Background

The neurodevelopmental hypothesis of schizophrenia suggests that interaction between genetic and environmental events occurring during critical early periods of neuronal growth may negatively influence the way by which nerve cells are laid down, differentiated, selectively culled by apoptosis and remodeled by expansion and retraction of dendrites and synaptic connections [1,2]. The Wnt family molecules play several roles in neuronal development by inducing cells to proliferate, differentiate, and survive [3,4]. In particular, Wnt signaling plays roles in regulating patterning during cortical development, axon remodeling, synaptic differentiation, clustering of synapsin I at presynaptic terminals [5-7] and the cytoarchitectural derangement that was observed in the brains of schizophrenics [8]. A mutation in the Wnt1 gene, one of the Wnt family genes, leads to abnormal cerebral development in mice [9], and mice deficient in Frizzled 3 (Fzd3), a receptor of Wnt ligands, showed loss of thalamo-cortical tracts and defects in corpus callosum development, abnormalities which were reported in schizophrenic patients [10-12]. Therefore, alteration of the Wnt/Fzd cascade may represent an aberrant neurodevelopment involved in schizophrenia [13].

Fzd3 is a required receptor in the Wnt-signaling pathway. In 2003, we reported a significant association between the gene encoding Fzd3 (*FZD3*) and susceptibility to schizophrenia [14]. Subsequent studies tried to replicate our findings, but the results were inconsistent. Yang et al. [15] revealed a significant association of the *FZD3* gene with schizophrenia in Han Chinese populations by a transmission disequilibrium test, and Zhang et al. [16] also found a significant association by a family-based case-control study. On the other hand, several studies failed to find significant evidence of a genetic effect of the *FZD3* gene on schizophrenia [17-19]. The inconsistencies in genetic studies in the relationship of the *FZD3* gene with schizophrenia may suggest heterogeneity of schizophrenia and a requirement for further studies using larger sample size. We consider that it may be also useful to investigate the role of the *FZD3* gene in other types of psychotic disorders for better understanding of the physiological roles of Fzd3 and the Wnt cascade in schizophrenia or psychotic conditions.

Repeated abuse of methamphetamine frequently predisposes to psychotic conditions. The clinical similarity between methamphetamine psychosis and schizophrenia has been pointed out, and methamphetamine psychosis has been considered to be a pharmacological model of schizophrenia, especially the paranoid subtype [20-22]. Thus, methamphetamine psychosis and schizophrenia resemble each other in a cross-section of clinical features, e.g., auditory hallucination and delusion, the longitudinal process of progressive exacerbation with acute relapses, good response to neuroleptics, and enduring vulnerability to relapse under stressors. Enhanced dopamine release in the striatum due to a challenge dose of methamphetamine was observed in schizophrenic patients and methamphetamine-sensitized rats, an animal model of methamphetamine psychosis [23-25]. These similarities between schizophrenia and methamphetamine psychosis in both symptomatology and pharmacological aspects may suggest that shared neural mechanisms are involved in both psychotic disorders. Therefore, in order to examine the roles of Fzd3 in mechanisms underlying the development of psychosis, we analyzed the *FZD3* gene in patients with methamphetamine psychosis.

Methods

Subjects

The subjects consisted of 188 patients with methamphetamine psychosis (158 male, 30 female; mean age ± SD, 36.6 ± 11.8) and 240 age-, gender-, and geographical origin-matched healthy controls (192 male, 48 female; mean age ± SD, 36.6 ± 10.6), who have no individual or family history of drug dependence or major psychotic disorders such as schizophrenia and bipolar disorders. All the subjects were unrelated Japanese, born and living in relatively restricted areas of Japan, northern Kyushu, Setouchi, Chukyo, Tokai, and Kanto. All subjects were out-patients or inpatients in psychiatric hospitals of the Japanese Genetics Initiative for Drug Abuse (JGIDA), a multicenter collaborative study group. Consensus diagnoses of methamphetamine psychosis were made by two trained psychiatrists according to the ICD-10 criteria on the basis of interviews and medical records. The patients with methamphetamine psychosis in the present study usually showed predominant positive symptoms such as delusion and hallucination. We excluded cases in which the predominant symptoms were of the negative and/or disorganized type in order to maintain the homogeneity of the patient group. The study protocol and purpose were explained to all subjects participating in the study, and written informed consent was obtained from all subjects. This study was approved by the Ethics Committee of each participating institute of JGIDA.

DNA analysis

We genotyped the three single nucleotide polymorphisms (SNPs), rs3757888 (SNP1) in the 3' flanking region, rs960914 (SNP2) in the intron 3, and rs2241802 (SNP3), a synonymous SNP in the exon5 of the *FZD3* gene that were analyzed in our previous study [14]. We also analyzed three additional SNPs, rs2323019 (SNP4) and rs352203 (SNP5) in the intron 5, and rs880481 (SNP6) in the intron 7 of the gene because a significant association with schizophrenia was reported by Yang et al. [15] and Zhang et al. [16]. Genotyping was performed by the PCR-

RFLP method. The genomic DNA was extracted from peripheral leukocytes using phenol-chloroform. Each polymorphic site was amplified by PCR (PCR primer sequence of each SNP is available on request) in a 15-μl volume containing 3% dimethyl sulfoxide and 0.75 units of Taq DNA polymerase (Promega Co., Japan) using a unique primer set. PCR reaction was performed under the following conditions: 95°C for 5 min, then 35 cycles of 30 s of denaturing at 95°C, 1 min of annealing at the appropriate temperature, and 30 s of extension, and final elongation at 72°C for 10 min. The PCR products were digested with the corresponding restriction enzyme for each polymorphism, Dde*I* for rs3757888, Rsa*I* for rs960914, Alu*I* for rs2241802, Ssp*I* for rs2323019, Nla*III* for rs352203, Eco32*I* for rs880481, and then electrophoresed on 3.0% agarose gels and stained with GelStar (TaKaRa Co., Japan). All genotyping was performed in a blinded fashion, with the control and cases samples mixed randomly. The genotyping of the SNPs were confirmed in part by direct sequencing or a TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA, U.SA.).

