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HLA gene polymorphism among Bangladeshi patients with end-stage renal disease awaiting kidney transplantation

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Article Info

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Abstract

Proper matching of HLA class I and class II antigens among donor and recipient is an important prerequisite for the long survival of a transplanted organ. To reveal the HLA gene polymorphism among end-stage renal disease (ESRD) patients and their donors, a total of 180 ESRD patients and 320 donors, referred by clinicians for HLA typing, were included in this study. HLA typing was performed using Polymerase Chain Reaction-Sequence Specific Primer (PCR-SSP). The most frequent alleles reported from both groups were, A*11, A*02 and A*33 in A locus; B*15:02, B*35 and B*52 in B locus and DRB1*15, DRB1*07 and DRB1*04 in DR locus. Frequencies of four alleles, A*26, B*57, B*40 and DRB1*11 were found to be higher in ESRD patients. The three locus haplotypes A*24, B*15:02, DRB1*15 were observed more frequently among recipients than in donors. The results were found to be in genetic equilibrium. Higher frequencies of certain alleles in recipients may be indicative of risk factor for renal disease. Further studies are needed to corroborate the findings of this study.

Introduction

Organ transplantation is considered as life enhancing and technologically advanced therapy now-a-days. Renal transplantation is the most standard and successful therapy for the end stage renal disease (ESRD). Compatibility of human leukocyte antigens (HLA) among the recipient and donor is an important factor for successful organ transplantation. These antigens are encoded by Major histocompatibility complex (MHC) genes which are located on short arm chromosome six, and represent about 1% of the whole genome. Different human population exhibit marked differences in the distribution of HLA alleles may be due to their extreme polymorphism and unique haplotype inheriting patterns. Thus, HLA haplotypes may serve as an important tool for studying the genetic background of different human populations.[2] HLA antigens are the major determinants used by the body's immune system for recognition and differentiation of self from non-self antigens. For this, MHC plays a vital role in solid organ and bone-marrow transplant success. HLA molecules expressed by transplanted organs are strongly immunogenic, and if not matched with donor HLA, are recognized as non-self and initiate T-cell proliferation and destruction of the transplanted organ.[3] HLA disparity is associated with graft failure, delayed immune reconstitution, graft versus-host disease (GVHD) and mortality. Hence, HLA-A, HLA-B and HLA-DR have known as major transplantation antigens.[1] Moreover, different alleles have been known to be associated with many autoimmune diseases as well as some renal diseases like IgA nephropathy, glomerulonephritis and diabetic nephropathy.[4-7] Although there has been several publications describing HLA distribution among chronic renal disease patients and the relation of HLA antigens with disease susceptibility from different populations, distribution of HLA antigen among ESRD patients from Bangladesh is not well documented. Therefore, this study aimed to evaluate alleles, haplotype and genotype frequencies in ESRD patients as well as their donors and to detect the susceptibilities of HLA antigens to end-stage renal disease.

Methods

Study Participants: A total of 180 adults with ESRD and 320 healthy individuals, advised for their HLA typing, were included in this study. All related information was obtained from the record registry of the laboratory. As age and gender does not influence an individual's HLA profile, the control group was not age and gender-matched with the patient group. Their mean age was 35±10.2 with lowest age 18 and highest 68 years.

DNA extraction: Five ml of whole blood samples were collected in ethylene diaminetetraacetic acid (EDTA) containing vial for DNA extraction and stored at -20ºC. Purified genomic DNA was extracted using EZ-10 Spin Column Genomic DNA extraction kit (Bio Basic Inc, Canada) according to manufacturer instructions. The purity and concentration of the DNA was estimated using NanoDrop1000 spectrophotometer (Thermo scientific) and stored at -20ºC until tested.

HLA-A, -B and –DRB1 Typing by Sequence Specific Primer based Polymerase Chain Reaction (PCR-SSP): HLA typing was carried out for 23 alleles of A, 40 alleles of B and 16 alleles of DRB1 locus, using PCR-SSP HLA kit (Micro SSPTM Generic HLA Class I and Class II DNA Typing Tray, One Lambda Inc., Canoga Park, CA). Amplification was done by thermal cycler GeneAmp PCR system 9700 (Applied Biosystems, USA). The amplified products were visualized and photographed under UV transillumination after 2% agarose gel electrophoresis. HLA alleles were assigned on the basis of the presence of allele specific bands in the gel. Interpretation of the results was carried out using the worksheets of HLA-A, HLA-B, and HLA-DR provided by the manufacturer.

