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HLA Antigen Distribution in Renal Transplant Recipients and Donors

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ABSTRACT

Background: HLA typing analysis is important in renal transplant patient. This study is the first report from Nepal to find out distribution of HLA A, B, DR antigen in live related renal transplant recipients and donors from Nepal. The aim of this study was to investigate the distribution of HLA in the live related renal transplant recipients and donors of Nepal.

Methods: In a retrospective study, HLA patterns were defined in 100 live related renal transplant recipients and donors. One year study is done from June 2011 to May 2012. The study was done by using sequence specific oligonucleotides primers and polymerase chain reaction and assay. Allele frequencies were obtained by direct counting.

Results: A total of 12 HLA-A, 15 HLA-B and 13 HLA-DRB1 alleles were identified at the four-digit level in the live related renal transplant recipients and donors of Nepal. High frequency alleles were HLA-A*11 (34.5%), A*24 (17%), A*33 (13%); HLA-B*15(27%), B*35(19%), B*40 (10%); HLA-DRB1*15 (33.5%), DRB1*12 (21.4%) and DRB1*04 (7.32%).

Conclusions: These results showed considerable heterogeneity in both HLA class I and class II antigens. To reduce the risk of allograft rejection, transplantation from HLA matched donors is recommended.

Keywords: allele; HLA antigen distribution; renal transplant.

INTRODUCTION

Renal transplant has become the standard care for the fatal renal diseases and the success of such transplantations correlates with the degree of HLA compatibility between recipients and donors.

However, to find out matched donor and recipient, is a difficult task as HLA locus is highly polygenic and polymorphic in nature. Human leukocyte antigens are encoded by major histocompatibility complex (MHC) located on short arm of chromosome six. HLA molecule is associated with allograft rejection.[1] When matched donor is not found in a family then search may be performed to find out unrelated donors. Therefore, the information about frequencies with which a particular HLA haplotype occurs in a population is important.

In the present work, the distribution of HLA-A, -B, -DR is obtained in the live related renal transplant recipients and donors of Nepal for the first time to determine HLA antigen frequencies.

METHODS

This is a retrospective study. Ethical approval of research was given by the institute where study was carried out. This study used data from patients whose samples had already been taken and processed; hence, there was no additional risk. The confidentiality of the information was strictly protected. The samples had been taken after obtaining verbal informed consent from the patients or their families and through medical request. A total number of 100 renal transplant recipients and their prospective live related donors' HLA- A, B and DR

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phenotypes were analyzed that was referred to Arrogya foundation, Pulchowk, Lalitapur, Nepal from June 2011 to May 2012. Nepal's first HLA laboratory was established in June 3, 2011 in Arogya foundation and we are doing HLA typing since then.

DNA Extraction: Genomic DNA was isolated from whole blood containing ethylenediaminetetraacetic acid (EDTA), using a Genomic DNA Isolation Kit, according to the manufacturer's instructions (Qiagen QIAVac 96 GmbH, Hilden). DNA typing of HLA Loci HLA-A, HLA-B and HLA DRB1 was performed on a Multi-Analyte Profiling system (xMAP) (Luminex HLA-SSO) using a Genprobe HLA typing kit according to the manufacturer's instructions.

Since the HLA types of our samples were molecularly defined, we used the 2009 HLA Dictionary (the IMGT HLA nomenclature reports-HLA, January 2009) to determine the serologic equivalents for HLA alleles. Allelic frequencies of HLA-A, -B and -DRB1 loci were estimated by the direct counting method.

RESULTS

Males outnumbered females, as recipients while the number of female donors was more. The donor-recipient profiles of 100 transplants (Figure 1). There was a female preponderance among donors 69.23% and male preponderance among recipients 87.5%. Since 1997 there has been an increase in transplants from biologically unrelated donors and the wife of the recipient has emerged as very common donor. When spousal transplants were considered as a subset, out of 47 transplants only four 3.8% were from husband to wife (Figure 1).

