Association Analysis of the Tryptophan Hydroxylase 2 Gene Polymorphisms in Patients with Methamphetamine Dependence/Psychosis

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Abstract: There is a growing evidence that serotoninergic systems modulate dopaminergic neurotransmission. We analyzed the association between the variations in the brain tryptophan hydroxylase 2 (*TPH2*) gene, a rate limiting enzyme for serotonin biosynthesis, and methamphetamine (METH) dependence/psychosis in a Japanese population. We found ten single nucleotide polymorphisms (SNPs) and two polynucleotide polymorphisms in *TPH2* gene exons and exon-intron boundaries. A total of 162 patients and 243 controls were used for the association analysis between these polymorphisms and METH dependence/psychosis. No significant differences were observed in either genotypic or allelic frequencies between METH dependent/psychotic patients and controls. A global test of differentiation among samples based on haplotype frequencies showed no significant association. With respect to latency of psychosis, prognosis of psychosis, and spontaneous relapse, we found no significant association with these SNPs. These results suggest that the *TPH2* gene variants may not be a factor in vulnerability to METH dependence/psychosis.

Keywords: Single nucleotide polymorphism, SNP, variation, serotonin, human, Japanese, MAP, abuse.

INTRODUCTION

Methamphetamine (METH) is a psychomotor stimulant with high liability for abuse, and METH abuse has become a very serious social problem in Japan [1]. Chronic METH abusers have been shown to have persistent dopaminergic deficits [2, 3]. In animals, amphetamine elevates extracellular dopamine levels in the mesolimbic circuits [4, 5]. There is growing evidence that serotonergic systems modulate dopaminergic neurotransmission. For example, the mesocorticolimbic dopamine system is under inhibitory control by the serotonin system, which exerts its actions *via* serotonin receptor subtypes [6, 7].

Acute and chronic administration of METH markedly decreases the activity of tryptophan hydroxylase (TPH) [8, 9], the rate-limiting enzyme in the biosynthesis of serotonin [10]. TPH2 (or neuronal TPH) was identified as a second isoform of TPH in 2003 [11, 12]. In contrast to TPH1, which is expressed predominantly in the pineal gland and the periphery, TPH2 mRNA is expressed in the raphe nuclei [11]. Since the identification of TPH2, there have been numerous association analyses between *TPH2* gene variants and psychiatric diseases. For example, associations have been observed between *TPH2* variants and bipolar disorder [13-18], suicidal behavior in major depression [19-21], the response to selective serotonin reuptake inhibitors (fluoxetine and/or citalopram) [22, 23] and emotional regulation in healthy subjects [24-28]. These reports indicate that polymorphic variants in the *TPH2* gene may have a role in the pathophysiology of a wide range of psychiatric disorders and emotional regulation. A recent study of heroin addiction also showed an association with *TPH2* variants in Hispanics and African-Americans [29].

The purpose of this study was (1) to identify novel sequence variations in all coding exons as well as exon-intron boundaries of the *TPH2* gene in Japanese, and (2) to investigate whether these polymorphisms and/or haplotypes were associated with METH dependence/psychosis.

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MATERIALS AND METHODS

Subjects

One-hundred sixty-two unrelated patients with METH dependence/psychosis (130 males and 32 females; mean age 37.4±12.0 years) meeting ICD-10-DCR criteria (F15.2 and F15.5) were used as case subjects; they were outpatients or inpatients of psychiatric hospitals. The 243 control subjects (168 males and 75 females; mean age 35.4±11.5 years) were mostly medical staff members who had neither personal nor familial history of drug dependence or psychotic disorders, as verified by a clinical interview. All subjects were Japanese, born and living in the northern Kyushu, Setouchi, Chukyo, Tokai, and Kanto regions. This study was approved by the ethical committees of each institute of the Japanese Genetics Initiative for Drug Abuse (JGIDA), and all subjects provided written informed consent for the use of their DNA samples for this research [30]. After informed consent was obtained, blood samples were drawn and genomic DNA was extracted by the phenol/chloroform method.

Defining Variants of the *TPH2* Gene

Initially, 16 METH dependent/psychotic patient samples were used to identify nucleotide variants within the *TPH2* gene (GenBank accession no. AC090109). Exons 1 to 11 and exon-intron boundaries were amplified by polymerase chain reaction (PCR) using a thermal cycler (Astec, Fukuoka, Japan), and the products were sequenced in both directions using BigDye terminators (Applied Biosystems, Foster City, CA) by an ABI Genetic analyzer 3100 (Applied Biosystems).

Genotyping of each polymorphism except in exon 11 was performed by PCR amplification using the relevant primers listed in Table **1** followed by sequencing using the same primers in both directions. Genotyping of polymorphisms in exon 11 was performed by PCR amplification using 9F and 11R primers followed by sequencing using 10F, 11F, and 11R primers.

Patient Subgroups

For the clinical category analysis, the patients were divided into two subgroups by three different clinical features. (A) Latency of psychosis from first METH intake: less than 3 years or more than 3 years. The course of METH psychosis varied among patients, with some patients showing psychosis sooner after the first METH intake, as previously reported [30, 31]. Because the median latency was three years, this time point was used as the cutoff in defining the two groups. (B) Duration of psychosis after the last METH intake: transient (<1 month) or prolonged (≧1 month). Some patients showed continuous psychotic symptoms even after METH discontinuation, as previously reported [30, 31]. Patients with the transient type showed a reduction of psychotic symptoms within one month after the discontinuation of METH consumption and the beginning of treatment with neuroleptics. Patients with the prolonged type showed a psychotic symptoms continued for more than one month even after the discontinuation of METH consumption and the beginning of neuroleptic treatment. (C) Spontaneous relapse: present or not. It has been well documented that once METH psychosis has developed, patients in the remission phase are liable to spontaneous relapse without reconsumption [30, 31].

Statistical Analysis

The Hardy-Weinberg equilibrium of genotypic frequencies in each SNP was tested by the chi-square test. The level of statistical significance was set at $\alpha = 0.05$. The allelic and genotypic frequencies of patients and control groups were compared using the chi-square test. Locus by locus linkage disequilibrium (LD) was evaluated by D' and r^2, which were calculated by the haplotype frequencies using the appropriate formula in the Excel program. A global test of differentiation among samples based on haplotype frequencies was performed using the Arlequin program available from http://anthropologie.unige.ch/arlequin [32].

Table 1. Primers Used in this Study

Exon	Forward		Reverse	
Exon 1	1F	CCT TAT GTA TTG TTC TCC ACC ACC	1R	GTT GAG CAC GCA GTG ATT GGC ACA
Exon 2	2F	CCA CTA GAT GAT GTC TTA GAC CAT	2R	CTG ACC TCC TAA CCT GGC AAT AGT
Exon 3,4	3F	GTA CTT GGC ACC TTG CTT AAG ATG	3R	TGG AAG TCT GCT CTC AGT TAT GGG
Exon 5	4F	GCT CAA CTA AGC CAT TCT GCT TAC	4R	GTA GCA CTT GGC ATG TGG CTC ACA
Exon 6	5F	GAT CCT TTC AGA CGC TCA TGT GCT	5R	CAT ACT CAT GTA GCC CAG CAC AGC
Exon 7	6F	GTG CGG TAA GCA TCA CTT TCG ATT	6R	CAG ATG AGG AGT CTG ATC CTT CAG
Exon 8	7F	GAA GTC CCA GCA TTG ATG AAC TGT	7R	GGC TAA GCT GAG TAA TTC TGA CAG
Exon 9	8F	CAG GAA GCG TAA GAC TCT TAG TAG	8R	GTC AGT AGG ATC ACT GCT AGC TCA
Exon 10, 11	9F	CCT GCA CAC AGG AGA GTT CCA TAT	9R	CAT GCT GGC AAC AAC ATA GTT CCA
	10F	CAA TCC CTA CAC ACA GAG TAT TGA	10R	CAT TCC AAC TGC TGT GTT ACC TCA
	11F	GAT CTA AGC CTT TCC TCT GTG TTC	11R	GAC ACA GAA ACA CAT GCA AGC ACT

RESULTS

To identify polymorphisms in the *TPH2* gene, all coding exons (1 to 11) and exon-intron boundaries were analyzed using genomic DNA from 16 Japanese METH-dependent/psychotic subjects. Ten single nucleotide polymorphisms (SNPs) and two insertion / deletion polymorphisms were identified. One polymorphism, Exon11+(C3) 500(C2), was novel (Table **2**). Two SNPs, rs7305115 (Exon7+A131G) and rs4290270 (Exon9+A57T), were synonymous mutations and Eon2+C18A was a non-synonymous mutation. Three linkage disequilibrium (LD) regions were found, rs11178998 (Exon1-A42G) to rs41265611 (IVS1+60 (I/D)), rs11179003 (IVS4+C4821T) to rs10879348 (IVS6+G144A), and rs4760816 (IVS6+C6106T) to rs7305115 (Exon7+A131G), in the sense that all genotypic patterns in all 16 samples analyzed were the same. Each one of the SNPs was chosen and a total of nine SNPs were genotyped for further analysis. LD mapping was analyzed by using SNPs having minor allele frequencies of over 10% in both samples (Table **4**). LD was observed from rs17110566 (IVS6+G152A) to rs17110747 (Exon11+G654A) and from rs4290270 (Exon9+A57T) to rs41317114 (IVS11+G128C) (Fig. **1** and Table **3**).

