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ORIGINAL INVESTIGATION

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Association of Ala72Ser polymorphism with COMT enzyme activity and the risk of schizophrenia in Koreans

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Abstract Catechol-*O*-methyltransferase (COMT) inactivates circulating catechol hormones, catechol neurotransmitters, and xenobiotic catecholamines by methylating their catechol moieties. The COMT gene has been suggested as a candidate gene for schizophrenia through linkage analyses and molecular studies of velocardio-facial syndrome. A coding polymorphism of the COMT gene at codon 108/158 (soluble/membrane-bound form) causing a valine to methionine substitution has been shown to influence enzyme activity, but its association with schizophrenia is inconclusive. We have screened 17 known polymorphisms of the COMT gene in 320 Korean schizophrenic patients and 379 controls to determine whether there is a positive association with a nonsynonymous single-nucleotide polymorphism (rs6267) at codon 22/72 (soluble/membrane-bound form) causing an alanine-to-serine (Ala/Ser) substitution. With the Ala/Ala genotype as a reference group, the combined genotype (Ala/Ser and Ser/Ser)-specific adjusted odds ratio was 1.82 (95% CI = 1.19–2.76; $P = 0.005$), suggesting the Ser allele as a risk allele for schizophrenia. However, the Val/Met polymorphism was not associated with an increased risk of schizophrenia in Koreans (OR = 0.88, 95% CI = 0.64–1.21; $P = 0.43$). The Ala72Ser substitution was correlated with reduced COMT enzyme activity. Our results support previous reports that the COMT haplotype implicated in schizophrenia is associated with low COMT expression.

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Introduction

Schizophrenia is a genetically complex mental disorder affecting approximately 1% of the world population (Bromet and Fennig 1999). As for other complex diseases, both genetic susceptibility and environmental factors appear to be involved in the causation of schizophrenia. Family and adoption studies suggest that schizophrenia has a significant genetic component (Tsuang 2000); however, the inheritance pattern is complex with low penetrance. So far, numerous candidate genetic loci have been identified through linkage or association studies or chromosomal aberrations in various populations (Karayiorgou et al. 1995; Straub et al. 1995; Brzustowicz et al. 1999; Brzustowicz et al. 2000; Millar et al. 2000; Stefansson et al. 2002). However, few have turned out to be reproducible in other populations.

Altered dopaminergic transmission has been suggested to play a significant role in schizophrenia (Carlsson 1988). Catechol-*O*-methyltransferase (COMT) is a candidate gene that could influence dopamine transmission; it catalyzes the transfer of the methyl group from *S*-adenosylmethionine to 3-hydroxyl group

of catechol or substituted catechols in the presence of Mg^{2+} (Axelrod and Tomchick 1958). The candidacy of COMT for schizophrenia is based on the following:

1) its central role in the metabolism of dopamine and noradrenaline,
2) linkage for schizophrenia on chromosome 22q (Karayiorgou et al. 1995; Schwab et al. 1995),
3) its chromosomal location in the microdeletion found in velo-cardio-facial syndrome (Dunham et al. 1992; Morrow et al. 1995), which is associated with a high incidence of schizophrenia (Murphy et al. 1999).

The level of COMT enzyme activity is genetically polymorphic in human red blood cells (RBC) and liver, with a range of activity of three- to four-fold (Weinshilboum and Raymond 1977; Boudikova et al. 1990). Individual variations in COMT enzyme activity have suggested the presence of common polymorphism(s) in the human COMT gene (Boudikova et al. 1990; Weinshilboum et al. 1974). A common polymorphism causing a change of valine at codon 158 (membrane-bound form; codon 108 of soluble form) to methionine in the COMT protein was identified through a comparison of the published sequences (Bertocci et al. 1991; Lundstrom et al. 1991), and thus, amino acid residue 158 was suggested as being responsible for the high and low activity variants of COMT (Grossman et al. 1992). Later, the 158Met allele was shown to be associated with a three- to four-fold variation in hepatic COMT enzyme activity (Lachman et al. 1996) and about a two-fold variation in RBC COMT activity (Syvanen et al. 1997). An enzyme-kinetics study performed with recombinant COMT variants produced in bacteria showed that the variants had similar catalytic activities, but that the 158Met-containing enzyme was more thermolabile (Lotta et al. 1995).

The COMT Val158Met polymorphism has been studied in many populations for association with schizophrenia; however, the results are equivocal (Daniels et al. 1996; Strous et al. 1997a, 1997b; Lachman et al. 1998; Egan et al. 2001). Studies performed in Asian populations have failed to show statistically significant positive association (Chen et al. 1997; Ohmori et al. 1998; Chen et al. 1999; Liou et al. 2001; Park et al. 2002). However, these Asian studies were limited by the small sample sizes. Li et al. (1996, 2000) have genotyped Val158Met polymorphism in 178 trios consisting of Han Chinese schizophrenic subjects and their parents and concluded that the COMT polymorphism might not have a major effect on susceptibility to schizophrenia. Therefore, we decided to investigate the possible association of COMT polymorphism with Korean patients with schizophrenia taking advantage of the dense single-nucleotide polymorphism (SNP) map now available following the human genome project. We tried to increase power by testing more markers through a haplotype-based approach and increasing the sample size. Here, we present a positive association with a nonsynonymous SNP that lies at codon 72 (membrane-bound form; codon 22 of soluble form) in the COMT gene and that causes an alanine-to-serine (Ala/Ser) substitution, and a correlation of 72Ser with reduced enzyme activity.

