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Research Article

Association Study of Dopamine β-Hydroxylase Gene with Methamphetamine Psychosis

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Abstract Dopamine is a key molecule in the pathophysiology of methamphetamine (METH) psychosis. We examined the association between METH psychosis and the dopamine β-hydroxylase (*DBH*) gene, which modulates dopaminergic cascades. Six polymorphisms, rs1989787, rs1611115, rs1108580, rs5320, rs1611125, and rs6271, of the *DBH* gene were genotyped. These polymorphisms were not associated with METH-seeking behaviors of patients with METH psychosis ($N = 216$) or healthy controls ($N = 328$), but rs1611125 affected one of the clinical phenotypes of METH psychosis. Individuals with the G/G homozygote of rs1611125 had a significant risk for spontaneous relapse of METH psychosis ($P = .02$, odds ratio $= 2.2$). In haplotype analyses, rs1108580-rs5320-rs1611125 was revealed to be associated with METH psychosis ($P = .01$). Having G-Ala-G was a significant risk factor, while A-Thr-A was a protective factor for METH psychosis (odds ratio were 9.9 and 0.16, resp.). Our present findings indicated that the *DBH* gene may play an important role in METH psychosis.

Keywords substance abuse; methamphetamine; dopamine β-hydroxylase; case-control association

1. Introduction

Illicit drug use is a serious health and social concern worldwide. The development of substance abuse and dependence is influenced by multiple factors, including pharmacological effects on mental status, as well as environmental and individual factors.

Among them, genetic factors were demonstrated to have large effects on substance dependence by family, twin, and adoption studies, and the heritability of substance abuse and dependence was estimated to be relatively high for psychostimulants such as amphetamines compared with sedatives and opiates [23]. In Japan, methamphetamine (METH), a member of the amphetamine family, continues to be the most widely abused illegal drug. The consumption of large amounts of METH for long periods easily produces psychotic symptoms, including ideas of reference, delusion of persecution, and visual and auditory hallucinations and delusions [17, 22]. Further consumption of METH may result in severe psychosis, liability to spontaneous relapse with reconsumption of METH or psychological stress, a gradually worsening prognosis. These psychotomimetic effects of METH consumption differ among individuals and the differences may be affected by individual genetic backgrounds [22]. Numerous studies have implicated dysfunction of central dopaminergic neurotransmission in the neurobiological mechanisms underlying METH psychosis. Sato et al. [17] revealed that chronic administration of METH induced a lasting change in the brain dopaminergic system using animal models. In humans, neuroimaging studies have repeatedly revealed that enhanced dopaminergic transmission is potential underlying pathophysiology of METH psychosis [18, 19].

Dopamine β-hydroxylase (DBH) catalyzes the conversion of dopamine to norepinephrine and is important in regulating the ratio of the neurotransmitters, dopamine, and norepinephrine [20]. DBH activity is measurable in serum or plasma, and while it is characterized by wide

individual variation [24], it does not change after physical activity [7]. Family and twin studies have demonstrated that plasma DBH activity is a highly heritable trait and that heredity accounts for over $\sim 90\%$ of human plasma DBH activity variation or $\sim 80\%$ of DBH activity variation [15]. The gene encoding DBH is located on chromosome 9q34, and is composed of 12 exons with a length of approximately 23 kb [9]. Several polymorphisms, including rs1989787 (-2073C/T) [2], rs161115 (-970C/T; previously called -1021C/T) [1,10,28], rs1108580 (444$*$G/A) [5], rs1611125 (IVS4+601T/C) [28], and rs6271 (1603C/T) [21, 28], were found to have significant correlations with DBH activity and levels in plasma and cerebrospinal fluid. Numerous studies have implicated low DBH activity as a risk factor for psychotic symptoms in several psychiatric disorders, such as schizophrenia, psychotic depression, and substance-induced psychosis [3,4,8,12,13,14,16,26,27]. In addition, rs5320 (Ala211Thr), a non-synonymous variant of the *DBH* gene, has recently been revealed to influence nicotine dependence in a Japanese population [6].

