Increased Frequency of HLA-DR2 in Patients with Autoantibodies to Epidermolysis Bullosa Acquisita Antigen: Evidence that the Expression of Autoimmunity to Type VII Collagen Is HLA Class II Allele Associated

W. Ray Gammon, M.D., Eugene R. Heise, Ph.D., William A. Burke, M.D., Jo-David Fine, M.D., David T. Woodley, M.D., and Robert A. Briggaman, M.D.

Department of Dermatology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, (DTW,RAB); Department of Microbiology and Immunology, Bowman Gray School of Medicine, Winston-Salem, North Carolina (WRG,ERH); and Department of Dermatology, University of Alabama, Birmingham, Alabama, U.S.A. (WAB,JDF)

Epidermolysis bullosa acquisita (EBA) is a chronic blistering disease characterized by circulating and tissue bound IgG auto-antibodies to the basement membrane zone (BMZ) of stratified squamous epithelium. Recent studies have shown that antibodies recognize epitopes present in the noncollagenous carboxyl-terminal domain of type VII collagen, a BMZ matrix protein. Antibodies with identical specificity also have been detected in patients with the rare blistering disease, bullous systemic lupus erythematosus (bullous SLE), suggesting EBA and bullous SLE are immunologically related diseases. In this study we determined the major histo-compatibility antigen types of 29 EBA patients and 6 patients with bullous SLE. Analysis of the results showed HLA-DR2 was significantly increased in both black EBA patients, $P = 0.013$ (corrected, RR = 4.8) and white EBA patients, $P = 0.0008$ (corrected, RR = 13.1). Five of the six bullous SLE patients also were positive for the DR2 antigen, $P = 0.009$. These results show the expression of autoimmunity to type VII collagen is HLA class II allele associated and that EBA and bullous SLE are immunogentically related diseases. *J Invest Dermatol 91:228–232, 1988*

Epidermolysis bullosa acquisita is a chronic acquired blistering disease with distinctive clinical, pathological, and immunopathological features [1–3]. The disorder is characterized by circulating and tissue bound IgG autoantibodies (EBA antibodies) that bind specifically to the BMZ of stratified squamous epithelium.

Epidermolysis bullosa acquisita antibodies have been well characterized by a variety of immunologic techniques and found to react with 290 and 145 kD proteins (EBA antigens) extracted from normal human skin [2,4,5]. Recently it was shown that EBA antigens are components of type VII collagen, a matrix protein found in basement membranes of stratified squamous epithelia [6].

The specificity of EBA antibodies distinguishes EBA from all other blistering eruptions except bullous SLE. Recently, some patients with bullous SLE were found to have circulating and tissue bound IgG anti-BMZ autoantibodies that were indistinguishable from EBA antibodies by immunochemical and immunoultrastructural analyses [7]. Although bullous SLE shares some features with EBA, the former has distinctive epidemiologic, clinical, and pathologic features that are not typical of EBA [8,9]. These findings suggest that EBA and bullous SLE are distinctive but immunologically related diseases that have in common the predisposition to produce autoantibodies to type VII collagen.

A number of diseases with a strong autoimmune component occur more frequently in individuals with certain HLA alleles [10]. In those diseases, distinctive antibodies or T cells against self-components are demonstrable. The HLA alleles that are associated with autoimmune disease belong to the class II family of molecules, which includes the DR, DQ, and DP series of alloantigens. On this basis, we hypothesized that EBA might be HLA associated and predicted that an HLA-DR association at the population level would be found. Because of its association with autoantibodies to type VII collagen, we also predicted bullous SLE might share a specific HLA association with EBA. The data to be presented demonstrate that the frequency of HLA-DR2 is significantly increased in both black and white EBA patients. In a small group of black patients with bullous SLE, HLA-DR2 was more frequent than in controls. The results suggest that EBA and bullous SLE are immunogenetically related diseases and that either the HLA-DR2 gene itself is a factor in anti-type VII collagen autoantibody formation or HLA-DR2 serves as a marker for another gene that exists in linkage disequilibrium with HLA-DR2.

