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Impact of five SNPs in dopamine-related genes on executive function

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Objectives – Dopamine neurotransmission is a critical factor for executive function, which is controlled by the prefrontal cortex in humans. Although the contribution of genetic factors to the regulation of brain dopaminergic activity is widely acknowledged, identification of a genotype–phenotype association has not yet been clearly established. In this study, we therefore evaluated the effects of five functional single-nucleotide polymorphisms (SNPs) in specific genes related to dopamine neurotransmission on executive function in a general population. *Materials and methods* – Participants of the health examination at the Shimane Institute of Health Science were recruited for this study (n = 964). To evaluate executive function, the Frontal Assessment Battery (FAB) was administered. SNPs were genotyped using the *Taq*Man method. *Results* – A significant association was found between an SNP in the catechol-O-methyltransferase (*COMT*) gene (rs4680) encoding the low-activity Met allele and FAB score (P = 0.003). Of note, the flexibility subset of the FAB was associated with the SNP in *COMT* (P = 0.003) after adjustment for confounding factors. The generalized multifactor dimensionality reduction method identified that the combination of two SNPs in the *COMT* gene (rs4680) and the dopamine D4 receptor gene (rs1800955) had a significant effect on FAB score. *Conclusions* – Our study indicates a contribution of rs4680 in the *COMT* gene to the variability in executive function, as assessed by the FAB. In addition, we have indicated that a complex gene–gene interaction between SNPs in the genes related to dopamine neurotransmission may influence executive function in a general population.

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Key words: dopamine neurotransmission; executive function; prefrontal cortex; single-nucleotide polymorphisms; the Frontal Assessment Battery

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Introduction

Executive function refers to the ability to plan and perform goal-directed actions, which requires the integration of sensory input, internal states including emotion and cognition, and motor output, as well as the ability to anticipate the consequences of one's actions. The prefrontal cortex (PFC) has long been identified as the critical hub in the control processes of execution, coordinating complex behaviors through reciprocal cortical and subcortical networks. This hypothesis was supported by the fact that impairment of executive control was observed in patients with lesions in the frontal lobes (1), as well as in those with schizophrenia and attention-deficit/hyperactivity disorder, psychiatric disorders presumed to affect PFC function (2, 3).

The dopaminergic system has been shown, in both human and non-human primates, to play a critical role in executive function controlled by the PFC (4). Consequently, genes associated with brain dopaminergic activity have been commonly studied in association with executive function. The dopamine D2 receptor gene (*DRD2*) region is one of the most extensively investigated gene regions associated with dopamine receptor function. A previous study has shown that a single-nucleotide polymorphism (SNP) in *DRD2* (rs6277) affects mRNA stability and, therefore, receptor expression

(5), and this finding was confirmed in an *in vivo* study (6). Dopamine D3 (*DRD3*) and D4 receptor (*DRD4*) genes have also been implicated in prefrontal functions (7, 8). Previous research has shown that an SNP in *DRD3* (rs6280) is associated with altered dopamine-binding affinity, predicting a possible functional effect (9), and an SNP in *DRD4* (rs1800955) has been reported to influence transcriptional efficiency (8). However, the behavioral phenotypes resulting from these SNPs have not yet been elucidated.

Dopamine catabolism is another important factor for regulating brain dopaminergic activity. Catechol-O-methyltransferase (COMT) and dopamine β-hydroxylase (DBH) are the major mammalian enzymes involved in the metabolic transformation of released dopamine in the PFC. The common SNP in the *COMT* gene, rs4680, has been reported to be associated with a decrease in enzymatic activity and dopamine catabolism, which ultimately results in increased availability of dopamine in the PFC (10). Previous studies have indicated that *COMT* (rs4680) is related to individual differences in several cognitive phenotypes, including executive function (11, 12). A study examining functional evidence of SNPs in the *DBH* gene showed that the C/T SNP (rs1611115) was associated with the transcription of DBH (13). This SNP has been shown to have an influence on cognition, including executive function (14).

