Current Trends in Immunology
Vol. 24, 2023

Original Article

Frequency of five-locus haplotypes of human leukocyte antigen genes in a Vietnamese population

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ABSTRACT

Genotypes and frequencies of human leukocyte antigen (HLA) alleles/haplotypes are diversified depending on ethnicity. The compatibility in genotypes of HLA genes between the donors and the recipients is very important in deciding the success of clinical transplantation therapies. In this study, frequency and distribution of five-locus haplotypes from a set of five HLA genes including HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 in 2076 cord blood units of Vietnamese were analysed and compared with those of other cohorts. The results of the study demonstrated that in a total of 1562 five-locus haplotypes, there were only 10 haplotypes with frequencies of over 1% (accounting for 23.0%), 23 haplotypes with frequencies of over 0.5% (accounting for 32.9%), 140 haplotypes with frequencies of over 0.1% (accounting for 56.1%), and the rest 1422 haplotypes with frequencies of below 0.1% (accounting for 43.9%). The highest five-locus haplotype was A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01 (5.9%), followed by A*29:01-B*07:05-C*15:05-DRB1*10:01-DQB1*05:01 (4.0%), and A*02:01-B*46:01-C*01:02-DRB1*09:01-DQB1*03:03 (3.1%). In addition, result from data mining analysis revealed that there was a very high level of similarity in five-locus haplotype frequencies between Vietnamese in this study and USA NMDP Vietnamese; however, there was a very low similarity in five-locus haplotype frequencies between different populations. This study provided important information about the frequency of five-locus (HLA-A-B-C-DRB1-DQB1) haplotypes in a large-size of cord blood samples of Vietnamese. It also suggests that cord blood/stem cell/tissue/organ transplantations should be only applied within the people in the same cohort.

KEYWORDS: human leukocyte antigen, five-locus haplotype frequency, cord blood, Vietnamese population.

INTRODUCTION

The human leukocyte antigen (HLA) plays very important roles in human immune system. Information about genotypes of HLA genes is very crucial for clinical applications. The compatibility about the HLA-system between the donor and the recipient is required when performing blood/stem-cell/tissue/organ transplantations. In general, the levels of similarity in genotypes of HLA genes decide the efficiencies of the transplantation therapies [1-4]. Practically, mismatch in HLA between the recipient and the donor is considered as a high risk factor for the development of graft-versus-host disease (GVHD) [5, 6]. HLA-A, HLA-B, HLA-C and HLA-DR have been identified as major transplantation antigens, which directly affect the outcomes of hematopoietic stem cell transplantation [7, 8]. HLA matching is also very important in kidney transplantation [9].

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Currently, cord blood is being exploited as an abundant and beneficial source of stem cells in transplantation therapies to treat various blood diseases such as anaemia, lymphoma, and leukaemia [10-13]. In Vietnam, many clinical bases have been established to collect, store and prepare cord blood for clinical applications. The National Institute of Haematology and Blood Transfusion (NIHBT) is one of the most important and the biggest organisations, which is contributing not only in collecting and storing of cord blood units but also performing of blood and/or stem cell transplantations in Hanoi, Vietnam. Previously, genotypes of four HLA genes including HLA-A, HLA-B, HLA-C and HLA-DRB1 in 3750 cord blood samples of Vietnamese (stored at NIHBT) [4], and genotype of HLA-DQB1 gene in 2076 cord blood samples of Vietnamese (stored at NIHBT) [14] had been identified by PCR-SSO. In this study we combined these two data sets to investigate the frequencies and distribution of five-locus (HLA-A-B-C-DRB1-DQB1) haplotypes in the 2076 Vietnamese cord blood samples, supplying important information about blood/stem cell transplantation programs. We also performed data mining to make a comparison on the similarity of five-locus haplotype frequencies between different populations.

2. MATERIALS AND METHODS

2.1. Population and sample collection

Cord blood samples of Vietnamese were collected and stored at −196 °C in liquid nitrogen tanks at the Umbilical Cord Blood Bank, National Institute of Haematology and Blood Transfusion, Vietnam. Clinically, cord blood samples were collected within 24 hours after birth. Before storing, cord blood samples were tested to ensure that the samples have no blood cluster or bizarre colours, mean corpuscular volume (MCV) of ≥ 95 fl, no abnormal haemoglobin, number of nucleated cells ≥ 109 cells/mL, and are negative for hepatitis C virus (HCV)/hepatitis B virus (HBV)/human immunodeficiency virus (HIV)/cytomegalovirus (CMV), as well as negative for bacteria.

