# Human Leukocyte Antigen Class I and II Variants in Yemeni Patients with Chronic Renal Failure

Mogahid Yahi'a Nassar[1,2], Hassan Abdulwahab Al-Shamahy[3,*], Abdullah Saleh Al-Samawi[4], Nagieb Waza'a Abu Asba[5], Ibrahiem Husain El-Nono[6], Haitham Abdulwahab Masood[7]

[1]Department of Clinical Pathology, Faculty of Medicine and Health Sciences, University of Science and Technology, [2]Laboratory Department, University of Science and Technology Hospital, [3]Department of Microbiology, Faculty of Medicine and Health Sciences, [4]Department of Pathology, Faculty of Medicine and Health Sciences, [5]Urology and Nephrology Center, Al-Thawra General Hospital; Department of Nephrology, Faculty of Medicine and Health Sciences, [6]Urology and Nephrology Center Al-Thawra General Hospital; Department of Urology, Faculty of Medicine and Health Sciences, Sana'a University, [7]HLA Typing Unit, Al-Thawra General Hospital, Sana'a, Yemen

## ABSTRACT

**Background**: Human leukocyte antigens (HLAs) are found to be significant genetic factors concerning the susceptibility of an individual to certain diseases. **Objective**: To determine the association between variants of class I (A and B) and class II (DRB1) HLA alleles and chronic renal failure (CRF), compared with healthy controls, in Yemen. **Methods**: A case-control study in the Urology and Nephrology Center at Al-Thawra University Hospital in Sana'a, Yemen was carried out between January 2013 and December 2015 and included 187 CRF patients, and 194 healthy controls visiting the same center for kidney donation. All CRF patients in the study were on haemodialysis. The control group was confirmed to be healthy following a clinical examination by specialist physicians. Among both patients and controls, HLA class I (A and B) and class II (DRB1) HLA typing was carried out by Sequence Specific Primers (SSP) polymerase chain reaction (PCR). **Results**: There was a significant protective function for HLA-A*30 gene (CRF 9.1% vs. con 16%, p=0.045) against CRF development. There was a high frequency of HLA-A*02, HLA-B*51 and HLA-DRB1*04 alleles in both patients and controls. **Conclusion**: No HLAs were located to have a significant association with genetic tendency to CRF in the current study population, however, certain HLA alleles, for instance in HLA-A*30, could be considered protective against CRF progress.

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**Keywords: Case-Control Study, HLA Alleles, Renal Diseases, Yemen**

*Corresponding author: Dr. Hassan A. Al-Shamahy, Department of Microbiology, Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen, e-mail: shmahe@yemen.net.ye

## INTRODUCTION

Chronic kidney disease (CKD) is a major worldwide public health problem (1). The number of patients with end-stage renal disease (ESRD) is growing significantly worldwide. In the United States, the incidence and prevalence rates per million population are estimated to increase by 32% and 70%, respectively, from 2000 to 2015 (2). In Canada, 1.9 to 2.3 million inhabitants have chronic kidney disease (3). In the United Kingdom, approximately 8.8% of the populations have symptomatic CKD (4). It has been identified that cardiovascular disease (CVD), hypertension, diabetes, infections and obstructive diseases, can influence the development of CKD (5-10). However, there is a need for further research to be carried out on the liability of the immune system in renal diseases, as this could be the origin or cause of the diseases and their progression (11). This theory is the result of investigations into positive relations between human leukocyte antigens (HLAs) and a broad variety of renal diseases (11). The studies on HLA and renal diseases demonstrate some significant associations with HLA Class I and Class II alleles. The procedures for associating HLA with renal disease have been developed since the late 1980s, mostly as a result of a more detailed knowledge of Class I and Class II molecules and their structure and function. HLA phenotypes are interrelated with an increased or reduced risk of alloantibody sensitization in ESRD candidates for first or repeat kidney transplantation (11). In addition, more than 40 diseases have well-established genetic linkages to HLA (12,13).

Chronic renal failure has become one of the major health problems and constitutes a significant cause of mortality in Yemen (14,15). The estimated annual incidence of ESRD in the Sana'a region is 385 per million population (15,16). There are many deficiencies in the diagnostic and therapeutic tools available. There is also a severe shortage in the total bed capacity of our seven dialysis centers, located in major towns, caring for end-stage renal disease patients on maintenance haemodialysis (14). Furthermore, there is a lack of statistics and other data related to kidney disease in Yemen, as well as an absence of adequate research in this field. Also in Yemen very few studies have been carried out on the scope of HLA antigens and their effect on different diseases (17). Therefore, this research was undertaken to evaluate the possible association of HLA antigen class I (A & B) and class II (DRB*01) with CRF in Yemeni patients, and in order to come up with recommendations for prevention and early recognition and diagnosis of factors leading to the development of chronic renal failure.

