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HLA alleles in British Caucasians with mucous membrane pemphigoid

F. Hübner[1], J. Setterfield[2], A. Recke[1], D. Zillikens[1], E. Schmidt[1,3], J. Dart[4],

and S. Ibrahim[3] and the MMP Study Group 2009[5]

[1]Department of Dermatology, University of Lübeck, Lübeck, Germany

[2]Guy's and St Thomas's NHS Foundation Trust and King's College London, United Kingdom

[3]The Lübeck Institut of Experimental Dermatology (LIED), University of Lübeck, Lübeck, Germany

[4]National Institute of Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom

[5]The Mucous Membrane Pemphigoid Study Group 2009-14

Moorfields Eye Hospital, London: Debbie Booth, Elaina Reid, Nicole Carnt, Stefano Gugliemetti, Vijay Shanmuganathan, Martin Watson, Valerie Saw, Mark Wilkins, Vicky McCudden, Saj Ahmad, Catey Bunce.

The UCL Institute of Ophthalmology, London: Virginia Calder, Waseem Naushin, Beverly Scott.

Guys and Thomas's Hospital, London: Stephen Challacombe, Mike Gleeson, Sarah Ali, William Gage.

Epivision (Ophthalmic Epidemiology Consultants), Penn, UK: Darwin Minassian.

The Royal National ENT Hospital, London: Valerie Lund, Guri Sandhu.

Correspondence to:

Saleh Ibrahim, PhD, Lübeck Institute of Experimental Dermatology, University of Lübeck,

Ratzeburger Allee 160, 23538 Lübeck, Germany, Phone: +49-451-3101-8450,

email: saleh.ibrahim@uksh.de

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Conflict of Interest

The authors state no conflict of interest.

Dear Editor,

Mucous membrane pemphigoid (MMP) is an autoimmune mucosal scarring disease having severe ocular morbidity (1). Disease susceptibility is associated with increased frequencies of HLA-DQB1*03:01, HLA-DRB1*11 and HLA-DRB1*04 and decreased frequencies of DQB1*02 (2). To explore correlations between clinical involvement and HLA-class-II alleles, we prospectively phenotyped a cohort of 55 British MMP patients, and 41 age/sex matched controls (Ethics approval reference 09/H0721/54).

Inclusion criteria have been described (3) and were pre-agreed clinical criteria with or without a positive direct immunofluorescence (DIF) study. HLA-typing used allele specific sequencing protocols (Protrans S3 HLA-DRB1* and HLA-DQB1* Cyclerstrips, Protrans, Hockenheim, Germany). Statistical analysis used Fisher's exact test (p), with Benjamini-Hochberg correction (p_c) defined as significant when $p_c < 0.05$.

The study dataset, with clinical and laboratory results, is provided in Table and Legend S1. Fifteen patients, 14 of them with ocular involvement, were DIF-negative of whom 7 had antibodies to basement membrane zone epitopes. MMP affected sites varied: 8 were ocular only, 10 oral only, 15 oral and ocular only and 22 multisite. Exons 2 and 3 in HLA-DQB1 were fully analysed in 54/55 patients and 39/41 controls (Table 1a). The frequency of HLA-DQB1*03:01 was increased (p_c = < 0.01) in 36/54 (67%) of MMP patients (13 homozygous and 23 heterozygous) compared to 13/39 (33%) controls (2 homozygous and 11 heterozygous, Table 1a**)**. Exon 2 of HLA-DRB1 was also fully analysed in 54/55 patients and 40/41 controls; HLA-DRB1*03:01 was decreased (p = < 0.01, p_c = 0.045, Table 1b). Additionally, we compared the frequency of HLA-DQB1*0301 with controls for different sites of involvement showing that HLA-DQB1*0301 was increased in all subgroups except for ocular only MMP. Compared to controls, DIF-positive MMP had significantly increased HLA-DQB1*0301 (p = 0.00009) but this difference was not significant for either DIF-negative MMP (p=0.113) or for DIF-positive ocular only MMP.

