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A single center study of protective and susceptible HLA alleles and haplotypes with end-stage renal disease in China

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ABSTRACT

Chronic kidney disease (CKD) is becoming a global public health problem and usually cause End-Stage Renal Disease (ESRD) in the end of progression. To analyze the associations of HLA-A, -B, -C, -DRB1 and -DQB1 alleles at high resolution with ESRD in Jiangsu province of China, a total of 499 unrelated patients with ESRD from the First Affiliated Hospital with Nanjing Medical University and 1584 healthy controls from Jiangsu Branch of Chinese Marrow Donor Program (CMDP) were genotyped at HLA-A, -B, -C, -DRB1 and -DQB1 loci. Statistical analysis was applied to compare the differences of HLA allele frequencies between patients with ESRD and healthy controls. As results, no protective allele at A locus was found and the susceptible alleles were A*11:01 and A*31:01. At B locus, B*15:01, B*55:02 and B*39:05 emerged as susceptible alleles, whereas no protective allele was found. At C locus, C*06:02 and C*07:01 emerged as protective alleles and no susceptible allele was found. At DRB1 locus, six alleles including DRB1*03:01, DRB1*04:03, DRB1*04:04, DRB1*04:05, DRB1*11:01 and DRB1*12:02 emerged as susceptible alleles, while DRB1*15:01 emerged as a protective allele. At DQB1 locus, DQB1*02:01, DQB1*03:01, DQB1*03:02 and DQB1*04:01 emerged as susceptible alleles, while DQB1*06:02 and DQB1*06:09 emerged as protective alleles. Haplotype A*11:01-C*03:03-B*15:01-DRB1*11:01-DQB1*03:01 containing four susceptible alleles was regarded as the most susceptible haplotype. The susceptible alleles and haplotypes might be used as some important risk classification markers. Besides, in the consanguineous renal transplantation, it would be very beneficial for the long-term survival of renal transplant patients to avoid the susceptible alleles and haplotypes in selecting optimal donors.

1. Introduction

Chronic kidney disease (CKD) is becoming a global public health problem, which usually cause End-Stage Renal Disease (ESRD) in the end of progression [1,2]. As of 2008, the total number of patients receiving renal replacement therapy was 2 million 31 thousand all over the world, with a 7% increase per year, far more exceeding the growth rate of the world population [3,4]. In China, the incidence of ESRD was a little higher and the annual incidence of ESRD that need hemodialysis therapy was estimated to be as high as 36.1 per million population [5]. Renal transplantation is recognized as the best treatment in clinical ESRD treatment so far and early diagnosis of CKD is vital to prevent the progression of ESRD.

Many factors, such as age, gender, genetics, race and hypertension have been found to be associated with progression of ESRD. Several emerging studies have described significant correlations between HLA and ESRD. Certain specific HLA alleles may influence the susceptibility to ESRD, other HLA alleles may confer protection to ESRD. Kidney disease might arise from the effects of HLA in the lymphoid organs or in the kidney. Different HLA allomorphs expressed by renal cells or renal mononuclear phagocytes might contribute mechanistically to renal disease [6]. However, previous studies were mostly performed at low resolution HLA typing. On the other hand, HLA polymorphism is restricted by region and race [7–9]. HLA polymorphism of Han ethnic in China has been divided into southern and northern population with the boundary of the Yangtze River. Jiangsu province owns its special geographical location. The Yangtze River runs across Jiangsu province, so that HLA polymorphism of Jiangsu province has its own special

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characteristics. Furthermore, with the development of HLA typing technology, high resolution HLA typing has become the trend of development, which can comply with the clinical needs better [10,11]. While little is known about the associations between HLA polymorphism and ESRD in the Jiangsu Han population at high resolution HLA typing.

To enrich the knowledge of HLA polymorphism in ESRD population of Jiangsu province and detect the susceptible or/and protective alleles or/and haplotypes to ESRD, patients with ESRD waiting for renal transplantation and unrelated healthy controls were analyzed at HLA-A, -B, -C, -DRB1 and -DQB1 loci at high resolution.

2. Subjects and methods

2.1. Subjects

The retrospective study investigated 499 unrelated patients with ESRD awaiting renal transplantation from January 2009 to May 2016 in the First Affiliated Hospital with Nanjing Medical University, which including 375 men and 124 women, ages ranged from 13 to 60 years, Han ethnic. General clinical characteristics, HLA typing and causes of ESRD were obtained from medical history of the hospital. Given that the studied patients were from Jiangsu province, volunteers from Jiangsu Branch Chinese Marrow Donor Program (CMDP) were used as controls for comparison analysis which consisted of 1584 unrelated healthy volunteers, including 909 men and 675 women, ages ranged from 18 to 45 years, Han ethnic and Jiangsu native. Both patients with ESRD and the controls were confirmed with the place of origin to be Jiangsu province and Han ethnic.