2.2. HLA genotyping

PCR-SSO was performed following the protocol of the LIFECODES HLA SSO kit. Based on the PCR-SSO principle, a number of kits such as WAKFlowHLA kit (Wakunaga, Hiroshima, Japan), LIFECODES HLA SSO kit (Luminex, USA) have been developed, and commercialized to identify human HLA alleles. In this study, HLA genotyping by PCR-SSO was performed in the National Institute of Hematology and Blood Transfusion. Particularly, genomic DNA (100 ng) extracted from cord blood were applied for genotyping by PCR sequence-specific oligonucleotide (PCR-SSO) using the LIFECODES HLA SSO kit on a Luminex 200 system, and analysed with Xponent 3.1 software linked to the International ImMunoGeneTics (IMGT) database library (version 3.43) to provide the well-documented allele [15-17]. Next generation sequening (NGS) may be the best choice for sequencing to identify HLA genotype; however, to apply NGS for genotyping a large number of samples, a huge budget is required. More importantly, although SSO-PCR using the LIFECODES HLA SSO kit has been in application since a long time, at present time, it is still widely used and accepted for HLA genotyping, especially when applying for medium-resolution HLA genotyping [18-19].

2.3. Data mining and statistical analysis

Published HLA haplotype data on the website http://www.allelefrequencies.net/ were exploited for comparisons among different populations. Diversity of HLA genotypes and population statistical analyses were conducted using Arlequin 3.5 software [20, 21].

3. RESULTS

3.1. Frequency of five-locus haplotypes

The information about the five-locus haplotypes is presented in Table 1 and the distribution of these haplotypes is shown in Figure 1. The results of the study demonstrated that a total of 1562 five-locus haplotypes were found; however, there were only 10 haplotypes with frequencies of over 1%, accounting for 23.0% (Table 1); 23 haplotypes with frequencies of over 0.5%, accounting for 32.9%; 140 haplotypes with frequencies of over 0.1%, accounting for 56.1%; and the rest of 1422 haplotypes with frequencies of below 0.1%, accounting for 43.9% (data not shown). The five-locus haplotype with the highest frequency was

Table 1. Frequency and cumulative frequency of five-locus (HLA-A-B-C-DRB1-DQB1) haplotypes, which had frequency > 1.0%, in cord blood samples of Vietnamese.

No	A	B	C	DRB1	DQB1	Freq. (Decimal)	Freq. (%)	Freq. (Cumulative)
1	11:01	15:02	08:01	12:02	03:01	0.059028	5.9028	0.059028
2	29:01	07:05	15:05	10:01	05:01	0.040073	4.0073	0.099101
3	02:01	46:01	01:02	09:01	03:03	0.031411	3.1411	0.130512
4	33:01	58:01	03:02	03:01	02:01	0.018944	1.8944	0.149456
5	24:02	15:02	08:01	12:02	03:01	0.018038	1.8038	0.167494
6	33:03	58:01	03:02	03:01	02:01	0.01621	1.621	0.183704
7	01:01	57:01	06:02	07:01	03:03	0.013478	1.3478	0.197182
8	33:01	44:03	07:01	07:01	02:02	0.011921	1.1921	0.209103
9	33:03	44:03	07:01	07:01	02:02	0.011302	1.1302	0.220405
10	11:01	38:02	07:02	12:02	03:01	0.010012	1.0012	0.230417

