Original Article

Prevalence of Human Leukocyte Antigen Alleles Polymorphism in North Indian Population

Abstract

Background: Human leukocyte antigens (HLA) are highly polymorphic glycoproteins required for immune response and recognizing self or non-self. Knowing the HLA diversity in a population may be helpful in the selection of organ allocation for transplantation. We aimed to retrospectively analyze the prevalence of HLA, A, B, C, DRB1, and DQA1 alleles frequency in the north Indian population. **Materials and Methods:** HLA antigen allele data were retrospectively analyzed from a transplant cohort of 2259 subjects. HLA-A, B, and DRB1 frequency were determined in 2259, HLA-C in 759 and DQA1 in 751 subjects. **Results:** The most abundant HLA-A antigen alleles were HLA-A*01(25.41%), HLA-A*02 (24.83%), HLA-A*11 (17.53%), HLA-A*24 (10.27%), HLA-A*03 (9.07%). HLA-B antigen alleles were HLA-B*35 (20.54%), HLA-B*15 (15.36%), HLA-B*40 (13.59%), HLA-B*07 (10.14%), HLA-B*44 (7.79). HLA-C antigen alleles were HLA-C*07 (28.06%), HLA-C*04 (20.42%), HLA-C*03 (15.55%), HLA-C*06 (13.04%), HLA-C*12 (5.27%). HLA-DRB1 alleles were HLA-DRB1*07 (21.60%), HLA-DRB1*04 (19.74%), HLA-DRB1*10 (13.15%), HLA-DRB1*03 (10.80%), HLA-DRB1*11 (8.63%). HLA-DQA1 antigen alleles were HLA-DQA1*03 (35.42%), HLA-DQA1*02 (30.89%), HLA-DQA1*05 (21.84%), HLA-DQA1* 06 (10.12%), HLA-DQA1*04 (1.07%). **Conclusion**: The most frequent HLA alleles were HLA-A*01(25.41%), HLA-B*35 (20.54%), HLA-C*07 (28.06%), HLA-DRB1*07(21.60%), HLA-DQA1*03(35.42%) in north Indian population.

Keywords: *Human leucocyte antigen, Alleles, DRB1, Frequency, PCR, SSO*

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Introduction

The human leukocyte antigen (HLA) is a highly polymorphic surface glycoprotein required for antigen presentation, discrimination of self from non-self, susceptibility to autoimmune disease development, progression and susceptibility to infections.[1-4] HLAs are encoded by genes located on the short arm of chromosome 6 within a stretch of 4 megabases, resulting in a co-dominant transfer of two alleles, close linkages among gene loci, and non-random association of alleles. The HLA gene at different loci codes for heterogeneous proteins, leading to recognition and immune response. Knowing the HLA details is important for organ donor–recipient selection for transplantation.[5,6] Other important applications include determining paternity, tracing population migration history ancestry, designing HLA-targeted vaccines, and allocating organs/tissues for transplantation.[7-9]

In India, HLA typing is predominately done for organ transplant purposes to establish the relationship between donor and recipients.[7] There is a huge admix of population and HLA diversity within the country[10], and knowing the HLA allele distribution in a local population is important for the successful deceased organ transplant program and organ allocation.[11,12]

Here we present results of a retrospective analysis of the prevalence of different HLA antigens alleles in the north Indian population from our cohorts of donors and recipients undergoing transplantation.

Materials and Methods

We retrieved HLA typing data from 1st January 2012 to 31st December 2022 of all kidney transplantation donors and recipients at our institute. The study was approved by the institute's ethics committee (2022-102-IMP-EXP-48). The data of individuals with incomplete HLA allele information were

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excluded. Since study is retrospective in nature, taking patients consent is not required. The HLA typing methods changed with the evolution of the HLA typing methodology at the institute. The HLA typing performed by serological methods was excluded. HLA typing by molecular methods, polymerase chain reaction (PCR) based methods, including PCR-sequence-specific oligonucleotide (PCR-SSO) probes and sequence-specific primers (PCR-SSP), were used for the HLA typing, allowing for higher resolution and more accurate results.

