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Interaction between catechol-O-methyltransferase (COMT) Val108/158Met and brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in age at onset and clinical symptoms in schizophrenia

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Summary Catechol-O-methyltransferase (COMT) gene is one of the candidate genes for schizophrenia because it codes an enzyme that participates in the metabolic inactivation of dopamine and noradrenaline and a limiting factor of dopamine metabolism in the prefrontal cortex. COMT gene lies on chromosome 22q11.2, which has been associated with schizophrenia susceptibility. A single-nucleotide polymorphism of COMT gene at position 108/158 results in an amino acid substitution from valine (val) to methionine (met), which modifies its enzymatic activity and may change the brain morphology and expressional behaviors. On the other hand, brain-derived neurotrophic factor (BDNF) plays a critical role in the development of mesolimbic dopaminergic-related systems. BDNF also contains a functional single-nucleotide polymorphism at codon 66 (Val66Met) of its prodomain and this polymorphism is responsible for schizophrenia susceptibility. In this study, we first investigated the relationship between COMT Val108/158Met polymorphism and age at onset as well as levels of clinical symptoms in 158 of chronic schizophrenia inpatients and then we investigated the gene-by-gene interaction between COMT Val108/158Met polymorphism and BDNF Val66Met polymorphism with age- and sex-matched control subjects ($n = 318$). We concluded that the COMT Val108/158Met polymorphism was not related to either the onset at age or the levels of clinical symptoms after long-term antipsychotic treatment in schizophrenia.

Keywords: Schizophrenia, catechol-O-methyltransferase, brain-derived neurotrophic factor, polymorphism, brief psychiatric rating scale, age at onset

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Introduction

Catechol-O-methyltransferase (COMT) gene has been considered to be one of the candidate genes for schizophrenia because it is an important enzyme that participates in the metabolic inactivation of dopamine and norepinephrine and it lies on chromosome 22q11 which has been associated with schizophrenia susceptibility (Owen et al., 2004). COMT gene contains a functional polymorphism, a single-nucleotide polymorphism at position 108/158 that results in change from valine (val) to methionine (met) and the COMT activity with Val108/158 has one fourth lower than that with Met108/158 (Lachman et al., 1996). In contrast to the striatum, dopamine transporters in the prefrontal cortex are expressed in low abundance and the variation in COMT activity has a neurobiological effect in that region (Bertolino et al., 2004). Some genetic studies have demonstrated the possible correlation between COMT Val158/108Met gene polymorphism and schizophrenia (Shifman et al., 2002; Chen et al., 2004), although some studies have failed to find any correlation (Munafo et al., 2005; Williams et al., 2005). Recently, it is reported that COMT Val108/158Met polymorphism is linked to the morphological changes in schizophrenia (Ohnishi et al., 2006).

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophic factor family that promotes the development,

regeneration, survival and maintenance of neurons (Maisonpierre et al., 1991). BDNF has also been demonstrated to modulate neurotransmitter syntheses, metabolism and release, postsynaptic ion channel fluxes, neuronal activities and long-term potentiation (Altar et al., 1997). A single-nucleotide polymorphism that results in valine (val) to methionine (met) substituition at codon 66 (Val66Met) in the prodomain of the BDNF gene was reported and 66Met BDNF has been shown to affect intracellular trafficking and activity-dependent secretion of BDNF (Egan et al., 2001). 66Met BDNF homozygotes had smaller hippocampal volume and lower scores in the Wechsler Memory Scale compared with 66Val homozygotes in normal control subjects (Egan et al., 2003). Although small size of hippocampus is reported in schizophrenia (Callicot, 1998), the results of genetic studies on the association between BDNF Val66Met polymorphism and schizophrenia have been controversial (Chen et al., 2006; Rosa et al., 2006). Recently, we reported that schizophrenic patients with Met66 BDNF had earlier onset and this BDNF polymorphism is associated with clinical symptoms in schizophrenia (Numata et al., 2006).

