Original research

Human leucocyte antigens associated with end-stage renal disease in Sri Lankan population

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Abstract

Introduction
Association between human leucocyte antigens and developing end-stage renal diseases has been shown in different settings. Such association has not been described for Sri Lankans in the recent past, especially with regards to the ethnicity. The aim of this study was to determine the association between HLA molecules and end-stage renal disease among patients awaiting renal transplantation, tested at National Blood Centre, Sri Lanka.

Methods
This retrospective study was carried-out at histocompatibility laboratory of National Blood Centre in 2017. HLA typing results of renal patients and donors were analysed retrospectively for one year. During this period, HLA typing was performed by serologically using lymphocytotoxicity test. Antigen frequencies of -A, -B, -C, -DR, and -DQ loci were calculated and compared between patients and donors according to the ethnicity. Relative Risk and 95% Confidence Intervals were calculated for antigens showing significant difference in frequencies.

Results
HLA typing results of 975 patients and 1174 donors were collected. HLA-A33, -A24, -A2, -A11, -B57, -B51, -C7, -C6, -DR15, -DR7, -DQ5, and -DQ6 were the commonest antigens among all patients and donors. Comparison of frequencies among two groups showed significant differences in -A26 and -C2 among Sinhalese, -B57 and -C3 among Moors and -B7 among Tamils.

Conclusion
HLA-A26 in Sinhalese and -B7 in Tamils were associated positively with end-stage renal disease while -B57 and -C3 in Moors and -C2 in Sinhalese were negatively associated antigens. A study based on molecular HLA typing is needed to identify alleles associated with renal diseases among Sri Lankans.

Keywords: human leucocyte antigen, antigen frequency, end-stage renal disease, Sri Lanka

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Introduction

End-stage renal disease (ESRD) is a devastating health issue in many countries worldwide [1]. People living in many parts of Sri Lanka, mainly in the North Central province, are also suffering from chronic kidney disease with unknown aetiology [2]. Though the exact causative factor responsible for ESRD is still unknown, associations have been described with old age, female gender, smoking, systolic blood pressure, and history of diabetes mellitus, hyperlipidemia, hypercholesterolemia and hyperuricemia [3]. Since the human leukocyte

antigen (HLA) system is a key element in immune recognition [4], many studies have focused on discovering HLA alleles/antigens linked with ESRD.

The HLA gene is a highly polymorphic region located in the major histocompatibility complex on chromosome 06. HLA gene is mainly divided into two classes; I and II. HLA class I includes three main loci: HLA-A, HLA-B, and HLA-C; HLA Class II includes HLA-DP, HLA-DQ, and HLA-DR (4). According to the latest updates of the HLA Nomenclature website, 19,587 class I alleles and 7,302 class II alleles were discovered by March 2020 [5].

Studies conducted in Venezuela [6], China [7], and Saudi Arabia [8] have reported positive and/or negative associations between HLA polymorphism and ESRD. However, few other studies failed to demonstrate such a relationship [9-11]. In addition, associations have been identified between HLA antigens and various pathologies leading to ESRD, such as anti-glomerular basement membrane disease [12] and IgA nephropathy [13]. To the best of my knowledge, such an association hasn't been described for Sri Lankans during the recent past; and has never been analysed, taking ethnicity into consideration. This study aimed to determine HLA antigens associated with ESRD among patients awaiting renal transplantation, tested at the National Blood Centre (NBC), Sri Lanka, for a period of one year.

Methodology

This retrospective descriptive study was carried out at the histocompatibility laboratory of NBC, Sri Lanka, in 2017. As the study group, HLA typing results of Sri Lankan patients with renal failure awaiting transplant, tested at the histocompatibility laboratory of NBC, were collected retrospectively for one year. Kidney donors of Sri Lankan origin, tested at the same laboratory during the study period, were taken as the healthy control group. The ethical clearance was obtained from the Faculty of Medicine, University of Colombo, Sri Lanka.