The HLA alleles of 782 subjects were analyzed using the PCR-SSP, and 1477 were determined using PCR-SSO methods. To bring uniformity in the reporting of molecular methods, the older reports of alleles nomenclature were converted into the new HLA nomenclature system, as per the HLA nomenclature committee of WHO 2010, using the international ImMunoGeneTics project (IMGT)/HLA portal.[12] We recorded the HLA prefix, antigen, and allele for analysis [Figure 1]. We have not recorded HLA-specific proteins, synonymous DNA substitution in the coding region, or the differences in the non-coding region. Alleles frequency was calculated using the formula = (n/2N). Where n is the sum of the individual alleles; N is the sum of the total individuals. 2-is the copy number of individual alleles. The phenotypic frequency was calculated by dividing the individual alleles by the sum of the total individuals multiplied by 100 (n/N x 100).[13]

Variables were analyzed with the SPSS software (IBM, corporation, Armonk, NY, USA), and results were tabulated as frequency and percentage.

Results

A data total of 2259 individuals (mean age 39.54 ± 12.26 years, 1023 females) were included in the study.

The most diverse HLA antigen alleles in the north Indian population were HLA-B (total allele count, 29), HLA-A (alleles count, 17), HLA-DRB1 (alleles count, 13), and HLA-C (allele count, 13), HLA-DQA1 (allele count, 06).

Human leukocyte antigen class I alleles frequency

The Class I, HLA-A allele frequency is shown in Table 1, HLA-B in Table 2 and HLA C in Table 3. The top five most abundant HLA-A1 antigen alleles were HLA-A*01 (pf,25.41%; af, 0.1270), HLA-A*02 (pf, 24.83%; af, 0.1242), HLA-A*11 (pf, 17.53%; af, 0.0876), HLA-A*24 (pf, 10.27%; af, 0.0514), HLA-A*03 (pf, 9.07%; af, 0.0454) [Table 1]. The frequency of five most abundant HLA-B1 alleles were HLA-B*35 (pf, 20.54%; af, 0.1027), HLA-B*15 (pf, 15.36%; af, 0.0768), HLA-B*40 (pf, 13.59%; af, 0.0680), HLA-B*07 (pf, 10.14%; af, 0.0507), HLA-B*44 (pf, 7.79%; af, 0.0390) [Table 2]. The five most abundant HLA-C1 antigen alleles were HLA-C*07 (pf, 28.06%; af, 0.1403), HLA-C*04 (pf, 20.42%; af, 0.1021), HLA-C*30 (pf, 15.55%; af, 0.0777), HLA-C*06 (pf, 13.04%; af, 0.0652), HLA-C*12(pf, 5.27%; af, 0.0264) [Table 3].

Table 1: Genotypic and phenotypic frequencies of HLA (N = 2259)

HLA-A1 locus alleles	#Phenotypic frequency %	Number of alleles (n)	$Alleles frequency
A*01	25.41	574	0.1270
A*02	24.83	561	0.1242
A*11	17.53	396	0.0876
A*24	10.27	232	0.0514
A*03	9.07	205	0.0454
A*30	3.81	86	0.0190
A*33	3.63	82	0.0181
A*26	1.99	45	0.0100
A*32	0.84	19	0.0042
A*68	0.66	15	0.0033
A*31	0.58	13	0.0029
A*23	0.49	11	0.0024
A*29	0.44	10	0.0022
A*25	0.31	7	0.0015
A*34	0.04	1	0.0002
A*43	0.04	1	0.0002
A*66	0.04	1	0.0002

$Alleles frequency was calculated using the formula = (n/2N), where n=is the sum of the individual alleles and N is the sum of the total individuals. 2-is the copy number of individual alleles. #The phenotypic frequency was calculated by dividing the individual alleles by the sum of the total individuals multiplied by 100 (n/N × 100). HLA: human leukocyte antigen