Association analyses were performed on these nine polymorphic positions using 162 METH dependent/psychotic patients and 243 controls. Genotypic frequencies in these

Table 2. ***TPH2*** **Gene Variants Found in the Japanese Population**

Position[1)]	Location	rs Number[2)]	SNP Name	Variation	Function
30029	5' side	rs11178998	Exon1-A42G	A/G	
30241	Intron 1	rs41265611	IVS1+60(I/D)	TCT/del	
32694	Exon 2		Exon2+C18A[3)]	C/A	nonsynonymous (Ser41Tyr)
40601	Intron 4	rs11179003	IVS4+C4821T	C/T	
63953	Intron 6	rs10879348	IVS6+G144A	G/A	
63961	Intron 6	rs17110566	IVS6+G152A	G/A	
69915	Intron 6	rs4760816	IVS6+C6106T	C/T	
70176	Exon 7	rs7305115	Exon7+A131G	A/G	synonymous (Pro312Pro)
113549	Exon 9	rs4290270	Exon9+A57T	A/T	synonymous (Ala375Ala)
123114	Exon 11		Exon11+(C3)500(C2)	C3/C2	
123268	Exon 11	rs17110747	Exon11+G654A	G/A	
123663	3' side	rs41317114	IVS11+G128C	G/C	

[1)] Position: nucleotide position number in the NCBI nucleotide database under accession number AC090109. [2)] rs number: NCBI SNP database. [3)] This SNP was reported as C2755A [14].

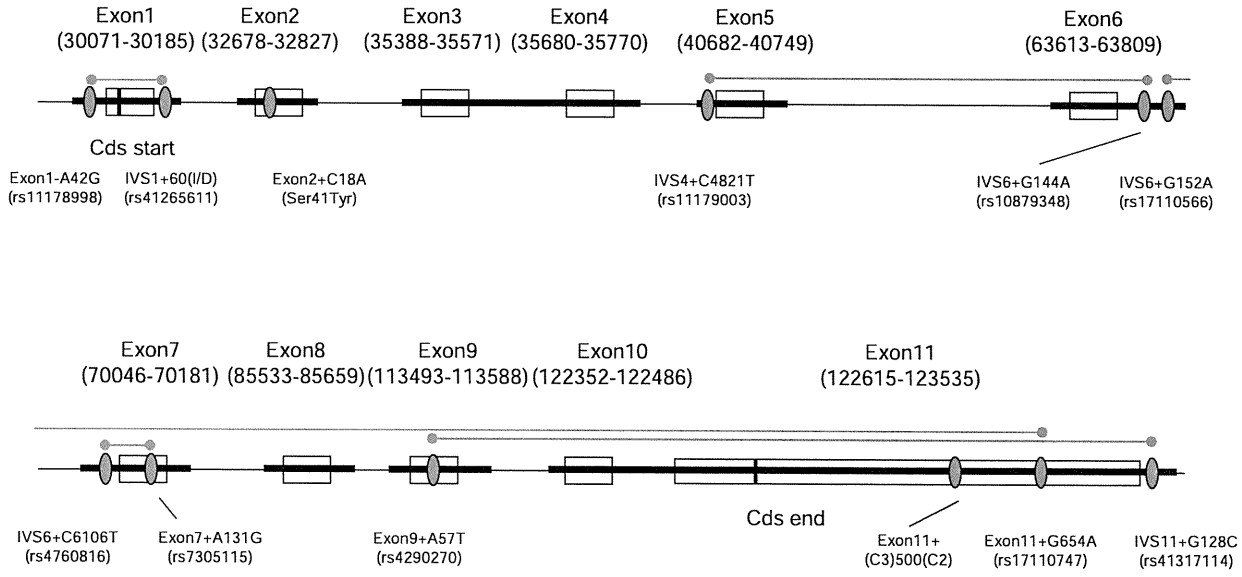

Fig. (1). Location and linkage disequilibrium mapping of the *TPH2* gene polymorphisms. All the coding exons and their regions were taken from the NCBI database under accession number AC090109. Red ovals indicate the polymorphic positions, solid black lines the analyzed regions, and solid red lines the LD block.

Table 3. Linkage Disequilibrium Mapping of the *TPH2* Gene

	rs17110566 (IVS6+G152A)	rs4760816 (IVS6+C6106T)	rs4290270 (Exon9+A57T)	rs17110747 (Exon11+G654A)	rs41317114 (IVS11+G128C)	
rs17110566		0.9392	0.6138	0.8581	0.0348	
rs4760816	0.9724		0.7301	0.9253	0.0092	
rs4290270	0.5262	0.5881		0.9284	0.6051	D'
rs17110747	0.8437	0.7885	0.9774		0.9399	
rs41317114	0.0111	0.2179	0.6284	0.9123		
			r^2			

D' and r^2 values for Control samples are shown in the upper right and lower left, respectively.

Table 4. Genotypic and Allelic Distribution of the *TPH2* gene SNPs in the METH Dependent/Psychotic Patients and the Control Groups

SNP	Group	Genotype (%)			P	Allele (%)		P
rs11178998 (Exon1-A42G)		A/A	A/G	G/G		A	G	
	METH	130 (80%)	29 (18%)	3 (2%)	0.102	289 (89%)	35 (11%)	0.617
	Control	197 (81%)	46 (19%)	0 (0%)		440 (91%)	46 (9%)	
Exon2+C18A		C/C	C/A	A/A		C	A	
	METH	146 (90%)	16 (10%)	0 (0%)	0.914	308 (95%)	16 (5%)	0.807
	Control	222 (91%)	21 (9%)	0 (0%)		465 (96%)	21 (4%)	
rs10879348 (IVS6+G144A)		G/G	G/A	A/A		G	A	
	METH	136 (84%)	26 (16%)	0 (0%)	0.975	298 (92%)	26 (8%)	0.920
	Control	206 (85%)	37 (15%)	0 (0%)		449 (92%)	37 (8%)	
rs17110566 (IVS6+G152A)		G/G	G/A	A/A		G	A	
	METH	123 (76%)	35 (22%)	4 (2%)	0.552	281 (87%)	43 (13%)	0.406
	Control	173 (71%)	64 (26%)	6 (2%)		410 (84%)	76 (16%)	
rs4760816 (IVS6+C6106T)		C/C	C/T	T/T		C	T	
	METH	28 (17%)	85 (52%)	49 (30%)	0.314	141 (44%)	183 (56%)	0.200
	Control	57 (23%)	121 (50%)	65 (27%)		235 (48%)	251 (52%)	
rs4290270 (Exon9+A57T)		A/A	A/T	T/T		A	T	
	METH	29 (18%)	80 (49%)	53 (33%)	0.840	138 (43%)	186 (57%)	0.777
	Control	49 (20%)	115 (47%)	79 (33%)		213 (44%)	273 (56%)	
Exon11+(C3)500(C2)		C3/C3	C3/C2	C2/C2		C3	C2	
	METH	159 (98%)	3 (2%)	0 (0%)	0.357	321 (99%)	3 (1%)	0.357
	Control	242 (100%)	1 (0%)	0 (0%)		485 (100%)	1 (0%)	
rs17110747 (Exon11+G654A)		G/G	G/A	A/A		G	A	
	METH	92 (57%)	63 (39%)	7 (4%)	0.956	247 (76%)	77 (24%)	0.888
	Control	136 (56%)	95 (39%)	12 (5%)		367 (76%)	119 (24%)	
rs41317114 (IVS11+G128C)		G/G	G/C	C/C		G	C	
	METH	119 (73%)	38 (23%)	5 (3%)	0.719	276 (85%)	48 (15%)	0.462
	Control	187 (77%)	50 (21%)	6 (2%)		424 (87%)	62 (13%)	

Table 5. Genotypic Distribution of the *TPH2* Gene SNPs in Clinically Subcategorized METH Subjects

SNP	Groups	Subgroup		N	Genotype			P
rs17110566 (IVS6+G152A)					G	G/A	A	
	Control			243	173	64	6	
	METH	Latency of Psychosis	<3 years	64	53	10	1	0.172
			≧3 years	67	47	18	2	0.966
		Prognosis of Psychosis	Transient (<1 month)	87	67	17	3	0.421
			Prolonged (≧1 month)	52	38	13	1	0.951
		Spontaneous Relapse	Not present	101	78	21	2	0.517
			Present	56	42	12	2	0.694
rs4760816 (IVS6+C6106T)					C	C/T	T	
	Control			243	57	121	65	
	METH	Latency of Psychosis	<3 years	64	13	35	16	0.771
			≧3 years	67	9	35	23	0.165
		Prognosis of Psychosis	Transient (<1 month)	87	15	39	33	0.125
			Prolonged (≧1 month)	52	7	34	11	0.107
		Spontaneous Relapse	Not present	101	19	51	31	0.577
			Present	56	8	30	18	0.306
rs4290270 (Exon9+A57T)					A	A/T	T	
	Control			243	49	115	79	
	METH	Latency of Psychosis	<3 years	64	8	35	21	0.338
			≧3 years	67	13	32	22	0.990
		Prognosis of Psychosis	Transient (<1 month)	87	16	37	34	0.541
			Prolonged (≧1 month)	52	6	34	12	0.058
		Spontaneous Relapse	Not present	101	17	52	32	0.712
			Present	56	10	27	19	0.923
rs17110747 (Exon11+G654A)					G	G/A	A	
	Control			243	136	95	12	
	METH	Latency of Psychosis	<3 years	64	35	28	1	0.438
			≧3 years	67	37	26	4	0.947
		Prognosis of Psychosis	Transient (<1 month)	87	52	31	4	0.827
			Prolonged (≧1 month)	52	26	25	1	0.366
		Spontaneous Relapse	Not present	101	57	41	3	0.712
			Present	56	32	21	3	0.970
rs41317114 (IVS11+G128C)					G	G/C	C	
	Control			243	187	50	6	
	METH	Latency of Psychosis	<3 years	64	49	15	0	0.411
			≧3 years	67	48	16	3	0.552
		Prognosis of Psychosis	Transient (<1 month)	87	65	19	3	0.852
			Prolonged (≧1 month)	52	38	13	1	0.767
		Spontaneous Relapse	Not present	101	77	21	3	0.966
			Present	56	38	17	1	0.282

N: Number of samples.
P: Significance values between the METH subjects and the controls.

