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ORIGINAL ARTICLE

Association analysis of *COMT* polymorphisms with schizophrenia and smooth pursuit eye movement abnormality

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Schizophrenia is a multifactorial disorder characterized by the contribution of multiple susceptibility genes that may act in conjunction with epigenetic processes and environmental factors. The catechol-*O*-methyltransferase (*COMT*) gene, which is located in the 22q11 microdeletion, has been considered as a candidate gene for schizophrenia because of its ability to degrade catecholamines, including dopamine. In a genetic analysis, neurophysiological endophenotype in schizophrenia, such as smooth pursuit eye movement (SPEM) disturbance, is considered to be a good trait marker, because it may be under more direct genetic control. This study was performed to examine the genetic association of *COMT* polymorphisms with the risk of schizophrenia and SPEM abnormality in a Korean population. Six single-nucleotide polymorphisms of *COMT* were genotyped by TaqMan assay. Their genetic effects on the risk of schizophrenia were analyzed in 354 patients and 396 controls using χ^2 analyses. Among the schizophrenic patients, 166 subjects were selected for association analyses of *COMT* polymorphisms with SPEM abnormality. From the six *COMT* polymorphisms, *rs6267* showed an association with the reduced risk of schizophrenia after correction ($P_{corr} = 0.02$). In analysis of SPEM abnormality, no significant associations were detected with COMT polymorphisms. The results of the present study provide the evidence that in a Korean population, *COMT* on the 22q11 locus is likely involved in the development of schizophrenia, but not in the SPEM function abnormality.
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INTRODUCTION

Schizophrenia (MIM 181500) is a multifactorial disorder characterized by the contribution of multiple susceptibility genes that may act in conjunction with epigenetic processes and environmental factors.[1]

The catechol-*O*-methyltransferase (*COMT*; MIM 116790) gene, which is located in the 22q11 microdeletion, has been considered as a candidate gene for schizophrenia because of its function of degrading catecholamines including dopamine.[2] The Val158Met functional polymorphism among the *COMT* polymorphisms leads to a fourfold reduction in enzyme activity,[3,4] and this variation of enzyme activity presumably affects the risk of schizophrenia. The associations between cognition in 22q11 deletion syndrome and *COMT* polymorphisms have been scrutinized in several studies, but the results have not been consistent and are as yet controversial.[5–9]

Schizophrenia is also recognized as a multifactorial disorder encompassing several intermediate phenotypes, each of which is likely affected by one or more genes. Defining and applying these endophenotypes in genetic studies is important for identifying schizophrenia-related genes, because they are likely under more direct genetic control.[10] Smooth pursuit eye movement (SPEM) disturbance, which can be used as a neurophysiological endophenotype, may be found in ~40–80% of patients with schizophrenia and <10% of healthy control subjects.[11] However, the genetic origin of the SPEM abnormality has been poorly understood, and relatively little research has been performed to answer these questions. The association of *COMT* rs4680 (G>A; Val158Met) with the SPEM abnormality in schizophrenia has been reported.[10] Patients with the A/A (Met/Met) genotype of *COMT* rs4680 showed poorer predictive pursuit eye movement than did patients with the G/G (Val/Val) genotype, but normal controls with the A/A (Met/Met) genotype showed better predictive pursuit eye movement than did patients with the G/G (Val/Val) genotype. In contrast, only male schizophrenia patients with the A (Met) allele showed less severity of

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SPEM functional abnormality in another study,[12] and subsequently no further study was performed to clarify this inconsistence.

In the present study, we analyzed the association of *COMT* polymorphisms with the risk of schizophrenia. We also analyzed the association of the SPEM abnormality with *COMT* polymorphisms among schizophrenic patients.

