphisms in patients with schizophrenia. Herein, serotonin-related genes included *TPH1* A218C and *TPH2* rs1352251.

METHOD

Subjects

The study was reviewed and approved by the institutional review board of Yonsei University College of Medicine at Severance Hospital, Seoul,

Clinical Points

- Levels of criminality in schizophrenic patients may be differentiated by a genetic method.
- Genetic examination in schizophrenic patients may lead to a better assessment and treatment for aggression followed by prevention of criminal behavior.
- Clinicians can refer potentially aggressive patients to therapists who are experts in aggression.

Korea. The purpose and procedures of the study were explained to all potential subjects, and informed consent was obtained from those who decided to participate. Participants were enrolled in the study between October 2005 and May 2008. One hundred thirty-three healthy subjects (53 men, 80 women) were recruited from medical residents and other hospital personnel. 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 an interview to confirm the absence of physical and psychiatric disorders and family history of psychiatric disorders. Specifically, volunteers were included in the group after psychiatrists confirmed that they had no abnormalities at their most recent regular physical check-ups. Also, none of the volunteers reported being treated for or having symptoms of physical or psychiatric disorders and family history of psychiatric disorders in the self-report questionnaires.

In addition, inpatients with diagnoses of schizophrenic disorder from the Forensic Mental Hospital (Gongju, Korea) were enrolled in this study. A semistructured interview was conducted during their admission to the Forensic Mental Hospital and diagnoses were made by 2 psychiatrists on the basis of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[29] criteria. The Hamilton Depression Rating Scale (HDRS)[30] was used to assess the severity of depression. The Life History of Aggression,[31] a revision of the Brown and colleagues' assessment[7] for life history of aggression, was also administered as an interview to assess history of aggression. The 11-item scale includes aggression, such as temper tantrums, physical fights, verbal fights, assaults on people (or animals), and assaults on property; self-directed aggression, such as self-injurious behavior and suicide attempts; and antisocial behavior, such as school disciplinary problems, problems with supervisors at work, antisocial behavior not involving the police, and antisocial behavior involving the police. Herein, each item is rated on a 5-point scale based on the number of occurrences of the behavior since adolescence, from 0 (none) to 5 (very frequent; more than 10 times).

Medical workups as needed were performed on all patients to rule out any medical disorders at the Forensic Mental Hospital. Patients with physical diseases or abnormal laboratory findings were excluded from the study. 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 99 crime-related schizophrenics (85 men, 14 women) who consisted of 57 homicidal (49 men, 8 women) and 42 nonhomicidal violent patients (36 men, 6 women). Nonhomicidal violent crime included any criminal conviction for assault, robbery, and arson but did not include simple stealing. The crime-related schizophrenics included 44 patients with paranoid schizophrenia and 55 with chronic undifferentiated schizophrenia. The mean ± SD age of crime-related schizophrenics was 36.8 ± 6.9 years, with a range of 21 to 55 years. The mean ± SD age of homicidal patients was 37.4 ± 6.7 years, with a range of 23 to 50 years, whereas for nonhomicidal patients it was 36.0 ± 7.2 years, with a range of 21 to 55 years.

Among the patients who completed the entire testing process, 11 subjects were excluded from the data analysis because they had either comorbid mental disorders or physical diseases: personality disorder (2 subjects), impulse control disorder (3 subjects), seizure disorder (3 subjects), and diabetes mellitus (3 subjects). Among the healthy subjects who completed the entire testing process, 3 subjects were excluded from the data analysis because they had dysthymic disorder (1 subject), adjustment disorder (1 subject), and diabetes mellitus (1 subject).

Single Nucleotide Polymorphisms Genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood using a Puregene DNA purification kit (Gentra, Minneapolis, Minnesota). Tryptophan hydroxylase (*TPH1* A218C and *TPH2* rs1352251) and *COMT* V158M polymorphisms were genotyped 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. Thermal cycle 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, Foste City, California), and allelic discrimination analysis was performed with an ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems, Foster City, California).

Statistical Analyses

A χ^2 test or *t* test was performed to compare demographic variables and the levels of psychological variables, such as depression and aggression, between 2 groups, such as crime-related schizophrenics and healthy subjects. Hardy-Weinberg equilibrium for all genotyping results was tested in both patients and healthy subjects using χ^2 test. Comparisons of genotype and allele frequencies between the 2 groups were also made using χ^2 test. Odds ratios (ORs) for crime-related schizophrenic disorder or homicidal group by genotype were determined by logistic regression analysis, controlling for sex and age.

