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Brief Research Communication

No Evidence for Association of Dopamine D2 Receptor Variant (Ser311/Cys311) With Major Psychosis

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We investigated a variant of the dopamine D2 receptor gene (Ser311/Cys311 substitution) in Caucasian patients with schizophrenia (n = 273), delusional disorder (n = 62), bipolar I affective disorder (n = 63), and controls (n = 255). No evidence for association between the receptor variant and any of the diseases was found, even when patients with younger age-of-onset (<25 years) were compared with controls. Furthermore, in a subgroup of schizophrenia patients whom we assessed for negative symptoms, those with the Cys allele did not differ from the remainder of the group. Also, the bipolar affective disorder patients with psychotic features did not show evidence for association with the receptor variant. Thus, our results do not provide evidence for an association between this D2 receptor variant and schizophrenia, or delusional disorder, or bipolar affective disorder.

KEY WORDS: schizophrenia, delusional disorder, bipolar affective disorder, dopamine D2 receptor, genetics

INTRODUCTION

Evidence that antipsychotic potencies of neuroleptics correlate with their affinity for the dopamine D2 receptor (DRD2) suggests the involvement of the DRD2 gene in the etiology of schizophrenia [Seeman, 1992]. Genetic association between a variant of the DRD2 receptor (a serine-to-cystine substitution at amino acid position 311, in the third cytoplasmic loop of the receptor, which is the region essential for coupling to G-proteins) and schizophrenia has been reported [Arinami et al., 1994]. The association was stronger in those patients with younger age of onset (AOO) (<25 years), or with fewer negative symptoms, or with family history of the disease. Several other groups tried to replicate this result, but did not find a significant association in Japanese [Hattori et al., 1994] and Caucasian samples [Asherson et al., 1994; Sobell et al., 1994; Shaikh et al., 1995]. The allele frequency of the Cys311 variant of the DRD2 receptor in control populations is low (0.8–3.5%), and thus a fairly large number of subjects is required to show a significant genetic association. This may be one reason why other groups have failed to replicate the initial positive result. Another reason for failure of replication may be that relevant clinical information was not sufficiently analyzed. AOO was studied only by Hattori et al. [1994], who examined a relatively small Japanese sample (n = 100). Clinical symptoms were not investigated by any of the four negative studies. Recently, Arinami et al. [1996] found further support for the association by assessing additional subjects with reduced negative symptoms, using another relatively small group of schizophrenia patients (n = 135). They also found an association between the receptor variant and mood-incongruent psychotic features in bipolar affective disorder patients. We investigated this receptor variant in 273 Caucasian schizophrenia patients and 255 controls. In addition, patients with delusional disorder or bipolar I affective disorder were studied in a preliminary way to investigate this receptor variant in other psychoses.

MATERIALS AND METHODS

All patients and controls were Caucasians of European origin. The affected subjects consisted of 273 un-

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related patients with schizophrenia (mean age ± SD, 32 ± 9 years), 62 unrelated delusional disorder patients (age, 51 ± 12 years), and 63 unrelated bipolar I affective disorder patients (age, 39 ± 10 years). The patients with schizophrenia were recruited from the clinics of Drs. Meltzer (Cleveland, n = 41), Lieberman (Long Island, n = 64), Hudson, Kennedy, and Bean (Toronto, n = 45), and Macciardi (Milan, n = 123). Patients with delusional disorder were from the research group of Dr. Macciardi. Bipolar disorder patients were recruited from the Toronto area through the Mood Disorders Program, Clarke Institute of Psychiatry (Dr. Joffe). Diagnoses of schizophrenia and delusional disorder were made according to DSM-III-R [1987]. For the diagnosis of bipolar I affective disorder, Research Diagnostic Criteria were used [Spitzer et al., 1977]. Information for the diagnosis was derived from the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-L) [Endicott and Spitzer, 1978] structured interview, or the Structured Clinical Interview for DSM-III-R. Schizophrenia patients from the clinics of Drs. Meltzer and Lieberman (n = 106) were treated with clozapine, and the majority had had poor response to classical neuroleptic treatment.

The unrelated control subjects (n = 176; mean age, 36 ± 10 years) were without major mental disorders. They were recruited from staff and nonpsychiatric patients at the clinics of Drs. Meltzer (n = 9), Lieberman (n = 83), Hudson (n = 21), and Macciardi (n = 63). Under the Haplotype Relative Risk design, untransmitted chromosomes from the biological parents of schizophrenia patients from Milan (n = 64) and Toronto (n = 15) also served as controls. Thus, a total of 255 controls (510 chromosomes) was used. Male vs. female ratios of subjects were close to 2:1 in schizophrenia, 1:2 in delusional disorder, and 1:1 in affective disorder and controls.

The method of genotyping was the same as in Arinami et al. [1994]. Statistical analyses were performed using chi-square analysis or Fisher's exact test.