SNPs were within the Hardy-Weinberg expectations. No significant differences were found in the allelic or genotypic frequencies of these SNPs between the METH dependent/psychotic patients and the controls (Table **4**). Since the minor allele frequency of the Exon11+(C3)500(C2) SNP was less than 1% in controls, this SNP was excluded from the haplotype analysis. No significant difference (P=0.448) was observed in a differentiation test between all pairs of samples based on haplotype frequencies by the Arlequin program.

Subcategory analyses were conducted on the clinical parameters (latency of psychosis, prognosis of psychosis, and spontaneous relapse). SNPs having minor allele frequencies of over 10% in both samples were used for this analysis: rs17110566 (IVS6+G152A), rs4760816 (IVS6+C6106T), rs4290270 (Exon9+A57T), rs17110747 (Exon11+G654A), and IVS11+G129C. No significant associations with clinical parameters were observed (Table **5**).

DISCUSSION

We analyzed the *TPH2* gene polymorphisms in a Japanese population and found ten SNPs and two insertion/deletion variants, among which one variant was novel. However, we failed to identify any variants or haplotypes in the *TPH2* gene examined in this study which were associated with METH dependence/psychosis.

Exon2+C18A is a nonsynonymous SNP and the corresponding amino acid is changed from Ser to Tyr at peptide position 41 (S41Y). This SNP was reported as C2755A by Lin and colleagues in a Han Chinese population [14]. They transfected plasmids containing full-lengthTPH2 protein–encoding sequences with two alternative alleles into SH-SY5Y cells and found that the amount of serotonin in SH-SY5Y cells expressing the 41Y allele was about 36% lower than in cells expressing the 41S allele. Despite the strong scientific rationale for studying polymorphisms in the *TPH2* gene in METH dependence/psychosis, we could not identify any variants or haplotypes associated with the phenotype. These results were comparable to those for cocaine use. Both cocaine and METH increase extracellular dopamine in the brain, and increased dopamine in the nucleus accumbens is thought to underlie the reinforcing effects of drugs of abuse [5, 33]. The association of cocaine dependence in subjects of African descent with TPH2 SNPs was analyzed by Dahl and colleagues, but they failed to identify any SNPs that were associated with the cocaine-dependent phenotype [34]. The disparity between these results and the previously reported results for heroin addiction [29] suggest that the *TPH2* gene has little effect in psychostimulants with the characteristics of indirect dopaminergic agonists.

Our results indicate that the *TPH2* gene variations may not be vulnerability factors in METH dependence/psychosis, and indeed that they are likely to make a small or no contribution to the development of METH dependence/psychosis.

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Association analysis of the GDNF gene with methamphetamine use disorder in a Japanese population

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ABSTRACT

Methamphetamine (MAP) dependence is a highly heritable and aberrant dopaminergic signaling that has been implicated in the disease. Glial cell line-derived neurotrophic factor (GDNF), which plays an important role in the survival of dopaminergic neurons, may be involved in this disorder. In this study, we examined the association between GDNF and MAP dependence using a Japanese population-based sample.
We selected eight single nucleotide polymorphisms (SNPs) in the GDNF locus for the association analysis. When patients with MAP dependence were divided into two subgroups consisting of multi-substance and MAP-only users, we detected a significant association between these two groups and the tagging SNP, rs2910704 (after Bonferroni's correction; allele P = 0.034). Thus, GDNF is likely to be related to the severity of MAP use in the Japanese population.

1. Introduction

Methamphetamine (MAP) dependence is a serious public health problem that has reached epidemic proportions worldwide (Elkashef et al., 2008). Repeated use of MAP induces a strong psychological dependence and results in the development of psychotic symptoms such as psychosis, attempted suicide, craving, and depression (Aoyama et al., 2006; Nakama et al., 2008). Numerous family and twin epidemiological studies have suggested that MAP dependence is a highly heritable disorder (the estimated heritability is 30–60%) (Kendler et al., 2005; Aoyama et al., 2006; Lichtenstein et al., 2009). Thus, a number of molecular genetic studies have been conducted worldwide to elucidate the vulnerable genes associated with this disorder (Aoyama et al., 2006; Kishi et al., 2010; Okochi et al., 2009).

Aberrant dopaminergic transmission has long been implicated in the development of MAP dependence (Freedman, 2003, Yui et al., 2000). It is well known that glial cell line-derived neurotrophic factor (GDNF) is one of the most potent neurotrophic factor influencing the dopaminergic function. (Carnicella and Ron, 2009). Indeed GDNF plays an important role in the survival and neurite outgrowth of midbrain dopaminergic neurons (Krieglstein et al., 1995; Lin et al.,

Abbreviations: MAP, methamphetamine; GDNF, Glial cell line-derived neurotrophic factor; DA, dopamine; UTR, untranslated region; SNP, single nucleotide polymorphism; GFRA, GDNF family receptor alpha; RET, rearranged during transfection; JGIDA, Japanese Genetics Initiative for Drug Abuse; S.D., standard deviation; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; LD, linkage disequilibrium; DAT, dopamine transporter.

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1993). Furthermore, GDNF modulates the activity/excitability of midbrain dopamine (DA) neurons (Yang et al., 2001; Wang et al., 2003) as well as DA uptake (Lin et al., 1993). These observations suggest that GDNF is important for the development and maintenance of DA signaling.

An animal study has provided direct evidence of the involvement of GDNF in MAP dependence. Reduction in the expression of *GDNF* potentiates MAP self-administration, enhances motivation for mice to take MAP, increases vulnerability to drug-primed reinstatement, and prolongs cue-induced reinstatement of MAP-seeking behavior that had been previously suppressed (Yan et al., 2007). Of note, GDNF is implicated not only in the control of MAP intake and seeking but also in drug abuse in general (Ghitza et al., 2010; Carnicella and Ron, 2009). Manipulations that modulate the amount of GDNF in the brain decrease cocaine-induced conditioned place preference and reduce cocaine and ethanol self-administration in rats (Carnicella et al., 2008; Messer et al., 2000; Green-Sadan et al., 2003, 2005).

Thus, changes in the expression or function of GDNF may affect dopaminergic signaling, favoring the development of MAP-seeking behaviors.

MAP-induced psychosis and schizophrenia (the paranoid type in particular) show very similar symptoms (Sato et al., 1992), and genetic association between *GDNF* and schizophrenia have been repeatedly reported (Lee et al., 2001; Michelato et al., 2003). To the best of our knowledge, however, the association of *GDNF* with MAP dependence has not been investigated. Therefore, our current study aimed to examine the possible association of SNPs in *GDNF* with susceptibility for MAP dependence in Japanese population.

2. Materials and methods

2.1. Participants

This study was approved by the ethics committees of each institution of the Japanese Genetics Initiative for Drug Abuse (JGIDA) including the Nagoya University Graduate School of Medicine and Fujita Health University. All patients were unrelated to each other and were ethnically Japanese. Written informed consent was obtained from each patient.

A total of 219 patients with MAP dependence (178 males, 41 females and mean age ± standard deviation (S.D.), 37.1 ± 11.8 years) and 383 normal controls (160 males, 223 females and mean age ± S.D., 40.0 ± 14.6 years) were genotyped. Patients with MAP dependence were diagnosed according to the ICD-10-DCR criteria, with the consensus of at least two experienced psychiatrists on the basis of empirical diagnostic interviews and review of medical records. Along with the case–control comparison, associations of five clinical features of the patients with MAP dependence were also examined, including age of first use, latency of psychosis, multi-substance use, prognosis of psychosis, and spontaneous relapse of psychotic symptoms (Morita et al., 2005).

A total of 106 patients (48.4%) consumed MAP before the age of 20 years, and 109 patients (49.8%) first consumed MAP after they were 20 years old. The latency of psychosis was less than 3 years after the first MAP consumption in 95 patients (43.4%), and 3 or more years in 82 patients (37.4%). A total of 60 patients (27.4%) abused only MAP during their lifetime, and 152 patients (69.4%) abused drugs in addition to MAP in the past or present. A total of 107 patients (48.9%) were diagnosed as the transient type, and 81 patients (37.0%) were diagnosed as the prolonged type. The numbers of patients with and without a history of spontaneous relapse were 80 (36.5%) and 130 (59.4%), respectively.

