ELSEVIER

Molecular Analysis of HLA Class II Polymorphisms among Different Ethnic Groups in Israel

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ABSTRACT: The Jewish population in Israel comprises of inhabitants of heterogeneous ethnic backgrounds. Genetic studies classify the Israeli Jewish population into two major groups: Ashkenazi from Central and Eastern Europe and Sephardic or non Ashkenazi, from the Mediterranean and North Africa. The present study was aimed at elucidating the differential influx of HLA class II alleles in Ashkenazi, in various non-Ashkenazi subgroups and in Israeli Moslem Arabs. Using the PCR-SSOP technique, a large number of alleles were detected at each of the loci examined (DRB1, DQA1 and DQB1).

In addition, gene frequencies, characteristic DR/DQ linkage disequilibria, population distances and their corresponding dendogram, were used to study the relationship between Israelis as a group, non Jewish Caucasians and Blacks. These populations could be grouped into three main clusters: the first consists of all the Israeli groups with the exception of the Ethiopian Jews; the second consists of non Jewish Caucasians, with a clear distinction seen between Israelis and non Jewish Europeans and U.S. Caucasians; the third, composed of Blacks, is distinctly different from the other populations. Ethiopian Jews were found to be closer to the Blacks than to any of the Israeli Jewish groups.

We have shown that Jews share common features, a fact that points to a common ancestry. A certain degree of admixture with their pre-immigration neighbors exists despite the cultural and religious constraints against intermarriage. *Human Immunology 60, 723–730 (1999).*

KEYWORDS: HLA; PCR; ethnic groups; gene frequency

INTRODUCTION

Two major historical upheavals had a decisive effect on the genetic makeup of the Jewish people. The first destruction of Jerusalem by Nebuchadnezzar of Babylon, took place in 586 BC, after which the Jews were exiled to Babylon. After return from this exile, the second destruction of Jerusalem took place in the year 70 AD, dispersing the Jews throughout the world for two thousand years [1]. Despite the religious and cultural constraints against intermarriage, genetic introduction from the populations within which the Jews resided was inevitable. The establishment of the State of Israel in this century, and the ingathering of Jews from all over the world created in Israel a population with fascinating genetic heterogeneity [2, 3]. Genetic studies define two major Jewish groups: Ashkenazi, from eastern and central Europe, a genetically homogeneous group, and non-Ashkenazi from Mediterranean, Asian, and North African countries, with more genetic heterogeneity [1].

The expulsion consequence of Jews from Spain in 1492 resulted in a massive influx of Spanish exiles to North Africa in general and especially to Morocco and Libya. The Iranian Jewry, whose origin goes back as early as the 6th century BC from Babylon, have lived throughout Persia and have had strong ties with the Babylonian Jewry. The first concrete figures appeared only in the 12th century when some 60,000 Jews were diffused into many provinces of Persia. During the 19th century there was discriminations against religious minorities, attitude which has improved since the turn of the century. The

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Iranian Jewry accounts today about 3.5% of the Jewish population in Israel originating from Iran mostly after the creation of the State of Israel in 1948. The Yemenite Jews were settled in Yemen following the migration from Jerusalem after the destruction of the Second Temple. Since then the Yemenite Judaism florished in Yemen until the victory of Islam. The first Jews from Yemen settled in Palestine at the end of the 19th century and assumed the dimensions of a vast exodus during the operation "Magic Carpet" immediately after the establishment of the state and account for about 4% of the Jewish population. In the past few years, thousands of Ethiopian Jews immigrated to Israel through two special rescue programs "Operation Moses" and "Operation Shlomo". Some historians claim that they originated from Jewish communities in upper Egypt, others regard them as descendants of some Semitic tribes from Southern Arabia. Most historians believe however they are descendants of the local African tribe Agau (ancient Ethiopians), whose ancestors were possibly converted to Judaism by Yemenite Jews brought into Ethiopian during the 1st centruy of Christianity. The Israeli Arabs, of Moslem religion, constitute a relatively homogeneous community.

The HLA system is the most polymorphic genetic system in Man. Showing the most polymorphism are HLA class II genes, localized in the second exon. These genes encode the peptide-binding groove of the cell surface heterodimer on antigen presenting cells. More than 230 alleles have been defined for the HLA-DRB, -DQA, and -DQB genes. The allelic distribution of this system was used to decipher the relationships and to calculate the genetic distances within the Jewish subgroups and between these groups and surrounding populations.

