Antibody response to myelin oligodendrocyte glycoprotein and myelin basic protein depend on familial background and are partially associated with human leukocyte antigen alleles in multiplex families and sporadic multiple sclerosis

Andreas Lutterotti[a], Markus Reindl[a], Christoph Gassner[b], Katharina Poustka[a], Kathrin Schanda[a], Florian Deisenhammer[a], Thomas Berger[a,*]

[a] Department of Neurology, University of Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria
[b] Central Institute of Blood Transfusion and Immunological Department, General Hospital and University Clinics, Anichstrasse 35, A-6020 Innsbruck, Austria

Abstract

We investigated the association of the antibody response to myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) with human leukocyte antigen (HLA) class II alleles in 41 patients with sporadic multiple sclerosis (MS) and 12 multiplex MS families. We found significantly increased antibody response to MOG and MBP in MS patients without any difference to asymptomatic relatives. HLA DRB1*04 was associated with IgM reactivity to MOG in MS patients, and DRB1*15 and DRB5 with anti-MOG IgA among asymptomatic relatives. We conclude that antibody responses to MOG and MBP depend on familial background. Moreover, the humoral immune reactivity against MOG is partially under control of certain HLA class II alleles.
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1. Introduction

Increased intrathecal immunglobulin synthesis in multiple sclerosis (MS) patients (Ebers and Paty, 1980) and the raised incidence of antibodies against myelin proteins such as myelin oligodendrocyte glycoprotein (MOG) (Sun et al., 1991; Xiao et al., 1991; Karni et al., 1999; Lindert et al., 1999; Reindl et al., 1999; Egg et al., 2001; Haase et al., 2001; von Budingen et al., 2001) and myelin basic protein (MBP) (Paterson et al., 1981; Newcombe et al., 1985; Olsson et al., 1990; Warren and Catz, 1994; Sellebjerg et al., 1995) in CSF and sera of MS patients suggest a relevant biological role for antibodies to these antigens in MS. Anti-MOG antibodies were found in sera of MS patients even at very early stages of the disease, whereas antibodies to MBP, the major protein component of myelin, accumulate over time (Reindl et al., 1999). Antibodies against MOG are able to cause demyelination in vitro (Kerlero de Rosbo et al., 1990; Menon et al., 1997; Besson Duvanel et al., 2001), in animal models (Schluesener et al., 1987; Linington et al., 1988; Amor et al., 1994; Adelmann et al., 1995; Genain et al., 1995; Johns et al., 1995; Raine et al., 1999; Stefferl et al., 1999; Genain and Hauser, 2001) and were found in active lesions of MS patients (Genain et al., 1999; Raine et al., 1999).

In experimental autoimmune encephalomyelitis (EAE), an animal model of MS, clinical expression was dependent on the anti-MOG antibody response (Stefferl et al., 1999). In addition, antibody responses to MOG and MBP were shown to be under genetic control in rodents (Stefferl et al., 1999; Yang et al., 2001). In humans, the human leukocyte antigen (HLA) has been found the only gene locus linked to MS in both sporadic MS and multiplex families in different populations (Tienari et al., 1993; Weinshenker et al., 1998).

To elucidate a possible genetic influence on the humoral immune response to MOG and MBP, we analyzed the sera

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of patients with sporadic MS and members of 12 multiplex families for antibodies against these antigens, and typed this cohort for HLA class II antigens.

2. Patients and methods

2.1. Study population and blood samples

Blood samples (EDTA treated whole blood and serum) were obtained between 1996 and 2001 and stored at -20 °C until use. All patients gave informed consent.

MS patients were diagnosed according to the criteria of Poser. The MS cohort included 41 patients with sporadic MS (sMS) and 24 patients with familial MS (fMS) sampled from 12 multiplex families. The control group consisted of 33 asymptomatic relatives (AR) of the fMS patients and 65 age- and gender-matched healthy controls (HC).

