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Further Association Study on Dopamine D2 Receptor Variant S311C in Schizophrenia and Affective Disorders

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The dopamine D2 receptor gene is a candidate gene for schizophrenia because the potency of certain neuroleptics correlates with their affinity for this receptor. Case-control studies in 291 schizophrenics, 78 patients with affective disorders, and 579 controls on an association of a molecular variant of S311C of the dopamine D2 receptor with psychiatric disorders were conducted. The frequency of individuals with S311C was significantly higher in schizophrenics with the absence of negative symptoms (17.1%, $P < 0.00001$), but similar in schizophrenics with the presence of negative symptoms (5.7%, $P = 0.46$) when compared with the controls (4.1%). The frequency of S311C was significantly higher in familial schizophrenics from one local area but not in those from other areas. It was significant that S311C was frequently present in patients with mood-incongruent psychotic affective disorders (33.3%, $P < 0.0001$), but not in those with other affective disorders. These data suggest that S311C might be one of the genetic factors for symptomatic dimensions of delusions and hallucinations and might be involved in underlying clinical heterogeneity in schizophrenia and affective disorders. © 1996 Wiley-Liss, Inc.

KEY WORDS: candidate gene, psychiatric disorders, S311C

INTRODUCTION

The clinical presentation of schizophrenia is characterized by marked variability in age and type of onset, premorbid adjustment, signs and symptoms, treatment response, and course of illness. Although roles of the genetic components for the liability to schizophrenia are evident, the question of whether genetic heterogeneity contributes to this clinical variability is unsolved. Family studies using multiplex families and twins support no genetically qualitatively distinct subtypes of schizophrenia but rather a quantitative tendency [Gottesman et al., 1982]. On the other hand, the consensus from recent family studies has shown that the boundary between schizophrenia and affective disorder is not distinct, and that schizophrenia-relevant spectrum disorders implicate schizotypal personality, schizoaffective psychoses, and affective disorders with mood-incongruent psychoses. It is likely that multiple genetic and environmental factors interact to produce a spectrum of these disorders [Gottesman, 1994].

The evidence for multiplicative interaction in the etiology of schizophrenia suggests that it will be useful to consider the analysis of schizophrenia as a multidimensional phenotype in which multiple symptomatic dimensions of underlying components interact to cause the manifest clinical heterogeneity [Cloninger, 1994]. Strauss et al. [1974] delineated positive, negative, and interpersonal aspects of the psychopathology of schizophrenia. These symptoms may occur together or apart, thereby reflecting independent quantitative dimensions of clinical and etiological variations among schizophrenics. Consequently, it should be useful to relate variation in candidate genes to such individual clinical syndromes of dimensions, rather than to schizophrenia as a symptomatically heterogeneous whole, because individual dimensions or components are likely to have a more simple genetic basis than schizophrenia as a heterogeneous whole [Cloninger, 1994].

The dopamine D2 receptor gene (*DRD2*) has been thought to be one of the candidate genes for schizophrenia because so-called typical neuroleptics bind D2 receptors with high affinity. Although no families have been found suggesting a linkage to *DRD2* [Moises et al., 1991; Coon et al., 1993, 1994; Su et al., 1993, the possibility of the existence of *DRD2* variants that have small effects on susceptibility to schizophrenia in a small pro-

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portion of multiplex pedigrees or that relate to schizophrenia as a modifier still remains. Searches for sequence variations in the coding region of the *DRD2* gene have been carried out with an independent detection of one missence variation, S311C, by Gejman et al. [1994] and Itokawa et al. [1993]. Gejman et al. [1994] reported no association of the variant with schizophrenia, whereas we reported data suggesting an association with some types of schizophrenia [Arinami et al., 1994]. Thereafter, several studies failed to find significantly increased frequencies of S311C in schizophrenics as a whole [Asherson et al., 1994; Laurent et al., 1994; Nanko et al., 1994; Nöthen et al., 1994; Shaikh et al., 1994; Sobell et al., 1994], though Shaikh et al. [1994] found a nonsignificant increased frequency of S311C in schizophrenics. None of these studies referred to the clinical symptoms of the schizophrenics studied.

Since the D2 receptor may play important roles in development and treatment of the symptoms of schizophrenia and since the S311C polymorphism is the only variant found in 170 schizophrenics in whom the total coding region of *DRD2* was analyzed so far [Sarkar et al., 1991; Itokawa et al., 1993; Gejman et al., 1994], S311C is worth examining in terms of its possible implication in syndromal heterogeneity of schizophrenia. We report data obtained from 291 schizophrenics, 78 affective disorder patients that include schizophrenia-relevant spectrum disorders, and 579 controls.