Materials and methods

Study subjects

In total, 320 patients with schizophrenia and 379 normal healthy controls were enrolled for the study. They were all ethnically Koreans. The patients with schizophrenia, all of whom met DSM-IV criteria (American Psychiatric Association 1994), were recruited from the Department of Psychiatry, Asan Medical Center, Seoul, Korea. Two psychiatrists made a diagnostic assessment separately. Diagnoses were established prior to the genetic analysis, and patients were not included if there was any disagreement in diagnosis at the consensus meeting.

Patients who had any history of head trauma, epilepsy, alcohol-related problems, or other evident pathologies of the central nervous system were excluded. The patient group consisted of 153 males and 167 females; their mean age was 32.6 ± 10.0 (mean $\pm$ SD). The normal controls were recruited from volunteers with no history of psychiatric problem, epilepsy, or alcohol-related problems; they consisted of 187 males and 192 females, with a mean age of 40.1 ± 14.0. Written informed consent was obtained prior to the study after the aims and procedures of the study had been explained. For genotyping, 10 ml venous blood was sampled from each patient and normal control. This study was approved by the Ethical Committee of Asan Medical Center.

SNP genotyping

Genomic DNA was isolated from peripheral blood leukocytes according to standard procedures with proteinase K-RNase digestion followed by phenol-chloroform extraction. The candidate SNPs selected from dbSNP were screened for identification of polymorphic markers by using a pooled DNA sequencing method (Lee et al. 2001). Every SNP was tested in four samples: three individual samples and a pool of 48 individuals. The markers were considered to be monomorphic only when the peak patterns in both directions were clear, without background signals of the minor allele. For polymorphic markers, genotyping was performed by DNA sequencing. Polymerase chain reaction (PCR) and DNA sequencing methods were as described elsewhere (Lee et al. 2001).

Measurement of COMT activity in red blood cell

Blood samples for the RBC COMT assay were drawn from 50 unrelated control and 38 case subjects. The control group consisted of 24 men (19–29 years old) and

26 women (20–34 years old), and the case group consisted of 17 men (19–48 years old) and 21 women (22–58 years old).

Erythrocyte soluble COMT activity was measured by the method of Gershon and Jonas (1975) with modification. Heparin-treated blood was centrifuged at 8,000*g* at 4°C, for 15 min. The serum was removed, and the RBCs were stored at −80°C before the analysis. For COMT activity measurement, 0.1 ml packed RBC was diluted with 0.9 ml ice-cold water and centrifuged for 10 min at 3,000*g* at 4°C. After removal of the sedimenting materials by centrifugation, 0.4 ml supernatant was incubated with 0.2 ml assay mixture for 1 h at 37°C. The assay mixture consisted of 80 mM phosphate buffer (pH 7.8), 5 mM $MgCl_2$, 1.28 nM *S*-adenosyl-L-[methyl−^{14}C] methionine (specific activity, 60 mCi/mM), and 1 mM 3, 4-dihydroxybenzoic acid in 1 ml total volume. After incubation for 1 h, the reaction was stopped by adding 0.1 ml 1 N HCl. To extract the enzymatically formed ^{14}C-homovanillic acid, 3 ml isoamyl alcohol was added and vortexed for 20 s, followed by centrifugation for 3,000*g* for 20 min. Subsequently, 1 ml organic phase was transferred to counting vials with 10 ml liquid scintillation cocktail solution (Ecolite, ICN). The radioactivity was determined by using a Packard liquid scintillation analyzer (Il, USA).

Enzyme activity was calculated as nanomoles ^{14}C-homovanillic acid formed per milliliter of packed RBC per hour. Duplicate determinations were performed for each blood sample. Blanks were prepared for each red blood sample without addition of dihydroxybenzoic acid.

Haplotype frequencies and statistical significance

The genotype frequencies were checked for consistency among cases and controls separately with those expected from Hardy-Weinberg equilibrium by using the commercial program SNP Alyze V 3.0 (Dynacom, Yokohama, Japan). The association between cases and controls was examined by comparing allele and genotype frequencies in different groups of subjects by using the χ^2 test. The logistic regression analysis was used to adjust for age and sex to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

The pairwise linkage disequilibrium (LD) values, D′, r^2, and *P*-values corresponding to χ^2 tests were calculated by using the SNP Alyze software package. Haplotype frequencies were estimated for cases and controls by using the SNP Alyze program, which uses an expectation-maximization (EM) algorithm to determine the maximum-likelihood frequencies of multi-locus haplotypes in diploid populations. The SNP Alyze program was employed to evaluate individual haplotype frequency differences between cases and controls and permutation test significance levels of haplotype profile differences. Analysis of variance (ANOVA) and the *t*-test were performed to compare RBC COMT activity between individuals of different genotypes. For a comparison of RBC COMT activity according to sex and age, an analysis of covariance (ANCOVA) was performed. All statistical tests were carried out by using SPSS for Windows (release 10.0). The χ^2 test was used to assess the significance of the resulting tables.