RESULTS

Genotype and allele frequencies in patients and controls are summarized in Table I. No significant differences in allele frequency were found between controls and any group of patients. Also, the Cys311 allele frequency varied from 0–3.9% across the different collection sites, and no significant differences were observed. No homozygotes with the cysteine allele were found among the patients, but there was one homozygote in the control subjects. This subject was male, 41 years old, and mentally healthy, although suffering from spastic paraplegia. No difference in allele frequencies was found between controls and schizophrenia or bipolar disorder patients with earlier AOO (<25 years).

We analyzed symptoms in a subgroup of schizophrenia patients (n = 66) using data from the SADS interview (n = 41) or the Scale for Assessment of Negative Symptoms (SANS) (n = 25) [Andreasen, 1982]. Five patients had the cysteine allele: 2 of them had higher levels, and 2 had the same levels of negative symptoms compared to the average of the patient group. Only 1 had reduced negative symptoms, 1.5 SD below average.

There was no difference in allele frequencies between the subgroup of bipolar patients with psychotic features (3.6%, 1 heterozygote out of 14 patients) and controls. Also, no difference was found between schizophrenia patients treated with clozapine vs. those without clozapine (1.9% vs. 2.4%) as compared to controls. Also, the responders in the clozapine-treated patients were not different from nonresponders, or from controls, in their frequency of the Cys311 allele.

DISCUSSION

We did not find any difference in the frequency of this DRD2 receptor variant (Cys311) between any group of patients vs. controls. The allele frequency of this Cys311 variant is low in our subjects (2.2% in 255 controls, 2.1% in 398 patients in total), consistent with other studies using Caucasians: 1.8% in 1,914 controls [Sobell et al., 1994], and 0.8% in 64 controls [Asherson et al., 1994]. Thus, a large number of subjects is required to definitively detect or refute an association with this receptor variant. We used 273 patients with schizophrenia and 255 controls. These numbers are sufficient when assuming that the Cys311 allele frequency in the population is 2.0% and the relative risk of the receptor variant for schizophrenia is 3.1, as in Arinami et al. [1994] (alpha = 0.05, power = 0.80). Thus, our results indicate that there is no evidence for

TABLE I. Genotypes and Allele Frequencies of DRD2 Receptor Variant (Ser311/Cys311) in Patients and Controls

	Genotypes		Allele frequency	
Group	Ser/Ser	Ser/Cys	Ser	Cys
Schizophrenia				
Total	261	12	534	12 (2.2%)
AOO < 25 years	102	8	212	8 (3.6%)
Delusional disorder[a]	60	2	122	2 (1.6%)
Bipolar I affective disorder				
Total	60	3	123	3 (2.4%)
AOO < 25 years	24	0	48	0 (0%)
Controls[b]	245	9	499	11 (2.2%)

[a] In delusional disorder patients, relevance of age of onset (AOO) was not analyzed, because only 3 patients had age of onset below 25 years.
[b] One homozygote for the Cys311 allele occurred in the non-HRR control group.

a role of this DRD2 receptor variant in susceptibility to schizophrenia. Furthermore, no evidence for an association between the receptor variant and bipolar affective disorder or delusional disorder was obtained, although the sample size of these patients was not large.

Arinami et al. [1994, 1996] found a stronger association using a subgroup of schizophrenia patients with reduced negative symptoms. However, in a subgroup of schizophrenia patients whom we assessed for negative symptoms, those with the Cys allele did not differ from the remainder of the group. Furthermore, examination of the other diagnoses (delusional disorder and bipolar I with psychosis) that can be considered under the broader designation of psychosis, and that have fewer negative symptoms than typical schizophrenia, showed no trend for a difference in allele frequencies compared to controls. These results provide evidence against the association between the Cys311 variant and psychotic disorders with fewer negative symptoms, although the sample size was relatively small. Also, the etiology of delusional disorder and psychotic features in affective disorder may well be completely different from that of schizophrenia. In addition, no evidence for association between response to clozapine and the receptor variant was obtained.

An association of the receptor variant with earlier AOO (<25 years) was also suggested by Arinami et al. [1994]. In our samples, however, no evidence for an association with lower AOO (<25 years) was obtained, either in schizophrenia or bipolar affective disorder, although the number of subjects, especially for bipolar affective disorder, was relatively small.

Arinami et al. [1994] reported three homozygotes of the Cys311 allele in their patients and no homozygotes in the controls, suggesting that homozygosity of this allele may increase susceptibility to schizophrenia. We found no homozygotes in patients but one homozygote in control subjects, and thus we cannot support this finding of Arinami et al. [1994].

In conclusion, our study provides no support for an association between the Cys311 DRD2 variant and schizophrenia in Caucasians, consistent with other studies in this ethnic group. No support was obtained for an association with lower AOO or reduced negative symptoms. Thus, the results of association may have resulted from other factors specific to the Japanese population [Arinami et al., 1994, 1996], or from specific clinical subtypes of psychoses. Another possibility is that the results of Arinami et al. were chance findings. We did not study family history in our patients, and further investigation of familial cases might be helpful.

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