2.2. Tagging SNP selection

GDNF is a trophic factor for dopaminergic neurons. The genomic structure of the *GDNF* locus covers a 24-kb interval at 5p12–p13.1. The locus contains three exons coding for a cDNA of 4.6 kb including large 5′- and 3′-UTRs (Grimm et al., 1998).

We first consulted the HapMap database (release #22/phase II; population: Japanese in Tokyo) to obtain SNPs throughout the entire coding region of *GDNF* as well as in the flanking regions 500 bp upstream and 500 bp downstream of the coding regions. Twenty-three SNPs were found in the HapMap Japanese sample.

The longest isoform was selected from the three alternately spliced isoforms of GDNF. We chose representative SNPs with the criteria of minor allele frequency (MAF) >0.10 and r^2>0.80, using Haploview version 3.32 software (http://www.broadinstitute.org/mpg/haploview) (Barrett et al., 2005), and defined these as tagging SNPs.

As a result, eight tagging SNPs were chosen. The gene structure of *GDNF* and the position of each SNP are shown in Fig. 1.

2.3. SNP genotyping

Genotyping of tagging SNPs was carried out using TaqMan assays (Applied Biosystems, Foster City, CA). TaqMan probes and Universal PCR Master Mix were obtained from Applied Biosystems. A 5-μl total reaction volume was used, and allelic-specific fluorescence was measured using the ABI PRISM 7900 Sequence Detector System (Applied Biosystems). Sequences of the individual primer pairs are available upon request. To exclude low-quality DNA samples or genotyping probes, data sets were filtered on the basis of tSNP genotype call rates (100% completeness) or deviation from the Hardy–Weinberg equilibrium (HWE) (P = 0.05) in the control sample. Participants whose percentage of missing genotypes was more than 10% or who had

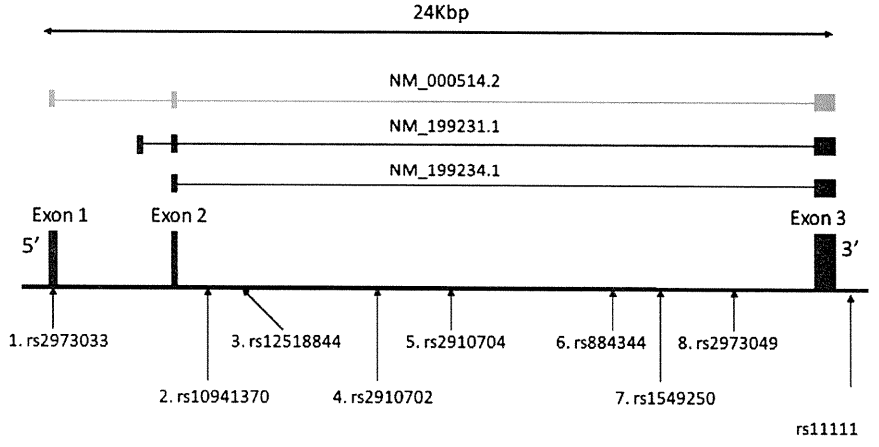

Fig. 1. Genomic structure of *GDNF* and the SNPs used in our association analysis. Vertical bars represent exons in *GDNF*, and the number under each arrow is the SNP ID.

Table 1
Association analysis of tagSNPs in *GDNF* with MAP dependence.

No.	SNP ID	M/m	Phenotype		N	Genotype			MAF	P-value		Global P-value
						M/M	M/m	m/m		Genotype	Allele	
1	rs2973033	A/G	MAP	Case	205	112	72	21	0.28	0.14	0.67	
	exon1			Control	381	202	155	24	0.27			
2	rs10941370	T/C	MAP	Case	204	78	94	32	0.39	0.82	0.79	
	intron2			Control	381	145	183	53	0.38			
3	rs12518844	G/A	MAP	Case	205	85	91	29	0.36	0.57	0.79	
	intron2			Control	381	154	183	44	0.36			
4	rs2910702	A/G	MAP	Case	206	85	101	20	0.34	0.55	0.93	
	intron2			Control	382	164	172	46	0.34			
5	rs2910704	G/C	MAP	Case	206	88	94	24	0.34	0.47	0.25	
	intron2			Control	381	143	190	48	0.38			0.46
6	rs884344	A/C	MAP	Case	205	128	69	8	0.21	0.40	0.18	
	intron2			Control	381	219	140	22	0.24			
7	rs1549250	G/T	MAP	Case	205	95	90	20	0.32	0.25	0.10	
	intron2			Control	381	198	158	25	0.27			
8	rs2973049	G/A	MAP	Case	205	51	111	43	0.48	0.24	0.96	
	intron2			Control	380	109	178	93	0.48			

M: major allele and m: minor allele.
MAF: minor allele frequency.

evidence of possible DNA contamination were excluded from the subsequent analyses. Finally, the clustering performance of the allelic discrimination assay was visually inspected for all SNPs.

2.4. Statistical analysis

Genotype deviation from HWE was evaluated with the χ^2-test. Genotypic association of SNPs that deviated from HWE was analyzed using Cochran–Armitage trend tests for the multiplicative model of inheritance (Balding, 2006). Genotypic and allelic associations were performed with SPSS version 14.0J (Tokyo, Japan) and Haploview software version 3.32, respectively. The significance level for all statistical tests was set at 0.05. Bonferroni's corrections were used for multiple comparisons; MAP P corrected = 0.05/48 [eight SNPs × two genetic analyses × three phenotypes (age of first use, multiple substance abuse and prognosis of psychosis)]. The linkage disequilibrium (LD) block was defined by Haploview 3.32. When the haplotype frequency in each block was over 5%, haplotypic analysis was performed with Unphased version 3.1.3 (Dudbridge, 2008), which was not a tagging SNP as defined by the Tagger program. Power calculations were performed using the genetic statistical package on a Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/) (Purcell et al., 2003).

3. Results

The genotypic and allelic frequencies of each SNP in patients with MAP dependence and normal controls are summarized in Table 1. The observed genotypic frequencies of all SNPs were within the distribution expected according to HWE. Neither the genotypic nor the allelic frequencies of the eight tagging SNPs for *GDNF* differed significantly between patients with MAP dependence and controls. As a result of LD analysis of 383 normal controls, one LD block was defined. The distribution of haplotypic frequencies at this block did not differ significantly between patients with MAP dependence and normal controls (global P value = 0.46). More than 80% power in detecting association was obtained when the prevalence of MAP dependence was set at 0.3% and the genotype relative risk was set at 1.40–1.45 under a multiplicative model of inheritance.

Next, we analyzed these cohorts based on the five clinical features of MAP dependence. First, a significant association was observed for rs2910704 (genotype, P = 0.01) between MAP-dependent patients whose age at first MAP consumption was younger than 20 years old and those who were older than 20 years at their first MAP consumption (Table 2). When patients with MAP dependence were divided into two subgroups of multi-substance and MAP-only users, a significant difference was observed between these two groups for the

Table 2
Genotype and allele frequencies of *GDNF* in the age of first use.

No.	SNP ID	M/m	Group	N	Genotype			MAF	P-value	
					M/M	M/m	m/m		Genotype	Allele
1	rs2973033	A/G	≧20 years	97	50	40	7	0.28	0.14	0.91
	exon1		<20 years	104	59	31	14	0.28		
2	rs10941370	T/C	≧20 years	97	41	42	14	0.36	0.65	0.44
	intron2		<20 years	103	37	50	16	0.40		
3	rs12518844	G/A	≧20 years	97	42	43	12	0.35	0.83	0.60
	intron2		<20 years	104	43	45	16	0.37		
4	rs2910702	A/G	≧20 years	97	39	49	9	0.35	0.91	0.96
	intron2		<20 years	105	44	50	11	0.34		
5	rs2910704	G/C	≧20 years	97	38	53	6	0.34	**0.01**	0.64
	intron2		<20 years	105	48	39	18	0.36		
6	rs884344	A/C	≧20 years	97	57	37	3	0.22	0.49	0.63
	intron2		<20 years	104	67	32	5	0.20		
7	rs1549250	G/T	≧20 years	97	45	43	9	0.31	0.90	0.97
	intron2		<20 years	104	50	43	11	0.31		
8	rs2973049	G/A	≧20 years	97	28	49	20	0.46	0.55	0.41
	intron2		<20 years	104	23	58	23	0.50		

Bold numbers represent significant P-values.
M: major allele and m: minor allele.
MAF: minor allele frequency.

Table 3
Association analysis of tagSNPs in *GDNF* in the multi substance use.

