The relationship between HLA-DRB1 alleles and optic neuritis in Irish patients and the risk of developing multiple sclerosis

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Aims: To investigate the role of the major histocompatibility complex in Irish patients with optic neuritis (ON) and determine whether HLA-DRB1 genotypes are a risk factor for the development of multiple sclerosis (MS) in such patients.

Method: All patients were Caucasian, had Irish ancestry and had MRI of brain and optic nerves within 2–3 weeks of presentation. Patients were referred to a neurologist if MRI findings were consistent with a diagnosis of MS. HLA-DRB1 allele and phenotype frequencies for 78 patients with a clinical diagnosis of acute ON were compared with those for 250 healthy bone marrow donors.

Results: An ON/MS positive patient was 3.4 times more likely than an ON/MS negative patient to be DRB1*15 positive. No difference in age profile was detected between ON/MS positive and ON/MS negative patients or between the ON male and female subgroups. No gender or HLA-DRB1 association was identified for ON/MS negative patients. Female gender was significantly increased among ON/MS positive patients with a *p* value of 0.0053.

Conclusions: DRB1*15 is a significant predisposing factor for ON. This ON patient cohort has also provided an opportunity to evaluate the relationship of HLA genotype with the risk of MS development. The findings of this study indicate that Irish individuals presenting with ON and who are HLA DRB1*15 positive have a higher risk than HLA DRB1*15 negative patients of presenting with MRI findings indicative of MS. This study has also demonstrated that female gender is a risk factor for developing MS in the Irish population.

Optic neuritis (ON) can be a general term that refers to any inflammatory optic neuropathy, but usually it denotes an acute disease of the optic nerve attributed to focal inflammation associated with demyelination. In the absence of any history or clinical signs of multiple sclerosis (MS) or any other explanation for the symptoms, ON is referred to as monosymptomatic or isolated.¹ Inflammation of the optic nerve may result from vascular disease, diabetes, ischaemia, exposure to chemicals such as lead, viral disease, syphilis, Lyme's disease, sarcoidosis, metastatic disease and malignant infiltration of the optic nerve.^{2–4}

ON is frequently both a clinical manifestation and symptom of MS.^{5–6} Approximately 20% of patients with MS have ON as the initial presenting symptom and 35–70% of ON patients progress to MS.⁴ MRI of the brain has revealed clinically silent lesions indicative of MS (periventricular, pericallosal, deep white matter and/or brain stem lesions) in 50–70% of patients with ON and 60–70% of ON patients have CSF findings characteristic of MS.⁴

ON and MS share striking similarities in incidence, worldwide distribution and human leukocyte antigen (HLA) associations as well as MRI and CSF diagnostic criteria.⁷ The lesions

observed in ON are virtually identical to those seen in MS.⁸ A study of childhood ON (94 cases under 16 years of age) suggests a lower risk of progression to MS (13% at 10 years, 26% by 40 years) compared to adults.⁹ Whilst it is evident that approximately half of adult ON patients will go on to develop MS, it is also apparent that others do not.^{10–12} An increased frequency of the MS-associated DR15 haplotype has been demonstrated in studies performed in Sweden,^{7 10 11 13 14} the USA,¹⁵ Denmark,⁶ the UK^{8 12} and Australia.¹⁶ In contrast, the frequency of both HLA DRB1*07 and DRB1*11 were found to be higher in Iranian patients.¹⁷ Interestingly, a study of 18 patients with intermediate uveitis in Wisconsin identified a significant positive association (72%) with DR15.¹⁸ This suggests that DR15 may be a common predisposing factor in a group of related disorders including ON, intermediate uveitis and MS.

Treatment of ON and other high risk patients with interferon β -1 α and intravenous methylprednisolone has shown a reduction in the conversion rate to MS.¹ These data suggest that obtaining an early diagnosis improves patient management since it allows early follow-up and therapeutic intervention at first clinical presentation. In this study we examined the DRB1*15 status of Irish patients presenting with a first attack of ON. Our aim was to determine whether or not patients presenting with acute ON and who carry the HLA DRB1*15 phenotype are at increased risk of developing MS.