Allele frequencies of HLA-A, -B and -DRB1 were calculated by the direct counting method.Two locus and three locus haplotype frequencies and genotype frequencies of HLA-A, -B and -DRB1 locus were determined by Hardy-Weinberg equilibrium test. Linkage disequilibrium (LD) andnormalized linkage disequilibrium between two locus haplotype were calculated by Lewontin methods. [8-9]. HLA-A, -B, -DRB1 allele'sfrequencies and HLA-A-B-DRB1haplotypes were compared between ESRD patients and controls by Pearson chi-square test. A 5% significance level was considered sufficient to reject the null hypothesis.

Results

A total of 17 alleles of A, 24 of B, 14 of DRB1 locus were detected from ESRD patients and 16 of A, 25 of B and 14 of DRB1 locus were detected from donors group (Tables-1- 3). On data analysis, allele frequency of A, B and DR loci did not differ significantly among patients and donors. The most frequent alleles found in both groups of HLA-A locus were

Table-I

Allele frequency of HLA-A locus in end stage renal disease (ESRD) patients and donors (N=500)

	Patients (n=180)			Donors (N=320)		Odd Ratio
HLA-A	Number	Antigen Frequency	HLA-A	Number	Antigen Frequency	(OR)
A*11	74	20.56	A*11	159	24.84	0.78
A*02	65	18.06	A*02	102	15.94	1.16
A*33	59	16.39	A*33	95	14.84	1.12
A*24	57	15.83	A*24	89	13.91	1.15
A*01	35	9.72	A*01	57	8.91	1.10
A*68	19	5.28	A*68	41	7.34	0.81
A*03	15	4.17	A*03	47	6.41	0.54
A*26	11	3.06	A*26	10	1.56	1.99
A*30	9	2.5	A*30	13	2.03	1.23
A*31	8	2.22	A*31	17	2.66	0.83
A*25	3	0.83	A*25	2	0.31	
A*29	2	0.56	A*32	2	0.31	
A*36	2	0.56	A*74	2	0.31	
A*74	1	0.28	A*25	1	0.16	
			A*29	1	0.16	
			A*36	1	0.16	
			A*69			
	1	0.16				

A*11, A*02 and A*33 (20.56%, 18.06%, 16.36% and 24.84%, 15.95%, 14.84% respectively) followed by A*24, A*01 and A*68. Moreover, A*74, A*29 and A*36 were found to be rare and in both groupswithafrequency of less than 1%. However, the common alleles in B locus found B*15:02, B*35, B*52 and B*44 with a frequency of greater than 8% in both groups. The least frequent allele observed were B*39, B*49, B*78, B*40:01 (Table-2). The polymorphism of DR locus revealed DRB1*15, DRB1*07, DRB1*04 and DRB1*12 as most frequent alleles in both groups (Table-3). However, allele comparison among the two groups revealed a positive association of ESRD with A*26 (OR:1.99), A*30 (OR:1.29), B*57(OR:1.54). DRB1*11(OR:1.69), DRB1*12 (OR:1.52) and a negative association with A*03 (OR:0.54), B*51(OR:0.52, B*40:02(OR:0.57), but the differences were not statistically significant (*P* value >0.05).

Haplotype analysis of the two locus (HLA-A and B) revealed 116 variation in patients and 138 variation in donors with two most frequent haplotypes A*11: B*15:02 and A*33: B*44 in both groups, followed by A*02: B*15:02, A*33: B*15:02, A*24: B*35 and A*11: B*35 in patients and A*11: B*35, A*02: B*35, A*11: B*52 in donors. The first 15 two locus haplotypes of both groups with a frequency of more the 1.5% is shown in Tables-4.

