

# HLA class II Genetic Diversity in Arabs and Jews of Iran

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## ABSTRACT

**Background:** Anthropological studies based on highly polymorphic HLA genes provide useful information for bone marrow donor registry, forensic medicine, disease association studies, as well as designing peptide vaccines against tumors, and infectious or autoimmune diseases. **Objective:** This study was designed to investigate the genetic relationship of Iranian Arabs and Jews using HLA-class II genetic diversity **Methods:** HLA-DRB1, DQA1, and DQB1 allele frequencies and haplotypes were determined in 134 Iranian Arabs from two different communities and 91 Iranian Jews using PCR/RFLP and PCR/SSP methods. **Results:** Neighbor-joining analyses showed a closer genetic relationship between Iranian Arabs and Iranian Jews than between either Iranian Arabs and Middle Eastern Arabs or Iranian Jews and other Jews. The results of AMOVA test also revealed no significant difference between these populations and other Iranians. **Conclusion:** It seems that, Iranian Arabs are originally from the Iranian gene pool and speak Arabic due to their encounter with Arabs. Iranian gene flow to immigrant Jews followed by their expansion in this country may also explain the close genetic relationship among different Iranian ethnic groups.

**Keywords:** HLA Polymorphism, Arabs, Jews, Iran

## INTRODUCTION

Despite being under strong selective pressure, highly polymorphic HLA genes are still used in anthropological studies because certain alleles are frequent only in specific populations and HLA genes are inherited as ancestral haplotypes that vary considerably among races (1). Extensive studies of global populations have shown that common HLA haplotypes are shared by populations in different geographical regions. Consequently, HLA data can be used to elucidate the genetic history of human populations (2).

In a clinical context, knowledge of the HLA allele distributions in various populations is critical for establishing bone marrow donor registries (3), forensic medicine (4), studies of HLA associated diseases (5), and peptide vaccine designation against tumors (6), infectious agents and autoimmune diseases (7).

The people of Iran, Europe, and India are known as Indo-Europeans whose ancestors lived probably in central and southern Russia. Some time around 2000 BC, these people migrated towards south and split into several branches including proto-Iranians who seem to be the direct ancestors of modern Iranians. However, different people with established civilizations inhabited this country long before Indo-European infiltration into this region (8).

Historically, Iranians have encountered different foreigners such as Macedonians (334 to 331 BC), Arabs (7th century), Turks (10th century), and Mongols (13th to 15th centuries) (8). Also, as a crossroad between Asia and Europe, Iran has been a host for various populations along the Silk Road (9). Therefore, the population of this country might be genetically admixed due to encountering other populations and immigrants from neighboring countries (10). This study was designed to investigate the genetic relationship between Iranian-Arabs and Iranian-Jews to find their affinity to the major Iranian sub-populations as well as to other Arabs and Jews.

## MATERIALS AND METHODS

**Characteristics of the Populations.** Iran is an ethno-linguistically diverse country, consisting of different groups including Pars, Turk, Kurd, Lur, Arab, and Baloch. Most of the Iranians are Muslims but Zoroastrians, Jews, and Christians are also living in this country (10). There are some different Arab communities in Iran who are mostly living in the south-western part of the country especially in Khuzestan province. An isolated Arab community is also living in Famoor near Parishan Lake in Fars. Jews are distributed in different parts of the country but most of them are localized in Fars province.

**Samples.** Blood samples were collected with informed consent from unrelated healthy individuals who belonged to two different Arab communities of Iran including 50 Khuzestani-Arabs and 84 Famoori-Arabs as well as 91 Iranian-Jews inhabiting in Shiraz, the capital of Fars province. All participants were third generation natives from selected ethnic groups. DNA was extracted from each sample using a salting out method (11).

**HLA Genotyping.** HLA-DQA1, DQB1 and DRB1 typing were performed by polymerase chain reaction-restriction fragment length polymorphism (PCR/RFLP) method (12). Samples with DRB1 heterozygote combinations that were not completely distin-

guishable by the above method were typed by PCR using sequence specific primers (PCR/SSP) (Biotest AG, Dreieich, Germany).