During the study period, HLA typing was performed in the laboratory via a serological method based on complement-dependent cytotoxicity technique [14]. For this purpose, commercially-available readymade typing plates (class I- One Lambda, class II- Bio-Rad), which contain sera with antibodies to all common HLA antigens, were utilised. All patients and donors were typed for HLA-A, -B, -C, -DR and -DQ loci.

Patients' and donors' demographic data and HLA typing results were collected from HLA request forms and laboratory worksheets, respectively. Frequencies of all detectable antigens in the five loci were calculated separately for both patient and donor groups considering their ethnicities. A 2 x 2 contingency table analysis was performed by Chi-Square test with Yates correction. $P < 0.05$ was considered as statistically significant. The strength of the association between HLA antigens and renal failure was estimated by Relative Risk (RR) and 95% Confidence Intervals (CI) which were calculated only for antigens having a significant difference between the patient and the donor groups. A relative risk value above 1 was taken as a positive association, while a value less than 1 was interpreted as a negative association.

Results

Of the 975 patients, 291 (30%) were females, and 684 (70%) were males. The patient population comprised 741 (75%) Sinhalese, 104 (10%) Tamil and 130 (13%) Moor patients. As the control group, the HLA typing results of 1174 donors were collected and comprised 399 (34%) females and 775 (66%) males. The donor group included 864 (73%) Sinhalese, 170 (14%) Tamils and 140 (11%) Moors.

Table 1, Table 2, and Table 3 summarise the antigen frequencies of HLA-A, -B, and -C loci, respectively. Frequencies of HLA class II antigens, -DR and -DQ, were shown in Table 4 and 5, respectively.

HLA-A1, -A2, -A11, -A24, and -A33 were among the most frequently occurring HLA-A locus antigens of patients and donors of all three races. In the HLA-B locus, HLA-B7, -B35, -B51 and -B57 were among the most frequent first five antigens of all categories. HLA-B51 was recorded as the highest antigen of patients of Moors origin, while HLA-B57 was the most frequently occurring antigen of all other categories. In the HLA-C locus, all groups had the frequency order of HLA-C7, -C6, -C3 and -C4. In HLA class II, HLA-DR7 and -DR15 were the most frequently occurring HLA-DR antigens in all patient and donor groups. HLA-DQ5, -DQ6, -DQ2 and -DQ7 was the HLA-DQ antigen frequency pattern seen in all categories.

Statistically significant differences in antigen distributions among patient and donor groups were detected with HLA-A26 (P-0.04) and HLA-C2 (P-<0.001) among Sinhalese, HLA-B7 (P-0.004) among Tamils, and HLA-B57 (P-0.04) and HLA-C3 (P-0.01) among Moors. Therefore, RR and 95% CI were calculated for those five occasions.

According to the results, HLA-A26 in Sinhalese (RR-1.4885, CI-1.029 to 2.153) and HLA-B7 in Tamils (RR-2.3228, CI-1.362 to 3.961) were positively associated with developing ESRD. HLA-B57 (RR-0.5821, CI-

0.357 to 0.949) and HLA-C3 (RR-0.4084, CI-0.213 to 0.784) in Moors and HLA-C2 in Sinhalese (RR-0.3928, CI-0.236 to 0.653) were negatively associated with developing ESRD.

Table 1: Distribution of HLA-A locus antigens in patients awaiting renal transplant and donors in relation to ethnicity

