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HLA types and their association with end-stage renal disease in Vietnamese patients

A cross-sectional study

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Abstract

End-stage renal disease (ESRD) is a significant public health issue with an estimated increasing burden over the next 10 years. Early prediction of patients with a high risk of ESRD progression is crucial to monitor and initiate appropriate interventions, of which HLA alleles have been proposed as promising biomarkers. This cross-sectional study described HLA profiles of a Vietnamese cohort and investigated the association between HLA alleles and ESRD. All ESRD patients who were waitlisted to receive kidney transplant and potential donors in a tertiary hospital from March 2018 to April 2020 were invited to participate in the study. A total of 458 participants were eligible, including 126 ESRD patients and 126 family-related donors, 98 ESRD patients and 108 unrelated donors. HLA typing was performed using Luminex-based PCR-SSO technology. We found HLA-A*02, A*11, A*24, B*15, B*07, DRB1*12, DRB1*09, DQA1*01, DQA1*06, DQB1*03 and DQB1*05 as the most common alleles, which is similar to the general Vietnamese population and other countries in East and South-east Asia. HLA-B*07 (P = .040), DQA1*06 (P = .031), and DQB1*03 (P = .036) were susceptible to ESRD, while HLA-B*27 (P = .024) and DQB1*02 (P = .006) were associated with a decreased risk of ESRD.

Abbreviations: ESRD = end-stage renal disease, HLA = human leukocyte antigen, OR = odds ratio, PCR-SSO = Polymerase Chain Reaction-Sequence Specific Oligonucleotide.

Keywords: ESRD, HLA, PCR-SSO, susceptible alleles, Vietnamese

1. Introduction

End-stage renal disease (ESRD) is the final, irreversible stage of chronic kidney disease, which has become a leading public health problem worldwide.[1] The global number of patients with chronic kidney disease was 752.7 million,[2] of which the number of ESRD patients requiring renal replacement therapy is estimated to be around 4.902 to 7.083 million worldwide.[1] The burden of ESRD is forecasted to continuously increase in the next 10 years.[3,4] As ESRD patients can only be managed by dialysis or kidney transplant, early prediction of patients with high risk of ESRD progression is crucial to monitor and initiate appropriate interventions.[5]

The progression from chronic kidney disease to ESRD was suggested to be independent of any intensive therapy and vary among patients.[6] Human leukocyte antigen (HLA) genes encode major histocompatibility complex proteins in humans and are responsible for immune system regulation. The association between HLA alleles and renal disorders has been described since 50 years ago.[7] In recent years, the association between HLA alleles and ESRD has been proposed, as several of both HLA class I and class II alleles were found as protective or risk factors of ESRD in a variety of studies worldwide.[6,8,9] The identification of such associated alleles is not only important for screening high risk ESRD patients, but also extends our understanding of the disease mechanism which could help to accelerate the development of more effective, safe and targeted therapies.[7] Moreover, the susceptible alleles can be avoided when selecting optimal donors to increase the post-transplant long-term survival for ESRD patients.[10]

Although a large number of ESRD-associated HLA alleles were reported, results among studies were inconsistent. This might be caused by limited sample size but also suggested the possibility of specific susceptible alleles or variations among different ethnic groups or races.[8] Genetic association studies conducted on different populations are therefore essential to provide more evidence on globally susceptible HLA alleles and identify new alleles associated with particular ESRD patients in a country or area. In this study, we described the HLA profiles of a Vietnamese cohort and investigated the association between HLA alleles and ESRD.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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2. Methods

2.1. Study subjects

A cross-sectional study was conducted in Cho Ray Blood Transfusion Center, Cho Ray Hospital in Ho Chi Minh City, Vietnam from March 2018 to April 2020. All ESRD patients who were waiting to receive kidney transplant during the period were included in the study.

The donors were all healthy subjects who registered for kidney donation and were selected based on Vietnam Organ Donation Law and guidelines from the Ministry of Health.[11] Inclusion criteria were healthy individuals aged 18 and above, who had normal shape and renal functions.[11] Exclusion criteria were donors who were diagnosed with acute infectious diseases, diabetes, hypertension, coronary artery disease, cancer, pregnant or overweight. A nephrologist was responsible for performing clinical examinations on all subjects. After completing the screening procedure they were all considered as potential donors and be included in the study. Donors who are blood relatives to the patients were matched with these patients and formed the family-related group. The rest of donors and patients were considered as the unrelated donors group.