In this retrospective study, ethical approval was obtained by the ethics commit of the First Affiliated Hospital with Nanjing Medical University (2018-SR-307).

2.2. DNA extraction and HLA genotyping

Genomic DNA was extracted from peripheral blood using TIANamp Blood DNA Kits according to the manufacturer's instructions (Tiangen Biotech (Beijing) Co., Ltd) and the concentration and purity of it was determined by Nanodrop spectrophotometer (Thermo NanoDrop Lite, Thermo Scientic, USA). The DNA samples were then stored at −20 °C until use. The samples of patients with ESRD were typed at HLA-A, -B, -C, -DRB1 and -DQB1 loci using polymerase chain reaction reversed sequence-specific oligonucleotide (PCR-rSSO) method with LABType HD typing kits according to the manufacturer's instructions (One Lambda, Canoga Park, CA, USA). The product signals were detected by Luminex-IS200 flow cytometer system (Luminex Corporation, Austin, TX, USA) and HLA genotyping was accomplished with software HLA Fusion 3.0 (One Lambda, Canoga Park, CA, USA).

The samples of controls were typed using polymerase chain reaction sequence based typing (PCR-SBT) methods with SeCore HLA Sequencing Kits according to the manufacturer's instructions (One Lambda, Canoga Park, CA, USA). The sequencing reaction was electrophoresed on ABI 3730XL DNA sequencer (Applied Biosystems, Foster City, CA, USA) and HLA genotyping was accomplished with software uTYPE (One Lambda, Canoga Park, CA, USA).

Given no identified high resolution genotyping, SeCore® GSSP (Group-Specific Sequencing Primers) kit was applied to resolve ambiguous allele combinations (One Lambda, Canoga Park, CA, USA). The PCR-rSSO method was applied because of necessity of clinical registration certificate of reagents in detecting clinical samples. Although two different methods were applied, the standard of high resolution HLA typing was the same and the genotyping results of the two groups could be unified.

2.3. Statistical analysis

HLA-A, -B, -C, -DRB1 and -DQB1 allele frequencies (AF) were determined for each allele in patients with ESRD and controls using the following formula: AF (%) = (n/2N) × 100, where n indicated the sum of a particular allele and N indicated the total number of individuals. The frequencies of HLA-A, -C, -B, -DRB1 and -DQB1 haplotypes were calculated by the expectation maximization (EM) algorithm using Arlequin software 3.5 (Switzerland) [12]. Statistical Package for the Social Sciences (OpenEpi with Version no. 20) was applied in the process of statistical analysis. The differences in allele percentages between patients with ESRD and controls were analyzed by cross tabulation using correction $\chi 2$ test or Fisher test. In the statistical process, P value was calculated according to the expected value. When the expected value was greater than 5, $\chi 2$ test was used directly. If one of the expected value was less than 1, the Fisher test was applied. In other cases, correction $\chi 2$ test was used. The strength of disease association to a particular allele was expressed by odds ratio interpreted as relative risk (RR) and 95% confidence intervals (95% CI). Statistical significance was set a priority at $P < 0.05$. Alleles with RR higher than 1.00 were considered to be positively associated with ESRD and emerged as susceptible alleles to ESRD. Alleles with RR lower than 1.00 were considered to be negatively associated with ESRD and emerged as protective alleles to ESRD.

3. Results

3.1. General characteristics of the study population

When patients were made a definite diagnosis of ESRD, most of their creatinine was too high to be punctured. Without a complete biopsy, the primary disease could not be provided and glomerulonephritis was the most common cause of ESRD in this study (Table 1).

3.2. HLA allele frequency at A, -B, -C, -DRB1 and -DQB1 loci in patients with ESRD and healthy controls

The common alleles obtained by genotyping at HLA-A, -B, -C, -DRB1 and -DQB1 loci with frequency more than 0.1% in patients with ESRD and healthy controls were summarized in Table 2–6 (If allele frequency was less than 0.1% in any of the two groups, this allele would be ignored in statistics).

In general, no significant difference between the patients with ESRD and the healthy controls was found at A locus. On the other hand, A*11:01 and A*31:01 showed significant positive associations with ESRD and emerged as susceptible alleles to ESRD (Table 2). At B locus, a no significant difference was found between the patients with ESRD and the healthy controls at B locus generally. However, B*15:01, B*55:02 and B*39:05 showed significant positive associations with ESRD and emerged as susceptible alleles to ESRD (Table 3). At C locus,

Table 1
Baseline characteristics of the study population.