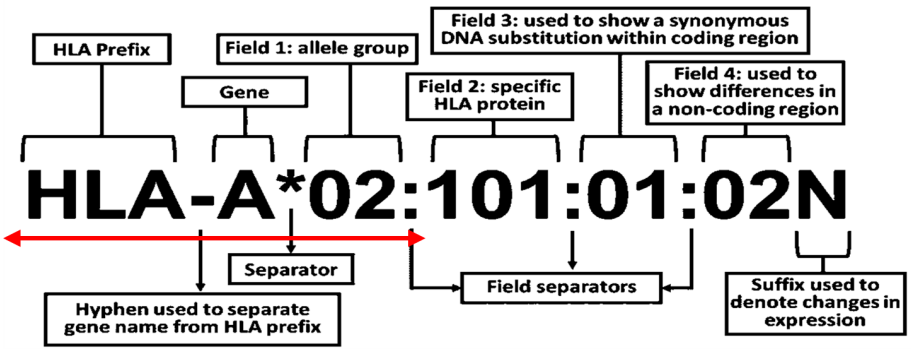

Figure 1: Schematic representation of human leukocyte antigen (HLA) nomenclature system. Red bar indicates the allele level reported in this article.

Table 2: Genotypic and phenotypic frequencies of HLA-B1 locus (N = 2259)

HLA-B1 locus alleles	#Phenotypic frequency %	Number of alleles (n)	$Alleles frequency
B*35	20.54	464	0.1027
B*15	15.36	347	0.0768
B*40	13.59	307	0.0680
B*07	10.14	229	0.0507
B*44	7.79	176	0.0390
B*37	4.65	105	0.0233
B*13	4.25	96	0.0213
B*52	3.90	88	0.0195
B*18	3.85	87	0.0193
B*27	3.81	86	0.0190
B*08	3.72	84	0.0186
B*51	1.95	44	0.0097
B*38	1.37	31	0.0069
B*39	1.15	26	0.0058
B*55	0.71	16	0.0035
B*57	0.58	13	0.0029
B*48	0.49	11	0.0024
B*50	0.44	10	0.0022
B*41	0.40	9	0.0020
B*53	0.31	7	0.0016
B*58	0.27	6	0.0013
B*46	0.22	5	0.0011
B*14	0.18	4	0.0009
B*47	0.09	2	0.0004
B*56	0.09	2	0.0004
B*45	0.04	1	0.0002
B*49	0.04	1	0.0002
B*54	0.04	1	0.0002
B*01	0.04	1	0.0002

$Alleles frequency was calculated using the formula = (n/2N), where n is the sum of the individual alleles and N is the sum of the total individuals. 2-is the copy number of individual alleles. #The phenotypic frequency was calculated by dividing the individual alleles by the sum of the total individuals' multiplied by 100 (n/N × 100), HLA: human leukocyte antigen

Human leukocyte antigen class II alleles frequency

The Class II HLA-DR and HLA-DQ frequencies are shown in Table 3. The frequency of the five most frequent HLA-DRB1 alleles were HLA-DRB1*07 (pf, 21.60%; af, 0.1080), HLA-DRB1*04 (pf, 19.74%; af, 0.0987), HLA-DRB1*10 (pf, 13.15%; af, 0.0657), HLA-DRB1*03 (pf, 10.80%; af, 0.0540), HLA-DRB1*11 (pf, 8.63%; af, 0.0432) [Table 4]. The frequency of the five most abundant HLA-DQA1 antigen alleles were HLA-DQA1*03 (pf, 35.42%; af, 0.1771), HLA-DQA1*02 (pf, 30.89%; af, 0.1545), HLA-DQA1*05 (pf, 21.84%; af 0.1092), HLA-DQA1*06 (pf, 10.12%; af, 0.0506), HLA-DQA1*04(pf, 1.07%; af, 0.0053) [Table 5].

Discussion

HLA typing is one of the most important laboratory work-ups before organ transplantation. Due to its highly

Table 3: Genotypic and phenotypic frequencies of HLA-C1 (N = 759)

HLA-C locus alleles	#Phenotypic frequency %	Number of alleles (n)	$Alleles frequency
C*07	28.06	213	0.1403
C*04	20.42	155	0.1021
C*03	15.55	118	0.0777
C*06	13.04	99	0.0652
C*12	5.27	40	0.0264
C*01	4.74	36	0.0237
C*02	4.08	31	0.0204
C*05	3.16	24	0.0158
C*15	2.50	19	0.0125
C*08	1.98	15	0.0099
C*14	0.92	7	0.0046
C*17	0.13	1	0.0007
C*18	0.13	1	0.0007