All families, patients and controls originated from the same geographic region in Western Austria. Each family had two affected family members. In six families the affected patients were parent–child pairs, four pairs were full sibs and in two families the affected pairs were half-sibs. On average 2.83 AR per family were examined (Table 2). A detailed history of previous and current signs and symptoms suggestive of MS was taken from all AR. None of the AR reported signs or symptoms suggestive for MS. In addition, neurological examinations of the AR were inconspicuous for MS. As MRI scans were not performed we defined this group as asymptomatic. The clinical and demographic data of all analyzed persons are given in Table 1. In the fMS group 6 (25.0%) patients were treated with interferon-β, 2 (8.3%) were treated with intravenous immunoglobulins, 2 (8.3%) with azathioprine and 14 (58.3%) had neither immunomodulatory nor immunosuppressive treatment. Of the sMS patients 25 (61.0%) were treated with interferon-β, 3 (7.3%) had intravenous immunoglobulins, 1 (2.4%) was treated with glatiramera-

cetate, 2 (4.9%) had treatment with azathioprine and 10 (24.4%) had no immunomodulatory or immunosuppressive treatment.

2.2. Determination of anti-MOG and anti-MBP antibodies

The human recombinant MOG Ig-domain and human myelin derived MBP were prepared as described before (Reindl et al., 1999). Anti-MOG and anti-MBP antibodies were analyzed by Western blot as previously described (Reindl et al., 1999; Egg et al., 2001) with minor modifications: Briefly, either 1-μg recombinant MOG–Ig or 2-μg MBP were loaded per lane and separated in 10% Bis–Tris (NuPage) SDS-polyacrylamide gels (Novex, San Diego, USA). Separated proteins were electrotransferred to nitrocellulose membranes (Hybond-C, Amersham, UK). Efficiency of transfer was monitored by the use of a prestained low range SDS-PAGE standard (Bio-Rad, Hercules, USA) and by staining of the filters with Ponceau S (Sigma, St. Louis, USA) after transfer. Blots were blocked with 2% milk powder in phosphate buffered saline (PBS) containing 0.05% Tween-20 (PBS–T). Blots were then dried, cut into 2-mm nitrocellulose strips using a membrane cutter (Novex) and probed with diluted human sera (1:1000 for IgG, 1:500 for IgM and 1:200 for IgA in 2% milk powder in PBS–T) overnight at 4 °C. Nitrocellulose strips were then washed three times with PBS–T and incubated with alkaline phosphatase conjugated anti-human IgG, IgM or IgA (all 1:5000; G6907, G5204 or G5415; all Axell, Westbury, USA) for 1 h at room temperature. After washing, bound antibodies were detected by p-nitro-blue-tetrazolium chloride and 5-bromo-4-chloro-3-indolyl phosphate (both Roche Molecular Diagnostics, Mannheim, Germany). Strips were then washed with distilled water, dried and the immunoreactivity of serum samples was then assessed by two independent investigators.

As controls, monoclonal antibodies to MBP (MAB381, Chemicon, Temecula, CA, USA) and MOG (8.18-C5,

Table 1
Clinical and demographic data

Group	Gender[a]		Age[b]	Disease course[a]			Duration[c]	Relapse[d]	EDSS[e]	Treatment[a,f]
	Men	Women		RR	SP	PP				
sMS	12 (29.3)	29 (70.7)	35.4 ± 09.1	36 (87.7)	3 (12.2)	0 (0.0)	7.1 ± 6.4	5.2 ± 3.5	2.3 ± 1.5	31 (75.6)
fMS	5 (20.8)	19 (79.2)	43.7 ± 13.5	12 (50.0)	8 (33.3)	6 (16.7)	15.0 ± 10.1	6.0 ± 6.8	3.7 ± 2.8	10 (41.7)
AR	20 (60.6)	13 (39.4)	47.8 ± 17.7							
HC	27 (41.5)	38 (58.5)	39.8 ± 14.5							

[a] Percentage in parentheses.
[b] Mean age given in years ± standard deviation (S.D.).
[c] Mean disease duration in years ± S.D.
[d] Mean total number of relapses ± S.D.
[e] Expanded Disability Status Scale given as mean ± S.D.
[f] Immunomodulatory or immunosuppressive treatment; RR: relapsing–remitting; SP: secondary-progressive; PP: primary–progressive; sMS: sporadic MS patients; fMS: familial MS patients; AR: asymptomatic relatives of multiplex families; HC: healthy controls.

Linington et al., 1988) and a positive and a negative human control serum were used.

In order to exclude any influence of clinical relapses or remissions and therapies on anti-MOG and anti-MBP antibodies, MS patients were repeatedly analyzed at least two times over a period of at least 3 years. Ten fMS patients could only be analyzed once. Of these fMS patients, only one patient had treatment with interferon-β and one was treated with intravenous immunoglobulins.