## MATERIALS AND METHODS

**Patients.** This case-control study was carried out over a three-year period between January 2013 and December 2015. The study was approved by the Department of Medical Microbiology and Clinical Immunology in the Faculty of Medicine and Health Sciences at Sana'a University, Yemen. Written consent was obtained from all of the included patients and controls. A total of 381 individuals were enrolled in the study; the patient group comprised 187 adults with CRF while the control group consisted of 194 healthy adult individuals. All patients and controls originated from Sana'a, Yemen. The patient group consisted of 124 males and 63 females (aged from 17 to 58 years) who had attended the Urology and Nephrology Center at Al-Thawra University Hospital, Sana’a, Yemen, for kidney transplantation. All CRF patients in the study were on

haemodialysis before they underwent kidney transplantation. The control group consisted of 124 males and 70 females (aged from 6 to 65 years) who had visited the Urology and Nephrology Center for kidney donation. They were confirmed to be healthy following a clinical examination by specialist physicians. As age and gender does not influence an individual's HLA frequency profile, the control group was not age- and gender-matched with the patient group. Both the patients and controls were required to undergo certain tests such as blood pressure, abdominal ultrasound, complete blood count (CBC), blood sugar, and kidney and liver function tests. In addition, a general urine examination and a 24-hour urine examination for protein detection and creatinine clearance were carried out. The results for all the aforementioned tests were normal in the control group.

**HLA Typing.** HLA genotyping was completed for each person in the patient and control groups and blood specimens from each individual were collected in sterile EDTA tubes. As the time of blood collection has no effect on the genotyping results, blood specimens were collected whenever patients arrived at the hospital. The blood specimens from both groups were used for HLA Class I (A and B) and Class II (DRB1) genotyping. The typing of all the subjects' HLA-A, -B, and -DRB1 alleles was identified using low-resolution BA Gene Sequence Specific Primers (SSP) polymerase chain reaction (PCR) kits (BAG Health Care GmbH, Lich, Germany). The tests were carried out according to the manufacturer's instructions. The genomic DNA of each sample was purified using the spin columns method of the QIAGEN DNA purification kit (QIAGEN, Hilden, Germany).

**Statistical analysis.** The statistical analysis of the results were performed by using SPSS Version 21.0 software where the frequencies and percentage (%) of the HLA-A, -B and -DRB1 were calculated. The association of CRF patients with HLA-I alleles was analyzed by comparing HLA-A, B and –DRB1 allele frequencies in CRF patients with the healthy Yemeni controls. Chi-Square test for 2×2 tables was used to define the differences between allele frequencies in patients and the control groups, using SPSS Version 21.0 software. The odds ratios (OR) with 95% confidence intervals (CI) were calculated and P values lower than 0.05 were considered significant.

## RESULTS

The age groups and genders of the individuals in the patient and control groups are shown in Table 1. The patients' mean age was 31.52 years (range: 17–58 years) and that of the controls was 29.8 years (6–65 years). A total of 124 patients (66.1%) were male and the remaining 63 patients (33.69%) were female. A 124 of the controls (63.9%) were male and the remaining 70 individuals (36.1%) were female (Table 1). The results showed that HLA-A*02 had the highest frequency among HLA-A alleles in the patients (54%) and the controls (54.6%). HLA-A*68 and HLA-A*01 were the next most frequent alleles in the patients. HLA-A*30, HLA-A*33, HLA-A*03 and HLA-A*23 were the next most frequent alleles in the controls. A comparison of the frequency of HLA-A alleles in the patients and controls showed higher frequencies of HLA-A*68 (OR=1.7; CI=0.92–3.34; p=0.086) and HLA-A*26 (OR=1.5; P=0.245) and lower frequencies of HLA-A*30 (OR=0.52; p=0.045) and HLA-A*28 (OR=0.12; p=0.051) in the CRF patients (Table 2).

