Dopamine Receptor Genetic Variation, Psychosis, and Aggression in Alzheimer Disease

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**Objective:** To examine if selected polymorphisms in the dopamine receptor genes DRD1, DRD2, DRD3, and DRD4 are associated with the presence of psychosis or aggressive behavior in patients with Alzheimer disease (AD).

**Design:** A cohort of patients with AD were longitudinally evaluated for behavioral symptoms and classified with regard to the presence of psychotic symptoms and physical aggression.

**Setting:** Alzheimer’s Disease Research Center.

**Patients:** Two hundred seventy-five elderly outpatients diagnosed as having probable AD.

**Results:** Among white patients, psychosis and aggression were both significantly more frequent in DRD1 B2/B2 homozygotes ($P < .02$), while psychosis was significantly more frequent in DRD3 1/1 or 2/2 homozygotes ($P < .05$). The joint risk for psychosis due to the DRD1 and DRD3 polymorphisms exceeded the risks due to either locus alone, suggesting an interaction. Neither the DRD2 S311C polymorphism nor the presence of long alleles for the DRD4 exon III repeat sequence was associated with psychosis or aggression.

**Conclusions:** Genetic variation in DRD1 and DRD3 genes may act to modify the course of AD, predisposing to the development of psychotic or aggressive symptoms. Confirmation in other samples of patients with AD is required.

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Behavioral syndromes including agitation, aggression, and psychosis occur in more than 80% of patients with Alzheimer disease (AD)1-4. When these syndromes occur, they are often highly distressing to both patients and caregivers, and can serve as the last straw leading to institutionalization.5,6 Currently, neuroleptics remain the only established pharmacotherapy for psychosis and agitation complicating dementia, though efficacy is modest.7,8 The use of neuroleptics (and other agents) in the treatment of behavioral syndromes in patients with AD has been largely on the basis of empirical extension of observed efficacy in other populations, without evidence of an underlying pathophysiological rationale.9

A series of recent in vivo and postmortem studies, however, indicate that a relative increase or preservation of presynaptic dopamine neurotransmission is associated with aggression in patients with AD.10-13 In contrast to aggression, psychosis in patients with AD (or the related dementia with Lewy bodies) does not appear to be associated with plasma homovanillic acid concentration,12 or with brain concentrations of dopamine, homovanillic acid, or the dopamine metabolite 3,4-dihydroxyphenylacetic acid.14-17 Because the net effect of dopamine in the synapse is dependent on the concentrations of both dopamine and its receptors (as well as postreceptor signal transduction mechanisms), the studies mentioned earlier do not exclude an association between psychosis in patients with AD and changes in dopamine receptor densities.

Despite the number of studies13,14,16-19 that have examined the associations of psychosis and aggression in patients with AD with neurochemical or neuropathologic changes, none have examined dopamine receptors. This absence of data is all the more surprising given that dopamine receptors are the major targets of neuroleptic agents.20 Moreover, the recent development of agonist and antagonist agents, selective among the dopamine receptor subtypes,21-25 provides a basis for the development of novel drug treatments if associations between specific dopamine receptors and aggressive or psychotic syndromes in patients with AD can be identified.
PATIENTS AND METHODS

PATIENTS

All patients were evaluated between April 8, 1986, and August 8, 1996, by the Clinical Core of the Alzheimer’s Disease Research Center of the University of Pittsburgh, Pittsburgh, Pa, using a comprehensive medical, neurologic, psychiatric, social work, and neuropsychological assessment that has been previously described. A total of 275 patients were identified from whom genetic material had been obtained and who had received, based on the above assessment, a diagnosis of probable AD by the National Institute of Neurological Disorders and Stroke criteria. We have previously reported neuropathologic confirmation in excess of 90% of such cases. Sufficient genetic material was available for DRD1 genotyping in 268 patients, for DRD2 genotyping in 267 patients, for DRD3 genotyping in 259 patients, and for DRD4 genotyping in 225 patients. The data presented in this study were obtained as part of clinical investigations of elderly patients according to protocols approved by the Biomedical Institutional Review Board of the University of Pittsburgh.