No.	SNP ID	M/m	Group	N	Genotype			MAF	P-value	
					M/M	M/m	m/m		Genotype	Allele
1	rs2973033	A/G	No	57	26	21	10	0.36	0.09	**0.03**
	exon1		Yes	141	82	48	11	0.25		
2	rs10941370	T/C	No	57	22	23	12	0.41	0.46	0.53
	intron2		Yes	140	54	66	20	0.38		
3	rs12518844	G/A	No	57	24	23	10	0.38	0.67	0.82
	intron2		Yes	141	57	65	19	0.37		
4	rs2910702	A/G	No	57	34	19	4	0.24	**0.007**	**0.01**
	intron2		Yes	142	50	77	15	0.38		
5	rs2910704	G/C	No	57	15	30	12	0.47	**0.003**	**0.0007**
	intron2		Yes	142	70	60	12	0.30		
6	rs884344	A/C	No	57	30	23	4	0.27	0.12	**0.04**
	intron2		Yes	141	94	43	4	0.18		
7	rs1549250	G/T	No	57	26	28	3	0.30	0.38	0.59
	intron2		Yes	141	65	60	16	0.33		
8	rs2973049	G/A	No	57	18	28	11	0.44	0.49	0.33
	intron2		Yes	141	33	77	31	0.49		

Bold numbers represent significant P-values.
M: major allele and m: minor allele.
MAF: minor allele frequency

tagging SNPs, rs2973033 (allele, P=0.03), rs2910702 (genotype, P=0.007 and allele, P=0.01), rs2910704 (genotype, P=0.003 and allele, P=0.0007), and rs884344 (allele, P=0.04) (Table 3). In addition, there was a significant difference between the transient type and the prolonged type for rs2973033 (allele, P=0.02) (Table 4). No significant differences were found in the latency of psychosis or spontaneous relapse of psychotic symptoms (data not shown). After Bonferroni's correction, three SNPs were no longer significant, but rs2910704 remained significant (allele, P=0.034) between multi-substance and MAP-only users (Table 3).

4. Discussion

Our results of the association analysis of MAP dependence suggest that *GDNF* may be related to the severity of MAP dependence in the Japanese population. There was no significant difference in the frequency of any of the tagging SNPs between MAP users and normal controls. However, when patients with MAP dependence were divided into two subgroups consisting of multi-substance and MAP-only users, a significant difference was observed between these two groups in the tagging SNP, rs2910704, even after Bonferroni's correction (allele, P=0.034). Multi-substance users in our study primarily used organic solvents and marijuana in addition to MAP, and the mechanism of action of these drugs is different from that of MAP (Aoyama et al., 2006). In our current study, we observed that the MAF of rs2910704 in MAP-only users (0.47) was higher than that of multi-substance users (0.30), and a similar trend was seen for the age of first use. In other words, rs2910704 may be associated with the severity of substance dependency, as we detected association with earlier age of onset (Table 2) and multiple substance abuse (Table 3). Interestingly, we found a significant association with this SNP that differed between MAP-only users and normal controls, suggesting the involvement of this SNP in MAP dependence. Further, this SNP was in strong LD with rs11111 ($r^2=1$), which is located 1.6 kb downstream of *GDNF* in the predicted 3′-UTR (ENCODE Gencode Manual Gene Annotations (level 1+2) (Feb., 2009)). The rs11111 SNP is associated with lower expression of *GDNF* in the brain but not in peripheral monoclonal blood cells as seen with SNPExpress (http://people.genome.duke.edu/~dg48/SNPExpress/) (Fig. 2, P=0.0026). Thus, patients with these SNPs may exhibit lower expression of *GDNF* and be more vulnerable to MAP abuse. This hypothesis is consistent with a report showing that reduction in the expression of GDNF potentiates MAP self-administration and enhances motivation for mice to take MAP (Yan et al., 2007).

Table 4
Genotype and allele frequencies of *GDNF* in the prognosis of psychosis.

No.	SNP ID	M/m	Group	N	Genotype			MAF	P value	
					M/M	M/m	m/m		Genotype	Allele
1	rs2973033	A/G	Transient	100	61	30	9	0.24	0.08	**0.02**
	exon1		Prolonged	75	33	31	11	0.35		
2	rs10941370	T/C	Transient	99	36	47	16	0.40	0.67	0.38
	intron2		Prolonged	75	31	35	9	0.35		
3	rs12518844	G/A	Transient	100	42	42	16	0.37	0.43	0.40
	intron2		Prolonged	75	33	35	7	0.33		
4	rs2910702	A/G	Transient	101	40	48	13	0.37	0.12	0.30
	intron2		Prolonged	75	31	41	3	0.31		
5	rs2910704	G/C	Transient	101	50	40	11	0.31	0.10	0.052
	intron2		Prolonged	75	25	39	11	0.41		
6	rs884344	A/C	Transient	100	66	31	3	0.19	0.37	0.16
	intron2		Prolonged	75	42	29	4	0.25		
7	rs1549250	G/T	Transient	100	47	39	14	0.34	0.17	0.27
	intron2		Prolonged	75	37	34	4	0.28		
8	rs2973049	G/A	Transient	100	26	50	24	0.49	0.39	0.76
	intron2		Prolonged	75	17	45	13	0.47		

Bold numbers represent significant P-values.
M: major allele and m: minor allele.
MAF: minor allele frequency.

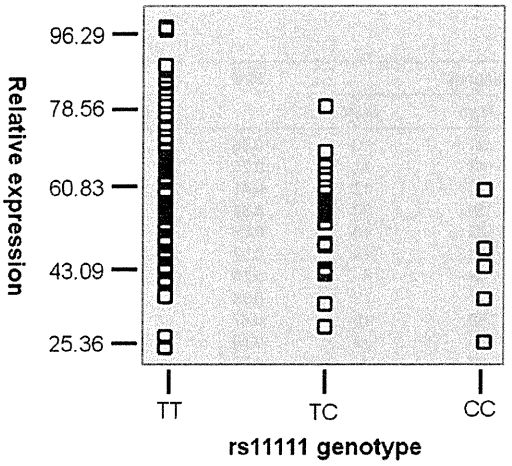

Fig. 2. Relationship between *GDNF* expression in the frontal cortex of human brain and the rs11111 genotype.

In addition, other associated SNPs were in strong LD with rs2910704, and reduced expression of *GDNF* may therefore be implicated in the prognosis of MAP use disorder. Recently, Boger et al. (2007) suggested that long-term consequences of MAP exposure in mice are exacerbated in GDNF heterozygous mice, which may explain the significant association of these SNPs with age of onset or prognosis of MAP use disorder. This group also found elevated dopamine transporter (DAT) activity in GDNF heterozygous mice, suggesting that examination of DAT binding in our patients may be of interest.

Our results had several limitations in terms of interpreting positive associations. A potential concern was population admixture, which is a known confounding factor for association. The Japanese population has rather low genetic diversity (Haga et al., 2002). However, even in such a genetically homogeneous population, a small amount of stratification may produce a spurious genetic association signal (Yamaguchi-Kabata et al., 2008). Another potential concern is the relatively small sample size and that the gender ratio in the MAP group was not replicated in the control group. This type of discrepancy may introduce a gender-specific effect that could have resulted in inflated p values. Thus, larger numbers of gender-matched samples and genomic controls are required.

5. Conclusion

We suggest that *GDNF* may be related to the severity of MAP use. Further studies using independent replication will be required to clarify the relationship between *GDNF* and MAP use disorder.

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〔特集：認知機能障害に対する治療をどう評価するか〕

シンポジウム特集「認知機能障害に対する治療をどう評価するか」

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統合失調症は陽性・陰性症状とともに記憶，遂行機能，注意，語流暢性など認知機能領域の障害を伴う．この認知機能障害は，精神病初回エピソードや顕在発症前の時点ですでに認められ，発症後も安定して存在することが知られている．また，認知機能障害は，社会適応や就労状況といった機能的転帰に影響し，長期的予後の予測因子にもなっている．以上から，認知機能障害は，統合失調症の中核症状の1つとして捉えられ，認知機能改善に向けた治療法の開発が望まれている．米国では，認知機能障害の治療法の開発を妨げていた認知機能評価尺度のばらつきを解消するため，信頼性・妥当性を有した包括的認知機能評価尺度であるMATRICSコンセンサス認知機能評価バッテリー（MCCB）を用いることが可能になった．本邦でも諸外国と比較可能なMCCB日本語版（MCCB-J）を用いることにより，統合失調症の認知機能障害に対する治療を包括的に評価できるようになった．

新潟リハビリテーション大学の佐藤　拓先生は東北大学を中心として開発を行ってきたMCCB-J下位検査のうち，本シンポジウムでは文化的・言語的な影響を受けやすいと予測されたマイヤー・サロヴェイ・カルーソー感情知能テスト：感情の管理（MSCEIT ME）と言語的ワーキングメモリを測定する語音声列課題（LNS）について紹介した．社会認知を測定するマイヤー・サロヴェイ・カルーソー感情知能テスト：感情の管理（MSCEIT ME）は統合失調症患者および健常者を対象にした解析を行い，MSCEIT MEの妥当性・信頼性の検討を個別に行った．さらに，MCCB-J全体の有効性を検討するため，統合失調症患者と健常者の認知機能の比較を行った結果を報告した．

統合失調症など精神疾患の認知機能障害に対する心理的手法として認知矯正療法があり，複数の手法が存在するが，鳥取大学の最上多美子先生はMedaliaらが開発したNeurocognitive and Educational Approach to Remediation（NEAR）が認知機能障害の改善に一定の効果を示すことを紹介された．本シンポジウムでは認知矯正療法は訓練法の違い，訓練スキルの違い，媒体の違い，標的認知機能の違い，治療者の役割の違い，標的領域の違いなどにより異なり，RCT研究で治療効果が示されている認知矯正療法の手法と効果について解説された．さらに認知矯正療法の効果に影響を与える要因としては，推奨された治療頻度の確保の重要性や戦略訓練が反復訓練に対して有効であることを示された．