MATERIALS AND METHODS

Study Subjects

The study population consisted of a total of five hundred and twenty-seven (527) unrelated healthy individuals residing in Israel: 119 Libyan Jews (LJ), 101 Iranian Jews (IJ), 122 Ethiopian Jews (EJ), 76 Yemenite (YJ) and 109 Israeli Arabs (IAR). These were compared to the 132 Ashkenazi (AJ) and 94 Moroccan Jews (MJ) previously studied by Roitberg-Tambur et al [4].

PCR-SSOP

PCR amplification. Genomic DNA was isolated from whole blood containing EDTA according to Miller's salting out procedure [5] with minor modifications.

Generic amplification of HLA-DRB1, -DQA1 and -DQB1, followed by group specific amplification of DR1-DRB1, DR2-DRB1, DR4-DRB1 and DR52 associated DRB1 were performed using oligonucleotide primers of the 12th International Histocompatibility Workshop (IHWS). In general, 50 μl of reaction mixture for each specific amplification was subjected to 35 cycles of PCR in an automated heated lid PCR thermal cycler (MJR, Watertown, Massachusetts, USA). PCR conditions differed in each specific amplification according to the reference protocols. A set of 24 DNA samples distributed by the 12th IHWS and locally selected panel cell DNA samples, served as controls for the HLA class II genotyping. PCR products were checked for amplification efficiency on 2% agarose gels visualized on a U.V. transilluminator.

Dot blot hybridization. PCR products were spotted onto an uncharged nylon membrane (Quiabrane, Quiagen) and denatured using an alkaline solution, neutralized and washed at room temperature. The membranes were then prehybridized for 2 h at 42°C in 10 ml of hybridization solution composed of 5 × SSC (0.9 M NaCl and 0.15 M sodium citrate), 0.5% casein, 0.1% N lauroylsarcosine, and 0.02% SDS at pH7.0. The filters were hybridized overnight in the same hybridization solution containing 3 pmoles/ml of the specific DIG labeled sequence specific oligonucleotide (SSO). After hybridization, the membranes were washed twice for 5 min. at room temperature (RT) in 2 × SSC with 0.1% SDS, once for 5 min at RT in a 3 M tetramethylammonium chloride (TMAC) solution (3 M TMAC, 50 mM TRIS-HCl pH 8.0, 2 mM EDTA, 0.1% SDS). The membranes were then submitted to two stringent washes with 3 M TMAC at 50-56°C for 10 min each with gentle agitation, washed, and blocked in solution B (1% Casein in 0.1 M Tris-HCl, 0.15 M NaCl pH 7.5) for 30–90 min, and then soaked in a dilute anti-digoxigenin-alkaline phosphatase Fab fragment in solution B (37.5 mμ/ml of anti DIG-AP) for 30 min and then washed to remove unbound antibody conjugate.

The probes were detected by chemiluminescence (CDP-Star, Boehringer Mannheim, Germany) followed by short exposure to x-ray films (Kodak). The oligonucleotide probe sequences and specificities are all from the 12th IHWS [6].

Statistical analysis. Gene frequencies (GF) were calculated using the formula $GF = 1 - \sqrt{1-AF}$, where AF is the allele frequency. The two locus haplotype frequencies were estimated and the delta values were calculated according to Cavalli-Sforza and Bodmer [7]; haplotype frequencies and delta values were expressed per 10,000 individuals. The significance of delta values was determined by chi-square testing of 2 × 2 contingency tables described from phenotypes.

The genetic distance between any two populations

TABLE 1. Gene frequency (%) of DRB1 alleles in various Israeli Jewish ethnic groups and Israeli Arabs.