Results

Single-locus analyses

The 17 SNPs in the COMT gene and their locations as tested in this study are summarized in Table 1 and Fig. 1, respectively. Polymorphic markers in the Korean population were identified in 51 individuals by using a pooled DNA sequencing method (Lee et al. 2001). Of the 17 SNPs screened, 10 SNPs (rs6268, rs6270,

Table 1 PCR primers for COMT genotyping

Primer set	rs number	Polymorphism	Product size (bp)	Left primer (5′–3′)	Right primer (5′–3′)
Set 1	rs737865	intron 1	254	AGGCACATCTAGACAAATCAG	AATGTTAGAGAAAGGGGAAGTC
	rs737864	intron 1			
Set 2	rs174686	intron 1	234	GAGGCACTAGGAAGAAGAACT	CAAGTAGCTGGGACTATAGGTG
Set 3	rs6268	intron 2	304	AGGCACACACCTGCTCTGTC	AGTGCCTCAGAAGCAGCAG
	rs6269	intron 2			
Set 4	rs6270	Cys34Ser	306	CTGCAGGAGGAGCACAGAG	CTGCTCGCAGTAGGTGTCAA
	rs4633	His62His			
Set 5	rs6267	Ala72Ser	158	ACAACCTGCTCATGGGTGAC	ACCCCAACCTTTCTTGTCG
	rs740602	Gln73Gln			
Set 6	rs5031015	Ala102Thr	248	CTCTCCACCTGTGCTCACCT	GCATGCACACCTTGTCCTT
	rs11544669	Leu112Leu			
	rs769223	Ala134Ala			
	rs4986871	Ala146Val			
	rs8192488	Ala146Ala			
Set 6	rs4680	Vla158Met	284	GGGCCTACTGTGGCTACTCA	TTTAGGGTTCTGGGATGACC
Set 7	rs12814	3′-UTR	279	GTGGACGGCCTGGAGAAG	GCTAGCCAGTGTTAGTAAAGAAGTCA
	rs14968	3′-UTR			

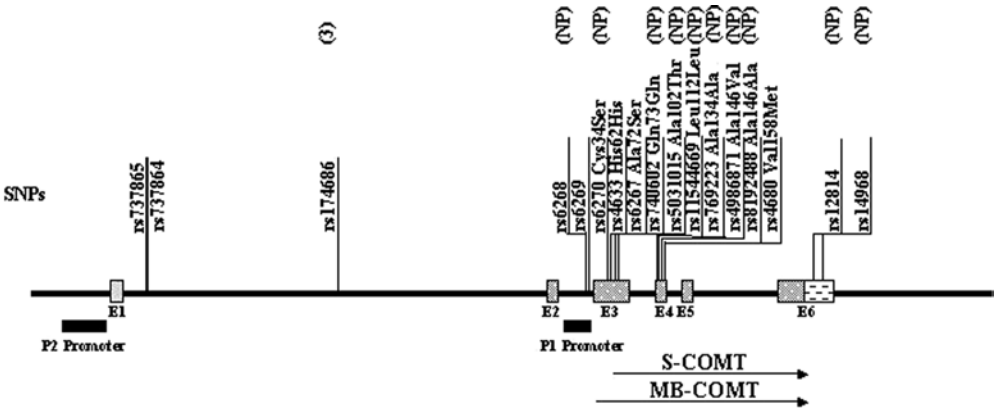

Fig. 1 Location of the 17 SNPs screened in the Korean population by using a pooled DNA sequencing method. Ten SNPs were not polymorphic (*NP*) and one SNP had three alleles (*3*). Five of the SNPs cause a nonsynonymous amino acid change (SNP rs6270:Cys34Ser; rs6267:Ala72Ser; rs5031015:Ala102Thr; rs4986871:Ala146Val; rs4680:Val158Met)

rs740602, rs5031015, rs11544669, rs769223, rs4986871, rs8192488, rs12814, and rs14968) were not polymorphic, and one SNP, rs174686, had three alleles in the Korean population. The selected polymorphic markers included two in the first intron (rs737865, rs737864), one in the second intron (rs6269), one causing His62His (rs4633), and two nonsynonymous SNPs, Ala72Ser and Val158-Met (SNPs rs6267 and rs4680, respectively). Polymorphic SNPs were scored by direct sequencing.

The pairwise LD pattern, measured by D′ and r^2 at the COMT gene (Lewontin 1988), is shown in Fig. 2. The *P*-values based on the χ^2 distribution indicated statistically significant LD among these markers ($P < 0.05$; data not shown). Two markers in the first intron, rs737865 and rs737864, and the remaining four markers were all in strong LD (D′ > 0.9; Fig. 2). The LD between SNP rs737865 and rs6267 was not significant in controls (D′ = 0.41). SNPs rs737865 and rs6269 were separated by 19,793 bp genomic sequence and showed a modest LD (D′ = 0.66). Strong LD was previously reported between the SNPs rs737865 and rs4633 (D′ = 0.84) and rs737865 and rs4680 (D′ = 0.85; Shifman et al. 2002; Bray et al. 2003); however, the LD was modest (D′ = 0.65, D′ = 0.75) in the Korean population.

