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Association between the polymorphism of HLA and ESRD in Dalian Han population located in north of China

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ABSTRACT

Background: End-stage renal disease (ESRD), the last stage of chronic renal failure, is a global health problem. The number of ESRD patients worldwide is increasing faster than the number of kidneys available per year for renal transplantation. Most of the ESRD patients are awaiting renal transplantation. The immune response to the transplanted kidney is directed mainly against mismatched human leukocyte antigen (HLA) glycoproteins expressed on donor tissues. Thus, the analysis of HLA allele and haplotype polymorphisms is valuable not only for identifying ESRD susceptibility factors but also to improve graft survival. Methods: In this study, 163 Han ESRD patients were recruited to participate. The blood samples were genotyped by sequence-specific oligonucleotide method. A group of 14,529 healthy Chinese Han individuals registered at the Dalian Blood Center as bone marrow donors, living in the same region and of the same ethnicity, were used as controls. Results: We found that only one allele, HLA-DRB1*12, showed a positive association with ESRD (p = 0.004, p_c = 0.028, odds ratio = 1.530, 95% confidence interval = 1.147–2.041); A*02-B*40-DRB1*09, A*02-B*40-DRB1*12, A*24-B*15-DRB1*12, and B*40-DRB1*12 were significantly more frequent in ESRD patients after Bonferroni correction ($p_c < 0.05$). Conclusion: They were potentially valuable predictors for evaluating the risk of ESRD in the Dalian Han population.

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Human leukocyte antigens; polymorphism; end-stage renal disease; susceptibility

Introduction

End-stage renal disease (ESRD), the last stage of chronic renal failure, is a global health problem (Levey et al., 2007). It has been defined as the permanent, total, or nearly total loss of renal function, making the patient dependent on renal replacement therapy such as dialysis or even a kidney transplant for continued survival (Alsuwaida et al., 2010). It is a devastating medical condition and the cost of treatment represents a significant economic burden (Mosaad et al., 2014). In the United States, the incidence of ESRD was 343 per million population (PMP) in 2000, and 453 PMP in 2015 (Gilbertson et al., 2005). A high prevalence is seen in China. At the end of 2008, it was estimated to be 88.9 PMP and the annual incidence was 36.1 PMP. In Liaoning province, where our blood center is located, the prevalence was 149 PMP, higher than the national average (Zuo and Wang, 2010). It is

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worth noting that the number of ESRD patients worldwide is increasing faster than the number of kidneys available per year for renal transplantation.

The HLA system is the most polymorphic genetic system described in humans and consists of several closely linked loci (Rey et al., 2015). Study of the HLA alleles and haplotype distribution patterns in populations suffering from a variety conditions is of great interest, since there molecules play critical roles in antigen presentation, tolerance, and self/non-self discrimination. They are especially important in terms of the immune response to the allograft after renal transplantation and have been studied as genetic markers associated with several diseases, particularly autoimmune (Giarola et al., 2012; Klein and Sato, 2000a, 2000b). However, little is known regarding possible associations between HLA alleles and haplotypes in northern Chinese Han ESRD patients. In order to enrich our knowledge in this field, we investigated the HLA-A, -B, and -DRB1 allele and haplotype frequencies of 163 Han ESRD patients living in Dalian (northern of China).

Materials and methods

Study population

A total of 163 Han ESRD patients (gender: 101 male/62 female; age range: 19–64; mean age ± SD: 41.55 ± 10.82) who were undergoing treatment at the Dalian Municipal Friendship Hospital between 2011 and 2017 while awaiting transplantation were recruited to participate in this study. The causes of ESRD in these patients are listed in Table 1. Ethics committee approval was received for this study from the Local Ethics Committee. Written informed consent was obtained from all individual participants who participated in this study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. A group of 14,529 healthy Chinese Han individuals registered at the Dalian Blood Center as bone marrow donors, living in the same region and of the same ethnicity, were used as controls (Shao et al., 2016). To avoid bias, only one member of each family was selected for the control group. As age and gender do not influence an individual's HLA frequency profile, the control group was not age- and gender-matched with the patient group.

