Major Histocompatibility Complex Susceptibility Genes for Dermatitis Herpetiformis Compared with Those for Gluten-sensitive Enteropathy

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Summary

Dermatitis herpetiformis (DH) shares some clinical features and major histocompatibility complex (MHC) markers with gluten-sensitive enteropathy (GSE). We compared MHC haplotypes in 27 patients with DH, 35 patients with GSE, and normal controls. As in GSE, the frequencies of two extended haplotypes, [HLA-B8, SC01, DR3] and [HLA-B44, FC31, DR7], were increased in patients with DH. Distributions of fragments of extended haplotypes, consisting of some but not all of the elements of complete extended haplotypes, were analyzed to attempt to localize a susceptibility gene. Besides complete extended susceptibility haplotypes, (DR3, DQ2) and (DR7, DQ2) fragments were most common in GSE. In contrast, DH showed only a few such fragments but many instances of the fragment (SC01). The differences in distribution of these fragments in the two diseases were highly significant ($P < 0.002$). HLA-DQ2 and DR3 had the highest odds ratios for GSE, but the highest odds ratio for DH was for the complotype SC01. These findings suggest that the MHC susceptibility gene for DH is between class II and complotype regions, closest to the complotype, whereas that for GSE is in the class II region.

Dermatitis herpetiformis (DH)[1] is a chronic pruritic papulo-vesicular disease of the skin characterized by the granular deposition of IgA in the dermal papillae and by patchy focal asymptomatic villous atrophy of the small intestine (1, 2). In Caucasian patients, there is a marked increase in HLA-B8, DR3, and DQ2 (3–7). These genes are components of the fixed conserved extended haplotype [HLA-B8, SC01, DR3] (8). The recent report of an increase in HLA-DP1 (9) in patients with DH who carry markers of this haplotype may be secondary to their known linkage disequilibrium in general (10, 11). A less striking increase in HLA-Dw7 in DH patients has also been reported (12). The same HLA markers have been noted to be increased in celiac disease (gluten-sensitive enteropathy [GSE]) (13–16). Moreover, patients with DH and GSE share a number of other features, such as jejunal atrophy correctable by elimination of gliadin from the diet, and the presence of anti-α-gliadin (17, 18) and antireticulin (19, 20) antibodies. We have reported family studies in GSE (21) that show that all increased available HLA markers are parts of two extended haplotypes: [HLA-B8, SC01, DR3] and [HLA-B44, FC31, DR7].

Previous studies of DH have almost exclusively reported HLA phenotypes in patients rather than haplotypes determined in family studies. Haplotype comparisons, including analysis for complotypes and other MHC genes, are critical to localizing candidate susceptibility genes, and we undertook such studies in patients with DH. We present these results in this report and compare these DH haplotypes with those derived from our earlier studies in GSE. Our results suggest that, despite the similarity of individual MHC allele markers for GSE and DH, the susceptibility genes for the two disorders are different. That for GSE appears to be in or near the HLA-DR/DQ region, whereas that for DH appears to be between complement and DR/DQ, closest to the complement region.

[1] *Abbreviations used in this paper:* DH, dermatitis herpetiformis; GSE, gluten-sensitive enteropathy.

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Materials and Methods

Samples. Blood from 27 randomly ascertained Caucasian patients with dermatitis herpetiformis and 147 of their first-degree relatives was collected into 7-ml Vacutainer tubes (Becton Dickinson & Co., Rutherford, NJ) containing 10.5 mg of potassium EDTA and into syringes containing 500–1,000 U of sodium heparin diluted with an equal volume of RPMI 1640. 25 patients were unrelated; 2 (43416 and 43417) were siblings. Lymphocytes were separated from heparinized blood by Ficoll-Hypaque centrifugation, frozen, and stored in vapor phase liquid nitrogen until thawed for HLA analysis. Plasma separated from blood anticoagulated with EDTA was stored at −80°C until just before analysis for complement types.