Total	499
Male/Female	375 (75.2%)/124 (24.8%)
Mean age at the time of end stage renal disease	13–60 y
1. Causes of end stage renal disease	
2. Glomerulonephritis	65 (13.0%)
3. Hypertensive nephropathy	39 (7.8%)
4. Diabetic nephropathy	32 (6.4%)
5. Interstitial nephritis	23 (4.6%)
6. ADPKD	9 (1.8%)
7. HSPN	8 (1.6%)
8. Obstructive nephropathy	5 (1.0%)
9. Autoimmune diseases	4 (0.8%)
10. Unknown	314 (62.9%)

Table 2
HLA-A allele frequency in patients with ESRD and healthy controls.

NO	Allele	ESRD (%)	Control (%)	RR	95% CI	*P*- value
1	01:01	3.5	4.5	0.812	0.152–4.349	0.165
2	02:01	11.8	14.2	0.849	0.085–8.484	0.055
3	02:03	2.0	2.6	0.821	0.204–3.307	0.316
4	02:05	0.2	0.2	1.041	0.850–1.276	0.727*
5	02:06	4.1	5.4	0.797	0.137–4.637	0.102
6	02:07	5.5	6.9	0.833	0.124–5.602	0.130
7	02:10	0.5	0.5	0.992	0.507–1.938	0.983
8	03:01	2.5	2.3	1.053	0.242–4.581	0.770
9	**11:01**	**21.7**	**15.1**	**1.386**	**0.108–17.869**	**9.433×10^{-7}**
10	11:02	1.9	1.5	1.138	0.313–4.137	0.532
11	23:01	0.5	0.3	1.490	0.830–2.674	0.476
12	24:02	18.5	16.5	1.110	0.090–13.629	0.141
13	24:07	0.1	0.2	0.595	0.551–0.642	0.873*
14	24:20	0.2	0.4	0.520	0.393–0.688	0.431*
15	26:01	2.6	2.5	1.032	0.232–4.596	0.856
16	29:01	0.5	0.8	0.693	0.339–1.416	0.344
17	30:01	7.5	8.9	0.862	0.110–6.777	0.156
18	**31:01**	**5.0**	**2.9**	**1.480**	**0.257–8.536**	**0.002**
19	32:01	1.4	1.5	0.971	0.295–3.194	0.901
20	33:03	8.8	10.5	0.856	0.100–7.318	0.109
21	68:01	0.5	0.9	0.629	0.305–1.298	0.232
22	69:01	0.2	0.3	0.640	0.492–0.833	0.686*

The *P* value using correction χ^2 test in the table was marked with * symbol.

overall no significant difference between the patient with ESRD and the healthy controls was observed. However, C*06:02 and C*07:01 showed significant negative associations with ESRD and emerged as protective alleles to ESRD (Table 4).

At DRB1 locus, in general, no significant difference between the patients with ESRD and the healthy controls was found. On the other hand, DRB1*03:01, DRB1*04:03, DRB1*04:04, DRB1*04:05, DRB1*11:01 and DRB1*12:02 showed significant positive associations with ESRD and emerged as susceptible alleles to ESRD. While DRB1*15:01 showed a significant negative association with ESRD and emerged as a protective allele to ESRD (Table 5). At DQB1 locus, generally speaking, no significant difference between the patients with ESRD and the healthy controls was observed. While DQB1*02:01, DQB1*03:01, DQB1*03:02 and DQB1*04:01showed significant positive associations with ESRD and emerged as susceptible alleles to ESRD. On the other hand, DQB1*06:02 and DQB1*06:09 showed significant negative associations with ESRD and emerged as protective alleles to ESRD (Table 6).

3.3. Haplotype frequency in patients with ESRD and healthy controls

The present study, as summarized in Tables 7 and 8, showed the common haplotypes with frequency more than 0.3%. The most frequent haplotype in both patients with ESRD and healthy controls was A*30:01-C*06:02-B*13:02-DRB1*07:01-DQB1*02:02. Haplotype of A*24:02-C*14:02-B*51:01-DRB1*09:01-DQB1*03:03 was also frequent in patients with ESRD and controls (ESRD 0.4% vs. Con 0.3%), which present a similar distribution of haplotypes between patients with ESRD and healthy controls. Haplotypes that contained susceptible alleles, such as A*11:01, B*15:01, DRB1*11:01, DQB1*03:01, DQB1*03:02 and DQB1*02:01, were A*11:01-C*03:03-B*15:01-DRB1*11:01-DQB1*03:01, A*24:02-C*03:02-B*15:18-DRB1*03:01-DQB1*02:01, A*11:01-C*07:02-B*40:01-DRB1*12:02-DQB1*03:01, A*11:01-C*04:01-B*15:01-DRB1*04:06-DQB1*03:02, A*30:01-C*06:02-B*13:02-DRB1*12:02-DQB1*03:01 and A*01:01-C*06:02-B*37:01-DRB1*10:01-DQB1*03:01. Among them, A*11:01-C*03:03-B*15:01-DRB1*11:01-DQB1*03:01 containing four susceptible alleles was regarded as the most susceptible haplotype to ESRD.

