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Distribution of MHC class II alleles in primary systemic vasculitis

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Distribution of MHC class II alleles in primary systemic vasculitis. Previous studies have shown a number of different associations between major histocompatibility complex (MHC) alleles and primary systemic vasculitis. Disease heterogeneity and the lack of specificity of certain MHC typing techniques may have contributed to the lack of consistency in those studies. We therefore studied a relatively homogeneous group of 94 patients with Wegener's granulomatosis, microscopic polyangiitis, or renal-limited vasculitis using molecular techniques that allow more precise assignment of MHC genotype. DNA was prepared from peripheral blood and DRB1 genotype determined by Taq restriction fragment length polymorphism. DQB1 and DPB1 genotype were assigned by polymerase chain reaction amplification followed by probing with allele-specific oligonucleotides. Specificity of associated anti-neutrophil cytoplasm antibodies (ANCA) was determined where possible by solid phase immunoassays using purified proteinase 3 (PR3) and myeloperoxidase (MPO). After correction for multiple comparisons there were no significant differences in the distribution of DRB1, DQB1 and DPB1 alleles between a local control group ($N = 90$ for DRB1, $N = 50$ for DQB1 and DPB1) and the patient group as a whole ($N = 94$) or two *a priori* defined subgroups (anti-PR3 positive, $N = 35$; anti-MPO positive, $N = 22$). We have therefore found no significant association between primary systemic vasculitis and any MHC class II allele. This, together with the fact that previous smaller studies have shown no consistent association, suggests that any such association is very weak, if it exists at all.

Products of the major histocompatibility complex (MHC) play a key role in the development of the immune (and autoimmune) response. By binding antigenic peptides and presenting them to T cells ($CD8^+$ T cells in the case of the products of the MHC class I loci A, B and C, $CD4^+$ cells in the case of the class II loci DP, DQ and DR) these molecules provide one of the critical signals necessary for T cell activation [1]. Different allelic forms of the MHC molecules differ in the repertoire of peptides that they are able to bind [2, 3]. This variability is one of the mechanisms underlying the association between particular MHC alleles and the ability to mount a particular immune (or autoimmune) response [4]. In humans, it is unusual to observe such associations in the response to exogenous antigens, which contain many potentially antigenic peptides and are therefore likely to be able to form at least some productive MHC molecule-peptide complexes. Autoimmunity is presumed to follow the breakdown of tolerance to a very limited number of self peptides, and MHC-disease associations are commonly observed [5]. Knowledge of such associations may identify key MHC molecules and, ultimately, self peptides which might allow the development of new therapeutic strategies; this has already been achieved in some animal models of autoimmunity [6]. Furthermore, analysis of MHC-disease associations may identify other linked genes with possible therapeutic consequences [7].

The primary systemic vasculitides, Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) [8], have long been suspected to have an autoimmune basis. The case for this has been strengthened by the finding of anti-neutrophil cytoplasm antibodies (ANCA) in a very high proportion of cases of WG [9], MPA [10], and renal-limited vasculitis [11]. The common clinical, histological and serological manifestations suggest that these three conditions are related, and belong to the same spectrum of disease. Among other factors, discrimination within this spectrum is possible on the basis of detailed ANCA specificity. WG is most closely associated with ANCA that produce a cytoplasmic staining pattern (cANCA) and that have specificity for proteinase 3 (PR3) [9, 12], while MPA and renal-limited vasculitis are usually associated with ANCA that exhibit a perinuclear staining pattern (pANCA) [9], the majority having specificity for myeloperoxidase (MPO) [11].

Autoimmune diseases are usually most closely associated with MHC class II alleles; with some exceptions [13], class I associations are secondary, and due to linkage disequilibrium within the MHC. We have therefore investigated the distribution of class II alleles in a series of patients with primary systemic vasculitis and renal-limited vasculitis. In other autoimmune diseases MHC associations may be closer with particular autoantibody specificities than with clinical patterns of disease [14]. We therefore defined two subgroups *a priori*: those with antibodies to PR3, and those with antibodies to MPO. Molecular techniques were used that allow typing at all three class II loci.

Methods

Patients and controls

The disease definitions used here were adapted from those developed at a recent consensus conference on nomenclature in systemic vasculitis [8].

Wegener's granulomatosis. Diagnosis requires clinical evidence of a chronic inflammatory process of more than six weeks duration affecting the respiratory tract, usually the upper airways, with or without involvement of other organs. This should be supported

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either by histology showing a granulomatous, necrotizing vasculitis of small and medium-sized vessels (such as capillaries, arterioles, venules and arteries) or cANCA positivity and/or reactivity for PR3 by ELISA.