Patients. All patients with DH had a history of and on physical examination had evidence of typical pruritic grouped vesicles on extensor surfaces of limb skin. The diagnosis of DH was confirmed by the presence of granular deposits of IgA by direct immunofluorescence microscopy in the dermal papillae of perilesional skin (22). 35 patients with GSE were studied, of which 24 were reported earlier (21).

MHC Marker Studies. HLA-A, B, DR, and DQ typing were by standard assays (23, 24). Plasma samples were analyzed for genetic polymorphism in C2 (25), in factor B (BF) (26), and in C4 (27) by methods previously described. Complotypes are haplotypes of specific alleles of these four closely linked loci and are designated in arbitrary order by their BF, C2, C4A, and C4B alleles, including Q0 for null alleles (28). Thus, FC30 stands for *BF*F, C2*C, C4A*3,* and *C4B*Q0.*

Haplotype Analysis. Alleles were assigned to haplotypes on the basis of family studies except for sequence-specific oligonucleotide-determined alleles, which were studied only in patients. The two DH-affected siblings were MHC haploidentical and thus contributed three independent disease haplotypes to the analysis.

Class II (HLA-DR, DQ, and DP) Allele Typing. Genomic DNA was isolated from PBL or from EBV-transformed cell lines of 17 DH patients and 10 GSE patients. Sequence-specific oligonucleotide (SSO) probe hybridization was carried out according to the protocols of the 11th International Histocompatibility Workshop (11). Briefly, PCR amplifications were carried out on 0.6-μg samples of purified genomic DNA in a 100-μl reaction mixture containing 50 pmol of each primer, 50 mM KCl, 10 mM Tris-HCl, pH 8.3, 0.2 mM of each deoxynucleotide, 2.5 U of *Taq* polymerase (Promega Biotec, Madison, WI), and 1.5 mM $MgCl_2$. The primers used were those recommended by the 11th Workshop. About 50 ng of amplified DNA was spotted on several nylon membranes. These were prehybridized at 54°C with hybridization buffer (50 mM Tris HCl, 3 M tetramethyl ammonium chloride, 2 mM EDTA, 0.1% SDS, 100 mg/ml heat-denatured herring sperm DNA, and 5× Denhardt's solution) for 1 h. The allele-specific oligonucleotides labeled with γ-[^{32}P]ATP were added. HLA-DRB1, -DQA1, -DQB1, and -DPB1 alleles were identified after incubation, washing, and autoradiography of the exposed membranes. Haplotype assignments were deduced from known linkage disequilibria for all loci but DPB1. The order of genes in the MHC from telomere to centromere is HLA-A, B, complotype, DR, DQ, and DP.

Statistical Analyses. Statistical significance of the differences in frequency of individual MHC alleles and extended haplotypes in the patient and control populations of haplotypes was estimated by χ^2 analysis or by Fisher's exact test, as appropriate. Since prior work has shown elements of [HLA-B8, SC01, DR3, DQ2] and [HLA-B44, FC31, DR7, DQ2] to be elevated among patients, no corrections were applied to p values for significance of differences in frequency from normals. Two kinds of control haplotypes were used, family and overall Caucasian controls (29).

Results

MHC Haplotypes in DH. MHC haplotypes occurring in 27 patients with DH are shown in Table 1. All but nine haplotypes contained elements of one or the other of two extended conserved MHC haplotypes, [HLA-B8, SC01, DR3] or [HLA-B44, FC31, DR7]. The patient haplotypes were arranged in Table 1 in relation to these extended haplotypes and their fragments from telomeric to centromeric. Two haplotypes, 42453b and 43655b, had elements of both extended haplotypes and are shown in each category. The arrangement permits the easy identification of fragments of the extended haplotypes. Thus, there were 22 instances of the complete [HLA-B8, SC01, DR3] extended haplotype and 10 examples of fragments of this haplotype. Of the fragments, there were two examples of (SC01, DR3) without B8, and single examples of B8 without SC01 or DR3, (B8, SC01) without DR3, and DR3 without SC01. In contrast, there are five cases of (SC01) without B8 or DR3. Because HLA-DQ2, in strong linkage disequilibrium with both DR3 and DR7, was also increased markedly (see below), these findings suggest that the susceptibility gene lies between the complotype region and HLA-DR/DQ.