$Alleles frequency was calculated using the formula = (n/2N), where n is the sum of the individual alleles and N is the sum of the total individuals. 2-is the copy number of individual alleles. #The phenotypic frequency was calculated by dividing the individual alleles by the sum of the total individuals' multiplied by 100 (n/N × 100). HLA: human leukocyte antigen

Table 4: Genotypic and phenotypic frequencies of HLA-DRB1 locus (N = 2259)

HLA-DRB1 locus alleles	#Phenotypic frequency %	Number of alleles (n)	$Alleles frequency
DRB1*07	21.60	488	0.1080
DRB1*04	19.74	446	0.0987
DRB1*10	13.15	297	0.0657
DRB1*03	10.80	244	0.0540
DRB1*11	8.63	195	0.0432
DRB1*15	8.32	188	0.0416
DRB1*13	6.95	157	0.0347
DRB1*14	5.27	119	0.0263
DRB1*12	4.47	101	0.0224
DRB1*09	1.06	24	0.0053

$Alleles frequency was calculated using the formula = (n/2N), where n is the sum of the individual alleles and N is the sum of the total individuals. 2-is the copy number of individual alleles. #The phenotypic frequency was calculated by dividing the individual alleles by the sum of the total individuals' multiplied by 100 (n/N × 100), HLA: human leukocyte antigen

polymorphic nature, the frequencies of alleles vary widely depending on the dominance of the ethnic groups in the community. It has mendelian inheritance and has long been used in determining paternity, tracing population, migration history, and ancestry.[14,15] Beyond this, every individual's immune system is tuned to the specific set of HLA and self-proteins; however, it is skewed when an allo-organ is transplanted to another person.[16-18] The recipient immune system recognizes the transplanted tissue or organ as non-self, leading to rejection and affecting graft survival.[19] It is well known that graft survival improves

Table 5: Genotypic and phenotypic frequencies of HLA-DQA1 (N = 751)

HLA-DQA1 locus alleles	#Phenotypic frequency %	Number of alleles (n)	$Alleles frequency
DQA1*03	35.42	266	0.1771
DQA1*02	30.89	232	0.1545
DQA1*05	21.84	164	0.1092
DQA1*06	10.12	76	0.0506
DQA1*04	1.07	8	0.0053
DQA1*01	0.67	5	0.0033

$Alleles frequency was calculated using the formula = (n/2N), where n is the sum of the individual alleles and N is the sum of the total individuals. 2-is the copy number of individual alleles. #The phenotypic frequency was calculated by dividing the individual alleles by the sum of the total individuals' multiplied by 100 (n/N × 100), HLA: human leukocyte antigen

with HLA matches between recipient and donor.[20] Beyond this, a marked HLA variability in susceptibility for communicable and non-communicable autoimmune diseases across ethnicity and geographical location has been reported.[21,22] The HLA alleles are significant determinants for immunogenic response to infection. There are associated risk factors for multiple non-kidney immunological diseases such as SARS-CoV-2 infection, cancer, myasthenia gravis, etc.,[21,23-25] and many other kidney diseases such as membranous glomerulopathy,[26] IgA nephropathy[27] complement 3 glomerulopathy,[28] and diabetic nephropathy.[29]

In this study, we found a higher prevalence of certain HLA alleles such as A*01, A*02, A*11, B*35, B*15, B*40, C*07, C*04, C*03, DRB1*07, DRB1*04, DRB1*10, DQA1*03, DQA1*02, DQA1*05. In our current study, the frequency of HLA-A*01, A*02, and DRB1*07 were comparable to that of HLA alleles from the middle central and South India data.[30,31] We have observed the prevalence of 24.83% of HLA-A*02 alleles in our population, while it was 50% in the UK population.[32] One study showed that HLA-A*01 alleles were strongly associated with acquiring viral infections such as Epstein–Barr virus (EBV) and Hodgkin lymphoma, in contrast to the HLA-A*02 allele, which had a protective effect from EBV infection.[33] A study has shown that HLA-A*02 alleles expressing peripheral blood mononuclear cells (PBMCs) respond to viral antigens and secret anti-HIV factors to regress HIV proliferation.[34] EBV and lymphoma are commonly observed in transplant scenarios,[35,36] and knowing the HLA beforehand may help understand the susceptibility to their viral infections. We have not studied any such association in the present study.