Statistical analysis

Statistical analysis of association was performed using SNPAlyze software (Dynacom Co., Japan). Deviation from Hardy-Weinberg equilibrium and case- control study were tested using the χ^2 test for goodness of fit and χ^2 test for dependence, respectively. Linkage disequilibrium (LD) was tested using the 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*-values were calculated based on 100,000 replications.

Results

The genotype distribution and allele frequencies of the each polymorphism are shown in Table 1. The genotype distributions of patients and control subjects did not deviate from Hardy-Weinberg equilibrium at any SNP examined. The allele frequencies of SNP1, SNP2, and SNP3

Table 1: Genotype and allele distribution of six SNPs of the FZD3 gene in controls and patients with methamphetamine (MAP) psychosis

		Genotype				*p*	Allele		*p*
SNP1	rs3757888	N	A/A	A/G	G/G		A	G	
Control		230	198(86.1)	31(13.5)	1(0.4)		427(92.8)	33(7.2)	
MAP Psychosis		186	151(81.2)	32(7.2)	3(1.61)	0.26	334(89.8)	38(10.2)	0.19
SNP2	rs960914	N	T/T	T/C	C/C		T	C	
Control		240	67(27.9)	130(54.2)	43(17.9)		264(55.0)	216(45.0)	
MAP Psychosis		185	45(24.3)	103(55.7)	37(20.0)	0.66	193(52.2)	177(47.8)	0.41
SNP3	rs2241802	N	A/A	A/G	G/G		A	G	
Control		240	49(20.4)	124(51.7)	67(27.9)		222(46.2)	258(53.8)	
MAP Psychosis		181	44(24.3)	97(53.6)	40(22.1)	0.34	185(51.1)	177(48.9)	0.16
SNP4	rs2323019	N	A/A	A/G	G/G		A	G	
Control		239	72(31.4)	113(49.3)	44(19.2)		257(56.1)	201(43.9)	
MAP Psychosis		186	45(24.1)	101(54.0)	41(21.9)	0.25	191((51.1)	183(48.9)	0.15
SNP5	rs352203	N	T/T	T/C	C/C		T	C	
Control		192	64(33.3)	98(51.1)	30(15.6)		226(58.9)	158(41.1)	
MAP Psychosis		176	49(27.8)	98(55.7)	29(16.5)	0.52	196(55.7)	156(44.3)	0.38
SNP6	rs880481	N	A/A	A/G	G/G		A	G	
Control		236	43(18.2)	123(52.1)	70(29.7)		209(44.3)	263(55.7)	
MAP Psychosis		186	30(16.1)	103(55.4)	53(28.5)	0.97	163(43.8)	209(56.2)	0.99

SNP, Single nucleotide polymorphism.
Numbers in parentheses indicate percentages.

were approximately same as those of our previous study [14]. The allele frequencies of SNP4, SNP5, and SNP6 in the present study also showed values similar to those of previous studies of Japanese and Chinese populations [16-18].

We found no significant difference between patients and controls in the frequencies of the genotype or allele at any single SNP of the *FZD3* gene. We estimated the pairwise LD between the six SNPs of the *FZD3* gene using the D' and r^2values as an index (Table 2). A D' range of 0.7–0.9 and a $r^2 > 0.3$ were found between SNP2, SNP3, SNP4, SNP5, and SNP6, but not between SNP1 and the other SNPs. This suggests that SNP2, SNP3, SNP4, SNP5, and SNP6 are in linkage disequilibrium and located within one LD block. Then, we performed case-control haplotype analysis using SNP2 to SNP6 (Table 3). Haplotype analyses revealed significant differences in patients and control subjects at SNP5-6, SNP4-5-6, SNP3-4-5-6, and SNP2-3-4-5-6, but not at SNP2-3, SNP3-4, SNP4-5, SNP2-3-4, SNP3-4-5, or SNP2-3-4-5. The largest χ^2 and smallest permutation *P* values were found in the haplotype analysis of SNP3-4-5-6 ($\chi^2 = 64.8$, permutation $p < 0.00001$). The estimated individual haplotypic frequencies of SNP3-4-5-6 are shown in Table 4. Eight kinds of haplotypes consisting of SNP3-4-5-6 with more than 1% overall frequency were identified. The estimated haplotype frequency of G-A-T-G and A-G-C-A of SNP3-4-5-6 were significantly lower in patients with methamphetamine psychosis than in controls ($p < 0.00001$ and $p = 0.0003$, respectively). Conversely, the A-G-C-G haplotype was significantly in excess in patients compared with controls ($p = 0.0246$). To avoid a type I error due to multiple comparison, Bonferroni's correction was applied to the results. G-A-T-G and A-G-C-A haplotypes were still significantly less frequent in the methamphetamine patients than in the controls, but A-G-C-G was not significantly different between the groups after correction. The odds ratios G-A-T-G and A-G-C-A haplotypes were 0.13 (95%CI; 0.043–0.36) and 0.086 (95%CI; 0.011–0.67), respectively. Accordingly, G-A-T-G and A-G-C-A haplotypes of SNP3-4-5-6 were negative risk haplotypes for methamphetamine psychosis.