METHODS

The EBA patient group consisted of 29 unrelated individuals born in the United States, of which 20 patients were from the southeastern U.S. The patients ranged in age from 5 to 76 years (Mean ± SD = 46.5 ± 19.3). This group consisted of 18 black and 11 white

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Reprint requests to: Dr. W. Ray Gammon, M.D., Department of Dermatology, CB# 7600, 137 NCMH, University of North Carolina, Chapel Hill, NC 27514

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EBA patients. There was a slight predominance of females (n = 16) to males (n = 13). All of the patients were diagnosed on the basis of previously published clinical, pathologic, immunohistologic, and immunoultrastructural criteria, including a chronic blistering disease, a subepidermal blister by routine histology, linear deposits of IgG at the BMZ by direct immunofluorescence, and IgG deposits on and beneath the lamina densa by direct immunoelectron microscopy [3].

A group of six unrelated patients with bullous SLE were also studied. This group consisted of 5 black females and 1 black male ranging in age from 8 to 25 years (Mean ± SD = 19.7 ± 6.5). Five were born in the southeastern U.S. and one was born in the Virgin Islands. All of these patients were diagnosed on the basis of previously published clinical, pathologic, immunohistologic, and immunoultrastructural criteria, including a diagnosis of SLE by criteria of the American Rheumatism Association, a blistering eruption, subepidermal blisters histologically, immune deposits at the BMZ by direct immunofluorescence, and immune deposits beneath the lamina densa by immunoelectron microscopy [8,9].

Immunohistologic, immunoultrastructural and immunochemical analyses of circulating anti-BMZ antibodies were performed on serum samples from all patients as previously described [4,5].

Tests for lymphocytotoxic antibodies were performed with serum obtained from 19 EBA patients. Each serum was tested neat, 1 : 2 and 1 : 5 using a standard assay method with nylon fiber purified T lymphocytes and B lymphocytes (cells + serum 30 min, 1 wash, complement 60 min) against a selected 45 member HLA typed panel. To determine if autoantibodies were generally elevated, the sera were tested for thyroid microsomal antibodies using a tanned erythrocyte hemagglutination method (Sera-Tek Kit, Fujirebio Inc, Tokyo, Japan).

Blood samples anticoagulated with beef lung heparin were shipped to the HLA laboratory where mononuclear cells were isolated using lymphocyte separation medium (Oraganon Teknika Corp., Malvern, PA), usually within 24 h of collection. HLA ABC typing was performed on 28 of the 35 patients using a standard lymphocyte microcytotoxicity assay and 140 antisera to define 16 A-locus, 27 B-locus, and 7 C-locus antigens [11]. HLA-DR, DQ typing was performed on all 35 patients with 70 antisera to define 11 DR and 3 DQ antigens using a standard two-color fluorescence technique [12].

HLA antigen frequencies of the two patient groups were compared with the frequencies of race matched healthy controls [10]. Fisher's Exact Probability (two-tailed) was used to determine statistical significance [10]. Because this is the first HLA study of EBA we corrected the probability (P) value for the multiple comparisons. For statistical analysis, some low frequency antigen subdivisions were grouped with the broad parent specificity. The P values were corrected for 39 class I and 14 class II HLA antigen comparisons. The Haldane modification of Woolf's formula was used to calculate the relative risk (RR) to avoid the introduction of bias resulting from the small number of patients positive for low frequency antigens [13]:

$$RR = \frac{(2h + 1)\,(2K + 1)}{(2H + 1)\,(2k + 1)}$$

where h and k are the number of patients positive and negative for the antigen, respectively, and H and K are the number of controls who are positive and negative for the antigen, respectively. The control antigen frequencies were those obtained during the eighth International Histocompatiblity Workshop [10].

RESULTS

Circulating EBA antibodies were detected in 18 of the 29 (62%) EBA patients and in 6 of 6 (100%) patients with bullous SLE (Table I). The difference is not statistically significant. In assays for lymphocytotoxic antibodies only 5 of 19 sera were reactive. Each of the five sera reacted with a single cell of the panel and thus could not be associated with any of the recognized HLA antigens (data not shown). Thyroid microsomal antibodies reached the clinically significant titer of > 1 : 100 in only one case. These results suggest that antibody production is not generally increased in EBA patients.