MATERIALS AND METHODS

Subjects

All individuals included in this study were of Korean ethnic origin; they consisted of 354 schizophrenia patients (176 males and 178 females) receiving stable doses of typical antipsychotic medications and 396 control subjects (224 males and 172 females). Schizophrenia patients were recruited from three Korean mental hospitals: the Keyo Hospital (Kyunggi-Do), the Jinju Mental Hospital (Jinju) and the Soonyoung Hospital (Gyeongsangnam Do). The age of the schizophrenic group was in the range of 23–76 years (mean age = 44.0 years; s.d. = 9.3). The schizophrenia diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (American Psychiatric Association, 1994).[13] These criteria were applied by two trained psychiatrists after an earlier clinical diagnosis of schizophrenia. Patients with complicating diagnoses of mental retardation, organic brain damage, drug or alcohol abuse, neurological disorders or autoimmune disorders, and those with low comprehension skills were excluded. Patients with drug side effects, such as tardive dyskinesia, extrapyramidal symptoms or oculogyric crisis, were also excluded from the study.

The population controls were unrelated healthy employees of the Center for Health Promotion of Seoul National University Hospital (Seoul, Korea), with an age range of 28–80 years (mean age = 54.6 years; s.d. = 9.3). Each population control subject was evaluated by a trained clinician using the Structured Clinical Interview for DSM-IV, non-patient edition (SCID-NP), to ensure that the individual did not have an ongoing or previous psychiatric illness. The institutional review board of each hospital approved the study, and all subjects provided an informed consent.

The measurement of SPEM

We evaluated SPEM of schizophrenia patients by electrooculographic (EOG) recordings of eye movement and calculated the natural logarithmic values of the signal-to-noise ratio (Ln S/N ratio). By this method, the global quantitative SPEM abnormality was scored and analyzed as the Ln S/N ratio, and the genetic association analysis was performed. A higher score on the Ln S/N ratio denotes good SPEM function and the lower score means poorer function. Subjects were seated in a darkened quiet room, in front of a 19-inch computer monitor at a distance of 40 cm. Patients were instructed to observe the moving target spot, as closely as possible, during the pursuit task. The green target spot (0.8 cm × 1 cm) appeared at the center of the computer monitor screen for 0.5 s and then moved horizontally back and forth in an 18.2 degree of visual arc to each side of the screen at a constant speed of 28.2 degree per sec. Using Biopac MP150 (BIOPAC Systems, Goleta, CA, USA), the electrophysiological analog signals of SPEM were amplified and sampled at 400 Hz and converted into digitized files. A measurement period of 15 s during the SPEM task was resampled at 4 Hz and passed through a 2 Hz low-pass filter. After application of Fast Fourier Transformation to the EOG data, the Ln S/N ratio was calculated from analysis of the power spectrum curves.

A total of 166 schizophrenia patients (81 males and 85 females) were analyzed for SPEM. Among them, each set of 87, 52 and 27 patients were recruited from the Keyo Hospital, the Jinju Mental Hospital and the Soonyoung Hospital, respectively. Subjects were selected among patients who agreed to participate and were able to understand the procedure of eye-tracking task. Schizophrenia patients were then divided into two groups for statistical analysis based on their SPEM function. The Ln S/N ratio (mean ± s.d.) of the good and poor SPEM function groups was 4.35 ± 0.29 and 3.20 ± 0.70, respectively.

Single-nucleotide polymorphism genotyping

Among the COMT polymorphisms previously examined in other studies,[14–16] six single-nucleotide polymorphisms (SNPs) were selected for validation in the Korean population, using the criteria of the International HapMap database, from over 10% of minor allele frequencies (MAFs) in the Asian population. The selected SNPs were genotyped using the TaqMan[17] assay. Genotyping quality control was performed in 10% of the samples by duplicate checking (rate of concordance in duplicates > 99%). The sequences and detailed descriptions of the primers used are summarized in Supplementary Table 2.