PSYCHIATRIC ASSESSMENT

Psychiatric evaluation included annual semistructured psychiatric interviews, with diagnoses established according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition. Psychopathologic features were also rated using the Consortium to Establish a Registry for Alzheimer Disease Behavioral Rating Scale for Dementia 51-Item Version (CBRS). Delusions were defined as a false belief, not attributable to membership in a social or cultural group, based on incorrect inference about external reality. Delusions were differentiated from confabulations due to cognitive impairment by their persistence and their resistance to persuasion or contrary evidence. Hallucinations were defined as sensory perceptions for which there was no reality basis and were differentiated from illusions and misidentifications. Because the CBRS was introduced during the enrollment of these patients, CBRS ratings were only available for 214 patients. The determination of the presence of psychosis (AD + P) or aggression (AD + A) was cumulative. That is, patients were categorized as AD + P if during any annual assessment they received a diagnosis (using the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition) of any dementia with delusions, a concurrent mood disorder with psychosis, or an organic hallucinosis; or if at any annual assessment any of the CBRS items measuring delusions or hallucinations (CBRS items 35-42 or 47-50) were rated as having been present for at least 3 to 8 days in the last month. Patients without these diagnoses and not having had at least 3 days of these symptoms in the last month were categorized as without psychosis (AD − P). Similarly, patients diagnosed as having a dementia with delirium, or a dementia with substance-induced delusions or hallucinations were categorized as AD − P. Because a history of aggression in patients with AD is not readily identified by a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition, patients considered to have AD + A were defined by receiving at any annual CBRS assessment a score indicating a history of any episode of physical aggression during the course of the illness (score >0 on CBRS item 31). Physical aggression was defined by physical contact with the object of aggression, whether another individual or an inanimate object (eg, throwing a chair or striking a wall). Threatening gestures or remarks, or the caregiver’s perception of being threatened, were not sufficient to be defined as physical aggression. Physical aggression, as opposed to verbal aggression or other agitation symptoms, was chosen because of its face validity and validated association with other neurochemical markers. The absence of physical aggression (AD − A) was defined as never receiving a score of more than 0 on CBRS item 31.

DOPAMINE RECEPTOR GENETIC ASSAYS

The DRD1, DRD2, DRD3, and DRD4 genotyping was performed using specific polymerase chain reaction protocols described elsewhere. DRD1 1.1 polymorphism described by Cichon et al because the high frequency of both alleles renders it amenable to association analysis. The DRD2 Ser311/Cys311 polymorphism was chosen because of 1 report associating it with schizophrenic psychosis in Japanese patients.

STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS for Windows release 7.5 (SPSS Inc, Chicago, Ill). Because of the multiple DRD4 genotype variants, for all statistical analyses of DRD4 patients were classified according to the presence of exon III repeat sequences containing 7 or more repeats. Thus, DRD4S indicates neither allele contains more than 7 repeats and DRD4L, 1 or both alleles contain more than 7 repeats. This classification scheme is derived from observed signal transduction differences in DRD4 receptors and has been previously validated in other behavioral association studies. Continuous data were compared using analysis of variance. Categorical data were compared using χ² analysis or Fisher exact test where appropriate.
clusions, 1 report in Japanese patients identified a significant association with a substitution of cysteine for serine at codon 311 of the DRD2 gene. This association was not replicated, however, in a population of European descent. Unlike DRD1 and DRD2, examination of DRD4 in individuals with schizophrenia has largely been restricted to a single polymorphism, a 48–base pair (bp) variable repeat sequence in exon III. No significant linkage or association of this polymorphism with schizophrenia has been identified.

In contrast to DRD1, DRD2, and DRD4, there has been a persistent association of a biallelic DRD3 Ball polymorphism with schizophrenia across studies (for a review see by Ninggaonkar et al). The nature of the exact association has varied. Some reports describe an excess of homozygosity for either allele in subjects with schizophrenia, while others have suggested that it is an excess frequency of allele 1 that accounts for the association. Interestingly, there is functional variation in the products encoded by the alleles at this polymorphism of the DRD3. Nevertheless, if present, the association between schizophrenia and the DRD3 gene is likely to explain only a fraction of the genetic cause of schizophrenia.