**Table 1. The frequencies of Yemeni chronic renal failure group and the control group according to their age groups and gender.**

| Character | Patient group | | Control group | | Total | |
|---|---|---|---|---|---|---|
| Age/Years groups: | No. | % | No. | % | No. | % |
| <20 | 30 | 16.0 | 24 | 12.4 | 54 | 14.2 |
| 21-35 | 93 | 49.7 | 122 | 62.9 | 215 | 56.4 |
| 36-50 | 51 | 27.3 | 44 | 22.6 | 95 | 24.9 |
| ≥51 | 13 | 13.0 | 4 | 2.1 | 17 | 4.5 |
| Gender: | | | | | | |
| Males | 124 | 66.3 | 124 | 63.9 | 248 | 65.1 |
| Females | 63 | 33.7 | 70 | 36.1 | 133 | 34.9 |
| Total | 187 | 49.1 | 194 | 50.9 | 381 | **100** |

**Table 2. HLA-A alleles frequency in chronic renal disease and healthy controls.**

| HLA-A alleles | Patient n=187 | | Control n=194 | | OR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | |
| HLA-A*01 | 26 | 13.9 | 21 | 12.3 | 1.33 | 0.72 to 2.45 | 0.362 |
| HLA-A*02 | 101 | 54.0 | 106 | 54.0 | 0.97 | 0.65 to 1.45 | 0.902 |
| HLA-A*0 3 | 21 | 11.2 | 26 | 13.4 | 0.81 | 0.44 to 1.51 | 0.519 |
| HLA-A*11 | 6 | 3.2 | 11 | 5.7 | 0.55 | 0.19 to 1.52 | 0.250 |
| HLA-A *23 | 22 | 11.8 | 24 | 12.4 | 0.94 | 0.50 to 1.75 | 0.855 |
| HLA-A *24 | 21 | 11.2 | 20 | 10.3 | 1.10 | 0.57 to 2.10 | 0.771 |
| HLA-A *25 | 2 | 1.1 | 3 | 1.5 | 0.68 | 0.11 to 4.16 | 0.684 |
| HLA-A *26 | 21 | 11.2 | 15 | 7.7 | 1.50 | 0.75 to 3.02 | 0.245 |
| HLA-A *28 | 1 | 0.5 | 8 | 4.1 | 0.12 | 0.01 to 1.00 | 0.051 |
| HLA-A *29 | 8 | 4.3 | 10 | 5.2 | 0.82 | 0.31 to 2.13 | 0.687 |
| HLA-A *30 | 17 | 9.1 | 31 | 16.0 | 0.52 | 0.28 to 0.98 | 0.045 |
| HLA-A *31 | 2 | 1.1 | 7 | 3.6 | 0.28 | 0.05 to 1.40 | 0.124 |
| HLA-A *32 | 12 | 6.4 | 16 | 8.2 | 0.76 | 0.35 to 1.65 | 0.494 |
| HLA-A *33 | 17 | 9.1 | 26 | 13.4 | 0.64 | 0.33 to 1.23 | 0.186 |
| HLA-A *34 | 2 | 1.1 | 0 | 0.0 | 5.24 | 0.25 to 109.93 | 0.149 |
| HLA-A *36 | 2 | 1.1 | 1 | 0.5 | 2.08 | 0.18 to 23.20 | 0.549 |
| HLA-A *66 | 2 | 1.1 | 1 | 0.5 | 2.08 | 0.18 to 23.20 | 0.549 |
| HLA-A *68 | 27 | 14.4 | 17 | 8.8 | 1.75 | 0.92 to 3.34 | 0.086 |
| HLA-A *69 | 3 | 1.6 | 4 | 2.1 | 0.77 | 0.17 to 3.50 | 0.740 |
| HLA-A*74 | 0 | 0.0 | 1 | 0.5 | 0.34 | 0.01 to 8.49 | 0.514 |
| HLA-A*80 | 0 | 0.0 | 1 | 0.5 | 0.34 | 0.01 to 8.49 | 0.514 |

$p \leq 0.05$ (significant), OR= odds ratio, 95%CI= 95% confidence interval.