HLA-A Antigens	Number and Percentage of antigens								
	Sinhalese			Tamils			Moors		
	Patients N=741 **n/%**	**Donors** N=864 **n/%**	**P value**	**Patients** N=104 **n/%**	**Donors** N=170 **n/%**	**P value**	**Patients** N=130 **n/%**	**Donors** N=140 **n/%**	**P Value**
1	126/8.3	154/8.9	0.72	20/9.6	50/14.7	0.11	27/10.4	29/10.4	0.89
2	179/12.1	214/12.4	0.83	27/13.0	50/14.7	0.66	36/13.8	49/17.5	0.29
3	90/6.1	89/5.2	0.28	16/7.7	16/4.7	0.20	19/7.3	19/6.8	0.94
11	180/12.1	204/11.8	0.80	28/13.5	40/11.8	0.65	29/11.2	29/10.4	0.87
23	14/0.9	17/1.0	0.94	5/2.4	7/2.1	0.97	2/0.8	0/0	-
24	236/15.9	266/15.4	0.71	34/16.3	42/12.4	0.23	55/21.2	54/19.3	0.66
25	0/0	1/0.1	0.35	1/0.5	0/0	-	0/0	0/0	-
26	60/4	47/2.7	**0.04**	9/4.3	13/3.8	0.94	10/3.8	8/2.9	0.68
29	9/0.6	6/0.3	0.41	2/1.0	2/0.6	0.98	0/0	1/0.4	-
30	0/0	1/0.1	-	0/0	0/0	-	1/0.4	1/0.4	0.51
31	49/3.3	80/4.6	0.07	7/3.4	16/4.7	0.58	14/5.4	11/3.9	0.54
32	27/1.8	21/1.2	0.20	8/3.8	7/2.1	0.32	4/1.5	8/2.9	0.45
33	312/21.1	351/20.4	0.63	20/9.6	43/12.6	0.34	39/15.0	45/16.1	0.82
36	2/0.1	0/0	-	0/0	0/0	-	0/0	0/0	-
68	61/4	65/3.8	0.67	7/3.4	13/3.8	0.96	7/2.7	6/2.1	0.89
X	137/9.2	208/12.1	0.01	24/11.5	41/12.1	0.96	17/6.5	20/7.1	0.91

N- Number of individuals, n- Number of antigens, X- Incidences of detecting single antigen

Table 2: Distribution of HLA-B locus antigens in patients awaiting renal transplant and donors in relation to ethnicity

HLA-B Antigens	Number and Percentage of antigens								
	Sinhalese			Tamils			Moors		
	Patients N=741 **n /%**	**Donors** N=864 **n/%**	**P value**	**Patients** N=104 **n/%**	**Donors** N=170 **n/%**	**P value**	**Patients** N=130 **n/%**	**Donors** N=139 **n/%**	**P value**
7	108/7.3	128/7.4	0.95	27/13	19/5.6	**0.004**	18/6.9	22/7.9	0.80
8	20/1.4	17/1	0.42	4/1.9	9/2.6	0.82	5/1.9	9/3.2	0.50
13	44/3	42/2.4	0.40	6/2.9	9/2.6	0.94	6/2.3	8/2.9	0.89
18	17/1.1	26/1.5	0.46	7/3.4	5/1.5	0.24	3/1.2	5/1.8	0.80
27	23/1.6	29/1.7	0.88	1/0.5	2/0.6	0.66	3/1.2	2/0.7	0.93
35	161/10.9	175/10.2	0.53	16/7.7	33/9.7	0.51	35/13.5	24/8.6	0.09
37	52/3.5	65/3.8	0.77	8/3.8	16/4.7	0.79	11/4.2	14/5	0.82
38	4/0.3	3/0.2	0.83	1/0.5	1/0.3	0.70	4/1.5	3/1.1	0.92
39	3/0.2	5/0.3	0.89	1/0.5	3/0.9	0.98	0/0	0/0	-
41	1/0.1	1/0.1	0.54	1/0.5	0/0	-	1/0.4	2/0.7	0.94
44	125/8.4	139/8.1	0.73	7/3.4	13/3.8	0.96	19/7.3	26/9.3	0.49
48	1/0.1	0/0	-	0/0	1/0.3	-	0/0	1/0.4	-
49	7/0.5	12/0.7	0.55	3/1.4	3/0.9	0.85	1/0.4	1/0.4	0.51
51	158/10.7	180/10.4	0.86	23/11.1	39/11.5	0.99	37/14.2	32/11.5	0.39
52	19/1.3	21/1.2	0.99	2/1	2/0.6	0.98	4/1.5	4/1.4	0.80
55	75/5.1	65/3.8	0.08	9/4.3	15/4.4	0.86	9/3.5	7/2.5	0.68
57	238/16.1	287/16.6	0.64	31/14.9	46/13.5	0.74	20/7.7	37/13.3	**0.04**
60	75/5.1	97/5.6	0.63	16/7.7	16/4.7	0.20	13/5	15/5.4	0.99
61	75/5.1	103/6	0.29	11/5.3	27/7.9	0.31	12/4.6	16/5.7	0.70
62	94/6.3	84/4.9	0.07	6/2.9	15/4.4	0.50	15/5.8	11/3.9	0.42
63	10/0.7	5/0.3	0.18	1/0.5	1/0.3	0.70	0/0	1/0.4	-
70	12/0.8	22/1.3	0.26	6/2.9	6/1.8	0.56	4/1.5	4/1.4	0.80
X	152/10.3	216/12.5	0.05	21/10.1	59/17.4	0.02	39/15	33/11.8	0.33

