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Genetic variation of *CHRNA4* does not modulate attention in Parkinson's disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder, characterised by cognitive decline and attentional impairment. Recently, variation in *CHRNA4* (rs1044396) has been shown to affect visual and auditory function, affecting speed and attention, in healthy adults. An association between *CHRNA4* variation and PD has not been shown. To determine the link between *CHRNA4* variation and attentional deficit in PD. A genotype-phenotype correlation between the common *CHRNA4*:rs1044396 variant and several baseline parameters of attention was carried out in a large cohort of PD cases ($n = 222$) and controls ($n = 159$). We identified significant associations to measures of attention in PD patients compared to controls. However, we found no significant link to *CHRNA4*:rs1044396 genotypes to baseline attention variables in PD or in controls. We conclude that *CHRNA4*:rs1044396 genotypes do not significantly influence the attentional deficit found in PD patients. Contrary to previous studies, we also found no significant influence in healthy age-matched controls.

Keywords

Parkinson's disease; Ageing; Cholinergic receptor; Attention

It is generally well known that many of our cognitive and perceptual functions decline as we age [9], however the extent of the age-related decline and the intra-individual variability remains unclear.

The role of acetylcholine in cognitive function is well documented and recent work indicates that variation in the gene *CHRNA4* (a member of the family of nicotinic acetylcholine receptors) may modulate attention and spatial scaling performance in humans [4,5]. More specifically, a single nucleotide polymorphism in the *CHRNA4* gene (rs1044396) appears to

have an effect on visual and auditory function, affecting speed and attention, in healthy adults [7].

Parkinson's disease (PD) is a neurodegenerative disorder characterised by a loss of midbrain dopaminergic (DA) neurons in the substantia nigra pars compacta. The aetiology of PD is likely caused by a complex combination of genetic and environmental factors. Cognitive decline, including attentional impairment, is a hallmark of both demented and non-demented PD cases. Convergent evidence from therapeutic intervention, neuroimaging and neuropathology studies in PD implicate degeneration of the subcortical cholinergic system in mediating attentional and executive dysfunction [2,10,11]. With this in mind, we examined the genetic effects of the *CHRNA4* polymorphism; rs1044396; on a range of neuropsychological measures, including attention, in a well characterised cohort of PD patients. We hypothesised that this polymorphism might have functional effects upon attention in PD.

We compared 222 community based cases with PD fulfilling UK-PD Society brain bank criteria for the diagnosis of PD [6] (mean age 71.41 years, SD = 8.04, 61% male) from the north east of England to an ethnically age and gender matched control group ($N = 159$, mean age 69.69 years, SD = 7.88, 46% male), with no clinical evidence of PD. All were of Caucasian origin. Four PD patients were taking a cholinesterase inhibitor and none were taking modafinil.

At baseline, all subjects underwent cognitive assessment, including the mini-mental state examination (MMSE) [8]. At baseline and follow-up, all subjects underwent Cognitive Drug Research (CDR, Goring-on-Thames, UK) computer based attentional tasks that included assessment of power of attention (PoA), continuity of attention (CoA), cognitive reaction time (CRT) and cognitive fluctuation (PowCV) [1], where higher scores represent worse attentional performance and directly reflect the ability to maintain concentration to a particular task [1,3]. Full ethical approval was gained for this work and informed consent obtained from all participants.

All subjects, 222 cases and 159 controls were genotyped for the *CHRNA4* polymorphism – rs1044396. Genotyping was done by primer extension of allele-specific extensions products by matrix-associated laser desorption/ionisation time-of-flight (MALDI-TOF, Sequeunom, San Diego, CA, USA) mass spectrometry. Genotypes were confirmed in 10% of random samples, by direct sequencing using an ABI3100 Genetic Analyser (Applied Biosystems).

Allele and genotype frequencies were compared using Pearson's χ^2 test. Multiple logistic regression was performed to look for interactions between the variables. All analyses were carried out using SPSS software version 17.0 (SPSS Inc.).

Comparisons of cognitive assessment between PD cases and controls revealed significant differences in MMSE, PoA and CoA ($P = 1.2 \times 10^{-9}$, 1.7×10^{-9} and 5.3×10^{-9} , respectively, Table 1). There was no significant difference between PD patient CRT or PowCV when compared to controls ($P = 0.737$ and 0.146 , respectively, Table 1).

