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Research Article

Association Study of *FYN* Gene Polymorphism and Methamphetamine Use Disorder

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Abstract Fyn kinase belongs to the Src family of tyrosine kinases and phosphorylates NMDA receptor subunits. The Fyn kinase gene, *FYN*, has been considered to be involved in the pathophysiologies of neuropsychiatric diseases. We examined three polymorphisms, rs706895, rs3730353, and rs6916861, of the *FYN* gene in 250 patients with methamphetamine use disorder and 275 controls. There were no significant differences between the patients and controls in genotype or allele distribution. In haplotype association analyses, the C-T haplotype at rs3730353-rs6916861 showed a significant association with methamphetamine use disorder. We also analyzed the clinical phenotypes of methamphetamine use disorder. Rs3730353 and rs6916861 showed a significant association with age at first consumption in genotype and allele distributions, and multiple-substance abuse status in the genotype distribution. The present study suggests that genetic variation of the *FYN* gene may be related to the severity of methamphetamine use disorder in a Japanese population.

Keywords methamphetamine; FYN; NMDA; clinical phenotype; haplotype

1. Introduction

Illicit drug abuse and dependence are serious social and health problems around the world. In Japan, methamphetamine has been a most popular illicit drug since World War II. Abuse of methamphetamine induces a strong psychological dependence and further consumption produces highly psychotic symptoms, including ideas of reference, delusion of persecution, and visual and auditory hallucinations [24, 26].

Conditioned place preference (CPP) and behavioral sensitization induced by methamphetamine treatment in rodents have been recognized as animal models of methamphetamine dependence and psychosis. Many lines of evidence have shown that A10 dopamine neurons in the ventral tegmentum area (VTA) projecting into the accumbens, amygdala, and prefrontal cortex play central roles in the induction of CPP and sensitization to methamphetamine [8, 15, 25]. Animal studies have revealed that glutamate and its N-methyl-D-aspartate (NMDA) receptors are essential to the development of CPP and sensitization in methamphetamine use disorder [29]. Methamphetamine administration enhanced glutamate release in the rat accumbens and VTA [30, 31]. Repeated amphetamine administration results in enhanced neuronal responsiveness to locally applied glutamate in the VTA [28, 34] and frontal cortex [20]. Repeated methamphetamine administration induces behavioral sensitization, which is blocked by coadministration of MK-801 (dizocilpine) and D, L-3 [(±)-2-carboxypiperazin-4-yl]-propyl-1-phosphonic acid, an NMDA-receptor antagonist, by systemic administration or microinjection into the VTA [1, 3, 7, 9]. These findings indicate that enhanced glutamate transmission via NMDA receptors due to methamphetamine administration is essential for induction of sensitization and conditioning to the drug. Therefore, it is possible that genomic variants of genes encoding molecules involved in glutamate signaling may affect individual susceptibility to methamphetamine use disorder. Based on this hypothesis, we previously

analyzed the genetic associations of several genes related to glutamate signaling, including the dysbindin gene, glycine transporter 1 gene, G72 gene, and serine rasemase gene, and found that all these genes were significantly associated with methamphetamine use disorder [10, 12, 17, 33].

Fyn kinase is a member of the Src family of tyrosine kinases and mediates phosphorylation of glutamatergic NMDA receptors, which is important for several brain functions including long-term potentiation, synaptic plasticity, and myelination [11, 13]. *Fyn*-knockout mice show various abnormal behaviors, such as impaired learning and memory [32], increased alcohol sensitivity and intolerance [2, 16], and increased fearfulness and defective maternal behavior [32]. Interestingly, Fyn is also reported to be involved in dopamine D2 receptor signaling. *Fyn*-deficit mice showed a significant reduction of catalepsy and muscle rigidity induced by a D2 receptor antagonist, haloperidol, compared with wild-type mice. Fyn activation and enhanced tyrosine phosphorylation of the NMDA receptor NR2B subunit were induced in the wild-type mice after haloperidol injection, but both responses were significantly reduced in *Fyn*-deficient mice. In addition, it was found that Fyn is required for the D2 receptor-mediated regulation of NMDA receptors in striatal neurons by using calcium imaging [5].

