

# ALLELE AND HAPLOTYPE FREQUENCIES IN PATIENTS WITH HEMATOPOIETIC STEMCELL TRANSPLANTATION IN NATIONAL CHILDREN'S HOSPITAL

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*HLA (Human Leukocyte Antigen) gene is located on chromosome 6's short arm, including several loci. HLA genotyping is necessary for transplantation, especially in hematopoietic stem cell transplantation. A cross-sectional study to determine the frequency of HLA-A, HLA-B, and HLA-DRB1 alleles of 122 patients admitted to the National Children's Hospital for Hematopoietic stem cell transplantation from the year between 2010 and 2020. The patients' HLA genotyping was performed by PCR-SSP method using Micro SSPTM Generic HLA Class I and II DNA Typing Tray (One Lambda). The results showed that the HLA-A locus has 12 alleles of which the highest frequency alleles are A\*11 (24.18%), A\*02 (23.36%), A\*33 (20.90%), and A\*24 (14.34%). HLA-B locus has 24 alleles in which the highest frequency alleles are B\*15 (24.59%), B\*58 (12.30%), B\*07 (9.02%), and B\*46 (8.20%). HLA-C locus has ten alleles of which the highest frequency alleles are C\*03 (24.59%), C\*07 (22.12%), and C\*04 (13.52%). HLA-DRB1 locus has 13 alleles of which the highest frequency alleles are DRB1\*12 (23.77%), DRB1\*03 (11.07%), DRB1\*15 (10.25%), and DRB1\*09 & DRB1\*07 (8.20%). There are 1984 haplotypes combined from 4 loci HLA-A, HLA-B, HLA-C, and HLA-DRB1, of which the highest frequency haplotypes are A\*11/B\*15/C\*08/DRB1\*12 (1.21%); A\*33/B\*58/C\*03/DRB1\*03 (1.06%); A\*11/B\*15/C\*04/DRB1\*12 (0.76%); A\*11/B\*15/C\*04/DRB1\*12 (0.71%), and A\*11/B\*15/C\*03/DRB1\*12 (0.71%). The study provides the frequencies of alleles and haplotypes of HLA genotypes in Hematopoietic Stem Cell Transplantation. This is very important information for choosing stem cell donors and establishing the stem cell bank.*

**Keywords:** HLA allele, HLA haplotype, Hematopoietic Stem Cell Transplantation, National Children's Hospital.

## I. INTRODUCTION

Major Histocompatibility Complex (MHC) was first introduced in the early 1990s. By 1958 it was first discovered in human and is also known as Human Leukocyte Antigen (HLA). The HLA gene cluster is located on the short arm of human chromosome 6, encoding protein molecules. HLA are categorized into three

groups: HLA class I, class II, and class III. Their function was originally known through graft rejections. Later, the important role of HLA in the immune system response was demonstrated: HLA class I, which is composed of HLA-A, HLA-B, and HLA-C, provides the presentation of endogenous antigens to CD8 T lymphocytes; HLA class II antigens, including HLA-DR, HLA-DP, HLA-DQ, present exogenous antigens for CD4 T cell; and HLA class III encodes some complementary proteins, cytokines. In addition, HLA also plays a role in other applications such as paternity testing, identification in

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forensic medicine, and disease and population characteristics.<sup>1-4</sup>

There is an increasing demand for hematopoietic stem cell transplantation (HSCT) currently. The best source of hematopoietic stem cells is from related donors because of the high HLA match rate and less GvHD, so the quality of life is better post-transplant. Also, associated donors are available faster than searching for an unrelated donor. However, for patients who have no HLA-matched siblings, finding an unrelated donor is very difficult. In Vietnam, there have not been many studies on the frequencies of HLA alleles, especially in patients requiring HSCT. Therefore, we carry out this study to determine the frequencies of Human Leukocyte Antigen alleles (HLA-A, HLA-B, HLA-C, HLA-DR) in patients with Hematopoietic stem cell transplantation in the Vietnam National Children's Hospital year from 2010 to 2020.