METHODS

Patients

A prospective study of 133 patients referred to the neuro-ophthalmic clinic at the Royal Victoria Eye and Ear Hospital in Dublin with a suspicion of ON between November 2003 and November 2005 was carried out. The study was approved by the ethics committee at the hospital. Informed consent was obtained from all patients. A clinical diagnosis of acute ON was established in 78 patients (21 male and 57 female; age range 15–64 years). All 78 patients selected were Caucasian and of Irish ancestry. Patients were excluded if they already had a diagnosis of MS or were of non-Irish origin. Patients with other infections or inflammatory causes of optic nerve neuropathy were excluded. All suspected cases of ON were referred for MRI of the brain and optic nerve within 2–3 weeks. Patients were referred to a neurologist if they had MRI findings consistent with demyelination. The diagnosis of clinically definite MS was based on clinical assessment, MRI and CSF examination. The 78 patients were subdivided according to McDonald criteria¹⁹ as either having MS (ON/MS positive) or not having MS (ON/MS negative). All 78 patients were typed for HLA-DRB1 genotypes.

Abbreviations: CI, confidence interval; HLA, human leukocyte antigen; MHC, major histocompatibility complex; MS, multiple sclerosis; ON, optic neuritis; OR, odds ratio; RPE, relative predispositional effect

Table 1 HLA-DRB1 allele frequencies in ON patients and controls

HLA- DRB1*	Controls vs ON (MS+/-) patients					Controls vs ON (MS+) patients				Controls vs ON (MS-) patients			
	Controls (2n=500)	Patients (2n=156)	Expected* (2n=156)	χ^2	p	Patients (2n=86)	Expected (2n=86)	χ^2	p	Patients (2n=70)	Expected (2n=70)	χ^2	p
01	53	8	16.54	4.4063	0.0358	3	9.116	4.1033	0.0428	5	7.42	0.7893	
03	85	23	26.52	0.4672		11	14.62	0.8963		12	11.9	0.0008	
04	101	23	31.51	2.2993		14	17.372	0.6545		9	14.14	1.8684	
07	82	24	25.58	0.0981		11	14.104	0.6831		13	11.48	0.2013	
08	7	3	2.18			2	1.204			1	0.98		
09	0	1	0.00			0	0			1	0		
10	0	1	0.00			1	0			0	0		
11	12	5	3.74			1	2.064			4	1.68		
12	6	3	1.87			2	1.032			1	0.84		
13	41	10	12.79	0.6094		4	7.052	1.3209		6	5.74	0.0118	
14	13	2	4.06	1.0422		0	2.236	2.2360		2	1.82	0.0178	
15	96	53	29.95	17.7354	<0.001	37	16.512	25.4214	<0.001	16	13.44	0.4876	
16	4	0	1.25			0	0.688			0	0.56		
(08/09/10/ 11/12/16)		13	9.05	1.7262		6	4.988	0.2053		1	4.06	2.3063	
Total	500	156	156	28.3840		86	86	35.5208		70	70	5.6833	

*The number of alleles expected in a sample of size 2n=156, where n=73, is derived from the number of alleles in a control sample of n=250 (2n=500).

Healthy controls

The control sample in this case-control study was comprised of 250 healthy Irish Unrelated Bone Marrow Registry donors. Individuals with non-Irish ancestry were excluded from this control sample. Controls were recruited at blood clinics throughout the Republic of Ireland between January 2001 and June 2002 on behalf of the Irish Unrelated Bone Marrow Registry. Females accounted for 55.6% of the donors tested. All of the donors were between 18 and 45 years of age at the time of recruitment. This control group was chosen as it represents an Irish population sample of healthy individuals in which one would not expect to see any effect on HLA frequencies due to disease. Donors with names suggestive of non-Caucasian parentage were not included in this cohort. Schipper²⁰ has previously employed this selection procedure.

HLA typing

All samples were initially HLA-DRB1 typed by PCR-SSO. Ambiguous SSO typings were resolved by PCR-SSP to a minimum of two-digit level. High resolution DRB1 typing was performed on all control samples using primer sets selected on the basis of the original SSO results.

Unresolved typings or suspected new alleles/variants were referred to the UK for confirmatory sequence-based typing.

Statistical analysis

HLA-DRB1 allele frequencies were determined by direct gene counting. χ^2 Analysis and the relative predispositional effect (RPE) method were used to compare allele frequencies in patient and control samples and to identify possible predisposing or protective alleles. Alleles identified by the RPE method as having possible association with ON were further examined for differences in phenotype frequencies between patients and controls using odds ratios (ORs). OR values and their 95% confidence intervals (CI) were calculated using the online interactive software JavaStat.