RESULTS

Demographic Data

There were significantly more men in the crime-related schizophrenic disorder group ($\chi^2_1 = 49.85$, $P < .0001$), homicidal group ($\chi^2_1 = 34.13$, $P < .0001$), and nonhomicidal group ($\chi^2_1 = 26.87$, $P < .0001$) compared to the healthy group. However, no significant difference was found in sex between the homicidal group and nonhomicidal group ($\chi^2_1 = 0.001$, $P = .97$). Each of the crime-related schizophrenic disorder group, homicidal group, and nonhomicidal group was significantly older than the healthy group (age, mean ± SD, 36.8 ± 6.9 vs 32.2 ± 7.6 years, $t_{230} = 4.42$, $P < .0001$; 37.4 ± 6.7 vs 32.2 ± 7.6 years, $t_{188} = 4.26$, $P < .0001$; 36.0 ± 7.2 vs 32.2 ± 7.6 years, $t_{173} = 2.56$, $P = .01$). However, no significant difference was found in age between the homicidal group and nonhomicidal group (37.4 ± 6.7 vs 36.0 ± 7.2 years, $t_{97} = 0.99$, $P = .32$).

Table 1. Allele and Genotype Distribution of Tryptophan Hydroxylase-1 (*TPH1*) and Catechol-*O*-Methyltransferase (*COMT*) in Healthy Subjects and Patients With Criminal Schizophrenia

	Healthy Subjects (n = 133)		Criminal Schizophrenics (n = 99)				
Variable	n (%)	Ratio of Group to Total Group, %[a]	n (%)	Ratio of Group to Total Group, %[a]	χ^2	*df*	*P*
TPH1							
A	147 (55.7)		94 (48.0)				
C	117 (44.3)		102 (52.0)		2.69	1	.10
TPH1							
AA	38 (28.8)	59.4	26 (26.5)	40.6			
AC	71 (53.8)	62.8	42 (42.9)	37.2			
CC	23 (17.4)	43.4	30 (30.6)	56.6	5.72	2	.06
TPH1[b]							
AC + AA	109 (82.6)		68 (69.4)				
CC	23 (17.4)		30 (30.6)		5.52	1	**.02**
COMT V158M							
G	193 (73.7)		143 (73.0)				
A	69 (26.3)		53 (27.0)		0.03	1	.87
COMT V158M							
GG	69 (52.7)	55.6	55 (56.1)	44.4			
GA	55 (42.0)	62.5	33 (33.7)	37.5			
AA	7 (5.3)	41.2	10 (10.2)	58.8	2.92	2	.23
COMT V158M							
GA + GG	124 (94.7)		88 (89.8)				
AA	7 (5.3)		10 (10.2)		1.93	1	.17

[a]The percentage shows either dominant or recessive phenotype allele.
[b]Logistic regression result represents effect of the *TPH1* CC genotype on risk of criminal schizophrenia after controlling for sex and age (OR, 2.69; 95% CI, 1.22 – 5.91; $P = .01$).
Abbreviation: OR = odds ratio.

Comparison of Levels of Depression and Aggression Between Crime-Related Schizophrenic Disorder Group and Healthy Group

Patients with crime-related schizophrenic disorder, those in the homicidal group, and those in the nonhomicidal group scored significantly higher on total HDRS mean ± SD scores than healthy subjects (10.4 ± 6.5 vs 3.5 ± 2.0, $t_{98} = 9.71$, $P < .0001$; 10.3 ± 6.4 vs 3.5 ± 2.0, $t_{56} = 7.52$, $P < .0001$; and 10.7 ± 6.6 vs 3.5 ± 2.0, $t_{36} = 6.29$, $P < .0001$; respectively). However, no significant differences were found in total HDRS mean ± SD scores between the homicidal group and nonhomicidal group (10.3 ± 6.4 vs 10.7 ± 6.6, $t_{86} = 0.25$, $P = .80$). In addition, the crime-related group, homicidal group, and nonhomicidal group scored significantly higher on total mean ± SD scores of the Life History of Aggression than the healthy group (10.8 ± 5.5 vs 1.7 ± 2.7, $t_{132} = 15.16$, $P < .0001$; 10.3 ± 5.5 vs 1.7 ± 2.7, $t_{68} = 11.35$, $P < .0001$; and 11.5 ± 5.8 vs 1.7 ± 2.7, $t_{40} = 10.03$, $P < .0001$; respectively). However, there were no significant differences in total mean ± SD scores of the Life History of Aggression between the homicidal group and nonhomicidal group (10.3 ± 5.5 vs 11.5 ± 5.8, $t_{92} = -1.00$, $P = .32$).