Statistics

We examined Lewontin's D' ($|D'|$) and the linkage disequilibrium (LD) coefficient r^2 between all pairs of bi-allelic loci.[18] Haplotypes were inferred using the algorithm, Haploview, developed by the Broad Institute (Cambridge, MA, USA).[19] χ^2-Tests were used to compare the observed numbers of each genotype with those expected for the population under Hardy–Weinberg equilibrium (HWE). The allelic distributions of polymorphisms and haplotypes among patients with schizophrenia and normal subjects were evaluated by χ^2-analyses (two-tailed). Multiple regressions were also used for association analyses of SPEM reliability. To correct for multiple testing, the effective number of independent markers was calculated using the software SNPSpD (http://genepi.qimr.edu.au/general/daleN/SNPSpD/), which is based on the spectral decomposition (SpD) of matrices of pair-wise LD values between SNPs.[20] The resulting number of independent marker loci of *COMT* (4.9998) was applied to correct for multiple testing. Statistical power of single associations was calculated with false-positive rate of 5%, disease lifetime prevalence of 0.4%,[21] given MAFs and sample sizes and assuming a relative risk of 1.3, using PGA (Power for Genetic Association Analyses) software.[22]

RESULTS

In this study, we analyzed the association of *COMT* polymorphisms with the risk of schizophrenia and SPEM abnormality using χ^2-tests. Six polymorphisms were selected among previously studied SNPs reported in the previous literatures.[14–16] The distribution of rs6267 in patients and rs4680 in controls significantly deviated from HWE (Supplementary Table 1). LDs among SNPs were measured by calculating Lewontin's D' and r^2 values (Supplementary Figure 1). With the exception of rs165599 because of its low linkage with other SNPs, analysis showed that five polymorphisms were parsed into two blocks with each block having storing LD spine. There were three major haplotypes (MAF > 5%) in each block. *COMT* BL1_ht1, BL1_ht2, BL2_ht2 and BL2_ht3 were not analyzed, because they were almost identical to rs740603, rs737865, rs4633 and rs6267, respectively. Haplotypes with MAF less than 5% were also excluded in further analysis.

In the initial analysis for the risk of schizophrenia, *COMT* rs6267 showed an association with the reduced risk of schizophrenia ($P = 0.004$ and $P_{corr} = 0.02$, Table 1) (MAF of patients versus controls; 0.068 versus 0.110, respectively). In the analysis of abnormality of SPEM quality, although rs165599 showed marginal association with schizophrenia and abnormality of SPEM quality, no significant associations were detected (Table 2).

DISCUSSION

Velo–cardio–facial syndrome is known to be caused by the microdeletion of the 22q11 locus,[23] and many studies have focused on the association between genes on the microdeletion locus of 22q11 and schizophrenia. *COMT* has been an attractive candidate gene for schizophrenia because of its biological function, including degradation of catecholamines, and the gene's location in the locus.[2] The *COMT* Val-158 allele of rs4680 has garnered particular attention regarding susceptibility to schizophrenia, because its physiological effect on prefrontal information processing might add to or interact with other causes of prefrontal malfunction for those at risk for schizophrenia.[24] Although *COMT* has been established as a candidate gene for the risk of schizophrenia, the association of *COMT* polymorphisms is still controversial. In an Ashkenazi Jewish population, rs737865 and rs165599 rather than rs4680 (Val158Met), showed significant

Table 1 Association analysis of *COMT* polymorphisms with the risk of schizophrenia in a Korean population

