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# Dopamine D4 Receptor Gene Polymorphisms and Neuroleptic Response in Schizophrenia

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**Background:** Dopamine D4 receptor (DRD4) gene polymorphisms are associated with various pharmacologic activities. This study investigated whether polymorphisms of 48-bp tandem repeats in the exon 3 of the DRD4 gene are related to neuroleptic response.

**Methods:** The neuroleptic response at the acute stage of schizophrenia was assessed in 80 (48 men, 32 women) schizophrenic patients. The negative symptoms at remission were also rated. DRD4 genotype was established using the polymerase chain reaction. Patients with genotypes containing an allele with only two repeats (2-2, 2-3, 2-4, 2-6) were assigned to group I (n = 38). Those homozygous for four 48-bp repeats were assigned to group II (n = 42).

**Results:** Thirteen (34.2%) of the 38 group I subjects and 26 (61.9%) of the 42 group II subjects had good neuroleptic response during acute stage treatment ( $\chi^2 = 6.12$ ,  $df = 1$ ,  $p < .02$ ). In remission, the rates of negative symptoms of blunt affect, avolition, and global negative rating were higher in group I than in group II. This was more prominent in men than in women.

**Conclusions:** The presence of homozygous four 48-bp repeats in both alleles in exon 3 of the DRD4 gene is associated with good neuroleptic response during acute treatment, and with a lower prevalence of negative symptoms at remission, especially in male schizophrenic patients. Biol Psychiatry 1998;44:483-487 © 1998 Society of Biological Psychiatry

**Key Words:** Dopamine, dopamine D4 receptor, receptor gene, neuroleptic response, schizophrenia, negative symptoms

## Introduction

The dopamine D4 receptor (DRD4) gene has been cloned and localized to the tip of the short arm of chromosome 11 (Gelernter et al 1992). The structural and pharmacologic characteristics of DRD4 are similar to those of the D2 and D3 receptors (Van Tol et al 1991). Genetic polymorphisms of the 48-bp repeat in exon 3 of the DRD4 gene have been studied for possible association and/or linkage with schizophrenia (Barr et al 1993; Shaikh et al 1994; Macciardi et al 1994; Maier et al 1994; Daniels et al 1994; Petronis et al 1995; Hong et al 1997). All these studies showed negative results, indicating that DRD4 was not related to genetic etiology of schizophrenia.

The neuroleptic response of schizophrenia has been thought to be due to the blocking effect of neuroleptics on the D2 receptor and related receptor families (Seeman and Lee 1975). Atypical neuroleptics, such as clozapine, were found to have a higher affinity for the D4 receptor than the D2 or D3 receptors (Van Tol et al 1991). The repeat number of a 48-bp sequence expressed in the third cytoplasmic loop of DRD4 affects the pharmacologic activities of this receptor (Iversen 1992). Variants with a greater number of repeats have higher affinity for clozapine and spiperone (Van Tol et al 1991). The relationship of DRD4 gene polymorphisms and clozapine treatment response in refractory schizophrenic patients has been studied, and controversial results have not yet been resolved (Shaikh et al 1993, 1995; Rao et al 1994; Kennedy 1994; Kennedy et al 1995; Rietschel et al 1996; Kohn et al 1997). This allele-related pharmacologic variation suggests that polymorphisms of the DRD4 gene might be related to the pathophysiological mechanism mediating the neuroleptic treatment response in the acute state of schizophrenia.

The density of D4 receptors is higher in the striatum of schizophrenic patients than in that of normal subjects (Seeman et al 1993). Because of the complex link (Seeman et al 1989) interactions (Meltzer 1995) between different dopamine receptors through the G-protein system, and the increased density of DRD4, it is reasonable to investigate a possible relationship between neuroleptic treatment response in schizophrenia and polymorphisms of the DRD4

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gene. Neuroleptic response has been studied under the dopamine hypothesis (Bowers 1991). A group with good neuroleptic response was found to have a higher pretreatment homovanillic acid level (Bowers 1991; Chang et al 1993). Different pharmacologic mechanisms or different subtypes of patients were studied based on this kind of pharmacologic study (Chang et al 1993). The real nature is still unknown. In this study, we examined whether the neuroleptic response of schizophrenic patients was related to variations of the number of 48-bp repeats in exon 3 of the DRD4 gene that encodes the third cytoplasmic loop of the D4 receptor.

