Association of the human leucocyte antigen region with susceptibility to Parkinson's disease

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ABSTRACT

Objective The core pathology of Parkinson's disease (PD) is a loss of the dopaminergic neurons in the nigro-striatal pathway, but this is only part of a more widespread pathological process, the nature of which is unknown. Recent data suggest a possible role for inflammation in this disease process. The Human Leucocyte Antigen (HLA) region is one of the most important genetic susceptibility factors in many immune-mediated diseases but has not been extensively investigated in PD.

Methods The authors typed the HLA class II loci HLA-DRB1 and -DQB1 in 528 patients with Parkinson's disease and 3430 controls from the UK.

Results The authors observed an association of HLA-DRB1 with susceptibility to Parkinson's disease. In particular, HLA-DRB1*03 was more common in patients compared with controls.

Conclusions These data suggest a possible role of the HLA region in susceptibility to Parkinson's disease and as such are consistent with other evidence supporting the role of an inflammatory process in the cellular loss in Parkinson's disease, especially of the nigral dopaminergic neurons.

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative condition of the central nervous system (CNS) characterised by a movement disorder and a range of non-motor symptoms. The core pathology is a loss of the dopaminergic neurons in the nigro-striatal pathway, but this is only part of a more widespread pathological process, the nature of which is unknown. However, there has been much recent interest in the genetic basis of PD as well as a possible role of inflammation in this cell loss. The observation of a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) in animal models and epidemiological studies underscores the role of neuroinflammation in PD.[1] In vivo positron emission tomography has shown enhanced binding of [^{11}C](R)-PK11195, a marker selectively expressed by activated microglia, in PD patients compared with controls.[2] A specific and localised activation of Human Leucocyte Antigen (HLA)-positive microglia has indeed been seen in the affected brain areas of PD patients[3] and in members of a family suffering from frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).[4] Previous association studies investigating HLA loci in PD have provided conflicting results but were limited in size.[5–8] Several studies have investigated the adjacent Tumour Necrosis Factor α gene (TNFA) and have shown a trend towards association of a promoter polymorphism with susceptibility to PD.[9–15] Given that a common allele with a large effect is unlikely in sporadic PD, large study populations are required to have any power of identifying true susceptibility genes. We therefore sought to investigate the role of the HLA class II region in susceptibility to PD in a well-characterised and large cohort of PD patients and controls.

METHODS

Our study population consisted of 530 patients with PD of Caucasian ancestry recruited through a specialist PD research clinic. All of these patients met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for PD, except that family history was not used as an exclusion criterion, and were diagnosed by a clinician expert in movement disorders. Individuals (n=2) carrying the known *LRRK2* G2019S mutation were excluded from the study. In the patient group, the male-to-female ratio was 3:2, the mean age of disease onset was 63 years (range 25–91), the mean age at recruitment was 70 years (range 37–105), the mean UPDRS score was 24, and 14% reported a family history of one or more first-degree relatives with parkinsonian symptoms. All patients gave written informed consent, and ethics approval for this study was granted by the local research ethics committee (Cambridge, UK).

HLA typing for the HLA-DRB1 and -DQB1 loci in the cases was performed with low-resolution typing based on PCR with sequence-specific primers.[16] HLA specificities were assigned using WHO nomenclature. Control HLA data were obtained from up to 3430 individuals from the British 1958 Birth Cohort DNA Collection (data deposited by John Todd, University of Cambridge and published online (http://www.b58cgene.sgul.ac.uk/)). These individuals were of white ethnicity and originating from England (86%), Scotland (10%) and Wales (4%). Analysis was performed with a χ^2 test with rare alleles (<5%) grouped together.

RESULTS

Comparison of our study population of 528 British PD cases with the control dataset from the UK 1958 birth cohort (N=3430) showed a significant difference in the distribution of HLA-DRB1

Table 1 Distribution of Human Leucocyte Antigen (HLA)-DRB1 and -DQB1 specificities

Locus	Specificity	Cases	Controls	p Value
HLA-DRB1	01	122 (0.116)	818 (0.119)	0.73
	03	183 (0.173)	977 (0.142)	0.0083
	04	174 (0.165)	1350 (0.197)	0.014
	07	156 (0.148)	1030 (0.150)	0.84
	11	66 (0.063)	424 (0.062)	0.93
	13	95 (0.090)	681 (0.099)	0.34
	15	143 (0.135)	996 (0.145)	0.40
	Other	117 (0.111)	584 (0.085)	
HLA-DQB1	02	292 (0.277)	1688 (0.251)	0.071
	03	331 (0.313)	2341 (0.347)	0.031
	04	19 (0.018)	153 (0.023)	–
	05	182 (0.172)	994 (0.148)	0.036
	06	232 (0.220)	1562 (0.232)	0.38

Specificities with frequencies <5% were not individually considered for analysis. Overall p values for association are 0.0076 for HLA-DRB1 and 0.03 for HLA-DQB1.

specificities (overall χ^2=19.2, 7 df, p=0.0076). HLA-DRB1*03 was found to be over-represented in patients compared with controls (p=0.0083, OR=1.26, 95% CI 1.06 to 1.50) (table 1). Carriers for DRB1*03 were more common among patients compared with controls: 33.0% (N=175) versus 26.7% (N=912), respectively (p=0.0017). This corresponds to an OR of 1.37 (95% CI 1.12 to 1.67) for carriers versus non-carriers of the DRB1*03 allele.

Consistent with the established linkage disequilibrium between HLA-DRB1 and -DQB1, a trend for association with borderline significance was also observed at the DQB1 locus (overall χ^2=10.74, 4 df, p=0.030) (table 1).

DISCUSSION

Our investigation of 528 patients with PD and more than 3000 controls suggests that the HLA region may be contributing to susceptibility to PD. More specifically, HLA-DRB1*03 was over-represented in PD cases compared with controls (p=0.0083), and HLA-DRB1*03 carriers were more common among PD patients compared with controls (p=0.0017). The latter observation remains significant after a Bonferroni studywide correction factor not taking into account the dependency between tests (N=15).

Association studies such as this may be prone to false-positive findings due to population stratification. Whereas the HLA region is one of the few loci for which geographical variation within the UK has been observed in the Wellcome Trust Case Control Consortium,[17] no significant geographical variation was seen for DRB1*03. Therefore, we believe that population stratification is an unlikely explanation for our findings on the HLA-DRB1 gene and susceptibility to PD.

Several studies have investigated polymorphisms in the promoter of the TNFA gene, located near HLA-DRB1.[9–15] A trend towards association with susceptibility to PD has been observed for the TNFA -308G/A variant (rs1800629)[9 11–15] and for a correlated SNP (rs2857595, r2=0.78 with rs1800629) that was included in one of the genome-wide association studies.[18] Notably, the rs1800629*A allele, which was increased in PD patients compared with controls, is present on the most common DRB1*03 ancestral haplotype in Caucasians,[19] rendering these observations consistent with these data. HLA typing resolution in our study was limited to two digits. However, the HLA-DRB1*03 specificity corresponds to just one common subtype (HLA-DRB1*0301) in Caucasian populations.[19] HLA-DRB1*03 has been established as a risk factor for multiple sclerosis, a neurological disorder with a strong inflammatory component, and for several other immune-mediated disorders.[16]

Further investigation of the HLA region in large study populations will be required to assess the role of this region in and to fine-map the effects of specific alleles on susceptibility to PD as suggested in our study. These findings may have important implications towards our understanding of the pathogenesis of the disease, and in particular the involvement and genetic control of any inflammatory component in that process.

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Competing interests None.

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