MATERIALS AND METHODS

Subjects

The schizophrenics analyzed in this study were 291 unrelated Japanese patients (166 males and 125 females) with a mean ± S.D. age of 44.9 ± 13.1. Except for 11 postmortem brain samples [Toru et al., 1988], 280 cases were recruited from patients who were being treated at 8 hospitals in the Kanto area (Tokyo, Kawasaki, and Chiba), Fukushima Prefecture, and Nagano Prefecture in Japan (Table I). Most of the patients in Nagano were selected for their family histories of psychiatric disorders, but the patients in the other areas were not selected on that basis. All patients satisfied ICD-10 or DSM-III-R criteria for schizophrenia.

The subjects with affective disorders were unrelated patients with bipolar affective disorders (n = 34, 18 males and 16 females, age 55.4 ± 12.8), major depression (n = 33, 13 males and 20 females, age 59.9 ± 11.4), and dysthymia (n = 11, 4 males and 7 females, age 58.2 ± 13.3), who were being treated at 4 hospitals in the Kanto and Fukushima areas. All the patients gave us informed consent for this study.

The control subjects consisted of 579 unrelated Japanese with a mean ± S.D. age of 49.2 ± 11.5. Among them, 135 hospital staff members and 10 postmortem controls were psychosis free, but the other apparent healthy controls were not evaluated for psychiatric disorders by psychiatrists (Table I).

TABLE I. Distribution of S311C-Positive Controls and Schizophrenics

	Population							
	Kanto (Tokyo area)		Fukushima		Nagano		Total	
	Number of Cys311-positive subjects/number examined (%)							
Controls								
Total	22/533	(4.1)	2/16	(12.5)	0/30	(0.0)	24/579	(4.1)
Postmortem brain samples	2/10	(20.0)					2/10	(20.0)
Parents of hypercholesterolemic children	6/200	(3.0)					6/200	(3.0)
Government employees	6/142	(4.2)					6/142	(4.2)
Hospital staff members free from psychosis	3/89	(3.4)	2/16	(12.5)	0/30	(0.0)	5/135	(3.7)
Patients treated for coronary heart disease	5/92	(5.4)					5/92	(5.4)
Schizophrenics								
Total	13/149	(8.7)*	5/109	(4.6)	8/33	(24.2)**	26/291	(8.9)**
Postmortem brain samples	2/11	(18.2)					2/11	(18.2)
Patients receiving treatment	11/138	(8.0)	5/109	(4.6)	8/33	(24.2)**	24/280	(8.6)*
Both positive sx. and negative sx present[a]	2/69	(2.9)	0/47	(0.0)	2/11	(18.2)	4/127	(3.1)
Positive sx. absent and negative sx present[a]	2/29	(6.9)	0/27	(0.0)	3/14	(21.4)*	5/70	(7.1)
Positive sx. present and negative sx absent[a]	2/14	(14.3)	4/22	(18.2)	3/6	(50.0)**	9/42	(21.4)****
Both positive sx and negative sx absent (remissions)	5/26	(19.2)***	1/13	(7.7)	0/2	(0.0)	6/41	(14.6)**
Patients with schizophrenic first-degree relatives	1/18	(5.6)	1/8	(12.5)	5/18	(27.8)**	7/44	(15.9)**
Patients without schizophrenic first-degree relatives	10/120	(8.3)	4/101	(4.0)	3/15	(20.0)*	17/236	(7.2)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, ****$P < 0.00001$ vs. the controls in each area

[a]Positive symptoms were assessed by items of delusions and hallucinations, and negative symptoms were assessed by items of poverty of speech, affective flattening, or psychomotor retardation of the Manchester Scale. Presence of positive or negative symptoms was defined as the morbid rating (2,3, or 4) of at least one of these items.

Among the subjects, 156 patients including the postmortem samples as well as 300 controls were those on whom we have previously reported [Arinami et al., 1994].

Analytical Procedures

The S311C polymorphism was typed with the polymerase chain reaction assay [Arinami et al., 1994]. A modified primer to introduce an artificially restriction site for enzyme *Asu*I was used. S311C and S311 were distinguished by fragments with 126 base pairs (bp) and 148 pb, respectively. *Bal*I polymorphism in the first exon of the dopamine D3 receptor gene (*DRD3*) and the 48 bp repeat polymorphism in the dopamine D4 receptor gene (*DRD4*) were determined according to Lannfelt et al. [1992] and Shaikh et al. [1993], respectively.