N- Number of individuals, n- Number of antigens, X- Incidences of detecting single antigen

Table 3: Distribution of HLA-C locus antigens in patients awaiting renal transplant and donors in relation to ethnicity

HLA-C Antigens	Number and Percentage of antigens								
	Sinhalese			Tamils			Moors		
	Patients N=741 **n /%**	**Donors** N=864 **n/%**	**P value**	**Patients** N=104 **n/%**	**Donors** N=170 **n/%**	**P value**	**Patients** N=130 **n/%**	**Donors** N=140 **n/%**	**P value**
1	78/5.3	74/4.3	0.22	7/3.4	15/4.4	0.70	13/5	11/3.9	0.69
2	19/1.3	59/3.4	**<0.001**	2/1	4/1.2	0.85	8/3.1	10/3.6	0.93
3	170/11.5	190/11	0.71	16/7.7	33/9.7	0.51	11/4.2	29/10.4	**0.01**
4	166/11.2	177/10.3	0.41	15/7.2	30/8.8	0.61	30/11.5	22/7.9	0.19
5	10/0.7	10/0.6	0.90	1/0.5	0/0	-	4/1.5	2/0.7	0.61
6	235/15.9	242/14	0.15	39/18.8	57/16.8	0.63	36/13.8	43/15.4	0.70
7	289/19.5	353/20.5	0.54	48/23.1	68/20.1	0.45	55/21.2	61/21.8	0.94
X	514/34.7	618/35.8	0.54	80/38.4	132/38.9	0.99	103/39.6	102/36.5	0.50

N- Number of individuals, n- Number of antigens, X- Incidences of not detecting antigen

Table 04: HLA-DR locus antigen distribution in relation to ethnicity

HLA-DR antigens	Number and Percentage of antigens								
	Sinhalese			Tamils			Moors		
	Patients N=741 **n /%**	**Donors** N=864 **n/%**	**P**	**Patients** N=104 **n/%**	**Donors** N=170 **n/%**	**P**	**Patients** N=130 **n/%**	**Donors** N=140 **n/%**	**P**
1	30/2	46/2.7	0.28	3/1.4	3/0.9	0.85	3/1.2	3/1.1	0.74
3	8/0.5	7/0.4	0.76	1/0.5	1/0.3	0.70	0/0	0/0	-
4	103/7	132/7.7	0.49	20/9.6	36/10.6	0.82	28/10.8	28/10	0.87
7	263/17.7	324/18.8	0.49	30/14.4	49/14.4	0.90	44/16.9	50/17.9	0.83
8	13/0.9	21/1.2	0.44	3/1.4	5/1.5	0.73	1/0.4	3/1.1	0.66
9	2/0.1	1/0.1	0.89	0/0	0/0	-	0/0	0/0	-
10	139/9.4	132/7.7	0.08	21/10.1	31/9.1	0.81	17/6.5	23/8.2	0.56
11	48/3.2	72/4.1	0.19	8/3.8	12/3.5	0.96	12/4.6	9/3.2	0.53
12	76/5.1	79/4.6	0.51	7/3.4	9/2.6	0.82	12/4.6	17/6.1	0.57
13	157/10.6	156/9	0.15	22/10.6	41/12.1	0.69	27/10.4	28/10	0.99
14	176/11.9	199/11.5	0.79	16/7.7	26/7.6	0.88	29/11.2	30/10.7	0.97
15	258/17.3	325/18.8	0.32	40/19.2	70/20.3	0.78	50/19.2	45/16.1	0.39
17	59/4	54/3.1	0.22	13/6.3	21/6.2	0.88	5/1.9	12/4.3	0.18
18	4/0.3	3/0.2	0.83	2/1	0/0	-	0/0	0/0	-
X	146/9.9	173/10	0.92	22/10.6	36/10.6	0.88	30/11.5	32/11.4	0.92