The significant findings of the analysis are summarized in Table II. None of the HLA-A,B,C antigens were significantly increased in either white or black EBA patients as compared to race matched controls. HLA-ABC typing was available in three of the six patients with bullous SLE. All three patients typed as HLA-A32, whereas this antigen has a frequency of 3% in the control population. This difference is statistically significant, P = 0.002 (corrected).

HLA-DR2 was found in significantly increased frequency in both white and black EBA patients. The increased frequency was statistically significant in both the white (P = 0.0008, corrected) and black EBA patients (P = 0.018, corrected). Because DR2 and DQwl occur in strong linkage disequilibrium in the general population it is not surprising that all 26 patients with DR2 also expressed the DQwl specificity. The RR calculations indicate that the risk of developing EBA is 13.05 times more frequent in white DR2 positive individuals than in white DR2 negative individuals. In blacks the RR of developing EBA was 4.81 in DR2 positive individuals. Of the DR2 negative EBA patients, the DR antigens found most often were DR4 in white patients and DR5 and DR7 in black patients. However, we do not attach any significance to this observation at present. All six of the bullous SLE patients were black. Five of the six patients were HLA-DR2 positive (83%) compared to 28.5% of controls (Table II). This difference is statistically significant before correcting the P value but not after correcting for 14 determinations.

In the general population, certain HLA-A,B,C,DR combinations are nonrandomly associated and segregate as haplotypes in families. Because family studies are required to determine segregating haplotypes, we could not define the DR2 haplotype in EBA patients. However, it is of interest that three of the 18 black EBA patients and 1 of the 6 bullous SLE patients possessed DR2,Cw4,A2 as part of their phenotype. The DR2,Cw4,A2 combination exhibits positive gamete association (lineage disequilibrium) in the black population. Of the eight most common DR2 haplotypes in blacks, only four might exist as haplotypes based on examination of the phenotypic data of 24 black patients. Among healthy North American whites, the DR2,B7 haplotype occurs in high frequency (520 per 10,000 haplotypes). The DR2,B7 combination was observed in only three of nine white EBA patients. The phenotypic combination of DR2, B18, A25 occurred in only one EBA patient. When this combination occurs as a haplotype, the individual often is found to be deficient in complement component 2. Although complement levels were not routinely measured in these patients, it is unlikely that genetic C2 deficiency would be an important feature of the disease.

DISCUSSION

This study extends our preliminary report that HLA-DR2 is statistically associated with EBA and bullous SLE and provides evidence for a genetic predisposition to those disorders [14].

Epidermolysis bullosa acquisita is a distinctive but uncommon blistering disease that affects stratified squamous epithelia of skin and mucous membranes. It occurs in children and adults of both sexes and all racial and ethnic groups [3,15,16]. It is distinguished from all other bullous diseases by its clinical, pathologic, and immunologic features. Clinical features include skin fragility, spontaneous and trauma-induced blisters and erosions, and healing with scars and milia. The histology of lesions is characterized by dermal-epidermal separation at the BMZ and, in most patients, inflammation in the upper dermis. It is characterized immunologically by circulating and tissue-bound IgG anti-BMZ autoantibodies with distinctive immunoultrastructural and immunochemical features [1–3].

Circulating EBA antibodies that were present in 62% of EBA patients in this study are characterized immunoultrastructurally by binding to sites on and just beneath the lamina densa and immunochemically by binding to 290 and 145 kD proteins (reducing conditions) extracted from human dermis-lamina densa [3–5]. Tissue-bound EBA antibodies are defined by their deposition on and just beneath the lamina densa [3].