Table 3
HLA-B allele frequency in patients with ESRD and healthy controls.

NO	Allele	ESRD (%)	Control (%)	RR	95% CI	*P*- value
1	07:02	1.2	2.1	0.642	0.113–3.660	0.079
2	07:05	0.5	0.8	0.717	0.207–2.483	0.394
3	08:01	0.3	0.5	0.624	0.214–1.819	0.497*
4	13:01	3.9	4.3	0.924	0.112–7.623	0.589
5	13:02	7.5	9.3	0.816	0.067–9.930	0.063
6	**15:01**	**7.5**	**4.5**	**1.513**	**0.179–12.796**	**1.337×10^{-4}**
7	15:02	1.9	2.1	0.930	0.162–5.345	0.724
8	15:05	0.2	0.3	0.695	0.311–1.553	0.799*
9	15:07	0.5	0.5	0.994	0.351–2.811	0.987
10	15:11	1.8	2.3	0.829	0.138–4.972	0.369
11	15:12	0.2	0.1	1.393	0.985–1.970	0.952*
12	15:17	0.2	0.3	0.641	0.273–1.503	0.689*
13	15:18	1.7	1.5	1.095	0.224–5.364	0.673
14	15:25	0.4	0.4	1.044	0.426–2.557	0.845*
15	15:27	1.2	1.0	1.116	0.275–4.533	0.667
16	18:01	0.1	0.4	0.277	0.105–0.732	0.204*
17	27:04	1.4	0.9	1.338	0.345–5.181	0.217
18	27:05	1.5	1.1	1.286	0.312–5.304	0.269
19	35:01	2.8	2.8	0.979	0.148–6.493	0.902
20	35:03	0.9	0.8	1.107	0.313–3.913	0.729
21	35:05	0.3	0.2	1.254	0.670–2.346	0.938*
22	37:01	2.0	2.1	1.006	0.179–5.647	0.976
23	38:01	0.4	0.2	1.675	0.967–2.901	0.412*
24	38:02	2.1	2.2	0.951	0.160–5.665	0.795
25	39:01	1.7	1.5	1.078	0.218–5.335	0.727
26	**39:05**	**0.5**	**0.1**	**2.625**	**2.144–3.215**	**0.032***
27	40:01	9.7	8.1	1.187	0.105–13.398	0.082
28	40:02	1.8	1.5	1.181	0.246–5.662	0.427
29	40:03	0.3	0.2	1.394	0.805–2.414	0.788*
30	40:06	3.3	3.9	0.881	0.113–6.880	0.419
31	44:02	0.4	0.7	0.615	0.181–2.087	0.263
32	44:03	4.3	3.9	1.096	0.140–8.561	0.509
33	46:01	7.5	9.4	0.808	0.066–9.883	0.051
34	48:01	1.9	2.0	0.966	0.172–5.421	0.865
35	50:01	0.5	0.4	1.161	0.455–2.960	0.917*
36	51:01	6.3	5.3	1.164	0.127–10.638	0.196
37	51:02	1.5	1.1	1.314	0.323–5.337	0.231
38	52:01	3.7	3.2	1.129	0.159–8.021	0.416
39	54:01	4.2	3.7	1.120	0.147–8.527	0.421
40	55:01	0.1	0.1	0.835	0.590–1.180	0.751*
41	**55:02**	**3.2**	**1.9**	**1.500**	**0.276–8.147**	**0.010**
42	56:01	0.1	0.3	0.378	0.169–0.846	0.421*
43	57:01	1.2	2.0	0.669	0.120–3.725	0.112
44	58:01	5.4	6.7	0.829	0.081–8.534	0.135
45	59:01	0.3	0.3	1.139	0.570–2.279	0.924*
46	67:01	0.6	0.6	1.002	0.325–3.088	0.996

The *P* value using correction χ^2 test in the table was marked with * symbol.

4. Discussion

The results of the present study supported the idea that polymorphism of HLA-A, -B, -C,-DRB1 and -DQB1 could influence the susceptibility to ESRD. At A locus in the current study, the susceptible alleles were A*11:01 and A*31:01. Similarly, a significant susceptibility association was found between ESRD and A*11, A*33 in Azerbaijan republic [13]. In addition, patients with microscopic polyarthritis and renal involvement in Greeks had increased frequency at A*11 [14]. In Cantonese from China [15], the frequency of A*24 in patients with ESRD was significantly higher than in the controls and A*24:02 was the second frequent allele in the current study with frequency of 18.6%, while there was no statistical difference between the patients with ESRD and the controls. On the other hand, A*26 had a significant negative association with ESRD and emerged as a protective allele to ESRD in Saudi Arabians, but no consistence with the current study [16]. In short, A*11:01 as a susceptible allele in the present results was consistent with in Azerbaijan Republic and Greeks.