The *FYN* gene is localized in the long arm of chromosome 6 (6q21), adjacent to a region suggested to be linked with neuropsychiatric disorders [4]. Ishiguro et al. performed a mutation study of the 5′-flanking region, all coding exons, and exon-intron junctions of the *FYN* gene in a Japanese population and found three single nucleotide polymorphisms (SNPs), rs706895 (−93A/G), rs3730353 (IVS10+37T/C), and rs6916861 (Ex12+1162T/G) [6]. Previous studies have focused on the association between these three SNPs and several neuropsychiatric disorders, including schizophrenia [6, 18], bipolar disorder [23], alcoholism [6, 19, 22], and Alzheimer's disease [27]. These three SNPs of the *FYN* gene may be associated with methamphetamine use disorder; however, we know of no study of the association between methamphetamine use disorder and variants of the *FYN* gene.

In this study, we investigated whether three SNPs of the *FYN* gene, rs706895, rs6916861, and rs3730353, are associated with methamphetamine use disorder in a Japanese population.

2. Materials and methods

2.1. Subjects

The subjects comprised 250 patients with methamphetamine use disorder (200 male and 50 female; mean age ± standard deviation (SD), 37.5 ± 11.8) and 275 age-, gender-, and geographical-origin matched healthy controls (214 male and 61 female; mean age ± SD, 37.1 ± 13.1). All subjects were unrelated Japanese born and living in relatively restricted areas of Japan. All patients were out- or inpatients at psychiatric hospitals of the Japanese Genetics Initiative for Drug Abuse (JGIDA). Consensus diagnoses of the patients were made by two trained psychiatrists according to ICD-10-DCR criteria on the basis of unstructured interviews and medical records. The patients were diagnosed with F15.2 (methamphetamine dependence), and 92.8% of patients had a comorbid diagnosis of F15.5 (methamphetamine psychosis). The controls had no individual or family history of drug dependence or major psychotic disorders such as schizophrenia or bipolar disorder. This study was approved by the ethics committee of each JGIDA institution. The study protocol and purpose were explained to all subjects who participated in the study, and written informed consent was obtained from each subject. This study was approved by the Ethics Committees of the participating institutions.

2.2. Clinical phenotypes

Clinical observation has revealed substantial inter-individual differences in certain phenotypes of methamphetamine-taking behavior and psychosis that seem to be regulated, at least in part, genetically. We divided patients into the following subgroups according to five clinical phenotypes: (1) age at first consumption of methamphetamine (younger or older than 20 years), (2) multiple-substance abuse status (presence or absence), (3) latency to the onset of psychotic symptoms after the first consumption (less than or more than 3 years), (4) prognosis of methamphetamine psychosis after therapy (transient type: psychotic symptoms disappear within one month due to treatment with an antipsychotic, or prolonged type: psychotic symptoms lasted more than one month even after discontinuance of methamphetamine use and treatment with an antipsychotic), and (5) spontaneous relapse to a psychotic state (presence or absence of spontaneous relapse without reconsumption of methamphetamine). The rationale and methods of the subgrouping were described previously [26].

2.3. Genotyping

Peripheral blood was obtained from the subjects, and genomic DNA was extracted from peripheral leukocytes using a standard procedure. We selected three SNPs, rs706895, rs3730353, and rs6916861, of the *FYN* gene for genetic association analyses.

The concentration and purity of DNA samples were assessed using a Nano Drop1000 spectrophotometer (Thermo Scientific, MA, USA). The concentration of DNA samples was adjusted to 20 ng/μL. The purity was estimated from the ratio of the absorbance values measured at wavelengths of 260 nm and 280 nm (defined as a 260/280 ratio between 1.8 and 2.0). Genotyping was performed by TaqMan technology on a Stratagene Real Time QPCR

Table 1: Genotype and allele distribution of three single nucleotide polymorphisms of *FYN* gene in control subjects and patients with methamphetamine use disorder.

	N	Genotype (%)			P-value	Allele (%)		P-value	HWE	
rs706895		A/A	A/G	G/G		A	G		P-value	χ^2
Controls	275	96 (34.9)	132 (48.0)	47 (17.1)		324 (59.0)	226 (41.0)		.99	0.00
Patients	247	86 (34.8)	123 (49.8)	38 (15.4)	.85	295 (59.7)	199 (40.3)	.79	.68	0.18
rs3730353		T/T	T/C	C/C		T	C			
Controls	272	122 (44.9)	119 (43.7)	31 (11.4)		363 (66.7)	181 (33.3)		.92	0.01
Patients	242	101 (41.7)	100 (41.4)	41 (16.9)	.19	302 (62.4)	182 (37.6)	.15	.09	2.96
rs6916861		T/T	T/G	G/G		T	G			
Controls	265	118 (44.5)	120 (45.3)	27 (10.2)		356 (67.2)	174 (32.8)		.77	0.09
Patients	250	103 (41.2)	109 (43.6)	38 (15.2)	.23	315 (63.0)	185 (37.0)	.16	.37	0.79

HWE: Hardy-Weinberg equilibrium.