HLA genotyping

Five milliliter of whole peripheral blood samples was collected in ethylenediaminetetraacetic acid anti-coagulant tubes. Genomic DNA was extracted using a QIAamp blood kit (QIAgen, Hilden, Germany) according to the manufacturer's protocol. HLA-A, -B, and

Table 1. Causes of end-stage renal disease within the patients.

Primary disease	*n*	%
Chronic glomerulonephritis	124	76.1
Hypertensive nephrosclerosis	25	15.3
Diabetic nephropathy	7	4.3
IgA nephropathy	2	1.2
Polycystic kidney disease	1	0.6
Chronic pyelonephritis	1	0.6
Other	3	1.8

-DRB1 loci were genotyped by sequence-specific oligonucleotide method according to the manufacture's introductions (One Lambda, Canoga Park, CA, USA). The product signals could be detected by a Luminex-IS200 flow cytometer system (Luminex Corporation, Austin, TX, USA), and the results were analyzed using HLA Fusion software, version 3.0 (One Lambda). The HLA alleles were assessed using HLA nomenclature release 3.15.0 (IMGT/HLA database).

Statistics analysis

HLA-A, -B, and -DRB1 allele frequencies were obtained by direct counting method. Hardy–Weinberg equilibrium (HWE) at each locus was tested using ARLEQUIN software package, version 3.5.2.2 (Excoffier and Lischer, 2010; Guo and Thompson, 1992). This software was also used to estimate haplotypic frequencies based on the expectation-maximization (EM) algorithm. The comparison analysis using Fisher's exact test and the relative risk estimate evaluated by odds ratio (OR) at the 95% confidence interval (CI) was performed by SPSS version 21.0. Only allele groups with frequencies >5% in cases were analyzed for Bonferroni correction. Corrected probability values (p_c) were determined by multiplying individual p values by the number of comparisons made at the allele and haplotype levels: 5 for A and B alleles, 7 for DRB1 alleles, and 10 for three- and two-locus haplotypes. The p value of less than 0.05 was considered statistically significant difference.

Results

HWE test at HLA-A, -B, and -DRB1 loci

No significant deviation was found from HWE at HLA-A, -B, and -DRB1 loci in Han ESRD patients (p = 0.21 for HLA-A, 0.36 for HLA-B, and 0.19 for HLA-DRB1).

Comparison of allele frequencies between ESRD patients and controls

A total of 49 different alleles were found in Han ESRD patients, including 13 HLA-A alleles, 23 HLA-B alleles, and 13 HLA-DRB1 alleles. The allele frequencies in ESRD patients and controls are summarized in Table 2. We found that only one allele, HLA-DRB1*12, showed a positive association with ESRD (p = 0.004, p_c = 0.028, OR = 1.530, 95% CI = 1.147–2.041).

Comparison of haplotype distributions between ESRD patients and controls

A total of 600 HLA-A-B-DRB1, 153 HLA-A-B, and 177 HLA-B-DRB1 haplotypes were identified in Han ESRD patients following the EM algorithm analyses. The top 10 three- and two-locus haplotypes found in Dalian Han ESRD patients are listed in Table 3, comparing their frequencies with the control group. The data indicated that 8 three-locus haplotypes and 3 two-locus haplotypes showed a positive association with ESRD. In order to find protective haplotypes, the 10 predominant three- and two-locus haplotypes found in controls were also investigated, and their frequencies compared with those seen in ESRD patients (Table 4). This analysis revealed that A*02-B*46-DRB1*09 was

Table 2. The frequencies and associations of HLA-A, -B, and -DRB1 alleles between Dalian Han ESRD patients and controls.