The patients' clinical data regarding age, age at onset, history of marriage, number of children, outpatient or inpatient treatment, inpatient period (days), neuroleptics prescribed, and schizophrenia in first-degree relatives were based on the medical records. Clinical symptoms were assessed according to the Manchester Scale [Krawiecka et al., 1977] by 8 of the authors (M.I., J.A., H.S., Y.O., A.I., K.O., H.S., and M.T.). Except for 18 cases, 136 patients additionally examined in this study were assessed by psychiatrists different from those who assessed the 156 patients reported in our previous paper. One (T.A.) of the authors who did not assess clinical symptoms summed up the data. Clinical features of the patients with affective disorders were based on the medical records.

Comparisons were made by the two-tailed 2×2 χ^2 test with Yates' correction and, in cases where the expected cell values were less than 5, Fisher's Exact Test for dichotomous dependent variables. Continuous dependent variables between S311C-positive and -negative patient groups were assessed by the Wilcoxon Test.

RESULTS

Findings in the previous paper [Arinami et al., 1994] showed marginally significant increases of homozygotes for S311C and of the S311C allele in the schizophrenics compared with the controls, significant increases of the S311C allele in the familial schizophrenics and in the schizophrenics whose age at onset was less than 25 compared with the controls, and significantly less severe negative symptoms of the S311C-positive patients compared with those of the S311C-negative patients. Since most of these positive findings in the previous report emerged post hoc, only findings replicated in the new samples by the analyses according to the same criteria are more likely to be true. In the newly examined 135 schizophrenics and 279 controls, less severe negative symptoms and thought disorders of the S311C-positive patients than those of the S311C-negative patients were replicated: average ± SEM scores of the items of affective flattening, psychomotor retardation, thought disorder, and poverty of speech in the patients with S311C vs. those without S311C were 1.3 ± 0.3 vs. 2.0 ± 0.1 ($P = 0.02$), 1.3 ± 0.2 vs. 1.7 ± 0.1 ($P = 0.08$), 0.9 ± 0.3 vs 1.6 ± 0.1 ($P = 0.02$), and 0.9 ± 0.3 vs. 1.4 ± 0.1 ($P = 0.06$), respectively. Scores of the items of positive symptoms such as delusion and hallucination were not different between the two groups: 1.6 ± 0.3 vs. 1.8 ± 0.1 ($P = 0.58$), 1.3 ± 0.3 vs. 1.6 ± 0.1 ($P = 0.35$). On the other hand, findings on homozygotes for S311C and patients with a younger age at onset were not replicated. The S311C allele frequencies of 0.044 (12 of 272 chromosomes) in the schizophrenics and of 0.067 (4 of 60) in the schizophrenics with schizophrenic first-degree relatives were higher than 0.025 (14 of 558) in the controls. However, the differences were not significant and all the familial schizophrenics with S311C were Nagano patients. Thus, consistent findings between the previous subjects and the newly examined subjects suggest possible associations of S311C with a less severity of negative symptoms and familial schizophrenia in limited areas.

In the combined samples, the frequencies of the presence of S311C were significantly different ($P = 0.01$) between patients and controls (Table I). However, this difference was mainly due to frequent S311C in the Nagano patients. The frequencies of the S311C-positive cases excluding the postmortem samples were not significantly different in the Fukushima and Kanto areas compared with the controls. However, the frequency of S311C-positive patients was significant in the subgroup of the patients who lacked morbid negative symptoms in all 3 populations. We defined the presence of negative symptoms as a morbid rating (2, 3, or 4) in at least one item of either poverty of speech, affective flattening, or psychomotor retardation of the Manchester Scale at the time of the examination. The frequency of S311C in the patients with negative symptoms was similar to that in the controls. Parameters (average ± SEM) possibly relating to negative symptoms such as age, dose of antipsychotics as chlorpromazine equivalent prescribed, and number of days of the current admission (inpatients only) of the S311C-positive patients vs. the S311C-negative patients were 42.1 ± 2.5 vs. 44.7 ± 2.5, 1,566 ± 281 vs. 1,249 ± 97, and 2,979 ± 1,121 vs. 4,579 ± 350, respectively. Although the difference in the number of days of the current admission was not significant, it was considerable. The hospitalization between these two groups is analyzed and presented in a later paragraph.

The frequency of S311C-positive patients was not significant in the subgroup of the patients who had or not morbid positive symptoms. However, S311C-positive familial schizophrenics had severe positive symptoms compared with S311C-negative familial cases, though the difference was not significant.