Table 2: Pairwise Linkage Disequilibrium between six SNPs of the FZD3 gene

	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6
SNP1		**0.840**	0.557	0.379	**0.853**	**0.706**
SNP2	0.057		**0.760**	**0.915**	**0.970**	**0.749**
SNP3	0.031	**0.532**		**0.834**	**0.831**	**0.729**
SNP4	0.012	**0.829**	**0.627**		**0.982**	**0.760**
SNP5	0.052	**0.841**	**0.542**	**0.843**		**0.788**
SNP6	0.036	**0.377**	**0.389**	**0.387**	**0.367**	

Linkage disequilibrium was tested using χ^2 test. Upper right and lower left diagonals show D' and r-square values, respectively. D'>0.7 and r-square>0.3 were shown in bold.

Discussion

We revealed that the *FZD3* gene is significantly associated with the vulnerability to psychosis induced by methamphetamine abuse, and two haplotypes of the *FZD3* gene comprising SNP3-4-5-6 (rs2241802-rs2323019-rs352203-rs880481) were identified as potent negative risk factors for methamphetamine psychosis. The G-A-T-G and A-G-C-A haplotypes potently reduce the risks of predisposition to psychosis after methamphetamine abuse to one seventh to one eleventh. In our previous study of schizophrenia [14], distribution of the SNP2 genotypes and haplotypes comprising SNP2-SNP3 was significantly associated with schizophrenia. Zhang et al. [16] reported that the haplotype comprising SNP4-SNP5-SNP6 was associated with schizophrenia in a Chinese population. These findings indicate that genetic variants of the *FZD3* gene may affect susceptibility to two analogous but distinct psychoses, endogenous psychosis of schizophrenia and substance-induced psychosis. This may imply that Fzd3 is involved in a liability to psychotic symptoms such as hallucination and delusion irrespective of whether they are due to schizophrenia or methamphetamine psychosis.

Dopamine is a key molecule in the pathophysiology of both schizophrenia and methamphetamine psychosis. Enhanced dopamine release in the terminals of mesolimbic dopamine projections was demonstrated *in vivo* in patients with schizophrenia, and the amount of the increase in dopamine was positively associated with the emergence or worsening of psychotic symptoms [25]. Similar phenomena were demonstrated in mesolimbic and mesocortical terminals in animal models of methamphetamine psychosis [23]. Wnt1 was found to be expressed in close vicinity to developing midbrain dopamine neurons, which are the origins of the mesolimbic and mesocortical dopamine pathways. Wnt1 regulates the genetic network leading to establishment of the midbrain progenitor domain in the ventral midbrain during embryonic development and of the subsequent terminal differentiation of midbrain dopamine neurons [26,27]. It is possible that differences in Wnt signaling due to genetic variants of the *FZD3* gene affect the development of dopamine neurons of the mesolimbic or mesocortical pathway in early brain development and susceptibility to these two dopamine-related psychoses in adulthood.

Another molecule that potentially links Fzd3 and these two related psychoses is glycogen synthesis kinase-3 (GSK-3), a serine/threonine kinase that is a downstream component of the Wnt/Fzd cascades. Binding of Wnt ligands to Fzd family receptors leads to activation of the intracellular protein disheveled, which inactivates GSK-

Table 3: Haplotype analysis of the FZD3 gene

	1SNP	2SNP	3SNP	4SNP	5SNP
SNP ID	Permutation p-value				
SNP2 (rs960914T>C)	0.41				
		0.16			
SNP3 (rs2241802G>A)	0.16		0.22		
		0.15		0.35	
SNP4 (rs2323019A>G)	0.15		0.15		**<0.00001**
		0.072		**<0.00001**	
SNP5 (rs352203T>C)	0.38		**0.00001**		
		0.00002			
SNP6 (rs880481A>G)	0.99				

Haplotype analysis was performed by permutaion method. Bold values represent significant p values.

3β. This in turn leads to the stabilization and accumulation of β-catenin, which translocates to the nucleus where it interacts with nuclear transcription factors for the genes involved in neuronal development. Briefly, GSK-3β mediates Wnt/Fzd signaling cascades. Dysregulation of GSK-3β and 3α is one of promising neurodevelopmental hypotheses of schizophrenia [13,28]. GSK-3 is also regulated by dopamine signaling through protein kinase B [29]. Several studies showed, but not consistently, that GSK-3 protein levels and activities are altered in schizophrenic brains [30,31] and lymphocytes [32,33]. Several genes, e.g., *DISC1* and *NRG1*, which have been repeatedly shown to be associated with susceptibility to schizophrenia, are involved in GSK-3/Wnt regulatory pathways [28]. Recently, the gene encoding DKK4, a component of the GSK-3/Wnt signaling cascade, was shown to be associated with schizophrenia. DKK4 inhibits Wnt-Fzd binding, resulting in inactivation of GSK-3 [34]. On the other hand, amphetamine also affects GSK-3 activity. Administration of amphetamine to mice increased Ser9 phosphorylation of GSK-3β, resulting in a reduction of its activity in the frontal cortex and striatum [35], and GSK-3 gene knockdown mice showed a reduced response to amphetamine [36]. Intriguingly, psychotomimetics of two different classes, phencyclidine and D-lysergic acid, also had the same effects on GSK-3β, which may imply that substance-induced psychosis might be the result of a reduction in GSK-3 signaling. In contrast, chronic treatment with typical and atypical neuroleptics that ameliorate the psychotic symptoms of schizophrenia and methamphetamine psychosis increase the levels and activities of GSK-3 [37]. It was also found that chronic neuroleptic treatment increased β-catenin in the ventral midbrain, whereas amphetamine decreased it [38]. These findings indicate that the altered GSK-3/Wnt signaling is involved in liability to expression of positive psychotic symptoms such as the hallucinations and delusions in patients suffering from both schizophrenia and methamphetamine-induced psychosis. This hypothesis may be supported by our present and previous findings because the *FZD3* gene was significantly associated with not only schizophrenia but also methamphetamine psychosis.