Microscopic polyangiitis. There should be clinical evidence of a chronic inflammatory process affecting at least two organ systems (one is typically the kidneys) supported by histology and/or ANCA positivity (indirect immunofluorescence or anti-PR3 or anti-MPO autoantibodies). The histological lesion is a non-granulomatous necrotizing vasculitis of small vessels (such as capillaries, arterioles, venules and arteries), but arteritis of small and medium-sized arteries may also occur. Renal disease is manifested by a pauci-immune, necrotizing, crescentic glomerulonephritis.

Renal-limited vasculitis. The definition is the same as for microscopic polyangiitis without evidence of extra-renal disease.

Patients presenting with one of these diagnoses listed above, or under follow-up, were included in the study. Ninety local healthy individuals were used as controls for DR typing, and a randomly selected subset of 50 of these as controls for DQ and DP typing.

ANCA indirect immunofluorescence (IIF)

ANCA IIF was determined using a fluorescein-isothiocyanate conjugated (FITC) mouse anti-human immunoglobulin (F200, DAKO, Denmark; binds to IgG, IgA and IgM) and a FITC conjugated rabbit anti-human IgM (F203, DAKO). Positive sera were, when possible, classified as having a cytoplasmic (cANCA) or peri-nuclear (pANCA) pattern [9]. In some cases the immunofluorescence could not be definitely assigned to either category and this IIF was classified as indeterminate.

Anti-MPO and anti-PR3 ELISA

MPO was obtained from Calbiochem (La Jolla, CA, USA). PR3 was prepared using minor modifications of published methods. Neutrophils were obtained by sedimentation of red cells with a methylcellulose-hypaque gradient (2% methylcellulose, 34% hypaque in distilled water). The supernatant was centrifuged at 250 g for 10 minutes, and remaining red cells lysed by resuspending in 0.83% NH_4Cl, 10 mM $KHCO_3$, 0.1 mM EDTA for 10 minutes. After washing with phosphate-buffered saline (PBS), granules were isolated from the neutrophils by nitrogen cavitation [15]. Granule pellets were suspended in cold 0.1 M sodium acetate buffer, pH 4.2, and disrupted by six freeze/thaw cycles. Following centrifugation at 10,000 g for 20 minutes, PR3 was isolated from the supernatant by column chromatography on Orange A and Bio-Rex 70 [16].

For the ELISA, antigens were coated onto Dynatech microtiter plates by incubation at 37°C for two hours (MPO 0.01 U/ml, PR3 0.2 μg/ml in 0.05 M sodium bicarbonate buffer, pH 9.5). Samples were diluted 1:50 in PBS/0.05% Tween 20/1% gelatin and incubated in duplicate on the plates for one hour at 37°C. After washing, bound antibody was detected with alkaline phosphatase-conjugated goat anti-human IgG (1:3000, Jackson Immuno-Research Laboratories Inc.) followed by alkaline phosphatase substrate (Sigma). Results were calculated as the net absorbance at 405 nm (average absorbance in antigen coated wells minus average absorbance in antigen free wells) expressed as a percentage of a known positive sample included on the same plate. A sample was designated positive if the binding was greater than three standard deviations above the mean, derived from 30 normal control sera.

MHC class II allele typing

The methods used in this study have been described previously [17]. DNA was extracted from peripheral blood samples. For DR typing, DNA was digested using Taq I and electrophoresed on an agarose gel. The fragments were transferred to a nylon membrane using the Southern blot method and then hybridised serially with ^{32}P-labeled DQA1 and DRB1 probes. The results were determined by visual inspection [18]. For DQ and DP typing, the DQB1 and DPB1 regions were amplified using the polymerase chain reaction, transferred to a nylon membrane using dot-blotting [19], and then probed with ^{32}P-labeled oligonucleotide probes. Restriction fragment length polymorphism patterns or binding combinations of oligonucleotide probes not corresponding to known alleles were designated as untyped.

Statistics

Analysis was by chi squared test (two tailed) on 2 × 2 contingency tables with Yates' correction. A correction for multiple comparisons was made by multiplying the *P* values by the number of different alleles found at each locus.

Results

A total of 94 patients were successfully typed at at least two of the three class II loci and form the basis of this report.

Seven patients were classified as having renal-limited vasculitis. Histological confirmation was available for all seven, and six were pANCA positive; of the six, three were anti-MPO positive, including one patient double positive for anti-PR3.

Thirty-one patients were classified as having microscopic polyangiitis. Histological confirmation was available for 26; of the other five, four were pANCA positive (one also anti-MPO positive), and one cANCA positive. In this group as a whole, 17 were anti-MPO positive, including one double positive for anti-PR3, and one patient was positive for anti-PR3 alone.

Fifty-six patients were classified as having Wegener's granulomatosis. Histological confirmation was available for 43; of the other 13, four were cANCA and anti-PR3 positive, six cANCA positive alone, one cANCA, anti-PR3 and anti-MPO positive, one pANCA and anti-PR3 positive and one cANCA and anti-MPO positive. In this group as a whole, 32 were anti-PR3 positive, including one double positive for anti-MPO, and one patient was positive for anti-MPO alone.