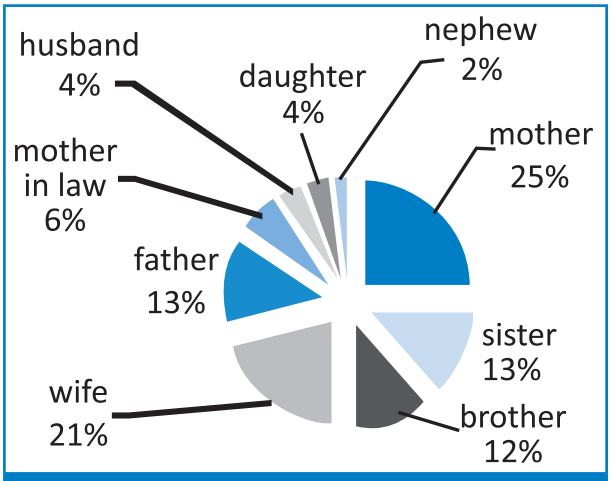

Figure 1. Donor profile

Allele frequencies: It was possible to determine 12, 15, and 13 alleles of the HLA A-B-DRB1 loci, respectively, in the renal patients and donors studied. The most frequent alleles in the HLA-A locus were A*11 34.5(%), A*24 17(%), A*33 13(%), A*02 11(%), and A*03 7(%); followed by A*31, A*01, A*68, A*32, A*29, A*26, and A*30 with frequencies over 0.5(%) (Table 1).

Table 1. HLA A allele frequencies (n=200).

HLA A	N	Percent
1	8	4
2	22	11
3	14	7
11	69	34.5
24	34	17
26	1	0.5
29	3	1.5
30	1	0.5
31	10	5
32	4	2
33	26	13
68	8	4

Table 2. HLA B Allele frequencies (n=200).

HLA B	N	Percent
7	9	4.5
13	10	5
15	54	27
18	6	3
35	38	19
37	1	0.5
38	5	2.5
40	20	10
44	7	3.5
48	12	6
51	5	2.5
52	7	3.5
55	10	5
57	5	2.5
58	11	5.5

Table 3. HLA DRB1 Allele frequencies (n=200).

HLA DRB1	N	Percent
1	12	6.28
3	10	5.23
4	14	7.32
7	7	3.66
8	3	1.57
9	2	1.04
10	11	5.75
11	9	4.71
12	41	21.46
13	2	1.04
14	13	6.8
15	64	33.5
16	3	1.57

The most frequent alleles observed in Nepalese renal transplant recipients and donors, in the HLA- B locus were B*15 27(%), B*35 19(%), B*40 10(%) (Table 2).

All the HLA-DR known allele were DRB1*15 33.5(%), DRB1*12 21.4(%), DRB1*04 7.3(%), DRB1*14 6.8(%), and DRB1*01 6.2(%); followed by DRB1*10, DRB1*03, DRB1*11, DRB1*07, DRB1*08, DRB1*16, DRB1*09 and DRB1*13 with frequencies over 1(%) (Table 3).

DISCUSSION

Nepal has successfully conducted kidney transplantation in August 2008 and has entered into the new phase of kidney transplantation after legalization in 2002 (2058/10/22 BS).

Kidney transplantations correlate with the degree of HLA compatibility between recipients and donors. To find out matched donor and recipient, is a difficult task as HLA locus is highly polygenic and polymorphic in nature. Human leukocyte antigens are encoded by major histocompatibility complex (MHC) located on short arm of chromosome six. HLA molecule binds and presents peptide to T lymphocytes in cell mediated immune response and plays a key role in shaping the T cell repertoire and is also associated with allograft rejection. HLA antigens are inherited in a co-dominant manner from parents to the offspring. In the live related transplants there are only 25% chances that two sibs would be hundred percent identical and 50% chances would be that they will share one haplotype and 25% would be that they will not share any of the haplotype.[1] Therefore, the information about frequencies with which a particular HLA haplotype occurs in a population is important.