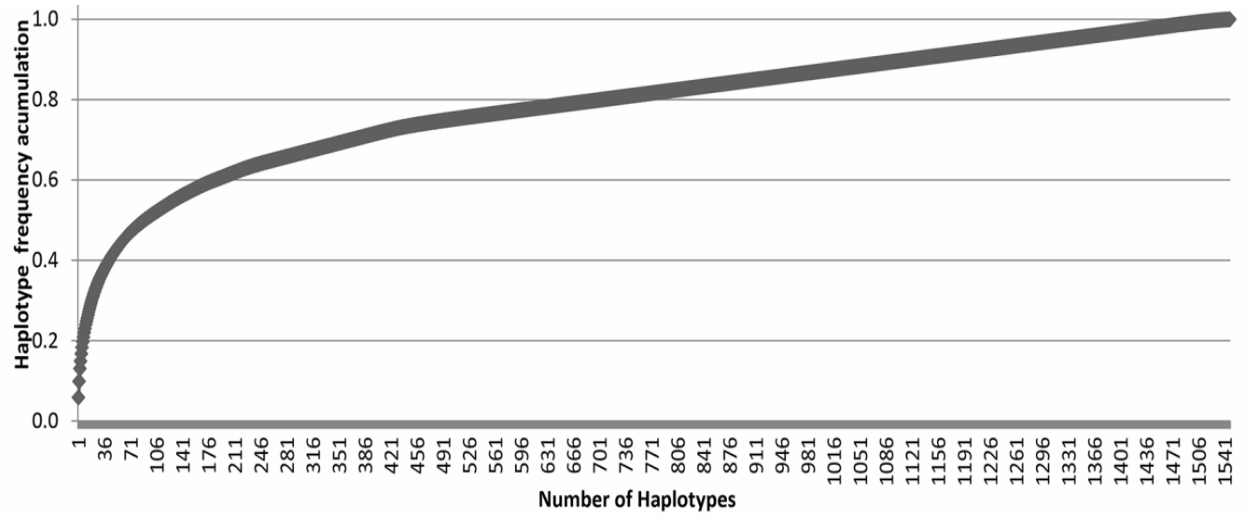

Figure 1. Frequency accumulation of five-locus haplotypes in cord blood samples of Vietnamese.

A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01 (5.9%), followed by A*29:01-B*07:05-C*15:05-DRB1*10:01-DQB1*05:01 (4.0%), and A*02:01-B*46:01-C*01:02-DRB1*09:01-DQB1*03:03 (3.1%).

3.2. Distribution of five-locus haplotypes

The frequency accumulation of five-locus haplotypes is also shown in Figure 1 and Figure 2. This indicated that there were diverse combinations in five loci to form a big number of haplotypes; however, many of them were low-frequent haplotypes. The numbers of haplotypes covering the corresponding 25%, 50%, 75%, 90%, 95%, and 100% haplotypes were 13, 90, 500, 1120, and 1328, respectively. This shows that 90 highest haplotypes (accounting for only 5.76%) out of a total of 1562 can cover 50% haplotype frequency accumulation; but 1472 haplotypes (accounting for 94.24%) out of a total of 1562 is needed to cover the last 50% haplotype frequency accumulation (Figures 1 and 2). This meant that the distribution of the haplotype did not follow a normal distribution.

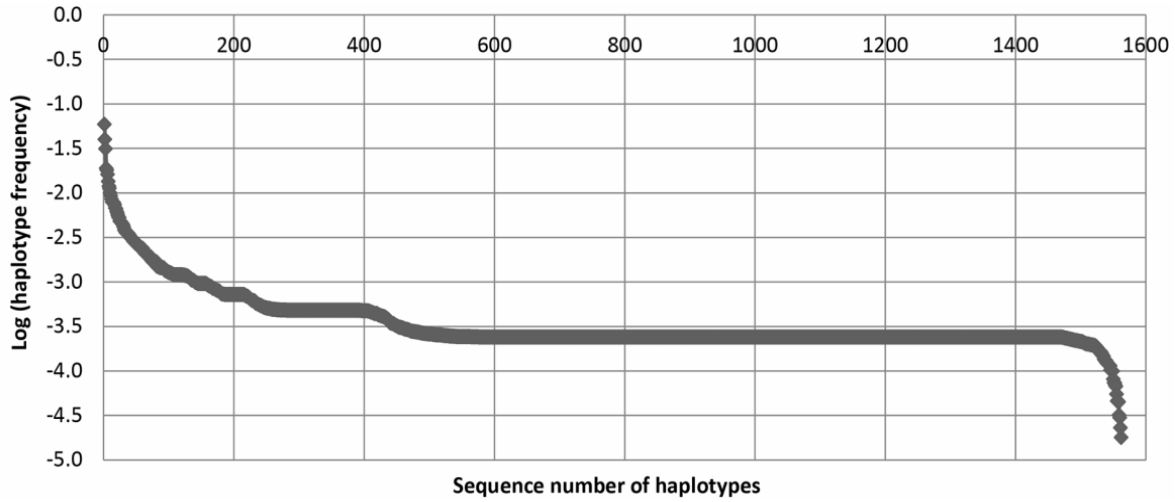

Figure 2. Curves showing the haplotype frequency of five-locus haplotypes in descending order.

