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SHORT REPORT

Dopamine D4 receptor polymorphism and idiopathic Parkinson's disease

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Patients with idiopathic Parkinson's disease (IPD) are described as having markedly decreased novelty seeking characteristics. Since recent publications suggest an association between the dopamine D4 receptor polymorphism and novelty seeking, we investigated this polymorphism in a group of 122 patients with IPD and 127 healthy control subjects. We found similar allele and genotype frequencies in both groups and no association with the age of onset of symptoms. Therefore, the dopamine D4 receptor polymorphism does not confer genetic susceptibility to IPD and cannot explain the decreased novelty seeking in IPD patients.

Keywords: Parkinson's disease; dopamine receptor; dopamine D4 receptor; polymorphism; susceptibility gene; association study; novelty seeking

Introduction

Recent studies have found an association between a polymorphism of the exon III repeat sequence of the dopamine D4 receptor gene (*D4DR*) and the trait of novelty seeking in normal volunteers.[1–5] Individuals with long alleles of this polymorphism scored significantly higher in tests of novelty seeking than subjects with short alleles, supporting earlier suggestions that interindividual variation in novelty seeking might be mediated through genetic variability in dopaminergic transmission.[6]

Patients with idiopathic Parkinson's disease (IPD) are also reported to have markedly lower scores in tests for novelty seeking compared with controls.[7] Whilst this finding may be related to brain dopamine deficiency in IPD, an alternative hypothesis is that decreased novelty seeking in IPD patients is in part genetically determined by the D4DR polymorphism. This could explain the frequently reported features of decreased novelty seeking in the premorbid Parkinsonian personality and raises the question whether D4DR polymorphism may act as a genetic susceptibility gene for IPD. Beside the decreased novelty seeking in IPD patients, the *D4DR* gene is a biologically reasonable candidate gene for the following reasons:

(i) the different alleles differently influence the binding of the ligand to the receptor which is higher for long alleles;[8]

(ii) D4DR receptors show a particular concentration in the limbic system[9] and

(iii) dopamine mediates the explorative behaviour at least in animal studies.[10]

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For these reasons the present study was performed to compare D4DR allele frequencies in a cohort of IPD patients and healthy controls.

Subjects and Methods

We investigated 122 (55 females and 67 males) unrelated Caucasian patients (age 68 ± 10 years) with IPD diagnosed according to the UK Parkinson's Disease Society Brain Bank (UKPDS BB) criteria.[11] Patients were recruited consecutively from our PD clinic and in-patient wards. Written informed consent was obtained from each patient. One hundred and twenty-seven healthy blood donors from the same geographical area served as control group.

Genomic DNA was extracted by standard procedures from whole blood. The 48 bp repeat polymorphism at the third exon of the *D4DR* gene[9] was analysed by PCR amplification using the protocol and primers recently described.[9] Laboratory personnel performing the genotyping were completely unaware of the patient/control status. Long D4DR alleles consisted of six to eight 48 bp repeats and short alleles of two to five repeats.

The Pearson's χ^2 test and the likelihood-ratio χ^2 test were used to compare the frequencies of D4DR alleles and genotypes between patients and controls. Power analysis revealed that we have 80% power to detect a difference of 9% in the frequency of long alleles and 16% in the frequency of genotypes including at least one long allele. We compared the age at onset of the disease between subjects with at least one long allele and those with only short alleles by the unpaired *t* test.

Results

Table 1 shows the D4DR allele frequencies in 122 patients with IPD and 127 healthy controls. There was no significant difference in the number of long alleles (alleles with six to eight 48 bp repeats) between patients and controls. When we compared the genotype frequency between the two groups we observed a higher frequency of 4/4 genotypes in the patient group which, however, did not reach significance (43.4% *vs* 34.6%) (Figure 1). The frequency of genotypes including at least one long allele was also similar in patients and controls (32.8% *vs* 33.9%).

Finally we compared the age at onset of symptoms of patients with at least one long allele with those having only short alleles. There was no significant difference for age at onset between the two patient groups (60 ± 10 *vs* 59 ± 15 years).

Table 1 Allele frequencies of the D4DR gene polymorphism in 122 patients with idiopathic Parkinson's syndrome (IPD) and 127 control subjects

D4DR alleles	*IPD* n=*244 alleles*	*Controls* n=*254 alleles*
allele 2	0.098	0.126
allele 3	0.054	0.055
allele 4	0.672	0.603
allele 5	0.000	0.031
allele 6	0.008	0.004
allele 7	0.156	0.173
allele 8	0.012	0.008
alleles combined[a]		
allele 2–allele 5	0.824	0.815
allele 6–allele 8	0.176	0.185

[a]Pearson's χ^2-test: χ^2=0.065, df=1, p=0.80.