**Data Analyses.** Allele and haplotype frequencies and analysis of molecular variance (AMOVA) were examined by Arlequin 2.000 (<http://anthro.unige.ch/arlequin>). Significant variation of allele frequencies among the studied ethnic groups was calculated by nonparametric test of Chi-square using SPSS version 11.5. Neighbor-joining tree was conducted using MEGA2 (<http://www.megasoftware.net>) based on Nei's genetic distances (13) which were calculated by DISPAN (<http://www.bio.psu.edu/People/faculty/Nei/Laboratory/Programs.html>).

## RESULTS

In this study, the results of HLA-DRB1, DQA1 and DQB1 allele frequencies and haplotypes of 134 Iranian-Arabs from two different communities and 91 Iranian-Jews were presented. The results were also compared with our previous reports on Baloch (14), Pars and Zoroastrian subpopulations of Iran (15), as well as Middle Eastern Arabs and Jewish populations (Table 1). Allele frequencies at the three HLA class II loci were presented in Table 2. In this study, DRB1\*0404, \*0406, \*0410, \*0411, \*0802, \*0803, \*1304, \*1402, \*1403, \*1404, DQA1\*0601 and DQB1\*0302, and \*0401 were not found in any of the studied populations. As shown in Table 2, in spite of DQA1\*0501 which was the most frequent allele in the three studied populations, the distribution of the predominant alleles in DRB1 and DQB1 loci was not the same as DRB1\*0701 and DQB1\*0201 in Khuzestani-Arabs, DRB1\*0301 and DQB1\*0602/3 in Famoori-Arabs, and DRB1\*1103/4 and DQB1\*0301 in Jews were the most common alleles. The frequency of DQA1\*0301 and DQB1\*0201 and \*0303 alleles in Khuzestani-Arabs; DRB1\*0301, \*1301, DQA1\*0401, DQB1\*0502 and \*0602/3 alleles in Famoori-Arabs; and DRB1\*1103/4 and DQB1\*0301 alleles in Jews were significantly higher than the corresponding alleles in the other two studied populations.

**Table 1. List of the populations used for comparison in this study**

| Population     | Reference |
|----------------|-----------|
| Ashkenazi-Jews | 16        |
| Bahraini-Arabs | 17        |
| Balochis       | 14        |
| Ethiopian-Jews | 16        |
| Israeli-Arabs  | 16        |
| Jordanians     | 18        |
| Lebanese       | 17        |
| Libyan-Jews    | 16        |
| Moroccan-Jews  | 16        |
| Parsees        | 15        |
| Saudi-Arabs    | 19        |
| Yemenite-Jews  | 16        |
| Zoroastrians   | 15        |