A probability value (p) derived from a two-tailed Fisher's exact (F) test was used to indicate the significance of each OR value. Gender and age differences between patient categories and controls were also examined using odds ratios. As the frequencies of 13 HLA DR alleles were compared between patient and control samples, p values associated with odds ratios were corrected according to the Bonferroni method by using a multiple of 13 to obtain the p cor values

Table 2 Comparison of the number of HLA-DRB1 alleles in ON(MS+) patients and controls using the RPE method

DRB1*	Controls vs ON (MS+) patients					<DRB1*15			
	Controls (2n=500)	Patients (2n=86)	Expected* (2n=86)	χ^2	p	Patients (2n=49)	Expected (2n=49)	χ^{2*}	p*
01	53	3	9.116	4.1033	0.0428	3	6.4282	1.8283	0.1763
03	85	11	14.62	0.8963		11	10.309	0.0463	
04	101	14	17.372	0.6545		14	12.25	0.2500	
07	82	11	14.104	0.6831		11	9.9455	0.1118	
08	7	2	1.204			2	0.849		
09	0	0	0			0	0		
10	0	1	0			1	0		
11	12	1	2.064			1	1.4554		
12	6	2	1.032			2	0.7277		
13	41	4	7.052	1.3209		4	4.9728	0.1903	
14	13	0	2.236	2.2360		0	1.5767	1.5767	
15	96	37	16.512	25.4214	<0.001	0	0.4851		
16	4	0	0.688			6	3.5173	1.7524	
(08/09/10/ 11/12/16)		6	4.988	0.2053					
Total	500	86	86	35.5208		49	49	5.7558	

*The number of alleles expected in a sample of size 2n=86, where n=43, is derived from the number of alleles in a control sample of n=250 (2n=500).

RESULTS

HLA-DRB1 allele and phenotype frequencies for 78 ON patients and 250 healthy unrelated bone marrow registry donors were compared. Comparisons of allele frequencies by χ^2 analysis and the RPE method are detailed in tables 1 and 2. Odds ratios, relative risk and calculated p values for HLA-DRB1 phenotype frequency comparisons are detailed in table 3. Gender comparisons are shown in table 4.

χ^2 Analysis of allele frequencies identified DRB1*15 as a possible susceptibility allele for ON and DRB1*01 as a possible protective allele. Further analysis by the RPE method indicated that the apparent protective effect of DRB1*01 was a result of the relatively high frequency of DRB1*15 alleles in the patient group. The DRB1*15 allele was the only class II allele showing a significant difference in frequency between ON patients and controls. This difference between ON patients and controls can be attributed to the MS positive subgroup of ON patients. There were no significant HLA-DRB1 allele frequency differences between the ON/MS negative patient group and the control population (tables 1 and 2).

The odds of finding a DRB1*15 positive individual among the ON/MS positive patients was 3.4 times higher than finding a DRB1*15 positive patient among the ON/MS negative subgroup. There was no significant association between the DRB1*15 phenotype and ON in the MS negative group. While the gender distribution between the ON/MS positive and ON/MS negative subgroups differs significantly, there is no association between the DRB1*15 phenotype and gender in either the control or patient groups (tables 2 and 3). The number of females to male ratio (6:1) was significantly higher in the ON/MS positive subgroup when compared with the MS negative group. There was no significant difference in gender composition between controls and the ON/MS negative subgroup. No gender or HLA-DRB1 association was identified for ON patients who were MS negative. Both female gender and carriage of the DRB1*15 phenotype were found to be significantly increased among ON/MS positive patients.

DISCUSSION

The major histocompatibility complex (MHC) system is responsible for control of the immune response, in that antigen presentation occurs in the context of the MHC antigens.

These antigens are a product of the MHC genes (subdivided into class I, II and III) and are expressed on a variety of cells. Class I genes are known as HLA-A, -B and -C. Class II genes are termed HLA-D. MHC genes are polymorphic and are responsible for some traits which distinguish one individual from another. Many studies have revealed an association between disease susceptibility and specific HLA alleles (eg, ankylosing spondylitis and HLA-B27, birdshot retinochoroidopathy and HLA-A29). The pathogenesis of these diseases is thought to be a result of autoimmune mechanisms. Also, autoimmune

mechanisms may have a major role in the pathogenesis of MS, and a recent study²¹ identifies various co-existing autoimmune diseases in families with several members with MS, suggesting that MS may arise on a background of generalised susceptibility to autoimmunity.