Although the contribution of genetic factors to the regulation of brain dopaminergic activity is widely acknowledged, the resultant cognitive phenotypes have not yet been identified. The aim of this study, therefore, was to investigate the effects of five functional SNPs (rs6277, rs6280, rs1800955, rs4680, and rs1611115) on executive function. We focused on these five SNPs because of their putative functional significance in association with dopamine transmission. In this study, we assessed executive function using the Frontal Assessment Battery (FAB). The FAB is a recently developed battery for the assessment of frontal lobe functions, which has been reported to be a valid and reliable screening test for evaluating executive dysfunction (15). This finding was further confirmed by reported correlations between FAB scores and brain perfusion in the PFC (16).

Materials and methods

Study population

This study was approved by the Ethical Committee of the Shimane University School of Medicine, Japan. From November 2001 to July 2006, a total of 1630 Japanese subjects voluntarily participated in the health checkup system in the Shimane Institute of Health Science. The checkup system included the collection of medical, neurologic, and psychiatric history, formal neurologic examinations by an experienced neurologist, neuropsychologic testing, magnetic resonance imaging scans of the head, and blood tests. We selected 964 neurologically normal subjects (513 men and 451 women) aged 41–88 years (mean, 59.7 ± 5.2) from these participants for this study. The criteria for subject exclusion were as follows: any history of neurologic or psychiatric diseases such as cerebrovascular diseases, including transient ischemic attack, dementia, depression, or other psychiatric diseases (n = 397); and missing data (n = 269). Hypertension was defined as blood pressure levels $\geq$140/90 mmHg or by the use of antihypertensive drugs. Total serum cholesterol and fasting plasma glucose levels were measured in blood samples taken after overnight fasting. Diabetes was defined as a fasting blood glucose level $\geq$126 mg/dl, a random blood glucose level $\geq$200 mg/dl, or by the use of oral antidiabetic drugs. Hyperlipidemia was defined as a serum cholesterol level $\geq$220 mg/dl or by the use of lipid-lowering drugs. A smoker was defined as any subject whose smoking index (cigarettes per day × years) exceeded 200. Regular alcohol consumption was defined as >58 ml of alcohol consumed per day. All participants provided informed consent.

Cognitive function

Executive function was assessed using the FAB, which is a composite tool consisting of six subtests, namely, categorization, flexibility, programming, resistance to interference, inhibitory control, and forced movement (15). Okabe's Intelligence Scale (Okabe's Test), which is a shortened and modified Wechsler Adult Intelligence Scale-Revised for the Japanese aged population, was used for assessing general intelligence, including orientation, semantic memory, calculation, forward and backward digit span, and paired association memory (17). The test is scored out of a total of 60 points, and its reliability and validity have been reported (17).

SNP genotyping

Fasting venous blood samples were obtained from all study participants. Genomic DNA was extracted from peripheral blood leukocytes using

a standard phenol/chloroform method. All SNPs were genotyped using the *Taq*Man SNP Genotyping Assay in a 384-well microplate format (Applied Biosystems, Foster, CA, USA). Briefly, 20 ng of DNA was amplified in a total volume of 5 μl containing an MGB probe (Applied Biosystems) and 2.5 μl of *Taq*Man universal polymerase chain reaction master mix (Applied Biosystems). Allelic discrimination analysis was performed on the ABI Prism 7900HT Sequence Detection System (Applied Biosystems). To ensure the quality of the genotyping, SNP-specific control samples were added to each 384-well plate.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). ANOVA was used in the univariate analysis. The fitness of the allele and genotype frequencies determined using the Hardy–Weinberg equilibrium was evaluated using the chi-square test. Multivariate linear regression analysis was used to test the individual effects of each SNP on FAB score and the effects of rs4680 in *COMT* on each FAB subset, after adjustment for gender, age, education duration, Okabe's test score, hypertension, hyperlipidemia, diabetes, and drinking habits. The proportion of variance explained by each significant factor was estimated by η^2, a ratio of sum-of-squares of the effect divided by total sum-of-squares. To investigate the influence of gene–gene interactions on FAB score, we employed the generalized multifactor dimensionality reduction (GMDR) (18) as an extension of the multifactor dimensionality reduction method developed previously by other research groups (19). Briefly, the n-dimensional space formed by a given set of SNPs is reduced to a single dimension to analyze n-way interactions, and score-based statistics are calculated to classify multifactor cells into two different groups (either high-risk or low-risk). The score is calculated using the target phenotype (i.e., the FAB score in this case) and covariates. If the sum of the score for a particular genotype set exceeds a threshold, the genotype set is categorized as high-risk and *vice versa*. The GMDR software selects the best reproduction combination of SNPs to categorize high- and low-risk genotypes using cross-validation consistency (CVC), and statistical significance of the model is examined by a permutation test. The score data are shuffled randomly to construct a new virtual data set that is tested by GMDR. This procedure is repeated 1000 times to obtain an adequate empirical significance level in the particular data set. In this study, we used gender, age, education duration, Okabe's test score, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits as covariates in our gene–gene interaction analyses.