At B locus of the current research, B*15:01, B*55:02 and B*39:05 emerged as susceptible alleles to ESRD. Similarly, alleles of B*15 and B*55 were found to be associated with susceptibility to ESRD in several

Table 4
HLA-C allele frequency in patients with ESRD and healthy controls.

NO	Allele	ESRD (%)	Control (%)	RR	95% CI	*P*- value
1	01:02	15.5	15.5	1.007	0.064–15.775	0.929
2	01:03	0.7	0.8	0.946	0.273–3.277	0.867
3	01:06	0.2	0.1	1.398	0.989–1.977	0.948*
4	02:02	1.2	0.8	1.328	0.368–4.787	0.262
5	03:02	5.6	6.9	0.851	0.082–8.869	0.180
6	03:03	8.1	6.9	1.152	0.111–11.996	0.162
7	03:04	8.1	8.6	0.958	0.082–11.177	0.675
8	04:01	6.8	6.0	1.095	0.112–10.700	0.411
9	04:03	0.6	0.8	0.837	0.242–2.901	0.619
10	05:01	0.4	0.7	0.643	0.194–2.134	0.309
11	**06:02**	**11.2**	**14.0**	**0.826**	**0.056–12.299**	**0.029**
12	**07:01**	**0.8**	**1.8**	**0.520**	**0.098–2.752**	**0.032**
13	07:02	13.3	11.5	1.140	0.085–15.385	0.106
14	07:04	0.5	0.9	0.653	0.178–2.400	0.273
15	07:06	0.5	0.9	0.653	0.178–2.400	0.273
16	08:01	8.2	8.3	0.996	0.087–11.421	0.968
17	08:03	0.3	0.7	0.501	0.151–1.663	0.163
18	12:02	4.4	3.9	1.109	0.141–8.698	0.441
19	12:03	1.5	1.0	1.343	0.336–5.372	0.192
20	14:02	5.0	4.3	1.133	0.137–9.347	0.322
21	14:03	2.8	2.4	1.132	0.184–6.979	0.458
22	15:02	3.4	2.9	1.145	0.170–7.724	0.373
23	15:05	0.4	0.7	0.643	0.194–2.134	0.309

The *P* value using correction χ^2 test in the table was marked with * symbol.

Table 5
HLA-DRB1 allele frequency in patients with ESRD and healthy controls.

NO	Allele	ESRD (%)	Control (%)	RR	95% CI	*P*- value
1	01:01	1.3	2.3	0.632	0.105–3.795	0.058
2	**03:01**	**4.7**	**3.2**	**1.358**	**0.193–9.555**	**0.018**
3	04:01	0.5	0.8	0.717	0.207–2.484	0.392
4	**04:03**	**2.4**	**1.1**	**1.683**	**0.397–7.141**	**0.003**
5	**04:04**	**1.8**	**1.0**	**1.509**	**0.377–6.037**	**0.046**
6	**04:05**	**7.9**	**5.7**	**1.284**	**0.135–12.245**	**0.014**
7	04:06	2.9	2.7	1.071	0.165–6.943	0.675
8	04:07	0.1	0.2	0.694	0.439–1.097	0.954*
9	04:10	0.4	0.4	0.926	0.350–2.449	0.921
10	07:01	10.4	12.6	0.847	0.060–11.952	0.066
11	08:02	0.1	0.5	0.260	0.095–0.711	0.170*
12	08:03	6.9	8.7	0.824	0.070–9.656	0.074
13	09:01	13.2	13.9	0.958	0.065–14.187	0.595
14	10:01	2.6	1.9	1.252	0.227–6.913	0.194
15	**11:01**	**7.0**	**4.1**	**1.478**	**0.183–11.914**	**3.030×10^{-4}**
16	12:01	2.8	3.5	0.835	0.112–6.218	0.279
17	**12:02**	**10.7**	**7.1**	**1.384**	**0.130–14.680**	**2.526×10^{-4}**
18	13:01	1.0	1.7	0.647	0.125–3.364	0.114
19	13:02	4.9	6.2	0.821	0.083–8.149	0.122
20	13:12	0.3	0.2	1.251	0.669–2.340	0.941*
21	14:03	0.9	0.5	1.568	0.572–4.293	0.120
22	14:04	0.6	0.3	1.473	0.628–3.455	0.419
23	14:05	1.7	2.2	0.821	0.140–4.820	0.353
24	14:07	0.5	0.3	1.606	0.803–3.211	0.369
25	14:54	2.1	1.8	1.124	0.211–6.002	0.542
26	**15:01**	**7.5**	**11.1**	**0.714**	**0.054–9.442**	**0.001**
27	15:02	2.6	3.2	0.856	0.121–6.053	0.369
28	15:04	0.1	0.2	0.694	0.439–1.097	0.954*
29	16:02	1.1	1.6	0.724	0.142–3.694	0.221

The *P* value using correction χ^2 test in the table was marked with * symbol.

regions. For example, in Cantonese from China, the frequency of B*55 in patients with ESRD was significantly higher than that in the controls and B*55:02 was the most common subtype in B*55 according to the HLA frequency of Cantonese population [15,17]. In Central China, B*15 showed significantly different frequency in patients and healthy groups, acted as a susceptible allele to ESRD [18]. In the Saudi Arabian population, alleles positively associated with ESRD were B*15, B*18, B*49 [16]. In another study from Zulia and Venezuela, B*38, B*51, B*53, B*15 (62) alleles were positively associated with ESRD [19]. In brief,

Table 6
HLA-DQB1 allele frequency in patients with ESRD and healthy controls.