**Table 2. Distribution of HLA-DRB1, DQA1, and DQB1 allele frequencies in Arabs and Jews of Iran**

|        | Khuzestani<br>Arabs | Famoori<br>Arabs | Jews          |        | Khuzestani<br>Arabs | Famoori<br>Arabs | Jews          |
|--------|---------------------|------------------|---------------|--------|---------------------|------------------|---------------|
| DRB1   | 2n=100              | 2n=168           | 2n=182        | DQA1   | 2n=100              | 2n=168           | 2n=182        |
| 0101   | 0.010               | 0.006            | 0.011         | 0101/2 | 0.220               | 0.256            | 0.198         |
| 0102   | 0.020               | 0.024            | 0.016         | 0103   | 0.100               | 0.220            | 0.115         |
| 0301   | 0.110               | <b>0.195*</b>    | 0.060         | 0201   | 0.210               | —                | 0.159         |
| 0302   | 0.030               | 0.065            | —             | 0301   | 0.180*              | 0.024            | 0.049         |
| 0401   | 0.010               | —                | —             | 0401   | 0.010               | 0.065*           | —             |
| 0402   | 0.050               | 0.006            | 0.022         | 0501   | <b>0.280</b>        | <b>0.435</b>     | <b>0.479</b>  |
| 0403   | 0.040               | 0.012            | 0.027         | Total  | 1.000               | 1.000            | 1.000         |
| 0405   | —                   | 0.006            | —             |        |                     |                  |               |
| 0409   | 0.030               | —                | 0.005         |        |                     |                  |               |
| 0701   | <b>0.210</b>        | —                | 0.156         |        |                     |                  |               |
| 0801   | —                   | 0.012            | —             |        |                     |                  |               |
| 0901   | 0.040               | —                | —             |        |                     |                  |               |
| 1001   | 0.040               | —                | 0.005         | DQB1   | 2n=100              | 2n=168           | 2n=182        |
| 1101   | 0.050               | 0.030            | 0.099         | 0201   | <b>0.370*</b>       | 0.208            | 0.192         |
| 1102   | —                   | 0.018            | 0.005         | 0301   | 0.150               | 0.196            | <b>0.442*</b> |
| 1103/4 | 0.110               | 0.149            | <b>0.360*</b> | 0303   | 0.160*              | 0.048            | 0.049         |
| 1201   | —                   | 0.048            | —             | 0402   | 0.010               | 0.054            | —             |
| 1202   | —                   | 0.006            | —             | 0501   | 0.050               | 0.018            | 0.027         |
| 1301   | 0.040               | 0.166*           | 0.033         | 0502   | 0.070               | 0.119*           | 0.016         |
| 1302   | 0.020               | 0.018            | 0.060         | 0503   | 0.030               | 0.054            | 0.066         |
| 1303   | —                   | —                | 0.022         | 0601   | 0.060               | 0.030            | 0.071         |
| 1305   | —                   | 0.006            | 0.005         | 0602/3 | 0.080               | <b>0.273*</b>    | 0.066         |
| 1401   | 0.030               | 0.030            | 0.060         | 0604   | 0.020               | —                | 0.071         |
| 1405   | —                   | 0.012            | 0.005         | Total  | 1.000               | 1.000            | 1.000         |
| 1501   | 0.040               | 0.060            | 0.011         |        |                     |                  |               |
| 1502   | 0.050               | 0.006            | 0.022         |        |                     |                  |               |
| 1601   | 0.040               | 0.012            | 0.016         |        |                     |                  |               |
| 1602   | 0.030               | 0.089            | —             |        |                     |                  |               |
| 1605   | —                   | 0.024            | —             |        |                     |                  |               |
| Total  | 1.000               | 1.000            | 1.000         |        |                     |                  |               |

The most frequent alleles are shown in bold

\*significantly increased frequencies

DRB1\*0701-DQA1\*0201-DQB1\*0201 with a frequency of 19% was the most common haplotype in Khuzestani-Arabs but it was not observed as one of the public haplotypes in Famoori-Arabs while it was the second frequent haplotype in Jews with a frequency of 14.8%. DRB1\*0301-DQA1\*0501-DQB1\*0201 (18.5%) and DRB1\*1103/4-DQA1\*0501-DQB1\*0301 (29.7%) were the most common haplotypes in Famoori-Arabs and Jews, respectively (Table 3).

AMOVA was performed to estimate the distribution of genetic diversity within and among Arabs and Jews of Iran when considered as one group and compared with previously studied Iranian subpopulations. The results of AMOVA revealed that the main variation components (95.54%) were contributed by the within-population level and the genetic differentiation ( $F_{ST}$ ) was about 0.045 (Table 4).

**Table 3. Haplotype frequencies (HF) of the most frequent DRB1-DQA1-DQB1 haplotypes in Arabs and Jews of Iran**

| Khuzestani-Arabs   |       | Famoori-Arabs      |       | Jews             |       |
|--------------------|-------|--------------------|-------|------------------|-------|
| DRB1-DQA1-DQB1     | HF    | DRB1-DQA1-DQB1     | HF    | DRB1-DQA1-DQB1   | HF    |
| 0701-0201-0201     | 0.190 | 0301-0501-0201     | 0.185 | 1103/4-0501-0301 | 0.297 |
| 0301-0501-0201     | 0.110 | 1301-0103-0602/3   | 0.167 | 0701-0201-0201   | 0.148 |
| 1103/4-0501-0301   | 0.100 | 1103/4-0501-0301   | 0.131 | 1101-0501-0301   | 0.093 |
| 1502-0103-0601     | 0.050 | 1602-0101/2-0502   | 0.083 | 1401-0101/2-0503 | 0.055 |
| 0402-0301-0303     | 0.050 | 1501-0101/2-0602/3 | 0.054 | 1103/4-0103-0601 | 0.049 |
| 0403-0301-0303     | 0.040 | 1201-0501-0301     | 0.048 | 1302-0101/2-0604 | 0.049 |
| 1601-0101/2-0502   | 0.040 | 0302-0401-0402     | 0.048 | 0301-0501-0201   | 0.038 |
| 1301-0103-0602/3   | 0.040 | 1401-0101/2-0503   | 0.030 | 1301-0103-0602/3 | 0.033 |
| 1101-0501-0301     | 0.040 |                    |       |                  |       |
| 1001-0101/2-0501   | 0.040 |                    |       |                  |       |
| 0901-0301-0201     | 0.030 |                    |       |                  |       |
| 1602-0101/2-0502   | 0.030 |                    |       |                  |       |
| 1501-0101/2-0602/3 | 0.030 |                    |       |                  |       |

