Comparative analysis of the HLA-DR and -DQ alleles revealed differences in the allelic distribution among both sexes, and HLA-DRB1 and -DQB1 genotyping was done by the PCR sequence-specific primer technique. Comparative analysis of the HLA-DR and -DQ alleles revealed differences in the allelic distribution among Bahraini and Lebanese subjects. Analysis of the 25 HLA-DRB1 alleles that have been investigated showed that the DRB1*040101-DRB1*110101 alleles were more frequent among Lebanese, whereas DRB1*030101 and DRB1*160101 alleles were more frequent among Bahrainis. Similarly, of the seven HLA-DQB1 alleles analyzed, the presence of DQB1*0201 was more frequent among Bahrainis, whereas DQB1*030101 was more frequent among Lebanese. The DRB1*160101-DQB1*050101 (0.1318 versus 0.0379%) and DRB1*030101-DQB1*0201 (0.1202 versus 0.0321%) haplotypes were more frequent among Bahrainis, while the DRB1*110101-DQB1*030101 (0.3142 versus 0.1198%) and DRB1*040101-DQB1*0302 (0.1416 versus 0.0278%) haplotypes were more frequent in Lebanese subjects. Furthermore, a high prevalence of the DRB1*040101-DRB1*110101-DQB1*0302-DQB1*030101 (12.63 versus 1.35%, P = 0.015) and the homozygous DRB1*110101-DRB1*110101-DQB1*030101-DQB1*030101 (7.37 versus 0.00%, P = 0.046) genotypes was seen among Lebanese, and DRB1*070101-DRB1*160101-DQB1*0201-DQB1*050101 (6.76 versus 0.00%, P = 0.034) was seen more frequently among Bahraini subjects. Our results underline significant differences between these two populations in HLA class II distribution, provide basic information for further studies of major histocompatibility complex heterogeneity among Arabic-speaking countries, and serve as a reference for further anthropological studies.

The gene frequencies of HLA class II alleles were studied in 95 healthy Lebanese Arab and 72 healthy Bahraini Arab subjects. Our aim was to establish the genetic relationship between Bahraini and Lebanese Arabs in terms of HLA class II gene and haplotype frequencies and to compare these results with frequencies for other countries with populations of Caucasian and non-Caucasian descent. Subjects were unrelated and of both sexes, and HLA-DRB1 and -DQB1 genotyping was done by the PCR sequence-specific primer technique. Comparative analysis of the HLA-DR and -DQ alleles revealed differences in the allelic distribution among Bahraini and Lebanese subjects. Analysis of the 25 HLA-DRB1 alleles that have been investigated showed that the DRB1*040101-DRB1*110101 alleles were more frequent among Lebanese, whereas DRB1*030101 and DRB1*160101 alleles were more frequent among Bahrainis. Similarly, of the seven HLA-DQB1 alleles analyzed, the presence of DQB1*0201 was more frequent among Bahrainis, whereas DQB1*030101 was more frequent among Lebanese.

The major histocompatibility complex (MHC) plays a key role in self-nonself recognition and is broadly divided into highly polymorphic class I (HLA-A, -B, and -C) and class II (HLA-DP, -DQ, and -DR) loci, which are subdivided into distinct regions (refer to the IMGT/MLA database for up-to-date listings of these genes [23]). For example, HLA-DRB1, with more than 315 known alleles, and DPB1, with more than 99 alleles (19), represent the most polymorphic protein-encoding regions of the human genome (19, 23). In addition to their role in conferring immune identity, genetic distances and correspondence analysis demonstrated that patterns of allele and haplotype distribution of class I and class II loci are racially and geographically restricted, thereby allowing their use for population and evolution studies (8, 21).

Comparative analysis of the HLA class II DR and DQ alleles and haplotypes has revealed differences in the distribution of these alleles among different ethnic groups and reflected ancient and recent admixtures between different populations (9, 21, 25). This has significant implications for analyzing human migration trends throughout history (14). Studies of the HLA origin of Arabs are scanty, but studies of related eastern and western Mediterranean groups including Turks, Iranians, Jews, Lebanese, and others suggest a common ancestry (6, 8, 24). Variation in HLA class II distribution among these populations can be explained by the admixture of the ancient population with invading and migratory societies, which may have given rise to present-day racial and ethnic groups (8).