Based on the above rationale, we hypothesized that variants of the *DBH* gene would be related to development of METH psychosis. We therefore undertook the present study to evaluate the association between the *DBH* gene and METH psychosis in a Japanese population.

2. Methods

2.1. Subjects

The subjects comprised 216 unrelated patients with METH psychosis (175 males and 41 females, mean age $\pm$ standard deviation (SD), 37.2 ± 11.9 years) who met the ICD-10-DCR criteria (F15.5). They were outpatients or inpatients of psychiatric hospitals of the Japanese Genetics Initiative for Drug Abuse (JGIDA). The healthy controls were 328 normal, unrelated, age-, sex-, and geographical origin-matched individuals (260 males and 68 females, mean age $\pm$ SD, 37.0 ± 13.7 years). Most were medical staff members who had no past or family history of substance dependence or major psychotic disorders. All subjects were Japanese, born and living in restricted areas of Japan, including northern Kyushu, Setouchi, Chukyo, Tokai, and Kanto, where the genetic background is considered to represent a relative unity. This study was initiated after receiving approval of the ethical committees of the participating institutions of the JGIDA. Written informed consent was obtained from all participants.

2.2. Clinical phenotypes

Clinical observation has revealed substantial interindividual differences in certain phenotypes of METH-taking behavior and psychosis that seem to be regulated, at least in part, genetically, and the rationale and methods of the subgrouping were previously described [22]. In brief, the patients with METH psychosis were divided into five subgroups according to the following clinical phenotypes: multisubstance-abuse status, age at first consumption of METH, latency to the onset of psychotic symptoms after the first consumption of METH, prognosis of psychosis after therapy, and spontaneous relapse to a psychotic state.

2.3. Genotyping

Peripheral blood was obtained from the subjects, and genomic DNA was extracted from peripheral leukocytes using a standard procedure. We selected six polymorphisms, rs1989787, rs1611115, rs1108580, rs5320, rs1611125, and rs6271, of the *DBH* gene. Genotyping of the six *DBH* gene polymorphisms was performed using TaqMan technology on an ABI7500 Real Time PCR system (Applied Biosystems, CA, USA). All genotyping was performed in a blinded fashion, with the control and case samples mixed randomly.

2.4. Statistical analysis

Statistical analysis of association was performed using SNPAlyze software (Dynacom Co., Japan). Deviation from Hardy-Weinberg equilibrium and the case-control study were tested using a χ^2 test. Linkage disequilibrium (LD) was tested using a χ^2 test, and D' and r^2 values were made the index in the authorization of LD. Case-control haplotype analysis was performed by the permutation method, and permutation P were calculated based on 100,000 replications.

3. Results

Rs6271 showed monomorphism, and rs1989787 deviated from Hardy-Weinberg equilibrium ($\chi^2 = 6.13$, $P = .01$) in the present Japanese population. Rs1611115, rs1108580, rs5320, and rs1611125 did not deviate from Hardy-Weinberg equilibrium (rs1611115, $\chi^2 = 0$, $P = 1.0$; rs1108580, $\chi^2 = 0.06$, $P = .81$; rs5320, $\chi^2 = 0.12$, $P = .73$; rs1611125, $\chi^2 = 1.52$, $P = .22$). Accordingly, subsequent analyses were done at four polymorphisms of the *DBH* gene, rs1611115, rs1108580, rs5320, and rs1611125. The genotype distribution and allele frequencies for each polymorphism of patients with METH psychosis and control subjects are shown in Table 1. We found no significant differences in genotypic or allelic distribution at any polymorphism of the *DBH* gene between the patients and controls.

We estimated the pairwise LD between the four SNPs of the *DBH* gene using the D' and r^2 values as an index, and it revealed that rs1611115, rs1108580, rs5320, and rs1611125 showed a strong LD (D' ranging between 0.82 and 1) with each other (Table 2). We then analyzed the haplotype distribution for every combination of the four polymorphisms (Table 3). Haplotypes consisting of rs1108580-rs5320-rs1611125 and rs1611115-rs1108580-rs5320-rs1611125 showed a significant association with METH psychosis (global permutation $P = .01$ and .04, resp.). Among them, we found the most significant

Table 1: Genotype and allele frequencies of four single nucleotide polymorphisms of *DBH* gene in patients with METH psychosis and controls.