Allele	Ashkenazi Jews (AJ) (N = 132)	Moroccan Jews (MJ) (N = 94)	Libyan Jews (LJ) (N = 119)	Iranian Jews (IJ) (N = 101)	Ethiopian Jews (EJ) (N = 122)	Yemenite Jews (YJ) (N = 76)	Israeli Arabs (IAR) (N = 109)
DRB1*							
0101	1.9	0.5	0.0	0.5	0.4	1.3	2.3
0102	10.0	4.4	2.1	2.0	11.3	0.7	1.9
0103	1.1	0.5	0.0	0.0	0.0	0.0	0.0
1501	2.7	3.2	0.8	2.0	2.5	2.0	3.3
1502	3.1	7.2	1.7	7.7	0.4	2.0	5.7
1503	0.0	0.0	0.0	0.0	10.4	0.0	0.5
1601	1.1	1.6	0.0	0.5	0.0	2.0	0.9
1602	0.8	0.0	2.1	1.0	0.0	0.0	0.0
03011	7.1	2.7	5.6	8.3	13.2	12.0	9.6
0302	0.4	0.5	0.0	0.0	0.0	0.0	0.0
0401	1.9	0.0	0.8	0.0	2.1	0.0	0.9
0402	8.3	2.7	3.0	5.1	0.0	7.5	2.8
0403	1.9	2.7	3.4	3.0	5.1	6.1	8.1
0404	1.5	0.0	5.6	1.5	2.5	1.3	0.9
0405	0.4	2.2	2.6	2.5	2.5	2.7	1.4
0406	0.0	3.2	2.1	0.0	0.0	1.3	0.0
0408	1.9	0.0	0.0	0.0	0.0	0.0	0.0
1101	6.3	5.5	9.3	3.0	2.9	3.4	10.7
1102	0.4	1.1	0.0	0.0	2.1	0.0	0.9
1103	0.8	1.1	3.0	0.0	0.4	0.0	0.5
1104	12.5	11.9	10.7	21.0	0.4	9.0	9.6
1201	3.1	0.5	0.0	2.5	0.0	6.1	0.5
1301	3.5	8.9	7.4	1.0	0.8	5.4	3.3
1302	4.3	3.2	3.9	15.0	16.0	4.0	3.7
1303	0.0	0.0	5.2	3.5	6.8	2.7	7.6
1304	0.4	0.0	0.0	0.0	0.0	0.0	0.0
1305	3.1	2.2	0.8	2.0	0.0	0.7	0.5
1309	NT	NT	0.0	0.0	0.0	0.0	0.5
1401	2.7	4.9	1.7	2.5	0.0	3.4	3.7
1404	NT	NT	0.8	0.0	0.0	0.0	0.5
1406	NT	NT	0.4	0.0	0.0	0.0	0.0
0701	13.0	18.8	26.7	8.8	12.3	22.1	12.8
0801	0.0	0.5	0.0	0.0	0.4	0.7	0.5
0802	0.4	0.0	0.0	0.0	0.0	0.0	0.5
0803	0.0	1.1	0.0	0.0	0.0	0.0	0.0
08041	0.0	0.0	0.0	0.0	5.1	0.0	1.4
0901	0.4	0.0	0.0	0.5	0.0	0.0	0.0
1001	2.3	7.2	0.8	3.0	1.7	4.0	4.7

was calculated as follows: first, for each of the three HLA loci, we calculated the per-locus genetic distance, using the approach suggested by Nei [8]. Thus, for locus j (j = 1,2,3), the distance between populations A and B, say, is

$$d_j(A,B) = 1 - \frac{\sum_i x_i y_i}{\sqrt{\sum_i x_i^2}\sqrt{\sum_i y_i^2}},$$

(where x_i and y_i are the frequencies of allele i in each population). The overall distance $D(A,B)$ between populations A and B was then taken as the Euclidean measure of the three locus distances:

$$D(A,B) = \sqrt{d_1(A,B)^2 + d_2(A,B)^2 + d_3(A,B)^2}.$$

These distances served to construct a population tree, using the unweighted pair group clustering method [9].

RESULTS

HLA Allele Frequencies in Israeli Jews

Table 1 lists the gene frequency of the DRB1 alleles of all the groups studied. Out of 180 known DRB1 alleles, 38 were detected using oligotyping. The most prominent allele was found to be DRB1*0701, varying in frequency from 8.8% in IJ to 26.7% in LJ. Next came DRBI*1104, that varied from as low as 0.4% in EJ to as high as 12.5% in AJ. In the DR1 cluster, the prominent allele was DRB1*0102, present in 10% of AJ and 11.3%

TABLE 2. Gene frequency (%) of DQ alleles in various Israeli Jewish ethnic groups and Israeli Arabs.