## II. METHODS

### 1. Subjects and Methods

This was a cross-sectional study. The 122 patients were assigned to receive hematopoietic

stem cell transplantation in the period 2010 - 2020. 2ml peripheral blood of the patient was collected for DNA extraction using QIAamp DNA Mini Kit (Qiagen). HLA genotyping (with four loci HLA-A, HLA-B, HLA-C, HLA-DR) was performed by PCR-SSP method using Micro SSP™ Generic HLA Class I and II DNA Typing Tray (One Lambda). The data of HLA alleles and haplotypes were collected.

Patients were invited to join this study, and the parents and/or guardians of the children were informed. Only the patients who voluntarily consented to participate in the study were recruited after supplying written informed consent.

### 2. Statistical analysis

Statistical analyses were conducted with Microsoft Excel 2016 and Medical statistics software Stata 14.

## III. RESULTS

### 1. HLA allele frequency characteristics

The HLA alleles of 4 loci (HLA-A, HLA-B, HLA-C, and HLA-DRB1) were analyzed in all 122 patients, with 244 alleles for each locus.

**Table 1. The frequency of HLA-A alleles**

Allele	n	%	Allele	n	%
A*11	59	24.18	A*26	6	2.46
A*02	57	23.36	A*31	5	2.05
A*33	51	20.90	A*03	2	0.82
A*24	35	14.34	A*30	2	0.82
A*29	14	5.74	A*34	2	0.82
A*01	9	3.69	A*68	2	0.82

Twelve alleles of HLA-A were found. The allele has the highest frequency of encountering:

A\*11 (24.18%), A\*02 (23.36%), A\*33 (20.90%), and A\*24 (14.34%).

**Table 2. The frequency of HLA-B alleles**

Allele	n	%	Allele	n	%
B*15	60	24.59	B*54	5	2.05
B*58	30	12.30	B*55	5	2.05
B*07	22	9.02	B*18	3	1.23
B*46	20	8.20	B*48	2	0.82
B*38	16	6.56	B*39	2	0.82
B*40	16	6.56	B*56	2	0.82
B*35	14	5.74	B*50	1	0.41
B*44	10	4.10	B*52	1	0.41
B*13	9	3.69	B*73	1	0.41
B*57	8	3.28	B*45	1	0.41
B*51	8	3.28	B*14	1	0.41
B*27	6	2.46	B*37	1	0.41

Twenty-four alleles of HLA-B were found. Allele has the highest rates of encountering: B\*15 (24.59%), B\*58 (12.30%), B\*07 (9.02%), B\*46 (8.20%), and B\*38 & B\*40 (6.56%).

**Table 3. The frequency of HLA-C alleles**

Allele	n	%	Allele	n	%
C*03	60	24.59	C*15	24	9.84
C*07	54	22.13	C*06	11	4.51
C*04	33	13.52	C*12	4	1.64
C*01	30	12.30	C*14	2	0.82
C*08	25	10.25	C*05	1	0.41

Ten alleles of HLA-C were found. The allele has the highest rates of encountering: C\*03 (24.59%), C\*07 (22.13%), C\*04 (13.52%), C\*01 (12.30%), and C\*08 (10.25%).

**Table 4. The frequency of HLA-DR alleles**

Allele	n	%	Allele	n	%
DRB1*12	58	23.77	DRB1*14	17	6.97
DRB1*03	27	11.07	DRB1*13	14	5.74
DRB1*15	25	10.25	DRB1*08	10	4.10

Allele	n	%	Allele	n	%
DRB1*09	20	8.20	DRB1*10	9	3.69
DRB1*07	20	8.20	DRB1*16	8	3.28
DRB1*11	18	7.38	DRB1*01	4	1.64
DRB1*04	17	6.97			

Thirteen alleles of HLA-DRB1 were found. The allele has the highest rates of encountering: DRB1\*12 (23.77%), DRB1\*03 (11.07%),

DRB1\*15 (10.25%), and DRB1\*09 & DRB1\*07 (8.20%).