Table-II

Allele frequency of HLA-B locus among study participants (N=500)

HLA-B	Patients(N=180)		HLA-B	Donors (N=320)		Odd Ratio (OR)
	Number	Antigen Frequency		Number	Antigen Frequency	
B*15:02	72	20	B*15:02	109	17.03	1.21
B*35	49	13.61	B*35	92	14.38	0.93
B*44	32	8.89	B*44	71	11.09	0.78
B*52	34	9.44	B*52	55	8.59	1.1
B*40:02	17	4.72	B*40:02	51	7.97	0.57
B*51	10	2.78	B*51	33	5.16	0.52
B*57	27	7.5	B*57	32	5	1.54
B*07	19	5.28	B*07	31	4.84	1.09
B*37	13	3.61	B*37	25	3.91	0.92
B*13	16	4.44	B*13	24	3.75	1.19
B*38	16	4.44	B*38	22	3.44	1.3
B*15:01	16	4.44	B*15:01	21	3.28	1.37
B*40:01	5	1.39	B*40:01	18	2.81	
B*27	8	2.22	B*27	16	2.5	
B*58	8	2.22	B*58	11	1.72	
B*18	3	0.83	B*18	9	1.41	
B*08	1	0.28	B*08	5	0.78	
B*55	6	1.67	B*55	4	0.63	
B*56	2	0.56	B*56	3	0.47	
B*15:17	1	0.28	B*63	3	0.47	
B*39	1	0.28	B*39	1	0.16	
B*78	2	0.56	B*78	1	0.16	
B*45	1	0.28	B*45	1	0.16	

Table-III

Allele frequency of HLA-B locus among study participants (N=500)

	Patients(N=180)			Donors (N=320)		Odd Ratio
HLA-DRB1	Number	Antigen Frequency	HLA-DRB1	Number	Antigen Frequency	(OR)
DR*15	137	38.06	DRB1*15	216	33.75	1.20
DR*07	57	15.83	DRB1*07	129	20.16	0.74
DR*04	34	9.44	DRB1*04	79	12.34	0.74
DR*12	42	11.67	DRB1*12	51	7.97	1.52
DR*10	27	7.5	DRB1*10	45	7.03	1.07
DR*01	11	3.06	DRB1*01	23	3.59	0.84
DR*13	11	3.06	DRB1*13	21	3.28	0.93
DR*1404	9	2.5	DRB1*1404	19	2.97	0.83
DR*11	15	4.17	DRB1*11	16	2.5	1.69
DR*03	6	1.67	DRB1*03	13	2.03	0.81
DR*14	6	1.67	DRB1*14	11	1.72	
DR*09	1	0.28	DRB1*09	9	1.41	
DR*16	3	0.83	DRB1*16	6	0.94	
DR*08	1	0.28	DRB1*05	1	0.16	

Table-IV

Two locus haplotype (HLA-A and B) frequencies (>0.015) among study participants (N=500)

	Patients (N=180)			Donors (N=320)			
HLA-A	HLA-B	Number	Frequency	HLA-A	HLA-B	Number	Frequency
A*11	B*15:02	17	0.047222	A*11	B*15:02	42	0.065625
A*33	B*44	16	0.044444	A*33	B*44	27	0.042188
A*2	B*15:02	12	0.033333	A*11	B*35	21	0.032813
A*33	B*15:02	12	0.033333	A*2	B*35	20	0.031250
A*24	B*35	11	0.030556	A*11	B*52	18	0.028125
A*11	B*35	11	0.030556	A*3	B*35	17	0.026563
A*2	B*38	10	0.027778	A*33	B*15:02	17	0.026563
A*11	B*52	9	0.025000	A*2	B*15:02	15	0.023438
A*24	B*15:02	9	0.025000	A*11	B*44	12	0.018750
A*11	B*44	7	0.019444	A*11	B*40:02	12	0.018750
A*2	B*35	7	0.019444	A*24	B*15:02	12	0.018750
A*33	B*57	6	0.016667	A*24	B*35	11	0.017188
A*2	B*7	6	0.016667	A*24	B*40:02	11	0.017188
A*1	B*15:02	6	0.016667	A*2	B*7	10	0.015625
A*31	B*15:02	6	0.016667	A*2	B*40:2	10	0.015625