In a north Indian cohort study of HLA class I molecule, HLA-A*01 alleles frequency was reported to be highest (47.5%) in Haryana, A*10 was highest (71.42%) in Bihar, A*02 was (34.88%) in Punjab, 39.28% in UP residents, with 25.41% HLA-A*01, 24.83% HLA-A*02.[10] The sample size in the study was only 360 individuals, and a limited number of individuals were selected from each region, including those from the respective state, which may have inflated the higher prevalence of these alleles. The frequency of HLA-B*13 was 4.25% in our cohort. HLA-B*13 is reported to be associated with 7.29 fold higher risk of non-melanoma skin cancer in Brazilian renal transplant patients,[25] while the frequency of HLA-B*45 (0.042%) and B*50 (0.44%) was lower in our cohort. A lower B*45 and B*50 alleles were associated with a higher risk of skin cancer than those without it.[25] There is no concordant data on skin cancer from India related to these HLA alleles.[37] Malignancy is the third most common cause of mortality in renal transplant patients, and about 5–6% of the patients develop malignancy in the post-transplant period.[38] The A*11 alleles prevalence was 17.53% in our cohort, similar to the South Indian cohort[39] and relatively lower compared to the Rajasthani population (60%),[10] and Bangladeshi population (25.4%).[13] This suggests more considerable genetic variability for different HLA alleles among various states of India and Bangladesh. Similarly, the prevalence of A*24 alleles was 10.27% in our cohort, which is strongly linked with inflammatory diseases, Myasthenia Gravis,[21] whereas A*08 showed a protective association from Myasthenia Gravis, A*08 was not detected in our cohorts. The prevalence of B*07 and DQA1*03 alleles was 10.14% and 35.42%, respectively, and both of the alleles were associated with the increased risk of human papillomavirus in cervical cancer patients.[40] Another study showed a higher prevalence of B*07, DRB1*01, and DRB1*07 alleles associated with inflammatory bowel Crohns disease.[41] Renal transplant patients frequently experience episodes of diarrhea that may be linked with B*07 alleles. However, none of the reports in RTRs suggest that B*07 is associated with diarrhea. HLA DRB1*04 frequency was 19.74% in our cohort, and in a study, DRB1*04 was found to be associated with rheumatoid arthritis.[42] Arthritis is a common problem in North Indian females.[43]

Many abundant alleles may be due to selection pressure against microbial infection.[44] However, there is no definite evidence of a link between HLA alleles and a specific microbial infection. Some studies have shown a prevalence of specific alleles in certain endemic regions.[44,45] Northern India witnesses three seasonal variations in a year and a very high prevalence of microbial diseases like hepatitis, tuberculosis, typhoid, malaria, meningitis, and chikungunya, which may show the selection of specific HLA alleles.[46]

Thus, the diversity of HLA reports from our study may help design the antibodies panel against the predominant HLA alleles for screening of the cadaveric organ allocation, stratification of organ transplant recipient risk of allograft rejection, susceptibility for infection and occurrence of autoimmune disease in the north Indian population.

A limitation of the study is that it remains limited to the analysis of the frequency of different HLA alleles in

our patient population. Further, the resolution was up to the alleles group level. We have not measured any functional impacts of HLA alleles polymorphism, such as DSA formation, immune cell frequency, infection risk, and cytokines level associated with any specific alleles. However, we have analyzed a big pool of 2259 samples, which may help screen suitable organ donors and design HLA-targeted vaccines for the north Indian population. It may also help specify donor-specific anti-HLA antibodies and the availability of possible matched donors if panel reactive antibodies are available.

The study may be expanded to include higher HLA allele resolution. High-resolution HLA typing may help in epitope matching, which has been shown to improve graft survival. The association of HLAs with graft survival, infections, autoimmunity, and cancers in the post-transplantation period, etc, can be explored in the future, where the Indian data are sparse. HLA typing with functional analysis may help determine the exact significance of HLA alleles on human health.

Conclusion

HLA-B was the most polymorphic antigen, having 29 alleles. The most frequent HLA alleles were HLA-A*01(25.41%), HLA-B* 35 (20.54%), HLA-C*07 (28.06%), HLA-DRB1*07(21.60%), HLA-DQA1*03(35.42%) in north Indian population.

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Conflicts of interest

There are no conflicts of interest.

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