NO	Allele	ESRD (%)	Control (%)	RR	95% CI	*P*- value
1	**02:01**	**4.8**	**3.1**	**1.399**	**0.201–9.746**	**0.009**
2	02:02	8.5	10.3	0.847	0.066–10.833	0.093
3	**03:01**	**22.2**	**16.5**	**1.309**	**0.081–21.141**	**4.949×10^{-5}**
4	**03:02**	**7.4**	**5.6**	**1.248**	**0.133–11.737**	**0.035**
5	03:03	15.5	16.1	0.967	0.061–15.436	0.656
6	03:05	0.3	0.1	2.088	1.705–2.557	0.310*
7	03:13	0.2	0.2	0.926	0.495–1.733	0.790*
8	**04:01**	**7.5**	**5.5**	**1.282**	**0.138–11.925**	**0.017**
9	04:02	0.6	1.4	0.508	0.109–2.354	0.053
10	05:01	4.4	4.9	0.913	0.103–8.068	0.501
11	05:02	3.0	3.7	0.852	0.112–6.491	0.322
12	05:03	4.4	3.5	1.192	0.160–8.881	0.191
13	06:01	10.5	11.7	0.910	0.067–12.398	0.296
14	**06:02**	**4.7**	**9.3**	**0.554**	**0.046–6.713**	**4.135×10^{-6}**
15	06:03	1.0	1.8	0.628	0.119–3.323	0.090
16	06:04	2.9	2.8	1.025	0.154–6.841	0.878
17	**06:09**	**1.9**	**3.3**	**0.632**	**0.087–4.578**	**0.022**

The *P* value using correction χ^2 test in the table was marked with * symbol.

Table 7
HLA-A, -C,-B, -DRB1 and -DQB1 haplotype frequency in patients with ESRD.

NO	Haplotype	Frequency (%)
1	30:01-06:02-13:02-07:01-02:02	0.8
2	02:07-01:02-46:01-09:01-03:03	0.6
3	32:01-12:02-52:01-15:02-06:01	0.5
4	11:01-06:02-13:02-07:01-02:02	0.5
5	**11:01-03:03-15:01-11:01-03:01**	0.4
6	24:02-14:02-51:01-09:01-03:03	0.4
7	02:01-06:02-13:02-07:01-02:02	0.4
8	24:02-06:02-13:02-07:01-02:02	0.4
9	24:02-03:02-15:18-03:01-02:01	0.3
10	24:02-03:04-13:02-07:01-02:02	0.3
11	11:01-07:02-40:01-12:02-03:01	0.3
12	11:01-04:01-15:01-04:06-03:02	0.3
13	30:01-06:02-13:02-12:02-03:01	0.3
14	33:03-03:02-58:01-13:02-06:09	0.3
15	01:01-06:02-37:01-10:01-03:01	0.3
16	24:02-08:01-40:06-15:01-06:02	0.3
17	33:03-06:02-58:01-13:02-06:09	0.3
18	02:07-01:02-13:02-07:01-02:02	0.3
19	02:01-04:01-15:27-04:06-03:02	0.3

Table 8
HLA-A, -C, -B, -DRB1 and -DQB1 haplotype frequency in healthy controls.

NO	Haplotype	Frequency (%)
1	30:01-06:02-13:02-07:01-02:02	1.3
2	30:01-06:02-46:01-08:03-02:02	0.3
3	11:01-06:02-13:02-07:01-06:01	0.3
4	33:03-06:02-58:01-07:01-02:02	0.3
5	02:01-03:04-13:01-12:02-03:01	0.3
6	11:01-04:01-15:01-04:06-03:02	0.3
7	24:02-14:02-51:01-09:01-03:03	0.3
8	33:03-06:02-58:01-13:02-02:02	0.3

B*55:02 as a susceptible allele was consistent with Cantonese and B*15:01 as a susceptible allele was consistent with Central China. In Egyptians, HLA-B*35 was significantly higher in patients with ESRD [20], which was not consistent with the current research.

At C locus in the present study, C*06:02 and C*07:01 showed significant negative correlations with ESRD and emerged as protective alleles to ESRD. In Saudi Arabian patients, C*02 was found to be associated negatively with ESRD, which was not consistent with the current research [16].