Three locus haplotype (A and B locus of MHC class I and DRB1 locus of MHC class II gene) analyses observed 236 and 320 variations of haplotypes among patients and donors respectively. The first 20 variations found A*11: B*15:02: DRB1*15 was the most frequent haplotypes in both groups. Among the recipient group, A*24: B*15:02:DRB1*15 was the second most frequent haplotype, followed by A*11: B*52:DRB1*15, A*33: B*44: DRB1*15 and A*33: B*15:02: DRB1*15. Moreover, among donor group, A*33: B*44: DRB1*07, A*33: B*44: DRB1*15, A*02: B*35: DRB1*07, A*11: B*15:02: DRB1*12 were the haplotypes after the most frequent one (Table-V).

Table-IV

Two locus haplotype (HLA-A and B) frequencies (>0.015) among study participants (N=500)

Patients (N=180)			Donors (N=320)		
Haplotypes (A:B:DRB1)	Number	Observed frequency	Haplotypes (A:B:DRB1)	Number	Observed frequency
*11:*15:02:*15	9	0.025	*11:*15:02:*15	23	0.0359
*24:*15:02:*15	8	0.0222	*33:*44:*07	10	0.0156
*11:*52:02*15	7	0.0194	*02:*35:*07	9	0.0141
*33:*44:*15	6	0.0167	*33:*15:02:*15	9	0.0141
*33:*15:02:*15	6	0.0167	*11:*44:*07	8	0.0125
*11:*15:02:*12	5	0.0139	*11:*52:*15	8	0.0125
*02:*38:*15	5	0.0139	*11:*40:02:*15	8	0.0125
*02:*15:02:*12	5	0.0139	*11:*15:02:*12	8	0.0125
*02:*15:02:*15	5	0.0139	*24:*40:02:*15	7	0.0109
*31:*15:02:*15	5	0.0139	*02:*15:02:*15	7	0.0109
*33:*44:*07	5	0.0139	*33:*44:*15	6	0.0094
*26:*52:*15	4	0.0111	*03:*35:*15	6	0.0094
*33:*57:*15	4	0.0111	*68:*52:*15	6	0.0094
*33:*40:02:*15	4	0.0111	*11:*35:*15	5	0.0078
*11:*35:*15	3	0.0083	*01:*44:*07	5	0.0078
*11:*37:*10	3	0.0083	*24:*40:01:*15	5	0.0078
*11:*44:*04	3	0.0083	*24:*15:02:*15	5	0.0078
*11:*44:*07	3	0.0083	*02:*35:*15	5	0.0078
*01:*37:*10	3	0.0083	*02:*44:*07	5	0.0078
*01:*75:*12	3	0.0083	*11:*35:*12	4	0.0062

Allele frequencies of HLA-A-A, HLA-B-B and HLA-DRB1 genotype in patients group showed that the highest frequency for HLA-A antigens were A11: A33, A2: A33, A1: A11, for HLA-B antigens were B75: B75, B35: B44, B35: B75 and for HLA-DR antigens were DR7: DR15, DR15: DR15, DR4: DR15 respectively. Among the donor group, HLA-A, HLA-B and HLA-DR were A2: A11, A11: A11, A11: A24; B35: B75, B75: B75, B44: B75; DR7: DR15, DR15: DR15, DR4: DR15 respectively (Figure 1-3).