Of the 16 haplotypes related to [HLA-B44, FC31, DR7], there were 3 instances of the complete extended haplotype. Of the 13 cases of fragments, 5 had HLA-B44 and complotypes other than FC31, 6 had DR7 but not FC31 (2 of these had SC01), 2 had (FC31, DR7) but not HLA-B44, there was 1 instance of (FC31) alone, and 6 with (DR7, DQ2) alone. These findings are consistent with the possibility that a susceptibility gene lies in the complotype-DR/DQ region of the MHC. In keeping with these conclusions was the finding that all (27/27) patients carried SC01 or FC31 and almost all carried HLA-DQ2 (26/27) and DR3 or DR7 (26/27).

MHC Class II Alleles Defined by Sequence-specific Oligonucleotide Typing. HLA-DRB1, DQA1, and DQB1 alleles are listed in Table 2 for patients with DH. In all instances, the DQA1 and DQB1 alleles present conformed to the DRB1 alleles predicted from known essentially invariable linkage disequilibria in Caucasians. Of the 27 DH patients, 21 carried the DRB1*0301, DQA1*0501, DQB1*0201 haplotype found on all HLA-DR3 haplotypes and instances of [HLA-B8, SC01, DR3]. Of the six patients who did not, three were DRB1*11, DQA1*0501, DQB1*0301/DRB1*07, DQA1*0201, DQB1*0201 heterozygotes, and one each were heterozygotes for DRB1*0103, DQA1*0101, DQB1*0501/DRB1*07, DQA1*0201, DQB1*0201; DRB1*0101, DQA1*0101, DQB1*0501/DRB1*04, DQA1*0301, DQB1*0302, and DRB1*04, DQA1*0301, DQB1*0302/DRB1*07, DQA1*0201, DQB1*0303. The overall distribution of DR specificity homozygotes and heterozygotes was not different from that predicted from the Hardy-Weinberg distribution.

The frequency of HLA-DPB1*0101 (6/28) was increased ($p < 0.003$) among DH haplotypes compared with the fre-

Table 1. *MHC Haplotypes in Patients with DH*

Haplotype No.	HLA- A	B	Complotype	HLA-DR	Haplotype No.	HLA- A	B	Complotype	HLA-DR
Haplotypes related to [HLA-B8, SC01, DR3]:									
42306a	2	8	SC32	4	Haplotypes related to [HLA-B44, FC31, DR7]:				
41019a	1	8	SC01	3	41019c	2	44	SC30	1
42290a	1	8	SC01	3	42290c	24	44	FC30	6
42372c	1	8	SC01	3	42297c	2	44	SC31	5
42388d	1	8	SC01	3	42439b	32	44	FC(3,2)0	1
42394d	1	8	SC01	3	43998b	28	44	SC31	7
42439a	1	8	SC01	3	42359a	23	44	FC31	7
42445c	1	8	SC01	3	43376a	26	44	FC31	7
42447a	1	8	SC01	3	42372d	11	44	FC31	7
43342b	1	8	SC01	3	42297d	3	7	FC31	7
43406a	1	8	SC01	3	43398a	2	7	FC31	7
43411a	1	8	SC01	3	42388c	2	57	FC31	5
43411c	1	8	SC01	3	43352b	3	47	FC91,0	7‡
43416a	1	8	SC01	3	42453b	2	13	SC01	7*
43998a	1	8	SC01	3	42312a	1	57	SC61	7‡
44026b	1	8	SC01	3	42338c	2	13	SC31	7
42399a	2	8	SC01	3	43655b	11	8	SC01	7*
43352a	2	8	SC01	3					
42306b	2	8	SC01	3					
42301a	3	8	SC01	3					
42394c	11	8	SC01	3					
43342a	24	8	SC01	3	Other haplotypes:				
42338a	25	8	SC01	3	43406c	23	7	SC31	1
43655b	11	8	SC01	7*	43902a	11	56	SC31	1
43417d	2	7	SC01	3	43416c	3	7	SC61	2
43376c	11	27	SC01	3	42301b	3	7	SC31	2‡
42312b	2	49	SC01	4	42399d	25	18	S042	2‡
43902c	2	49	SC01	4	44026a	1	60	SC31	4
42447c	3	7	SC01	1	43655a	2	51	SC30	5
42453b	2	13	SC01	7*	43398c	1	35	SC42	6
42359b	2	61	SC01	5	42445a	3	35	SC42	6
42453a	1	7	SC31	3					