In view of the heterogeneity of the Arab population, which comprises people of distinct ethnic backgrounds and whose origins can be classified according to their area of habitation (North Africa, Arabian peninsula, and eastern Mediterranean), the present study was aimed at elucidating the diversity in HLA class II allele distribution among two distinct Arab communities, Bahrain and Lebanon. Bahrain is an island located in the Arabian Gulf whose inhabitants derive their origin from three major roots: Jaafar 1 Arab, Sunni Arab, and Iranians (4). Lebanon is located in the eastern Mediterranean, and its population consists of Christians (Catholic, Maronite, Greek Orthodox, and Coptic) and Moslems (Sunni, Shi'ite, and Druze). This study provides basic information for further studies of the MHC differences between Arabs of distinct origins...
and will serve as a reference for further anthropological studies, as well as for studies of associations between HLA and disease.

MATERIALS AND METHODS

Subjects. The samples used in this study included 95 healthy unrelated Leb-

Table 1. HLA-DRB1* allele distribution among Lebanese and Bahraini Arabs

| DRB1 allele | Bahrain# | Lebanese# | P | Pc | OR |
|-------------|----------|-----------|---|----|----|
| 010101      | 0.014    | 0.010     | 0.058 | 0.017 | 0.055 | 1.371 | 0.243 |
| 0103        | 0.000    | 0.000     | 0.005 | 0.005 | 1.000 | 25.000 | 0.000 |
| 030101      | 0.139    | 0.029     | 0.032 | 0.013 | 0.001 | 0.033 | 4.585 |
| 030201      | 0.007    | 0.007     | 0.021 | 0.010 | 0.289 | 7.233 | 0.320 |
| 0310        | 0.021    | 0.012     | 0.005 | 0.005 | 0.192 | 4.811 | 4.087 |
| 040101      | 0.049    | 0.018     | 0.179 | 0.028 | <0.001 | 0.002 | 0.171 |
| 040302      | 0.000    | 0.000     | 0.005 | 0.005 | 1.000 | 25.000 | 0.000 |
| 0412        | 0.007    | 0.007     | 0.000 | 0.000 | 1.000 | 25.000 |
| 070101      | 0.090    | 0.024     | 0.063 | 0.018 | 0.331 | 8.264 | 1.524 |
| 080101      | 0.035    | 0.015     | 0.011 | 0.007 | 0.122 | 3.056 | 3.470 |
| 080201      | 0.007    | 0.007     | 0.011 | 0.007 | 0.730 | 18.249 | 0.655 |
| 090102      | 0.014    | 0.010     | 0.005 | 0.005 | 0.406 | 10.146 | 2.686 |
| 100101      | 0.076    | 0.022     | 0.032 | 0.013 | 0.029 | 0.736 | 3.245 |
| 110101      | 0.160    | 0.031     | 0.268 | 0.035 | <0.001 | 0.003 | 0.286 |
| 120101      | 0.007    | 0.007     | 0.032 | 0.013 | 0.116 | 2.890 | 0.209 |
| 130101      | 0.021    | 0.012     | 0.037 | 0.014 | 0.388 | 9.695 | 0.547 |
| 130701      | 0.042    | 0.017     | 0.005 | 0.005 | 0.020 | 0.502 | 8.546 |
| 130702      | 0.035    | 0.015     | 0.000 | 0.000 | 0.000 | 0.000 |
| 140101      | 0.042    | 0.017     | 0.037 | 0.014 | 0.818 | 20.443 | 1.143 |
| 1402        | 0.007    | 0.007     | 0.000 | 0.000 | 1.000 | 25.000 |
| 1415        | 0.007    | 0.007     | 0.005 | 0.005 | 0.843 | 21.079 | 1.324 |
| 1416        | 0.000    | 0.000     | 0.005 | 0.005 | 1.000 | 25.000 |
| 150101      | 0.076    | 0.022     | 0.047 | 0.015 | 0.103 | 2.564 | 2.267 |
| 160101      | 0.139    | 0.029     | 0.037 | 0.014 | <0.001 | 0.010 | 4.835 |

# DRB1* alleles were assessed by PCR-SSP.

# DQB1* alleles were assessed by PCR-SSP.

# A total of 95 Lebanese and 72 Bahraini subjects were analyzed. Allele frequency was determined as frequency = number of an allele/total number of alleles per group.

