

INVESTIGATIVE REPORT

Lichen Planopilaris is Associated with HLA DRB1*11 and DQB1*03 Alleles

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There are no studies of the possible association of the human leukocyte antigen (HLA) system with lichen planopilaris (LPP). To determine whether the HLA system is associated with LPP, 40 consecutive Jewish Israeli patients with LPP (study group) and 252 volunteers (controls) were typed for DRB1* and DQB1* loci by molecular methods. Compared with controls, the study group had a significantly higher frequency of the DRB1*11 allele (62% vs. 21%, corrected *p*-value (*pc*)=0.001) owing to increased frequencies of DRB1*11: 01 and DRB1*11: 04. The DQB1*03 allele was also expressed at a significantly higher frequency in the study group (70% vs. 33%, *pc*=0.0005); specifically, the frequency of DQB1*03: 01 was increased. The majority (82.5%) of the patients were of non-Ashkenazi origin. We conclude that LPP appears to be over-represented in non-Ashkenazi Jewish patients and is associated with an increased frequency of HLA DRB1*11 and DQB1*03 alleles. These findings suggest that immunogenetic factors play a role in LPP. *Key words: major histocompatibility complex; alopecia; lichen planopilaris; ethnicity.*

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Lichen planopilaris (LPP), which is thought to be a follicular form of lichen planus (LP), is a rare inflammatory T-cell-mediated disorder that selectively involves the hair follicles (1). Clinically, LPP usually involves the scalp and is characterized by areas of scarring alopecia with various degrees of perifollicular inflammation and violaceous papules, erythema and scaling (2). Histologically, findings typically include decreased terminal and vellus hair density, absent inner root sheath desquamation, and reduction in, or absence of, arrector pili muscle and sebaceous glands, along with perivascular and perifollicular lymphocytic infiltrate in the reticular dermis and mucinous perifollicular fibroplasia (3). The aetiology of LP in general and LPP in particular is unknown, although an autoimmune origin is suspec-

ted. Despite extensive studies of the human leukocyte antigen (HLA) system in T-cell-mediated diseases (4), including LP (5–24), little is known about the possible role of the HLA system in LPP.

The aim of the present study was to investigate the potential association of specific major histocompatibility complex (MHC) alleles with LPP.

METHODS

The study group comprised 40 consecutive Jewish patients in Israel (21 women, 19 men) with clinically and histologically confirmed LPP attending the Department of Dermatology of a tertiary medical centre from 2003 to 2013. Their findings were compared with a control group of 252 apparently healthy, unrelated Jewish volunteers, of whom 132 were Ashkenazi (originating from European countries, except the Balkans) and 120 non-Ashkenazi (from North Africa (Morocco, Algeria, Tunisia, Libya) and the Middle East (Iran, Iraq, Syria, Egypt, Yemen, Turkey)) (25). The study was approved by the local institutional review board, and all subjects provided informed consent to undergo venipuncture for HLA typing.

High- and intermediate-resolution molecular typing of HLA A*, B* and DRB1*, DQB1* was performed using the SSP method (One Lambda, Canoga Park, CA, USA) and the Luminex SSO method (GenProbe, San Diego, CA, USA), respectively. Associations of HLA alleles with LLP were studied by comparing class I and class II allele frequencies between patients and controls. Each allele was counted, and the total for each group was twice the number of subjects. Fisher's exact test was performed for each antigen or allele separately, using a 2 × 2 table (present or not present in patients and controls). The level of significance was set at *p* < 0.05. The corrected *p*-value (*pc*) was calculated by multiplying the *p*-values by the number of alleles tested for each locus. To determine whether the severity of LPP (active or burned out) was correlated with certain HLA associations, we constructed a severity score based on the percentage of scalp or body surface involving either inflammatory lesions or scarring alopecia, as follows: < 10%: mild disease; > 10%: severe disease.

RESULTS

All patients had cicatricial alopecia. In 9 patients, other hair-bearing areas of the body were involved in addition to the scalp. Mean ± standard deviation (SD) age at diagnosis was 54 ± 13 years (median 55, range 27–82 years), and mean ± SD duration of disease was 5 ± 4 years (median 4, range 1–18 years). Thirty-three

patients (82.5%) were of non-Ashkenazi origin: 9 (22.5%) from Iran, 10 (25%) from Iraq and 14 (35%) from other Asian countries and North Africa. The remaining 7 patients (17.5%) were of Ashkenazi origin. This rate is considerably lower than the ~50% rate of Ashkenazim in the Israeli Jewish population (26).

