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# Human leukocyte antigen variation among Iranian renal transplant recipients

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**ABSTRACT**

*Background:* HLA typing analysis is important in renal transplant patients.
*Objectives:* We made a plan to determine the most frequent HLA antigens in Iranian kidney transplant patients.
*Patients and Methods:* In a retrospective cross sectional study, HLA patterns were defined in 512 kidney transplant recipients (67% male and 33% female) from different transplant centers of Tehran, Iran between 2008 and 2011 by microcytotoxicity assay.
*Results:* The studies samples were of different ethnic groups of the Iranian kidney transplants. Considerable variations were observed in each HLA sub class. A2, A1, A3, A24 and A26 were the most frequent HLA-A antigens. Among HLA-B, the predominant antigens were B35; B13, B15, B13 and B18. The most frequent HLA-DR antigens were DR 4, DR11, DR1, DR3 and DR15. DQ1 showed the highest frequency and followed by DQ3 and DQ2.
*Conclusions:* These results showed considerable heterogeneity in both HLA class I and class II antigens, which reflects recent admixture of this group with neighboring Middle East populations.

Original Article

*Implication for health policy/practice/research/medical education:*
In a retrospective cross sectional study, HLA typing was defined in 512 kidney transplant recipients, 67% of them were male, and 33% were female, from different transplant center of Tehran, Iran between 2008 and 2011. The results suggest that both class I and class II polymorphisms of the study subjects depict considerable heterogeneity, which reflects recent admixture of this group with neighboring middle east populations.

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## 1. Background

The human leukocyte antigen (HLA) system is being widely used in genetic studies because it is more polymorphic than the rest of the non-DNA markers together. HLA is the most informative genetic system known to date (1).Several researchers have focused on HLA as a potential risk allele in the pathogenesis of some diseases (2-4). On the other hand, HLA polymorphism is kind of epidemiological risk factor for some diseases. In addition, it is clear that the HLA complex will have to be increas-

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ingly considered in relation to pharmacological responses (5). The major barrier to acceptance of renal transplants from living-related donor can be the mismatch of antigens of the HLA system. Graft survival is superior in sibling pairs having both the same serologically defined HLA antigens and a nonreactive in vitro mixed lymphocyte proliferative response when compared to randomly match deceased donors treated with the same immunosuppressive drugs (6). Polymorphism in the HLA system is used as a tool for anthropological studies, as genetic distances and correspondence analysis demonstrated that the allele and haplotype distribution of class I and class II loci are racially and geographically restricted (7, 8).This prompted the use of HLA class I and class II phenotype and haplotypes in different ethnic groups for the analysis of the origin, migration and the degree of admixture of populations (9). HLA gene and haplotype frequencies have been described in different racial groups (10).

Shankarkumar and Ghosh reported a scenario can be envisaged where polymorphisms associated with transplant outcome are tested prior to transplantation at the same time as HLA typing (11) and also a few studies have also emerged from Iran, which report HLA antigen frequencies (12). For example, aghdaei reported that HLA polymorphisms are necessary to define polymorphism as a valuable clinical marker and sugesst furthermore studies are required (13).

## 2. Objectives

HLA polymorphism studies, especially in renal transplantation, seem to be very important and we therefore made a plan to determine the most frequent polymorphism in Iranian kidney transplant patients.

## 3. Patients and Methods

### *3.1. Patients*

In a retrospective cross sectional study, HLA typing in 512 kidney transplant recipients from different transplant center of Tehran, Iran between 2008 and 2011 were analyzed. All measurements were performed in a single laboratory. Ethical approval of research was confirmed by Local Ethic Committee of University.

### *3.2. HLA typing*

HLA typing was conducted by using the standard microlymphocytotoxicity test using commercially available reagents from One Lambda Inc. (CA, USA). In brief, whole blood sample (10 mL) was collected in acid citrate dextrose (ACD) tubes and T and B lymphocytes were separated by T- and B-immunomagnetic beads (Dynal, Oslo, Norway/One Lambda Inc., CA, USA) and incubated with HLA-specific class I and class II antisera, respectively. This was followed by incubation with rabbit complement, and then ethidium bromide/acridine orange stain was added. The reactions were scored using a fluorescent microscope that estimates the percentage of cell death according to the American Society of Histocompatiblity and Immunogenetics (ASHI) Standard Readings.

### *3.3. Statistical Analysis*

The SPSS version 17.0 for Windows was used in all the analysis. Quantitative variables were expressed as mean ± SD, while qualitative variables were shown by number and percentage. A p value less than 0.05 was regarded as a significant level and 95% confidence interval was also considered to be a reliable estimate.

## 4. Results

### *4.1. Demographic status*

The study samples were of different ethnic

groups of the Iranian kidney transplants. Sixty-seven percent of them were male, 33% were female, 17% were transplanted from deceased donors and 83% received a kidney from a living kidney donor, majority of them were living unrelated donors (Table 1).

**Table 1:** Baseline Characteristics of patients.

| Variable | |
|---|---|
| Number of patients, n | 512 |
| Age of recipients, yr. | 39±17 |
| Sex of Donor (male/female), % | 67/33 |
| Donor source (DD/LD), % | 17/83 |

### *4.2. HLA -A, -B, -DR and -DQ serological tissue typing results*

Considerable polymorphism was observed at each locus; at the A locus, 15 different antigens out of 27 known antigens were observed. A2, A1, A3, A24 and A26 were the most frequent antigens (Table 2).