CHRNA4:rs1044396 genotyping revealed no direct relationship to the onset of PD, when comparing genotypes or alleles (Pearson's $P = 0.558$ and $P = 0.532$, respectively, Table 2).

When comparing mean baseline variables to *CHRNA4*:rs1044396 genotypes we found no significant associations with MMSE, PoA, and CoA scores in cases or controls (Table 3). However, we did find a significant difference in the mean CRT scores of PD patients when compared to *CHRNA4*:rs1044396 genotype ($P = 0.040$, Table 3) and the mean PowCV scores of controls when compared to *CHRNA4*:rs1044396 genotype ($P = 0.038$, Table 3), although correcting for multiple testing removed the statistical significance of these observations. There also appeared to be a trend towards lower CoA scores when the cohort was combined, although the P value did not reach significance ($P = 0.072$, Table 3).

As previous studies have shown that the *CHRNA4*:rs1044396 genotype TT has the strongest effect on attention [7], we performed analysis of CC:CT versus TT genotypes on baseline variables (Table 4). Tests of association did not reveal any link between the CC:CT or TT genotype with MMSE, PoA or CoA; however there was a significant association with CRT and TT homozygous PD patients ($P = 0.043$, Table 4), again not reaching significance after correcting for multiple significance testing. The previously identified association between PowCV scores and controls was improved when comparing CC:CT versus TT genotypes ($P = 0.010$, Table 4), although this would not reach significance after correction for multiple significance testing.

As previous studies have shown a link to TT-homozygotes and cognitive decline, which may evolve to dementia [7], we compared a subset of our subjects (143 PD cases and 96 age and gender matched controls) who had been evaluated for dementia on the basis of DSM-IV assessment and a MMSE ≥ 26 . We found no significant association between *CHRNA4*:rs1044396 genotypes and the presence of dementia, however (Table 5).

Multiple logistic regression analysis did not reveal any additional significant results after correction for multiple significance testing.

The results indicate that *CHRNA4*:rs1044396 genotypes do not have a strong effect on attention, and its progression to dementia, in PD. Previous work has shown that the rs1044396 TT allele has an adverse effect on the ability of healthy individuals to perform complex attention tasks [7]. Whilst an association with cognitive decline (and attention) is evident in PD, a possible reason for our lack of *CHRNA4* genetic association could be the younger mean age of our study group. Alternatively, the effects of medication could mask a possible genetic effect in the PD group. There was no evidence of an association between attention and levodopa equivalents dose after correction for multiple significance testing, however, and only four patients were taking cholinomimetic drugs.

Reinvang et al. (2009) found their most striking effect was in patients aged 70–79 years [7]. Another potential confounding, and perhaps more likely, factor may be PD disease progression itself. If the effect of *CHRNA4* genotype on attention is weak in healthy individuals, then it may be masked in a PD cohort whose attention capacity is already markedly reduced due to disease itself or its treatment. It is interesting perhaps that we did not see significant evidence of attention decline in controls, although this may reflect the

size of our study. It is conceivable that a larger study of similar design might reveal subtle differences between the groups.

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Table 1

Analysis of PD status and mean baseline variables (where; SD is standard deviation of the mean; *P* is Pearson's probability; PD is PD cases; Con is controls. MMSE is Mini-Mental State Examination; PoA is power of attention; CoA is continuity of attention; CRT is cognitive reaction time).

Variable	Mean score (SD)		<i>P</i>
	PD	Con	
MMSE	25.6 (2.2)	27.6 (3.8)	1.2×10^{-9}
PoA	1569 (363)	1348 (183)	1.7×10^{-9}
CoA	63.0 (11.1)	69.5 (4.9)	5.3×10^{-9}
CRT	160.0 (139)	164.8 (81)	0.737
PowCV	59.08 (12.6)	54.12 (16.1)	0.146

Table 2

Analysis of PD status and *CHRNA4*:rs1044396 genotypes (where; PD is PD cases; Con is controls and *P* is Pearson's probability and *P** is Fisher's probability).