Table 2: Linkage disequilibrium (LD) by χ^2 test.

	rs706895	rs3730353	rs6916861
rs706895		0.384	0.387
rs3730353	0.117		0.96
rs6916861	0.116	0.914	

Right-upper and left-lower diagonal sides showed D' and r-square values, respectively.

System Mx3000P (Applied Biosystems, CA, USA). PCR was carried out in 16 μL of a solution containing approximately 0.2 μL TE buffer, 0.2 μL ready-to-use PCR probe (Applied Biosystems), 2 μL genomic DNA, 8 μL Brilliant II FAST QPCR Master Mix (Agilent Technologies, CA, USA), and 5.6 μL DNAase-free water. PCR cycling conditions consisted of an initial incubation at 95 °C for 2 min, followed by 40 cycles of 92 °C for 30 s, and 60 °C for 1 min, as the annealing/elongation step. An experienced researcher conducted the genotyping and read out the data, and the genetic variants were verified by repeated PCR.

2.4. Statistical analyses

Statistical analyses were performed using Statcel software for Windows version 2.0 (OMS Publishing Co., Saitama, Japan). Associations between categorical variables were analyzed using χ^2 tests and continuous variables were analyzed using Mann-Whitney's U-test. Deviation from Hardy-Weinberg equilibrium (HWE) and the case-control association was examined by χ^2 test. SNPs with HWE below the statistical significance level defined as P-value .05 in either cases or controls were excluded from further analyses. We evaluated pairwise linkage disequilibrium (LD) among the SNPs by χ^2 test, D' value, and r^2. In haplotype analysis, we calculated the permutation P-value by using 100,000 simulations to avoid the possibility of a large error in the χ^2 test when the haplotype frequency was extremely small. To avoid misleading global haplotype results due to rare haplotypes, we limited haplotypes to those having frequencies of at least 1%. These statistical analyses were performed by using the software SNPAlyze (Dynacom Co., Chiba, Japan). The statistical significance was defined as $P < .05$.

Table 3: Haplotype frequencies of *FYN* gene of control subjects and patients with methamphetamine use disorder.

rs3730353/rs6916861 Haplotype	Controls Frequency	Patients Frequency	Permutation P-value
T-T	0.638	0.665	.061
C-G	0.342	0.324	.214
T-G	0.011	0.009	.617
C-T	0.009	0.002	.008

Global permutation P-value = .048.

3. Results

The genotype distribution and allele frequency for each polymorphism of patients with methamphetamine use disorder and control subjects are shown in Table 1. The three SNPs, rs706895, rs3730353, and rs6919861, of the *FYN* gene did not deviate significantly from HWE. There were no significant differences in genotype or allele distribution of any polymorphisms examined between the two groups.

Table 2 shows the results of the pairwise LD among the three SNPs of the *FYN* gene using D' and r^2 values as an index; we found that rs3730353 and rs6916861 showed a strong LD (D' value = 0.960). In this LD block, we analyzed the haplotype distributions, and found a significant association between the haplotypes of the patients with methamphetamine use disorder and controls (global permutation P-value = .048) (Table 3). The haplotype consisting of rs3730353-rs6916861 showed that the C-T frequency was significantly higher in control subjects than in patients with methamphetamine use disorder (permutation P-value = .008).

To investigate the association of the *FYN* gene with methamphetamine-taking behaviors and psychosis, we examined the association of the *FYN* gene with several clinical phenotypes, including the age at first consumption of methamphetamine, multiple substance abuse status, latency to onset of psychosis after abuse, prognosis of psychosis after therapy, and spontaneous relapse even without reconsumption of methamphetamine, which show individual variation and may in part be regulated genetically (Table 4).

Table 4: Subgroups of methamphetamine use disorder by clinical characteristics.