Association Between Genotype Frequency of the Serotonin-Related Gene or *COMT* Gene Polymorphisms and Crime-Related Schizophrenic Disorder

All SNPs were found to be in Hardy-Weinberg equilibrium in both the patient and healthy samples, except genotypes of *TPH2* rs1352251 polymorphism in the healthy group ($\chi^2 = 17.08$, $P < .0001$) and *COMT* polymorphism in the homicidal group ($\chi^2 = 35.09$, $P < .0001$). Power analysis showed that for the detection of a main effect for *TPH1* and *COMT* genotype, the power was 64% and 30% at $\alpha = .05$, respectively.

From the genotype ratio of each group to total groups in Table 1, the A allele of *TPH1* was considered the dominant phenotype, whereas C allele was considered the recessive phenotype. Therefore, genotypes were grouped into AC + AA and CC to determine the effects of dominant and recessive genotypes on risk of crime-related schizophrenic disorder. Frequency of *TPH1* CC genotype was significantly higher than that of A-carrier genotype in patients with crime-related schizophrenic disorder. We then compared the ORs for crime-related schizophrenic disorder between the 2 groups using logistic regression analysis. Because older age and male gender were significantly associated with crime-related schizophrenic disorder in this study, ORs were adjusted for these 2 variables. As a result, *TPH1* CC genotype had 2.7-fold higher odds of crime-related schizophrenia compared with A-carrier genotype (OR, 2.69; 95% CI, 1.22 – 5.91, $P = .01$). The homicidal group also had significantly higher frequency of the *TPH1* CC genotype than the healthy group (Table 2). The result of logistic regression analysis after controlling for sex and age was as follows: *TPH1* CC genotype had 3.4-fold higher odds of homicidal schizophrenia compared with A-carrier genotype (OR, 3.38; 95% CI, 1.40 – 8.18; $P = .007$).

However, no significant differences were found in the frequencies of *TPH1* genotype between nonhomicidal schizophrenics and healthy subjects, nor were any significant

Table 2. Allele and Genotype Distribution of Tryptophan Hydroxylase-1 (*TPH1*) in Healthy Subjects, Patients With Homicidal Schizophrenia, and Patients With Nonhomicidal Schizophrenia

Variable	Healthy Subjects (A) (n = 133), n (%)	Homicidal Schizophrenics (B) (n = 57), n (%)	Nonhomicidal Schizophrenics (C) (n = 42), n (%)	Statistics A vs B	Statistics A vs C	Statistics B vs C
TPH1						
A	147 (55.7)	48 (42.1)	46 (56.1)	$\chi^2_1 = 5.88$, $P = .02$	$\chi^2_1 = 0.004$, $P = .95$	$\chi^2_1 = 3.74$, $P = .05$
C	117 (44.3)	66 (57.9)	36 (43.9)			
TPH1[a]						
AA	38 (28.8)	12 (21.1)	14 (34.2)	$\chi^2_2 = 8.43$, $P = .01$	$\chi^2_2 = 1.24$, $P = .54$	$\chi^2_2 = 3.29$, $P = .19$
AC	71 (53.8)	24 (42.1)	18 (43.9)			
CC	23 (17.4)	21 (36.8)	9 (21.9)			

[a]A vs B: *TPH1* AC + AA vs CC ($\chi^2_1 = 8.40$, $P = .004$; $P = .012$ after Bonferroni correction; logistic regression analysis controlling for sex and age: OR, 3.38; 95% CI, 1.40 – 8.18; $P = .007$).