Allele	Ashkenazi Jews (AJ) (*N* = 132)	Moroccan Jews (MJ) (*N* = 94)	Libyan Jews (LJ) (*N* = 119)	Iranian Jews (IJ) (*N* = 101)	Ethiopian Jews (EJ) (*N* = 122)	Yemenite Jews (YJ) (*N* = 76)	Israeli Arabs (IAR) (*N* = 109)
DQA1*							
0101	17.4	18.8	5.6	7.7	13.6	9.7	12.2
0102	9.6	10.1	7.0	20.4	28.7	7.5	11.7
0103	9.6	14.9	9.3	11.6	0.8	9.0	9.1
0201	12.5	18.8	26.7	8.8	12.3	22.1	12.8
03	16.5	11.3	17.5	12.7	10.8	18.1	14.9
0401	0.4	0.5	0.0	0.0	0.4	0.7	0.9
05	28.8	25.6	35.2	38.7	29.9	32.3	37.2
0601	0.4	0.0	0.0	0.0	0.0	0.0	0.0
DQB1*							
0501	14.7	13.7	3.0	5.6	13.2	6.1	9.1
0502	2.7	1.6	2.1	2.0	0.0	2.0	2.8
05031	2.3	5.5	2.6	2.5	0.0	3.4	4.2
0601	3.5	8.3	1.7	8.8	0.8	2.7	6.6
0602	4.3	2.7	0.8	1.0	6.4	2.0	2.3
0603	6.7	11.3	7.4	3.5	7.2	6.1	3.7
0604	0.8	2.2	2.6	11.6	5.5	2.0	3.3
06051	3.1	5.3	1.3	3.0	9.9	1.3	0.9
02	18.4	23.5	33.3	18.0	24.3	39.1	23.4
0301	24.1	23.5	29.6	28.9	20.6	19.1	29.6
0302	13.8	6.0	13.0	7.7	5.5	14.2	10.2
03032	0.0	0.0	1.3	0.5	3.3	0.0	0.5
0304	0.0	0.0	0.0	0.5	0.0	0.0	0.5
0305	NT	NT	0.8	0.0	0.0	0.0	1.9
0402	1.1	2.2	2.6	0.5	2.5	4.0	1.4

of EJ, and almost absent in YJ (0.7%). In the DR2 group, the DRB1*1502 had the highest frequency in IJ and in MJ, 7.7% and 7.2%, respectively. This allele was almost absent in EJ (0.4%). A high prevalence of DRB1*1503 in EJ (10.4%) was found, as opposed to the total absence of this allele in the other Jewish groups. Within the DR4 cluster, the DRB1*0401 allele was very rare while DRB1*0402 was frequent in AJ (8.3%) and in YJ (7.5%) but absent in EJ.

Among the DR13 positive individuals, the DRB1*1301 allele was present at frequencies of 8.9, 7.4% and 5.4% in MJ, LJ and YJ, respectively and DRB1*1302 was more prevalent in IJ (15%) and in EJ (16%). In contrast, most of DR13 positive Israeli Arabs were found to carry the DRB1*1303 allele (7.6%). None of the remaining DRB1 alleles were present at a high frequency in any of the groups studied.

Table 2 summarizes the gene frequencies of the DQA1 alleles. The highest frequency was found for DQA1*05 in all the groups, due to its linkage with all the DR3, DR11, DR12 and DR13 alleles. The high prevalence of DQA1*0201 in all the groups is essentially due to its linkage disequilibrium with DRB1*0701.

Table 2 also presents the gene frequencies of the DQB1 alleles. In descending order, the most common allelic variants were: DQB1* 0301>02>0302>0501, with minor changes in rank within each group. Linkage disequilibrium may also account for the differences in the DQB1 allele distribution among the groups.

HLA class II linkage disequilibria in Israeli Jews. Since family studies were not performed, the associations between the different HLA class II loci are merely putative. Estimated two loci (DRB1-DQB1) and DQA1-DQB1 haplotype frequencies, with their p values, are presented in Table 3. The most common DRB1-DQB1 haplotype was DRB1*0701-DQB1*02. The next most frequent were DRB1*1104-DQB1*0301 and DRB1*03011-DQB1*02. The haplotype DRB1*1104-DQB1*0301 was, however, almost absent in EJ while the DRB1*0701-DQB1*02 was two-to three-fold higher in LJ and YJ than in the other groups.