Group	<u>Frequency</u>			<i>P</i>
	CC	CT	TT	
PD	38	87	97	0.558
Con	21	63	75	

Group	<u>Frequency</u>		<i>P*</i>
	CC:CT	TT	
PD	125	97	0.532
Con	84	75	

Group	<u>Frequency</u>		<i>P*</i>
	C	T	
PD	163	281	0.317
Con	105	213	

Table 3

Analysis of CHRNA4:rs1044396 on mean baseline variables (where; SD is standard deviation of the mean; *P* is ANOVA probability; PD is PD cases; Con is controls and Comb. is PD + Con. MMSE is Mini-Mental State Examination; PoA is power of attention; CoA is continuity of attention; CRT is cognitive reaction time).

Variable	rs1044396		Mean (SD)			<i>P</i>
			CC	CT	TT	
MMSE	CC v CT v TT	PD	24.74 (4.3)	26.20 (3.5)	26.05 (3.2)	0.111
		Con	28.14 (2.2)	27.87 (2.3)	27.44 (2.2)	0.353
		Comb.	26.02 (4.0)	26.92 (3.2)	26.68 (2.9)	0.207
PoA	CC v CT v TT	PD	1602 (502)	1582 (351)	1503 (264)	0.201
		Con	1420 (236)	1326 (167)	1350 (184)	0.211
		Comb.	1545 (442)	1483 (319)	1450 (249)	0.180
CoA	CC v CT v TT	PD	60.7 (14.5)	64.3 (9.1)	63.9 (10.1)	0.227
		Con	67.8 (5.7)	70.0 (5.2)	69.6 (4.1)	0.310
		Comb.	62.9 (12.8)	66.5 (8.3)	65.9 (9.0)	0.072
CRT	CC v CT v TT	PD	117.5 (206)	160.3 (124)	186.8 (119)	0.040
		Con	184.9 (83.0)	164.2 (78.7)	156.6 (83.7)	0.486
		Comb.	138.3 (180)	161.8 (109)	176.5 (109)	0.152
PowCV	CC v CT v TT	PD	53.35 (6.4)	62.24 (15.8)	57.19 (17.3)	0.273
		Con	64.66 (10.7)	52.43 (13.85)	52.76 (10.49)	0.038
		Comb.	59.38 (10.4)	57.74 (15.6)	55.23 (14.7)	0.501

Table 4

Analysis of combined CC:CT versus TT rs1044396 genotypes on mean baseline variables (where; SD is standard deviation of the mean; *P* is *T*-test probability; PD is PD cases; Con is controls and Comb. is PD + Con. MMSE is Mini-Mental State Examination; PoA is power of attention; CoA is continuity of attention; CRT is cognitive reaction time).

Variable	rs1044396		Mean (SD)		<i>P</i>
			CC:CT	TT	
MMSE	CC:CT v TT	PD	25.77 (3.8)	26.0 (3.2)	0.575
		Con	27.94 (2.2)	27.44 (2.3)	0.168
		Comb.	26.68 (3.4)	26.68 (2.9)	0.990
PoA	CC:CT v TT	PD	1588.5 (400)	1503.1 (264)	0.077
		Con	1348.8 (188)	1350.9 (184)	0.952
		Comb.	1500.8 (357)	1450.9 (249)	0.157
CoA	CC:CT v TT	PD	63.2 (11.1)	63.9 (10.1)	0.640
		Con	69.5 (5.3)	69.6 (4.1)	0.910
		Comb.	65.5 (9.0)	65.8 (9.0)	0.744
CRT	CC:CT v TT	PD	147.4 (154)	186.8 (119.3)	0.043
		Con	169.1 (79.6)	156.7 (83.7)	0.417
		Comb.	155.2 (132.7)	176.5 (109.0)	0.121
PowCV	CC:CT v TT	PD	60.6 (14.9)	57.2 (17.4)	0.457
		Con	55.4 (14.1)	52.7 (10.5)	0.010
		Comb.	58.1 (14.7)	55.2 (14.79)	0.447

Table 5

Analysis of combined CC:CT versus TT rs1044396 genotypes on the presence of PD with dementia (where; SD is standard deviation of the mean; *P* is Pearson's probability and *P** is Fisher's probability; PD is PD cases; Con is controls).

Dementia		<u>Frequency</u>			<i>P</i>
		CC	CT	TT	
PD	Y	11	13	25	0.205
	N	18	39	37	
Con	Y	1	6	8	0.697
	N	12	29	40	

Dementia		<u>Frequency</u>		<i>P*</i>
		CC:CT	TT	
PD	Y	24	25	0.214
	N	57	37	
Con	Y	7	8	1.000
	N	41	40	