At DRB1 locus in the present study, DRB1*03:01, DRB1*04:03, DRB1*04:04, DRB1*04:05, DRB1*11:01 andDRB1*12:02 emerged as

susceptible alleles and DRB1*15:01 emerged as a protective allele to ESRD. In Cantonese from China, the frequency of DRB1*04 in patients with ESRD were significantly higher than that in the controls [15]. In Dalian Han population of China, DRB1*12 showed a positive association with ESRD [21]. In Taiwanese, DRB1*03 and DRB1*11 represented susceptible risk for the development of ESRD [22]. In Sichuan and Beijing Han population of China, DRB1*04 was significantly associated with primary IgAN [23]. In brief, DRB1*04:03, DRB1*04:04 and DRB1*04:05 as susceptible alleles were consistent with Cantonese and Central China (DRB1*04). DRB1*11:01 as a susceptible allele was consistent with Central China and Taiwanese (DRB1*11). DRB1*03:01 as a susceptible allele was consistent with Taiwanese (DRB1*03). In Saudi Arabian population, the allele positively associated to the ESRD was DRB1*03 [16], which was consistent with the current study. On the other hand, DRB1*15:01 regarded as a susceptible allele had a strong postive correlation with ant glomerular basement membrane nephritis in Japanese patients, which was contrary to the present research [24].

At DQB1 locus in the present study, DQB1*02:01, DQB1*03:01, DQB1*03:02 and DQB1*04:01 emerged as susceptible alleles to ESRD. Similarly, DQB1*03(8) was found to be associated to a marginally greater risk in Saudi Arabian patients with ESRD [16], which was consistent with the current research.

Many of the susceptible alleles reported in the study cohort were known to be associated with specific kidney diseases. For example A*11 was positive correlation with microscopic polyarthritis and renal involvement in Greeks, DRB1*04 was significantly associated with primary IgAN in Sichuan and Beijing Han population of China. In addition, DRB1*03:01 conferred risk of membranous nephropathy in Han Chinese and DRB1*11:01 conferred risk of MPO-AAV in a Chinese population [25,26]. Patient samples would be expanded and kidney disease classification would be differentiated in the future.

Except for the susceptible alleles, an important susceptible haplotype A*11:01-C*03:03-B*15:01-DRB1*11:01-DQB1*03:01 carrying four susceptible alleles was found, which was much more important in predicting the progression of ESRD. Comparing with donor selection on the basis of number/type of HLA mismatches, donor selection on the basis of HLA haplotype mismatches was more important [27,28]. Besides, in the consanguineous renal transplantation, it would be very beneficial for the long-term survival of renal transplant patients to avoid the susceptible alleles, haplotypes in selecting optimal donors.

Results from the present study should be confirmed in further investigations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.09.001.