	Patient $2N = 326$	Control $2N = 29{,}058$				Patient 2 $N = 326$	Control $2N = 29{,}058$		
Allele	Frequency		p	p_c	Allele	Frequency		p	p_c
A*01	0.030675	0.041469	NS	NS	B*46	0.061350	0.075194	NS	NS
A*02	0.306748	0.316815	NS	NS	B*48	0.039877	0.034276	NS	NS
A*03	0.046012	0.041400	NS	NS	B*50	0.009202	0.007984	NS	NS
A*11	0.187117	0.173240	NS	NS	B*51	0.070552	0.071168	NS	NS
A*23	0.003067	0.003200	NS	NS	B*52	0.030675	0.034035	NS	NS
A*24	0.177914	0.164533	NS	NS	B*54	0.046012	0.032762	NS	NS
A*26	0.036810	0.031902	NS	NS	B*55	0.015337	0.019822	NS	NS
A*29	0.009202	0.007399	NS	NS	B*56	0.003067	0.003717	NS	NS
A*30	0.092025	0.071822	NS	NS	B*57	0.009202	0.015314	NS	NS
A*31	0.030675	0.038027	NS	NS	B*58	0.039877	0.049281	NS	NS
A*32	0.012270	0.015555	NS	NS	B*67	0.006135	0.008638	NS	NS
A*33	0.064417	0.082525	NS	NS	DRB1*01	0.027607	0.027290	NS	NS
A*68	0.003067	0.009361	NS	NS	DRB1*03	0.036810	0.039817	NS	NS
B*07	0.024540	0.034655	NS	NS	DRB1*04	0.128834	0.108645	NS	NS
B*08	0.003067	0.009257	NS	NS	DRB1*07	0.104294	0.110297	NS	NS
B*13	0.144172	0.117730	NS	NS	DRB1*08	0.076687	0.066350	NS	NS
B*15	0.119632	0.144711	NS	NS	DRB1*09	0.144172	0.132975	NS	NS
B*18	0.003067	0.004680	NS	NS	DRB1*10	0.024540	0.013869	NS	NS
B*27	0.030675	0.020373	NS	NS	DRB1*11	0.061350	0.063012	NS	NS
B*35	0.046012	0.051208	NS	NS	**DRB1*12**	**0.174847**	**0.121619**	**0.004**	**0.028**
B*37	0.027607	0.014110	NS	NS	DRB1*13	0.042945	0.066453	NS	NS
B*38	0.036810	0.023952	NS	NS	DRB1*14	0.049080	0.069585	NS	NS
B*39	0.012270	0.018205	NS	NS	DRB1*15	0.128834	0.160438	NS	NS
B*40	0.184049	0.148806	NS	NS	DRB1*16	0.006135	0.019650	NS	NS
B*44	0.036810	0.048696	NS	NS					

N: Number of individuals; NS: not significant; p value was calculated by Fisher's exact test; p_c: p corrected; p value after Bonferroni correction with the number of comparison = 5 for A and B alleles, 7 for DRB1 alleles. Significant associations are indicated in bold; odds ratio (95% confidence interval): 1.530 (1.147–2.041).

significantly less frequent in ESRD patients. However, some of the above mentioned comparisons of haplotype distributions were no longer statistically significant following Bonferroni corrections. Only A*02-B*40-DRB1*09, A*02-B*40-DRB1*12, A*24-B*15-DRB1*12, and B*40-DRB1*12 were significantly more frequent in ESRD patients ($p_c < 0.05$).

Discussion

The worldwide incidence and prevalence of ESRD have markedly increased since the mid-1980s (Almogren et al., 2012). Several factors have been identified which can influence the development of ESRD, including gender, ethnicity, genetic factors, lipid profile, hypertension, and smoking (De Menthon et al., 2009). Kidney transplantation is the treatment of choice for ESRD because it prolongs survival, decreases morbidity and improves the quality of life of the patient (Jordan and Pescovitz, 2006; Port et al., 1993; Russell et al., 1992). The immune response to the transplanted kidney is directed mainly against mismatched HLA glycoproteins expressed on donor tissues (Kosmoliaptsis et al., 2014). Thus, the analysis of HLA allele and haplotype polymorphisms is valuable not only for identifying ESRD susceptibility factors but also to improve graft survival.

Table 3. Top 10 frequent three- and two-locus haplotypes in Dalian Han ESRD patients compared with controls.