The present results were still significant even after a Bonferroni correction, although it is possibly a chance finding due to less power. The power analysis showed that our

Table 4: Haplotype frequencies from positive permutation analyses

Haplotype	Frequency		Permutation p-values	Odds ratio (95%CI)
(SNP3-4-5-6)	Controls	MAP Psychosis		
G-A-T-A	0.3523	0.4148	0.0889	
A-G-C-G	0.3178	0.3970	0.0246	1.42 (1.14–1.76)
G-A-T-G	0.1542	0.0243	<0.00001	0.13 (0.07–0.22)
A-A-T-G	0.0382	0.0635	0.1283	
A-G-C-A	0.0625	0.0070	0.0003	0.086 (0.03–0.24)
A-G-T-G	0.0211	0.0354	0.2791	
G-G-C-G	0.0196	0.0379	0.1678	
A-A-T-A	0.0169	0.0090	0.4565	

Haplotypes with overall frequencies are less than 1% were eliminated.

present sample size had more than 80% power to detect a significant difference at 0.05 of any SNP examined, but it must have less power for haplotype analyses. Therefore, our findings should be confirmed in studies using a larger number of subjects and different populations. It may also be useful for further investigation of the roles of Fzd3 in psychoses to examine the genetic association of the *FZD3* gene with other types of psychoses, e.g., cocaine-induced paranoia or delusional type of bipolar disorders.

Conclusion

We examined genetic association of *FZD3* and found that two kinds of *FZD3* haplotypes showed strong associations with methamphetamine psychosis. Having the G-A-T-G or A-G-C-A haplotype of rs2241802-rs2323019-rs352203-rs880481 was a potent negative risk factor (odds ratios were 0.13 (95%CI; 0.07–0.22) and 0.086 (0.03–0.24), respectively) for methamphetamine psychosis. Our present and previous findings indicate that genetic variants of the *FZD3* gene affect susceptibility to two analogous but distinct dopamine-related psychoses, endogenous and substance-induced psychosis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HU conceived of the study, reviewed the manuscript and supervised all management, analysis, and interpretation of the data. MKi, YO, TK supervised by MT and MKo, genotyped samples and analyzed data, and MKi drafted manuscript and produced all tables. HU organized collaboration of Japanese substance abuse group, and HU, TI, MY, NU, NI, IS and NO collected genome samples and informed consents. HU and SK managed research expense. All authors read and approved for final manuscript.

Acknowledgements

We thank the Zikei Institute of Psychiatry (Okayama, Japan) and the Ministry of Health, Labor, and Welfare of Japan.

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The Dysbindin Gene (*DTNBP1*) Is Associated with Methamphetamine Psychosis

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Background: The dysbindin (*DTNBP1* [dystrobrevin-binding protein 1]) gene has repeatedly been shown to be associated with schizophrenia across diverse populations. One study also showed that risk haplotypes were shared with a bipolar disorder subgroup with psychotic episodes, but not with all cases. *DTNBP1* may confer susceptibility to psychotic symptoms in various psychiatric disorders besides schizophrenia.

Methods: Methamphetamine psychosis, the psychotic symptoms of which are close to those observed in schizophrenia, was investigated through a case (n = 197)–control (n = 243) association analyses of *DTNBP1*.

Results: *DTNBP1* showed significant associations with methamphetamine psychosis at polymorphisms of P1635 (rs3213207, $p = .00003$) and SNPA (rs2619538, $p = .049$) and the three-locus haplotype of P1655 (rs2619539)-P1635-SNPA (permutation $p = .0005$). The C-A-A haplotype, which was identical to the protective haplotype previously reported for schizophrenia and psychotic bipolar disorders, was a protective factor ($p = .0013$, odds ratio [OR] = .62, 95% confidence interval [CI] .51–.77) for methamphetamine psychosis. The C-G-T haplotype was a risk for methamphetamine psychosis ($p = .0012$, OR = 14.9, 95% CI 3.5–64.2).

Conclusions: Our genetic evidence suggests that *DTNBP1* is involved in psychotic liability not only for schizophrenia but also for other psychotic disorders, including substance-induced psychosis.

Key Words: Akt1, *DTNBP1*, dysbindin, methamphetamine psychosis, substance dependence

A genetic variation of the dystrobrevin-binding protein 1 (*DTNBP1*) gene has recently been shown to be associated with schizophrenia in several independent studies. Straub *et al.* (1) revealed original evidence for a positive genetic association between schizophrenia and variants in a gene on 6p22.3, dysbindin (*DTNBP1*), which is located within one of several promising loci revealed by a genomewide linkage scan. Many replication studies showed consistent findings in different populations, for example, German (2), Irish (3), Chinese (4), Swedish/German/Polish (5), UK/Irish (5), Bulgarian (6), American (7), Scottish/Chinese (8), and Japanese (9), although the significantly associated alleles and haplotypes were not always consistent among populations. Two postmortem studies also revealed that dysbindin protein or its mRNA level was reduced in the dorsolateral prefrontal cortex and in presynaptic glutamatergic terminals of the hippocampus of schizophrenia patients (10,11). These findings suggest that the dysbindin is involved in the pathogenesis of schizophrenia.

Recently, Raybould *et al.* (12) examined three loci of the *DTNBP1* gene in a large sample of patients with bipolar disorder, another endogenous psychosis, in UK Caucasians, and found that the *DTNBP1* gene was not associated with all cases of bipolar disorder but was associated with a subgroup of bipolar disorder characterized by the complication of psychotic features during episodes. The risk and protective haplotype were identical to those found in their previous schizophrenia study (13). Therefore, they speculated that the *DTNBP1* genetic variation influences susceptibility to schizophrenia and bipolar psychosis across the Kraepelinian dichotomy.