# Determined by Fisher’s exact test.

# Pc = corrected P value for the number of alleles tested (n = 25), calculated using the Bonferroni method.

RESULTS

Frequencies of the HLA-DRB1 alleles. We found significant DRB1 allelic differences between Lebanese and Bahraini Arabs, 7 of 25 loci being significantly different (P < 0.05). When we applied the Bonferroni correction, differences were significant for four loci. These comprised DRB1*030101 (0.139 versus 0.032%; Pc = 0.033) and DRB1*160101 (0.139 versus 0.035%; Pc = 0.011), which were significantly more frequent in Bahraini than in Lebanese subjects (Table 1), and DRB1*040101 (0.179 versus 0.049%; Pc = 0.002) and DRB1*110101 (0.368 versus 0.160%; Pc = 0.003), which were more frequent among Lebanese than among Bahraini subjects (Table 1).

Frequencies of the HLA-DQB1 alleles. Similarly, significant DQB1 allelic differences were seen between Lebanese and Bahraini Arabs, four of seven loci being significantly different (P < 0.05). With the Bonferroni correction, differences were significant for only two loci. These comprised DQB1*0201 (0.257 versus 0.158%; Pc < 0.001; OR = 4.267), which was

Table 2. HLA-DQB1* allele distribution among Lebanese and Bahraini Arabs

| DQB1 allele | Bahrain# | Lebanese# | P | Pc | OR |
|-------------|----------|-----------|---|----|----|
| 0201        | 0.257    | 0.036     | 0.158 | 0.084 | <0.001 | <0.001 | 4.267 |
| 030101      | 0.160    | 0.031     | 0.379 | 0.035 | <0.001 | <0.001 | 0.245 |
| 0302        | 0.097    | 0.025     | 0.168 | 0.027 | 0.034 | 0.239 | 0.455 |
| 0303        | 0.028    | 0.014     | 0.026 | 0.012 | 0.934 | 6.538 | 1.059 |
| 0401        | 0.035    | 0.015     | 0.053 | 0.016 | 0.423 | 2.939 | 0.634 |
| 050101      | 0.292    | 0.038     | 0.205 | 0.029 | 0.012 | 1.084 | 2.220 |
| 060101      | 0.132    | 0.028     | 0.084 | 0.020 | 0.144 | 1.009 | 1.788 |

# DQB1* alleles were assessed by PCR-SSP.

# A total of 95 Lebanese and 72 Bahraini subjects were analyzed. Allele frequency was determined as frequency = number of an allele/total number of alleles per group.

# Determined by Fisher’s exact test.

# Pc = corrected P value for the number of alleles tested (n = 7), calculated using the Bonferroni inequality method.
The frequencies of DRB1*040101-DQB1*0302 (0.1416 versus 0.0278; \(P = 0.046\)) genotypes were observed more frequently in Lebanese than in Bahraini subjects (Table 5). Among the Bahraini subjects tested, extensive heterogeneity was seen in genotype distribution, with DRB1*070101/160101-DQB1*0201/050101 (6.76 versus 0.00%; \(P = 0.034\)) appearing to be most commonly present (Table 5).

**HIA class II diversity.** The differences at the HLA class II DRB and DQB loci were further investigated using \(F_{str}\) and Nei genetic distance and identity measurements. When class II alleles from Bahraini and Lebanese Arabs were compared, overall average genetic differentiation between populations (estimated with the \(F_{str}\), a measure of genetic differentiation over subpopulations) was 0.026 for DRB1 and 0.029 for DQB1 (Table 6). Nei genetic distance and identity were 0.287 and 0.751, respectively. Collectively, this suggested that the identity between Bahraini and Lebanese Arabs was not high.

