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# Protective and Susceptible HLA Class I Genes in Patients with End-Stage Renal Disease

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**Abstract:** The role of the HLA system in the pathophysiology of primary renal disease is intriguing, but not completely resolved. According to the results of studies links between HLA haplotype and renal failure has been reported. This study was conducted to determine protective and susceptible role of HLA class I genes in end stage renal disease patients. Subjects of this study were 77 individuals from Azerbaijan republic referred to Iran Red Crescent Society clinic in Baku of which were assigned into 2 group, case and control, based on renal disease. Case group were 26 patients with end stage renal disease candidate for renal transplant and controls were 51 healthy subjects. Typing of HLA class I was performed by serologic method. There was no significant difference in age and sex between control and patient groups. The most frequent detected HLA antigens were A2 (41.6%), A3(28.6%), A24(26%) from A loci and B35 (46.8%), B51 (29.9%), B18 (13%) from B loci. Significant association was found between susceptibility to ESRD and HLA-A33, A11, B49 ($p<0.05$). The findings support the idea that polymorphism of HLA class I may influence the susceptibility to ESRD. We suggested HLA antigen distribution will identify the high-risk patients who are candidates for transplantation.

**Key words:** HLA, ESRD, protective, susceptible, renal disease, patients

## INTRODUCTION

Chronic Kidney Disease (CKD) is a worldwide public health problem (Obrador and Pereira, 2008). End Stage Renal Disease (ESRD) as a frequent result of CKD represents a clinical state or condition in which there has been irreversible loss of endogenous renal function (Braunwald *et al*., 2001). According to the published statistics by Obrador and Pereira (2008), the total cost of the ESRD program in the United States was approximately $32.5 billion in 2004 and the projected number of ESRD patients by the year 2010 has been estimated to be 651,330 and the total Medicare ESRD program cost in excess of $28 billion dollars. Findings of Richard *et al.* (2005) on epidemiological changes of ESRD during the last decade showed an increasing incidence and prevalence. Although, the exact reasons for the growth of the ESRD program are unknown, it is postulated that changes in the demographics of the population, differences in disease burden among racial groups and under-recognition of earlier stages of CKD and of risk factors for CKD, may partially explain this growth (Obrador and Pereira, 2008). Findings of Peralta *et al.* (2006) and Freedman *et al.* (1993, 1994) indicates epidemiological differences of ESRD by race but reasons for this are unclear (Peralta *et al*., 2006). Disorders with clear-cut monogenic inheritance comprise a small but important component among the etiologies of CKD. Both candidate locus and genome-wide strategies have been used to pinpoint genes that contribute to the risks for development of these disorders (Braunwald *et al*., 2001). This study was conducted to determine protective and susceptible role of HLA class I genes in end stage renal disease patients.

## MATERIALS AND METHODS

Subjects of this study were the individuals referred to Iran Red Crescent Society clinic in Baku, Azerbaijan Republic. All of the subjects were Azerbaijani and from different part of the country. The subjects were selected from those who had or not ESRD. Using sequential sampling method, seventy seven individuals were assigned into 2 groups, case and control. Case patients were 26 subjects with ESRD candidate for renal transplant and controls were 51 healthy subjects. HLA typing was performed in Department of Immunology of Azerbaijan

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Medical University, using serologic method and based on manufacture's instruction (Euro clone, Italy). Collected data were analyzed by SPSS software version 11.5. Student t-test was used to compare means of independent groups. Chi-square test was used to test the HLA differences between the patients and control groups. The level of significance in all cases was set at a 2 tailed $p<0.05$.

## RESULTS AND DISCUSSION

Mean age of patients and controls were 32.37±10.71 and 34.14±9.64, respectively. There was no significant difference in age and sex between control and patient groups. The most frequent detected HLA antigens in all of subjects were A2 (41.6%), A3 (28.6%), A24 (26%) from A loci, B35 (46.8%), B51 (29.9%), B18 (13%) from B loci. According by groups the most frequent HLA were A2(38.5%), A3(26.9%), A11(26.9%), B35 (38.5%), B51(34.6%) and B27(15.4%) in case and were A2(43.1%), A3(29.4%), A24(27.5%), B35 (51%), B51(27.5%), B44(15.7%) in control group but there was no significant differences between groups for these results. However, a significant association was found between ESRD and HLA-A11, A33, B49 (Table 1, $p<0.05$).

The major histocompatibility complex (HLA) is a large group of genetic loci on the short arm of chromosome 6 that were originally discovered through research on models of transplant compatibility. A number of these loci encode the human leukocyte antigens HLA class I and HLA class II, which we now know to be key molecules in the antigen presentation system at the core of adaptive immunity (Thursz, 2001). HLA molecules play a key role in the selection and establishment of the antigen-specific T cell repertoire (Kasper *et al*., 2005). There are several prominent disease associations with HLA class I alleles (Braunwald *et al*., 2001). According to the report of 6th transplantation congress on nephrology (Verona, Italy) by Oldrizzi and Maschio (1997) role of the HLA system in the pathophysiology of primary renal disease is intriguing, but not completely resolved. Findings of Freedman *et al*. (1993) indicate the presence of a first-degree relative with ESRD can increase an African American's risk for developing ESRD nine fold.

Table 1: Distribution of HLA-A11, A33 and B49 in case and control groups

| | HLA 11 | | HLA 33 | | B49 | |
|---|---|---|---|---|---|---|
| Group | Number | (%) | Number | (%) | Number | (%) |
| Case | 7 | 26.9 | 2 | 7.7 | 2 | 7.7 |
| Control | 5 | 9.8 | 0 | 0 | 0 | 0 |
| Total | 12 | 15.6 | 2 | 2.6 | 2 | 2.6 |

In our analytical descriptive study, HLA class I genetic effects on the presence of ESRD was evaluated. Findings of the study demonstrated an association between HLA-A11, A33, B49 and ESRD.

It is shown that development of ESRD is associated with different HLA alleles (Korotkova *et al*., 2006). Results of Freedman *et al.* (1994) study suggest that the risk of ESRD among African-Americans due to chronic glomerulonephritis is 4 times more often than whites. These results indicate that HLA-DR3 and HLA-DR5 are positively associated with ESRD in patients of both races and that HLA-DR7 is negatively associated in whites. According to the results of Doxiadis *et al.* (2001), the antigens HLA-B35 and DR5 were significantly increased in the patients with relative risk values of 1.385 and 1.487, respectively. In another research HLA phenotypes identified as independent risk factors associated with protection against alloantibody sensitization in ESRD were DR1, 4, 7; B12 (44.45) and A1,2. The only independent susceptibility allelotype was A36 (Heise *et al*., 2001).

In our study we also found the most frequent HLA A2, B35 and B51 in patients with ESRD. In a study by Ozdemir *et al*. (2004) in Turkey the most frequent HLA for class I in ESRD patients were B56, A2, A34, A1, A23, A24 and B61 while in other study (Chen *et al*., 1996) decreased frequencies of HLA-B27, B40 ($p<0.05$) and an increased frequency of HLA-B35 ($p<0.05$) were found in patients with ESRD compared with healthy controls. Schena (Bari, Italy) focused on the correlations between HLA haplotype and clinical of presentation in various forms of glomerulopathy. HLA B12 haplotype is more common in minimal changes disease. Adult patients with HLA4 frequently progress to renal failure (Oldrizzi and Maschio, 1997).

Our findings support the idea that polymorphism of HLA class I may influence the susceptibility to ESRD. We suggested HLA antigen distribution will identify the high-risk patients who are candidates for transplantation.

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