Abuse of large amounts of methamphetamine for long periods easily produces psychotic symptoms, such as delusions of reference, persecution, and poisoning, as well as auditory and visual hallucinations (14–16). Further consumption of methamphetamine may result in severe psychosis, liability to relapse with reconsumption of methamphetamine or psychological stress, and a gradually worsening prognosis. Clinical similarities between methamphetamine psychosis and schizophrenia in a cross-section of clinical features have been noted; these include auditory hallucination and delusion, the longitudinal process of progressive exacerbation with acute relapses, relatively good response to neuroleptics, and enduring vulnerability to relapse to stressors, especially in the paranoid type of schizophrenia. Indeed, methamphetamine psychosis has long been considered a pharmacologic model of schizophrenia (17,18), and shared molecular mechanisms could be involved in these psychotic disorders. Based on this rationale, it is possible that the *DTNBP1*

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Received January 6, 2007; revised February 17, 2007; accepted March 14, 2007.

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2007.03.019

BIOL PSYCHIATRY 2008;63:191–196

gene may influence susceptibility to substance-induced psychoses in the same manner that influence susceptibility to schizophrenia and bipolar psychosis disorders. To examine this hypothesis, we investigated the association between *DTNBP1* and methamphetamine psychosis in a case–control analyses.

Methods and Materials

Subjects

The subjects consisted of 197 patients (162 male, 35 female; mean age ± SD, 38.1 ± 12.6) with methamphetamine psychosis (MAP) and 243 age-, gender-, and geographic-origin-matched healthy control subjects (193 male, 50 female; mean age ± SD, 37.2 ± 12.0) who had no individual or family history of drug dependence or major psychotic disorders such as schizophrenia and bipolar disorders. All the subjects were unrelated Japanese who were born and lived in relatively restricted areas of Japan. All patients were outpatients or inpatients in psychiatric hospitals of the Japanese Genetics Initiative for Drug Abuse (JGIDA). Consensus diagnoses of methamphetamine psychosis were made by two trained psychiatrists according to the ICD-10 criteria on the basis of unstructured interviews and medical records. All healthy control subjects were also psychiatrically screened based on unstructured interviews. The study protocol and purpose were explained to all subjects participating in the study, and written informed consent was obtained from all subjects. This study was approved by the Ethics Committee of each participating institute of JGIDA.

The patients with methamphetamine psychosis were divided into subgroups according to three clinical phenotypes that may indirectly indicate the severity of and liability to psychosis:

1. *Latency to onset of psychotic state after initial methamphetamine consumption:* Median latency was 3 years; 99 (54.4%) of patients developed psychotic symptoms within 3 years of the first methamphetamine abuse, and 83 (45.6%) patients did after 3 or more years.
2. *Duration of the psychotic state after therapy:* Methamphetamine-induced psychosis (transient type) will usually subside within 10 days to 1 month following discontinuance of consumption and beginning of pharmacologic therapy with antipsychotics such as haloperidol or risperidone. Some patients show sustained (longer than 1 month) psychotic symptoms (prolonged type), however, regardless of detoxification from methamphetamine and adequate antipsychotic therapy (16,19). In our study, 107 (56.6%) patients showed the transient type of psychosis, and 82 (43.4%) patients showed the prolonged type of psychosis.
3. *Complication of spontaneous psychosis:* Once methamphetamine psychosis has developed, some remitted patients may experience spontaneous relapse due to nonspecific stresses, such as severe fatigue or life problems, without consumption of methamphetamine. The observation period for the presence or absence of spontaneous relapse was at least 1 year and averaged 12.3 ± 11.1 years. Eighty-three patients (42.8%) experienced spontaneous relapse, and 111 (57.2%) did not.

As to multisubstance abuse status, 37.2% patients concurrently abused other illicit drugs in addition to methamphetamine. Cannabinoids were most frequently abused (34.0%), followed by LSD (14.1%), cocaine (13.1%), opioids (12%), and hypnotics (9.9%). More than 60% of patients abused only methamphetamine, but about half had a past history of organic solvent abuse in their teenage years. All clinical data were obtained from interviews with patients and their families. Urine examination was not applied.

DNA Analysis

We genotyped the three single nucleotide polymorphisms (SNPs), P1655 (rs2619539), P1635 (rs3213207), and SNPA (rs2619538) of the *DTNBP1* gene that were examined previously by O'Donovan's group and were shown to have a significant association with both schizophrenia and psychotic bipolar disorders (12,13). They showed in the schizophrenia study that these three locus haplotypes showed the most significant results among 26 significantly associated haplotypes constructed by combinations of 9 SNPs of *DTNBP*. P1655 and P1635 were two of the markers that had provided the most significant results in the study by Straub *et al.* (1), and SNPA was reported to be significantly associated with schizophrenia in a Japanese population (9).

The genomic DNA was extracted from peripheral leukocytes using the phenolchloroform method. Genotyping was performed by the polymerase chain reaction (PCR)–restriction fragment length polymorphism method. Each polymorphic site was amplified by PCR in a volume of 15 mL containing 3% dimethyl sulfoxide and .75 units of Taq DNA polymerase (Promega, Japan) using a unique primer set (P1655 [mismatch]; 5′-ATCAGGCAAAATGATGTACTGC-3′, 5′-GCCTTTTAAATAATCCTATTAGCTATGAGAGT-3′, P1635; 5′-CTTTATGCAATAAGTATTCCTG-3′, 5′-GTATACCCTGTTTTAAGCAGAC-3′, SNPA; 5′-CCTGTTTCTCAACTTAGTACAC-3′, 5′-CCTTTATCTTATTTAACTCCTG-3′). PCR reaction was performed under the following conditions: 95°C for 5 min, then 35 denaturing cycles of 30 sec each at 95°C, 1 min of annealing at the appropriate temperature, and 30 sec of extension, and final elongation at 72°C for 10 min. The PCR products were digested with the corresponding restriction enzyme for each polymorphism, *Hin*fI for P1655, *Bse*NI for P1635, and *Cai*I for SNPA, and then electrophoresed on 3.0% agarose gels and stained with ethidium bromide. All genotyping was performed in a blinded fashion, with the control and case samples mixed randomly. Part of the genotyping of P1655, P1635, and SNPA was confirmed by direct sequencing and a TaqMan SNP genotyping assay (C_16036968_10), respectively.