In this study, we performed a case-control study with COMT Val108/158Met polymorphism, and then examined whether any association exists between this polymorphism and clinical symptoms or onset age in schizophrenic patients. We also investigated the gene-by-gene interaction between COMT Val108/158Met polymorphism and BDNF Val66Met polymorphism.

Materials and methods

We used the same DNA samples as our previous study (Numata et al., 2006) from 159 inpatients (115 male and 44 female; mean age: 53.9 ± 12.8 years, mean duration of hospitalization: 12.1 years) with schizophrenia from nine psychiatric hospitals in the neighboring area of Tokushima Prefecture in Japan (population: about 820,000). All patients were Japanese and biologically unrelated. The diagnosis of schizophrenia was made by at least two experienced psychiatrists according to DSM-IV criteria (American Psychiatric Association, 1994). Clinical symptoms and antipsychotic- induced adverse effects were evaluated when blood samples were taken by the Brief Psychiatric Rating Scale (BPRS) scores (Overall and Goham, 1962) and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) (Inada et al., 2002). The age at first psychotic episode was used as age at onset (mean ± SD: 25.9 ± 8.3 years) by referring to the patient's medical records. Inter- rater reliability for the BPRS and the DIEPSS was $r = 0.81$ ($p < 0.01$). If the first degree relatives of the patient were diagnosed as schizophrenia, we considered the patient as family history plus. In our samples, 72 patients received atypical and 44 patients received typical and others received both types of antipsychotics. Age- and sex-matched controls were selected from volunteers after assessing the psychiatric problems. All control subjects were Japanese, unrelated to each other, and living in Japan. All subjects signed written informed consent to participate in this study approved by the institutional ethics committees.

Genomic DNA was extracted according to standard procedures. Genotyping of COMT Val108/158Met polymorphism was performed with taqman probe according to the manufacture's instruction with ABI 7500 (Applied Biosystems, Tokyo, Japan).

Hardy-Weinberg equilibrium was tested with HWDIAG (Rogatko et al., 2002). Frequency analysis was performed with Fisher's exact test. To evaluate associations between the genotypes and age at onset, Kaplan-Meier analyses were used for survival curves. Spearman correlation coefficients (two-tailed) were used to evaluate whether clinical symptoms of schizophrenia was correlated with Met allele dose-dependency of COMT Val108/158Met polymorphism. Group mean comparisons of the BPRS among genotypic COMT Val108/158Met polymorphism were performed with the Kruskal-Wallis statistic. Multiple linear regression was performed to explore determinants of age at onset. To determine the independent and combined effects of COMT and BDNF genotypes to the BPRS scores in schizophrenia, comparisons between groups were performed by two-way ANOVA followed by multiple comparison testing using the Tamhane correction. The criterion for significance was set at $p < 0.05$ for all of the tests. Data are presented as mean ± standard deviation.

Results

The effect of COMT Val108/158Met polymorphism in schizophrenia

COMT data were available for 158 subjects (114 males and 44 females, genotyping was failed in one subject) and 318 controls (230 males and 88 females). Genotype and allele

Table 1. *Frequency of catechol-O-methltransferase and brain-derived neurotrophic factor genotypes and alleles in patients with schizophrenia and in healthy comparison subjects*

Snp	Group	Genotype			Hardy-Weinberg equilibrium	*p*-Value	Allele		*p*-Value
		Val/Val	Val/Met	Met/Met			Val	Met	
COMT Val106/156Met									
	sch ($n = 158$) (%)	59 (37.3)	85 (53.8)	14 (8.9)	0.092	0.057	203 (64.2)	113 (35.8)	0.16
	cont ($n = 317$) (%)	151 (47.6)	134 (42.3)	32 (10.1)	0.970		436 (68.8)	198 (31.2)	
BDNF Val66Met									
	sch ($n = 159$) (%)	65 (40.9)	68 (42.8)	26 (16.3)	0.528	0.40	198 (62.3)	120 (37.7)	0.16
	cont ($n = 317$) (%)	113 (35.7)	138 (43.5)	66 (20.8)	0.950		364 (57.4)	270 (42.6)	

sch Schizophrenia; *cont* control subjects. Hardy-Weinberg equilibriums are estimated by HWDIAG. *p*-values are calculated by Fisher's exact test.