2.2. DNA extraction

Whole blood samples (2 mL) were collected from participants and stored in EDTA anticoagulant tube at 2 to 6°C. Genomic DNA was isolated using QIAamp DNA mini kit (Qiagen, Germantown, MD). DNA was extracted from whole blood. The extraction procedure was conducted followed manufacturer's protocol.

2.3. HLA typing using PCR-SSO

HLA typing on class I (HLA-A, -B) and class II (HLA-DRB1, -DQB1, and DQA1) of One Lambda were performed using Polymerase Chain Reaction-Sequence Specific Oligonucleotide method (PCR-SSO) using Luminex technology (Luminex, Austin, TX). Target DNA was PCR amplified using biotinylated locus specific primers. The PCR product was denatured and hydridised to a panel of complementary oligonucleotides conjugated to fluorescently coded microspheres. Each microsphere was coupled with single probe sequence that was capable of hydridizing with the biotin labeled complementary amplicons. A flow analyzer quantified the fluorescence signal from R-Phycoerythrin-Conjugated Streptavidin labeled amplicons and hybridized to the microspheres and classified the signal based on the unique color for each of microsphere. HLA fusion 3.0 program (One Lambda, Los Angeles, CA) was used to analyze the result.

2.4. Statistical analysis

All analyses were performed using R software version 4.1.2. Continuous variables were presented using mean ± standard deviation. Frequency and percentage were used to describe categorical data. Allele frequencies of HLA-A, -B, -DRB1, -DQB1, and DQA1 were computed by (n/2N)*100, of which n is the total count of an allele and N is the total number of individuals. Logistic regression model with generalized estimating equations (GEE) was used to examine allelic association. Statistical significance was defined as $P < .05$.

2.5. Ethics

This study was approved by the Ethics Review Committee of Cho Ray Hospital, Ho Chi Minh City, Vietnam (approval number: 1111/CN-HĐĐĐ, November 16, 2020). Written informed consent was obtained from all participants.

3. Results

A total of 458 participants were enrolled in the study, of which 98 ESRD patients and 108 unrelated donors, and 126 ESRD patients came with their 126 related donors. Most ESRD patients were men (66.7% and 64.3%) with mean age of 34.1 ± 9.5 years and 41.0 ± 9.7 years, respectively. The majority of unrelated donors were men with mean age of 38.2 ± 11.9 years, while most related donors were women at a higher age (mean: 52.1 ± 8.8 years) (Table 1).

HLA profiles were similar between ESRD patients and healthy donors. At the HLA-A and HLA-B loci, A*02, A*11, A*24 and B*15, B*07 were the most frequently found among both recipients (24.5%, 32.1%, 16.7%, 26.1%, 12.7%, respectively) and donors (22.4%, 29.8%, 18.2%, 23.4%, 9.9%) (Table 2). At HLA-DRB1, HLA-DQA1 and HLA-DQB1 loci, DRB1*12, DRB1*09, DQA1*01, DQA1*06, DQB1*03 and DQB1*05 were the most common alleles in all study groups (34.3%, 11.0%, 32.2%, 27.8%, 57.1%, 22.5% among recipients and 28.2%, 12.0%, 36.1%, 22.6%, 50.0%, 27.7% among donors, respectively) (Table 3).

HLA-B*07 (OR = 1.951 [1.032–3.688]), DQA1*06 (OR = 1.630 [1.044–2.545]) and DQB1*03 1.515 (1.027–2.235) were risk alleles of ESRD ($P < .05$). Conversely, HLA-B*27 (OR = 0.175 [0.039–0.793]), DQB1*02 (OR = 0.337

Table 1

Demographic characteristics of participants.