Table 3. Allele and Genotype Distribution of Catechol-*O*-Methyltransferase (*COMT*) in Healthy Subjects and Patients With Nonhomicidal Schizophrenia

Variable	Healthy Subjects (n = 133), n (%)	Nonhomicidal Schizophrenics (n = 42), n (%)	χ^2	*df*	*P*
COMT V158M					
G	193 (73.7)	61 (72.6)			
A	69 (26.3)	23 (27.4)	0.04	1	.85
COMT V158M					
GG	69 (52.7)	24 (57.1)			
GA	55 (42.0)	13 (31.0)			
AA	7 (5.3)	5 (11.9)	3.08	2	.21

differences found between homicidal schizophrenics and nonhomicidal schizophrenics (Table 2). There were also no significant differences in the frequencies of *COMT* genotype between crime-related schizophrenics and healthy subjects (Table 1), nor were any significant differences found between nonhomicidal schizophrenics and healthy subjects (Table 3).

DISCUSSION

This study found that patients with crime-related schizophrenic disorder, those in the homicidal group, and those in the nonhomicidal group had significantly higher levels of depression, such as high HDRS scores, and more frequent episodes of aggression, such as high total scores of the Life History of Aggression, than healthy subjects. Logistic regression analysis revealed that *TPH1* CC genotype had 2.7-fold higher odds of crime-related schizophrenia compared with A-carrier genotype after controlling for sex and age (OR, 2.69; 95% CI, 1.22 – 5.91; $P = .01$). In addition, *TPH1* CC genotype had 3.4-fold higher odds of homicidal schizophrenia compared with A-carrier genotype after controlling for sex and age (OR, 3.38; 95% CI, 1.40 – 8.18; $P = .007$). Therefore, *TPH1* CC recessive genotype is likely to be a genetic risk factor for criminal behavior, especially homicidal behavior in patients with schizophrenia.

In previous studies, a genetic variation in *TPH* has been associated with aggression and anger-related traits in volunteers. One study[9] found that the A218C and A779C SNP in the *TPH* gene may be associated with anger-related traits in German samples. Manuck et al[14] demonstrated an association between 218A polymorphism and psychometric measures of aggression in nonselected volunteers. However, New et al[15] showed an association of measures of aggression with the 218C polymorphism in personality-disordered patients. In addition, it was reported that the number of impulsive behavioral tendencies was related to the presence of the 218C allele in nonpsychotic, nonorganic inpatients.[16]

Previously, a significant excess of the low activity *COMT* homozygote was found in the homicidal schizophrenia group compared with controls, and the *COMT* gene was known to be associated with the severity of aggression in patients with schizophrenia.[22,24,25] However, in this study, no significant differences were found in the frequencies of *COMT* genotype between criminal schizophrenics and healthy controls. Therefore, our study failed to detect an association between *COMT* and criminal behavior in schizophrenia, as some other studies have not shown.[26,27]

In addition, no significant differences were found in the frequencies of *TPH1* and *COMT* genotypes between nonhomicidal schizophrenics and healthy subjects, nor were any significant differences found in the frequencies of *TPH1* genotype between homicidal schizophrenics and nonhomicidal schizophrenics. These findings suggest that nonhomicidal, violent schizophrenics are not likely to be associated with *TPH1* and *COMT* genotypes. In these cases, criminal behavior may be related to epigenesis, such as early traumatic environment, psychosocial stress, and substance abuse.[32]

Data relevant to genotype frequencies of *TPH2* rs1352251 were removed from the results because the SNP of *TPH2* rs1352251 was not in the Hardy-Weinberg equilibrium for the healthy group, so it was therefore considered inappropriate to use these data for group comparison. In addition, data relevant to *COMT* V158M genotype in homicidal schizophrenics were removed because the SNP of *COMT* V158M was not in the Hardy-Weinberg equilibrium for the homicidal group.

One limitation of this study was the absence of a control group that included schizophrenics who do not exhibit criminal behavior or nonschizophrenics who exhibit criminal behavior. In addition, another limitation was the small sample size.

In conclusion, these results indicate that *TPH1* CC recessive genotype is likely to be a genetic risk factor for criminal behavior, especially homicidal behavior in patients with schizophrenia. However, *COMT* gene polymorphism was not associated with criminal behavior in schizophrenic patients. Future studies need to include a larger sample of subjects and a higher number and more variety of serotonin-related gene polymorphisms.

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