Shown are all specificities assigned to haplotypes by family study.
* Listed twice as related to both [HLA-B8, SC01, DR3] and [HLA-B44, FC31, DR7].
‡ Extended haplotypes other than those above.

quency of 3 of 105 among random normal Caucasian haplotypes in our laboratory. 2 of the 3 DPB1*0101 among control chromosomes were carried by [HLA-B8, SC01, DR3] and 18 of 52 [HLA-B8, SC01, DR3] homozygous typing cell haplotypes carried DPB1*0101 ($p < 2 \times 10^{-7}$), indicative of strong linkage disequilibrium between DPB1*0101 and [HLA-B8, SC01, DR3]. Six of six instances of the DPB1*0101 allele occurred in patients who carried DR3 haplotypes, of which five were the complete extended haplotype [HLA-B8, SC01, DR3] and one was the (SC01, DR3) fragment.

MHC Specificity and Haplotype Frequencies in Patients with DH Compared with Control Haplotypes. Table 3 gives the frequencies in patients with DH of MHC alleles and extended

Table 2. *HLA-DRB1, DQA1, DQB1, and DPB1 Alleles in Patients with DH*

	First haplotype			Second haplotype			
Patient	DRB1	DQA1	DQB1	DRB1	DQA1	DQB1	DPB1
43902	0101	0101	0501	04	0301	0302	ND
43342	0301	0501	0201	0301	0501	0201	ND
43411	0301	0501	0201	0301	0501	0201	ND
43406	0301	0501	0201	0101	0101	0501	0101/1201
42439	0301	0501	0201	0101	0101	0501	0301/0401
42399	0301	0501	0201	1501	0102	0602	0101/1901
43416	0301	0501	0201	1501	0102	0602	0401/0401
42306	0301	0501	0201	04	0301	0201	0101/0301
43998	0301	0501	0201	07	0201	0201	0101/1101
42447	0301	0501	0201	07	0201	0201	0301/0401
43376	0301	0501	0201	07	0201	0201	0101/1001
42453	0301	0501	0201	07	0201	0201	0401/0501
43352	0301	0501	0201	07	0201	0201	0101/1501
43398	07	0201	0201	0103	0101	0501	0301/0402
42312	07	0201	0303	04	0301	0302	0401/0401
42359	07	0201	0201	11*	0501	0301	0301/0401
43655	07	ND	0201	11*	ND	0301	0401/0701

DRB1-DQA1-DQB1 haplotype assignments deduced from known linkage disequilibria. Because linkage relationships of DR,DQ-DPB1 alleles are weaker, no assignments were made.
* 1101 or 1104.

haplotypes of interest or those showing significant differences from the frequencies in control haplotypes. There were striking increases in the frequencies of the extended conserved MHC haplotype [HLA-B8, SC01, DR3] and all of its elements, including HLA-B8, SC01, C4A*Q0, HLA-DR3, and HLA-DQ2.

Comparison of MHC Haplotypes in Patients with DH with Those in Patients with GSE. Table 4 lists MHC haplotypes in 35 patients with GSE. In the two groups of patients, only HLA-A29 was higher in GSE ($p = 0.012$) and only HLA-DR1 was higher in DH ($p = 0.018$) among all alleles and extended haplotypes compared. These differences were only nominally significant and lost significance after correction for the number of comparisons. HLA-DRB1, DQA1, and DQB1 alleles observed among GSE patients were those predicted by known linkage disequilibria with generic DR types.