Such a situation is consistent with the hypothesis that DRD3 genotype might serve to unmask psychotic symptoms in individuals predisposed by other neurodevelopmental or neurodegenerative changes. We tested this hypothesis in individuals with AD, the prototype neurodegenerative disorder, by examining the association between the DRD3 polymorphism and psychosis in 275 elderly outpatients diagnosed as having probable AD. In the absence of prior studies of dopamine receptor gene polymorphisms and psychotic or aggressive symptoms in individuals with AD, we similarly examined the association of these symptoms with polymorphisms in DRD1, DRD2, and DRD4.

**RESULTS**

Demographic and clinical characteristics at the time of initial presentation and dopamine receptor genotype frequencies of the 275 patients with probable AD are presented in **Table 1**. Despite the relatively young mean age at onset of AD, 193 patients (70%) were 65 years or older at onset of their AD. Although the majority of patients were evaluated only at baseline, 132 patients (48%) were evaluated for a median of 2 annual follow-up visits (range, 1-9 years of follow-up). Only 27 patients (10%) had a history of psychiatric illness predating the onset of AD. These consisted of major depression (n = 19), generalized anxiety disorder (n = 3), dysthymic disorder (n = 2), depressive disorder not otherwise specified and posttraumatic stress disorder (n = 1), alcohol dependence (n = 1), and paranoid personality disorder (n = 1). No patient had a prior diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder. The DRD3 distribution differed significantly between races ($\chi^2 = 11.4; P = .004$), consistent with reports in other patient and control groups. The DRD1 distribution also differed significantly between races ($\chi^2 = 11.4; P = .003$). No association between race and DRD2 or DRD4 was found. DRD4L was significantly associated with better cognitive function at initial assessment ($F = 4.9; P = .03$). No other significant associations between dopamine receptor genotype and demographic or clinical variables were detected.

The association of dopamine receptor genotype with AD + P and AD + A was then examined. A total of 81 (29.5%) of 275 patients were categorized as AD + P. A

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Race, No. (%)</th>
<th>Sex, No. (%)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age, y</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Age at Onset, y</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>B1/B1 (n=31)</td>
<td>75 ± 8</td>
<td>71 ± 8</td>
<td>30 (12)</td>
</tr>
<tr>
<td>B1/B2 (n=126)</td>
<td>73 ± 8</td>
<td>69 ± 8</td>
<td>124 (49)</td>
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<tr>
<td>B2/B2 (n=111)</td>
<td>72 ± 8</td>
<td>68 ± 8</td>
<td>97 (39)</td>
</tr>
<tr>
<td>Ser311/Ser311 (n=252)</td>
<td>73 ± 8</td>
<td>69 ± 8</td>
<td>235 (94)</td>
</tr>
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<td>Ser311/Cys311 (n=14)</td>
<td>70 ± 11</td>
<td>67 ± 11</td>
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<td>65 ± 3</td>
<td>63</td>
<td>1 (0.0)</td>
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<tr>
<td>1/1 (n=119)</td>
<td>74 ± 8</td>
<td>70 ± 8</td>
<td>117 (48)</td>
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<tr>
<td>1/2 (n=104)</td>
<td>72 ± 8</td>
<td>68 ± 8</td>
<td>96 (39)</td>
</tr>
<tr>
<td>2/2 (n=36)</td>
<td>72 ± 8</td>
<td>67 ± 8</td>
<td>31 (13)</td>
</tr>
<tr>
<td>DRD4S: ≤4.6/≤4.6 (n=28)</td>
<td>72 ± 8</td>
<td>67 ± 8</td>
<td>27 (13)</td>
</tr>
<tr>
<td>DRD4L: ≤4.6/≥4.7, ≥4.7/≥4.7 (n=197)</td>
<td>73 ± 8</td>
<td>69 ± 8</td>
<td>183 (87)</td>
</tr>
<tr>
<td>Total 275</td>
<td>73 ± 8</td>
<td>69 ± 8</td>
<td>258 (94)</td>
</tr>
</tbody>
</table>