S311C was increased in familial schizophrenics who had at least one first-degree relative with schizophrenia. However, this was due to the increased frequency of S311C in familial cases in the Nagano patients. To evaluate hidden population stratification and inbreeding, we genotyped *Bal*I polymorphisms in *DRD3* and a 48 bp repeat polymorphism in *DRD4* in the 33 Nagano patients and 30 controls residing in the same area. The homozygous state of either allele of the D3 polymorphism has been proposed to be associated with schizophrenia, although this has caused some controversy [Crocq et al., 1992; Jönsson et al., 1993; Nanko et al.,

TABLE II. Marital Status of the Schizophrenic Subjects Aged Over 30 at the Examination*

	Cys311		
	Presence	Absence	*P*
Total			
Married	8	30	
Divorced	2	11	0.02
Unmarried	7	99	
Negative symptoms of schizophrenia			
Absence			
Married	5	8	
Divorced	2	3	0.21
Unmarried	3	12	
Presence			
Married	3	30	
Divorced	0	8	0.27
Unmarried	4	87	

*Comparisons were made between married and unmarried by Fisher's exact test.

1993; Nimgaonkar et al., 1993; Nöthen et al., 1993a, b; Yang et al., 1993; Di Bella et al., 1994; Mant et al., 1994; Saha et al., 1994]. Studies on the D4 polymorphism and schizophrenia have also been reported [Shaikh et al., 1993; Sommer et al., 1993; Daniels et al., 1994; Macciardi et al., 1994]. Each allele frequency and genotype of these polymorphisms in the Nagano patients was similar to those in the controls and did not deviate from Hardy-Weinberg equilibrium (data not shown). Thus, the possibility of the hidden population stratification and inbreeding was not suggested.

To evaluate the interpersonal aspects of the psychopathology of schizophrenia, the present marital status was compared in those patients older than 30 (Table II). It is significant that the S311C-positive patients were more frequently married compared with the S311C-negative patients. These data suggest that there was less severe interpersonal impairment in the S311C-positive schizophrenics, particularly those who lacked negative symptoms.

In the patients with affective disorders, the frequency of the presence of S311C was not significantly different when compared with the controls (Table III). Mood-incongruent psychotic affective illness has been proposed to be a distinct subtype of affective illness, and it is listed as one of the schizophrenia-relevant spectrum disorders [Kendler, 1991]. When the patients with affective disorders were divided into the presence and absence of episodes with mood-incongruent psychosis, S311C appears to be frequently found among the patients with mood-incongruent psychotic affective disorders: 33% (95% confidence interval 13.8–60.9%) of the patients with mood-incongruent psychotic affective disorders had the variant, whereas a prevalence for the variant in the patients with nonpsychotic affective disorders was similar to that in the controls. S311C was not found in 4 bipolar patients with mood-congruent psychotic symptoms. One in 6 patients with S311C and 2 in 70 without it had a schizophrenic first-degree relative.

DISCUSSION

There are 2, the short (D2S) and the long (D2L), isoforms of the D2 receptor that are produced by alternative splicing. The site of S311C locates in the cytoplasmic third loop of both isoforms and, in D2S, it locates in the middle of the cytoplasmic third loop. S311 is conserved in the rat, mouse, and frog. No homologous amino acid sequence correspondent to the sequence spanning S311 exists in other subtypes of human dopamine receptors, D1, D3, D4, and D5. Although consequences for the receptor function due to S311C are still under investigation, our study on the D2 receptor expressed in Chinese hamster ovary cells has shown significantly less sequestration of the S311C type of D2S compared with that of the wild type of D2S (manuscript in preparation).

Shaikh et al. [1994] documented possible good responses to clozapine and typical antipsychotic drugs of S311C-positive patients. Crawford et al. found that a patient homozygous for S311C was best responded to clozapine among the S311C-positive patients (personal communication). Clozapine binds with high affinity to the D4 receptor. However, it binds to D2S with an affinity comparable to that for D4 receptors [Malmberg et al., 1993]. An association between S311C and good responses to antipsychotic treatment is an intriguing hypothesis.