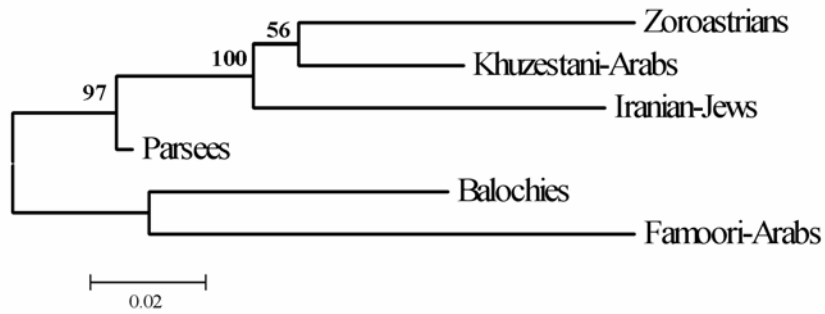
HF higher than 0.025 are listed

**Table 4. Summary of AMOVA analysis based on HLA-DRB1, DQA1, and DQB1 allele frequencies when Arabs and Jews of Iran are considered as one group and compared to Pars, Zoroastrian, and Baloch subpopulations of Iran**

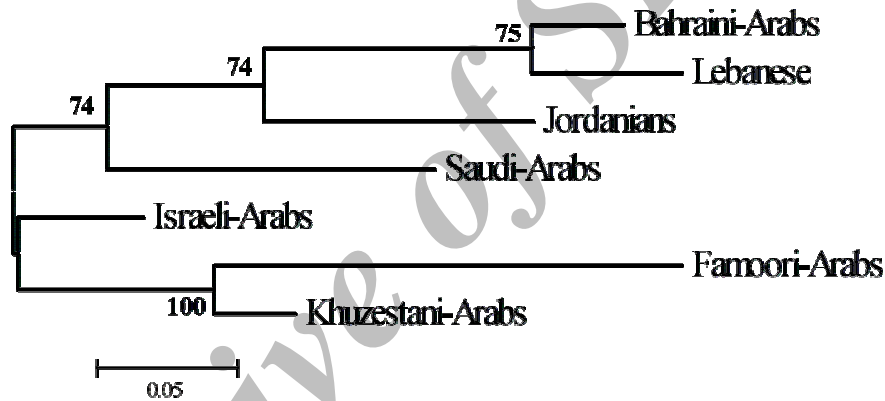
| Source of Variation             | d.f     | Sum of Squares | Variance Components | Percentage of variation |
|---------------------------------|---------|----------------|---------------------|-------------------------|
| Among groups                    | 1       | 11.359         | 0.00328             | 0.26                    |
| Among populations within groups | 4       | 37.084         | 0.05354             | 4.20                    |
| Within populations              | 918     | 1118.041       | 1.21791             | 95.54                   |
| Total                           | 923     | 1166.484       | 1.27473             |                         |
| <b>Fixation Indices</b>         |         |                |                     |                         |
| FST                             | 0.04458 |                |                     |                         |
| FSC                             | 0.04211 |                |                     |                         |
| FCT                             | 0.00258 |                |                     |                         |

FCT =  $\sigma^2a / \sigma^2T$ , FSC =  $\sigma^2b / \sigma^2T$ , FST =  $\sigma^2a + \sigma^2b / \sigma^2T$ 