2.3. HLA typing

DNA was isolated from leukocytes by the salting-out method (GenomicPrep™ Blood Kit/Amersham Pharmacia Biotech, Uppsala, Sweden). HLA typing was performed for class II genes using polymerase chain reaction (PCR) amplification with sequence-specific primers in a low resolution kit (Olerup SSP-Combi Tray, Saltsjöbaden, Sweden). PCR products were analyzed by agarose gel electrophoresis and interpreted using the Helmberg SCORE Software (Geno Vision, West Chester, PA, USA).

2.4. Statistical evaluation

Statistical analysis [frequencies, Odds ratios (OR), means, standard deviations, medians] and significance of group differences (Fishers exact test, Chi-square test) was performed using the GraphPad InStat statistical analysis program (GraphPad Software, San Diego, CA, USA). P-values < 0.05 were considered as statistically significant and are given as $p < 0.05$ (significant), $p < 0.01$ (very significant) and $p < 0.001$ (highly significant). Transmission Disequilibrium Test (TDT) was used according to Spielman et al. (1993). The TDT counts the numbers of transmissions and non-transmissions from heterozygous parents to affected offspring and tests the statistical deviation from the expected 50:50 rate of

transmission using a Chi-square test with one degree of freedom. The level of significance was set at $p < 0.05$.

3. Results

3.1. Frequencies of anti-MOG antibodies

The frequencies of anti-MOG and anti-MBP antibodies were comparable with those found in previous studies from our laboratory (Reindl et al., 1999; Egg et al., 2001).

The overall incidence of antibody responses to MOG (Table 3a) was significantly more frequent among multiplex families compared to HC. This difference was significant for both, fMS ($p < 0.01$) and AR ($p < 0.001$). There was also a significant difference of the antibody response to MOG between AR and sMS ($p < 0.05$).

When comparing the immunglobulin isotypes, we found a significantly higher percentage of IgG antibody responses to MOG in AR ($p < 0.001$) when compared to HC, whereas there was no significant difference in the fMS and sMS group compared to HC. This seems to be an age-dependent effect as the anti-MOG IgG antibody response rises with age. In the HC group the mean age of MOG IgG positive individuals (50.3 ± 14.2 years) is significantly ($p < 0.01$) higher compared to MOG IgG negative individuals (36.9 ± 13.3 years). IgM is the predominant isotype among MS families compared to HC ($p < 0.001$). IgA antibodies were significantly more frequent among all members of multiplex families compared to HC ($p < 0.01$). Incidences of anti-MOG IgM and IgA were not age-dependent. There was no influence of gender on the antibody response.

To test for a difference of antibody responses between individual families we performed a Chi-square test, which detected no significant difference for anti-MOG and anti-MBP antibody responses (Table 2). This was still not

Table 2
Antibody responses to MOG and MBP in MS multiplex families

Family	n	Affected	MOG				MBP			
			IgG	IgM	IgA	Ig All	IgG	IgM	IgA	Ig All
01	4	2 (50%)	3 (75%)	3 (75%)	1 (25%)	3 (75%)	2 (50%)	4 (100%)	0 (0%)	4 (100%)
02	2	2 (100%)	0 (0%)	1 (50%)	0 (0%)	1 (50%)	1 (50.0%)	1 (50.0%)	0 (0%)	1 (50%)
03	5	2 (40%)	3 (60%)	4 (80%)	0 (0%)	4 (80%)	1 (20%)	1 (20%)	0 (0%)	2 (25%)
04	5	2 (40%)	3 (60%)	4 (80%)	2 (40%)	5 (100%)	3 (60%)	4 (80%)	3 (60%)	4 (80%)
05	9	2 (22%)	3 (33%)	4 (44%)	5 (56%)	5 (56%)	4 (44%)	4 (44%)	2 (22%)	6 (67%)
06	4	2 (50%)	1 (25%)	3 (75%)	0 (0%)	3 (75%)	0 (0%)	0 (0%)	1 (25%)	4 (100%)
07	6	2 (33%)	1 (17%)	4 (67%)	1 (17%)	4 (67%)	3 (50%)	4 (67%)	0 (0%)	4 (67%)
08	4	2 (50%)	2 (50%)	4 (100%)	2 (50%)	4 (100%)	2 (50%)	4 (100%)	2 (50%)	4 (100%)
09	8	2 (25%)	2 (25%)	7 (88%)	2 (25%)	7 (88%)	1 (13%)	5 (63%)	1 (13%)	6 (75%)
10	6	2 (33%)	3 (50%)	4 (67%)	2 (33%)	5 (83%)	4 (67%)	5 (83%)	1 (17%)	5 (83%)
11	2	2 (100%)	1 (50%)	2 (100%)	1 (50%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)	2 (100%)
12	2	2 (100%)	1 (50%)	2 (100%)	2 (50%)	2 (100%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)