Table I. Age, Sex, Ethnicity, EBA Antibody Status, and HLA Phenotypes of Patients with Autoantibodies to Type VII Collagen

Patient Number	Age, Sex, Ethnicity	Circulating EBA Antibody	HLA- A	B	C	DR	DQ
		Epidermolysis Bullosa Acquisita Group					
1	54,F,B	−	2,x	w42,53	w4,x	5,6	1,3
2	30,M,B	+	2,28	7,w53	w4,x	2,8	1,3
3	54,F,B	−	28,x	w35,53	w3,w4	2,8	1,3
4	30,F,B	−	23,w30	w42,x	w2,x	3,5	2,3
5	57,F,B	+	NT	NT	NT	2,8	1,3
6	73,F,B	−	NT	NT	NT	7,x	1,2
7	46,F,W	+	2,x	17,x	x,x	2,7	1,2
8	40,M,W	+	NT	NT	NT	2,x	1
9	50,M,W	+	2,3	8,37	x,x	2,3	1
10	66,M,W	−	NT	NT	NT	2,3	1
11	28,M,B	−	3,23	8,w58	NT	2,3	1
12	65,F,B	+	3,11	8,w57	NT	2,4	1,3
13	56,F,B	+	2,3	w53,57	w4,x	2,7	1,3
14	59,M,W	−	1,x	8,x	w7,x	2,5	1,3
15	17,M,B	+	2,28	8,44	3,4	2,w6	1,3
16	64,F,B	−	2,23	7,w53	w4,x	2,3	1,2
17	06,F,B	−	2,x	15,35	w3,7	4,x	3
18	54,F,B	+	28,w34	8,17	x,x	2,w11	1
19	62,M,W	+	3,11	7,w62	x,x	2	1
		Epidermolysis Bullosa Acquisita Group					
20	60,M,W	+	1,2	7,8	w6,x	2,w6	1
21	76,M,B	+	2,23	w45,w53	x,x	w6,w9	1,3
22	59,M,B	+	2,x	7,w51	x,x	2,7	1,2
23	62,F,B	+	1,23	17,x	x,x	2,8	1
24	23,M,B	−	29,w34	w42,w49	w6,x	2,3	1,2
25	12,M,W	+	1,3	7,8	x,x	2	1
26	33,F,W	+	2,31	8,35	x,x	4,5	3
27	17,F,W	+	23,18	x,x	x,x	2,8	1
28	56,F,W	−	11,w31	22,40	x,x	4,x	3
29	41,F,B	+	28,33	7,14	x,x	7,w11	1
		Bullous Eruption of SLE Group					
1	08,F,B	+	2,w32	7,w53	w4,x	2,8	1,3
2	17,F,B	+	NT	NT	NT	7,x	2
3	20,F,B	+	2,w32	w45,w50	w2,x	2,8	1,2,3
4	25,M,B	+	NT	NT	NT	2,x	1,2
5	25,F,B	+	NT	NT	NT	2,7	1,2
6	23,F,B	+	1,w32	7,w53	w4,x	2,8	1

NT: alleles not tested; F: female; M: male; W: white; B: black.

Recent studies have provided evidence that the 290- and 145-kD proteins recognized by EBA antibodies in extract of human dermis-lamina densa are type VII collagen alpha chains and the noncollagenous carboxyl-terminal domain of those chains, respectively [17]. Those studies showed that monoclonal and polyclonal EBA antibodies react with the carboxyl-terminal domain of type VII procollagen extracted from epithelial cell lines and that monoclonal and polyclonal antibodies to the carboxyl-terminal domain of type VII procollagen recognize the 290- and 145-kD proteins extracted from human dermis-lamina densa. In addition, studies have shown that the antigens recognized by both types of antibodies have the same tissue distribution and ultrastructural location within the BMZ [18–21].

The features of EBA antibodies have made it possible to distinguish them from circulating and tissue-bound IgG anti-BMZ autoantibodies in all other bullous diseases except bullous SLE. We previously showed that anti-BMZ antibodies from some of those patients have features indistinguishable from EBA antibodies, including reactivity with 290- and 145-kD proteins extracted from dermis-lamina densa [7].