**Table 2:** Frequencies of class I antigens (A loci) of the study subjects (n = 512).

| HLA – A type | Frequency | Percent |
|---|---|---|
| A 1 | 99 | 18.3 |
| A 2 | 138 | 25.6 |
| A 3 | 80 | 14.8 |
| A 11 | 65 | 12.0 |
| A 23 | 8 | 1.5 |
| A 24 | 62 | 11.5 |
| A 26 | 16 | 3.0 |
| A 29 | 9 | 1.7 |
| A 30 | 12 | 2.2 |
| A 32 | 10 | 1.9 |
| A 68 | 5 | 0.9 |
| Other | 8 | 1.5 |

At the HLA-B locus, the predominant antigens observed in Iranian population were B35, B13, B15, B13 and B18 (Table 3).

**Table 3:** Frequencies of class I antigens (B loci) of the study subjects (n = 512).

| HLA – B type | Frequency | Percent |
|---|---|---|
| B 7 | 24 | 4.4 |
| B 8 | 36 | 6.7 |
| B 13 | 49 | 9.1 |
| B 14 | 25 | 4.6 |
| B 15 | 38 | 7.0 |
| B 18 | 35 | 6.5 |
| B 27 | 15 | 2.8 |
| B 35 | 129 | 23.9 |
| B 37 | 7 | 1.3 |
| B 38 | 27 | 5.0 |
| B 40 | 9 | 1.7 |
| B 41 | 20 | 3.7 |
| B 44 | 16 | 3.0 |
| B 49 | 11 | 2.0 |
| B 50 | 13 | 2.4 |
| B 51 | 30 | 5.6 |
| B 52 | 11 | 2.0 |
| B 55 | 8 | 1.5 |
| Other | 9 | 1.7 |

As shown in table 4, all the HLA-DR known antigens have been detected in the Iranian population and were DR 4, DR11, DR1, DR3 and DR15 (Table 4).

**Table 4:** Frequencies of class II antigens (DR loci) of the study subjects (n = 443).

| HLA – DR type | Frequency | Percent |
|---|---|---|
| DR 1 | 50 | 9.3 |
| DR 3 | 72 | 13.3 |
| DR 4 | 82 | 15.2 |
| DR 7 | 59 | 10.9 |
| DR 8 | 6 | 1.1 |
| DR 9 | 6 | 1.1 |
| DR 10 | 8 | 1.5 |
| DR 11 | 81 | 15.0 |
| DR 12 | 5 | 0.9 |
| DR 13 | 36 | 6.7 |
| DR 14 | 6 | 1.1 |
| DR 15 | 29 | 5.4 |
| DR 16 | 3 | 0.6 |

Concerning HLA-DQ polymorphisms, DQ1 showed the highest, and following were DQ3 and DQ2 (Table 5). In the DQ locus, DQ1, DQ3 and DQ2 were the most frequent specificities (Table 5).

**Table 5:** Frequencies of class II antigens (DQ loci) of the study subjects (n = 443).

| HLA – DQ type | Frequency | Percent |
|---|---|---|
| DQ 1 | 50 | 9.3 |
| DQ 3 | 72 | 13.3 |
| DQ 4 | 82 | 15.2 |
| DQ 7 | 59 | 10.9 |

## 5. Discussion

A few studies in the histocompatibility complex of Iranian had been done previously (14-16). The present study provides data on the incidence, inheritance, and haplotype association of WHO-recognized HLA-A, -B, -DR and -DQ locus antigens in this population. In contrast to our expectations, a wide variety of HLA antigens were found, with most of the antigens occurring at low frequency and most individuals were heterozygous. It is unclear whether there has been some selective advantage of major histocompatibility complex heterozygosis in the population, or whether the heterozygosis reflects recent tribal admixture. In this study, we observed high frequency of HLA-A2, A30, A3, A24, A1 and A68, respectively. There were very few HLA studies in Middle East populations, A2, A30 and A1 were high frequency in Jordanian population (1, 7), which was relatively the same finding of our study. Similarly, A2, A24, and A30 were found in high frequency among Tunisians and A2 among those in UAE and geographically related Middle East, Iranians and Asians, all living in the UAE (17). There are clear reductions in the normal frequencies of A36, A43, A66 and A69 antigens in the A locus among the study subjects compared to other black populations in Jordan and Pakistan near Iran.

Results obtained in class II antigen typing suggested that the most prevalent DR antigens in our study were DR 3 and DR 4 and DR 11, which were also the reported in all healthy population in Iran (18). Most of the serologically well-defined specificities were present in this population. The linkage disequilibria seen in other populations (19) were also found here but with a few exceptions. DR1 showed a significant decrease in Iranian subjects compared to the other ethnic groups (14, 18).

In this study, the most common DR2 split was DR11, which was also reported in Turkey (20), Lebanese (21), Jordan (7). DR3, which is present in our study subjects with second place, was observed in Saudi (22) and in Kuwait (23) .DR17 was the most common DR3 subgroup (88%), a subgroup most often seen in Caucasians, while DR18 subgroup was observed in South African Blacks (7), which was similar to our finding. DR4 was usually observed in association with DQ03, DR53 and DQ04, DR53 (24).

## 6. Conclusions

These results suggest that both class I and class II polymorphisms of the study subjects depict considerable heterogeneity, which reflects recent admixture of this group with neighboring middle east populations.

## Authors' contributions

BE and ZR designed and performed the research. MT and ZR analyzed the data and wrote some parts of paper. BE provided extensive intellectual contribution and reviewed the manuscript. MT and ZR reviewed the draft too. BE prepared the manuscript.

## Conflict of interest

The author declared no competing interests.

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