認知機能の変化に加え，認知機能の評価尺度以上の表面的妥当性を持ち，機能的に意味があるco-primaryな評価尺度の必要性が指摘されている．岩城クリニックの兼田康宏先生は，日常生活機能と直接関連する認知機能障害の程度を評価する目的で開発された統合失調症認知評価尺度（Schizophrenia Cognition Rating Scale, SCoRS）の日本語版を作成された．SCoRSはUniversity of California at San Diego Performance-Based Skills Assessment（UPSA）とともに米国MATRICSアウトカム委員会により機能的に意味があるco-primaryな評価尺度の候補として推薦されている．本シンポジウムでは認知機能との相関が強いUPSAと，面接に基づく認知機能評価尺度でより認容性/実用性に優れていたSCoRSについて紹介された．

認知機能の障害の度合いは，心理社会的介入などの治療による就労への可能性や地域社会への適応度を予測し，患者の長期入院の必要性や就労の可否などの機能的転帰（community functioning measures）と強く関連することが知られている．福島大学の住吉チカ先生はMCCB-Jの開発に伴い，社会生活機能を測る方法として日本語版Modified SFS/SAS（MATRICS-PASS用）を作成された．日本語版Modified SFS/SASは，日本語版SFS（根本，2008）に沿いつつ，頻度・程度項目については英語版Modified SFS/SAS同様，アンカーポイントを設け，また基本的に自己記入式でも行えるよう作成された．本シンポジウムでは，機能的転帰の概念，評価方法，および各国への移植における問題について紹介された．

統合失調症患者の認知機能障害の特徴，機能的転機に深く関与するco-primaryの評価，社会生活機能の3つの関連性を明らかにし，社会参加・就労の維持を目指した統合失調症患者へのより有効な治療・介入方法へつなげることが期待される．

〔特集：認知機能障害に対する治療をどう評価するか〕

MATRICSコンセンサス認知機能評価バッテリー日本語版の開発への取り組み*

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要約：統合失調症の認知機能障害は，就労への可能性やコミュニティへの適応度，長期入院の必要性などの機能的転帰を左右するとされ，認知機能改善に向けた治療が重視されている．米国では，国立精神保健研究所（NIMH）主導のもと，7つの認知機能領域（処理速度，注意/覚醒，ワーキングメモリ，言語学習，視覚学習，推論と問題解決，社会認知）を測定するMATRICSコンセンサス認知機能評価バッテリー（MCCB）が開発された．MCCBの下位テストは，再テスト信頼性，繰り返し用いる評価尺度としての有用性，機能的転帰との関連性，および忍容性と実用性に優れたものから選定された実証的証拠のあるテストであった．MCCBは認知機能障害の改善薬の評価法の1つとして米国食品医薬品局（FDA）に承認され，統合失調症の認知機能改善薬の治験における標準的な評価法として推奨されている．本邦へのMCCB導入は，アカデミックバージョンの日本語版の開発から始められた．本稿では，米国で開発されたMCCBについて概説した上で，研究用に開発されたMCCB日本語版の下位テストに関するパイロット研究の紹介を行った．

キーワード：MATRICSコンセンサス認知機能評価バッテリー（MCCB），認知機能，日本語版，統合失調症

認知機能障害は統合失調症の中核症状の1つであり，多くの研究において機能的アウトカムとの関連が指摘されている（Green, 1996; Green et al, 2000, 2004a）．そのため，認知機能障害は精神薬理学における重要な治療ターゲットとしてみなされており（Marder and Fenton, 2004），認知機能障害の改善に関する研究が盛んに行われている．

認知機能の改善を目指した薬物，もしくは心理社会的介入法の開発には，科学的なコンセンサスのとれた認知機能評価バッテリーを開発することが必須である．これまで，認知機能の評価には，認知の各領域を評価する検査を目的に応じて組み合わせた神経心理学的テストバッテリー（NTB）が用いられていたが，NTBは使用する研究者や施設間でのばらつきが大きく，得られた結果の比較が困難になっていた（兼田，2009）．そのような現状を踏まえて，米国では国立精神保健研究所（NIMH）が中心となり，米食品医薬品局（FDA），学界，製薬企業と共同でMeasurement and Treatment Research to Improve Cognition in Schizophrenia（MATRICS）と呼ばれるプロジェクトが企画された（Marder and Fenton, 2004）．このプロジェクトでは，統合失調症患者の認知機能改善薬の治験には不可欠な，科学的なコンセンサスを反映したNTB（MATRICSコンセンサス認知機能評価バッテリー；MCCB）の開発が行われた．

本稿では，まず米国で開発されたMCCBについて概説した後，研究用に開発されたMCCB日本語版に関するパイロット研究について紹介する．

MATRICSコンセンサス認知機能評価バッテリー（MCCB）

MCCBは，統合失調症で障害される認知機能領域を簡潔に評価するために開発されたNTBである（Nuechterlein and Green, 2006）．MCCBに採用されたテストのほとんどは，従来から統合失調症の認知機能の測定に用いられているものであったが，下記のプロセスを経て選択および標準化された（Green et al, 2004b; Nuechterlein and Green, 2006）．

まず第1に，MCCBで評価される認知機能領域が決定された．MATRICS神経認知委員会の小委員会が統合失調症と関連する精神疾患を対象とした研究のレビューを行い，そのレビューから7つの認知機能領域が同定された（Nuechterlein et al, 2004）．そのうちの1つである「言語理解」は，統合失調症においては障害が顕著ではないためにバッテリーから除かれ，残りの6つの領域が小委員会によって推薦された．この6つの領域に，近年，統合失調症の認知機能障害の領域として注目されている「社会認知」が加えられ（Kern et al, 2007），MCCBでは「処理速度」，「注意/覚醒」，「ワーキングメモリ」，「言語学習」，「視覚学習」，「推論と問題解決」，「社会認知」の7つの領域を評価することになった（Nuechterlein and Green, 2006）．

次に，7つの認知機能領域を評価する個々のテストを選択するための基準が決定された（Green et al, 2004b）．選択基準には（1）再テスト信頼性，（2）繰り返し用いる評価尺度としての有用性，（3）機能的アウトカムとの関連性，（4）薬物治療に対する反応性，（5）忍容性と実用性が含め

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られていたが，専門家が最も重視していた基準は再テスト信頼性であった（Kern et al, 2004）．上記の選択基準を満たす認知機能テストを選抜するために90以上のテストが推薦されたが，MATRICS 神経認知委員会は認知機能領域ごとにテストを絞り，20のテストによって構成されるβバッテリーを作成した（Nuechterlein and Green, 2006）．

このβバッテリーから最終的なテストバッテリーを決定するため，176人の統合失調症患者を対象としたMATRICS心理測定・標準化研究（MATRICS Psychometric and Standardization Study; MATRICS-PASS）が実施された（Nuechterlein et al, 2008）．この研究で得られた結果と前述の選抜基準を鑑み，最終的なテストバッテリーに含めるテストが決定された．次に，MATRICS-PASSの第2段階として，採用されたテストがコミュニティから募った健常者300人に実施され，共通の規準データの収集が行われた（Kern et al, 2008）．

上記のプロセスを経て開発されたMCCBは，7つの認知機能領域を測定する10のテストで構成されている．個々のテストの詳細については，Nuechterlein and Green (2006) によるMCCBのマニュアルを参照されたい．MCCBの実施にかかる所要時間は約65分で（Nuechterlein et al, 2008），個々のテストのT-scoreだけでなく，7つの認知機能領域と総合的な認知機能のT-scoreを算出することができる．MCCBは認知機能障害の改善薬の評価法の1つとしてFDAに承認され，統合失調症の認知機能改善薬の治験における標準的な評価法として推奨されている（Nuechterlein and Green, 2006）．

MCCB日本語版の開発とパイロット研究

MCCBはもともと英語版のみが利用可能であったが，現在は中国語，ドイツ語，ヒンディ語，ロシア語，スペイン語などに翻訳されている．本邦では曽良と兼田が中心となり，MATRICS Assessment, Inc.と各テストの原著者の許可を得た上でMCCB（アカデミックバージョン）の日本語への翻訳が行われた（兼田・曽良，2009；佐藤ら，2010）．日本語版の開発にあたっては，ワーキングメモリの領域を測定する語音整列課題（Gold et al, 1997）には言語的調整が必要であった．また，社会認知の領域を測定するMayer-Salovey-Caruso情動知能テスト：感情の管理（Mayer et al, 2002）に関しては，得点化のための規準データが米国を中心とした欧米圏で集められているため，得点化に日本人の規準データを用いても原版と同様の結果が得られるかどうかを検討する必要があった．以下では，両テストについての概説，およびパイロット研究の紹介を行う．