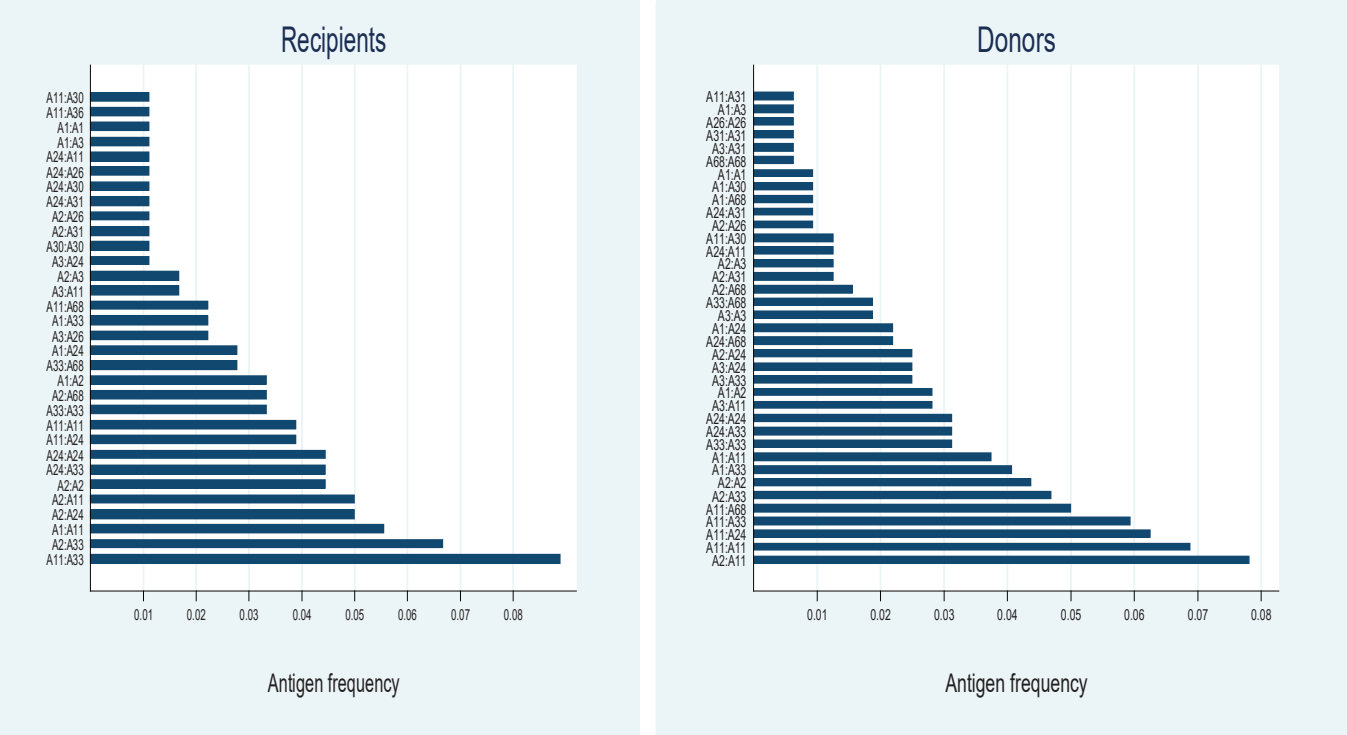

Figure - 1: HLA A-A antigen frequencies among patients and donors.