4. DISCUSSION

Hematopoietic stem cell (HSC) transplantation has been widely and effectively used to treat various diseases, especially blood cancers as well as other hematological disorders [21-25]. The main problem limiting allogeneic HSC transplantation is due to lack of suitable donors, who have HLA match with the recipient. If the donor is a close relative, such as a sibling, and having a perfect HLA match, it should be the ideal donor to provide HSC for grafting [26]. Prior to stem cell or organ transplantation, donors and recipients are required to screen for crucial factor, human leukocyte antigen (HLA), to ensure donor-recipient matching in order to minimize GVHD and transplant rejection. To date, more than 1,250 HLA alleles have been identified for six HLA loci, including HLA-A, HLA-B, HLA-C, HAL-DP, HLA-DQ, and HLA-DR, of which HLA-A, HLA-B, and HLA-C correspond to the major histocompatibility complex class I (MHC-class-I) and HLA-DP, HLA-DQ, and HLA-DR correspond to the major histocompatibility complex class II (MHC-class-II) [27, 28]. The more HLA antigens coincide, the higher the success rate of transplants. In summary, HLA well-matching between the donor and the recipient is extremely important for the survival of the transplant [27, 28].

In this study, 2076 healthy Vietnamese women, who delivered their children at NHIB in the period 2016-2020, participated. Nowadays, stem cell sources from cord blood and/or marrow are very beneficial for transplantation programs worldwide. The National Marrow Donor Program (NMDP) has been established since 1986 in the United States. NMDP has recruited a large numbers of un-related marrow donors [29, 30]. NMDP gives many benefits for stem cell/organ transplatation programs by increasing the chance to find out HLA-matched donor from unrelated donors [31]. In this study, we also got information on HLA from NMDP website to make comparisons about HLA frequencies and distributions in different cohorts.

To have an overlook on the frequency of five-locus haplotypes from different populations, we did a data mining of the website http://www.allelefrequencies.net/ and made a comparison of the frequency of five-locus haplotypes of Vietnamese population collected in this study with those of USA NMDP Vietnamese population as well as with USA NMDP Chinese, USA NMDP Korean, and USA NMDP Japanese populations [32-36]. The three highest frequencies of five-locus haplotypes of these populations are presented in Table 2. The result demonstrated that there was not much difference in the frequency of haplotypes between the Vietnamese selected in this study (sample size of 2076) and USA NMDP Vietnamese (samples size of 43450). Particularly, these two Vietnamese populations shared the same genotypes of the first and the second highest haplotypes with almost equal frequencies (5.9% *vs* 5.6%, and 4.0% *vs* 4.8%, respectively).

Table 2. The three five-locus haplotypes with high frequencies in different populations.

Haplotypes	The highest frequency (%)	Sample size	Cohort	Citation source
A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	5.9	2076	Vietnamese	This study
A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	5.6	43540	USA Vietnamese	[32, 33]
A*33:03-B*58:01-C*03:02-DRB1*03:01-DQB1*02:01	4.6	99672	USA Chinese	[34]
A*33:03-B*44:03-C*14:03-DRB1*13:02-DQB1*06:04	3.5	77584	USA Korean	[35]
A*24:02-B*52:01-C*12:02-DRB1*15:02-DQB1*06:01	7.8	24582	USA Japanese	[36]
Haplotypes	**The 2nd high frequency (%)**	**Sample size**	**Cohort**	**Citation source**
A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	4.0	2076	Vietnamese	This study
A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	4.8	43540	USA Vietnamese	[32, 33]
A*33:03-B*58:01-C*03:02-DRB1*03:01-DQB1*02:01	4.0	99672	USA Chinese	[34]
A*33:03-B*44:03-C*14:03-DRB1*13:02-DQB1*06:04	2.7	77584	USA Korean	[35]
A*24:02-B*52:01-C*12:02-DRB1*15:02-DQB1*06:01	3.9	24582	USA Japanese	[36]
Haplotypes	**The 3rd high frequency (%)**	**Sample size**	**Cohort**	**Citation source**
A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	3.1	2076	Vietnamese	This study
A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	3.7	43540	USA Vietnamese	[32, 33]
A*33:03-B*58:01-C*03:02-DRB1*03:01-DQB1*02:01	2.5	99672	USA Chinese	[34]
A*33:03-B*44:03-C*14:03-DRB1*13:02-DQB1*06:04	2.6	77584	USA Korean	[35]
A*24:02-B*52:01-C*12:02-DRB1*15:02-DQB1*06:01	3.5	24582	USA Japanese	[36]