1. 語音整列課題

語音整列課題（Letter-Number Span; LNS）は，数字および文字を昇順に並べ替える（例：「J-5-T-2」→「2-5-J-T」）課題である（Gold et al, 1997）．この課題の文字にはアルファベットが用いられていたため，日本語版では文字を日本人にとってなじみ深い五十音に変更する必要があった．住吉ら（2009）は，原版と文字・数字操作の課題負荷が同質になるように，また日本語における数字と五十音の発音，および五十音表の特性を考慮して日本語版を作成した．住吉らは統合失調症患者および健常者に，作成した日本語版とアルファベット版を同時に実施し，両課題の等価性を確認している．

2. Mayer-Salovey-Caruso情動知能テスト：感情の管理

Mayer-Salovey-Caruso情動知能テスト（MSCEIT）は，Mayer et al（2002）が情動知能（Emotional Intelligence; EI）の個人差を測定するために開発した能力モデルの尺度である．MSCEITには情動知能に関する4つの下位尺度があるが，統合失調症患者を対象としたMATRICS-PASSでは，部門1：感情の知覚（Perceiving Emotions; PE）と部門4：感情の管理（Managing Emotions; ME）がβバッテリーに含められた（Nuechterlein and Green, 2006; Nuechterlein et al, 2008）．MATRICS-PASS研究においてPEよりMEの方が機能的アウトカムと関連が強いことから，最終的なバッテリーにはMEが採択された（Nuechterlein and Green, 2006; Nuechterlein et al, 2008）．

MSCEIT MEは，セクションDとHの2つの課題から構成されている（Mayer et al, 2002）．セクションDでは，自己の感情を意思決定に組み込む能力を測定する．この課題では，感情を制御しなければならない状況下で，ある結果を得るために選択肢の行動がどの程度有効であるかを回答者に評価させる．セクションHでは，他者が関わる意思決定に感情を組み込む能力を測定する．この課題では，他者が関わる状況において，ある結果を得るためにはどの行動が効果的であるかを回答者に評価させる．どちらの課題も回答者にシナリオを提示して，そのシナリオの状況下で，ある行動がどの程度効果的であるかを評価させる課題である．

上記の課題で得られた回答を採点する方法として，2つの採点方法がある（Mayer et al, 2002）．1つ目は一般的コンセンサスによる採点方法であり，各項目への反応を採点するために，規準データにおける回答分布を利用する．この方法では，ある項目に対して規準となるサンプルの70%がAを選択していたら，Aの反応に対して.70の得点が与えられる．もしBを20%が選択していたら，Bへの反応は.20の得点が与えられる．もう1つは専門家のコンセンサスによる採点方法であり，規準データの代わりに21名の感情研究の専門家のサンプルのデータを用いる．MCCBでは2つの採点方法のうち，一般的コンセンサスによる方法が採用されている（Nuechterlein and Green, 2006）．

Mayer et al (2002) の原版では，5,000 人のデータを米国の人口分布に合わせて重みづけた規準データを用いている．このデータを用いて日本語版の得点化を行うことも可能であるが，同質な集団の規準データを用いる方が文化的な交絡を最小化することができる (Roberts et al, 2006)．そのため，オーストラリア人の規準データによって得点化した Roberts et al (2006) と同様，我々は得点化に本邦の規準データを用いることにした．

佐藤ら (2009) は MSCEIT 日本語版のパイロット研究として，大学生を対象者に規準データの収集を行った．284 名の回答を基準データとして，各参加者の得点を一般的コンセンサスによる採点方法で算出したところ，その平均値 (M=.32, SD=.04) は原版 (Mayer et al, 2002) の平均値 (M=.45, SD=.08) と比べると低かった．つまり，本邦の大学生のデータでは，原版に比べると大多数の回答が 1 つの選択肢に収束しなかったと考えられる．ただし，ここで得られた平均値は，スペイン語版を作成した Extremera et al (2006) の平均値 (M=.33, SD=.09) と同程度であることを付記しておく．

次に MSCEIT ME の得点の性差を検討したところ，男性の得点 (M=.31, SD=.04) より女性 (M=.33, SD=.03) の得点が高かった (t=4.67, p<.001, Cohen's d=0.56)．この結果は，原版の Mayer et al (2002) の結果，およびスペイン語版を検討した Extremera et al (2006) の結果と一致している．

また，上記のデータのうち 128 名は，5 因子パーソナリティ検査である NEO-FFI 日本語版 (下仲ら，1999) を同時に評定していた．MSCEIT ME の得点と NEO-FFI の下位尺度の相関係数を算出したところ，調和性とのみ有意な正の相関が確認された (r=.23, p<.01)．調和性は利他性・共感性に関連するパーソナリティ傾向であるため，5 因子の中で調和性との相関が最も強い結果は予測通りと言えた．ただし，その相関係数の絶対値は小さく，Mayer et al (2004) のレビューで示された結果とほぼ同値であった (表)．Mayer et al (2004) はこの結果から，MSCEIT はパーソナリティと別個の概念を測定していると主張している．本邦でも 5 因子パーソナリティ傾向との相関係数が低いことから，日本語版もパーソナリティとは別個の概念を測定していると考えられる．

さらに，Sato et al (2010) は，統合失調症患者 20 名と健常者 10 名を対象に，前述の規準データで重みづけた MSCEIT ME 得点の比較を行った (図)．その結果，統合失調症患者の得点 (M=.29, SD=.03) は健常者の得点 (M=.33, SD=.04) に比べて低いことが確認された (t=−2.65, p<.05, Cohen's d=1.02)．この結果は，原版の MSCEIT ME を用いて統合失調症の社会認知を検討した研究 (Kee et al, 2009; Eack et al, 2010) に合致するものであった．

以上のように，パイロット研究では原版を用いた先行研究に合致する結果が得られている．ただし，これらの研究で用いられた規準データは大学生のサンプルで構成されている．一般的コンセンサスを利用した MSCEIT ME の得点は，規準データの質によって直接的に左右されるため，本邦でも大規模な規準データを収集したうえで，統合失調症患者を対象とした MSCEIT ME の再テスト信頼性，および機能的アウトカムと関連性を検討する必要がある．

おわりに

本稿では，米国で開発された MCCB の概説，および研究用に開発された MCCB 日本語版のパイロット研究の紹介を行った．紹介したパイロット研究は個々のテスト (LNS および MSCEIT ME) についての検討であったが，曽良を中心とする研究グループでは研究用の MCCB を用いて統合失調症患者および健常者のデータを集積し，日本語版の信頼性，妥当性，および機能的アウトカムとの関連性の検討を進めている．また，(財)精神・神経科学振興財団の主導で MCCB 日本語版の標準化研究も 2009 年にスタートしている．これらの研究をもとに最終的な MCCB 日本語版が完成すれば，本邦での認知機能の改善を目指した薬

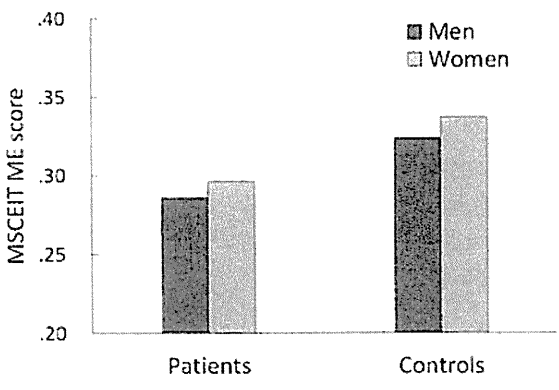

図 統合失調症患者と健常者の MSCEIT ME 得点の比較 (Sato et al, 2010 より)．

表 MSCEIT ME 得点と 5 因子パーソナリティ傾向の相関

	神経症傾向	外向性	開放性	調和性	誠実性
佐藤ら (2009)	.01	.08	.15	.23**	−.03
Mayer et al (2004)	−.07**	.11***	.15***	.24***	.13***

注) Mayer et al (2004) の相関係数は，MSCEIT および MEIS と 5 因子パーソナリティ傾向との相関を報告した 5 つの研究 (N=1,584) で得られた相関係数を重みづけた平均値である．**p<.01, ***p<.005

物や心理社会的介入法の開発がより一層促進されるであろう．

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Abstract: Taku SATO[*1] and Ichiro SORA[*2] ([*1] Faculty of Allied Health Science, Niigata University of Rehabilitation, 2-16 Kamino-Yama, Murakami, 958-0053 Japan; [*2] Department of Biological Psychiatry, Tohoku University Graduate School of Medicine) *Approaches to the development of the Japanese academic version of the MATRICS Consensus Cognitive Battery.* Jpn. J. Neuropsychopharmacol., 31: 241-244 (2011).

Cognitive impairment is related to functional outcome (e.g., work skills and community activities) in patients with schizophrenia; therefore, many researchers view these impairments as important treatment targets for psychopharmacological treatment. To stimulate the development of new treatments for cognitive impairments, the US National Institute of Mental Health's (NIMH's) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative developed a standard cognitive battery, i.e., the MATRICS Consensus Cognitive Battery (MCCB). In Japan, the MCCB has been initially translated as an academic version. This paper describes the process of developing the Japanese academic version and focuses on pilot studies on subtests of this battery.