The dendrogram presented in Fig. 1 summarizes the genetic distances between the different Jewish ethnic groups studied and between Israeli Arabs and two previously analyzed Jewish groups, namely Ashkenazi and Moroccan Jews [4]. These data were compared to those of European and American Caucasians as well as of two Black populations: South African and North American [14], data presented in Table 4. This dendrogram reveals that these populations, with the exception of the Ethiopian Jews, could be clustered into three major groupings:

TABLE 3. Selected haplotype frequency (%) of HLA class II two-loci in various Israeli Jewish ethnic groups and Israeli Arabs.

Haplotype	Ashkenazi Jews (AJ) ($N = 132$)	Moroccan Jews (MJ) ($N = 94$)	Libyan Jews (LJ) ($N = 119$)	Iranian Jews (IJ) ($N = 101$)	Ethiopian Jews (EJ) ($N = 122$)	Yemenite Jews (YJ) ($N = 76$)	Israeli Arabs (IAR) ($N = 109$)
DRB1*-DQB1*							
0102-0501	10.0[a]	4.4	2.1	2.0	10.8[a]	0.7	1.9
1502-0601	2.7	7.2	1.7	7.7	0.4	2.0	5.7[b]
1503-0603	0.0	0.0	0.0	0.0	6.3	0.0	0.0
03011-02	6.6[a]	2.7	5.6	7.7	13.6[a]	12.0	9.6[a]
0402-0302	8.3[a]	2.7	3.0	5.1[b]	0.0	7.5[b]	2.8
0404-0302	1.1	0.0	5.1	1.0	0.0	1.3	0.9
0406-0402	0.0	4.2	0.0	0.0	0.0	0.0	0.0
1101-0301	4.7	5.5	9.3	3.0	2.9	3.4	8.1
1103-0301	0.8	1.1	3.0	0.0	0.4	0.0	0.5
1104-0301	8.4	9.8[a]	10.7[a]	18.2[b]	0.4	8.1[a]	9.6
1104-0603	2.7	1.7	0.0	1.6	0.0	0.9	0.0
1201-0301	3.1	0.5	0.0	2.5	0.0	6.1	0.5
1301-0603	3.1	7.7	7.7[b]	7.4	0.8	5.4[b]	3.3
1302-0604	0.8	1.0	2.6	11.6[b]	5.5	2.0	3.3
1302-06051	2.7	0.5	1.3	3.0	9.5[a]	1.3	0.5
1303-0301	0.0	0.0	5.2	3.5	6.4	2.7	7.6
1305-0301	3.1	1.5	0.8	2.0	0.0	0.7	0.5
1401-0501	2.3	4.9	1.7	2.5	0.0	3.4	3.7
0701-02	11.6[a]	18.8[a]	24.7[a]	8.8[a]	8.2	22.1[a]	12.2[b]
0801-0402	0.0	0.0	0.0	0.0	0.0	0.0	0.9
08041-0301	0.0	0.0	0.0	0.0	5.1	0.0	0.9
1001-0501	2.3	7.2[a]	0.8	3.0	1.7	4.0	4.7
DQA1*-DQB1*							
0101-0501	14.7[a]	13.0[a]	3.0	5.6[a]	13.2[b]	6.1[b]	8.6[a]
0101-05031	2.3	4.8	2.6	2.5	0.0	3.4	4.2
0102-0602	3.0	2.1	0.8	1.0	6.4	2.0	2.3
0102-0603	0.6	1.9	0.0	1.6	6.1	0.0	0.5
0102-0604	0.8	2.2	2.6	11.6[b]	5.5	2.0	3.3
0102-06051	2.7	0.5	1.3	3.0	9.5	1.3	0.9
0103-0601	2.6	6.4[a]	1.7	8.8[b]	0.0	2.7	5.7
0103-0603	5.8	8.7[a]	7.4[a]	2.4	0.8	6.1[c]	3.3
0201-02	11.6[a]	18.8[a]	24.7[a]	7.7	7.4	22.1[a]	12.2[b]
03-0302	13.4[a]	6.0	13.0[b]	7.7[b]	5.5	14.2[a]	10.2[a]
05-02	5.5	1.7	0.2	9.3	14.0[a]	13.7	9.6
05-0301	22.0[a]	22.1[a]	29.6[a]	28.9[a]	17.5[b]	21.4[a]	29.0[a]

[a] $p < 10^{-5}$; [b] $p < 10^{-6}$; [c] $p < 10^{-7}$.