N-Number of individuals, n-Number of antigens, X-Single antigen detecting incidences, P- P value

Table 05: HLA-DQ locus antigen distribution in relation to ethnicity

	Number and Percentage of antigens

HLA-DQ antigens	Sinhalese			Tamils			Moors		
	Patients N=741 n /%	Donors N=864 n/%	P	Patients N=104 n/%	Donors N=170 n/%	P	Patients N=130 n/%	Donors N=140 n/%	P
2	191/12.9	219/12.7	0.89	27/13	44/12.9	0.90	28/10.8	35/12.5	0.62
4	8/0.5	6/0.3	0.57	3/1.4	1/0.3	0.32	0/0	2/0.7	-
5	380/25.6	399/23.1	0.10	47/22.6	69/20.3	0.59	67/25.8	56/20	0.13
6	216/14.6	274/15.9	0.33	34/16.3	63/18.5	0.59	36/13.8	46/16.4	0.47
7	148/10	176/10.2	0.89	25/12	34/10	0.54	28/10.8	31/11.1	0.97
8	98/6.6	116/6.7	0.96	13/6.3	26/7.6	0.65	23/8.8	26/9.3	0.97
9	81/5.5	110/6.4	0.31	12/5.8	18/5.3	0.96	7/2.7	12/4.3	0.44
X	360/24.3	424/24.6	0.90	47/22.6	85/24.7	0.59	71/27.3	72/25.7	0.74

N-Number of individuals, n-Number of antigens, X-Single antigen detecting incidences, P- P value

Discussion

In the present study, HLA typing results of ESRD patients awaiting renal transplant and kidney donors awaiting organ donation were collected for one-year duration and analysed. As cadaveric organ donation is still not mandatory in Sri Lanka, the majority are awaiting live donor renal transplantations. Once diagnosed with end-stage renal failure and decided to undergo a renal transplant, patients are first referred for HLA investigations. At the time of the study, HLA typing was performed only at the histocompatibility laboratory of NBC; thus, this study population represents the entire country.

The current study identified HLA-A33, -A24, -A11, -A2 and -A1 as the most frequently occurring HLA-A locus antigens of both patient and donor categories in all three races. This finding was similar to the previously published data of Sri Lanka in 2008, except having -A9 instead of -A11 within the first five antigens [15].

When analysing frequencies concerning ethnicity, HLA-A33 had the highest frequency among Sinhalese, while -A24 was the most common among Moors. In Tamils, HLA-24 has the highest frequency among patients, whereas -A1 and -A2 were the top antigens in donors. These findings show some similarities with other populations' data. Publications from India reported high frequencies of HLA-A*24, -A*02, -A*33, and -A*11 among Dravidian tribal communities [16] and HLA-A*1, and -A*2 among West Central Indians [17]. HLA-A*02, -A*24, and -A*11 were frequently seen in China [18] and Malaysia [19]. A study conducted on Saudi Arabians reported HLA-A*1, -A*2, -A*3, -A*24, -A*31, -A*30 and -A*68 as having highest frequencies [8].

HLA-B57 and -B51 were the top in the frequency lists of HLA-B locus antigens among all categories. HLA-B57 was the most frequently occurring antigen among all except Moors patients, in whom HLA-B51 was recorded as the highest. The previous work on the Sri Lankan population reported HLA-B15, -B7 and -B35 as the commonest antigens in all ethnic categories [15]. Published data of other populations are also quite different to the present results; for example, -B*35 in West Central India [17], -B*15, -B*35, and -B*18 in Malaysia [19] and -B*13, -B*15, and -B*40 in China [18] had highest percentages. HLA-B*7, -B*8, -B*15, -B*18, and -B*35 were the commonest alleles of Saudi Arabians [8].