		Genotype (%)			P	Allele (%)		P
rs1611115	N	C/C	C/T	T/T		C	T	
Controls	320	223 (69.7)	85 (26.6)	12 (3.7)		531 (83.0)	109 (17.0)	
Patients	207	130 (62.8)	71 (34.3)	6 (2.9)	0.16	331 (80.0)	83 (20.0)	0.22
rs1108580	N	A/A	A/G	G/G		A	G	
Controls	326	265 (81.3)	57 (17.5)	4 (1.2)		587 (90.0)	65 (10.0)	
Patients	211	158 (74.9)	49 (23.2)	4 (1.9)	0.20	365 (86.5)	57 (13.5)	0.07
rs5320	N	Ala/Ala	Ala/Thr	Thr/Thr		Ala	Thr	
Controls	259	196 (75.7)	59 (33.8)	4 (1.5)		451 (87.1)	67 (12.9)	
Patients	199	159 (79.9)	36 (18.1)	4 (4.0)	0.45	354 (88.9)	44 (11.1)	0.39
rs1611125	N	G/G	G/A	A/A		G	A	
Controls	287	213 (74.2)	63 (22.0)	11 (3.8)		489 (85.2)	85 (14.8)	
Patients	189	138 (73.0)	48 (25.4)	3 (1.6)	0.28	324 (85.7)	54 (14.3)	0.82

HWE: Hardy-Weinberg equilibrium.

Table 2: Linkage disequilibrium of four polymorphisms of *DBH* gene.

	rs1611115	rs1108580	rs5320	rs1611125
rs1611115		**1**	**0.82**	**1.00**
rs1108580	0.03		**0.83**	**0.92**
rs5320	0.02	**0.66**		**0.95**
rs1611125	0.04	**0.67**	**0.76**	

Linkage disequilibrium (LD) by χ^2 test.
Right upper and left lower diagonals show D' and r-square values, respectively. $D' > 0.8$ and $r^2 > 0.3$ were shown in bold.

Table 3: Haplotype analyses of *DBH* gene.

	1 locus	2 loci	3 loci	4 loci
rs1611115	0.19			
		0.77		
rs1108580	0.09		0.14	
		0.07		0.04
rs5320	0.39		0.01	
		0.29		
rs1611125	0.75			

Table 4: Haplotype frequencies of *DBH* gene.

	rs1108580/rs5320/rs1611125		
Haplotype	Controls	Patients	Permutation P
A-Ala-G	0.855	0.828	.29
G-Thr-A	0.100	0.104	.83
G-Ala-A	0.013	0.02	.55
A-Thr-A	0.021	0.003	.04
A-Ala-A	0.004	0.020	.07
G-Ala-G	0.002	0.019	.0008

difference between patients with METH psychosis and control subjects at a 3-loci haplotype that consisted of rs1108580-rs5320-rs1611125. The frequency of each haplotype consisting of rs1108580-rs5320-rs1611125 is shown in Table 4. The estimated haplotype frequency of G-Ala-G of rs1108580-rs5320-rs1611125 was significantly higher in patients with METH psychosis than controls ($P = .0008$). Conversely, the A-Thr-A haplotype was significantly lower in patients than controls ($P = .04$).

To investigate further the roles of DBH in the pathophysiology of psychosis and drug-taking behaviors, we examined the association of the *DBH* gene with several clinical phenotypes of METH psychosis, the age at first consumption of METH, latency to onset of psychosis after abuse, prognosis of psychosis after therapy, spontaneous relapse even without reconsumption of METH, and multiple substance abuse status, that show individual variation and may in part be regulated genetically. There was a significant difference in allelic distribution of rs1611125 of the *DBH* gene between the two subgroups divided by spontaneous relapse even without reconsumption of METH (Table 5). The subset of patients complicated by spontaneous relapse to a psychotic state after complete remission of METH psychosis showed the A allele more frequently than those without the complication of spontaneous relapse ($P = .02$). The other polymorphisms, rs1611115, rs1108580, and rs5320, of the *DBH* gene did not show association with either phenotype.