This is the first study to investigate the role of the major histocompatibility complex in ON in this Irish population. This study has employed PCR methods to confirm the recognised association of ON with the DR15 phenotype in this Irish patient group. This susceptibility association with the DR15 phenotype has previously been identified in ON studies performed in Sweden,^{1 3 11 13 14} the USA,⁵ Denmark,⁶ the UK^{8 12} and Australia.¹⁶

Since approximately 20% of MS patients have ON as an initial presenting symptom and 35–70% of ON patients go on to develop MS,⁴ several studies have been performed to investigate the prognostic value of different indicators for disease progression to MS. Numerous studies have conclusively shown that the presence of both oligoclonal IgG bands and abnormal lesions on MRI have a strong positive predictive value for the development of MS in monosymptomatic ON patients.^{3 4 6–8 10 22} Other risk factors including younger age, recurrence of ON, female gender, winter onset and non-specific neurologic symptoms, have also been identified in different studies as increasing the risk of MS.^{3 11 12 16 23 24}

In this study DRB1*15 was shown to have a phenotype frequency of 59.0% in the ON patient group and was identified as a significant susceptibility factor for ON irrespective of MS status (OR = 2.646, $p = 0.0003$, $p_{\text{cor}} = 0.0039$). This finding is in agreement with previous studies of HLA-DRB1 genes which indicate that the DR15 association with ON is intermediate or similar to MS when compared with controls.^{6 8 10–12 13 14} We have also identified a significant susceptibility association between the HLA DRB1*15 and the ON patients who were diagnosed with MS (OR = 4.756, $p < 0.001$, $p_{\text{cor}} = 0.0013$). This observation relates to the very high phenotype frequency of DRB1*15 in the ON/MS positive subgroup (72.1%) when compared with the ON/MS negative patient group (42.9%). This remarkably high phenotype frequency is one of the highest reported to date for any ON/MS study using DNA typing methods. In addition, the odds of identifying a DRB1*15 positive individual among the ON/MS positive patients was 3.4 times higher than finding a DRB1*15 positive patient in the ON/MS negative subgroup. The DRB1*15 phenotype frequency (72.1%) and odds ratio (4.756, $p_{\text{cor}} = 0.0013$) identified for the ON/MS positive subgroup were notably higher than those observed for MS patient groups from Donegal (53.43%, OR = 2.32, $p_{\text{cor}} = 0.0420$) and Wexford (57.78%, OR = 3.84, $p_{\text{cor}} = 0.0014$).²⁵ These findings clearly indicate that the combination of ON and carriage of the DRB1*15 phenotype is a risk factor for the future development of MS in this population.

Table 3 Comparison of HLA DRB1*15 phenotype frequencies

Comparison	DRB1*15 positive Number (%)	DRB1*15 negative Number (%)	OR/RR	(95% CI)	F test p	F test p cor
Controls	88 (35.2)	162 (64.8)	OR	2.646 (1.576 to 4.442)	0.0003	0.0039
ON patients	46 (59.0)	32 (41.0)	RR	1.675 (1.292 to 2.101)		
Controls	88 (35.2)	162 (64.8)	OR	4.756 (2.349 to 9.616)	<0.001	<1.0013
ON (MS+) patients	31 (72.1)	12 (27.9)	RR	2.048 (1.559 to 2.482)		
Controls	88 (35.2)	162 (64.8)	OR	1.381 (0.680 to 2.804)	0.4527	
ON (MS-) patients	15 (42.9)	20 (57.1)	RR	1.218 (0.772 to 1.756)		
ON (MS+) patients	31 (72.1)	12 (27.9)	OR	3.444 (1.352 to 8.777)	0.0115	
ON (MS-) patients	15 (42.9)	20 (57.1)	RR	1.797 (1.147 to 2.910)		
Controls (male)	36 (32.7)	74 (67.3)	OR	1.215 (0.720 to 2.050)	0.5026	
Controls (female)	52 (37.1)	88 (62.9)	RR	1.135 (0.809 to 1.607)		
ON patients (male)	12 (57.1)	9 (42.9)	OR	1.193 (0.441 to 3.241)	0.7971	
ON patients (female)	35 (61.4)	22 (38.6)	RR	1.075 (0.750 to 1.719)		

RR, relative risk.