Discussion

There is growing evidence of significant genetic contribution to IPD. Recent studies proposed different genes for IPD in different families[12–18] and it became apparent that several genes might be involved independently; for review see Nussbaum and Polymeropoulos.[19]

The present study investigated the D4DR receptor polymorphism as another candidate for increased

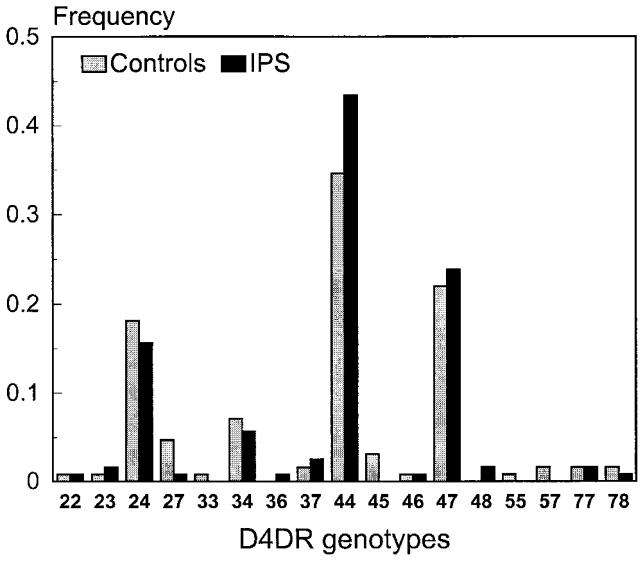

Figure 1 *Frequencies of the dopamine D4 receptor (D4DR) genotypes in 122 patients with idiopathic Parkinson's disease (IPD) and 127 control subjects. The frequency distribution is not significantly different between patients and controls (by likelihood ratio χ^2 test).*

genetic susceptibility to IPD because of its possible role in the expression of personality traits: short alleles were described in some[1–5] but not all[20–23] studies to be associated with decreased novelty seeking. This personality trait was found to be decreased in patients with IPD[7] and was regarded as part of their premorbid personality.[24] To reduce a possible effect of gross motor impairment on the novelty seeking score in IPD patients, equally disabled orthopaedic and rheumatology patients served as controls in the study by Menza *et al*.[7]

Using a large group of patients with IPD we were neither able to show an association between the disease state itself nor the age at onset of symptoms and the D4DR receptor polymorphism. It therefore seems that the *D4DR* receptor gene is not a susceptibility gene for Parkinson's disease in the population we investigated. This is in contrast to a recent study of 92 IPD patients which reported a higher frequency of genotypes with long alleles compared with 47 controls.[25] However, the sample size, especially of the controls, raises doubts about the statistical power of this study.[25] A further small study in a Japanese population was also unable to detect differences between IPD patients and controls in the D4DR polymorphism.[26] However, a markedly different D4DR allele distribution in Japanese control subjects with ≥ 98% short alleles[3,26,27] makes it difficult to detect a significant difference between patients and controls. This therefore justified the investigation of the polymorphism in IPD patients and controls of European origin where the frequency of short alleles is usually between 75% and 85%.[27]

The association between the D4DR polymorphism and novelty seeking was recently discussed controversially[1–5,20–23] and has still to be determined. If there indeed exists an association, we conclude from the present study that the decreased novelty seeking in patients with IPD cannot be explained by this polymorphism since we observed similar allele and genotype frequencies in patients and controls.

Our study, however, could be limited by not assessing novelty seeking in patients and controls and therefore not totally excluding a selection bias. The high number of patients, the consecutive recruitment, and the selection of a control group from the same geographical area might have minimised this possibility.

In summary, the similar D4DR allele frequency in patients and controls suggests that this gene is not a susceptibility gene for Parkinson's disease and that the decreased novelty seeking in patients with IPD cannot be explained by genetic variation in the D4DR receptor.