All tested cases and controls were well matched for gender ($P = 0.7046$). The mean age of schizophrenic patients was 32.6 years (range 14–67), and the mean age of the control group was 40.1 years (range 19–74). Since SNP rs737864 was in complete LD with rs737865, only rs737865 was typed in cases and controls. The results of single-locus analyses with five SNPs in the COMT gene are summarized in Table 2.

As shown in Table 2, only SNP rs6267, which encodes the Ala72Ser polymorphism, showed statistically significant difference in allele frequencies between the cases and controls, whereas five other polymorphisms did not. Table 3 shows the same results analyzed according to sex. The allele and genotype frequencies between men and women were not significantly different, except for SNP rs6267 (Table 3).

In the Caucasian subjects, SNP rs737865 was found to be significantly associated with schizophrenia risk (Shifman et al. 2002); however, the frequency of the CC homozygote of rs737865 was not statistically different between the Korean cases and controls (8.44% in cases, 8.97% in controls). Neither the TC nor the CC genotype was associated with an increased risk of schizophrenia (adjusted OR = 0.94, 95% CI = 0.68–1.30; adjusted OR = 0.96, 95% CI = 0.54–1.71, respectively), when using the TT genotype as a reference group. The frequencies of rs6269 AG heterozygotes or GG homozygotes were similar in the cases and controls (46.3% and 48.5%, 11.6% and 12.7%, respectively) and were not associated with schizophrenia upon adjustment for age and sex (adjusted OR = 0.86, 95% CI = 0.61–1.20; adjusted OR = 0.85, 95% CI = 0.51–1.42, respectively). The difference of allele frequencies between men and women were 8% in the cases (G allele frequency = 0.31 in women vs. 0.39 in men) and 4% in the controls (G allele frequency = 0.35 in women vs. 0.39 in men) (Table 3); however, the differences were not statistically significant ($P = 0.054$ within the cases, $P = 0.32$ within the controls; data not shown). Neither the differences in genotype frequencies within the cases ($P = 0.051$) nor those within the controls ($P = 0.33$) were

Fig. 2 Pairwise LD (the *D′*-value is given *above* the *diagonal*; the r^2-value is given *below* the *diagonal*)

Control	rs737865	rs6269	rs4633	rs6267	rs4680
rs737865		0.66	0.65	0.41	0.75
rs6269	0.32		1.00	1.00	0.90
rs4633	0.07	0.21		1.00	0.92
rs6267	0.01	0.04	0.03		1.00
rs4680	0.09	0.17	0.83	0.03	

Case	rs737865	rs6269	rs4633	rs6267	rs4680
rs737865		0.66	0.71	0.52	0.75
rs6269	0.35		1.00	1.00	0.82
rs4633	0.07	0.17		1.00	0.91
rs6267	0.01	0.07	0.04		1.00
rs4680	0.08	0.12	0.80	0.04	

Table 2 Single-locus analyses of the COMT polymorphisms and association with schizophrenia

Locus	Case		Control		Adjusted OR (95% CI)[a]	*P*-value
	N	%	*N*	%		
Total subjects	320	100	379	100		
rs737865						
TT	157	49.1	182	48.0	1.00	
TC	136	42.5	163	43.0	0.94 (0.68–1.30)	0.71
CC	27	8.4	34	9.0	0.96 (0.54–1.71)	0.89
TT	157	49.1	182	48.0	1.00	
TC/CC	163	50.9	197	52.0	0.94 (0.69–1.29)	0.72
Frequency	T = 0.70/ C = 0.30		T = 0.70/ C = 0.30			
rs6269						
AA	135	42.2	147	38.8	1.00	
AG	148	46.3	184	48.5	0.86 (0.61–1.20)	0.37
GG	37	11.6	48	12.7	0.85 (0.51–1.42)	0.53
AA	135	42.2	147	38.8	1.00	
AG/GG	185	57.8	232	61.2	0.86 (0.62–1.18)	0.34
Frequency	A = 0.65/ G = 0.35		A = 0.63/ G = 0.37			
rs4633 (His62His)						
CC	184	57.5	207	54.6	1.00	
CT	116	36.3	146	38.5	0.89 (0.64–1.24)	0.50
TT	20	6.3	26	6.9	0.92 (0.48–1.76)	0.81
CC	184	57.5	207	54.6	1.00	
CT/TT	136	42.5	172	45.4	0.90 (0.66–1.23)	0.50
Frequency	C = 0.76/ T = 0.24		C = 0.74/ T = 0.26			
rs6267 (Ala72Ser)						
GG	251	78.4	329	86.8	1.00	
GT	65	20.3	49	12.9	1.75 (1.14–2.68)	0.01
TT	4	1.3	1	0.3	4.80 (0.52–44.16)	0.17
GG	251	78.4	329	86.8	1.00	
GT/TT	69	21.6	50	13.2	1.82 (1.19–2.76)	0.005
Frequency	G = 0.89/ T = 0.11		G = 0.93/ T = 0.07			
rs4680 (Val158Met)						
GG	183	57.2	208	54.9	1.00	
GA	113	35.3	140	36.9	0.87 (0.63–1.21)	0.41
AA	24	7.5	31	8.2	0.93 (0.51–1.69)	0.82
GG	183	57.2	208	54.9	1.00	
GA/AA	137	42.8	171	45.1	0.88 (0.64–1.21)	0.43
Frequency	G = 0.75/ A = 0.25		G = 0.73/ A = 0.27			