Table 4 Comparison of gender distribution among ON patients

	Male, number (%)	Female, number (%)	OR (95% CI)	F test (p)
Controls	110 (44.0)	140 (56.0)	2.133 (1.224 to 3.713)	0.008
ON patients	21 (26.9)	57 (73.1)		
Controls	110 (44.0)	140 (56.0)	4.845 (2.02 to 11.589)	0.0002
ON (MS+) patients	6 (14.0)	37 (86.0)		
Controls	110 (44.0)	140 (56.0)	1.048 (0.518 to 2.118)	1
ON (MS-) patients	15 (42.9)	20 (57.1)		
ON (MS+) patients	6 (14.0)	37 (86.0)	4.625 (1.586 to 13.396)	0.0053
ON (MS-) patients	15 (42.9)	20 (57.1)		

The strong association between DRB1*15 and ON in patients diagnosed with MS and the absence of this association in MS negative patients is particularly striking and is indicative of heterogeneity within the ON patient group. Hillert¹³ interpreted similar findings by suggesting that DRB1*15 is a risk factor for dissemination of the demyelination process. Similarly, Frederiksen *et al*⁶ also proposed that the DRB1*15 heterodimer plays a predisposing role in the initial formation of demyelinating lesions but also indicated that other susceptibility genes may contribute to disease progression to MS.

Several studies have established that there is heterogeneity in HLA class II associations with ON in different Caucasian populations. A prospective study of 146 British patients has shown that ON patients who had the HLA-DR3-DQ2 phenotype were 26 times more likely to develop MS.¹² A subsequent study of patients in Sweden confirmed a minor association of the DR3-DQ2 haplotype with ON using the RPE method.¹³ On the basis that the DRB1*03-DQB1*02 haplotype had been positively associated with MS in the Swedish population,^{13, 26} this suggested that haplotype may be a marker for developing MS. A study of 82 Australian patients has shown that 45% of patients with ON alone expressed the DR4 antigen.¹⁶ This result led the authors to speculate that this phenotype may protect against the formation of demyelinating lesions. This finding has not been confirmed in other studies.

The higher number of female patients (73.1%) compared with males was not unexpected. This finding concurs with several ON studies in Caucasian populations of Northern European descent^{4, 6, 13, 22} and with a previous study of 127 cases in Northern Ireland of whom 73% were also female.²³ Our study also identified a significant gender difference between the ON/MS positive and ON/MS negative patient groups. However, there was no association between gender and carriage of the DRB1*15 phenotype in either the patient or control groups. The odds of being female in the ON/MS positive group was four times higher than being female in the ON/MS negative group. This confirmed a significant positive association between female gender and development of MS and is in agreement with an Australian study which also indicated that female gender was a risk factor for MS development.¹⁶ Similarly, a study of Swedish patients identified lower conversion rates in men.¹³ However, more recent studies^{3, 10} have shown that gender is not a risk factor for MS development in ON patients.

This novel study has identified DRB1*15 as a significant susceptibility factor for ON in patients of Irish descent. This ON patient cohort has also provided an opportunity to evaluate the relationship of HLA genotype with the risk of MS development. The findings of this study indicate that MS occurred in significantly more ON patients carrying the DRB1*15 phenotype than in those who were DRB1*15 negative. In addition, this study has also demonstrated that female gender is a risk factor for the development of MS in the Irish population. Several prospective studies indicate that approximately half of all cases of isolated ON will progress to MS. The increased availability of effective drug therapies has emphasised the importance of prognostic markers for

the future development of MS in patients diagnosed with ON. Clinical data indicate that proactive treatment of MS at its earliest clinical manifestation, often ON, is of therapeutic benefit.¹ It is anticipated that introduction of HLA-DRB1 typing at first clinical presentation will identify patients for early follow-up and therapeutic intervention. In addition, absence of the DRB1*15 susceptibility phenotype may also be used to identify patients with a lower risk of MS development. Significantly, some observers³ have recently questioned the need for early treatment on the basis of the improved prognosis for patients with acute monosymptomatic ON. It remains to be seen whether the evidence provided by this preliminary study justifies the introduction of HLA-DRB1 typing of ON patients at first clinical presentation.

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