Some studies have described a correlation of HLA-DQB1*03:01 with ocular and oral MMP or in ocular only MMP, whereas others have shown HLA-DQB1*03:01 to be associated with multisite MMP (2). In this study the association of HLA-DQB1*0301 with MMP was lower than in the largest reported study (2) ($pc < 0.00000028$), possibly due to our inclusion of 8 patients without detectable tissue-bound or serum antibodies, who were excluded from the latter study (2). In ocular only MMP 50% are DIF negative but have a phenotype that both progresses and responds to therapy in the same way as DIF positive cases (3,4). DIF-negative ocular MMP may result from inadequate test sensitivity, because of the small volumes of tissue involved, to dominance of an autoreactive T cell mediated over a autoantibody mediated disease (4) or because this is a different disease subset. We included our DIF-negative cases because to leave these out of this analysis disregards a group of cases which do not fit criteria for any other disease.

In our prospectively characterized cohort the association with HLA-DQB1*0301, HLA-DQB1*02, and HLA-DRB1*11 was corroborated whereas HLA-DRB1*0301 was identified as a potentially protective allele which requires confirmation in a larger study.

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Table 1a

HLA-DQB1	patients (n=54)	patients in %	controls (n=39)	controls in %	p-value	pc
HLA-DQB1*02	9	16.6	18	46.2	**< 0.01**	**< 0.01**
HLA-DQB1*03	48	88.9	20	51.3	**< 0.01**	**< 0.01**
HLA-DQB1*04	4	7.4	6	15.4	0.31	0.39
HLA-DQB1*05	13	24	11	28.2	0.81	0.81
HLA-DQB1*06	13	24	18	46.2	**0.04**	0.07
HLA-DQB1*02						
HLA-DQB1*02:01	6	11.1	9	23.1	0.15	n. d.
HLA-DQB1*02:02	3	5.5	7	17.9	0.09	n.d.
HLA-DQB1*03						
HLA-DQB1*03:01	36	66.6	13	32.1	**< 0.01**	**0.01**
HLA-DQB1*03:02	7	13	2	5.1	0.29	0.63
HLA-DQB1*03:03	4	7.4	2	5.1	1	1
HLA-DQB1*03:05	0	0	1	2.6	0.42	0.63
HLA-DQB1*03:19	1	1.8	0	0	1	1
HLA-DQB1*03:22	0	0	1	1.3	0.42	0.63

Table 1b

HLA-DRB1	patients		controls		p-value	pc
	(n=54)	in %	(n=39)	in %		
HLA-DRB1*01	10	18.5	12	30	0.23	0.48
HLA-DRB1*0301[1]	7	13	15	37.5	**< 0.01**	**0.046**
HLA-DRB1*04	20	37	7	17.5	**0.04**	0.15
HLA-DRB1*05	0	0	1	2.5	0.43	0.59
HLA-DRB1*07	5	9.3	10	25	0.05	0.14
HLA-DRB1*08	3	5.5	4	10	0.45	0.59
HLA-DRB1*09	3	5.5	0	0	0.27	0.48
HLA-DRB1*11	25	40.7	7	17.5	**< 0.01**	**0.046**
HLA-DRB1*12	3	5.5	1	2.5	0.63	0.75
HLA-DRB1*13	13	24	6	17.5	0.31	0.5
HLA-DRB1*14	1	1.8	0	0	1	1
HLA-DRB1*15	9	16.6	14	35	0.05	0.14
HLA-DRB1*16	1	1.8	0	0	1	1
HLA-DRB1*11						
HLA-DRB1*11:01/11:97	12	22.2	5	12.5	0.29	n. d. .
HLA-DRB1* 11:01/11:97 or 11:04	2	3.7	0	0	0.5	n. d..
HLA-DRB1*11:02 or 11:36 or 11:48	1	1.85	0	0	1	n. d.
HLA-DRB1*11:03	2	3.7	0	0	0.5	n. d.
HLA-DRB1*11:03 or 11:11	2	3.7	0	0	0.5	n. d.
HLA-DRB1*11:04	6	11.1	2	5	0.46	n. d..

Table 1a: Distribution of HLA-DQB1 among patients and controls
Table 1b: Distribution of HLA-DRB1 among patients and controls

In the first step of the analysis the gene frequencies for the allel groups of HLA-DQB1 (2 - 6) and HLA-DRB1 (1, 3-5, 7- 9, and 11-16) were compared and in the second step, only significant alleles were further analysed regarding specific HLA-protein (e. g. HLA-DRB1*11) and compared. The p-value is given for comparisons of HLA gene frequencies, between cases and controls, using Fishers Exact test for each allele. The P_c value is the probability value after using the Benjamini-Hochberg correction for multiple testing.

n. d. not done
[1] all patients with HLA-DRB1*03 expressed the specific protein HLA-DRB1*0301