In the patient population as a whole, histological confirmation of the diagnosis in the form of necrotizing vasculitis and/or crescentic glomerulonephritis was available for 76 patients (81%). Vasculitis was generalized in 74 (79%) and renal-limited in seven (7%). Disease was persistent in 20 of the 69 patients (29%) for which this information was available. A total of 85 patients (90%) were positive for ANCA by IIF at some stage (55 cANCA, 29 pANCA, 1 indeterminate); the majority of the nine negative patients had localized and/or inactive disease.

The distribution of alleles in the whole population studied is presented in Table 1. Thirty-five patients were positive for anti-PR3 antibodies, and 22 for anti-MPO antibodies (these numbers include three patients that were positive for both specificities); the distribution of alleles in these two *a priori* defined subgroups is shown in Tables 2 and 3. Table 4 presents the comparisons in which the chi squared statistic was > 1 together with the associated uncorrected *P* values. In no case did the chi squared statistic

Table 1. Frequency (%) of MHC class II alleles in patients with primary small vessel vasculitis

	Patients (N = 94)	Controls (N = 90)		Patients (N = 94)	Controls (N = 50)		Patients (N = 94)	Controls (N = 50)
DR1	17	19	DQ*0401/0402	1	8	DPB*0101	21	18
DR2	31	27	DQ*0201	35	34	DPB*0201/0801	38	30
DR3	29	37	DQ*0501	45	28	DPB*0301	22	18
DR4	44	37	DQ*0602	16	24	DPB*0401	75	60
DR5	16	17	DQ*0301	57	50	DPB*0402	20	24
DR6	12	19	DQ*0302	28	26	DPB*0501	5	4
DR7/9	30	21	DQ*0303	8	10	DPB*0601	3	0
DR8	10	4	Untyped	1	4	DPB*0901	5	10
Untyped	1	12				Untyped	1	6

Table 2. Frequency (%) of MHC class II alleles in patients with anti-PR3 antibodies

	Patients (N = 35)	Controls (N = 90)		Patients (N = 35)	Controls (N = 50)		Patients (N = 35)	Controls (N = 50)
DR1	17	19	DQ*0401/0402	3	8	DPB*0101	17	18
DR2	34	27	DQ*0201	37	34	DPB*0201/0801	34	30
DR3	29	37	DQ*0501	37	28	DPB*0301	11	18
DR4	57	37	DQ*0602	17	24	DPB*0401	86	60
DR5	14	17	DQ*0301	69	50	DPB*0402	26	24
DR6	6	19	DQ*0302	29	26	DPB*0501	9	4
DR7/9	29	21	DQ*0303	3	10	DPB*0601	3	0
DR8	9	4				DPB*0901	9	10

Table 3. Frequency (%) of MHC class II alleles in patients with anti-MPO antibodies

	Patients (N = 22)	Controls (N = 90)		Patients (N = 22)	Controls (N = 50)		Patients (N = 22)	Controls (N = 50)
DR1	18	19	DQ*0201	23	34	DPB*0101	18	18
DR2	27	27	DQ*0501	50	28	DPB*0201/0801	36	30
DR3	18	37	DQ*0602	9	24	DPB*0301	27	18
DR4	54	37	DQ*0301	59	50	DPB*0401	68	60
DR5	9	17	DQ*0302	27	26	DPB*0402	23	24
DR6	14	19	DQ*0303	14	10	DPB*0501	5	4
DR7/9	36	21	Untyped	5		DPB*0601	5	0
DR8	9	4				DPB*0901	9	10

achieve significance after correction for multiple comparisons, and indeed in only one case (DPB*0401 in patients with anti-PR3 antibodies) was this significant before correction.

Discussion

We have found no difference in the distribution of DRB1, DQB1 or DPB1 alleles between our patient and control populations. There was a possible suggestion of an increased incidence of DPB*0401 in patients with anti-PR3 antibodies, but because of the multiple comparisons involved this should be interpreted with caution. Our conclusions must be qualified somewhat because the RFLP typing method used for the DR locus will conceal some allelic complexity, and we may not have identified rare alleles present as heterozygotes at the DQ and DP loci. However, given the very similar distribution of alleles between the patient and control populations, we regard it as unlikely that a more detailed analysis would reveal significant differences.