Our center performs live related renal transplant's HLA typing. Most of the time donor and recipient are siblings 24.99%, parent's vs offspring 25%, and offspring vs parents 3.8%. Thirteen 24.9% are spousal donors (wife 11 and husband 2). Only 1.9% are other donors like cousins. This study almost corresponds to the study done by Agrawal S et al.[2]

The present study is the first investigation of the HLA status of the live related renal transplant recipients and donors of Nepal. All the groups shared the most common haplotypes, many of them frequently. Analyses of HLA distribution patterns are necessary for the estimation of the likelihood of obtaining matched donors for individuals requiring transplants. It has been widely recognized that transplants between haplotypically matched patients and donors have a better rate of survival and that having donors of the same ethnic backgrounds minimizes the risk of allelic differences that may result in graft-versus-host disease or graft rejection. Thus to increase the probability of finding HLA-matched unrelated donors such studies of HLA polymorphism and haplotype distribution among different geographical areas are of great significance. Beside the study done by Dulal RK also found that the percentage of unrelated donor 69.69% has outnumbered related donor 29.43%.[3]

Male recipients 87.5% outnumbered female recipients, whereas female donors outnumbered males in the ratio 2: 1 in this study, which is similar to that of Panigrahi et al.[4] where 86 % of recipients were males.

Our results show that HLA-A*11 34.5(%), A*24 17(%), A*33 13(%); HLA-B*1527(%), B*3519(%), B*40 10(%); HLA-DRB1*15 33.5(%), DRB1*12 21.4(%) and DRB1*04 7.32(%) are more frequently seen HLA-A, B and DR antigen in renal transplant recipients and donors. While studies on HLA allelic diversity of among 838 population groups from Asia (272), Western Europe (147), South and Central America (107), North America (79), Pacific (59), sub-Saharan Africa (55), Eastern Europe (56), Middle East (34), North Africa (21) and Australia (8) of the world have revealed that some common alleles such as HLA A*02 20-28(%), B*40 5-20(%), and DRB1*15 10-18(%) are seen in Asian countries such as Afghanistan, Armenia, Azerbaijan, Bahrain, Bangladesh, Bhutan, Brunei Darussalam, Cambodia, China, East Timor, Georgia, India, Indonesia, Iran, Iraq, Israel, Japan, Jordan, Kazakhstan, Lebanon, Malaysia, Maldives, Middle East, Mongolia, Myanmar, North Korea, Oman, Pakistan, Philippines, Qatar, Saudi Arabia, Singapore, South Korea, Srilanka, Syria, Taiwan, Tajikistan, Thailand, Turkmenistan, UAE, Uzbekistan, Vietnam and Yemen.[5]

The study on Gurkha population also revealed the higher allele frequency of A*02 and A*11.[6] Similarly, the higher frequency of A*24 is also observed in the majority of the South Indian, Northern Indian populations and Bangladeshi Bengali population.[7-9]

The frequent alleles such as A*02 and A*11 and A*24 observed in the study done by Singh B et al correlated with Bangladeshi Bengalis. Among HLA-B locus alleles the most common alleles of Bangladeshis such as B*44, B*40, B*51 were not found to be in higher frequencies amongst the Bengalis in their study.[10] It could be explained that allele and haplotype distribution in the HLA system differ from one ethnic group to another or between the members of the same ethnic group living in different geographic areas, as shown in previous studies.[10]

However, we need large sample size to get overall picture of HLA antigen distribution among Nepalese population

living in Nepal. The large amount of data involving both HLA Class I and Class II will be required to know the phyogenetic history of Nepal population. The present study provides data on the incidence, inheritance and haplotype association of WHO recognized HLA-A, B and DR locus antigens in renal transplant patients and donors.

Beside, polymorphism in the HLA system is also used as a tool for anthropological studies, as genetic distances and correspondence analysis demonstrated that the allele and haplotype distribution of class I and class II loci are racially and geographically restricted.[11,12]

CONCLUSIONS

These results suggest that wide variety of HLA antigen distribution is present in renal transplant patients and donors. Such data may help to choose better donor candidates from ethnic groups which are genetically closer to the recipient

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