	Related donor		Unrelated donor	
	Donor (N = 126)	Recipient (N = 126)	Donor (N = 108)	Recipient (N = 98)
Age (yr)				
Mean ± SD	52.1 ± 8.8	34.1 ± 9.5	38.2 ± 11.9	41.0 ± 9.7
Median (IQR)	54 (47–59)	33 (27–39)	36 (29–48)	40 (34–48)
Range	28–68	17–67	20–69	21–65
Age group (yr)				
<18	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
18–30	3 (2.4)	45 (35.7)	35 (32.4)	12 (12.2)
31–40	11 (8.7)	52 (41.3)	31 (28.7)	38 (38.8)
41–50	35 (27.8)	19 (15.1)	23 (21.3)	35 (35.7)
51–60	55 (43.7)	7 (5.6)	13 (12.0)	10 (10.2)
>60	22 (17.5)	1 (0.8)	6 (5.6)	3 (3.1)
Sex				
Male	57 (45.2)	84 (66.7)	69 (63.9)	63 (64.3)
Female	69 (54.8)	42 (33.3)	39 (36.1)	35 (35.7)

Table 2

HLA class I typing of donors and ESRD patients.

	Related donor			Unrelated donor		
	Donor (N = 252)*	Recipient (N = 252)*	*P* value	Donor (N = 216)*	Recipient (N = 196)*	*P* value
HLA-A						
1	7 (2.8)	4 (1.6)	.367	3 (1.4)	4 (2.0)	.611
2	64 (25.4)	68 (27.0)	.685	42 (19.4)	43 (21.9)	.532
3	2 (0.8)	1 (0.4)	.570	4 (1.9)	1 (0.5)	.246
11	74 (29.4)	82 (32.5)	.441	65 (30.1)	62 (31.6)	.735
23	1 (0.4)	0 (0.0)	–			
24	39 (15.5)	44 (17.5)	.548	45 (20.8)	31 (15.8)	.191
26	3 (1.2)	4 (1.6)	.704	7 (3.2)	5 (2.6)	.678
29	24 (9.5)	22 (8.7)	.757	12 (5.6)	19 (9.7)	.116
30	5 (2.0)	3 (1.2)	.481	2 (0.9)	6 (3.1)	.139
31	1 (0.4)	2 (0.8)	.570	2 (0.9)	4 (2.0)	.358
32	1 (0.4)	0 (0.0)	–	1 (0.5)	0 (0.0)	–
33	25 (9.9)	17 (6.7)	.200	29 (13.4)	19 (9.7)	.240
34	2 (0.8)	4 (1.6)	.421	3 (1.4)	0 (0.0)	–
68	1 (0.4)	1 (0.4)	1.000	1 (0.5)	0 (0.0)	–
74	3 (1.2)	0 (0.0)	–	0 (0.0)	1 (0.5)	–
36				0 (0.0)	1 (0.5)	–
HLA-B						
7	30 (11.9)	28 (11.1)	.780	17 (7.9)	28 (14.3)	**.040**
13	12 (4.8)	13 (5.2)	.837	13 (6.0)	8 (4.1)	.375
14	1 (0.4)	0 (0.0)	–	1 (0.5)	0 (0.0)	–
15	62 (24.6)	66 (26.2)	.682	48 (22.2)	51 (26.0)	.368
18	6 (2.4)	4 (1.6)	.526	4 (1.9)	2 (1.0)	.488
27	6 (2.4)	9 (3.6)	.435	12 (5.6)	2 (1.0)	**.024**
35	14 (5.6)	14 (5.6)	1.000	9 (4.2)	2 (1.0)	.068
37	2 (0.8)	2 (0.8)	1.000	4 (1.9)	0 (0.0)	–
38	17 (6.7)	14 (5.6)	.579	10 (4.6)	16 (8.2)	.146
39	7 (2.8)	6 (2.4)	.779	3 (1.4)	3 (1.5)	.905
40	12 (4.8)	16 (6.3)	.438	20 (9.3)	17 (8.7)	.835
41	1 (0.4)	0 (0.0)	–			–
44	2 (0.8)	3 (1.2)	.655	6 (2.8)	1 (0.5)	.113
46	18 (7.1)	20 (7.9)	.736	18 (8.3)	22 (11.2)	.324
48	5 (2.0)	5 (2.0)	1.000	2 (0.9)	3 (1.5)	.580
51	10 (4.0)	8 (3.2)	.632	8 (3.7)	10 (5.1)	.490
52	1 (0.4)	4 (1.6)	.213	4 (1.9)	2 (1.0)	.488
53	1 (0.4)	1 (0.4)	1.000			
54	5 (2.0)	10 (4.0)	.199	8 (3.7)	6 (3.1)	.720
55	5 (2.0)	4 (1.6)	.737	3 (1.4)	5 (2.6)	.400
56	9 (3.6)	4 (1.6)	.171	5 (2.3)	3 (1.5)	.567
57	9 (3.6)	6 (2.4)	.435	3 (1.4)	5 (2.6)	.400
58	17 (6.7)	14 (5.6)	.579	18 (8.3)	9 (4.6)	.131
67	0 (0.0)	1 (0.4)	–			–
45			–	0 (0.0)	1 (0.5)	–