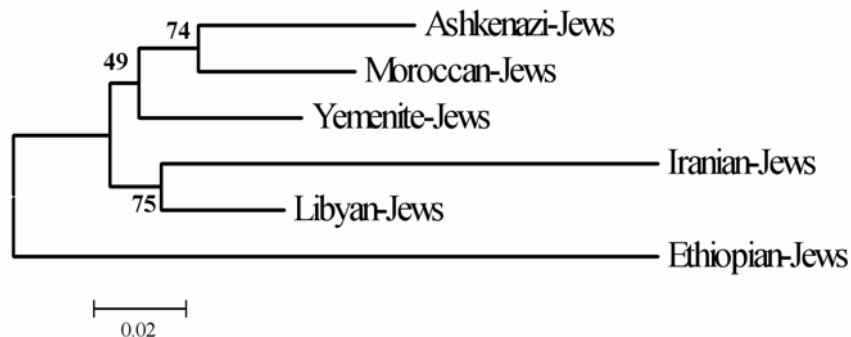
Neighbor-joining trees based on Nei's genetic distances according to the HLA class II allele frequencies are illustrated in figures 1-4. Figure 1 illustrates the genetic relationship between Arabs and Jews of Iran and other Iranian subpopulations. As shown, different communities of Iranian-Arabs are not strongly related to each other. Comparison of Iranian-Arabs with Middle Eastern Arabs shows that Khuzestani-Arabs and Famoori-Arabs are located in the same cluster and are well separated from other Arabs (Figure 2). Figure 3 illustrates a closer genetic relationship among Iranian-Jews and non-Ashkenazi Jews. The genetic relationship of Iranian-Jews to Iranian-Arabs which are well separated from other Jews and Arabs is shown in figure 4.



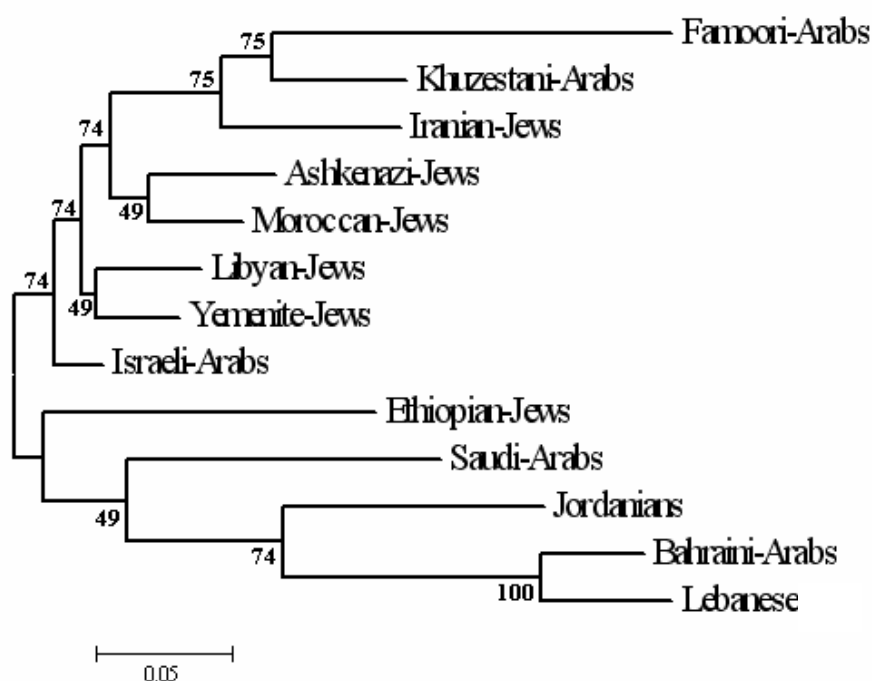
**Figure 1.** Neighbor-joining tree linking six Iranian subpopulations using Nei's genetic distances based on HLA-DRB1, DQA1, and DQB1 allele frequencies. Numbers by internal branches represent bootstrap values (%) based on 1000 replications.



**Figure 2.** Neighbor-Joining tree showing the genetic relationship between Iranian Arab communities and Middle Eastern Arabs using Nei's genetic distances based on HLA-DRB1 and DQA1 allele frequencies. Numbers by internal branches represent bootstrap values (%) based on 1000 replications (the sources of data from other populations were from references in Table 1).