In the present study, HLA-DR15, -DR7, and -DR14 were found to be the most frequent HLA-DR locus antigens in both patient and donor groups. HLA-DR15, followed by -DR7, had the highest frequencies among all participants except the donors of Moors origin, in whom the order was reversed. Similar to the results of this work, HLA-DRB1*15 and -DRB1*7 were the most highly occurring alleles in those living in Central India [17]. In China [18] and Malaysia [19], HLA-DR12 was also among the frequent antigens. Saudi Arabian frequencies were different to the above results, as -DRB1*1 and -DRB1*3 were at the top of the frequency order [8].

Antigen frequency comparison of the current study showed that HLA-A26 among Sinhalese and HLA-B7 among Tamils were significantly higher in the patient group than the controls demonstrating positive associations with developing ESRD. Donor frequency of HLA-C2 among Sinhalese and HLA-B57 and HLA-C3 among Moors were significantly higher than the patient categories; thus, they were negatively associated with developing ESRD. In 2012, Sergio Rivera et al. reported HLA-B38, -B51, -B53, -B62 as positively associated antigens and HLA-A9, -B12, -B17, -B40, -B48 as negatively associated antigens with ESRD in Venezuela [6]. HLA-A*24, -B*55, -B*54, -B*40, and -DRB1*04 alleles in ESRD patients in China were significantly higher than those among controls [7]. Alleles positively associated with ESRD among Saudi Arabians were HLA-B*15, -B*18, -B*49, and -DRB1*03. In contrast to the finding of the current study, HLA-A26 had been identified as a protective allele for Saudi Arabian; HLA-B*39 and -B*50 were the other reported protective alleles [8]. Ciou-Sia Dai et al. summarised the results of 32 studies carried-out in 19 different countries. The results of those studies were far different from the current work except for detecting -C2 as a protective factor among the Saudi population. Apart from that,

almost all studies identified ESRD-associated HLA class II alleles/antigens [11]. In the current study, the distribution of -DR and -DQ antigens were not significant.

This is the first instance that identified HLA antigens linked with ESRD among Sri Lankans. This knowledge is much important to identify those with a genetic predisposition to ESRD and to take preventive measures early. However, the current study focused on the patients with renal failure as a whole without specifically focusing on the aetiologies leading to ESRD. In addition to that, this study was carried out on HLA typing data obtained from a serologic method. One of the major limitations of this method is the unavailability of antisera specific for all possible HLA antigens. For example, among the patients and donors of the current study, the incidences of detecting a single antigen in a given locus had been reported as around 10% in -A, -B, and -DR loci, 24% in -DQ locus and 35% in -C locus. Therefore, it can affect the antigen frequencies in all loci. More accurate typing results can be generated through molecular technologies. Since the histocompatibility laboratory currently practices molecular methods for HLA typing, a similar study can be conducted to compare the results.

Conclusion

This study reports HLA antigens positively and negatively linked with ESRD in the Sri Lankan population from the results derived from the serological HLA typing method. A future study based on molecular typing results will allow the comparison of the results of the two methods and to assess the genetic variation of identified antigens involved with ESRD.

Conflicts of Interests

There are no conflicts of interest.

References

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2020; 395:709–33. DOI: 10.1016/S0140-6736(20)30045-3.

2. Wanigasuriya K. Aetiological factors of Chronic Kidney Disease in the North Central Province of Sri Lanka: A review of evidence to-date. *J Coll Comm Phys. Sri Lanka.* 2012;17(1):15-20. DOI:10.4038/jccpsl.v17i1.4931.

3. Xue L, Lou Y, Feng X, Wang C, Ran Z, Zhang X. Prevalence of chronic kidney disease and associated factors among the Chinese population in Taian, China. *BMC Nephrol.* 2014;15:205. DOI: 10.1186/1471-2369-15-205.

4. Cruz-Tapias P, Castiblanco J, Anaya JM. Major histocompatibility complex: Antigen processing and presentation. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, Levy RA, Cervera R, editors. Autoimmunity From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press; 2013. p. 169-184.