A genetic component to the pathogenesis of Wegener's granulomatosis is suggested by the occasional reports of occurrence of the disease in related individuals [20–23]. However, previous studies of the distribution of MHC alleles have produced conflicting results. An initial report found no association with any of 24 class I specificities [24]. Subsequently, an association with the class I allele B8 was found (present in 38.7% of patients vs. 18.9% of controls; $P < 0.01$, but probably not corrected for multiple comparisons [25]). A later study found a very similar increased frequency of B8 but this was not significant after correction [26]. There was, however, a significant association between Wegener's granulomatosis and DR2 ($P_{corr} < 0.008$). There were no other significant associations between Wegener's granulomatosis and the other MHC alleles that were examined, nor between polyarteritis nodosa and Churg-Strauss vasculitis and any allele.

The first study to employ molecular typing techniques used RFLP analysis to determine DR types, in addition to standard serological typing for class I A and B locus alleles, in 41 patients with Wegener's granulomatosis [27]. No significant associations were found, although the greatest difference was a frequency of 43.9% for DR15 (a subtype accounting for almost all DR2 types in the population studied) in patients compared to 30% in controls. A study of 27 patients with Wegener's granulomatosis using serological techniques found a significant increase in DR1 ($P_{corr} = 0.04$) [28].

Table 4. Alleles with chi squared statistic > 1

Group	Allele	Chi squared	*P* value (uncorrected)
All patients	DR6	1.326	0.2496
	DR7/9	1.392	0.238
	DR8	1.144	0.2847
	DQB*0401/2	2.844	0.0917
	DQB*0501	3.152	0.0758
	DPB*0401	3.054	0.0805
Patients with anti-PR3 antibodies	DR4	3.528	0.0603
	DR6	2.448	0.1177
	DQB*0301	2.197	0.1382
	DPB*0401	5.377	0.0204 (P_c = 0.1632)
Patients with anti-MPO antibodies	DR3	1.959	0.1616
	DR4	1.666	0.1968
	DR7/9	1.492	0.222
	DQB*0501	2.364	0.1242
	DQB*0602	1.321	0.2505

The previous largest study to date used exclusively molecular techniques to examine the distribution of DRB1, DQA1 and DQB1 alleles in 59 patients with ANCA-positive vasculitis [29]. This found a significant increase in the frequency of the DQw7 (DQB*0301) allele: 53% in patients versus 27.8% in controls, $P_{corr} < 0.0025$. Our study found a very similar frequency for this allele (57%), and if we use the same control group (1103 British Caucasoids typed by Bidwell) then we would also find that this increased frequency is highly significant. However, the DQB*0301 allele was also found in 50% of our local control population. Furthermore, a similar frequency has been found in a number of independent patient groups typed using exactly the same techniques as used in this study (39% in Graves' disease [17], 46% in alopecia areata [30], 45% in Hashimoto's thyroiditis [31], 38% in primary biliary cirrhosis [32]), although a reduced frequency of 15% was found in autoimmune Addison's disease [33]. The DQB*0301 allele can be difficult to detect using RFLP analysis [34], which was the method used by Bidwell. Because Spencer et al were aware of this problem they used a polymerase chain reaction-allele specific oligonucleotide method to detect DQB*0301 [29]. It may be significant that the studies using this more accurate method report a rather similar frequency for DQB*0301, which is higher than that found by Bidwell using different methodology.

The only previous study to examine serologically defined subgroups found no suggestion of any difference between patients with a cANCA pattern on indirect immunofluorescence and those with a pANCA pattern [29]. Because these patterns (particularly pANCA) encompass a number of different antigenic specificities, their use as a grouping factor for immunogenetic analysis may blur any associations with specific autoantibodies. Despite our use of specific assays we were only able to detect a possible association between DPB*0401 and anti-PR3 antibodies. Because of the multiple comparisons and subgroups (albeit defined *a priori*) this association may well have arisen by chance alone. A separate study would be needed to determine whether or not it is a true association. The rather low proportion of seropositive cases in our population reflects the fact that many patients were in remission, and that strict criteria were used to define specific binding in the ELISA. In addition, a proportion of samples typed by IIF in the past were unavailable for analysis by specific ELISA.

The lack of an association between the MHC and primary systemic vasculitis, despite improved definition of patient subgroups and use of molecular techniques for MHC typing, may indicate significant differences in pathogenesis as compared to diseases (such as membranous nephropathy [35] and anti-glomerular basement membrane disease [36]) that do manifest such an association. The association between infection and relapse of vasculitis [37], the seasonal incidence and occasional preceding viral illness [38], and the response in some cases to anti-microbial therapy alone [39] all draw attention to the role of infection. If vasculitis is precipitated by an abnormal or exaggerated response to infection [9] then, for the reasons outlined above, it would be unusual to observe any particular MHC association with this response.

In conclusion, we have found no significant association between primary systemic vasculitis and any MHC class II allele. This, together with the fact that previous smaller studies have shown no consistent association, suggests that any such association is very weak, if it exists at all. This may or may not have implications for the underlying pathogenesis, but suggests that therapeutic strategies targeted at a particular MHC molecule or self-peptide are unlikely to be applicable to this group of diseases.

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