Although EBA and bullous SLE appear to share anti-BMZ antibodies of identical specificity, some of their clinical and pathologic

Table II. Statistically Interesting Associations Between Disease and HLA Antigens

Ethnicity	Patient Group FR. + (% +)		Controls Fr. + (% +)		Fisher's Exact P(uncorr)	Relative Risk
			HLA-DR2 in Epidermolysis Bullosa Acquisita Patients			
Black	12/18	66.7	92/323	28.5	0.0013	4.81
White	9/11	81.8	290/1145	25.3	0.00006	13.05
			HLA-DR2 in Bullous Eruption of SLE Patients			
Black	5/6	83.3	92/323	28.5	0.0095	100.7
			HLA-Aw32 in Bullous Eruption of SLE Patients			
Black	3/3	100.0	11/365	3.0	0.00004	215.7

Fr. +: Number of patients with the antigen/number tested.

features are different [7–9]. Skin fragility, a predilection for trauma-sensitive skin, and healing with scars and milia are not features of bullous SLE. Blisters in bullous SLE may show a predilection for sun-exposed sites and often respond dramatically to sulfone therapy, which are not features of EBA. Bullous SLE affects a younger patient population and is of shorter duration than EBA. Furthermore, the histology of blisters in bullous SLE more closely resembles dermatitis herpetiformis than EBA. Although there are similarities, both diseases appear to share autoimmunity to type VII collagen and an association with the DR2 haplotype.

We considered the possibility that the increased frequency of DR2 in bullous SLE patients might be due to their SLE. Although we cannot exclude that possibility, it appears unlikely because SLE seems to be primarily associated with DR3 and B8; reports of an association with DR2 have been inconsistent; and all our patients were black and several studies have found that DR2 is not increased in black patients [22–29].

Although other autoimmune blistering diseases (herpes gestationis, cicatricial pemphigoid, and pemphigus vulgaris) have been found to be associated with various HLA haplotypes, this is the first report of an association of an autoimmune blistering disease(s) with DR2 [30–34]. It may be of interest that EBA and bullous SLE are not the only diseases characterized by autoimmunity to a collagen and an association with DR2. Goodpasture's syndrome, which is characterized by autoantibodies to glomerular basement membrane, has been shown to be associated with DR2 and the antibodies have been found to react with epitopes in the carbolyl-terminal, noncollagenous domain of type IV collagen [35–37]. That raises the possibility that a common HLA allele may be involved in regulating autoimmunity to basement membrane collagens in EBA, bullous SLE, and Goodpasture's syndrome.

In conclusion, we have found that the HLA class II haplotype DR2, is significantly increased in black and white EBA patients and appears to be increased in black bullous SLE patients. This finding suggests that genetic factors are involved in predisposing to both disorders. The findings that both diseases appear to share an association with the same DR haplotype and autoimmunity to the same BMZ autoantigen suggest that the same gene may predispose to autoimmunity to type VII collagen in both diseases. That gene could be DR2 or a gene linked to DR2. The finding that DR2 was not present in all patients suggests that it is simply a marker for the gene(s) that predisposes to EBA and bullous SLE. A DR2 association suggests that immunogenetic factors are involved in predisposing to type VII collagen autoimmunity and that DR2 or a linked, class II gene is responsible. Because class II gene products are involved in antigen recognition, the development of autoimmunity to type VII collagen could be regulated by a specific DR2 linked allelic variant capable of recognizing and presenting normal or abnormal type VII collagen to helper T cells. That hypothesis can be tested once sufficient amounts of purified type VII collagen are available.

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Fifth International Conference on Behçet's Disease

The Fifth International Conference on Behçets's Disease will be held at the Mayo Clinic in Rochester, Minnesota, on September 14 and 15, 1989. At previous meetings held overseas there were very few conributors from North America. Perhaps this is because the disease is uncommon here. Most of the conributors were from Japan or the Mediterranean countries where the disease is more common. At the London Conference in 1985 a program chairman publicly lamented, "Where are the Americans?" For this reason we have chosen to alert a select group of North American investigators 15 months in advance of the conference. Dr. J. D. O'Duffy and Dr. R. S. Rogers will be co-chairmen of the meeting. We hope that this notice may stimulate abstracts. Further notices and abstract deadlines will follow.