**Figure 3.** Neighbor-Joining tree showing the genetic relationship among Jews using Nei's genetic distances based on HLA-DRB1 and DQB1 allele frequencies. Numbers by internal branches represent bootstrap values (%) based on 1000 replications (the sources of data from other populations were from references in Table 1).



**Figure 4.** Neighbor-Joining tree showing the genetic relationship between Jews and Arabs using Nei's genetic distances based on HLA-DRB1 and DQB1 allele frequencies. Numbers by internal branches represent bootstrap values (%) based on 1000 replications.

## DISCUSSION

In this study, the genetic relationship between Iranian-Arabs and Iranian-Jews was investigated according to HLA class II allele and haplotype frequencies to find their genetic relationship to the major Iranian subpopulations as well as to other Arabs and Jews.

Comparison of Iranian-Arabs to Middle Eastern Arabs (Figure 2) suggests that Iranian-Arabs might be genetically from a different origin and those Arabs who came into Iran in the 7th century AD did not substantially contribute to the pre-existing genetic pool of this country however they had strong cultural, religious, and linguistic effects on some Iranian subpopulations. Moreover, genetic affinity of Iranian-Arabs to other Iranian ethnic groups might be the result of their common ancestry (Figure 1).

It seems that, Arabs of Khuzestan are not a national minority immigrant group but rather they are a native ethnic group which has roots in the history and geography of Iran. Historically, Khuzestan is one of the most ancient provinces of Iran referred to as ex-Elam where Indo-European tribes first settled, assimilating the native Elamite population, and thus laying the foundation for the future empires of Persia and Media (20, [http://en.wikipedia.org/wiki/Persian\\_Empire](http://en.wikipedia.org/wiki/Persian_Empire)).

The origin of Famoori-Arabs who have been living nearby Parishan Lake in Fars province is not clear but they are culturally more similar to the people of the Arabian Peninsula than Khuzestani-Arabs. As shown in figure 1, Famoori-Arabs are located in the vicinity of the Baloch subpopulation, whom some scholars believe to have originated from Semites of Syria (21). Therefore, Famoori-Arabs might have originated from the Semites and following the genetic drift and successive genetic admixture with the Iranian gene pool show more affinity to Iranians.

Iranian Jews are originally those who were deported from Jerusalem and forced to stay in Media and Susa. Around 680 BC, the next wave of Jews arrived to escape persecution from the Assyrians. Following the conquest of Babylon by Cyrus the Great, some of the Jews chose to immigrate to Persia (22). Genetically, Iranian-Jews show a closer relation to non-Ashkenazi than Ashkenazi Jews who are both similar to one another because of a certain level of shared ancestry (Figure 3).

Observed genetic divergence among Jewish communities can be explained by the genetic drift and/or admixture due to their successive exiles. On the other hand, genetic affinity of Iranian-Jews to other Iranian ethnic groups may be explained by gene flow from Iranian gene pool to Jews during the expansion followed by their migration to Iran. In the past, several groups of Jews were converted to Islam; some voluntarily, some due to social pressure, and some in hopes of improving prospects for themselves and their families (23). In Persia as well, during the Safavid dynasty of the 16th and 17th centuries following certain limitations, some of the Jews were converted to Islam (23). Later, some married other Iranians and in this way their genes might have been diluted in Iranian gene pool.

Figure 4 illustrates a close relation among the Arabs and Jews of Iran. The results of AMOVA also strongly suggest that genetic diversity among two Iranian-Arab communities and Iranian-Jews was mainly confined to intra-population variations. In this analysis,  $F_{ST}$  averaged 0.045 which indicates little subdivision among the specified Iranian subpopulations (Table 4).

More interestingly, the affinity of Iranian-Jews to Iranian-Arabs is more than their genetic relationship to other Arabs and Jews (Figure 4). If it could be considered that Iranian-Arabs belonged to the Iranian gene pool who just learned Arabic language, Iranian gene flow to immigrant Jews might explain this relationship.

Although the results of this study based on HLA class II genotyping showed some genetic relationships between Arabs and Jews of Iran, complementary data from HLA class I, mitochondrial DNA, Y chromosome and other nuclear markers will shed more light on the genetic history of Iranian subpopulations.

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