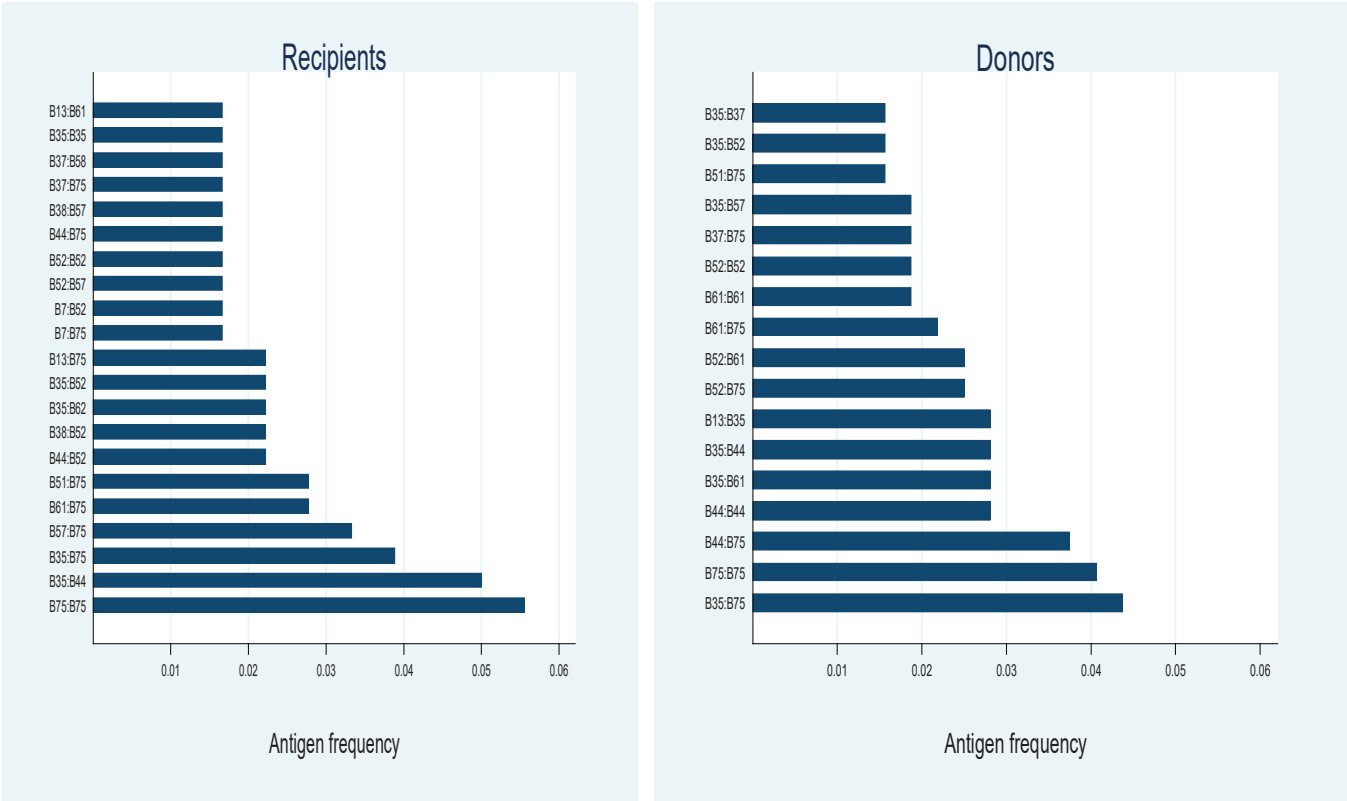

Figure - 2: HLA B-B antigen frequencies bar plot of patients and donors

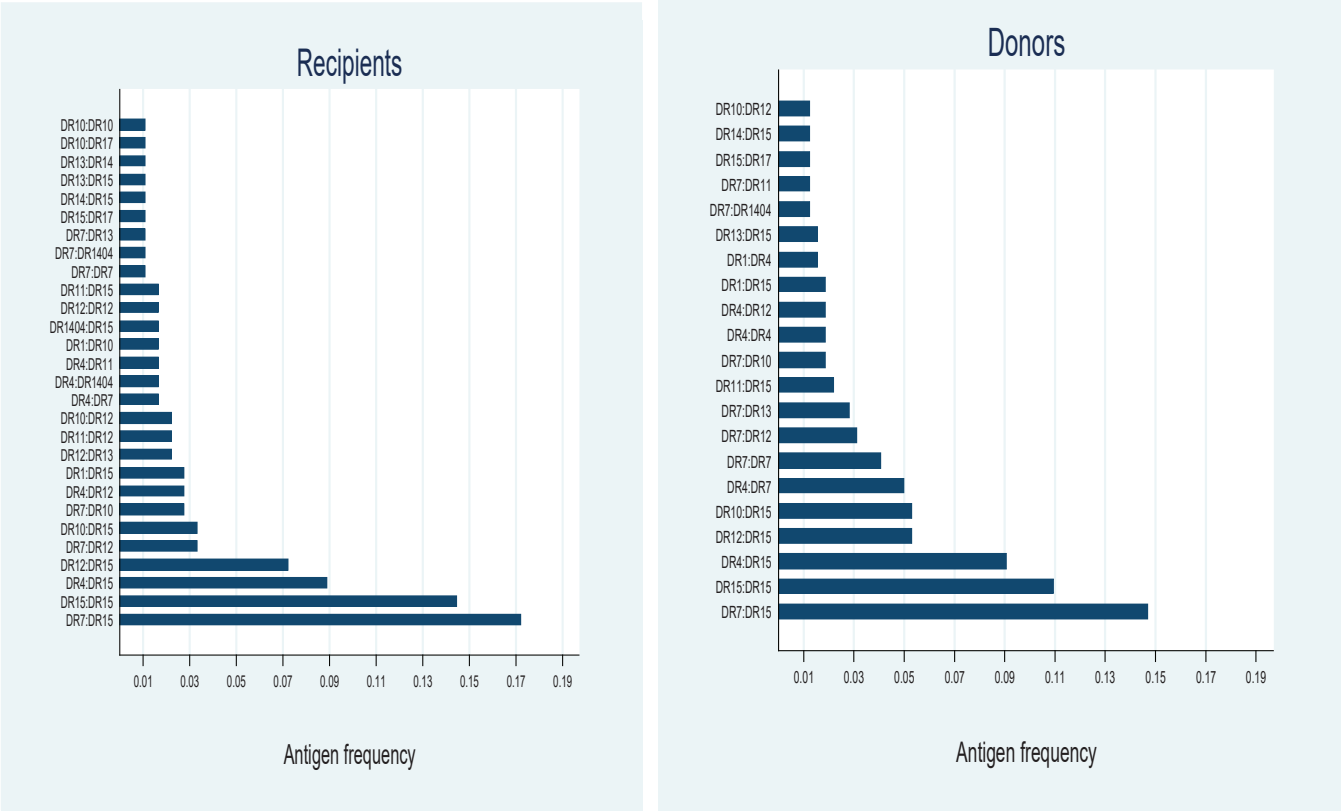

Figure - 3: HLA DRB1-DRB1antigen frequencies bar plot of patients and donors

Discussion

HLA molecules play a major role in regulation of the body's immune system by detecting self from non-self antigen and are thus considered as the major barrier for successful organ transplantation. The success of graft survival depends largely on well matching of HLA antigens of patient and donor. For this, analyses of HLA distribution patterns is necessary for the estimation of the likelihood of obtaining matched donors to increase the graft survival rate. Moreover, HLA system has been found to be associated with the pathogenesis of some renal diseases like, IgA nephropathy, glomerulonephritis, diabetic nephropathy and some autoimmune diseases and inflammatory bowel diseases. Thus, identification and analysis of the HLA polymorphism in ESRD patients is also important for the determination of a possible association of the disease with HLA system.

In this study, among ESRD patients and donors, A, B and DRB1 locus were found to be similar and both groups were in genetic equilibrium. The highest frequent allele detected in A, B and DRB1 locus of patients- A*11, B*15:02 and DRB1*15 were also be reported highest among donors of this study. Not only the highest one, the first four most frequent alleles of each three loci; A*11, A*02, A*33, A*24 of A, B*15:02, B*35, B*44, B*52 of B and DRB1*15, DRB1*07, DRB1*04, DRB1*12 of DRB1 locus were found to be in agreement within both groups. Additionally, these highest frequent alleles were also be reported highest from a previous study,[10] as well as from another population based study from Bangladesh.[11] As cadaveric transplant has not yet started in Bangladesh, most of the donors of this study were blood relatives of the patients. Moreover, racial diversity is less frequent in the Bangladeshi population, which may be the underlying cause of similar pattern of allele distribution among donors and patients. However, the relative occurrence of allele frequencies had shown some differences. The ESRD patients group had higher frequencies of A*26 (OR:1.99), A*30(OR:1.29), B*57(OR:1.54), B*15:01(OR:1.37) and DRB 1*11(OR:1.69) compared to the donor group. On the other hand, HLA A*03(OR: 0.54), B*51(OR:0.52) and B*40:02(OR:0.57) was observed less frequently among recipients than donors. Although these findings are not statistically significant, it may suggest some association of HLA alleles with the development of ESRD. DRB1*11, which was observed more frequent among ESRD patients in this study, was also reported significantly higher among ESRD patients from Taiwan.[12] A significant association with renal diseases of different A and B locus alleles were also reported from China, Iran, Arab, Egypt and Kuwait.[13-17] A positive association and protective role of some alleles was also reported from Venezuela.[18] However, the positively associated alleles from different countries are not

unique in distribution. This diversity in the findings of different researchers may be due to the irregularity in allele frequency among different ethnic groups and geographical locations.