Other groups have failed to find an increased frequency of S311C in familial cases [Asherson et al., 1994; Laurent et al., 1994; Nanko et al., 1994; Nöthen et al., 1994; Shaikh et al., 1994; Sobell et al., 1994]. In our study, the frequency of S311C was significantly fre-

TABLE III. Distribution of S311C-Positive Subjects With Affective Disorders

	Number of Cys311-positive subjects/ number examined(%)
Affective disorders	6/78 (7.7)
Bipolar affective disorder	4/34 (11.8)
Subgroup	
Presence of episodes with mood-incongruent psychosis	3/9 (33.3)*
Absence of episodes with mood-incongruent psychosis	1/25 (4.0)
Major depression	2/33 (6.1)
Subgroup	
Presence of episodes with mood-incongruent psychosis	1/3 (33.3)
Absence of episodes with mood-incongruent psychosis	1/30 (3.3)
Dysthymia	0/11 (0.0)

*$P < 0.01$ vs. the total controls.

quent in Nagano patients but was not significantly different between the patients and the controls in other areas. A hidden population stratification of Nagano samples may exist, though we did not find the evidence. Simple chance positive findings in Nagano samples or an association of S311C with schizophrenia in individuals living in this region is also possible. In the latter case, there could exist other unknown genetic and environmental backgrounds in a combination in which S311C increases the liability to schizophrenia. Further study in this region will address these questions.

The results of the present study appear to suggest that S311C is associated with a type of schizophrenia in which neither enduring negative symptoms nor interpersonal dysfunctions develop. However, it must be mentioned that our patient samples do not represent schizophrenics as a whole. They were recruited from those who gave us informed consent and most of the patients were receiving treatment at hospitals. Therefore, it is possible that relatively more patients who were stable and not severely ill, cooperative, and had a good relationship with their psychiatrists were included in this study. Since these characteristics were in line with those with which we propose that S311C is associated, there might be a bias toward more frequent S311C-positive patients in our samples, if the association is true.

Other groups have not found significantly increased frequencies of S311C in schizophrenics compared to controls [Asherson et al., 1994; Gejman et al., 1994; Laurent et al., 1994; Nanko et al., 1994; Nöthen et al., 1994; Shaikh et al., 1994; Sobell et al., 1994]. Therefore, it is possible that the positive results of ours were chance findings. These association studies have also shown a wide range of variations in the S311C allele frequency in the populations that could be used for the controls: from less than 0.01 in the United Kingdom [Asherson et al., 1994; Shaikh et al., 1994] and in Sweden [Friedman et al., 1994], 0.018 in Germany [Nöthen et al., 1994] and the United States [Sobell et al., 1994], to 0.035 in Utah (Byerley et al., personal communication) in Caucasians, and from 0.008 (Ohara et al., personal communication), 0.022 (the present study), to 0.035 [Nanko et al., 1994] in Japanese. Low and fluctuating allele frequencies of S311C among control samples would increase chance positive findings. At the same time, they increase the difficulty in detecting a weak association.

The present study showed an odds ratio for schizophrenics carrying S311C was 1.5 with 95% CI 0.8–2.8 comparing with the controls when Nagano patients who were selected mainly for their family history were excluded. Therefore, an association of S311C and schizophrenia might be very weak, even if it exits. The statistical power to allow detection or denial of this magnitude of relative risk requires a study analyzing more than 1,000 samples of patients and appropriate controls. Identification of the clinical characteristics with which S311C could be more strongly associated will help in having greater likelihood of revealing a definitive result. In this study, S311C was not found significantly in the schizophrenics with the presence of negative symptoms. Several studies suggested that psychotic symptoms differ from negative symptoms in the heritability [Kendler et al., 1986; Dworkin et al., 1988] and in the pathophysiology [Andreasen et al., 1991], though the negative/positive dichotomy has been criticized because of change in phenomenology over time and interdependency of positive and negative symptoms [Häfner and Maurer, 1991; Maurer and Häfner, 1991]. In all the geographical populations in this study, the frequencies of S311C were increased in the schizophrenics who lacked negative symptoms. Therefore, absence of negative symptoms might be the clinical characteristics of schizophrenia with which S311 is associated. This type of schizophrenia is a part of positive schizophrenia [Andreasen and Olsen, 1982] or nondeficit schizophrenia [Carpenter et al., 1993]. The absence of negative symptoms is one of the attributes of Crow's type I syndrome of schizophrenia in which the dopaminergic system is hypothesized to be involved [Crow, 1980]. It has been suggested that positive and negative symptoms are independent dimensions and genetically transmitted in family members of schizophrenics [Bassett et al., 1993].

In this study, the patients with mood-incongruent psychotic affective disorders also frequently had S311C. It might be postulated that S311C is one of the factors predisposing to mood-incongruent psychosis during episodes for affective disorders. The relevance of affective disorder with mood-incongruent psychosis to schizophrenia has been demonstrated [Farmer et al., 1987]. S311C might be one of the factors for positive symptoms of schizophrenia or other symptomatic dimensions of schizophrenia.

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