Statistical Analysis

Statistical analysis of association was performed using SNPAlyze software (Dynacom, Mobara City, Chiba, Japan). Deviation from Hardy–Weinberg equilibrium and the case–control study were tested using the χ^2 test. Linkage disequilibrium (LD) was tested using the 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 values were calculated based on 100,000 replications.

GenBank/EMBL Accession Numbers

Genome; NC_000006.10, NT_007592.14, MIM; 607145.

Results

The genotype distribution and allele frequencies for each polymorphism of patients with methamphetamine psychosis and control subjects are shown in Table 1. The genotype distributions of patients and control subjects did not deviate from the Hardy–Weinberg equilibrium at any of the three SNPs. We found a significant difference between patients and control subjects in the frequencies of the genotype or allele at P1635 and SNPA of

Table 1. Genotype and Allele Distribution of Three Single Nucleotide Polymorphisms of the *DTNBP1* Gene in Control Subjects and Patients with Methamphetamine (MAP) Psychosis

			Genotype				Allele		
		N	C/C	C/G	G/G	*p*	C	G	*p*
P1655	rs2619539								
Control		240	118 (49.2)	107 (44.6)	15 (6.2)		343 (71.5)	137 (28.5)	
MAP Psychosis		190	78 (41.0)	94 (49.5)	18 (9.5)	.17	250 (65.8)	130 (34.2)	.076
P1635	rs3213207		A/A	A/G	G/G		A	G	
Control		243	239 (98.4)	4 (1.6)	0 (.0)		482 (99.2)	4 (.8)	
MAP Psychosis		197	175 (88.8)	22 (11.2)	0 (.0)	.000025	372 (94.4)	22 (5.6)	.000030
SNPA	rs2619538		A/A	A/T	T/T		A	T	
Control		232	225 (97.0)	7 (3.0)	0 (.0)		457 (98.5)	7 (1.5)	
MAP Psychosis		197	182 (92.4)	15 (7.6)	0 (.0)	.046	379 (96.2)	15 (3.8)	.049

Numbers in parentheses indicate percentages.

the *DTNBP1* gene (P1635: genotype, $\chi^2 = 17.74$, $df = 1$, $p = .000025$; allele $\chi^2 = 17.20$, $df = 1$, $p = .000030$; SNPA: genotype $\chi^2 = 4.63$, $df = 1$, $p = .046$; allele $\chi^2 = 4.51$, $df = 1$, $p = .049$). The minor alleles of P1635 and SNPA, G and T alleles, respectively, were in excess in methamphetamine psychosis when compared with control subjects. To avoid a type I error due to multiple comparison, the Bonferroni correction was applied to the results. The G allele of P1635 was still significantly more frequent in the methamphetamine psychosis patients than in control subjects, but SNPA was not significantly different after correction. P1655 did not show significant differences in distribution of allele and genotype between groups.

Comparison between subgroups of the patients according to clinical phenotypes showed a significant difference in allelic and genotypic distribution of P1635 between the two subgroups divided by duration of psychotic state after therapy, transient and prolonged types (Table 2). The frequency of the minor allele G of P1635 was only 0.8% in control subjects, whereas it was 3.3% in patients with transient psychosis and 8.5% in patients with prolonged psychosis ($p = .027$, compared with transient psychosis). After Bonferroni correction, this was not significant. The other clinical phenotypes, psychosis latency and spontaneous relapse, were not associated with any SNP examined.

Estimation of the pairwise LD between the three SNPs of the *DTNBP1* gene using the D′ and r^2 values as an index showed that P1655, P1635, and SNPA have strong LD (D′ ranging between 0.65 and 1.0) with each other (Table 3). We then analyzed the three-marker haplotypes (Table 4) and found significant differences in patients and control subjects at P1655-P1635-SNPA ($\chi^2 = 27.8$, $df = 6$, global permutation $p = .0005$).

Table 2. Association of the *DTNBP1* Gene with Subgroups of Patients Divided by Clinical Phenotypes