Loci	Position	Amino acid change	Allele	Allele distribution		χ^2	P of χ^2	P_{corr}	Statistical power (%)
				SZO	PC				
rs737865 T>C	Intron1		T	489 (69.3%)	558 (70.6%)	0.333	0.56	1	91.84
			C	217 (30.7%)	232 (29.4%)				
rs740603 A>G	Intron1		A	377 (54.2%)	435 (55.3%)	0.206	0.65	1	94.75
			G	319 (45.8%)	351 (44.7%)				
rs4633 C>T	Exon3	H62H	C	499 (71.7%)	585 (74.4%)	1.402	0.24	1	89.81
			T	197 (28.3%)	201 (25.6%)				
rs6267 G>T	Exon3	A72S	G	**660 (93.2%)**	**701 (89.0%)**	**8.242**	**0.004**	**0.02**	65.84
			T	**48 (6.8%)**	**87 (11.0%)**				
rs4680 G>A	Exon4	M158V	G	495 (70.7%)	583 (74.2%)	2.222	0.14	0.68	89.94
			A	205 (29.3%)	203 (25.8%)				
rs165599 A>G	3′		A	398 (57.2%)	410 (52.2%)	3.751	**0.05**	0.26	94.76
			G	298 (42.8%)	376 (47.8%)				
BL1_ht3	—		—	584 (83.2%)	654 (83.2%)	0.000	0.99	1	80.08
			ht3	118 (16.8%)	132 (16.8%)				
BL2_ht1	—		—	261 (37.2%)	301 (38.3%)	0.196	0.66	1	94.22
			ht1	441 (62.8%)	485 (61.7%)				

Abbreviations: COMT, catechol-*O*-methyltransferase; MAF, minor-allele frequency; PC, population control; P_{corr}, corrected *P*-value; SNP, single-nucleotide polymorphism; SZO, schizophrenia patient. Haplotypes were constructed using five SNPs, including rs737865T>C, rs740603A>G, rs4633C>T, rs6267G>T and rs4680G>A. rs165599A>G was not used in haplotype construction because of its low linkage with other SNPs. BL1_ht1, BL1_ht2, BL2_ht2 and BL2_ht3 were not analyzed because they were almost identical to rs740603, rs737865, rs4633 and rs6267, respectively. Haplotypes with below 5% of MAF were also excluded in further analysis. To achieve the optimal correction for multiple testing of SNPs in linkage disequilibrium (LD) with each other, the effective number of independent marker loci (4.9998) in *COMT* was calculated using the software SNPSpD (http://genepi.qimr.edu.au/general/daleN/SNPSpD/), on the basis of the spectral decomposition (SpD) of matrices of pair-wise LD between SNPs.

Table 2 Association analysis of *COMT* polymorphisms with SPEM abnormality in two SPEM categories among Korean schizophrenic patients

Loci	Allele	Allele distribution		χ^2	P of χ^2	P_{corr}	Statistical power (%)
		Poor SPEM	Good SPEM				
rs737865 T>C	T	117 (68.8%)	107 (66.1%)	0.290	0.59	1	37.07
	C	53 (31.2%)	55 (34.0%)				
rs740603 A>G	A	84 (49.4%)	79 (48.8%)	0.014	0.91	1	39.24
	G	86 (50.6%)	83 (51.2%)				
rs4633 C>T	C	128 (75.3%)	119 (73.5%)	0.147	0.70	1	33.52
	T	42 (24.7%)	43 (26.5%)				
rs6267 G>T	G	154 (90.6%)	155 (95.7%)	3.177	0.07	0.37	11.24
	T	16 (9.4%)	7 (4.3%)				
rs4680 G>A	G	126 (74.1%)	116 (71.6%)	0.264	0.61	1	34.59
	A	44 (25.9%)	46 (28.4%)				
rs165599 A>G	A	83 (48.8%)	99 (61.1%)	5.042	0.02	0.12	38.46
	G	87 (51.2%)	63 (38.9%)				
BL1_ht3	—	133 (78.2%)	130 (80.3%)	0.203	0.65	1	28.65
	ht3	37 (21.8%)	32 (19.7%)				
BL2_ht1	—	62 (36.5%)	54 (33.3%)	0.358	0.63	1	36.81
	ht1	108 (63.5%)	108 (66.7%)				

Abbreviations: COMT, catechol-*O*-methyltransferase; Ln S/N ratio, logarithmic values of the signal-to-noise ratio; P_{corr}, corrected *P*-value; SPEM, smooth pursuit eye movement.
Good and Poor SPEM groups were divided at the Ln S/N ratio of 3.97.