1) All the Jewish ethnic groups, and the Israeli Arabs. In this grouping, the shortest genetic distance was seen between the Libyan and Yemenite Jews. The Ashkenazi and Moroccan Jews were found to be close to the Libyan and Yemenite Jews, as well as to Israeli Arabs. 2) Non-Jewish Caucasians: a clear distinction was found to exist between Jews and non-Jewish Caucasians. 3) The two populations of Blacks: this grouping falls totally apart from both the Jewish and non-Jewish Caucasians.

DISCUSSION

Israelis come from a wide variety of ethnic backgrounds. The genetic makeup of today's Jewish population is the product of the common ancestral gene pool and the introduction from the peoples among whom, over the ages, the Jews lived. During the last two decades, many studies have been conducted on both the ethnic affinities and the genetic relationships between various Jewish groups [10–13].

The HLA class II information obtained in this study was compared to information obtained at the 11th IHWS [14] pertaining to other populations around the world.

Our molecular analysis of the DR1 allelic variants showed that DRB1*0102 was the dominant subtype in most of the Jewish and Arab groups in Israel as opposed to DRB1*0101 which is the predominant allele in non-Jewish Caucasians. A similar pattern occured in DR2, where DRB1*1502 was found to be the most dominant allele among Israelis, whereas DRB1*1501 is more fre-

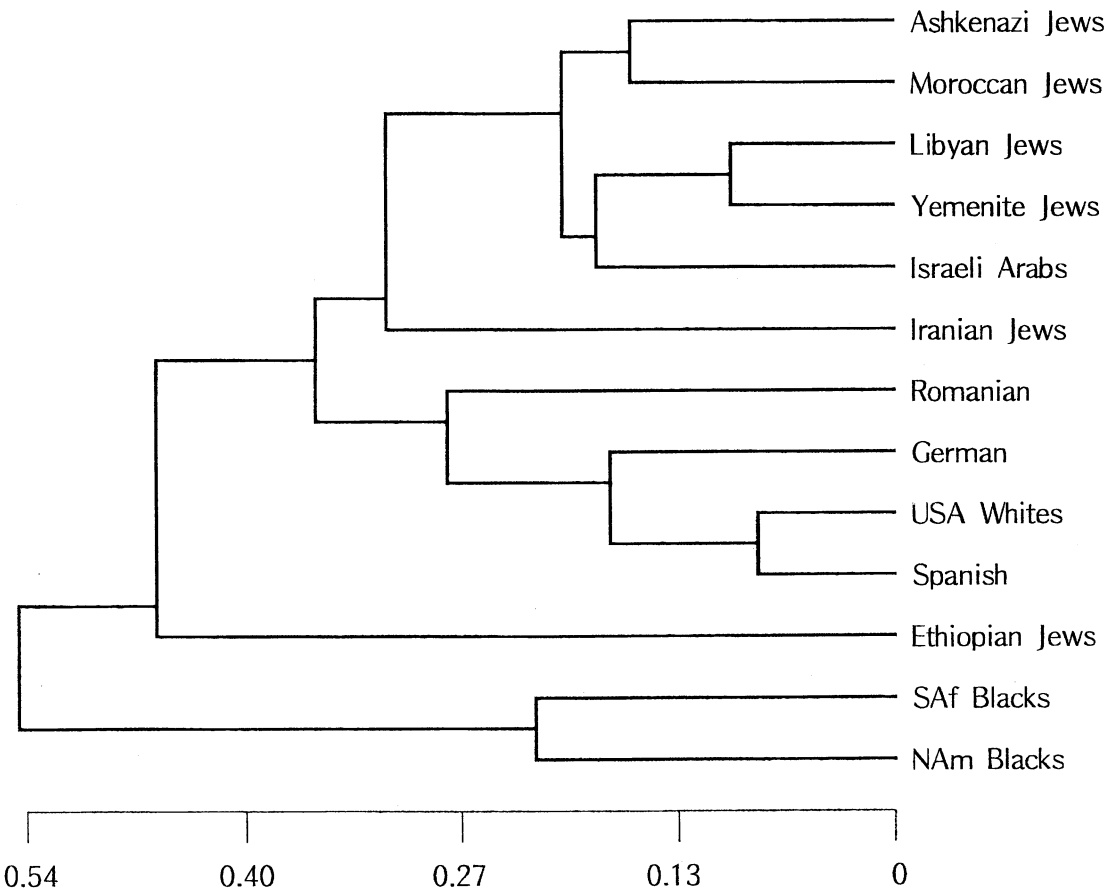

FIGURE 1 A population tree, based on the genetic distances for HLA class II allele distribution of Israeli, non-Jewish Caucasians and Black populations.