	Patient $2N = 326$	Control $2N = 29{,}058$			
Haplotype	Frequency		p	p_c	OR (95% CI)
A*30-B*13-DRB1*07	0.067485	0.050253	NS	NS	
A*02-B*40-DRB1*09	**0.037604**	**0.011982**	**0.001**	**0.01**	**3.153 (1.755–5.666)**
A*02-B*40-DRB1*12	**0.028697**	**0.007389**	**0.001**	**0.01**	**3.809 (1.937–7.488)**
A*24-B*15-DRB1*12	**0.021198**	**0.003830**	**3.57×10^{-4}**	**3.57×10^{-3}**	**5.723 (2.645–12.381)**
A*02-B*15-DRB1*04	0.020618	0.009876	0.047	NS	2.200 (1.031–4.694)
A*02-B*51-DRB1*09	0.019737	0.004784	0.006	NS	3.901 (1.710–8.898)
A*33-B*58-DRB1*03	0.018405	0.017972	NS	NS	
A*24-B*40-DRB1*04	0.018108	0.004942	0.007	NS	3.765 (1.651–8.583)
A*11-B*13-DRB1*12	0.017716	0.006199	0.018	NS	3.008 (1.324–6.835)
A*24-B*40-DRB1*12	0.017315	0.005745	0.013	NS	3.244 (1.426–7.378)
A*02-B*40	0.074535	0.051852	NS	NS	
A*30-B*13	0.073476	0.061153	NS	NS	
A*24-B*40	0.057503	0.042722	NS	NS	
A*24-B*15	0.043071	0.024764	0.047	NS	1.766 (1.029–3.032)
A*11-B*40	0.038222	0.033876	NS	NS	
A*33-B*58	0.036810	0.038324	NS	NS	
A*02-B*15	0.033664	0.060400	NS	NS	
A*02-B*46	0.030958	0.054959	NS	NS	
A*02-B*13	0.030148	0.021732	NS	NS	
A*02-B*51	0.029686	0.022427	NS	NS	
B*13-DRB1*07	0.079755	0.061365	NS	NS	
B*40-DRB1*12	**0.056766**	**0.021956**	**1.57×10^{-4}**	**1.57×10^{-3}**	**2.757 (1.723–4.411)**
B*40-DRB1*09	0.055640	0.033165	0.019	NS	1.804 (1.130–2.879)
B*15-DRB1*12	0.040147	0.025658	NS	NS	
B*13-DRB1*12	0.037378	0.026201	NS	NS	
B*15-DRB1*04	0.033907	0.029931	NS	NS	
B*40-DRB1*04	0.026669	0.017721	NS	NS	
B*51-DRB1*09	0.026124	0.016825	NS	NS	
B*46-DRB1*09	0.025556	0.032744	NS	NS	
B*54-DRB1*04	0.021472	0.014595	NS	NS	

N: Number of individuals; NS: not significant; p value was calculated by Fisher's exact test; p_c: p corrected; p value after Bonferroni correction with the number of comparison = 10 for three- and two-locus haplotypes; OR: odds ratio; CI: confidence interval. Significant associations are indicated in bold.

Table 4. Top 10 frequent three- and two-locus haplotypes in controls compared with Dalian Han ESRD patients.

	Patient $2N = 326$	Control $2N = 29{,}058$			
Haplotype[a]	Frequency		p	p_c	OR (95% CI)
A*02-B*46-DRB1*09	0.005360	0.024022	0.027	NS	0.251 (0.062–1.009)
A*02-B*15-DRB1*15	0.009202	0.016781	NS	NS	
A*02-B*13-DRB1*12	0.012503	0.013413	NS	NS	
A*33-B*58-DRB1*13	0.015337	0.012898	NS	NS	
A*33-B*44-DRB1*13	0.009202	0.012471	NS	NS	
A*02-B*46-DRB1*08	0.003067	0.012112	NS	NS	
A*11-B*15-DRB1*12	0.009202	0.011544	NS	NS	
A*11-B*15	0.029544	0.038966	NS	NS	
B*15-DRB1*15	0.017793	0.03394	NS	NS	
B*40-DRB1*15	0.019083	0.026734	NS	NS	
B*58-DRB1*03	0.021472	0.023079	NS	NS	

[a]The haplotype repeats with Table 2 were omitted.