[a]Adjusted by age and sex

statistically significant. However, statistically significant differences were found in the allele ($P = 0.04$) and genotype ($P = 0.042$) frequencies between men and women in total (data not shown).

The frequencies of rs4633 CT heterozygotes or TT homozygotes were similar between the cases and controls (36.3% and 38.5%, 6.3% and 6.9%, respectively) and were not associated with schizophrenia upon adjustment for age and sex (adjusted OR = 0.89, 95% CI = 0.64–1.24; adjusted OR = 0.92, 95% CI = 0.48–1.76, respectively). The frequency of rs4680 encoding the 158Met allele was similar in the cases and controls (25% and 27%, respectively), and the combined genotype (Val/Met and Met/Met) was not associated with a risk of schizophrenia upon adjustment for age and sex (adjusted OR = 0.88, 95% CI = 0.64–1.21).

Among the tested SNPs, SNP rs6267 showed an association with schizophrenia with the highest combined genotype (Ala/Ser and Ser/Ser)-specific adjusted OR of 1.82 (95% CI = 1.19–2.76; $P = 0.005$), suggesting that the Ser allele might be a risk allele for schizophrenia. This association was more prominent in female cases (adjusted OR = 1.93, 95% CI = 1.12–3.31; $P = 0.018$) than in males (adjusted OR = 1.81, 95% CI = 0.93–3.54; $P = 0.08$; Table 3). Statistically significant differences in the T allele (T allele frequency = 0.07 in normal female vs. 0.13 in female patient; $P = 0.008$) and genotype frequencies ($P = 0.006$) were found between female cases and controls, but not in male cases and controls (T allele frequency = 0.06 in normal male vs. 0.09 in male patient; $P = 0.15$, genotype; $P = 0.14$; Table 3).

Association analysis between COMT haplotype and schizophrenia risk

The SNP Alyze program was used to estimate haplotype frequencies in cases and controls separately. The results of five-locus estimated haplotype frequencies and their distribution in controls and cases are summarized in

Table 3 Allele frequencies of COMT polymorphisms according to sex

Locus	MAF[a]		Adjusted OR (95% CI)[b]	*P*-value[b]	Genotype[c]	Allele[d]
	Case	Control				
Study subjects (F/M)	167/153	192/187				
rs737865						
F	0.28	0.30	0.83 (0.55–1.27)	0.40	0.68	0.67
M	0.31	0.31	1.12 (0.70–1.78)	0.63	1.00	1.00
rs6269						
F	0.31	0.35	0.70 (0.46–1.08)	0.11	0.26	0.25
M	0.39	0.39	1.15 (0.71–1.86)	0.56	1.00	1.00
rs4633 (His62His)						
F	0.25	0.28	0.91 (0.59–1.40)	0.67	0.40	0.39
M	0.24	0.24	0.81 (0.51–1.30)	0.39	0.93	0.93
rs6267 (Ala72Ser)						
F	0.13	0.07	1.93 (1.12–3.31)	0.018	0.006	0.008
M	0.09	0.06	1.81 (0.93–3.54)	0.08	0.14	0.15
rs4680 (Val158Met)						
F	0.24	0.28	0.81 (0.53–1.24)	0.34	0.36	0.35
M	0.26	0.26	0.91 (0.57–1.44)	0.68	0.93	0.93

[a] *MAF* Minor allele frequency of SNP
[b] Adjusted by age. OR and *P*-value were computed for the combined genotypes of heterozygote and minor allele homozygote by using the major allele homozygote as a reference
[c] *P*-values are provided for testing genotypes in the case against those in the control group
[d] *P*-values are provided for testing allele frequencies in the case against those in the control group

Table 4. The EM algorithm predicted 11 different haplotypes in 640 (cases) and 758 (controls) chromosomes. Individual haplotype frequency differences between the groups were evaluated by chi-square tests of individual haplotypes by grouping all others together, with respect to their *P*-values. Permutation test significance levels for individual haplotype frequency comparisons between the case and control groups and the distribution of haplotypes between the cases and controls were also estimated. Haplotype E, which includes the rs6267 (72Ser), exhibited a statistically significant difference in haplotype frequency between the cases and controls (4.1%). However, the differences in overall haplotype distribution between the cases and controls following permutation test were not statistically significant ($P = 0.372$).