**2. HLA haplotype frequency characteristics**

**Table 5. The highest frequencies of HLA haplotypes**

Haplotype	n	%	Haplotype	n	%
A*11/B*15/C*08/DRB1*12	24	1.21	A*33/B*44/C*07/DRB1*07	7	0.35
A*33/B*58/C*03/DRB1*03	21	1.06	A*24/B*15/C*03/DRB1*03	7	0.35
A*11/B*15/C*04/DRB1*12	15	0.76	A*11/B*38/C*07/DRB1*11	6	0.30
A*11/B*15/C*03/DRB1*12	14	0.71	A*24/B*15/C*08/DRB1*12	6	0.30
A*02/B*15/C*08/DRB1*12	13	0.66	A*33/B*15/C*03/DRB1*15	6	0.30
A*33/B*58/C*03/DRB1*12	12	0.60	A*02/B*46/C*01/DRB1*11	6	0.30
A*02/B*15/C*08/DRB1*15	11	0.55	A*02/B*58/C*03/DRB1*03	6	0.30
A*33/B*58/C*03/DRB1*15	11	0.55	A*33/B*58/C*03/DRB1*13	6	0.30
A*02/B*46/C*01/DRB1*12	10	0.50	A*33/B*58/C*07/DRB1*03	6	0.30
A*02/B*15/C*07/DRB1*12	9	0.45	A*01/B*57/C*06/DRB1*07	6	0.30
A*33/B*15/C*03/DRB1*12	9	0.45	A*02/B*46/C*01/DRB1*15	6	0.30
A*02/B*15/C*01/DRB1*12	9	0.45	A*33/B*58/C*03/DRB1*07	6	0.30
A*02/B*46/C*01/DRB1*09	9	0.45	A*33/B*58/C*07/DRB1*07	6	0.30
A*11/B*15/C*08/DRB1*15	8	0.40	A*33/B*58/C*03/DRB1*14	5	0.25
A*33/B*58/C*03/DRB1*11	8	0.40	A*11/B*38/C*07/DRB1*04	5	0.25
A*02/B*15/C*04/DRB1*12	8	0.40	A*29/B*07/C*15/DRB1*10	5	0.25
A*24/B*15/C*03/DRB1*12	8	0.40	A*11/B*15/C*07/DRB1*12	5	0.25
A*11/B*15/C*03/DRB1*03	7	0.35	A*02/B*35/C*04/DRB1*12	5	0.25
A*24/B*58/C*03/DRB1*03	7	0.35	A*11/B*58/C*03/DRB1*11	5	0.25
A*33/B*15/C*03/DRB1*03	7	0.35	A*11/B*15/C*01/DRB1*12	5	0.25
A*11/B*58/C*03/DRB1*03	7	0.35	A*11/B*15/C*08/DRB1*07	5	0.25

One thousand nine hundred eighty-four haplotypes combined from 4 HLA loci (HLA-A, HLA-B, HLA-C, and HLA-DRB1). Some haplotypes have the highest rate: A\*11/B\*15/C\*08/DRB1\*12 (1.21%); A\*33/B\*58/C\*03/DRB1\*03 (1.06%); A\*11/B\*15/C\*04/DRB1\*12 (0.76%); A\*11/B\*15/C\*04/DRB1\*12 (0.71%), A\*11/B\*15/C\*03/DRB1\*12 (0.71%), and A\*02/B\*15/C\*08/DRB1\*12 (0.66%).

#### IV. DISCUSSION

In this study, we found 12 alleles of the HLA-A locus (Table 1), HLA-B being the most diverse locus with 24 alleles (Table 2), ten alleles of the HLA-C locus (Table 3), and 13 alleles of the HLA-DR locus (Table 4).