association with the risk of schizophrenia.[15] On the other hand, no *COMT* polymorphism was found to affect schizophrenia in the European, Japanese and Chinese populations.[16,25] In previous studies conducted in the Korean population, *COMT* rs4680 was reported to have no genetic effect on schizophrenia,[14,26] whereas rs6267 seemed to be a genetic factor for the risk of schizophrenia.[14] Lee *et al.* reported that the frequency of the T allele of rs6267 (Ala72Ser) was significantly higher in the Korean schizophrenia patients than in control subjects (10.2 versus 8.2%). On the other hand, a study conducted in the Japanese population reported that the significant association between this SNP and schizophrenia could not be found, for example, 10.2% in patients versus 8.2% in control subjects,[27] and 8.7% in patients versus 8.6% in control subjects.[28] It is hard to expound on the discrepancies among the results of the studies at this stage. However, if the relative risk was small and/or MAF was low, the possibility of a type II error as a result of insufficient statistical power might be possible. Further studies should be performed using larger samples in several populations.

Except for rs6267 in cases and rs4680 in controls (Supplementary Table 1), all the SNPs in this study were consistent with HWE. Although it would be hard to decipher the cause of deviation of rs4680 ($P = 0.040$), deviation of rs6267 could be attributed to association with the disease. In population-based case–control studies, there

is a possibility that the disease group may deviate from HWE because of selection bias. If there is indeed a gene–disease association, cases are not necessarily expected in HWE. Therefore, the deviation from HWE could be an additional evidence for the true association of this marker.

SPEM is initiated by the motion of an object's image across the retina, and smooth pursuit is generated to minimize the velocity error between the moving image and the fovea.[29] It has been proposed that two kinds of motion information processing, retinal perceptive motion signal processing and extraretinal predictive motion signal processing, drive SPEM. The extraretinal motion-processing deficit is thought to be directly related to the eye-tracking abnormality in schizophrenia.[30,31] Our method of measuring the SPEM function is a global measurement of the SPEM, which is adequate for genetic analysis. We were thus able to quantitatively calculate the degree of SPEM impairment based on the Ln S/N ratio of the SPEM curves. Schizophrenia patients were then divided into two groups, 'good' and 'poor,' according to their SPEM function using the Ln S/N ratio value of 3.97. As there were ~40–80% schizophrenic patients reported to have an incidence of SPEM, dividing the schizophrenia patients into two groups according to their SPEM function was justified under the hypothesis that 50% of patients have SPEM disturbance. In addition, we did not perform the association analysis of the SPEM function abnormality with *COMT* polymorphisms in normal controls. When considering the low incidence of SPEM impairment in normal controls ($<10\%$), the association analysis in normal control subjects could not retain statistical power.

In the recent genetic association studies of the *COMT* rs4680 (G>A) with SPEM abnormality,[10] schizophrenia patients with the A/A genotype (Met/Met) showed poorer predictive pursuit performance than those with G/G genotype (Val/Val). Interestingly, it has been suggested that in a gender-specific manner, *COMT* polymorphisms might be associated with eye-tracking abnormality in schizophrenia.[12] However, there was no significant association detected between *COMT* polymorphisms and the abnormality of SPEM quality in our subjects (Supplementary Table 3). Our result in this study regarding this inconsistency did not favor any previous report, because we found no association of *COMT* polymorphisms with SPEM severity in schizophrenia patients.

In summary, we scrutinized the association of six SNPs and four major haplotypes of *COMT* with the risk of schizophrenia and the abnormality of SPEM quality among schizophrenic patients in a Korean population. There was a significant association between *COMT rs6267* and the reduced risk of schizophrenia after correction ($P_{corr}=0.02$); however, no association was detected between *COMT* polymorphisms and SPEM abnormality in schizophrenia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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