Because so many of the DH patient haplotypes were related to [HLA-B8, SC01, DR3], analyses of the distribution of alleles and haplotypes were carried out after the removal of the complete [HLA-B8, SC01, DR3] haplotype from all patient and control haplotypes. The increases in patients' SC01, C4A*Q0, and HLA-DQ2 remained highly significant. In addition, the increase in [HLA-B44, FC31, DR7] among DH patient haplotypes was just significant (compared with family controls but not to overall controls) at $p < 0.05$. By themselves, these observations suggested that the chromosomal region between SC01 and HLA-DQ2 contains susceptibility gene(s) for DH.

Odds ratios for MHC alleles and haplotypes in the DH and GSE patient and control populations with and without patients positive for the complete [HLA-B8, SC01, DR3] extended haplotype were calculated and the results are given in Table 5. It is seen that for DH the highest odds ratio with and without the extended haplotype was that of SC01 followed by that of HLA-DQ2, whereas in GSE it was DQ2 followed by DR3.

The distribution of fragments of [HLA-B8, SC01, DR3] among 55 DH patient haplotypes (Table 1) was compared with those among 70 GSE patient haplotypes (Table 6). In DH, there were six haplotypes with SC01 but not DR3 and only one haplotype with DR3 but not SC01, whereas in GSE there were no haplotypes with SC01 but not DR3 and eight haplotypes with DR3 but not SC01 ($p < 0.002$), as shown in Table 6.

We had earlier noted that in patients with GSE, HLA-A1 was less frequently found on [HLA-B8, SC01, DR3] than on control haplotypes (Table 4). This phenomenon was not seen in patients with DH (Table 1), in whom 16 of 22 in-

Table 3. *Comparison of MHC Allele Frequencies in Patients with DH with Controls*

Allele	Patient frequency		Family control frequency		Normal control frequency		pt vs. fc	pt vs. nc
	No.	Fraction	No.	Fraction	No.	Fraction		
							P	*P*
HLA-A1	19	0.352	11	0.190	378	0.174	<0.05	0.0010
HLA-B8	24	0.444	4	0.069	265	0.122	<0.0001	0.0001
HLA-B15	0	0.000	5	0.086	121	0.056	<0.04	NS
HLA-DR2	3	0.056	7	0.121	354	0.162	NS	<0.02
HLA-DR3	23	0.426	7	0.121	290	0.133	0.0001	0.0001
HLA-DR4	4	0.074	6	0.103	373	0.171	NS	<0.02
C4A*Q0	29	0.537	7	0.121	360	0.165	0.0001	0.0001
C4A*2	0	0.000	1	0.017	133	0.061	NS	<0.04
C4A*3	18	0.333	37	0.638	1,319	0.605	0.0010	0.0001
C4B*1	45	0.833	37	0.638	1,530	0.702	0.02	NS
SC01	29	0.537	6	0.103	293	0.134	0.0001	0.0001
SC31	8	0.148	19	0.328	820	0.376	<0.03	0.0001
[B8,SC01,DR3]	22	0.407	3	0.052	192	0.088	<0.0001	0.0001
[B44,FC31,DR7]	3	0.056	0	0.000	63	0.029	NS	NS
Total	54		58		2,180			
DQ1	10	0.208	21	0.396	192	0.420	<0.05	0.004
DQ2	31	0.646	17	0.321	109	0.239	0.001	0.0001
DQ3	7	0.146	15	0.283	155	0.339	NS	0.006
Total	48		53		457			

Only alleles or haplotypes of interest or showing significant differences in frequency among the populations of haplotypes are shown.

stances carried HLA-A1, a similar fraction as in normal [HLA-B8, SC01, DR3] haplotypes (p = NS).

Discussion

Our observations strongly suggest that the major susceptibility genes within the MHC for GSE and DH are different, or at least has different locations, in spite of the fact that the two disorders share clinical features and similar MHC markers, including extended haplotypes. That for GSE appears to lie in the DR/DQ region, whereas that for DH is near the complotype region, perhaps between it and DR/DQ.

As previously reported (21), all of the HLA markers for GSE are derived from two conserved or extended haplotypes, [HLA-B8, SC01, DR3] and [HLA-B44, FC31, DR7]. It is evident that for both HLA-DR3, DQ2- and HLA-DR7, DQ2-bearing haplotypes that (DR, DQ) fragments of the complete extended haplotypes were specifically enriched over (HLA-B, complotype), (complotype), or (complotype, DR, DQ) fragments in GSE. These findings support the concept that a gene in the DR, DQ region, probably a class II gene, is the susceptibility gene for GSE.