Correlation between COMT genotype and RBC COMT activity

To explore the functional significance of the nonsynonymous SNP rs6267 (Ala72Ser polymorphism), we measured COMT enzyme activity in RBC in 38 case and 50 control participants for correlation with genotype. The distribution of RBC COMT activity in the 88 individuals is shown in Fig. 3. The mean COMT activity for the 88 individuals was 4.81 ± 1.89 (mean $\pm$ SD). An ANCOVA indicated that there was no difference in the COMT enzyme activity between the case and control groups in a given genotype ($P = 0.172$; data not shown). Women exhibited lower mean COMT activity than men (women: 4.56 ± 1.82, $n = 47$; men: 5.08 ± 1.96, $n = 41$); however, the difference was not statistically significant

Table 4 COMT haplotype frequency estimates in cases and controls

	rs737865	rs6269	rs4633 (H62H)	rs6267 (A72S)	rs4680 (V158M)	Case	Control	δ[a]	χ^{2}[b]	*P*-value[b]	Permutation *P*-value[c]
A:	T	A	C	G	G	0.270	0.264	0.005	0.074	0.786	0.789
B:	C	G	C	G	G	0.229	0.234	0.005	0.057	0.812	0.812
C:	T	A	T	G	A	0.210	0.227	0.017	0.517	0.472	0.484
D:	T	G	C	G	G	0.100	0.126	0.026	2.209	0.137	0.155
E:	**T**	**A**	**C**	**T**	**G**	**0.100**	**0.059**	**0.041**	**7.970**	**0.005**	**0.006**
F:	C	A	C	G	G	0.020	0.027	0.008	0.799	0.371	0.458
G:	C	A	T	G	A	0.018	0.020	0.002	0.129	0.720	0.776
H:	T	G	C	G	A	0.015	0.009	0.006	0.715	0.398	0.433
I:	C	A	T	G	G	0.013	0.015	0.002	0.105	0.746	0.797
J:	C	A	C	T	G	0.012	0.008	0.004	0.736	0.391	0.459
K:	T	A	C	G	A	0.005	0.010	0.005	1.530	0.216	0.239
											0.076[d]
											0.372[e]

[a] δ-values represent the differences of the haplotype frequency between the case and control groups
[b] χ^2 statistics and *P*-values were derived from simple 2×2 tables based on the frequency of each haplotype versus all others combined between the case and control groups
[c] Permutation test significance levels for individual haplotype frequency comparisons between the case and control groups
[d] Overall *P*-value obtained by comparing the haplotype distribution between the case and control groups
[e] Overall *P*-value based on 1,000 permutations

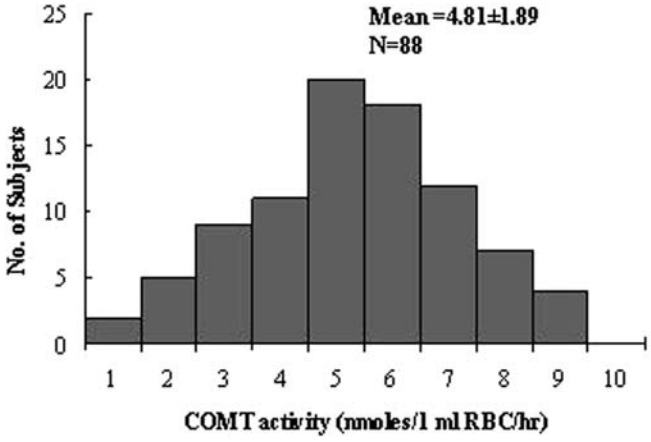

Fig. 3 Distribution of RBC COMT activity. Number of subjects with RBC COMT activity in successive 1 nM/1 ml RBC per hour increments are shown for 88 individuals

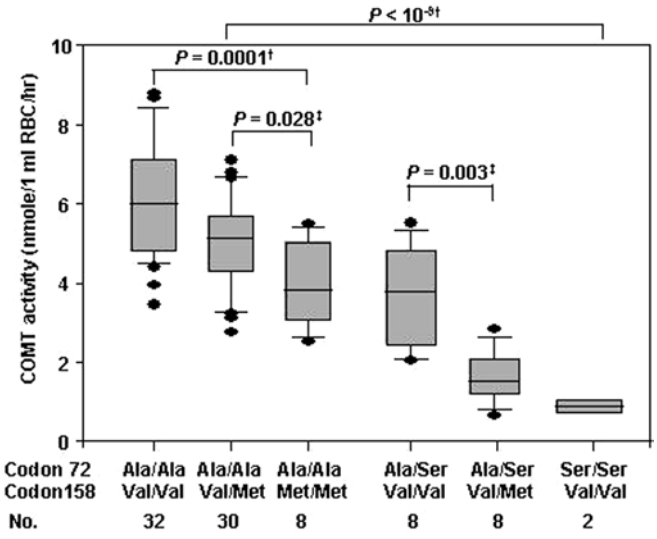

Fig. 4 RBC COMT activity by genotype. The mean COMT activities are indicated by *horizontal bars*. The CI of the mean value and the range are also indicated (*No.* number of study subjects). RBC COMT activities of three genotypes of each polymorphism were analyzed by ANOVA, and their *P*-values are indicated (*dagger*); comparisons of two genotypes by *t*-test and their *P*-values are also indicated (*double dagger*)

($P = 0.201$). The activity was also not different among the age groups ($P = 0.156$).