N: Number of individuals; NS: not significant; p value was calculated by Fisher's exact test; p_c: p corrected; p value after Bonferroni correction with the number of comparison = 10 for three- and two-locus haplotypes; OR: odds ratio; CI: confidence interval.

In this work, we investigated the HLA-A, -B, and -DRB1 alleles and haplotype distributions of 163 Han ESRD patients. The most straight forward observation is that

only HLA-DRB1*12 showed a significantly different frequency between the two groups, and no protective allele was found. This suggests that the HLA-DRB1*12 allele is a susceptibility marker for ESRD in the Dalian Han population. Moreover, the A*02-B*40-DRB1*09, A*02-B*40-DRB1*12, A*24-B*15-DRB1*12, and B*40-DRB1*12 haplotypes showed significantly different distributions between ESRD patients and controls, indicating that they were risk haplotypes for ESRD in the Dalian Han population. In contrast, no protective haplotypes were identified. Some haplotypes did not show any statistically significant associations after the Bonferroni correction. However, some of the trends in haplotype distribution seen in ESRD patients when compared with controls are noteworthy. For example, the haplotype A*02-B*51-DRB1*09 (p = 0.006, p_c = 0.06, OR = 3.901, 95% CI = 1.710–8.898) was more frequently seen in ESRD patients suggesting that this haplotype may also confer increased susceptibility.

Study performed by Dai et al. (2015) in southern China (Taiwan province) indicated that none of the HLA-A or -B alleles was positively associated with susceptibility to ESRD; DR3 and DR11 were identified as risk factors and DR8 as a protective allele. Cao et al. (2014) found that in the Cantonese population, the A*24, B*55, B*54, B*40, DRB1*04 alleles, and the A*11-B*27-DRB1*04 haplotype were significantly more frequent in ESRD patients. To our knowledge, the present study is the first to analyze the HLA-A, -B, and -DRB1 allele frequencies and haplotype distributions of ESRD patients in northern China. Our results are quite different from those observed in southern populations. A retrospective study describing the association of different HLA types with kidney diseases in worldwide populations also differs with our results (Dai et al., 2015). These apparently contradictory results after the analysis of specific loci in different global populations are a common outcome of genetic association studies. The possible reasons include different effects in different geographic locations and ethnic groups, different pathogeneses, referral bias, small sample sizes resulting in nonrepresentative populations, and various environmental triggering factors.

In the geographical context where this study was carried out, only the HLA-DRB1*12 allele was positively associated with ESRD. However, the high frequency A*02-B*40-DRB1*09 haplotype, lacking the DRB1*12 allele, was significantly more frequent in ESRD patients. On the contrary, the high frequency B*15-DRB1*12 haplotype, carrying the DRB1*12 allele, did not differ significantly between the two groups. A possible explanation is that certain alleles may actually have different functions in the context of different haplotypes. In a haplotype, it is not merely one allele that is responsible for the altered disease risk but rather interactions between multiple alleles which can modify the susceptibility to the disease. The mechanisms underlying these interactions are still unclear. Therefore, the most conservative way to approach this subject is to investigate the association of the entire haplotype with disease susceptibility, by comparing the frequencies between patients and healthy controls. In-depth studies are needed to understand the associated mechanisms.

The HLA system has a very high degree of polymorphism, and the allele and haplotype distributions vary in different geographic locations and ethnic groups (Rey et al., 2015). In order to obtain exact results, the sample size of our control group was very large (n = 14,529), and all the participants belonged to the same geographic region and ethnic group as the ESRD patients. The main limitation of this study was the small patient

sample size. However, our data provide initial information that can be used for further research on ESRD susceptibility.

In conclusion, this study shows that the HLA-DRB1*12 allele as well as the A*02-B*40-DRB1*09, A*02-B*40-DRB1*12, A*24-B*15-DRB1*12, and B*40-DRB1*12 haplotypes are potentially valuable predictors for evaluating the risk of ESRD in the Dalian Han population. For physicians planning the treatment of ESRD patients, it is essential to obtain molecular diagnostic information on HLA polymorphisms, in order to identify high-risk cases.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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