**DISCUSSION**

Analysis of HLA genes has provided invaluable tools for anthropological studies, and analysis of HLA loci and haplotypes, first by serology and later by molecular tools, has been reported for many societies. Insofar as Arabs represent a heterogeneous mixture of populations extending from the Arabian (Persian) Gulf to the Atlantic Ocean, and in view of the admixture brought about by the transmigration which trans-Arabia has witnessed throughout its history, this study was undertaken to analyze HLA class II usage among Bahraini and Lebanese Arab communities, the former situated in the eastern Arabian peninsula and the latter located in the eastern Mediterranean.

As expected, marked heterogeneity in HLA class II DR-DQ alleles and haplotypes was seen, with DRB1*030101 and DQB1*0201 being more prevalent among Bahrainis while DRB1*110101/040101 and DQB1*030101 were more prevalent among Lebanese Arabs, and also by genotype analysis, which clearly showed that the DRB1*040101-DRB1*110101-DRB1*0302- DQB1*030101 and DRB1*110101-DRB1*110101- DQB1*030101-DRB1*030101 genotypes were more frequent among Lebanese, while DRB1*070101-DRB1*160101- DQB1*0201- DQB1*050101 was more common among Bahrainis. This heterogeneity in HLA class II expression was subsequently confirmed by analysis of molecular variance and \(F_{str}\) measurements and also by calculating Nei genetic distance and identity, all of which indicated that the identity between these two populations was not high.

Among the DRB1 alleles analyzed we noted that DRB1*110101, a common allele of eastern Mediterranean countries including Greece, Bulgaria (16), Turkey (25) and Slovakia (12), had the highest frequency among Lebanon. In addition to the DRB1*110101 allele which they shared with the Lebanese, Bahraini also had unique DRB1 alleles including DRB1*030101 and DRB1*160101, which were present at significantly lower frequencies among healthy Lebanese. The similarity of the Lebanese alleles to those of the above-mentioned eastern Mediterranean countries as well as other countries, including Algeria (13) and Hungary (29), may be explained by the admixture brought about by the migration of Phoenicians.
(ancestors of present-day Lebanese) to North Africa and southern Europe.

Analysis of the Bahraini HLA class II alleles and haplotypes revealed some relatedness to their Lebanese counterparts and also to those of neighboring and distant ethnic groups, as exemplified by DRB1*1101 and DRB1*16011 (6, 27), which suggests the influence of these populations on this distinct Arab population. The strongest similarity that the Bahrainis had was with their related Arabian Gulf neighbors, as exemplified with DRB1*030101, which is also highly frequent among healthy Saudi (2) and Kuwaiti (3, 15) Arabs. Interestingly, the same alleles were highly frequent among Iranians (5), Indians (20), and Thais (28), an indication that Bahraini Arabs share some HLA components with populations of the Arabian Peninsula and the Indian subcontinent.

Perhaps the main feature of Arabs is the high diversity of DR-DQ associations. Most of the DR-DQ associations reported here for both Bahraini and Lebanese Arabs were also seen in other regions, though at different frequencies. These included DRB1*0701-DQB1*0201, which was common among Yemenite Jews (17), Moroccans (17), and Iranians (5); DRB1*0401-DQB1*0302, reported for Jordanian Arabs (24); and DRB1*1501-DQB1*06, which was reported for Tunisians (1). There were also certain haplotypes which were completely missing among these two Arabic-speaking populations but reported for other ethnic groups, including DRB1*0803-DQB1*0601 for Filipinos (11), DRB1*0401-DQB1*0401 for Koreans (22), and DRB1*16-DQB1*0602 for Japanese (7).

Data presented here, in defining the HLA profile among (eastern Mediterranean) Lebanese and (Arabian Peninsula) Bahraini Arabs, point to differences in the origins of these two distinct Arabic-speaking communities, brought about possibly by the admixture of the original inhabitants with neighboring and distant populations. These results provide information that can be used for future anthropological studies and also in the analysis of disease susceptibility and organ transplantation (18, 22).

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