*DRD: dopamine receptor (DRD1) and DRD3 genotype distribution differed significantly between races (both $P < .005$). In comparison with DRD4S, DRD4L was significantly associated with higher Mattis Dementia Rating Scale (MDRS) score at initial assessment ($P = .03$). No other significant associations were observed. Ser indicates serine; Cys, cysteine. †One patient was categorized as “other” for race.
smaller proportion of patients, 12 (5.6%) of 214, were categorized as AD + A. Results for DRD1 are presented in Table 2. Because of the significant association between DRD1 and race, these analyses were limited to the 251 whites among the patients for whom DRD1 genotyping was completed. The DRD1 distribution was significantly associated with the presence of psychosis ($\chi^2 = 8.7$; $P = .01$). This was due to a greater proportion of the B2/B2 homozygotes in the AD + P vs the AD − P group ($\chi^2 = 5.5$; $P = .02$). The associated odds ratio (OR) for AD + P among B2/B2 homozygotes vs all others was 1.9 (95% confidence interval [CI], 1.1-3.3). No significant increase in allele B2 frequency in patients with AD + P, however, was seen ($\chi^2 = 1.4$; $P = .20$). A similar association of DRD1 distribution and the presence of aggressive behavior was also observed ($\chi^2 = 6.8$; $P = .03$). Once again there was a greater proportion of B2/B2 homozygotes within patients with aggressive behavior ($\chi^2 = 6.4$; $P = .01$), with an associated OR of 6.3 (95% CI, 1.5-25.9). In contrast to psychosis, there was also a trend for allele B2 to be more frequent in aggressive patients ($\chi^2 = 3.6$; $P < .06$).

For DRD3, results are presented in Table 3. Because of the significant association between DRD3 and race, these analyses were limited to the 244 whites among the patients for whom DRD3 genotyping was completed. Although there was only a trend for DRD3 distribution to be associated with psychosis ($\chi^2 = 4.0$; $P = .10$), there was a greater proportion of homozygotes (1/1 and 2/2) vs heterozygotes among patients with psychosis ($\chi^2 = 4.0$; $P < .05$). The associated OR for AD + P among homozygotes (1/1 or 2/2) vs heterozygotes was 1.8 (95% CI, 1.0-3.3). Although this effect appeared to be largely due to an excess of 1/1 homozygotes, there was no significant increase in frequency of AD + P in 1/1 homozygotes vs all others ($\chi^2 = 2.8$; $P = .09$), nor a significant increase in allele frequency in the patients with psychosis (AD + P vs AD − P; $\chi^2 = 1.1$; $P = .30$). There was no association of DRD3 distribution with aggression ($\chi^2 = 1.6$; $P = .50$), nor was there evidence for an increased proportion of homozygotes (1/1 or 2/2) in aggressive patients ($\chi^2 = 0.0$; $P > .99$).

There was no association between DRD2 distribution and either AD + A or AD + P (both exact $P > .80$). Neither Cys311 allele frequency nor the presence of a Cys311 allele was associated with AD + A or AD + P in our patients (all $P > .40$). Similarly, DRD4L distribution demonstrated no association with psychosis ($\chi^2 = 0.1$; $P = .70$) nor with aggression (exact $P = 1.0$).

Because the above results suggested an association between AD + P and polymorphisms at both DRD1 and DRD3, we next examined the joint risk due to the associated alleles at both loci. There was no significant association between genotypes for these 2 receptors ($\chi^2 = 1.2$; $P = .90$). The cross-classification of DRD1 and DRD3 and the associated frequencies of AD + P are presented in Table 4. The joint OR was 4.3 (95% CI, 1.7-10.8). In comparison, the individual ORs were smaller: 3.6 (95% CI, 1.3-9.8) and 2.8 (95% CI, 1.2-6.9), respectively.