		Genotype				Allele		
	N	C/C	C/G	G/G	*p*	C	G	*p*
P1655								
Latency to Onset of Psychosis, <3Y	96	35 (36.5)	50 (52.1)	11 (11.4)		120 (62.5)	72 (37.5)	
Latency to Onset of Psychosis, ≥3Y	79	36 (45.6)	37 (46.8)	6 (7.6)	.41	109 (69.0)	49 (31.0)	.20
Transient MAP Psychosis	103	44 (42.7)	50 (48.6)	9 (8.7)		138 (67.0)	68 (33.0)	
Prolonged MAP Psychosis	79	29 (36.7)	42 (53.2)	8 (10.1)	.71	100 (63.3)	58 (36.7)	.46
Spontaneous Relapse; No	108	41 (38.0)	54 (50.0)	13 (12.0)		136 (63.0)	80 (37.0)	
Spontaneous Relapse; Yes	77	34 (44.1)	38 (49.4)	5 (6.5)	.40	106 (68.8)	48 (31.2)	.24
P1635		A/A	A/G	G/G		A	G	
Latency to Onset of Psychosis, <3Y	99	89 (89.9)	10 (10.1)	0 (.0)		188 (94.9)	10 (5.1)	
Latency to Onset of Psychosis, ≥3Y	81	71 (87.7)	10 (12.3)	0 (.0)	.63	152 (93.8)	10 (6.2)	.64
Transient MAP Psychosis	107	100 (93.5)	7 (6.5)	0 (.0)		207 (96.7)	7 (3.3)	
Prolonged MAP Psychosis	82	68 (82.9)	14 (17.1)	0 (.0)	.022	150 (91.5)	14 (8.5)	.027
Spontaneous Relapse; No	111	98 (88.3)	13 (11.7)	0 (.0)		209 (94.1)	13 (5.9)	
Spontaneous Relapse; Yes	82	73 (89.0)	9 (11.0)	0 (.0)	.87	155 (94.5)	9 (5.5)	.88
SNPA		A/A	A/T	T/T		A	T	
Latency to Onset of Psychosis, <3Y	99	91 (91.9)	8 (8.1)	0 (.0)		190 (96.0)	8 (4.0)	
Latency to Onset of Psychosis, ≥3Y	82	75 (91.5)	7 (8.5)	0 (.0)	.91	157 (95.7)	7 (4.3)	.910
Transient MAP Psychosis	108	102 (94.4)	6 (5.6)	0 (.0)		210 (97.2)	6 (2.8)	
Prolonged MAP Psychosis	82	73 (89.0)	9 (11.0)	0 (.0)	.170	155 (94.5)	9 (5.5)	.18
Spontaneous Relapse; No	110	104 (94.5)	6 (5.5)	0 (.0)		214 (97.3)	6 (2.7)	
Spontaneous Relapse; Yes	82	74 (90.2)	8 (9.8)	0 (.0)	.26	156 (95.1)	8 (4.9)	.27

Number in parentheses indicate percentages.

Table 3. Pairwise Linkage Disequilibrium Between Single Nucleotide Polymorphisms of the *DTNBP1* Gene

	P1655	P1635	SNPA
P1655		.9643	1.0000
P1635	.0128		.6519
SNPA	.0114	.3522	

Right upper and left lower diagonal showed D′ and r^2 values, respectively.

The estimated haplotype frequency of C-A-A of P1655-P1635-SNPA was significantly lower in patients with methamphetamine psychosis than in control subjects (p = .0013). Conversely, the C-G-T haplotype was significantly higher in patients than in control subjects (p = .0012). Permutation p values of these haplotypes remained significant even after Bonferroni correction. Odds ratios were .62 (95% confidence interval [CI] .51–.77) and 14.9 (95% CI 3.5–64.2), respectively, indicating that the C-A-A haplotype protected against development of methamphetamine psychosis. On the other hand, the C-G-T haplotype was a significant risk factor for development of methamphetamine psychosis.

Discussion

We found a significant association between the *DTNBP1* gene and methamphetamine psychosis in individual marker and haplotype-based case–control analyses. The G allele of P1635 was shown to be a risk factors for methamphetamine psychosis. Numakawa *et al.* (9) reported that the G allele of P1635 was a risk factor for schizophrenia in Japanese; other reports have shown that it was also overtransmitted in Irish (1) but not in German schizophrenia (2). We also found that the G allele of P1635 was in excess in a subgroup showing a prolonged psychotic state, indicating that the allele was a risk for a worse prognosis of psychosis or refractoriness to antipsychotic therapy in patients with methamphetamine psychosis. The T allele of SNPA also showed a nominally significant risk for methamphetamine psychosis. Although it did not remain significant after multiple comparison correction, one study of schizophrenia showed that it was a significant risk (9), whereas another did not (13). The most striking findings in our study were that analyses of a haploype constructed by P1655-P1635-SNPA of the *DTNBP1* gene revealed a strong association with methamphetamine psychosis (p = .0005). The C-A-A haplotype was significantly more common in control subjects than patients with methamphetamine psychosis (p = .0013), implying a substantial protective factor given the odds ratio of .62. The protective haplotype found in our study of methamphetamine psychosis was identical with that previously reported in studies of schizophrenia and psychotic bipolar disorders (12,13). This evidence may indicate that the C-A-A haplotype of *DTNBP1* reduces the liability of individuals who suffer from endogenous psychoses or substance abuse to complications of psychotic symptoms such as delusions and hallucinations. Another possibility should be also considered, however; the C-A-A haplotype may be associated with methamphetamine dependence but not methamphetamine psychosis because all the patients examined in our study suffered not only from methamphetamine psychosis but also dependence. Accordingly, these hypotheses should be examined in other psychotic disorders—for example, psychotic depression, organic psychoses, and cocaine paranoia—as well as in other dependence disorders. In contrast, the C-G-T haplotype was a significant risk for development of methamphetamine psychosis. The frequency of the C-G-T haplotype was small at about 3% in methamphetamine psychosis but almost absent in control subjects, resulting in a strong risk and an odds ratio of 14.9. This haplotype was absent in the UK/Irish studies. In these studies, the C-A-T haplotype was a risk for both schizophrenia and psychotic bipolar disorder; however, this haplotype was rare (<1%) in Japanese samples and was not a significant factor for methamphetamine psychosis. In addition, the UK/Irish studies showed the G-G-T haplotype was as rare as 3% in control subjects but completely absent in schizophrenia, indicating a potent protective factor against schizophrenia. Again, this haplotype was absent in our samples. Such inconsistencies between the present study and UK/Irish studies indicate that the influence of genetic variation of *DTNBP1* on susceptibility to psychiatric disorders differs among the three distinct disorders (i.e., methamphetamine psychosis, schizophrenia, and psychotic bipolar disorder), although the protective C-A-A haplotype was common to all of them. In addition, population differences in SNP frequencies may also affect results. For example, the minor allele frequency of SNPA was .02, which was consistent with another Japanese study (9), but UK/Irish samples showed a frequency of .45 (13). The P1655 frequency was .28 in our samples, which was similar to another Japanese sample (.31) but different from Caucasian samples (.47 in Straub's study [1] and .49 in Williams's study [13]).