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References

1 Ebstein RP, Novick O, Umansky R *et al*: Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. *Nat Genet* 1996; **12**: 78–80.
2 Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH: Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. *Nat Genet* 1996; **12**: 81–84.
3 Ono Y, Manki H, Yoshimura K *et al*: Association between dopamine D4 receptor (D4DR) exon III polymorphism and novelty seeking in Japanese subjects. *Am J Med Genet* 1997; **74**: 501–503.
4 Noble EP, Ozkaragoz TZ, Ritchie TL, Zhang X, Belin TR, Sparkes RS: D2 and D4 dopamine receptor polymorphisms and personality. *Am J Med Genet* 1998; **81**: 257–267.
5 Ebstein RP, Nemanov L, Klotz I, Gritsenko I, Belmaker RH: Additional evidence for an association between the dopamine D4 receptor (D4DR) exon III repeat polymorphism and the human personality trait of novelty seeking. *Mol Psychiatry* 1997; **2**: 472–477.
6 Cloninger CR, Svrakic DM, Przybeck TR: A psychobiological model of temperament and character. *Arch Gen Psych* 1993; **50**: 975–990.
7 Menza MA, Golbe LI, Cody RA, Forman NE: Dopamine-related personality traits in Parkinson's disease. *Neurology* 1993; **43**: 505–508.
8 Van Tol HH, Wu CM, Guan HC *et al*: Multiple dopamine D4 receptor variants in the human population. *Nature* 1992; **358**: 149–152.
9 Van Tol HHM, Bunzow JR, Guan HC *et al*: Cloning of the gene for human D4 receptor with high affinity for the antipsychotic clozapine. *Nature* 1991; **350**: 610–619.
10 Hooks MS, Kalivas PW: Involvement of dopamine and excitatory amino acid transmission in novelty-induced motor activity. *J Pharmacol Exp Ther* 1994; **269**: 976–988.
11 Hughes AJ, Daniel SE, Kilford L, Lees AJ: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatr* 1992; **55**: 181–184.
12 Polymeropoulos MH, Lavedan C, Leroy E *et al*: Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 1997; **276**: 2045–2047.

13 Yamamoto M, Kondo I, Ogawa N, Asanuma M, Yamashita Y, Mizuno Y: Genetic association between susceptibility to Parkinson's disease and α_1-antichymotrypsin polymorphism. *Brain Res* 1997; **759**: 153–155.
14 Gasser T, Muller-Myhsok B, Wszolek ZK *et al*: A susceptibility locus for Parkinson's disease maps to chromosome 2p13. *Nat Genet* 1998; **18**: 262–265.
15 Bandmann O, Vaughan J, Holmans P, Marsden CD, Wood NW: Association of slow acetylator genotype for N-acetyltransferase 2 with familial Parkinson's disease. *Lancet* 1997; **350**: 1136–1139.
16 Krüger R, Kuhn W, Müller T *et al*: Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease [letter]. *Nat Genet* 1998; **18**: 106–108.
17 Planté-Bordeneuve V, Taussig D, Thomas F *et al*: Evaluation of four candidate genes encoding proteins of the dopamine pathway in familial and sporadic Parkinson's disease: evidence for association of a DRD2 allele. *Neurology* 1997; **48**: 1589–1593.
18 Nakatome M, Tun Z, Shimada S, Honda K: Detection and analysis of four polymorphic markers at the human monoamine oxidase (MAO) gene in Japanese controls and patients with Parkinson's disease. *Biochem Biophys Res Commun* 1998; **247**: 452–456.
19 Nussbaum RL, Polymeropoulos MH: Genetics of Parkinson's disease. *Hum Mol Genet* 1997; **6**: 1687–1691.
20 Jönsson EG, Nöthen MM, Gustavsson JP *et al*: Lack of evidence for allelic association between personality traits and the dopamine D4 receptor gene polymorphisms. *Am J Psychiatry* 1997; **154**: 697–699.
21 Gelernter J, Kranzler H, Coccaro E, Siever L, New A, Mulgrew CL: D4 dopamine-receptor (DRD4) alleles and novelty seeking in substance-dependent, personality-disorder, and control subjects. *Am J Hum Genet* 1997; **61**: 1144–1152.
22 Pogue-Geile M, Ferrell R, Deka R, Debski T, Manuck S: Human novelty-seeking personality traits and dopamine D4 receptor polymorphisms: a twin and genetic association study. *Am J Med Genet* 1998; **81**: 44–48.
23 Vandenbergh DJ, Zonderman AB, Wang J, Uhl GR, Costa PT Jr: No association between novelty seeking and dopamine D4 receptor (D4DR) exon III seven repeat alleles in Baltimore Longitudinal Study of Aging participants. *Mol Psychiatr* 1997; **2**: 417–419.
24 Poewe W, Gerstenbrand F, Ransmayr G, Plorer S: Premorbid personality of Parkinson patients. *J Neural Transm* 1983; **19** Suppl.: 215–224.
25 Ricketts MH, Hamer RM, Manowitz P *et al*: Association of long variants of the dopamine D4 receptor exon 3 repeat polymorphism with Parkinson's disease. *Clin Genet* 1998; **54**: 33–38.
26 Nanko S, Ueki A, Hattori M *et al*: No allelic association between Parkinson's disease and dopamine D2, D3, and D4 receptor gene polymorphisms. *Am J Med Genet* 1994; **54**: 361–364.
27 Chang FM, Kidd JR, Livak KJ, Pakstis AJ, Kidd KK: The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Hum Genet* 1996; **98**: 91–101.