Bold values indicate statistical significance.

ESRD = end-stage renal disease, HLA = human leukocyte antigen.

*Number of alleles.

[0.154–0.736]) were found as protective alleles to ESRD progression (Tables 2–4).

4. Discussion

HLA alleles were known to be associated with a variety of kidney diseases.[7] Several studies have shown the association between HLA alleles and ESRD,[6,8,12] but findings have been inconsistent among works conducted in different countries, suggesting that susceptible HLA alleles could be specific to particular ethnic groups. Our study examined a wide range of both class I (-A, -B) and class II (-DR, -DQ) HLA alleles in Vietnamese ESRD patients, which will contribute to the understanding of ESRD-related genetic factors among Vietnamese and South-east Asians.

The HLA typing of ESRD patients in our study is similar to research conducted by Hieu et al[12] on Northern Vietnamese ESRD patients and the general Vietnamese Kinh population reported by Do et al[13] The most common alleles in each locus (HLA-A*11, B*15, DRB1*12, DQA1*01, and DQB1*03) are also consistent with typing results from research conducted on East[14–16] and South-east Asian populations.[17,18] These findings are different from the most common alleles found in ESRD patients living in countries outside of the regions. For example, HLA-A*02 and B*51 are the most frequent alelles among Kuwaiti and Saudi Arabian patients,[8,19] while in Pakistani patients, HLA-A*02, B*08, DRB1*03, DQA1*01, and DQB1*02 were reported.[9]

We found no association between HLA-A alleles and ESRD patients, which is consistent with other studies performed in Vietnam,[12] Taiwan[15] and China.[16] Some alleles of the HLA-A locus were found to be the risk factors to particular subsets of ESRD patients. For example, HLA-A*11 and A*01 were found to be associated with ESRD caused by glomerulonephritis, or HLA-A*01, A*25, A*30 were related to ESRD due to hypertension.[12] Since ESRD could result from complications of several chronic diseases, it is proposed that the cause of ESRD or

Table 3

HLA class II typing of donors and ESRD patients.