Even though MHC markers among DH patient haplotypes were very similar and the same extended haplotypes were increased as in GSE, the (SC01) fragment was specifically enriched over (B8, SC01), (SC01, DR3, DQ2), and (DR3, DQ2). Furthermore, there was only one haplotype with DR3 but not SC01, but six with SC01 but not DR3. SC01 had the highest odds ratio of any MHC marker in DH, including DQ2. All of these points support the conclusion that the DH susceptibility gene is near SC01. This was in contrast to GSE, in which DQ2 had the highest odds ratio.

The findings with respect to DH haplotypes related to [HLA-B44, FC31, DR7] were less clear cut in that both HLA-B44 and DR7 alone were often (and roughly equally) found and only one (FC31) alone occurred among patient haplotypes. Nevertheless, the presence of several instances of the (FC31, DR7, DQ2) fragment suggests that the susceptibility gene on this haplotype, too, may be between the complotypes and DR regions. Although ethnic differences between DH and GSE patients might affect the extent of fragmentation of the relevant extended haplotypes (30, 31), this would not in itself be expected to result in enrichment of some specific fragments over others.

Table 4. *MHC Haplotypes in Patients with GSE*

Haplotype no.	HLA- A	B	Complotype	HLA-DR
Haplotypes related to (HLA-B8, SC01, DR3):				
38756d	24	8	FC31	3*
40713a	3	7	SC01	3
35788c	1	8	SC01	3
37001b	1	8	SC01	3
38263c	1	8	SC01	3
38313a	1	8	SC01	3
38506a	1	8	SC01	3
38619a	1	8	SC01	3
38647c	1	8	SC01	3
39987a	1	8	SC01	3
40709c	1	8	SC01	3
40771a	1	8	SC01	3
42613c	1	8	SC01	3
42613d	1	8	SC01	3
44417c	1	8	SC01	3
11245c	2	8	SC01	3
11263c	2	8	SC01	3
38506c	2	8	SC01	3
40709a	2	8	SC01	3
40777a	2	8	SC01	3
43870c	2	8	SC01	3
38668c	3	8	SC01	3
38668a	24	8	SC01	3
35017a	24	8	SC01	3
37925a	25	8	SC01	3
11278a	28	8	SC01	3
11260a	28	8	SC01	3
34986c	32	8	SC01	3
38756c	29	8	SC01	3
38623a	34	8	SC01	3
35204a	2	18	F1C30	3‡
35788d	1	57	SC61	3
35811a	11	39	SC42	3
42136b	2	44	SC30	3*
38553c	3	7	SC31	3
40713c	2	44	SC(3,905)1	3*
42629d	26	63	S1C2(1,17)	3
Haplotypes related to (HLA-B44, FC31, DR7):				
42136b	2	44	SC30	3*
40713c	2	44	SC(3,905)1	3*
38584c	2	44	SC30	5
35204b	29	44	SC61	6
38756d	24	8	FC31	3*
11146c	29	44	FC31	7
11245a	29	44	FC31	7
11260c	29	44	FC31	7
38263a	29	44	FC31	7
11278c	2	44	FC31	7
38572c	2	44	FC31	7
38619c	2	44	FC31	7
38623c	28	44	FC31	7
37001d	25	18	FC31	7
37925c	26	45	FC01	7
40777d	30	58	FC01	7
11263a	33	44	SC31	7
11146a	1	57	SC61	7‡
34986a	30	13	SC31	7
36051a	2	13	SC31	7
35811c	24	22	SC31	7
38553a	29	14	SC31	7
40771c	2	62	SC33	7
42629b	–	51	S1C3,17	7
44440c	11	44	SC31	7
Other haplotypes:				
38584a	3	7	SC31	2‡
44417a	1	7	SC31	2‡
35017c	2	60	SB42	4‡
38647a	2	62	SB42	4‡
42136e	3	60	SC31	4
43870a	26	35	SC31	4‡
36051c	26	14	SC31	5
38313c	30	38	SC31	5
38572a	24	51	SC31	5
44440a	69	55	SC30	5
39987c	11	51	FC(3,2)0	6

* Listed twice as related to both [HLA-B8, SC01, DR3] and [HLA-B44, FC31, DR7].
‡ Extended haplotype other than those above.