Frequency of the overall antibody response to MOG and MBP in MS multiplex families. In each family, two MS patients and asymptomatic relatives were examined. There is no significant difference in antibody response to MOG and MBP between the families when comparing with a Chi-square test. n: number of tested individuals in the family.

significant after taking those families without asymptomatic relatives in this study out of the analysis.

3.2. Frequencies of anti-MBP antibodies

As shown in Table 3b, the overall incidence of anti-MBP antibodies was elevated in fMS ($p<0.001$) and AR ($p<0.001$) compared to HC. This antibody response was also higher among fMS when compared to sMS ($p<0.05$).

Similarly to anti-MOG antibodies, the predominant isotype among the families was IgM. There was a significant difference of the incidence of anti-MBP IgM comparing fMS ($p<0.001$) and AR ($p<0.001$) with HC. The frequency of this isotype was also raised in fMS ($p<0.01$) and AR ($p<0.05$) compared to the sMS group. There were no significant differences between the groups regarding IgG and IgA antibody frequencies. There was no influence of age or gender on the antibody response to MBP.

3.3. Comparison of the anti-MOG and anti-MBP antibody responses

To further evaluate any relation between the immune responses to MOG and MBP, the incidences of anti-MOG and anti-MBP antibodies were analyzed with respect to anti-MOG only, anti-MBP only, and anti-MOG and anti-MBP together. As Fig. 1 demonstrates, immune responses were similar in the sMS and the HC group, whereas there was a raised incidence of anti-MOG in combination with anti-MBP in fMS ($p<0.001$) and AR ($p<0.001$) compared to HC. We also found an increased incidence of anti-MOG in combination with anti-MBP in fMS ($p<0.05$) and AR ($p<0.05$) compared to sMS.
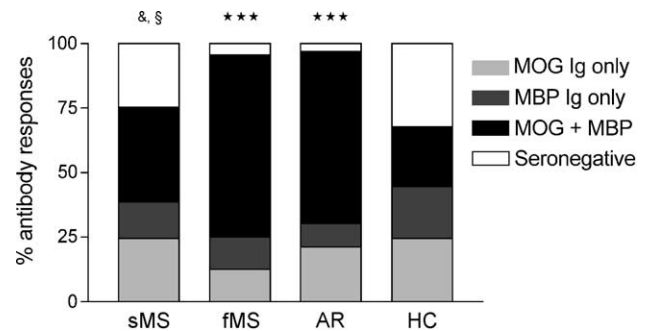

Fig. 1. Comparison of the anti-MOG and anti-MBP antibody response. sMS: sporadic MS; fMS: familial MS; AR: asymptomatic relatives; HC: healthy controls. There is a highly significantly raised incidence in antibody response to MOG in combination with MBP compared to HC in fMS ($p<0.001$) and AR ($p<0.001$). This antibody response is also significantly increased in fMS ($p<0.05$) and AR ($p<0.05$) compared to sMS patients. Statistically different (Fisher's exact test) from HC: ***$p<0.001$; from AR: [§]$p<0.05$; from fMS: [&]$p<0.05$.

3.4. Frequencies of HLA DQB1, DRB1, DRB3, DRB4 and DRB5 genotypes

HLA class II allele frequencies were compared to 299 organ donors (data not shown). There was a significant association of DQB1*06 ($p<0.05$), DRB1*15 ($p<0.001$) alleles and the DRB5 ($p<0.001$) locus with MS after correction for the number of comparisons made. We observed no significant differences in allele frequencies between fMS and AR. However, by TDT test DRB1*15 and DRB5 were shown to be transmitted significantly more often to affected offspring (data not shown). DRB3 was negatively associated with fMS compared to HC ($p<0.05$). A significant negative association in the frequency of DRB3 ($p<0.01$) and a positive association with DRB5 ($p<0.05$) were found when comparing AR and HC. There was no