	Related donor			Unrelated donor		
	Donor (N = 252)*	Recipient (N = 252)*	*P* value	Donor (N = 216)*	Recipient (N = 196)*	*P* value
HLA-DRB1						
1	1 (0.4)	1 (0.4)	1.000	1 (0.5)	0 (0.0)	–
3	12 (4.8)	9 (3.6)	.505	14 (6.5)	6 (3.1)	.115
4	27 (10.7)	32 (12.7)	.489	18 (8.3)	22 (11.2)	.324
7	13 (5.2)	8 (3.2)	.270	14 (6.5)	8 (4.1)	.283
8	8 (3.2)	9 (3.6)	.805	7 (3.2)	9 (4.6)	.481
9	30 (11.9)	31 (12.3)	.891	26 (12.0)	19 (9.7)	.447
10	22 (8.7)	25 (9.9)	.646	14 (6.5)	15 (7.7)	.643
11	5 (2.0)	10 (4.0)	.199	3 (1.4)	8 (4.1)	.106
12	73 (29.0)	84 (33.3)	.290	59 (27.3)	69 (35.2)	.085
13	11 (4.4)	6 (2.4)	.224	12 (5.6)	4 (2.0)	.077
14	13 (5.2)	9 (3.6)	.386	16 (7.4)	13 (6.6)	.759
15	33 (13.1)	25 (9.9)	.265	24 (11.1)	19 (9.7)	.639
16	4 (1.6)	3 (1.2)	.704	8 (3.7)	3 (1.5)	.186
18				0 (0.0)	1 (0.5)	–
HLA-DQA1						
1	86 (34.1)	80 (31.7)	.570	82 (38.0)	64 (32.7)	.261
2	13 (5.2)	8 (3.2)	.270	14 (6.5)	7 (3.6)	.186
3	56 (22.2)	60 (23.8)	.672	41 (19.0)	40 (20.4)	.716
4	12 (4.8)	19 (7.5)	.198	8 (3.7)	8 (4.1)	.843
5	25 (9.9)	22 (8.7)	.646	25 (11.6)	17 (8.7)	.333
6	60 (23.8)	63 (25.0)	.756	**46 (21.3)**	**60 (30.6)**	**.031**
HLA-DQB1						
1	0 (0.0)	3 (1.2)	–	1 (0.5)	0 (0.0)	–
2	16 (6.3)	15 (6.0)	.853	**27 (12.5)**	**9 (4.6)**	**.006**
3	135 (53.6)	145 (57.5)	.370	**100 (46.3)**	**111 (56.6)**	**.036**
4	15 (6.0)	17 (6.7)	.715	9 (4.2)	12 (6.1)	.370
5	67 (26.6)	58 (23.0)	.354	62 (28.7)	43 (21.9)	.116
6	19 (7.5)	14 (5.6)	.370	17 (7.9)	21 (10.7)	.321

Bold values indicate statistical significance.

ESRD = end-stage renal disease, HLA = human leukocyte antigen.

*Number of alleles.

Table 4

Odd ratios of susceptible and protective alleles.

HLA alleles	OR (95% CI)
B*07	**1.951 (1.032–3.688)**
B*27	**0.175 (0.039–0.793)**
DQA1*06	**1.630 (1.044–2.545)**
DQB1*02	**0.337 (0.154–0.736)**
DQB1*03	**1.515 (1.027–2.235)**

HLA = human leukocyte antigen, OR = odds ratio.

comorbidities could act as significant confounders to the relationship between HLA types and ESRD.[9]

We found HLA-DQA1*06 as a significant susceptible allele to ESRD, in contrast to a study from Noureen et al[9] on Pakistani ESRD patients that concluded it was a protective allele. The reason might be due to the difference in HLA typing between the two populations. HLA-DQA1*06 was among the most frequent alleles in the Vietnamese population (30.6% of ESRD patients and 21.3% of unrelated donors), while it is scarce in the Pakistani population (1.1% of ESRD patients and 2.9% of donors).[9] This could also explain the fact that the relationship between HLA alleles and ESRD may contradict across different ethnic groups, emphasizing the genetic background of a population should be taken into account when interpreting HLA association.

Allele DQB1*03 was found as a risk factor for ESRD in our research, consistent with studies conducted on patients from Turkey[20] and China.[10] The frequencies of HLA-B*27 and DQB1*02 among the control group were significantly higher than in the ESRD group. However, as these findings were not mentioned in the literature, it can be due to a hidden confounder and should be confirmed in further investigations.

5. Limitation

The main limitation of this study is low resolution HLA typing and small sample size, although we have collected all waitlisted ESRD patients in 3 consecutive years. Due to low resolution PCR-SSO, we were unable to discriminate HLA-B*40 into B*60(40) or B*61(40), or HLA-DRB1*03 into DRB1*17(3) or DRB1*18(3). Further research with higher resolution and larger sample size, preferably multi-center should be conducted to confirm our findings.

6. Conclusion

The most frequent alleles in each HLA locus were similar to the general Vietnamese population and other countries in East and South-east Asia. HLA-B*07, DQA1*06 and DQB1*03 were found as susceptible alleles to ESRD, while HLA-B*27 and DQB1*02 were associated with a decreased risk of ESRD.

Author contributions

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