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COMPARISON OF THE GENDER SPECIFIC HLA HAPLOTYPES DISTRIBUTION IN UZBEK PATIENTS WITH CHRONIC GLOMERULONEPHRITIS AND ESRD

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ABSTRACT

Chronic glomerulonephritis (CG), chronic renal failure (CRF) are the majority of instances to end stage renal disease (ESRD) which is the cause of renal replacement therapy. Our interest was to evaluate the possible associations of HLA class II haplotypes with ESRD according to gender specificity factors, in Uzbek population. The study was performed at the Institute of Immunology of the Academy of Sciences of Uzbekistan. We have examined 542 people of Uzbek nationality. The 225 people of these have been diagnosed with chronic glomerulonephritis, chronic renal failure complicated with end-stage, to whom the chronodialize was recommended. The control group consisted of 317 healthy individuals who are relatives of the first line of kinship. The patients were 51 female and 174 male. Among the donors were 163 male and 154 female. Positively associated haplotypes with ESRD in male patients were: DRB1*08-DQA1*01:03-DQB1*06:01, DRB1*13-DQA1*01:03-DQB1*06:02 and DRB1*14-DQA1*01:01-DQB1*05:03. The haplotypes positively associated with ESRD in female patients were: DRB1*14-DQA1* 01:01-DQB1*05:03, DRB1*15-DQA1*01:02-DQB1*06:02 and DRB1*16-DQA1*01:02-DQB1*05:02.

KEYWORDS: HLA, chronic renal failure CRF, CKD, ESRD, glomerulonephritis.

INTRODUCTION

End-stage renal disease (ESRD), the complete or almost complete failure of the kidneys to function, has become a worldwide public health problem, with increased risks of mortality and morbidity.[1, 2] Lots of risk factors have been reported to be susceptible to develop rapid progressive ESRD, including immunological and environmental factors.[3] The HLA system belongs to the major histocompatibility complex (MHC) in humans and it is located on chromosome 6p21.3. HLA genes encode cell surface molecules specialized to present antigenic peptides to T-cell receptors. MHC molecules are divided into two main classes: MHC class I and II. Class II MHC molecules are encoded by genes in the HLA-DP, HLA-DQ, or HLA-DR regions.[3, 4] Specific HLA types have been known to be associated with the pathogenesis of many autoimmune diseases, allergies, and inflammatory bowel disease.[5-8] The detection of specific HLA types has proven to be a valuable tool for the diagnosis or screening of ankylosing spondylitis, inflammatory bowel disease, and multiple sclerosis.[9-11] Several emerging studies have described significant correlations between HLA and some renal diseases such as diabetic nephropathy, IgA nephropathy, and glomerulonephritis.[12-14] Also it is well known, that not only single specificities can play role in the disease occurrence, but sometimes more there haplotypes are more in However, specific HLA types associated with ESRD have not been well documented. In this study, HLA class II polymorphisms of ESRD patients were compared to healthy relative donors (control group) in an effort to provide a better understanding of the etiology of this disease. Also we have divided both patients and control group by gender differences.

MATERIALS AND METHODOLOGY

The study was performed at the Republican Scientific Centre Of Immunology MOH RUz in the lab of human genomics named after Professor R.M. Ruzybakiev and SDC "Immunogen Test" in the period from 2010 to 2016y.y. The selection of patients in outpatient and inpatient treatment was carried out on the basis of RSCS named acad. V.V.Vahidov and SDC "Immunogen Test" at the Institute of Immunology of the AS of Uzbekistan. We have examined 542 people of Uzbek nationality. During the process of selecting individuals for this study we took into account their national identity in three generations, according to the recommendations VII Workshop on HLA (1977). The 225 people of these have been diagnosed with chronic glomerulonephritis, chronic renal failure complicated with end-stage, to whom the chronodialize was recommended. The control group consisted of 317 healthy individuals who are relatives of the first line of kinship. The patients were 51 female and

174 male. Among the donors were 163 male and 154 female.

The DNA Isolation was carried out using the method of alcohol-salt treatment by S. Miller et al (1988). HLA-typing of alleles of genes DRB1, DQA1 and DQB1 was performed using kits "of HLA-DNA-TECH" (« DNA Technology SPA», Moscow) using PCR mSSP method (polymerase chain reaction with sequence-specific primers) in modification of Institute of Immunology MOH RF (D.Yu. Trofimov, 1996) and with Q-PCR. As a result of the behavior of the reactions were determined following DRB1 specificities: DRB1 * 01, * 04, * 05, * 07, * 08, * 09, * 10, * 11, * 12, * 13, * 14, * 15, * 16, * 17 (Splits option * 03) * 18 (* Splits version 03). During the process of typing of the DQA1 locus the following specificities were found: * 0101, * 0102, * 0103, * 0201, * 0301, * 0401, * 0501, * 0601. On locus DQB1: * 0201, * 0301, * 0302, * 0303, * 0304, * 0305, * 0401/02 * 0501 * 0502/04 * 0503, * 0601, * 0602-08.