4. Discussion

We analyzed six polymorphisms of the *DBH* gene and found that these polymorphisms were not associated with METH-seeking behaviors, but that rs1611125 affected one of the clinical phenotypes of METH psychosis. Individuals with the G/G homozygote of rs1611125 had a significant risk for spontaneous relapse after complete remission of METH psychosis even without reconsumption of METH, and the risk was estimated to be more than 2-fold. In haplotype analyses, the haplotype of rs1108580-rs5320-rs1611125 was associated with METH psychosis (global permutation $P = .01$), and G-Ala-G was revealed to be a risk haplotype for development of METH psychosis ($P = .0008$). The frequency of G-Ala-G haplotype was small at about 2% in METH psychosis but almost absent in control subjects, resulting in a considerable risk and an odds ratio of 9.9. In contrast, A-Thr-A was a protective haplotype ($P = .04$)

Table 5: Clinical phenotypes of METH psychosis and rs1611125 of *DBH* gene.

Clinical phenotype		Genotype (%)			P	Allele (%)		P
rs1611125	N	G/G	G/A	A/A		G	A	
Multisubstance abuse								
Yes	136	99 (72.8)	36 (26.5)	1 (0.7)	0.22	234 (86.0)	38 (14.0)	0.83
No	47	35 (74.5)	10 (21.3)	2 (4.2)		80 (85.1)	14 (14.9)	
Age at first consumption								
< 20	99	72 (72.7)	26 (26.3)	1 (1.0)	0.75	170 (85.9)	28 (14.1)	0.99
≥ 20	88	65 (73.9)	21 (23.9)	2 (2.2)		151 (85.8)	25 (14.2)	
Latency to onset of psychosis								
< 3 years	91	66 (72.5)	22 (24.2)	3 (3.3)	0.24	154 (84.6)	28 (15.4)	0.41
≥ 3 years	85	64 (75.3)	21 (24.7)	0 (0.0)		149 (87.6)	21 (12.4)	
Prognosis of psychosis								
Transient	98	72 (73.5)	25 (25.5)	1 (1.0)	0.76	169 (86.2)	27 (13.8)	0.89
Prolonged	84	62 (73.8)	20 (23.8)	2 (2.4)		144 (85.7)	24 (14.3)	
Spontaneous relapse of psychosis								
Yes	85	69 (81.2)	15 (17.6)	1 (1.2)	0.05	153 (90.0)	17 (10.0)	0.02
No	101	66 (65.3)	33 (32.7)	2 (2.0)	(0.016)*	165 (81.7)	37 (18.3)	

*G/G vs. G/A+A/A.

and the frequency of A-Thr-A haplotype was about 2% in controls but almost absent in patients, implying a substantial protective factor given an odds ratio of 0.16. This finding suggests that the *DBH* gene may contribute to the liability for complication of psychotic symptoms after METH abuse.

Several previous studies suggested that variants of the *DBH* gene regulate the variations of plasma DBH activity. Zabetian et al. [28] have identified two novel polymorphisms, rs1611115 and rs1611125, that account for very low DBH activity using sequencing-based mutational analysis in three population samples of African Americans, European Americans, and Japanese. In particular, rs1611115 was strongly associated with plasma DBH and accounts for up to 52% of the variation in plasma DBH activity across populations of different geographic origins [10, 28]. Individuals who carried two copies of the T allele at rs1611115 showed very low plasma DBH, and those with two copied of the C allele showed higher mean levels [1, 28]. In their study, they also indicated that a non-synonymous polymorphism, rs6271, accounts for additional variations in plasma DBH after statistically allowing for rs1611115 in a European-derived population [21, 28]. However, they did not detect a polymorphism at rs6271 in Japanese samples, and the finding was consistent with our present study. Rs1108580 has been found to associate with plasma DBH activity in individuals of European heritage [5]. The A-allele of rs1108580 was associated with lower plasma DBH activity, while the G-allele was associated with higher activity. Recently, Chen et al. [2] found that a promoter polymorphism, rs1989787, was associated with plasma DBH activity after statistically accounting for rs1611115.

