INVESTIGATIVE REPORT

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

Lev PAVLOVSKY1,2, Moshe ISRAELI3, Eti SAGY1, Amy L. BERG2, Michael DAVID1,2, Avner SHEMER2,4, Tirza KLEIN2,3 and Emmilia HODAK1,2

1Department of Dermatology and 3Tissue Typing Unit, Rabin Medical Center, Beilinson Hospital, Petach Tikva, 1Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; and 2Department of Dermatology, Sheba Medical Center, Tel-Hashomer, Israel

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.

Accepted Apr 24, 2014; Epub ahead of print May 7, 2014


Emmilia Hodak, Department of Dermatology, Rabin Medical Center, Beilinson Hospital, Petach Tikva 49100, Israel. E-mail: hodake@post.tau.ac.il

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-
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%, \(pc=0.001\)), and in each of the subgroups, i.e. non-Ashkenazi and Ashkenazi, compared with the respective control subgroups (non-Ashkenazi, 61% vs. 23%, \(pc=0.001\); Ashkenazi, 71% vs. 19%, \(pc=0.001\)). 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 (\(pc=0.001\) and \(pc=0.0005\), 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 \((pc=0.02)\). 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%, \(pc=0.0005\)), and in both the non-Ashkenazi and Ashkenazi patient subgroups compared with the respective control subgroups (non-Ashkenazi, 68% vs. 30%, \(pc=0.0005\); Ashkenazim, 79% vs. 36%, \(pc=0.01\)).

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 \((pc=0.0002)\). The difference remained significant on separate comparison by ethnicity (non-Ashkenazim: 64% vs. 24%, \(pc=0.0002\); Ashkenazim, 71% vs. 22%, \(pc=0.0004\)). 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

<table>
<thead>
<tr>
<th>Allele</th>
<th>Ashkenazi</th>
<th>Non-Ashkenazi</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
<td>(p)-value</td>
</tr>
<tr>
<td>DRB1*01</td>
<td>0 13</td>
<td>132</td>
<td>NS</td>
</tr>
<tr>
<td>DRB1*03</td>
<td>0 6</td>
<td>NS</td>
<td>11 4</td>
</tr>
<tr>
<td>DRB1*04</td>
<td>1 16</td>
<td>NS</td>
<td>3 9</td>
</tr>
<tr>
<td>DRB1*07</td>
<td>14 12</td>
<td>NS</td>
<td>9 15</td>
</tr>
<tr>
<td>DRB1*08</td>
<td>0 0.3</td>
<td>NS</td>
<td>0 2</td>
</tr>
<tr>
<td>DRB1*10</td>
<td>0 2</td>
<td>NS</td>
<td>0 6</td>
</tr>
<tr>
<td>DRB1*11</td>
<td>71 19</td>
<td>&lt;0.0001</td>
<td>61 23</td>
</tr>
<tr>
<td>*:11:01</td>
<td>42 6</td>
<td>0.0002</td>
<td>17 6</td>
</tr>
<tr>
<td>*:11:02</td>
<td>0 0.4</td>
<td>NS</td>
<td>1 1</td>
</tr>
<tr>
<td>*:11:03</td>
<td>0 0.8</td>
<td>NS</td>
<td>0 1</td>
</tr>
<tr>
<td>*:11:04</td>
<td>29 12</td>
<td>NS</td>
<td>42 14</td>
</tr>
<tr>
<td>DRB1*12</td>
<td>0 4</td>
<td>NS</td>
<td>4 1</td>
</tr>
<tr>
<td>DRB1*13</td>
<td>7 12</td>
<td>NS</td>
<td>4 15</td>
</tr>
<tr>
<td>DRB1*14</td>
<td>0 3</td>
<td>NS</td>
<td>6 5</td>
</tr>
<tr>
<td>DQB1*02</td>
<td>14 17</td>
<td>NS</td>
<td>20 19</td>
</tr>
<tr>
<td>DQB1*03</td>
<td>79 36</td>
<td>0.0002</td>
<td>68 30</td>
</tr>
<tr>
<td>*:03:01</td>
<td>71 22</td>
<td>0.0002</td>
<td>64 24</td>
</tr>
<tr>
<td>*:03:02</td>
<td>7 13</td>
<td>NS</td>
<td>4 6</td>
</tr>
<tr>
<td>DQB1*04</td>
<td>0 1</td>
<td>NS</td>
<td>0 2</td>
</tr>
<tr>
<td>DQB1*05</td>
<td>0 19</td>
<td>NS</td>
<td>6 18</td>
</tr>
<tr>
<td>DQB1*06</td>
<td>7 14</td>
<td>NS</td>
<td>6 23</td>
</tr>
</tbody>
</table>

Level of significance: \(p<0.05\).

\(pc\): corrected \(p\)-value; NS: not significant.

*Acta Derm Venereol 95*
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 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 DQ1* 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.

REFERENCES


Acta Derm Venereol 95