quent in non-Jewish Caucasians. DRB1*1503 appeared at a singularly high frequency (10.4%) among the Ethiopian Jews, and should therefore be considered to be a specific HLA marker. This allele is present in North American Blacks [14]. Among the DR3 positive individuals analyzed in the present investigation, the vast majority carried DRB1*0301, whereas the DRB1*0302 allele was almost absent in all of the groups. A similar pattern is found for non-Jewish Caucasians, however, in both South African and North American Blacks, DRB1*0302 is present at the high frequencies of 18.8% and 7.2%, respectively.

With regard to the DR4 cluster, DRB1*0401 has been found to be the predominant allele in most of the non-Jewish sub-populations. This allele was very rare in the Israeli groups studied in this work. The other DRB1*04 alleles were poorly represented in the Jewish and Arab groups, except for DRB1* 0403, which was found to be very frequent in Yemenite Jews (6.1%) and in Israeli Arabs (8.1%). The DRB1*0402 allele, which is in strong linkage disequilibrium with DQB1*0302, is far more frequent in Ashkenazis (8.3%) than in all the other groups studied so far, including non-Jewish populations.

DR11 is a common allele among the Jews, as in Caucasians. When divided into its allelic variants, the predominant allele among the Israeli groups (except for EJ) was found to be DRB1*1104, as opposed to DRB1* 1101 in non-Jews.

HLA-DR13, which is rather widespread in various Jewish groups did not show an equal distribution pattern of its allelic variants in this study. Similar differences were found also for DQA1 and DQB1 profiles (Table 2). The Ashkenazi, Moroccan and Iranian Jews are the only groups known to share DRB1*1305 (2-3.1%), an allele that might have arisen as a consequence of a gene conversion event between DRw13-DQw6 and DRB1*1101 [15]. The presence of such a unique genetic incident in these distinct populations implies that this variant evolved in the ancient Jewish gene pool prior to the dispersion in the Diaspora.

The high incidence of DRB1*0701 was a common feature in all the Jewish populations studied. It was, how-

TABLE 4. Gene frequency (%) of DRB1 locus among various populations.