A large number of studies have investigated the association between plasma DBH activity, which is a highly heritable trait, and psychiatric disorders such as schizophrenia, substance-induced psychosis, and major depression. Yamamoto et al. [27] showed that individuals with the low-activity-related haplotype, including rs1108580, were over-represented in schizophrenic patients who exhibit poor response to antipsychotics, young age at onset, or poor level of global functioning. In addition, schizophrenic patients who have the low-activity-related haplotype including rs1108580 showed significantly higher scores on the Brief Psychiatric Rating Scale (BPRS) [25, 27]. With regard to substance-induced psychosis, Cubells et al. [3] reported that the low-activity-associated haplotype including rs1108580 was associated with cocaine-induced paranoia, and Kalayasiri et al. [8] indicated that patients with the TT genotype of rs1611115, which is strongly associated with low plasma DBH activity, showed an increased propensity to paranoia among chronic cocaine abusers. Studies of unipolar major depression with psychotic features (UDPF) also reported significant associations with low plasma DBH activity [4, 12, 14, 16]. Wood et al. [26] determined the genotypes of rs1108580 and revealed that the GG genotype of rs1108580, which promotes higher DBH activity, has a protective effect against the development of psychosis in depressed patients. Furthermore, low cerebrospinal fluid DBH activity was reported to be related to a higher risk for psychosis in alcoholics who were treated with disulfiram, which inhibits DBH [11]. These findings suggest that the *DBH* gene might affect the phenotypic expression of psychosis in the clinical course of psychiatric disorders such as schizophrenia, substance-induced psychosis, and major depression.

Our present study, consistent with the previous findings, revealed that the *DBH* gene affects the clinical course of METH psychotic symptoms. Rs1611125 is one of the functional polymorphisms that regulate DBH activity [28], and we found that this polymorphism has a significant effect on individual vulnerability to relapse of METH psychosis.

Individuals with the G/G homozygote of rs1611125 showed a significantly higher rate than individuals with the G/A or A/A genotype. In haplotype analyses, the haplotype consisting of rs1108580-rs5320-rs1611125 showed that G-Ala-G was a significant risk factor, and in contrast, A-Thr-A was a protective factor for METH psychosis. Ella et al. [6] reported that the A-allele in ACG (Thr) of rs5320 was protective against nicotine dependence in a Japanese population. Our samples of patients with METH psychosis showed a concordant tendency with the effect of rs5320 of the *DBH* gene. With regard to rs1108580, however, the A allele of this polymorphism has been consistently associated with lower plasma DBH activity [5] and worsens psychotic symptoms [3, 27], while our finding showed the opposite effect. The result may be due to population differences or our relatively small sample size. In addition, rs1611115 was considered strongly functional, accounting for 30–50% of the variance of DBH activity across various populations [3, 28], but the present study did not detect an association between rs1611115 and either METH psychosis or clinical phenotypes of METH psychosis. Cubells et al. demonstrated an association between the genotypes of rs1611115 and plasma DBH activity in UDPF patients, but they failed to detect an association between genotypes of rs1611115 and diagnosis in the same sample [4]. Although we did not demonstrate an association between rs1611115 and plasma activity in METH psychosis patients, it was possible that genotypes of rs1611115 are associated with plasma DBH activity in our Japanese METH psychosis samples. Further, we examined only six polymorphisms of the *DBH* gene because they have revealed functional variants. However, the *DBH* gene is large, and the function of polymorphisms may vary in different populations. Neighboring variants could also have a functional effect. Therefore, our findings must be confirmed in larger samples by examining additional variants to cover the entire *DBH* gene.

5. Conclusion

This study showed that genetic variants of the *DBH* gene may contribute to liability for complication of psychotic symptoms of METH psychosis. Taken together with previous findings, our findings suggest that genetic variants of the *DBH* gene affect the vulnerability to psychotic symptoms in endogenous and substance-induced psychosis.

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