Table I summarizes the HLA analysis. The DRB1*11 allele was expressed at a significantly higher frequency in the entire study than the control group (62% vs. 21%, $p=0.001$), and in each of the subgroups, i.e. non-Ashkenazi and Ashkenazi, compared with the respective control subgroups (non-Ashkenazi, 61% vs. 23%, $p=0.001$; Ashkenazi, 71% vs. 19%, $p=0.001$). On high-resolution analysis of DRB1*11, the frequencies of DRB1*11: 01 and DRB1*11: 04 alleles were found to be significantly higher in the study than the control group ($p=0.001$ and $p=0.0005$, respectively). Further analysis by ethnic background yielded a high frequency of DRB1*11: 01 in both the non-Ashkenazi and Ashkenazi patient subgroups relative to the respective control subgroups, whereas the difference in frequency of DRB1*11: 04 by ethnicity was significant only for the non-Ashkenazim (Table I).

Interestingly, 8 patients (20%) were found to be homozygous for DRB1*11: 04 compared with only 1.7% of the control group. This difference was statistically significant ($p<0.0001$). Furthermore, all 8 patients (100%) had severe disease compared with only 19 of the 32 patients (59%) of the non-homozygotes for DRB1*11: 04 ($p=0.04$). DRB1*01 was expressed

at a lower frequency in the patients than in the controls ($p=0.02$). Overall, the frequency of the HLA-DQB1*03 alleles (DQB1*03: 01–03: 02) was significantly higher in the patients than in the controls (70% vs. 33%, $p=0.0005$), and in both the non-Ashkenazi and Ashkenazi patient subgroups compared with the respective control subgroups (non-Ashkenazi, 68% vs. 30%, $p=0.0005$; Ashkenazi, 79% vs. 36%, $p=0.01$). High-resolution analysis of the DQB1*03 gene showed that the DQB1*03: 01 allele was specifically associated with LPP: 85% of the patients carried at least one DQB1*03: 01 allele, and the allele frequency in the study group was 65% compared with 23% in the control group ($p=0.0002$). The difference remained significant on separate comparison by ethnicity (non-Ashkenazim: 64% vs. 24%, $p=0.0002$; Ashkenazim, 71% vs. 22%, $p=0.0004$). Concurrently, the allele frequencies of DQB1*05 and DQB1*06 were significantly lower in the patient group than in the control group.

No between-group differences were found in frequencies of the HLA A* and B* alleles (data not shown).

DISCUSSION

The pathogenesis of LP in general and LPP in particular is unknown. The presumptive mechanism of the scarring alopecia in LPP is autoimmune lymphocytic inflammation of the bulge area of the hair follicle where the follicular stem cells are found (27). LPP is rare; the reported annual incidence rate from 4 tertiary

Table I. Frequencies (%) of HLA-DRB1 and HLA-DQB1 alleles in Ashkenazi and non-Ashkenazi Jewish patients with lichen planopilaris and control subjects

Allele	Ashkenazi			Non-Ashkenazi			Combined		
	Patients <i>n</i> =7	Controls <i>n</i> =132	<i>p</i> -value (<i>pc</i>)	Patients <i>n</i> =33	Controls <i>n</i> =120	<i>p</i> -value (<i>pc</i>)	Patients <i>n</i> =40	Controls <i>n</i> =252	<i>p</i> -value (<i>pc</i>)
DRB1*01	0	13	NS	0	6	0.05 (0.5)	0	9	0.002 (0.02)
DRB1*03	0	6	NS	11	4	NS	9	5	NS
DRB1*04	1	16	NS	3	9	NS	4	13	NS
DRB1*07	14	12	NS	9	15	NS	10	13	NS
DRB1*08	0	0.3	NS	0	2	NS	0	1	NS
DRB1*10	0	2	NS	0	6	NS	0	4	NS
DRB1*11	71	19	<0.0001 (0.001)	61	23	<0.0001 (0.001)	62	21	<0.0001 (0.001)
*11: 01	42	6	0.0002 (0.0008)	17	6	0.009 (0.04)	21	6	<0.0001 (0.001)
*11: 02	0	0.4	NS	1	1	NS	1	0.6	NS
*11: 03	0	0.8	NS	0	1	NS	0	1	NS
*11: 04	29	12	NS	42	14	<0.0001 (0.0005)	40	13	<0.0001 (0.0005)
DRB1*12	0	4	NS	4	1	NS	4	3	NS
DRB1*13	7	12	NS	4	15	0.02 (0.2)	5	13	0.03 (0.3)
DRB1*14	0	3	NS	6	5	NS	5	4	NS
DQB1*02	14	17	NS	20	19	NS	19	18	NS
DQB1*03	79	36	0.002 (0.01)	68	30	<0.0001 (0.0005)	70	33	<0.0001 (0.0005)
*03: 01	71	22	0.0002 (0.0004)	64	24	<0.0001 (0.0002)	65	23	<0.0001 (0.0002)
*03: 02	7	13	NS	4	6	NS	5	10	NS
DQB1*04	0	1	NS	0	2	NS	0	2	NS
DQB1*05	0	19	NS	6	18	0.019 (0.09)	5	19	0.0018 (0.009)
DQB1*06	7	14	NS	6	23	0.0013 (0.0065)	6	18	0.0056 (0.028)