Allele	Romanian ($N = 73$)	German ($N = 90$)	USA (Whites) ($N = 286$)	Spanish ($N = 154$)	South Af. Blacks ($N = 86$)	North Am. Blacks ($N = 132$)
DRB1*						
0101	7.5	6.7	7.2	6.3	1.7	1.9
0102	1.4	1.1	2.6	6.1	0.0	3.4
0103	0.0	0.0	1.1	2.6	0.0	0.0
1501	6.2	7.8	9.9	8.9	6.4	8.6
1502	4.7	1.1	0.7	1.3	0.0	0.8
1503	0.0	0.0	0.0	0.0	0.0	3.8
1601	12.1	1.1	0.9	2.0	0.0	0.0
1602	1.4	0.6	0.2	0.3	0.0	2.7
0301	11.3	9.4	9.3	6.3	5.5	7.0
0302	0.0	0.6	0.3	0.0	18.8	7.2
0401	4.1	8.1	6.6	5.4	2.9	1.5
0402	2.7	0.6	1.0	2.9	0.0	0.0
0403	1.4	0.6	1.9	1.3	0.0	0.0
0404	1.4	1.7	2.5	2.4	0.6	0.4
0405	0.7	0.6	0.7	2.0	0.6	0.8
0406	0.0	0.6	0.0	0.3	0.0	0.0
0407	0.0	1.1	1.0	0.6	0.0	1.1
0408	0.0	0.0	0.3	1.3	0.0	0.0
1101	7.2	9.2	4.2	1.0	20.5	8.2
1102	0.7	1.1	1.1	1.3	2.3	3.8
1103	0.0	1.2	1.4	0.0	0.6	0.8
1104	6.2	3.4	0.5	4.0	0.6	0.4
1201	2.1	2.2	1.8	0.0	4.7	3.9
1202	0.7	0.0	0.0	0.0	0.0	1.1
1301	4.4	4.5	4.8	4.2	3.5	4.2
1302	1.4	3.4	4.4	0.6	9.1	8.1
1303	1.4	1.1	1.4	0.6	0.6	3.0
1304	0.0	0.0	0.0	0.0	0.0	0.4
1305	0.0	0.0	0.2	0.0	0.0	0.0
1401	2.7	1.7	2.3	3.0	1.2	1.5
1402	0.0	0.6	0.9	0.0	0.6	0.0
1403	0.0	0.0	0.0	0.0	0.6	0.0
1404	0.0	0.0	0.2	0.0	0.0	0.0
1405	1.5	0.0	0.0	0.0	0.0	0.0
1701	8.2	12.3	14.6	18.9	7.6	9.8
0801	0.7	4.0	0.9	1.3	0.0	1.1
0802	0.0	0.6	0.5	0.0	1.2	0.0
0803	0.0	1.7	0.2	0.0	1.2	0.0
0804	0.0	0.0	0.2	0.6	0.6	7.0
0901	0.7	0.6	1.2	1.6	1.7	2.0
1001	2.1	0.6	2.7	1.6	2.3	1.9
Other	2.1	0.0	2.6	2.6	1.2	0.8
Blank	3.4	10.4	7.6	8.4	3.6	2.8

ever, most frequent in Libyan Jews and in Yemenite Jews, with an incidence of 26.7% and 22.1% respectively.

DR8 and DR9 alleles are present at very low frequencies, if at all, as in non-Jewish populations, with the exception of DRB1*0801, which was relatively frequent in Ethiopian Jews (5.1%) and present in North American Blacks.

The distribution of the various DQ allelles in the groups studied matches the distinct DRB1 alleles with which they are in strong linkage disequilibrium.

Comparison between HLA class II alleles between the different Jewish groups and other non-Jewish populations. Jewish HLA DRB1 frequencies show the following differences from other populations:

1. *Caucasians:* DRB1*1601, almost non-existent in Jews, appears at a high frequency (12.1%) in Rumanian Caucasians (Table 4).
   DRB1*1104, is very slightly represented in American Caucasians (0.5%), but is quite frequent in the

Jewish groups (between 9–21%), with the exception of Ethiopian Jews (0.4%).

2. *Blacks:* Comparisons were made with both South African and North American Blacks, as reported in the 11th IHWS [14]. The common characteristics between Blacks and Ethiopian Jews in DRB1 allele are: a) a high frequency of DRB1*1503 (10.4% in Ethiopian Jews vs. 3.8% in North American Blacks). This allele is non-existent in all other Jewish groups or in Caucasians; b) the absence of DRB1*0402 in Ethiopian Jews as well as in Blacks, c) a low frequency of DRB1*1104 in these groups; d) a high frequency of DRB1*0804 in Ethiopian Jews (5.1%) and in North American Blacks (7.8%).
3. Most of the Moroccan Jews originated in Spain some 500 years ago after the expulsion of Jews in 1492 [16]. We therefore compared the allele frequencies of Moroccan Jews to that of Spanish non-Jews (Table 4) (IHWS, 1992) with the following results: a) a lower frequency in Jews of DRB1*0101, DRB1*1501, DRB1*0401, b) a higher frequency in Jews of DRB1*1101 and DRB1*1104, DRB1*1301 and DRB1*1302 and DRB1*1001.

In conclusion, our data show that the Jewish groups differ in their HLA class II genetic makeup from non-Jewish Caucasians and Blacks with the exception of the Ethiopian Jews who are related to neither other Jews, Israeli Arabs, or non-Jewish Caucasians or Blacks.

This study may contribute to future epidemiological surveys of HLA and infectious diseases prevalent among non-Ashkenazi Jews and in particular Ethiopian Jews. The results of this study have direct implications on the search for unrelated hematopoietic stem cell donors for patients of Jewish and Arabic origins as well as for the study of the role of HLA genes in the predisposition to autoimmune diseases.

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