Clinical phenotype		Genotype (%)			P-value	Allele (%)		P-value
rs706895	N	A/A	A/G	G/G		A	G	
Age at first consumption								
< 20	127	45 (35.4)	64 (50.4)	18 (14.2)	.89	154 (60.6)	100 (39.4)	.72
$\geqq 20$	116	40 (34.5)	57 (49.1)	19 (16.4)		137 (59.1)	95 (40.9)	
Multisubstance abuse								
None or mild	149	53 (35.6)	72 (48.3)	24 (16.1)	.99	178 (59.7)	120 (40.3)	.95
Heavy	90	32 (35.6)	44 (48.9)	14 (15.5)		108 (60.0)	72 (40.0)	
Latency to onset of psychosis								
$<$ 3 years	110	39 (35.5)	56 (50.9)	15 (13.6)	.43	134 (60.9)	86 (39.1)	.95
$\geqq$ 3 years	99	39 (39.4)	42 (42.4)	18 (18.2)		120 (60.6)	78 (39.4)	
Prognosis of psychosis								
Transient	117	46 (39.3)	57 (48.7)	14 (12.0)	.31	149 (63.7)	85 (36.3)	.16
Prolonged	100	33 (33.0)	48 (48.0)	19 (19.0)		114 (57.0)	86 (43.0)	
Spontaneous relapse of psychosis								
Yes	119	43 (36.1)	63 (52.9)	13 (11.0)	.076	149 (62.6)	89 (37.4)	.20
No	106	37 (34.9)	46 (43.4)	23 (21.7)		120 (56.6)	92 (43.4)	
rs3730353	N	T/T	T/C	C/C		T	C	
Age at first consumption								
< 20	123	61 (49.6)	46 (37.4)	16 (13.0)	**.025**	168 (68.3)	78 (31.7)	**.006**
$\geqq 20$	116	38 (32.8)	54 (46.5)	24 (20.7)		130 (56.0)	102 (44.0)	
Multisubstance abuse								
None or mild	146	53 (36.3)	69 (47.3)	24 (16.4)	**.012**	175 (59.9)	117 (40.1)	.13
Heavy	89	47 (52.8)	25 (28.1)	17 (19.1)		119 (66.9)	59 (33.1)	
Latency to onset of psychosis								
$<$ 3 years	108	47 (43.5)	47 (43.5)	14 (13.0)	.63	141 (65.3)	75 (34.7)	.61
$\geqq$ 3 years	97	42 (43.3)	38 (39.2)	17 (17.5)		122 (62.9)	72 (37.1)	
Prognosis of psychosis								
Transient	118	53 (44.9)	47 (39.8)	18 (15.3)	.68	153 (64.8)	83 (35.2)	.42
Prolonged	95	37 (38.9)	42 (44.3)	16 (16.8)		116 (61.1)	74 (38.9)	
Spontaneous relapse of psychosis								
Yes	119	49 (41.2)	46 (38.6)	24 (20.2)	.44	144 (60.5)	94 (39.5)	.83
No	102	44 (43.1)	44 (43.2)	14 (13.7)		132 (64.7)	72 (35.3)	
rs6916861	N	T/T	T/G	G/G		T	G	
Age at first consumption								
< 20	126	60 (47.6)	51 (40.5)	15 (11.9)	**.049**	171 (67.9)	81 (32.1)	**.014**
$\geqq 20$	119	39 (32.8)	58 (48.7)	22 (18.5)		136 (57.1)	102 (42.9)	
Multisubstance abuse								
None or mild	150	55 (36.7)	74 (49.3)	21 (14.0)	**.029**	184 (61.3)	116 (38.7)	.37
Heavy	91	45 (49.5)	29 (31.8)	17 (18.7)		119 (65.4)	63 (34.6)	
Latency to onset of psychosis								
$<$ 3 years	110	44 (40.0)	51 (46.4)	15 (13.6)	.74	139 (63.2)	81 (36.8)	.079
$\geqq$ 3 years	100	44 (44.0)	41 (41.0)	15 (15.0)		129 (64.5)	71 (35.5)	
Prognosis of psychosis								
Transient	121	53 (43.8)	51 (42.2)	17 (14.0)	.70	157 (64.9)	85 (35.1)	.45
Prolonged	97	37 (38.1)	45 (46.4)	15 (15.5)		119 (61.3)	75 (38.7)	
Spontaneous relapse of psychosis								
Yes	123	50 (40.6)	51 (41.5)	22 (17.9)	.51	151 (61.4)	95 (38.6)	.56
No	103	42 (40.8)	48 (46.6)	13 (12.6)		132 (64.1)	74 (35.9)	