Results

Association of the five SNPs with FAB score

The relationship between the five SNPs and FAB score was analyzed in the study population. The genotype frequencies of the five SNPs were in agreement with the Hardy–Weinberg equilibrium. As shown in Table 1, the less frequent A allele in the *COMT* gene was associated with a significantly lower FAB score ($P = 0.0003$). We found no correlation between the other four SNPs and FAB score.

Multivariate linear regression analysis was used to determine the association between FAB score and each SNP, with gender, age, education duration, Okabe's Test score, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits serving as independent variables. Each SNP was tested separately for its association with FAB score. This analysis indicated that of all five SNPs, only that of *COMT* (rs4680) was associated with a decrease in FAB score ($F = 8.88$, $P = 0.003$, $\eta^2 = 0.03$, Table 2). The magnitude of the contribution of *COMT* (rs4680) to the FAB score accounted for 3% of variance on executive function.

Table 1 Association between fivr SNPs and the FAB score

Genes	(rs number)	Genotype	N (%)	FAB score (points)
DRD2	(rs6277)	CC	859 (89.1)	15.8 ± 1.3
		CT	100 (10.4)	15.8 ± 1.3
		TT	5 (0.5)	15.4 ± 0.8
				NS
DRD3	(rs6280)	AA	495 (51.4)	15.8 ± 1.3
		AG	403 (41.8)	15.8 ± 1.3
		GG	66 (6.8)	15.8 ± 1.6
				NS
DRD4	(rs1800955)	CC	353 (36.6)	15.7 ± 1.4
		CT	454 (47.1)	15.8 ± 1.3
		TT	157 (16.3)	15.9 ± 1.3
				NS
COMT	(rs4680)	GG	473 (49.1)	16.0 ± 1.2
		GA	414 (42.9)	15.7 ± 1.3
		AA	77 (8.0)	15.3 ± 1.5
				$P = 0.0003$
DBH	(rs1611115)	CC	675 (70.0)	15.8 ± 1.3
		CT	275 (28.5)	15.8 ± 1.3
		TT	14 (1.5)	16.0 ± 1.1
				NS

FAB, Frontal Assessment Battery; NS, not significant.

Table 2 Multiple linear regression model for the FAB score

SNPs	Genes	Major/ minor allele	MAF	Coefficient	*t*-value	*P*-value
rs6277	*DRD2*	C/T	0.057	−0.07	−0.560	NS
rs6280	*DRD3*	A/G	0.277	−0.02	−0.38	NS
rs1800955	*DRD4*	C/T	0.398	0.002	0.04	NS
rs4680	*COMT*	G/A	0.295	−0.22	−2.98	0.003
rs1611115	*DBH*	C/T	0.157	−0.0003	−0.00	NS

Adjusted for gender, age, education duration, Okabes test score, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits.
FAB, Frontal Assessment Battery; MAF, minor allele frequency; NS, not significant; SNP, single-nucleotide polymorphism.

Association of *COMT* (rs4680) with each FAB subset

To examine the association between each FAB subset and the SNP in *COMT* (rs4680), we performed multiple linear regression analysis with adjustment for gender, age, education duration, Okabe's Test score, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits. This analysis indicated that *COMT* (rs4680) was associated with a decrease only in the flexibility component of the FAB ($F = 8.83$, $P = 0.003$, $\eta^2 = 0.04$, Table 3). The magnitude of the contribution of *COMT* (rs4680) to the flexibility component of the FAB accounted for 4% of variance on executive function.