**Table 3. HLA-B alleles frequencies in chronic renal failure and healthy controls.**

| HLA-B alleles | Patient n=187 | | Control n=194 | | OR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | |
| HLA-B*07 | 13 | 7.0 | 12 | 6.2 | 1.13 | 0.50 to 2.55 | 0.762 |
| HLA-B*08 | 16 | 8.6 | 17 | 8.8% | 0.97 | 0.47 to 1.99 | 0.942 |
| HLA-B*13 | 9 | 4.8 | 7 | 3.6 | 1.35 | 0.49 to 3.70 | 0.559 |
| HLA-B*14 | 8 | 4.3 | 6 | 3.1 | 1.40 | 0.47 to 4.11 | 0.540 |
| HLA-B*15 | 6 | 3.2 | 9 | 4.6 | 0.68 | 0.23 to 1.95 | 0.475 |
| HLA-B*16 | 0 | 0.0 | 4 | 2.1 | 0.11 | 0.00 to 2.11 | 0.048 |
| HLA-B*18 | 9 | 4.8 | 8 | 4.1 | 1.17 | 0.42 to 2.94 | 0.745 |
| HLA-B*27 | 4 | 2.1 | 1 | 0.5 | 4.21 | 0.46 to 38.09 | 0.199 |
| HLA-B*35 | 17 | 9.1 | 29 | 14.9 | 0.56 | 0.30 to 1.07 | 0.079 |
| HLA-B*37 | 5 | 2.7 | 4 | 2.1 | 1.30 | 0.34 to 4.93 | 0.695 |
| HLA-B*38 | 3 | 1.6 | 2 | 1.0 | 1.56 | 0.25 to 9.47 | 0.625 |
| HLA-B*39 | 6 | 3.2 | 4 | 2.1 | 1.57 | 0.43 to 5.67 | 0.487 |
| HLA-B*40 | 6 | 3.2 | 4 | 2.1 | 1.57 | 0.43 to 5.67 | 0.487 |
| HLA-B*41 | 24 | 12.8 | 26 | 13.4 | 0.95 | 0.52 to 1.72 | 0.869 |
| HLA-B*42 | 2 | 1.1 | 5 | 2.6 | 0.40 | 0.07 to 2.13 | 0.288 |
| HLA-B*44 | 20 | 10.7 | 23 | 11.9 | 0.89 | 0.47 to 1.68 | 0.720 |
| HLA-B*45 | 7 | 3.7 | 7 | 3.6 | 1.03 | 0.35 to 3.02 | 0.944 |
| HLA-B*47 | 1 | 0.5 | 2 | 1.0 | 0.51 | 0.04 to 5.74 | 0.590 |
| HLA-B*49 | 10 | 5.3 | 8 | 4.1 | 1.31 | 0.50 to 3.40 | 0.574 |
| HLA-B*50 | 28 | 15.0 | 25 | 12.9 | 1.19 | 0.66 to 2.12 | 0.556 |
| HLA-B*51 | 71 | 38.0 | 68 | 35.1 | 1.13 | 0.74 to 1.72 | 0.554 |
| HLA-B*52 | 12 | 6.4 | 5 | 2.6 | 2.59 | 0.89 to 7.50 | 0.079 |
| HLA-B*53 | 28 | 15.0 | 29 | 14.9 | 1.00 | 0.57 to 1.75 | 0.994 |
| HLA-B*55 | 0 | 0.0 | 2 | 1.0 | 0.20 | 0.009 to 4.30 | 0.164 |
| HLA-B*57 | 13 | 7.0 | 20 | 10.3 | 0.65 | 0.31 to 1.34 | 0.246 |
| HLA-B*58 | 13 | 7.0 | 15 | 7.7 | 0.89 | 0.41 to 1.92 | 0.770 |
| HLA-B*60 | 1 | 0.5 | 0 | 0.0 | 3.12 | 0.12 to 77.29 | 0.308 |
| HLA-B*62 | 1 | 0.5 | 0 | 0.0 | 3.12 | 0.12 to 77.29 | 0.308 |
| HLA-B*64 | 0 | 0.0 | 1 | 0.5 | 0.34 | 0.01 to 8.49 | 0.326 |
| HLA-B*65 | 0 | 0.0 | 1 | 0.5 | 0.34 | 0.01 to 8.49 | 0.326 |
| HLA-B*70 | 0 | 0.0 | 1 | 0.5 | 0.34 | 0.01 to 8.49 | 0.326 |
| HLA-B*72 | 1 | 0.5 | 2 | 1.0 | 0.51 | 0.04 to 5.74 | 0.590 |
| HLA-B*73 | 2 | 1.0 | 6 | 3.1 | 0.33 | 0.06 to 1.70 | 0.188 |
| HLA-B*78 | 3 | 1.6 | 1 | 0.5 | 3.14 | 0.32 to 30.52 | 0.297 |
| HLA-B*81 | 1 | 0.5 | 1 | 0.5 | 1.03 | 0.06 to 16.71 | 0.979 |

p ≤ 0.05 (significant), OR= odds ratio, 95%CI= 95% confidence interval.