Table 2. *Genotypes of catechol-O-methl transferase Val108/158Met polymorphism and clinical symptoms of patients with chronic schizophrenia* ($n = 158$)

COMT genotypes	Val/Val	Val/Met	Met/Met
Age	53.3 ± 12.4	53.7 ± 13.4	57.4 ± 10.0
Age at onset	26.3 ± 8.1	25.8 ± 8.9	25.2 ± 4.8
Duration of disease (years)	27.0 ± 12.7	27.9 ± 14.1	32.1 ± 9.1
BPRS-total	40.2 ± 10.0	40.1 ± 9.6	41.8 ± 11.1
BPRS-positive	10.5 ± 4.2	10.1 ± 3.6	11.0 ± 4.6
BPRS-negative	11.4 ± 4.0	11.0 ± 4.3	11.3 ± 3.8
DIEPS	4.6 ± 3.9	4.2 ± 4.4	4.8 ± 2.9
Daily neuroleptic dosage (mg/day)	755.4 ± 534.1	729.2 ± 530.7	594.8 ± 377.4
Duration of hospitalization (years)	14.0 ± 13.5	11.0 ± 11.2	11.4 ± 11.9
Positive first-degree family history ($n = 33$)	48.5%	48.5%	3.0%

BPRS Brief Psychiatric Rating Scales; *DIEPSS* Drug Induced Extra-Pyramidal Symptoms Scale.

distributions of COMT Val108/158Met polymorphism are shown in Table 1. The genotypic distributions did not deviate from the Hardy-Weinberg equilibrium at this polymorphism in both groups. No association between schizophrenia and control subjects was found in genotype or allele frequencies. The mean onset ages were 26.3 ± 8.1 for COMT Val/Val, 25.8 ± 8.9 for COMT Val/Met and 25.2 ± 4.8 for COMT Met/Met. No significant differences were observed among genotypes (log rank statistic: 0.200, $p = 0.904$). No significant sex effect was observed in the effect of the COMT polymorphism on age at onset. The mean BPRS total scores were 40.2 ± 10.0 for COMT Val/Val and 39.9 ± 9.6 for COMT Val/Met, 41.7 ± 11.1 for COMT Met/Met and were not significantly different comparing these three genotypic groups with Kruskal-Wallis comparison ($p = 0.838$). No significant differences were demonstrated in the COMT genotype distributions between patients with positive and negative family history ($p = 0.186$). Neither chlorpromazine-equivalent dose nor the scores of the side effect scale, DIEPSS, showed significant Spearman's rank correlation with Met allele dose-dependency of COMT polymorphism ($p = 0.476$ and $p = 0.689$, respectively). No significant effects of sex or duration of illness were observed in the effect of the COMT polymorphism on BPRS, chlorpromazine-equivalent dose or DIEPSS.

Interaction between COMT Val108/158Met polymorphism and BDNF Val66Met polymorphism

We have previously reported Met66 BDNF homozygotes patients showed significantly earlier age at onset compared to Val66 BDNF homozygotes by the Kaplan-Meier analyses (log rank statistic: 7.51, $p = 0.023$), and that the BDNF polymorphism significantly affects clinical symptoms (Numata et al., 2006). The multiple regression analyses of age at onset were performed as dependent variables. Plausible predictors (sex, education, family history, marriage status and BDNF or COMT polymorphisms) were included in the original models. The final linear regression model included the number of BDNF 66Met alleles ($p = 0.022$) and marriage status ($p < 0.001$) as significant variables influencing age at onset in schizophrenia. COMT polymorphism was eliminated as a significant variable ($p < 0.2$). The dose of Met66 BDNF was weakly but significantly correlated with the onset age (Spearman: $r = 0.162$, $p = 0.042$). On the other hand, the COMT polymorphism was not significantly correlated with the onset age ($p = 0.824$).