Table 5. *Odds Ratios of MHC Alleles in Patients with DH and GSE with and without Removal of [HLA-B8, SC01, DR3]*

Allele	Dermatitis herpetiformis odds ratio		Gluten-sensitive enteropathy odds ratio	
	With [B8, SC01, DR3]	Without [B8, SC01, DR3]	With [B8, SC01, DR3]	Without [B8, SC01, DR3]
B8	9.8	3.4	7.5	0
SC01	37.8	99.6	8.7	1.7
DR3	10.6	5.4	14.7	11.4
[B8, SC01, DR3]	11.8	–	10.9	–
B44	1.1	1.1	1.8	5.0
FC31	1.3	2.5	1.8	0.8
DR7	2.0	19.1	3.5	5.6
[B44, FC31, DR7]	2.0	11.4	4.8	6.4
C4A*Q0	29.3	50.6	5.9	0.8
DQ2	35.9	6.8	46.9	34.0

Odds ratios are for subjects positive for the marker.

Table 6. *Extended Haplotype Fragment Distributions in Patients with DH and GSE*

Disease	SC01, not DR3,DQ2 no.	DR3,DQ2, not SC01 no.
DH	6	1
GSE	0	8

$p < 0.002$.

We believe that there are a number of susceptibility genes for DH and a number for GSE at a single locus for each disease acting in an essentially, but not simply, recessive manner. Others have found that DR4 haplotypes may contribute "minor" susceptibility to GSE (32). From our results, the major susceptibility markers for GSE are DR3, DQ2 and DR7, DQ2, and the minor markers are DR4, DQ7; DR5, DQ1; DR2, DQ1; and DR6, DQ1. We cannot, however, rule out 2 distinct MHC susceptibility loci (DQ and DP related) in GSE and three (complotype, DR/DQ, and DP related) in DH. Against the latter possibility is the presence primarily of (DR3, DQ2) and (DR7, DQ2) but not (FC31) or (SC01) in GSE and SC01, rather than chiefly class II fragments in DH patient haplotypes. If both DQ and complotype genes were required for recessive expression, the minimum fragment should contain both complotype and DQ susceptibility genes.

The relatively greater diversity of HLA-A alleles on [HLA-B8, SC01, DR3] haplotypes in GSE compared with the same haplotypes in DH patients or normals, in whom 75–80% of instances carry HLA-A1, may reflect the susceptibility gene localization results. Since there was enrichment for DR, DQ fragments in GSE, one might expect less homogeneity of the HLA-A region which is 2×10^6 base pairs telomeric to the class II region. It follows that if the susceptibility locus is near the complotype region, perhaps between the latter and DR, DQ, this may result in the observed higher HLA-A1 frequency on [HLA-B8, SC01, DR3] in DH than in GSE.

Recent studies have raised the possibility of specific HLA-DP alleles being associated with GSE (33–35) and DH (36). Our finding of an increase in the frequency of a specific DP allele, DPB1*0101, in both our GSE and DH patients over normal controls supports this possibility. We did not find increases in DPB1*04 and DPB1*03 alleles in GSE, as reported by Bugawan et al. (34), nor the increase in DP3 found by Kagnoff et al. (35), but confirmed the increase in DP1 found by this group. We found DPB1*0101 to be increased, particularly in association with HLA-DR3, suggesting that the [HLA-B8, SC01, DR3] extended haplotype often extends through DP in both GSE (34) and DH (9, 36, 37) patients as well as in normals (10). In this view, the increase in the DP marker may be because of known linkage disequilibrium between [HLA-B8, SC01, DR3] and DP1 (10, 11) (DPB1*0101) but may also reflect the possibility that the DP region contains a susceptibility gene (33).

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