Key words: MATRICS Consensus Cognitive Battery (MCCB), Cognitive function, Japanese version, Schizophrenia

(Reprint requests should be sent to T. Sato)

REVIEW

Quality of life and its predictors in people with schizophrenia

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Abstract : The author reviewed measurement of quality of life (QOL) of schizophrenia patients and the clinical factors related to their QOL. As schizophrenia patients were thought to be unable to assess their own QOL because of their cognitive impairment, objective QOL measures had been frequently used. However, nowadays, there is general agreement that symptomatically stabilized patients could assess their QOL by themselves. Therefore, researchers gradually have become interested in subjective QOL measure. Although most researchers often evaluate schizophrenia patients' QOL using only subjective or objective QOL measure, considering the fact that there is a discrepancy between the two types of measures, it is recommended to use both of them as complementary measures. As for clinical factors related to lowered QOL, several studies reported that depressive symptom was most associated with lowered subjective QOL, negative symptom was strongly related to lowered objective one and poor life skill was associated with both. Moreover, several studies found that cognitive dysfunctions in some cognitive domains were related to lowered objective QOL but the effects of them were much smaller than those of negative symptoms. It is suggested that improving depressive and negative symptoms and life skills may contribute to enhancement of QOL of schizophrenia patients. J. Med. Invest. 58 : 167-174, August, 2011

Keywords **:** *schizophrenia, quality of life, life skill, cognitive function*

INTRODUCTION

Schizophrenia is a disease that can devastate the lives of people who suffer from it, and people with it suffer distress, disability, reduced productivity, and lowered quality of life (QOL). Over the past two decades, the concept of QOL has become an important attribute in patient care and research in psychiatry area (1-3).

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Although there seems to be no unanimous definition of QOL at the moment, there is general agreement that QOL consists of access to resources and opportunities, fulfillment of life's roles, level of functioning and a sense of well being or life satisfaction (4, 5). As QOL is today regarded one of the most important outcome measures, it is important to clarify the clinical factors associated with lowered QOL. Doing so can lead to more sophisticated treatment strategies.

In this article, the author reviewed some existing articles on measurement of QOL of schizophrenia patients and clinical factors associated with QOL.

MEASUREMENT OF QUALITY OF LIFE

Recently, there has been increasing interest in QOL of people with schizophrenia, and now, QOL measures are included routinely in most studies of intervention or outcome (5, 6). However, not a few problems have been identified with the implement of the instruments. Such problems include the definition of the concept of QOL and the approach for measurement of it. Although there is no unanimous definition of QOL, the World Health Organization defines QOL as individuals' perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (7).

QOL of people with schizophrenia has been measured from two different viewpoints. One is a self-rated measurement of QOL (subjective QOL) and the other is an interviewer-rated measurement of QOL (objective QOL). Although, according the definition by the World Health Organization, individuals' perception of QOL seems to be vital, QOL of schizophrenia patients had been frequently assessed with objective QOL measures. Because of schizophrenia patients' cognitive impairment, they had been thought to be unable to evaluate their own QOL by themselves. However, nowadays, there is general agreement that stabilized schizophrenia patients could assess their QOL by themselves (8).

Objective measures of QOL usually include indicators of health and living conditions, sociodemographic items and role functioning in society, whereas subjective measures of QOL do indicators of life satisfaction in general and within different life domains (5). For example, the Quality of Life Scale (QLS) (9), one of the most frequently used objective QOL measures, was specifically constructed to measure QOL of people with schizophrenia. The QLS is a 21-item scale from a semistructured interview providing information on symptoms and functioning during the preceding 4 weeks. The QLS has four subscales, Intrapsychic foundations, Interpersonal relations, Instrumental role, and Common objects and activities. Intrapsychic foundations subscale items elicit judgments about intrapsychic elements in the dimensions of cognition, conation, and affectivity seen as near the core deficit of schizophrenia. Interpersonal relations subscale relates to various aspects of interpersonal and social experience. Instrumental role subscale focuses on the role of worker, student, or housekeeper/parent. Common objects and activities subscale is based on the assumption that a robust participation in the community is reflected in the possession of common objects and the engagement in regular activities (9).

As for subjective QOL instruments, although not a few subjective QOL instruments exist to assess health-related QOL, it is said that they can sometimes overlook the QOL concerns of specific patients groups. Recently, Wilkioson *et al.* (10) constructed schizophrenia disease specific subjective QOL instrument that is called the Schizophrenia Quality of Life Scale (SQLS). The SQLS consists of three scales that are Psychosocial, Motivation and energy, and Symptoms and side-effect. Lower scores indicate higher QOL. The Japanese version of it is often used in studies in Japan (11).

RELATION BEWEEN SUBJECTIVE AND OBJECTIVE QUALITY OF LIFE MEASURES

Researchers have been paying attention to the relation between subjective and objective QOL measures. Although many studies used only one of them, if they reflect different aspects of QOL and have different predictors, doing so is likely to introduce bias in the results. However, there are only a few studies investigating the relation between them.

Using the Quality of Life Interview which contains subjective and objective measures, Dickerson *et al.* (12) studied 72 outpatients with schizophrenia and demonstrated that there were few significant correlations between subjective and objective QOL indicators of specific life areas. Fitzgerald *et al.* (5) found that life satisfaction and objectively rated QOL are not closely related, and concluded that subjective and objective QOL had different determinants in patients with schizophrenia.

To explore the relationship between subjective and objective QOL measures, we conducted a strict research using schizophrenia disease specific subjective and objective QOL measures (13). In the cross-sectional study, 99 symptomatically stabilized outpatients with a DSM-IV diagnosis of schizophrenia were assessed with the SQLS (10, 11) and the QLS (9). The correlations between the scores on scales of the SQLS and the QLS total and subscales in the study are shown in Table 1. The score of the Motivation and energy scale correlated significantly with the QLS total score, Interpersonal relations, Instrumental role, Intrapsychic foundations, and Common Objects and activities subscales. Moreover, the score of the Psychosocial scale showed a

Table 1 Correlation between Schizophrenia Quality of Life Scale and Quality of Life Scale (N=99) (from Ref.13 Tomotake M, *et al.* Psychol Rep 99, 477-487, 2006)

		SQLS		
		Psychosocial	Motivation and energy	Symptoms and side-effects
QLS	Total	-.20 *	-.40 ***	-.16
	Interpersonal relations	-.19	-.42 ***	-.16
	Instrumental role	-.19	-.28 **	-.14
	Intrapsychic foundations	-.19	-.39 ***	-.14
	Common objects and activities	-.10	-.25 *	-.14

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
SQLS=Schizophrenia Quality of Life Scale, QLS=Quality of Life Scale.

significant but weak correlation with the QLS total score. The score of the Symptoms and side-effects scale did not correlate significantly with the QLS scores.

Considering these results indicating that there were only a few significant correlations between the SQLS and the QLS scores, researchers should use both of subjective and objective QOL measures as complementary outcome measures in order to avoid introducing bias.

RELATION BETWEEN CLINICAL SYMPTOMS AND QUALITY OF LIFE

As for the clinical symptoms associated with subjective QOL, Dickerson *et al.* (1998) found that schizophrenia patients' subjective QOL measured by the Quality of Life Interview was significantly related to the depression factor in the Positive and Negative Syndrome Scale (PANSS). Huppert *et al.* (14) also found that more severe depression as rated on the Brief Psychiatric Rating Scale (BPRS) was associated with lower subjective QOL measured by the Quality of Life Interview. Other similar studies support the significant association of depressive symptom with subjective QOL (5, 15). As for subjective well-being which is the main component of subjective QOL, Norman *et al.* (16) reported that the General Well-Being Scale score was significantly related to positive symptom, particularly reality distortion. These results suggest that depressive and positive symptoms may be important factors influencing schizophrenia patients' subjective QOL. Moreover, other clinical factors such as anxiety, extrapyramidal adverse effects, and patients' subjective responses and attitudes towards antipsychotic treatment have been found to be significantly associated with subjective QOL (1, 14, 15).

Clinical factors related to objective QOL also have been investigated, and several research groups reported that negative symptom was much more closely related to objective QOL than was positive symptom (5, 16). As the studies used the QLS which was originally designed to assess deficit symptoms of schizophrenia, it may stand to reason that fewer negative symptoms were associated with better QOL assessed by the QLS. However, some studies showed the significant associations of positive symptom and other clinical factors with the QLS (17-20).

We investigated the relationship between several clinical factors (duration of illness, number of hospitalization, dose of neuroleptics, positive symptom, negative symptom, extrapyramidal symptom, and depressive symptom) and QOL in outpatients with schizophrenia (13). The results of stepwise regression analyses on the SQLS and the QLS in the study are shown in Table 2. Psychosocial scale score was predicted independently by the Calgary Depression Scale for Schizophrenia (CDSS) score, the BPRS positive symptoms score, dose of neuroleptics, and the BPRS negative symptoms score. The CDSS score contributed significantly to the prediction of the Motivation and energy scale score. Symptoms and side-effects scale score was predicted independently by the BPRS positive symptoms score, the CDSS score, and dose of neuroleptics. The QLS total score was predicted independently by the BPRS negative symptoms score and the BPRS positive symptoms score. The BPRS negative symptoms score and duration of illness contributed independently to the prediction of the Interpersonal relations subscale. Instrumental role subscale was predicted independently by the BPRS negative symptoms score and the BPRS positive symptoms score. The Intrapsychic foundations subscale was also predicted by the BPRS negative symptoms score and the