5. Robinson J, Barker DJ, Georgiou X, Cooper MA, Flicek P, Marsh SG. IPD-IMGT/HLA Database. *Nucleic Acids Res.* 2020;48:D948-55. DOI: 10.1093/nar/gkz950.

6. Rivera PS, Márquez G, Cipriani AM, Hassanhi M, Villalobos CC, Fuenmayor A, et al. HLA class I association with progression to end-stage renal disease in patients from Zulia, Venezuela. *Inmunología.* 2012;31(2):37-42. DOI: 10.1016/j.inmuno.2011.12.001.

7. Cao Q, Xie D, Liu J, Zou H, Zhang Y, Zhang H, et al. HLA polymorphism and susceptibility to End-Stage Renal Disease in Cantonese patients awaiting kidney transplantation. *PLoS One.* 2014;9(6):e90869. DOI:10.1371/journal.pone.0090869.

8. Hamdi NM, Al-Hababi FH, Eid AE. HLA class I and class II associations with ESRD in Saudi Arabian population. *PLoS One.* 2014;9(11):e111403. DOI: 10.1371/journal.pone.0111403.

9. Agrawal S, Singh AK, Sharma RK. HLA gene and haplotype frequency in renal transplant recipients and donors of Uttar Pradesh (North India). *Indian J Nephrol.* 2001;11:88-97.

10. Almogren A, Shakoor Z, Hamam KD. Human leucocyte antigens: their association with end-stage renal disease in Saudi patients awaiting transplantation. *Br J Biomed Sci*. 2012; 69(4):159-63. DOI: 10.1080/09674845.2012.12069145.

11. Dai CS, Chu CC, Chen SF, Sun CY, Lin M, Lee CC. Association between human leucocyte antigen subtypes and risk of end stage renal disease in Taiwanese: a retrospective study. *BMC Nephrol.* 2015;16:177. DOI: 10.1186/s12882-015-0165-7.

12. Zhou XJ, Lv JC, Zhao MH, Zhang H. Advances in the genetics of Anti-Glomerular Basement Membrane Disease. *Am J Nephrol.* 2010;32:482-90. DOI: 10.1159/000321324.

13. Feehally J, Farrall M, Boland A, Gale DP, Gut I, Heath S, et al. HLA has strongest association with IgA Nephropathy in genome-wide analysis. *J Am Soc Nephrol.* 2010; 21(10):1791–7. DOI: 10.1681/ASN.2010010076.

14. Phelan DL, Morris GP. The HLA system. In: Harmening DM, editor. Modern Blood Banking and Transfusion Practices. Philadephia: F A Davis Company; 2012. p. 475-94.

15. De Alwis WM. Frequencies of HLA antigens in patients and donors, typed at histocompatibility laboratory of the National Blood Centre, Colombo, Sri Lanka [dissertation for a MD]. Colombo: Post Graduate Institute of Medicine, University of Colombo; 2008.

16. Thomas R, Banerjee M. HLA-A allele frequency and haplotype distribution in the Dravidian tribal communities of South India. *Indian J Hum Genet.* 2005;11:140-4. DOI:10.4103/0971-6866.19533.

17. Patel JS, Patel MM, Koringa PG, Shah TM, Patel AK, Tripathi AK, et al. Human leukocyte antigen alleles, genotypes and haplotypes frequencies in renal transplant donors and recipients from West Central India. *Indian J Hum Genet.* 2013;19(2):219-32. DOI: 10.4103/0971-6866.116122.

18. Li XF, Zhang X, Chen Y, Zhang KL, Liu XJ, Li JP. An analysis of HLA-A, -B, and -DRB1 allele and haplotype frequencies of 21,918 residents living in Liaoning, China. *PLoS One.* 2014;9(4):e93082. DOI: 10.1371/journal.pone.0093082.

19. Dhaliwal JS, Shahnaz M, Too CL, Azrena A, Maiselamah L, Lee YY, et al. HLA-A, -B and -DR allele and haplotype frequencies in Malays. *Asian Pac J Allergy Immunol*. 2007;25(1):47-51.