The study group of 88 individuals was categorized on the basis of the presence of 72Ser or 158Met (Table 5). As reported previously, the Val/Met polymorphism had an effect on COMT enzyme activity in Korean subjects (Table 5, Fig. 4). Compared with the subjects with Val/Val, a statistically significant difference was found in those carrying Val/Met or Met/Met (Fig. 4). The Ala/Ala and Val/Met heterozygotes and Ala/Ala and Met/Met homozygotes were correlated with a COMT activity of 4.81 ± 1.22 and 3.98 ± 1.11, respectively, which are about 79% and 65% of the enzyme activity of the Ala/Ala and Val/Val homozygotes (6.11 ± 1.47; $P = 0.0001$; Fig. 4). More significant reduction in the enzyme activity was associated with the Ala/Ser heterozygotes or Ser/Ser homozygotes compared with Ala/Ala ($P < 10^{-9}$; Fig. 4): the Ala/Ser and Val/Val heterozygotes and Ser/Ser and Val/Val homozygotes were correlated with a COMT activity of 3.72 ± 1.31 and 0.88 ± 0.24, respectively, which are about 61% and 14% of the enzyme activity of the Ala/Ala and Val/Val homozygotes (Table 5). Enzyme activity appeared to be even lower when both polymorphisms were present: the COMT activity of those carrying Ala/Ser and Val/Met was 1.64 ± 0.69, which was lower than those carrying Ala/Ser or Val/Met alone and about 27% of those carrying Ala/Ala and Val/Val.

Discussion

Ethnic differences in the frequency of COMT Ala/Ser and Val/Met polymorphisms

We have identified a nonsynonymous SNP rs6267 (Ala/Ser polymorphism) of COMT; this SNP appears to affect the enzyme activity in the Korean population. The marker has been described as being monomorphic in a large Israeli population (Shifman et al. 2002) and in Caucasian-Americans and African-Americans (Shield et al. 2004). However, it seems to be polymorphic in the Japanese (Saito et al. 2001) and Korean populations. Ethnic differences in COMT enzyme activity and the frequency of the Val/Met polymorphism have been reported. Rivera-Calimlim and Reilly (1984) showed that the frequency of high RBC COMT activity of the Asians was significantly greater than that of the Caucasians. Subsequent studies reported that the frequency of the codon 158Met low activity allele was lower in Asian than in Caucasian, viz., 0.27 in Korean in contrast to 0.54 in Caucasians (McLeod et al. 1998; Palmatier et al. 1999). Identification of a second COMT functional polymorphism, 72Ser, appeared to increase the population frequency of Koreans with low COMT activity, but not to the level of Caucasians. Since our study tested known SNPs in the Korean population, further extensive SNP identification of COMT gene needs to be carried out in Asian populations to identify additional SNPs that might affect COMT activity. It remains to be seen whether ethnic differences in COMT enzyme activity are solely attributable to differences in the frequencies of the COMT low activity alleles, 158Met and 72Ser, in the various populations.

Correlation of Ala/Ser and Val/Met variations with COMT enzyme activity

We have explored the potential functionality of a nonsynonymous SNP rs6267 (Ala/Ser polymorphism) by correlating the COMT genotype with RBC COMT activity. Neither Val/Met nor Ala/Ser variation is conserved among the species. The mouse and rat COMT

Table 5 Distribution of RBC COMT activities in subjects of various genotypes. Values are given as mean ± SD[a]. The number of samples are given in *brackets*

	AA change	Codon 72			
		Ala/Ala	Ala/Ser	Ser/Ser	Total
Codon 158	Val/Val	6.11 ± 1.47 (32)	3.72 ± 1.31 (8)	0.88 ± 0.24 (2)	5.40 ± 1.97 (42)
	Val/Met	4.81 ± 1.22 (30)	1.64 ± 0.69 (8)		4.32 ± 1.77 (38)
	Met/Met	3.98 ± 1.11 (8)			3.98 ± 1.11 (8)
	Total	5.40 ± 1.48 (70)	2.68 ± 1.47 (16)	0.88 ± 0.24 (2)	4.81 ± 1.89 (88)

[a]COMT activity (nM/1 ml RBC/h)

sequences have Pro and Leu at amino acid positions 72 and 158, respectively. The two polymorphisms, Val/Met and Ala/Ser, were separated by 1,008 bp of genomic sequence and were in complete LD. Although the Val/Met polymorphism was reported to cause a three- to four-fold reduction in enzyme activity compared with the activities of Ala/Ala and Val/Val homozygotes in some studies, we did not observe these levels of reduction, perhaps because of the differences in ethnicity or biochemical assay. The Ala/Ser variation was associated with a more dramatic reduction in enzyme activity than was the well-studied Val/Met polymorphism. When both polymorphisms were present, enzyme activity appeared to be lower than that with a single polymorphism, suggesting an additive effect of the polymorphisms on enzyme activity. However, since these observations are based on an association between a COMT genotype and plasma enzyme activity levels, and since our RBC data refers to the soluble form of the enzyme when the predominant form in the brain is the membrane-bound form (Lundstrom et al. 1991), a more detailed analysis with recombinant enzymes will be necessary to characterize the effects of 72Ser and/or 158Met on actual COMT enzyme activity.