However, on the other hand, we did not find any similarity in five-locus haplotype frequency in Vietnamese cohort and in the other cohorts including Chinese, Korean, and Japanese.

When comparing the frequency and the distribution of five-locus haplotypes between a big size of sample (2076, in this study) and a small size sample (170) [37] in two Kinh Vietnamese subpopulations, it showed that, in the10 highest frequent five-locus haplotypes, only the first and the second rank haplotypes shared the same haplotype information, and the others were totally different (Table 3). Moreover, the frequency accumulation of 5 highest five-locus haplotypes of the big-size sample subpopulation was only 23%, while that of small-size sample subpopulation was 29%. This demonstrated that the sample size affected on frequency and the

Table 3. The ten five-locus haplotypes with high frequencies in two different sample-size populations.

No	Haplotypes [37]	Haplotype frequency	Sample size
1	A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	7.0000	170
2	A*29:01-B*07:05-C*15:05-DRB1*10:01-DQB1*05:01	4.7000	
3	A*33:03-B*58:01-C*03:02-DRB1*03:01-DQB1*02:01	3.5000	
4	A*33:03-B*44:03-C*07:01-DRB1*07:01-DQB1*02:01	2.6000	
5	A*01:01-B*57:01-C*06:02-DRB1*07:01-DQB1*03:03	2.1000	
6	A*02:07-B*46:01-C*01:02-DRB1*09:01-DQB1*03:03	2.0000	
7	A*02:07-B*46:01-C*01:02-DRB1*12:02-DQB1*03:01	1.8000	
8	A*11:01-B*46:01-C*01:02-DRB1*09:01-DQB1*03:03	1.8000	
9	A*24:07-B*35:05-C*04:01-DRB1*12:02-DQB1*03:01	1.8000	
10	A*02:03-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	1.7000	
	Frequency accumulation (%)	**29**	
No	**Haplotypes [in this sudy]**	**Haplotype frequency**	**Sample size**
1	A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	5.9028	2076 (in this study)
2	A*29:01-B*07:05-C*15:05-DRB1*10:01-DQB1*05:01	4.0073	
3	A*02:01-B*46:01-C*01:02-DRB1*09:01-DQB1*03:03	3.1411	
4	A*33:01-B*58:01-C*03:02-DRB1*03:01-DQB1*02:01	1.8944	
5	A*24:02-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01	1.8038	
6	A*33:03-B*58:01-C*03:02-DRB1*03:01-DQB1*02:01	1.6210	
7	A*01:01-B*57:01-C*06:02-DRB1*07:01-DQB1*03:03	1.3478	
8	A*33:01-B*44:03-C*07:01-DRB1*07:01-DQB1*02:02	1.1921	
9	A*33:03-B*44:03-C*07:01-DRB1*07:01-DQB1*02:02	1.1302	
10	A*11:01-B*38:02-C*07:02-DRB1*12:02-DQB1*03:01	1.0012	
	Frequency accumulation (%)	**23**	

distribution of locus haplotypes, even in the same ethnic groups.

5. CONCLUSION

The result of this study indicated that Vietnamese population has high level similarity in five-locus haplotype pattern and different populations have their own characteristics in HLA genotypes and therefore have differences in frequency and distribution in multi-locus haplotypes. Consequently, it suggests that blood/stem cell/tissue/organ transplantations may be appropriately applied only among the people of the same population.

ACKNOWLEDGMENTS

We thank Vietnam National Institute of Haematology and Blood Transfusion (NIHB) for the support.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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