The most numerous HLA-B allele in the patients (38%) and controls (35.1%) was HLA-B*51. HLA-B*50, HLA-B*53, HLA-B*35 and HLA-B*41 were the next most frequent alleles in the patients and controls. On the other hand, the HLA-B*60, *62, *64, *65,

*70, *72 and *81 alleles were among the least expressed HLA-B alleles in both the patients and controls. HLA-B*35 (OR=0.56; P=0.079), and HLA-B*57 (OR=0.65; P=0.24) were also observed at a lower frequency in the patients compared to the controls (Table 3).

The results showed that DRB1*04 DRB1*13, and DRB1*03 had the highest frequency among DRB1 alleles in the patients (36.9%, 26.7% and 26.2%, respectively) and controls (37.1%, 24.7% and 31.4%, respectively). DRB1*07 was the next most frequent allele in the patients (22.5%) and controls (24.7%). A comparison of the frequency of DRB1 alleles among those in the patient and control groups showed higher frequencies of DRB1*08 in the controls (7.2%) (OR=0.42; p=0.087), while in the patients it was 3.2% (p=0.079). The results therefore reveal no significant associations, but might indicate a possible protective function for DRB1-*08 (Table 4).

**Table 4. HLA-DR alleles frequencies in patients with chronic renal failure and healthy controls**

| HLA-DR alleles | Patient N = 187 | | Control N = 194 | | OR | 95% CI | p-value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | |
| HLA-DR* 01 | 27 | 14.4 | 28 | 14.4 | 1.00 | 0.56 to 1.77 | 0.998 |
| HLA-DR*0 3 | 49 | 26.2 | 61 | 31.4 | 0.77 | 0.49 to 1.20 | 0.259 |
| HLA-DR *04 | 69 | 36.9 | 72 | 37.1 | 0.99 | 0.65 to 1.50 | 0.965 |
| HLA-DR *07 | 42 | 22.5 | 48 | 24.7 | 0.88 | 0.54 to 1.41 | 0.600 |
| HLA-DR *08 | 6 | 3.2 | 14 | 7.2 | 0.42 | 0.16 to 1.13 | 0.079 |
| HLA-DR*09 | 2 | 1.1 | 1 | 0.5 | 2.08 | 0.18 to 23.20 | 0.549 |
| HLA-DR *10 | 29 | 15.5 | 25 | 12.9 | 1.24 | 0.69 to 2.20 | 0.463 |
| HLA-DR *11 | 29 | 15.5 | 20 | 10.3 | 1.59 | 0.86 to 2.93 | 0.132 |
| HLA-DR *12 | 0 | 0.0 | 3 | 1.5 | 0.14 | 0.00 to 2.84 | 0.088 |
| HLA-DR *13 | 50 | 26.7 | 48 | 24.7 | 1.11 | 0.70 to 1.75 | 0.656 |
| HLA-DR *14 | 12 | 6.4 | 11 | 5.7 | 1.14 | 0.49 to 2.65 | 0.759 |
| HLA-DR *15 | 32 | 17.1 | 24 | 12.4 | 1.46 | 0.82 to 2.59 | 0.193 |
| HLA-DR *16 | 13 | 7.0 | 18 | 9.3 | 0.73 | 0.34 to 1.53 | 0.407 |

p ≤ 0.05 (significant); OR= odds ratio; 95%CI = 95% confidence interval.

## DISCUSSION

Chronic renal failure is a slow progressive loss of kidney function over a period of several years. Eventually the patient suffers permanent kidney failure. The condition often goes undetected and undiagnosed until the disease is well advanced and kidney failure is fairly imminent. Because of the importance of the role of immune response in the processing of CRF, the HLA genes are potentially a contributory factor. The detection and analysis of HLA polymorphism are important for the study of the CRF susceptibility (19,20). Many studies have been performed worldwide on the HLA

complex and disease, but this type of research is still in its infancy in Yemen. Indeed, this was only the second study in Yemen on HLA typing, following an earlier one aimed mainly at investigating the association between HLA (A, B, CW and DRB1) antigen and HESRF in comparison with its status healthy individuals (21). In this study, the male-to-female patient ratio was 2:1. The high prevalence of renal diseases among males could be as a result of physiological differences between genders and of the higher susceptibility among males to diseases which can lead to renal failure. The higher prevalence of such CRF among males in this study was in harmony with the findings of another study, which reported a male-to-female ratio of 2:1.14. The present study also concurred with that of Al-Rohani (10), who reported that the male gender was a risk factor for CRF. Another possible reason could be the statistically small sample size of females in the study, partly due to the fact that for socio-cultural reasons Yemeni females have less access than males to medical services (22).