Recently, Shield et al. (2004) found COMT with the 158Met allele exhibiting low levels of COMT polypeptide in transfected cell lines and liver biopsies. The 158Met COMT enzyme displayed a 70%–90% decrease in the level of immunoreactive protein when compared with wild-type COMT. Since we did not measure the COMT levels having the 72Ser allele, we cannot rule out the possibility that the 72Ser allele modulates the protein level and/or enzyme activity. Further studies will be necessary to characterize the effects of 72Ser and/or 158Met alleles on COMT function and levels.

COMT polymorphism and risk for schizophrenia

By genotyping five SNPs of the COMT gene in the Korean subjects, we were able to show a positive association between the COMT gene and schizophrenia. Of the five SNPs tested, SNP rs6267 only showed a positive association with schizophrenia with the combined genotype (Ala/Ser and Ser/Ser)–specific adjusted OR of 1.82 (95% CI = 1.19–2.76; $P = 0.005$), suggesting that the Ser allele might be a risk allele for schizophrenia. Furthermore, haplotype E, which includes rs6267 (72Ser), showed a statistically significant difference in haplotype frequency between the cases and controls (Table 4). The *P*-values obtained in this study are not exceptionally significant when corrected for multiple testing. Nevertheless, given prior published results, our study can be treated as a replication in a distinct and independent population. In this context, the *P*-value for rs6267 is significant. As far as we are aware, this is the most statistically significant association of any known COMT polymorphisms with schizophrenia of Asian origins. In Koreans, the well-known Val/Met polymorphism is not associated with an increased risk of schizophrenia (OR = 0.88, 95% CI = 0.64–1.21; $P = 0.43$).

The COMT Val108/158Met polymorphism has been examined repeatedly for an association with schizophrenia, but results have been inconsistent. Recently, a meta-analysis of case-control and family-based studies of the association between the Val/Met polymorphism and schizophrenia has concluded that the Val allele might be a small but reliable risk factor for schizophrenia for people of European ancestry, but the influence on the risk in Asian populations remains unclear (Glatt et al. 2003). Our data suggest that the inconsistent result in Asian data could be attributable to the polymorphism at amino acid residue 72. It remains to be seen whether this data is reproducible in other Asians.

While this work was in progress, a highly significant association was reported between a COMT haplotype and schizophrenia in a large Israeli sample, but no association was present between the Val/Met polymorphism and schizophrenia (Shifman et al. 2002). A subsequent analysis of allele-specific expression by using mRNA from human brain has shown that the haplotype implicated in schizophrenia susceptibility is associated with low COMT expression (Bray et al. 2003). Unfortunately, direct comparisons between our and the previous studies are not possible because of the differences in the tested markers and their frequencies in cases and controls. However, our results of the significant association with the 72Ser allele appear to be consistent with these reports.

Our finding that an association of the 72Ser allele was more prominent in females cases (adjusted OR = 1.93, 95% CI = 1.12–3.31; $P = 0.018$) than in males (adjusted OR = 1.81, 95% CI = 0.93–3.54; $P = 0.08$) prompted us to analyze the COMT activity based on gender. There

was no agreement among the earlier studies as to the differences in COMT enzyme activity in relation to sex (Boudikova et al. 1990; Gershon and Jonas 1975; Lewander et al. 1981), although recent studies have shown that COMT expression is regulated by estrogen through the estrogen-responsive elements in its promoter region (Xie et al. 1999). We found that men had a higher mean RBC COMT activity (5.08 ± 1.96) than women (4.56 ± 1.82); however, the difference was not statistically significant ($P = 0.201$).

Sexually dimorphic effects of COMT on genetic susceptibility to affective disorder, obsessive-compulsive disorder (OCD), and schizophrenia have been proposed (Gershon and Jonas 1975; Cohn et al. 1970; Karayiorgou et al. 1997). However, results have not been consistent for schizophrenia: some workers have reported that a high COMT activity (158Val) allele is associated with female patients (Kremer et al. 2003), whereas others have reported that a low COMT activity (158Met) allele appears to be associated with aggressive behavior in schizophrenia (Strous et al. 2003). Sex-specific effects of the associated alleles examined by Shifman et al. (2002) appear to down-regulate COMT expression (Bray et al. 2003). Although the alleles involved are not consistent, our finding of a significant association in female cases is compatible with previous suggestions of a sex-specific genetic component in schizophrenia (Shifman et al. 2002; Kremer et al. 2003).

In conclusion, we have found, in COMT, a SNP that is associated with reduced COMT activity and a risk of schizophrenia in Koreans. Our data support the view that the reduced COMT activity is related to the development of schizophrenia and other mental diseases. Numerous family-based and/or case-control association studies of COMT with mental diseases have been published with data concerning either COMT activity or COMT genotypes. However, comparisons among them are difficult because of the differences in population and study design. Large population-based studies are necessary to establish associations of COMT with schizophrenia in both genetic and enzyme activity analyses.

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