Marked difference in allelic distribution of different loci in different ethnic population may be due to the extreme polymorphism of major histocompatibility complex (MHC) genes. Thus, comparison of HLA genotypes among different populations may be important because the probability of incompatibility at the allele level will be affected by different origins of recipients and donors.[19] For this reason, we compared the more frequently observed alleles from this study with the findings of similar studies from surrounding Asian population and found it to be comparable with alleles detected among donors and recipients from Nepal[20] different states of India and Pakistan,[21-23] Mayanmar[24] and other oriental people of South Asian countries like China, Thailand, Malayasia and Vietnam.[25-28] However, when compared with the world population, frequently reported alleles of Asian people were observed to be less frequent in Hispanics, Caucasians and North African population.[29]

In this study, analysis of antigen expression of HLA-A-A, B-B and DRB1-DRB1 genotype revealed higher frequency of A11/A33, B75/ B75 and B35/ B44 antigens in patients (0.10, 0.056, 0.050) compared to donors (0.06, 0.045, 0.030). These findings suggest that these types may have some association with renal disease. A study from West Central India also reported variations in antigen distribution among donors and recipients[30] A review of different HLA and renal disease associated studies summarized possible protective and risk associated alleles of A, B and DRB1 locus.[31] However, there are marked variation of HLA antigen distribution among different ethnicity and geographical location, thus, protective and risk antigen will also be varied accordingly, but this issue needs further investigation.

HLA haplotype carries more specific information than HLA allele frequencies. In this study, the most common haplotypes observed in the two locus HLA-A- B haplotype were A *11-B*15:02 and A*33- B*44 with a frequency of 0.065 and 0.042, respectively among donors and 0.047 and 0.044, respectively among patients. The A*11- B*15:02 haplotype is predominant among Mayanmar Rakhain, Mayanmar Kayah[29] as well as other Asian people, including Sri-Lanka,[32] Malaysia Peninsular Malay[27] and Oriental people of South East Asian countries including Vietnam[28] and China.[25] Moreover, the common three locus haplotypes, A*11- B*15:02-DRB1*15 distribution observed in this present study has also been reported frequent from Mayanmar Rakhine population and other oriental people.[29] In Uttar Pradesh (North India), A2-B7; A3-B51 was found the common alleles in both renal transplant recipients and donors (North India)[33]; A2-B40; A9-B35 was common in Maharastra (Western India)[34]; A*02-B*61; A*01-B*57 was common in west central India[30]; A*24, B*35, DRB1*15 was common in Telangana and Andhra Pradesh,[35] while among the Bengali population of Siliguri and adjoining areas of West Bengal, A*01-B*37; A*01-B*40, A*29-B*40 was common.[36] All of these reported haplotypes were found to be less frequent in this study as well as in our previous study. Haplotype analysis of this study indicates that Bangladeshi people have more influence of the Oriental people than Caucasoid.[29]

The result of this study suggests that a wide variety of HLA antigen distribution is present in ESRD patients and donors in Bangladesh. Many immune suppressive drugs are used to prevent graft rejection, but HLA matching plays the vital role in graft survival rate. A study on the effect of HLA-A, -B and –DR matching on survival of adult renal transplant recipients by analyzing the records of 189141 adult transplant patients who had received organs from deceased donors found that the hazard ratios are significantly linear for HLA mismatch.[37] Bangladesh is planning to start cadaver transplant very soon. If haplotype identical cadaver renal transplant is required, large registries are to be created for end stage renal disease patients. The data of this study will be helpful in creating a national registry and organ sharing network for Bangladeshis. In addition to renal transplant, patients in need of hematopoietic stem cell transplantation will also benefit by finding suitable donors.

Conclusion

Haplotype and allele frequency observed in this study indicates that both patients and donor groups are in genetic equilibrium. Higher frequency of some alleles found in patients and donors may have some susceptible and protective role in end stage renal disease development. However, none of these were found to be significant statistically. Further studies are needed to corroborate the findings of this study.

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