References

[1] J.L. Holley, Advance care planning in CKD/ESRD: an evolving process, Clin. J. Am. Soc. Nephrol. 7 (2012) 1033.
[2] M.D. Okusa, G.M. Chertow, D. Portilla, Nephrology AKIAGotASo: the nexus of acute kidney injury, chronic kidney disease, and World Kidney Day 2009, Clin. J. Am. Soc. Nephrol. 4 (2009) 520.
[3] A.N. Karopadi, G. Mason, E. Rettore, C. Ronco, The role of economies of scale in the cost of dialysis across the world: a macroeconomic perspective, Nephrol. Dial. Transplant. (2014) gft528.
[4] ESRD Patients in 2012: A Global Perspective. Fresenius Medical Care.
[5] L. Zuo, M. Wang, Current burden and probable increasing incidence of ESRD in China, Clin. Nephrol. 74 (2010) S20.
[6] K.J. Robson, J.D. Ooi, S.R. Holdsworth, J. Rossjohn, A.R. Kitching, HLA and kidney disease: from associations to mechanisms, Nat. Rev. Nephrol. 14 (2018) 636.
[7] G. Yang, Y.J. Deng, S.N. Hu, D.Y. Wu, S.B. Li, J. Zhu, et al., HLA-A,-B, and-DRB1 polymorphism defined by sequence-based typing of the Han population in Northern China, Tissue Antigens 67 (2006) 146.
[8] E. Trachtenberg, M. Vinson, E. Hayes, Y.M. Hsu, K. Houtchens, H. Erlich, et al., HLA class I (A, B, C) and class II (DRB1, DQA1, DQB1, DPB1) alleles and haplotypes in the Han from southern China, Tissue Antigens 70 (2007) 455.
[9] M. Maiers, L. Gragert, W. Klitz, High-resolution HLA alleles and haplotypes in the United States population, Hum. Immunol. 68 (2007) 779.
[10] N. Cereb, H.R. Kim, J. Ryu, S.Y. Yang, Advances in DNA sequencing technologies for high resolution HLA typing, Hum. Immunol. 76 (2015) 923.
[11] M. Gowda, S. Ambardar, N. Dighe, A. Manjunath, C. Shankaralingu, Comparative analyses of low, medium and high-resolution HLA typing technologies for human populations, J. Clin. Cell. Immunol. 7 (2016) 2.
[12] L. Excoffier, H.E. Lischer, Arlequin suite ver 3.5: a new series of programs to perform population genetics analyses under Linux and Windows, Mol. Ecol. Resour. 10 (2010) 564.
[13] P.P. Davood, N. Farhadi, M. Najafizadeh, Protective and susceptible HLA Class I genes in patients with end-stage renal disease, Res. J. Biol. Sci. 3 (2008) 1344.
[14] C. Papasteriades, D. Hatziyannakos, M. Siakotos, H. Pappas, K. Tarassi, N. Nikolopoulou, et al., HLA antigens in microscopic polyarteritis (MP) with renal involvement, Dis. Markers 13 (1997) 117.
[15] Q. Cao, D. Xie, J. Liu, H. Zou, Y. Zhang, H. Zhang, et al., HLA polymorphism and susceptibility to end-stage renal disease in Cantonese patients awaiting kidney transplantation, PLoS One 9 (2014) e90869.
[16] N.M. Hamdi, F.H. Al-Hababi, A.E. Eid, HLA class I and class II associations with ESRD in Saudi Arabian population, PLoS One 9 (2014) e111403.
[17] P. Qin Qin, F. Su, W. Xiao Yan, Z. Xing, P. Meng, W. Chengya, et al., Distribution of human leucocyte antigen-A,-B and-DR alleles and haplotypes at high resolution in the population from Jiangsu province of China, Int. J. Immunogenet. 38 (2011) 475.
[18] W. Shang, Y. Shen, S. Gao, G. Feng, Y. Feng, Z. Wang, et al., Comparison of HLA-A,-B and-DRB1 loci polymorphism between kidney transplants of uremia patients and healthy individuals in Central China, PLoS One 11 (2016) e0165426.
[19] S. Rivera, G. Márquez, A.M. Cipriani, M. Hassanhi, C.C. Villalobos, A. Fuenmayor, et al., HLA class I association with progression to end-stage renal disease in patients from Zulia, Venezuela. Inmunol. 31 (2012) 37.
[20] E. El-Gezawy, H. Baset, K. Nasif, A. Osama, H. AbdelAzeem, M. Ali, et al., Human leukocyte antigens as a risk factor for the primary diseases leading to end stage renal disease in Egyptian patients, Egypt. J. Immunol./Egypt. Assoc. Immunol. 18 (2010) 13.
[21] L.-N. Shao, Y. Yang, S.-T. Zhang, S.-H. Zhou, Y. Duan, Q.-L. Meng, et al., Association between the polymorphism of HLA and ESRD in Dalian Han population located in north of China, Immunol. Invest. 47 (2018) 212.
[22] C.-S. Dai, C.-C. Chu, S.-F. Chen, C.-Y. Sun, M. Lin, C.-C. Lee, Association between human leucocyte antigen subtypes and risk of end stage renal disease in Taiwanese: a retrospective study, BMC Nephrol. 16 (2015) 177.
[23] Y. Jiyun, L. Guisen, Z. Li, S. Yi, L. Jicheng, L. Fang, et al., The genetic variants at the HLA-DRB1 gene are associated with primary IgA nephropathy in Han Chinese, BMC Med. Genet. 13 (2012) 33.
[24] W. Kitagawa, H. Imai, A. Komatsuda, N. Maki, H. Wakui, Y. Hiki, et al., The HLA-DRB1* 1501 allele is prevalent among Japanese patients with anti-glomerular basement membrane antibody-mediated disease, Nephrol. Dial. Transplant. 23 (2008) 3126.
[25] Z. Cui, L.J. Xie, F.J. Chen, Z.Y. Pei, L.J. Zhang, Z. Qu, et al., MHC Class II risk alleles and amino acid residues in idiopathic membranous nephropathy, J. Am. Soc. Nephrol. 28 (2016) 1651.
[26] H. Luo, M. Chen, R. Yang, P.C. Xu, M.H. Zhao, The association of HLA-DRB1 alleles with antineutrophil cytoplasmic antibody-associated systemic vasculitis in Chinese patients, Hum. Immunol. 72 (2011) 422.
[27] S. Takemoto, F.K. Port, F.H. Claas, R.J. Duquesnoy, HLA matching for kidney transplantation, Hum. Immunol. 65 (2004) 1489.
[28] C.D. Miles, D.E. Schaubel, D. Liu, F.K. Port, P.S. Rao, The role of donor-recipient relationship in long-term outcomes of living donor renal transplantation, Transplantation 85 (2008) 1483.