We performed two way ANOVA analyses in clinical symptoms because we could not find linear correlation between the BDNF polymorphism and BPRS scores (Numata et al., 2006). By two-way ANOVA followed by multiple comparison testing using the Tamhane correction, BDNF Val66Met polymorphism significantly affects the BPRS in our schizophrenic in-patients samples ($p = 0.040$), however, there was no significant effect seen with COMT Val108/158Met polymorphism to the BPRS ($p = 0.845$). There were no significant effects of DIEPSS or the medication dose in genotypes of either gene.

Discussion

We determined whether any association exists between COMT Val108/158Met polymorphism and clinical variables of schizophrenia and investigated the interaction between COMT Val108/158Met polymorphism and BDNF Val66Met polymorphism. The genotypic frequencies of two polymorphisms of those genes in our sample were almost the same ratio as those of the precedent reports of Japanese samples (Inada et al., 2003; Kunugi et al., 2004).

COMT Val108/158Met polymorphism was not related to either the onset age or the levels of clinical symptoms that remained after long-term antipsychotic treatment in our sample. It has been reported that an association between COMT Met/Met genotype and schizophrenia patients with aggressive behavior as well as suicidal behavior (Nolan et al., 2000; Strous et al., 2003). A possible interaction between low activity COMT and poor response to conventional neuroleptics has been suggested (Illi et al., 2003). However, the lack of association between this COMT polymorphism and clinical variables of schizophre-

nia in this study is consistent with previous reports (Herken et al., 2003; Strous et al., 2006). No significant effects of age at onset or duration of illness were observed in the effect of the COMT polymorphism on the BPRS.

Since COMT knockout mice are known to have increased brain dopamine, especially in the frontal cortex and to show aberrant behavior (Gogos et al., 1998), there may be a distinct effect of the functional single nucleotide polymorphism, COMT Val108/158Met, in human behaviors and diseases. Several studies have revealed that subjects with COMT Met/Met homozygotes performed better than COMT Val/Val homozygotes on executing the Wisconsin Card Sorting Test (WCST), a test associated with prefrontal cortical function (Egan et al., 2001; Malhotra et al., 2002). Ohnishi et al found that this COMT polymorphism is associated with morphological changes in schizophrenia, particularly in the limbic and paralimbic systems (Ohnishi et al., 2006). More extensive studies on the association between the COMT polymorphism and clinical variables are necessary.

Schizophrenia is a complex psychiatric disorder with multiple factors including genetic inheritances. We hypothesized that gene-by-gene interaction might contribute to the different effects of COMT Val108/158Met polymorphism on clinical variables of schizophrenia. We have previously found that the BDNF gene Val66Met polymorphism is related to the onset age of schizophrenia and also influences to the levels of clinical symptoms that are refractory to long-term ordinary antipsychotic treatment in the same sample (Numata et al., 2006). Gourion et al. reported that interaction between BDNF Val66Met and dopamine D3 receptor Ser9Gly polymorphisms was significantly associated with an earlier emergence of psychosis by three years (Gourion et al., 2005). So we investigated the gene by gene interaction between COMT Val108/158Met polymorphism and BDNF Val66Met polymorphism, but the COMT Val108/158Met $\times$ BDNF Val66Met genotype interactions were not detected in this study. However, The BDNF Val66Met polymorphism still indicates a weak but significant effect to onset age and the BPRS even after adjusting for the COMT genetic effect. Kaufman et al. reported that children with one or two of Met66 BDNF alleles are vulnerable to environmental stress in depression (Kaufman et al., 2006). We suggest that the schizophrenic patients with Met66 BDNF might also show vulnerability to environmental stress and suffer the disease earlier.

Our study has several limitations. First, the BPRS is a cross sectional rating scale but not a life time scale, although our patients showed little fluctuation in their symptoms at the time of the interview under long-term antipsychotic treatment. Second, all the patients were long-term inpatients and might not represent schizophrenic patients in general. Third, the sample size is relatively small. Larger studies will be needed to confirm these results.

In summary, our finding suggests that, unlike BDNF Val66Met polymorphism, COMT Val108/158Met polymorphism is not related to the onset age of schizophrenia and does not influence to the levels of clinical symptoms that are refractory to long-term ordinary antipsychotic treatment at least in the Japanense population.

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