Gene–gene interaction analysis

Investigation into the interaction between the five SNPs in their effects on the FAB score, using GMDR, identified a significant two-locus model involving *COMT* and *DRD4*, after adjustment for gender, age, education duration, Okabe's Test score, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits (CVC: 10/10, test accuracy: 61.1, $P = 0.001$, Table 4). All of the other models including three or more loci were not significant.

Table 3 Association between *COMT* (rs4680) and each FAB subtest

FAB subsets (response variable)	Coefficient	*t*-value	*P*-value
Categorization	−0.08	−2.09.	0.03
Flexibility	−0.16	−2.97	0.003
Programming	−0.001	−0.09	NS
Resistance to interference	−0.01	−1.11	NS
Inhibitory control	−0.07	−2.07	0.04
Forced movement	0.004	1.44	NS

Adjusted for gender, age, education duration, Okabes test score, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits.
FAB, Frontal Assessment Battery; NS, not significant.

Table 4 Best gene–gene interaction models of the five SNPs in the study population

Locus number	Best combination	CVC	Test accuracy (%)	*P*-value
2	*COMT, DRD4*	10/10	61.1	0.001
3	*COMT, DRD4, DRD3*	9/10	54.7	NS
4	*COMT, DRD4, DRD3, DBH*	9/10	52.7	NS
5	*COMT, DRD2, DRD4, DRD3,DBH*	10/10	52.1	NS

Analysis by the Generalized Multifactor Dimensionality Reduction method with adjustment for gender, age, education duration, Okabes test score, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits.
CVC, cross-validation consistency; SNP, single-nucleotide polymorphism.

Discussion

In this study, we showed that *COMT* (rs4680) was associated with a decrease in FAB score. Of note, the flexibility subset of the FAB was associated with that SNP after adjustment for confounding factors such as gender, age, education duration, hypertension, hyperlipidemia, diabetes, smoking habits, and drinking habits in this healthy population. It is important to underscore that, although the observed effects of *COMT* (rs4680) on executive function are robust, this SNP accounted for no more than 4% of the total variance, in accord with the literature (20). However, cognition including executive function is a complex trait and is therefore likely to be underpinned by many genes, each with a relatively small effect. In other words, small effects of multiple factors may exercise a clinically meaningful influence on executive function. Therefore, while engendering a cautious attitude, the observed effects of *COMT* (rs4680) cannot be dismissed as too small and therefore irrelevant.

The SNP in *COMT* (rs4680) refers to a G-to-A change at codon 158, resulting in a valine (Val) to methionine (Met) substitution. The Met allele leads to a three- to four-fold reduction in COMT activity, which results in increasing levels of dopamine in the PFC (10). Previous studies have shown that the Met allele of the *COMT* gene is related to better executive function, as assessed using the Wisconsin Card Sorting Test (WCST), in healthy adults and in those with psychoses such as schizophrenia (21–23). In particular, Egan et al. examined the executive function using the WCST in a cohort of subjects including healthy adults, schizophrenics, and unaffected siblings (23). As the COMT effect was similar across all subject groups and independent of psychiatric diagnosis or risk status, the COMT genotype was concluded to modulate typical as well as impaired prefrontal cognition. Although the results of the

present study appear to be inconsistent with these reports, one possible explanation for this discrepancy is that high levels of dopamine in the PFC do not always enhance cognitive performance, including executive function, which is called the 'inverted U' functional response (24). The 'inverted U' functional response dictates that when dopamine levels are either too high or too low, cognition is adversely affected. Because of the putative inverted-U-shaped relationship between dopamine levels and PFC function, the relationship between COMT activity and PFC function is more complicated. In our study, the age of the subjects was greater than that reported in previous studies conducted in the healthy population (21, 22). Age-related loss of dopaminergic neurons or nerve terminals has been reported (25), which results in the upregulation of dopamine synthesis (26, 27). This upregulation may compensate for the age-related deficit in the dopaminergic system. Thus, in older individuals, the low-activity Met allele, which results in an increase in dopamine synthesis, may cause superoptimal dopamine function and a relative decrease in FAB score. Because of the inverted-U-shaped relationship, which is optimal for young people, may not be optimal for older people. Thus, the effect of *COMT* (rs4680) is dependent on other factors that also affect dopaminergic tone. Actually, in patients with Parkinson's disease (28), which is associated with a relative hyperdopaminergic state within the PFC compared to the striatum, it is the Met allele rather than the Val allele that is linked to relatively impaired PFC performance. These findings suggest that whether the Met allele or the Val allele is associated with improved PFC performance depends in large part on the background on which the polymorphism exerts its effect.