## Methods and Materials

Eighty (48 men, 32 women) schizophrenic patients from community treatment settings of the Department of Psychiatry, National Taiwan University and an affiliated hospital, the Provincial Taoyuan Psychiatric Hospital, were recruited. Written informed consent was obtained prior to study. The clinical diagnosis was ascertained using the Psychiatrist Diagnostic Assessment method (Hwu and Yang 1987), following DSM-III-R (American Psychiatric Association 1987) criteria of schizophrenia. The data from patient charts and clinical interviews were combined for final diagnostic assessment. The mean age of onset of nonspecific symptoms was 20.7 years; the mean age of onset of severe impairment in social function was 22.4 years. Twenty-six percent of the patients had received  $\leq 9$  years of education, 46% had received 10–12 years, and 28% had received  $> 12$  years. The mean dose of neuroleptic medication for acute stage treatment in the study hospitals was 1150 (SD 755) mg/day of chlorpromazine equivalent dose. The acute treatment response was assessed based on patient records at discharge and clinical interviews. In assessing the degree of response, positive symptoms of delusion, hallucination, bizarre behavior, and thought process/form disorders were rated as 0–3 (absence to marked), based on the vividness and frequency of these symptoms, and also their influence on social function. If no positive symptom (rated 0) was present after acute stage treatment, the treatment response was regarded as good. If any positive symptom (rated 1–3) remained, the response was considered poor. The interrater reliability test for the assessment method of this rating scale revealed a Spearman rank correlation coefficient of 1.0 (Hwu 1994).

The clinical psychopathological symptoms were rated at remission, using a Chinese positive and negative symptom rating scale (Hwu 1994), which was composed of four positive symptom items (delusion, hallucination, unusual behavior, and thought process/form disorders) and four negative symptom items (blunt affect, avolition, alogia, and asociality), following the definition of Andreasen (1984a, 1984b). The positive and negative symptoms were rated on a 6-point scale, ranging from 0 to 5 (degree of severity of symptoms). The interrater reliability test showed a satisfactory Spearman rank correlation coefficient of .73–.92 (Hwu 1994). A positive symptom was considered to

be present if its rating was above 0. A negative symptom rating of 1 was considered mild and not of clinical significance. Thus, a negative symptom was considered to be present if its rating was  $\geq 2$ .

The social function of schizophrenic patients was assessed using a community life scale (Hwu 1991). The interrater reliability was satisfactory, as shown by an intraclass correlation coefficient of .67–.95 (Hwu et al 1987). The social function scale was composed of four dimensions of daily activity: achievement, interpersonal relationships, daily time arrangement, and daily family life function. Each dimension was rated 1–7, ranging from the worst (score 1) to the best (score 7). A score of 4 was considered marginal.

Genomic DNA isolated from lymphocytes was analyzed by polymerase chain reaction (PCR) with oligodeoxynucleotide primers specific for part of the D4 sequence (Shaikh et al 1993). Each PCR was done in a 25- $\mu$ L mixture that contained 50 mmol/L KCl, 10 mmol/L Tris-HCl pH 8.3, 0.5 mmol/L  $MgCl_2$ , 10% dimethylsulphoxide (DMSO), 200  $\mu$ mol/L each of deoxyadenosine triphosphate, deoxythymidine triphosphate, and deoxycytidine triphosphate, 50  $\mu$ mol/L of deoxyguanosine triphosphate, 150  $\mu$ mol/L of 7-deazaguanosine, 0.5  $\mu$ mol/L of each primer, 100 ng template DNA, and 0.6 U of Dynazyme (Finnzymes oy, Espoo, Finland). This mixture was denatured at 95°C for 5 min, followed by 30 cycles of amplification (90°C, 1 min; 52°C, 1 min; 72°C, 2 min), and elongation at 72°C for 5 min. PCR products were detected by 2% ethidium-bromide stained agarose gel electrophoresis and ultraviolet photography.

Patients homozygous for the two 48-bp repeat (2-2), as well as those with two-repeat allele and one three (2-3), one four (2-4), or six (2-6) repeat allele were classified as group I. Patients homozygous for the four 48-bp repeat allele were classified as group II. Differences between groups were tested using the chi-square test for nonparametric data, and the independent *t* test for parametric data. The level of statistical significance was set at  $p < .05$ . The statistical analysis was done using the SPSS PC+ package (Norusis 1990).