For evaluating of the results obtained, we held the statistical processing of the data, with the help of Arlequin 3.5.2.2 software package, Excel 2007, SISA and a number of formulas to calculate the OR (Odds Ratio) is the index of relative risk, EF (Etiologic fraction) - etiologic fraction, PF (Preventive fraction) - preventive fraction, $\chi 2$-confidence index Pearson, 95% CI-confidence interval.

RESULT AND DISCUSSION

As the aim of the study was to analyze the difference between the distribution of 3 loci haplotypes of HLA DRB1*-DQA1*-DQB1* depending on gender features, we have genotyped DNA samples 174 Uzbek male patients with ESRD and the 163 healthy male individuals in the control group who are relatives of the first line of kinship for the patients. Table 1 shows the comparison between the frequency of HLA Class II 3 loci haplotypes in males. We calculated haplotypes frequencies, etiological fractions (EF), preventive fractions (PF), and OR (Odds Ratio) is the index of relative risk. The sum of all possible haplotypes in ESRD male patients was 276 and in healthy male donors sum of all possible haplotypes was 246.The haplotypes positively associated with ESRD in male patients were: DRB1*08-DQA1*01:03-DQB1*06:01 (OR≤8,628; EF≤0,0228), DRB1*13-DQA1*01:03-DQB1*06:02 (OR≤2,399; EF≤0,0754) and DRB1*14-DQA1*01:01-DQB1*05:03 (OR≤10,608; EF≤0,0286). Only one haplotype DRB1*04-DQA1*03:01-DQB1*03:02 was found as a negatively associated haplotype (OR≤0,106; PF≤6,793).

Table1. The main significant haplotypes in ESRD Uzbek male

HLA haplotypes DRB1*/DQA1* /DQB1*	Frequencies				OR	EF	PF	χ^2	*Pc*
	ESRD Male, n=174		Donors Male, n=163						
	PhF	HF	PhF	HF					
04/03:01/03:02	12	0,0345	26	0,0849	0,106		6,793	6,484	0,01
08/01:03/06:01	9	0.0258	7	0,0032	8,628	0,0228		5,983	0,014
13/01:03/06:02	45	0.1293	19	0.062	2,399	0,0754		9,881	0,001
14/01:01/05:03	11	0,0316	1	0,0032	10,608	0,0286		7,841	0,005

Also, we have genotyped 51 female with ESRD and 122 healthy female. The sum of all possible haplotypes in ESRD female patients was 142 and in healthy female donors sum of all possible haplotypes was 255. As it is shown in Table2, we have observed 4 significant haplotypes. The haplotypes positively associated with ESRD in female patients were: DRB1*14-DQA1*01:01-DQB1*05:03 (OR≤4,9387; EF≤0,0312), DRB1*15-DQA1*01:02-DQB1*06:02 (OR≤4,6931; EF≤0,108) and DRB1*16-DQA1*01:02-DQB1*05:02 (OR≤9,9183; EF≤0,0352). Only one haplotype DRB1*11-DQA1*05:01-DQB1*03:01 was found as a negatively associated haplotype (OR≤0,3821; PF≤1,498).

Table2. The main significant haplotypes in ESRD Uzbek female

HLA haplotypes DRB1*/DQA1* /DQB1*	Frequencies				OR	EF	PF	χ^2	*Pc*
	ESRD Female, n=51		Donors Female, n=122						
	PhF	HF	PhF	HF					
11/05:01/03:01	5	0,049	29	0,1184	0,3821		1,498	3,959	0,04
14/01:01/05:03	4	0,0392	2	0,0081	4,9387	0,0312		4,062	0,04
15/01:02/06:02	14	0,1372	8	0,0327	4,6931	0,108		13,185	0,0002
16/01:02/05:02	4	0,0392	1	0,004	9,9183	0,0352		6,229	0,01

So, as we can see, there is only one common haplotype for the both male and female, it is positively associated haplotype DRB1*14-DQA1*01:01-DQB1*05:03. We found, that the other six significant haplotypes are different for male and female. This result shows us again

the important role of analyzing the data with the considering of the gender factor.

Due to the important role of the immune response genes located on HLA are potentially plays an important role in the development and progression of glomerulonephritis, CKD and ESRD processing. The identification and analysis of HLA polymorphism are important not only for the study of the ESRD susceptibility or protection against it, but also for the renal transplantation in ESRD patients. This study provides useful information for the selection of donor kidneys in Uzbek ESRD patients, we can assume that grafted kidney In these patients may survive better through selecting donor kidneys without susceptible haplotypes of ESRD, although the efficacy of the prognosis this data for the kidney transplantation need be supported by further investigations.

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