The findings of this present study revealed the phenotypic and gene frequencies of HLA-A, HLA-B, and DRB1 genes in 381 Yemenis (187 patients and 194 controls). The patients, as compared to the controls, had lower frequencies of certain HLA genes such as HLA-A*30, HLA-A*31, HLA-A*33, HLA-B*35, HLA-B*57 and HLA-DRB1*08. Despite this, there was no statistically significant difference between the renal failure patients and the controls; this suggests that there are no HLA genes predisposing to CRF. This result is in agreement with those of Agrawal *et al.* (23) and of Prasanavar and Shankarkumar (24), who determined that HLA and haplotype frequencies were not significantly different in renal transplant patients and healthy donors. However, the results of our study were dissimilar to those of Crispim *et al.*, who described associations of Class I and II HLA antigens with CRF (26). The antigens positively associated with renal failure in Crispim *et al.* were HLA-A*78 and HLA-DR*11 (26).

The most numerous HLA-B allele in patients was HLA-B*51. This allele was articulated in the CRF patients at a similar frequency in comparison to the controls (20.9% versus 19.2%). This result is similar to that reported among the Egyptian (CRF 69.5% vs. healthy 63.2%), Turkish (CRF 43.4% vs. healthy 43.8%) and Saudi Arabian populations (CRF 25.86% vs. con 26.67%) (27-30).

In the current study, a comparison of the frequency of HLA-A alleles in the patients and controls showed considerably higher frequencies of HLA-A*30 among the controls (16%; P=0.045), while among the patient group it was 9.1% (P=0.045); indicating the possible protective function of HLA-A*30 (Table 2). This result is different from those reported in Saudi Arabia (22) and Egypt (20) in which HLA- A*26 (CRF 5.14% vs. con 9.52%, $p<0.05$, CRF 2.89% vs. con 13.6%, p=0.03 respectively) was suggested the protective function. However, as yet, there have been no reported findings regarding the protective function of HLA-A*30 alleles in renal diseases in access medical journals (30,31). The results of this study demonstrate that HLA-A*02, HLA-A*68, HLA-B*51, HLA-B*53, HLA-DRB1*04, DRB1*13 and DRB1*03 have the highest frequency among HLA-alleles in both the patients and controls in the studied population (Tables 2 to 4). This result matches those of studies performed on the frequency of HLA in Jordanian, Egyptian, Saudi Arabian, Kuwaiti, Iraqi, Emirati and Lebanese populations (27,29,31-36). In addition, the antigen frequencies in the current study were compared with those from kidney recipients and kidney donors of other ethnic groups (i.e. African-Americans, Caucasians, Asians and Hispanics) included in the UNOS renal registry data on HLA-A, B and DR loci. This comparison showed that while the population in the current study differed from the other ethnic groups in other respects,

there was a similarity with Hispanics and Caucasians in that the highest frequencies among HLA alleles in the studied population were roughly comparable to those in these two ethnic groups (23). Finally, the diversity in the findings of different researchers may be due to the huge irregularity in the frequency of HLA alleles present in different populations or ethnic groups. A further cause may be the unequal relationship between these HLA alleles and other nearby genes involved in accommodating the immune response. An example of this is reported by Ranganath *et al.,* who stated that polymorphism in genes encoding certain cytokines, including IL-6, IL-4 and tumor necrosis factor, may be affected in the progression to renal failure (37).

In conclusion, in our study, although there is no highly significant association of any of the HLA, class I and class II alleles with the Yemeni CRF patients, HLA-A*30 showed a significant negative association with CRF and emerged as a possible protective allele against the development of CRF. HLA-A*02, HLA-B*51 and HLA-DRB1* 04 are the most frequent alleles in both CRF patient and control groups, but without significant association with CRF development.

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