## Results

Of the 80 study subjects, 38 (48%) were group I and 42 (32%) were group II. The genotypes of the group I patients were 2-2 (3 cases), 2-3 (1 case), 2-4 (33 cases), and 2-6 (1 case). There were 22 (46%) men in group I and 26 (54%) in group II. Women were evenly distributed among group I and group II. Sixteen women (50%) belonged to each group. There were no differences between groups in educational level, economic status of the family, mean dose of neuroleptic medication, mean age of onset of nonspecific symptoms (20.3 years old versus 21.1 years), or mean age of onset of severe functional impairment (22.5 years old versus 22.4 years).

Group II patients had a significantly higher rate of good neuroleptic response during acute stage treatment than group I patients ( $\chi^2 = 6.12$ ,  $df = 1$ ,  $p < .02$ ) (Table 1).

Table 1. Comparison of Neuroleptic Response in Schizophrenic Patients with Different Repeat Numbers of the DRD4 Gene 48-bp Repeat

Neuroleptic response	Group I (%) <sup>a</sup>	Group II (%) <sup>b</sup>	Statistics
Total cases			$\chi^2 = 6.12$
Good	13 (34.2)	26 (61.9)	df = 1
Poor	25 (65.8)	16 (38.1)	$p < .02$
Men			$\chi^2 = 5.99$
Good	5 (22.7)	15 (57.7)	df = 1
Poor	17 (77.3)	11 (42.3)	$p < .02$
Women			$\chi^2 = 1.17$
Good	8 (50.0)	11 (68.8)	df = 1
Poor	8 (50.0)	5 (31.3)	$p < .30$

<sup>a</sup>Group I genotypes include one allele with two 48-bp repeats and the other with 2, 3, 4, or 6 repeats.

<sup>b</sup>Patients with group II genotype were homozygous for four 48-bp repeats.

This difference was also significant among men, but not women; however, in group II, there was a tendency for the women to have a higher rate of good response.

In remission, group I patients had a higher rates of negative symptoms, although the difference was not statistically significant (Table 2). This tendency was more prominent in the men. Differences between groups in the items of blunt affect, avolition, and global negative rating reached statistical significance in men; in women, there was no difference. No differences in the prevalence of positive symptom items were found.

The social function scores tended to be lower in group I patients, although the difference was not statistically significant (Table 3). The differences between groups in achievement and time arrangement nearly reached statistical significance.

Table 3. Mean Social Function Assessment in Schizophrenic Patients with Different Repeat Numbers of the DRD4 Gene 48-bp Repeat

Social function assessment	Group I (SD) <sup>a</sup>	Group II (SD) <sup>b</sup>
Achievement score	2.7 (1.8)	3.4 (1.6) <sup>c</sup>
Interpersonal relationship score	3.2 (1.4)	3.7 (1.3)
Time arrangement score	2.9 (1.7)	3.6 (1.6) <sup>c</sup>
Family life score	3.1 (1.6)	3.7 (1.5)

<sup>a</sup>Group I genotypes include one allele with two 48-bp repeats and the other with 2, 3, 4, or 6 repeats.

<sup>b</sup>Patients with group II genotype were homozygous for four 48-bp repeats.

<sup>c</sup> $p < .10$ .

## Discussion

This study revealed that patients with DRD4 genotype (4-4) had a higher rate of good neuroleptic response than group I patients (genotypes 2-2, 2-3, 2-4, and 2-6) during the acute stage treatment of schizophrenia. Group I was composed of various genotypes, with one allele having two repeats of the 48-bp tandem unit; the other allele had two, three, four, or six 48-bp tandem repeats. The only patient with genotype 2-6 had a good neuroleptic response. While this patient belonged to group I, he might be considered as having the high number of 48-bp repeat units.