Table 3

(a) Anti-MOG antibody response in sMS, fMS, AR and HC

Group	n	Number and percentage (in parentheses) of seropositive cases			
		IgG anti-MOG	IgM anti-MOG	IgA anti-MOG	All anti-MOG[1]
sMS	41	16 (39.0%)	24 (58.5%)*	8 (19.5%)	25 (61.0%)[§]
fMS	24	6 (25.0%)	19 (79.2%)***	8 (33.3%)**	20 (83.3%)**
AR	33	17 (51.5%)**	23 (69.7%)**	10 (30.3%)*	29 (87.9%)***
HC	65	14 (21.5%)	22 (33.8%)	6 (9.2%)	30 (46.2%)

(b) Anti-MBP antibodies in sMS, fMS, AR and HC

Group	n	Number and percentage (in parentheses) of seropositive cases			
		IgG anti-MBP	IgM anti-MBP	IgA anti-MBP	All anti-MBP
sMS	41	13 (31.7%)	14 (34.1%)[§,&&]	9 (22.0%)	21 (51.2%)[&]
fMS	24	10 (41.7%)	17 (70.8%)***	6 (25.0%)	20 (83.3%)***
AR	33	12 (37.5%)	20 (62.5%)***	6 (18.2%)	25 (75.8%)***
HC	65	16 (24.6%)	11 (16.9%)	9 (13.8%)	25 (38.5%)

n: number of patients investigated. Statistically different (Fisher's exact test) from HC: *$p<0.05$, **$p<0.01$, ***$p<0.001$; from AR: [§]$p<0.05$; from fMS: [&]$p<0.05$, [&&]$p<0.01$.
sMS: sporadic MS patients; fMS: familial MS patients; AR: asymptomatic relatives of multiplex families; HC: healthy controls; 1: positive if either IgG or IgM or IgA or any combination of these occurred.

Table 4
Anti-MOG antibodies and HLA genotypes in sporadic MS, familial MS and asymptomatic relatives

Phenotype	n	Ig[a]	HLA-positive		HLA-negative		OR[b]
			Ig +	Ig −	Ig +	Ig −	
DRB1*04	65[c]	IgM (43)	13	0	30	22	19.9
DRB1*15	33[d]	IgA (10)	9	8	1	15	16.9
DRB5	33[d]	IgA (10)	9	9	1	14	14.0

n: number of individuals investigated.
[a] Ig isotype and number of Ig positive in parentheses.
[b] Odds ratio (all $p < 0.01$).
[c] fMS + sMS.
[d] AR.

significant difference in allele or phenotype frequencies between fMS and sMS (data not shown).

3.5. Association of HLA class II genotypes with antibodies to MOG and MBP

To avoid false positive association due to the polymorphism of HLA class II alleles and the relatively low number of individuals examined, we considered only p values of < 0.01 to be statistically significant.

When combining all MS patients, there was a significant association between anti-MOG IgM antibody response and the DRB1*04 allele (OR:19.9; $p < 0.01$) (Table 4). There was no statistically significant association with any Ig isotype for any MS group alone. Comparing HLA phenotype frequencies and the antibody response to MOG in AR revealed a significant positive association of DRB1*15 (OR:16.8; $p < 0.01$) and the DRB5 (OR:14.3; $p < 0.01$) locus with anti-MOG IgA antibodies.

There was a trend towards a negative association of anti-MOG IgG and DRB1*15 ($p < 0.05$) and DRB5 ($p < 0.05$), respectively, when considering all patients. No significant association of HLA class II phenotypes with antibody response to MBP was detected.

4. Discussion

In this study we investigated the incidence of antibody responses against MOG and MBP in patients with sporadic MS and in multiplex families and their relation to the HLA.

In previous studies (Reindl et al., 1999; Egg et al., 2001) from our laboratory, antibodies to MOG and MBP were shown to be raised among MS patients compared to other noninflammatory neurological diseases and healthy controls. Consistent with these previous reports, we found raised antibody responses against MOG and MBP among MS patients compared to healthy controls. A new finding was the significantly increased humoral immune response to both myelin antigens in asymptomatic relatives of multiplex MS families without any difference in the overall antibody response to MOG and MBP. Furthermore, virtually all anti-

MOG and anti-MBP antibody responses were significantly higher in fMS and AR compared to sMS. This is consistent with other immune-mediated diseases as systemic lupus erythematodes (SLE), primary Sjögren's syndrome (SS), primary antiphospholipid syndrome (APS) and rheumathoid arthritis (RA), in which increased incidences of autoantibodies were found among first degree and, to a lesser extent, second degree relatives of patients (Arnett et al., 1989; Tishler et al., 1992; Radway-Bright et al., 2000). It is suggested that autoantibody-mediated diseases may in part result from a familial susceptibility, either by genetically determined B cell dysregulation (van der Linden et al., 2001) or genetically determined cytokine expression (Grondal et al., 1999).