The relationship between abnormal dysbindin function and methamphetamine psychosis is unclear. The *DTNBP1* gene encodes a 40-Kd coiled-coil-containing protein that binds to β-dystrobrevin to form dystrophin-associated protein complex (DPC), which is found in postsynaptic densities of the brain (20). *DTNBP1*, however, is particularly expressed in certain axon terminals, notably, mossy fiber synaptic terminals in the cerebellum and hippocampus independent of DPC (20). Talbot *et al.* (10) found that patients with schizophrenia displayed a presynaptic DTNBP1 reduction in the hippocampus, and an inversely correlated increase in vesicular glutamate transporter-1 occurred in the same schizophrenia cases, suggesting a relationship between glutamatergic neurotransmission and DTNBP1. Evidence in vitro showed that overexpression of DTNBP1-enhanced glutamine release accompanied by an increase of presynaptic machinery SNAP25 and synapsin 1 and a knockdown of DTNBP1 by siRNA-reduced glutamate release. Reduced expression of DTNBP1 in schizophrenic brains may result in hypofunction of the glutamatergic system in the brain, which has been promising hypothesis for the pathophysiology of schizophrenia (21,22). Based on the clinical similarity between methamphetamine psychosis and schizophrenia, it has been assumed that shared neural mechanisms, not only dopamine systems but also gluta-

Table 4. Haplotype Frequencies of the *DTNBP1* Gene of Control Subjects and Methamphetamine (MAP) Psychosis

Haplotype P1655-P1635-SNPA	Controls Frequency	MAP Psychosis Frequency	Permutation p
C-A-A	.7101	.6046	.0013
G-A-A	.2741	.3315	.076
C-G-T	.0022	.0318	.0012
C-G-A	.0023	.0178	.11
C-A-T	.0073	.0055	.83
G-G-A	0	.0089	.15
G-A-T	.0039	0	.18

Haplotype analysis was performed by the permutation method. The global permutation p value was .0005.

mate systems, may be involved in the two psychotic disorders. Many lines of evidence from experimental studies using behavioral sensitization by repeated psychostimulant treatment, which has been recognized as an animal model of methamphetamine psychosis (18), showed pivotal roles of N-methyl-D-aspartate (NMDA) receptors and glutamate systems in the development of behavioral sensitization. Thus repeated administration of amphetamine or cocaine produces behavioral sensitization with enhanced efflux of glutamate in the ventral tegmental area (VTA) and accumbens, which are key brain structures for sensitization phenomena (23,24). NMDA receptor antagonists, including the noncompetitive antagonist MK-801, prevent behavioral sensitization to amphetamines when administered systemically or microinjected into the VTA (25–28). In contrast, phencyclidine, another NMDA antagonist, exacerbates amphetamine-induced abnormal behaviors and a hyperdopaminergic state in the prefrontal cortex and striatum (29–31). Amphetamines can also directly inhibit the NMDA receptor complex (32). Although the roles of NMDA receptors and glutamatergic systems in animal models of methamphetamine psychosis seem to be complex, our findings may indicate that variants of *DTNBP1* affect susceptibility to methamphetamine psychosis by implication of glutamatergic neurotransmission. In addition, DTNBP1 was shown to enhance phosphorylation of AKT protein by PI3-kinase and protect against neuronal cell death. Impaired PI3-kinase-Akt signaling and a genetic association with the *AKT1* gene were found in schizophrenia (20,33,34). Previously, we also found a significant association of the *AKT1* haplotype with the same patients of methamphetamine psychosis (35). It is possible that DTNBP1 confers susceptibility to methamphetamine psychosis via the PI3-kinase-Akt signaling cascade. In vitro evidence of interaction between dysbindin and dopamine system was recently reported. Kumamoto *et al.* (36) found that mRNA of disbindin expressed in the mouse substantia nigra, that suppression of dysbindin expression in PC 12 cells resulted in an increase of dopamine release, and that overexpression of dysbindin produced a tendency to decrease dopamine release. This finding suggests that dysbindin dysfunction may induce susceptibility to methamphetamine psychosis through interaction with dopamine systems.

Alternatively, the effect of DTNBP1 on cognitive ability should be considered. In an analysis of the phenotype–haplotype relationship, Williams *et al.* (13) found that the C-A-A protective haplotype was significantly associated only with higher educational attainment. A longitudinal study of childhood and adolescent antecedents of drug and alcohol problems in adulthood showed that, for both males and females, educational attainment was directly associated with a reduced risk for substance use problems (37). In this respect, higher educational attainment due to carrying the C-A-A haplotype might be involved in a reduced risk for methamphetamine psychosis, and the phenotype of higher educational attainment might be a common protective factor in methamphetamine psychosis and schizophrenia. Further studies are required to confirm this possibility.

Although our results remained significant after Bonferroni correction, it is possible that this was a chance finding resulting from reduced power due to small sample size. Analysis showed, however, that our sample size for the three SNPs had powers of .9994, 1.0000, and .9594 to detect an effect size (w = .1892, .5388, and .1263, respectively), with a significance level of .05 to detect significant associations in allelic analysis between control subjects and subjects with methamphetamine psychosis. Our total sample size is therefore large enough statistically, and it is unlikely that our positive findings results from reduced power. When methamphetamine psychosis patients are divided into subgroups according to clinical phenotypes, however, the statistical power may be reduced. It is possible that a rare haplotype C-G-T as a risk for methamphetamine psychosis may result from a chance fluctuation. In addition, a false-positive association owing to population stratification could not be excluded in this study despite careful matching of control subjects and patients. Our findings should be confirmed in larger samples and in different populations.

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan; a grant from the Ministry of Health, Labor, and Welfare of Japan; and from the Zikei Institute of Psychiatry (Okayama, Japan).

The authors have no conflicts of interest to declare.

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