Level of significance: $p<0.05$.

pc: corrected *p*-value; NS: not significant.

hair research centres in the USA varied from 1.15% to 7.59% (28). The literature on the ethnic predilection of the disease is sparse; in the 3 largest case series from North American institutions, the majority of patients were Caucasian, commensurate with the percentage of Caucasians in the general population (2, 29, 30).

The association between HLA antigens and LP has been studied extensively, but the findings differ by disease variants (7, 11–13, 15) and by populations studied (6, 8, 9, 16, 17). For example, serological typing of HLA DR1 was positive in 80% of American patients with generalized cutaneous LP compared with 25% of healthy controls (21). By contrast, in Italian patients, no HLA antigen was found to be significantly associated with secondary LP (hepatopathy or other autoimmune disorder-related LP) or with primary mucosal LP (15). In patients with primary cutaneous LP, with or without mucosal lesions, a significant increase was noted in HLA-DR1 and DQ1 antigen frequency, and a significant decrease in HLA-DQ3 antigen frequency (15). A British study reported a significant association of vulvovaginal gingival syndrome, a severe form of mucosal LP, with the HLA DQB1*02: 01 allele (7). Interestingly, in Jewish patients with oral erosive lichen planus, there was a significant association of the disease with HLA-DR2 and a decrease in DR4 frequency (16). HLA-DRB1*01: 01 was found to be associated with a genetic susceptibility for LP in the Mexican Mestizo population (6). To our knowledge, the present study is the first to examine the association of HLA and LPP.

The findings of the current study yielded an ethnic predisposition for LPP in non-Ashkenazi Jews and an association of LPP with specific HLA DRB1* and DQB1* alleles: DRB1*11 and DQB1*03. The association in the patient group was remarkable: 85% carried at least 1 DQB1*03: 01 allele. Interestingly, studies have reported increased frequencies of the same allele in another T-cell-mediated disease, mycosis fungoides (MF) (25), in which hair-follicle involvement is a common histopathological finding (31). Moreover, in our study, there was a correlation between homozygosity for DRB1*11: 04 and disease severity. HLA allele frequencies are known to differ between Jews and many other populations (32), representing one of the traits that accounts for the genetic uniqueness of the Jewish people (33). Moreover, the prevalence of autoimmune diseases, such as type 1 diabetes and pemphigus, apparently differs between Ashkenazi and non-Ashkenazi Jews (34, 35). For these reasons, we included only Jewish subjects in the control group and, specifically, only Jews of Ashkenazi and non-Ashkenazi origin. The comparison of the ethnic subgroups of patients and controls highlights the novelty of our findings, as it indicates that these allele frequencies are indeed linked to the disease and not a product of selection bias due to the ethnic background of the patients.

The DRB1*11: 01 and DRB1: 11: 04 alleles, which were significantly increased in our patients with LPP, are known to be highly associated with DQB1*03: 01 due to linkage disequilibrium (36). Therefore, we were unable to determine whether both DRB1* and DQB1* loci are involved in the pathophysiology and manifestation of LPP, or if LPP is associated with only one of these loci, with the other being an accompanying locus as part of a commonly inherited haplotype. It is noteworthy that HLA DQB1*03 gene is a well-recognized susceptibility gene for the most common form of autoimmune non-cicatricial alopecia (alopecia areata) (37, 38) and plays a possible pathophysiological role in the collapse of immune privilege (37). Furthermore, in a study of patients with LPP, increased transcription of HLA DRB1 and DQB1 genes was found in affected, but not in unaffected, tissue (39).

Our study was limited by its relatively small size. In general, studies of HLA-disease associations are fraught with problems unless large populations are included. Therefore, further large studies are needed to establish the association of the HLA system and LPP in general and in the Jewish population in particular.

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