There were significant differences in the genotype and allele distributions of rs3730353 (genotype: $P = .025$, allele: $P = .006$; the odds ratio is 1.69) and rs6916861 (genotype: $P = .049$, allele: $P = .014$; the odds ratio is 1.58) of the *FYN* gene between patients with methamphetamine use disorder whose age at their first consumption of methamphetamine was younger than 20 years and those who were older than 20 years at first consumption of methamphetamine. When patients with methamphetamine use disorder were divided by multisubstance status, there were also significant differences in the genotype distributions of rs3730353 ($P = .012$) and rs6916861 ($P = .029$) of the *FYN* gene.

4. Discussion

The present study revealed that the *FYN* gene may be related to the severity of methamphetamine use disorder in a Japanese population. The *FYN* gene did not affect susceptibility to methamphetamine use disorder, but it was associated with several clinical phenotypes of methamphetamine dependence and psychosis. Carriers of the T allele of rs3730353 were younger in age at first consumption of methamphetamine, and these T allele carriers had a tendency to abuse multiple illegal drugs other than methamphetamine. We also found that carriers of the T allele of rs6916861 were younger at first consumption of methamphetamine, and they also had a tendency to abuse multiple illegal drugs. These findings suggested that rs3730353 and rs6916861 of the *FYN* gene may be involved with the severity of methamphetamine use disorder because we detected an association between earlier age of onset and multiple substance abuse status. In addition, our present study showed that the haplotype of rs3730353-rs6916861 was associated with methamphetamine use disorder. The frequency of the C-T haplotype of rs3730353-rs6916861 was about 1% in controls but almost absent in patients, implying that the C-T haplotype was a protective factor.

The three SNPs investigated in our present study are neither missense nor nonsense mutations, but the possible functional effects of these SNPs have not been identified. Rs3730353 is located in intron 10 and rs6916861 is in the 3′ UTR, and these intronic SNPs are usually considered nonfunctional. However, recent studies showed that intronic RNAs can actually be processed to smaller RNAs, snoRNAs, or miRNAs, which control various levels of gene expression in physiology and development, including transcription, RNA splicing, editing, translation, and turnover [14]. It is possible that rs3730353 and rs6916861 affect *FYN* gene expression and result in susceptibility to or severity of methamphetamine use disorder.

The present study is the first association study analyzing the possible relationship between *FYN* gene polymorphisms and methamphetamine use disorder, and thus we cannot compare our results with others. However, the two SNPs rs3730353 and rs6916861 were reported to be associated with the percentage of perseverative errors in the Wisconsin Card Sorting Test, regarded as the most important index of working memory, which depends on prefrontal cortex functions [21]. In addition, Szczepankiewicz et al. found an association between the two SNPs, rs3730353 and rs6916861, and bipolar disorder, particularly with type I illness and early age of onset [23]. These findings suggest that these two SNPs of the *FYN* gene may relate to the function of the glutamatergic system and pathogenesis of several psychiatric disorders.

We did not detect an association of rs706895 with methamphetamine use disorder or any clinical phenotype. Rs706895 is located in the promoter region near the transcriptionally active site and may affect gene expression. Recent studies of a Caucasian population have showed that rs706895 was associated with alcohol dependence. It has been shown that the C allele of rs706895 is a risk allele for alcohol dependence [19,22]. However, in our present study, there was no association between rs706895 and methamphetamine use disorder in a Japanese population. The dissociation may be due to differences in the substances of abuse and ethnic differences in the distributions of genotype and alleles. The minor allele frequency of rs706895 was 41.0% in our Japanese samples, while it was 21–22% in Caucasian samples [19,22].

The main limitation of our present study is that the sample size is not large enough to exclude the possibility of a type I error due to insufficient power. Our findings must be replicated in a larger independent sample and other populations.

5. Conclusion

This study suggested that the *FYN* gene may be related to the severity of methamphetamine use disorder. Further studies using independent replication will be required to clarify the relationship between the *FYN* gene and methamphetamine use disorder.

Competing interests The authors declare that they have no competing interests.

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