To our knowledge, this is the first study to examine the association of behavioral symptoms among patients diagnosed as having AD with dopamine receptor polymorphisms. We found that psychosis occurred more frequently in patients with AD who were homozygous for DRD1 allele B2 and who were homozygous for either DRD3 allele. Similarly, aggression was more prevalent in patients with AD who were homozygous for DRD1 allele B2; however, aggression was not associated with DRD3. Neither aggression nor psychosis during the course of AD was associated with the Ser311/Cys311 polymorphism in the DRD2 gene nor with the presence of long alleles for the DRD4.

Clearly, caution must be used in interpreting any genetic association studies in the absence of independent replication because of the possibility of type I error. This admonitory note is particularly relevant for the current finding of an association of DRD1 with psychosis, as similar associations have not been found in schizophrenia.4 Offsetting such a concern, however, is the recognition that the significant associations of DRD1 genotype with AD + P, but not with AD + A, would persist after correcting for multiple comparisons. Similarly, though our finding of increased psychosis risk in patients with AD who are homozygous for either DRD3 allele is counterintuitive, the convergence of this finding with replicated results in schizophrenia would suggest that the observed association of DRD3 with AD + P is not due to type I error. The concurrence of findings for DRD3 in these 2 disparate disorders, AD and schizophrenia, further suggests that the D1 receptor may play a role in the genesis of psychotic symptoms not specific to diagnosis per se. Confirmation of such a hypothesis would require replication of the current find-
ings in patients diagnosed as having other disorders in which a proportion of affected individuals demonstrate psychotic features, eg, patients with major depression with and without psychotic features.

The mechanisms by which alleles at DRD1 and DRD3 may increase the risk for psychosis in patients with AD are not known. The observed polymorphism in the DRD3 leads to a substitution of glycine (allele 2) for serine (allele 1) in the extracellular N-terminal region of the receptor. We have previously suggested that the association of homozygosity with psychosis is an artifact of statistical power, with the true causal relationship being accounted for by the presence of an increased frequency of allele 1 in patients with psychosis. Consistent with such a mechanism, in vivo studies of the neuroendocrine response to apomorphine challenge have shown a significantly greater increase in corticotropin and cortisol in subjects who were 1/1 or 1/2 than in 2/2 subjects. One report using an in vitro expression system to examine the receptors encoded by each of the DRD3 alleles did not find differences in receptor density, although receptors encoded by allele 1 demonstrated a significantly lower affinity for dopamine. Less is known about how the observed polymorphism in DRD1, a substitution of G for A 48 bp upstream of the coding region and downstream of identified promoters, might lead to an increased psychosis or aggression risk. The proximity of the base pair substitution to the coding region suggests it may affect posttranscriptional processing and possibly therefore alter receptor expression. Clarification awaits direct measurement of D1 and D3 receptor density and affinity, in conjunction with receptor genotyping, in brains from AD + P and AD + A patients.

The relatively brief duration of follow-up CBRS ratings conducted in the majority of our patients should be noted. This limitation is most telling with regard to the categorization of patients as AD + A, which occurred among only 6% of our sample. This rate is low compared with the previously reported rate of AD + A among patients with AD. The relatively brief duration of follow-up CBRS ratings in our study represents less of a limitation to the findings with regard to AD + P. Unlike the longitudinal course of aggression in patients with AD, psychotic syndromes (other than misidentification delusions) occur around the time of initial presentation and persist. Consistent with such a time course, AD + P occurred in 35% of our patients, a rate consistent with published reports of psychotic symptom prevalence in outpatients with AD.

In summary, we report the first study to examine dopamine receptor genetic variation and behavioral symptoms in patients with AD. Our findings suggest that DRD1 and DRD3 polymorphisms are associated with psychotic symptoms in patients with AD. Furthermore, DRD1 is associated with aggressive behavior. Although clearly preliminary, if replicated these observed associations provide important leads to a more selective pharmacotherapy of psychosis and aggression in patients with AD as pharmacologic agents selective among the dopamine receptor subtypes become available.

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Table 4. Cross-Classification of DRD1 and DRD3 With Associated Frequency of AD ± P in 239 White Patients for Whom Both Genotypes Were Available*
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REFERENCES


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