Another possible explanation for our findings is that, in cognitive processing, *COMT* (rs4680) may affect tonic and phasic dopaminergic neurotransmission. Tonic stimulation of dopamine D1 receptors stabilizes and maintains relevant information, whereas phasic stimulation of dopamine D2 receptors underlies 'cognitive flexibility', such as updating and manipulating information (4). Our results show that, after adjustment for confounding factors, an SNP in *COMT* (rs4680) mainly affects the cognitive flexibility of human executive function, thus altering the balance between tonic and phasic neurotransmission. Furthermore, adjustment for age and education duration is of particular importance, as cognitive flexibility is known to be related to general/fluid intelligence (29) and to decline with increasing age (30). Interestingly, recent report has suggested that the Val158Met genotype may differentially affect cognitive stability and flexibility (31). In particular, Met carriers may show comparatively high cognitive stability but comparatively low cognitive flexibility (32). Moreover, the WCST, as shown in previous reports (23), is a complex task involving multiple cognitive functions, which is likely to limit its ability to discriminate between cognitive stability and cognitive flexibility. Further studies evaluating the correlation between FAB score and cognitive flexibility are warranted.

Using the GMDR approach, which can be used to detect the genetic contribution of multiple genes on executive function, we confirmed a significant gene–gene interaction between *COMT* and *DRD4* in influencing executive function. To our knowledge, this is the first study indicating that complex gene–gene interactions may significantly contribute to executive function in the healthy population. These results indicate that the significant joint contribution of these two genes in humans may be responsible for the well-documented experimental evidence observed in *in vitro* studies (8, 10). *DRD4* and *COMT*, which regulate dopaminergic activity by the suppression of signal transduction and degradation, respectively, are major limiting factors for dopaminergic neurotransmission. Taken together, the functional relationship between *DRD4* and *COMT* may explain why polymorphisms in these genes have a statistical interaction in affecting executive function. The dopamine D4 receptor is expressed in the hippocampus as well as in the PFC (33), and the hippocampus, in addition to the PFC, is also considered to be critical for executive function (34). Previously, it has been reported that the performance of executive function tasks is significantly associated with hippocampus size (35). Therefore, our results may reinforce the notion that executive function is mediated by the concerted actions of dopamine/noradrenaline in the frontal cortex and hippocampus.

This study has certain limitations. First, because it was a hospital-based cohort study, selection bias cannot be fully excluded. It would therefore be important to confirm these findings in a population-based study before definitive conclusions can be made about the role of dopamine-related genes in executive function. Second, although several polymorphisms have been identified in each gene, we analyzed only one SNP for each gene. Nevertheless, we believe that the choice of the five SNPs investigated here does not invalidate our findings because of their putative functional significance. Finally, FAB performance

may also be influenced by other skills such as verbal and visuospatial ability. However, the FAB is one of the easiest screening tests to administer and can be completed at the bedside without the need for any tools or instruments; we believe that the simplicity of this test makes it a valuable tool. Further comprehensive assessment of executive function, including measures such as set-shifting, working memory, and verbal fluency, should be performed in future research.

In conclusion, our study highlights the contribution of *COMT* (rs4680) to the variability in executive function, as assessed by the FAB. Moreover, we have indicated a complex gene–gene and gene–environment interaction between SNPs involved in dopamine neurotransmission in the PFC and executive function. Further functional analyses are warranted to elucidate the biologic plausibility of the complex gene–gene interactions identified in this study.

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None.

Conflicts of interests

None of the authors have any conflicts of interest to declare.

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