To elucidate a genetic control of these antibody responses, we performed HLA class II typing in patients and asymptomatic relatives. The HLA is the only gene locus shown to be linked and associated with MS in different populations (Tienari et al., 1993; Weinshenker et al., 1998). HLA DRB1*15 DQB1*06 is the putative haplotype, conferring disease susceptibility in sporadic MS and multiplex families (Olerup and Hillert, 1991; Compston, 2000). Studies in animal models have demonstrated genetic control of the antibody response to MOG and MBP to be partially under influence of the major histocompatibility complex (MHC) (Stefferl et al., 1999; Yang et al., 2001). The relevance of this findings is underlined by reports that clinical expression of EAE is modulated by MHC (Weissert et al., 1998). Only recently has it been demonstrated that MOG peptide reactive T cells occur with high frequency, both in MS patients and their healthy siblings. The dominant epitopes recognized by MOG reactive T cell clones differed in HLA identical siblings, suggesting that epigenetic factors or non HLA genes play a major role in shaping the T cell repertoire to this antigen (Koehler et al., 2002).

HLA DRB1*04 was found to be associated with MS in sporadic disease and in nuclear families (Marrosu et al., 1988; Weinshenker et al., 1998; Laaksonen et al., 2002). It was also shown that the immunodominant HLA DRB1*04 restricted T-cell epitope of MOG in transgenic mice was also presented by human B-cells expressing HLA DRB1*04 (Forsthuber et al., 2001). We found a positive association of HLA DRB1*04 with the occurrence of anti-MOG IgM antibodies in MS patients. In contrast, the allele was not associated with any antibody response in AR. Thus, the association between HLA DRB1*04 and anti-MOG IgM antibodies seems to be specific in MS patients. This is also consistent with previous reports on associations of antibody responses with HLA class II alleles in other autoimmune diseases (Arnett et al., 1989; Tishler et al., 1992). Due to limitations in the typing resolution used in this study, it is not possible to define HLA DRB3/4/5 alleles. Therefore, we cannot exclude that a specific DRB1*04 haplotype accounts for the association of the DRB1*04 allele with anti-MOG IgM.

In AR the HLA DRB1*15 allele and the DRB5 locus were positively associated with anti-MOG IgA antibody expression. Likewise, the previously described HLA DRB3/4/5 typing resolution is too low to deduce a specific DRB1*15 DRB5 haplotype. Interestingly, there was a trend towards negative association with IgA when considering all families together. It might be speculated that these IgA antibodies have a protective effect in multiplex families, as HLA DRB1*15 is associated with disease susceptibility in these families and considering reports that IgA deficiency is associated with autoimmunity in humans (Liblau and Bach, 1992; Rankin and Isenberg, 1997). Alternatively, this may reflect a secondary finding, due to an intrinsic difference in serum cytokine levels, such as TGF-β, which on one hand has been shown to favor IgA switching, and on the other hand exerts a immunosuppressive effect (Rieckmann et al., 1995; Letterio and Roberts, 1998). Finally, we found no association of anti-MBP antibodies with HLA class II alleles in any group. Consequently, the genetic influence of the antibody responses against myelin antigens might differ between MOG and MBP in humans, corresponding to the suggestion in EAE (Yang et al., 2001). Although we are aware that the number of individuals examined is relatively low, we feel that there is evidence for a partially modulating effect of HLA class II alleles on the antibody response to MOG.

In conclusion, we found that antibodies against MOG and MBP were increased among MS patients compared to healthy controls. We showed that the anti-MOG antibody response is partially associated with certain HLA class II alleles. Finally, the antibody response against these antigens in multiplex families was dependent on the familial background and not on disease status in multiplex families. However, whether the MS phenotype in these multiplex families reflects a reaction to common environmental triggers or is controlled by shared genes in and outside the HLA in remains to be elucidated.

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