The relationships between the genotype group and positive or negative symptoms, as well as social function at remission, were also examined. Group II had a lower frequency of negative symptoms and also tended to have higher mean scores for social function than group I. This suggests that schizophrenia in patients with the group II genotype might have a different pathophysiological mechanism than in group I patients. Although the 48-bp repeat polymorphisms of DRD4 have no linkage with schizo-

Table 2. Negative Symptoms in Schizophrenic Patients with Different Repeat Numbers of the DRD4 Gene 48-bp Repeat

Symptom	Men		Women		Total	
	Group I <sup>a</sup> (n = 22)	Group II <sup>b</sup> (n = 26)	Group I <sup>a</sup> (n = 16)	Group II <sup>b</sup> (n = 16)	Group I <sup>a</sup> (n = 38)	Group II <sup>b</sup> (n = 42)
Blunt affect	15 <sup>c</sup> (68.2)	9 (34.6)	7 (43.8)	8 (50.0)	22 <sup>d</sup> (57.9)	17 (40.5)
Avolition	16 <sup>c</sup> (72.7)	11 (42.3)	10 (62.5)	10 (62.5)	26 (68.4)	21 (50.0)
Alogia	14 (63.6)	11 (42.3)	9 (56.3)	9 (56.3)	23 (60.5)	20 (47.6)
Asociality	17 <sup>d</sup> (77.3)	14 (53.8)	9 (56.3)	11 (68.8)	26 (68.4)	25 (59.5)
Global negative rating	18 <sup>c</sup> (81.8)	14 (53.8)	10 (62.5)	9 (56.3)	28 <sup>d</sup> (73.7)	23 (54.8)

<sup>a</sup>Group I genotypes include one allele with two 48-bp repeats and the other with 2, 3, 4, or 6 repeats.

<sup>b</sup>Patients with group II genotype were homozygous for four 48-bp repeats.

<sup>c</sup> $p < .05$ .

<sup>d</sup> $p < .10$ .

phrenia etiology, they might have pathophysiological meaning in the clinical manifestations of schizophrenic symptoms.

In group II, the higher rate of good neuroleptic response during acute stage treatment was more prominent in men. The lower prevalence of negative symptoms in group II patients was also found only in men. If the 48-bp tandem repeat polymorphisms of the DRD4 gene play a significant role in the pathophysiological mechanism of schizophrenic clinical manifestations, gender has to be considered as a significant mediating variable. The role of gender in schizophrenic clinical manifestations is well known (Goldstein et al 1989; Lewis 1992; Seeman and Lang 1990; Häfner et al 1991). Gender difference in the pathophysiological manifestation of DRD4 polymorphism is therefore an important subject for future investigation.

As dopamine receptors are the main target sites for neuroleptic treatment for the positive symptoms of schizophrenia (Carlsson 1988), polymorphisms of dopamine receptor genes may mediate the response to treatment. Previous studies (Bowers 1991; Chang et al 1993) suggested that a high pretreatment plasma level of homovanillic acid (HVA) was associated with a good neuroleptic response. The relationship between a higher pretreatment HVA level and a higher 48-bp repeat number of the DRD4 gene needs to be explored in the future.

We used patient records and clinical interview data for the assessment of neuroleptic response during acute stage treatment. The interrater reliability of this assessment was satisfactory; however, this is a retrospective approach. A prospective study using an operationalized rating scale should be done. Our study group in Taiwan is currently proceeding with this kind of study (Hwu 1994) using the Positive and Negative Symptom Scale (PANSS) (Kay et al 1986; Cheng et al 1996) for symptom rating.

We did not find a significant difference between groups in the rates of positive symptoms in patients in remission. This is consistent with the results of another study using a different study sample (Lin and Hwu 1993), suggesting that a good neuroleptic response at the acute stage represents a quick neuroleptic response. The positive symptoms subside eventually. This quick neuroleptic response has also been studied in another schizophrenic sample (Hwu and Chang 1994); as in the present study, patients with quick neuroleptic response also had better social function at follow-up.

In summary, we conclude that alleles with a homozygous four 48-bp tandem repeat in the exon 3 of the DRD4 gene are associated with a quick neuroleptic response during treatment at the acute stage, and a lower rate of negative symptoms at remission.

In spite of this conclusive clinical remark, the appropriate biological relevance has to be explored further. The

pharmacologic properties of the 48-bp repeat polymorphism of the DRD4 gene were studied in an in vitro experiment (Asghari et al 1994), and the results showed that the binding profiles for all ligands were similar among different forms of the human and rat D4 receptors and repeat deletion mutants. If this study's results were to stand true, the authors would expect that this 48-bp polymorphism might have linkage disequilibrium with other polymorphisms of the DRD4 gene, such as 12-bp deletion/insertion polymorphism of exon 1, or poly G polymorphism of intron 1, which have been found to have polymorphism in a Chinese population (Chang et al 1997). Further genotype studies using these two DRD4 gene polymorphisms and haplotype analysis would be a meaningful approach.

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