For the HLA-A locus, we found that in patients needing hematopoietic stem cell transplantation (HSCT), the most common allele was A\*11 (24.18%), followed by A\*02 (23.36%), A\*33 (20.90%), A\*24 (14.34%), A\*29 (5.74%). Some studies have also shown that A\*11 is common in the HLA-A locus in Vietnam and other Asian populations.<sup>5,6</sup> In 2007, B.K. Hoa et al. studied 170 Vietnamese Kinh people in Vietnam and found that A\*11 accounted for the highest frequency (22.9%). Research by H.Q. Huy et al. (2000) on 91 Vietnamese Kinh people also showed the highest rate of allele A\*11 (24.73%).<sup>7,8</sup> A study on umbilical cord blood by T.N. Que et al. (2022) on 3750 cord blood samples of Vietnamese Kinh people provided a proportion for A\*11 that was 25%, and a similar study on cord blood samples by N.T. Binh et al. (2021) showed the frequency of HLA-A\*11 (25,2%).<sup>9,10</sup> The following four alleles, A\*02, A\*33, A\*24, and A\*29, were the highest frequency allele group in the Vietnamese population.<sup>9,10</sup> However, there was a clear difference in the French people; A\*02 was the most common allele. This is one of the characteristics of the HLA allele distribution

specific to race or ethnicity.

We found locus HLA-B alleles in all patients. This locus has the most diverse number of alleles of the loci studied, with 24 alleles. In this study, the B\*15 allele had a frequency of 24.59% in patients. Allele B\*58, which had the second-highest frequency, was 12.30% in patients, followed by B\*07 and B\*46, whose frequencies were larger than 8,20%. Allele B\*15 is also the most common allele of the Vietnamese Kinh people in other studies, similar to that of the Javanese and Timo.<sup>5, 9, 10</sup> In the survey of umbilical cord blood samples, T.N. Que et al. showed that B\*15 was also the most common allele but only accounted for 15.1%, while B\*46 (10.7%), B\*58 (7.65%) are also quite common.<sup>10</sup> But in this study, the frequency of B\*07 is not as high as in our study and N.T. Binh et al.<sup>9</sup> In H.Q. Huy's study, B\*15 had the highest frequency of 14.2%, and B\*07 had the second-highest rate (9.3%). However, in this study, the frequency of B\*46 is not high, only 3.8%. Our study's allele B\*58 had a high frequency of 12.30%, ranked second, but B\*58 did not appear in this study. Instead, B\*70 with a high frequency, 5.4%, but this allele was not detected.<sup>8</sup> B\*38 in our study had quite a high frequency of 6.5%, similar to T.N. Que's (7.65%), but H.Q. Huy's had a lower rate of 2.7%.<sup>8,10</sup> In other ethnic groups, there is a clear difference in the distribution of this gene locus. In the study of French people, the most common allele was B\*07; in the Chinese, the allele with the highest frequency was B\*40 (14.5%); in our study, it only accounted for 6.5%.<sup>11,12</sup>

In our study, the top two frequent alleles were C\*03 and C\*07, with frequencies of 24.59% and 22.13%. In contrast, C\*04 showed a frequency of 13.52% (ranked 3rd). Our results are consistent with B.K. Hoa et al. (2008). B.K. Hoa et al. also indicated C\*03 as the most common HLA-C

allele in the Vietnamese Kinh population, with 18.0%.<sup>7</sup> The most common alleles found were C\*01 and C\*04, with frequencies of 16.8% and 11.8%, respectively. Similar results were also obtained in M.D. Do et al. (2020) worked on 202 samples of the Vietnamese Kinh population.<sup>13</sup> C\*03 was also the most predominant allele, with 21.8%, followed by C\*01 at 13.37% and C\*04 at 12.88%. In studies of other populations, the results, however, experience many differences. The allele C\*06 was the most commonly found in Saudis, with a frequency of 22.1%, followed by C\*07 and C\*04 with 19.6 and 11.2%, as shown in the research of Hajeer et al.<sup>14</sup> In the work of the Serbian population by Andric et al. (2014), C\*07, C\*12, and C\*04 alleles were the most abundant (24.84%, 13.52%, and 13.52%, respectively).<sup>15</sup> Meanwhile, Chen et al. (2019) study on Chinese people showed frequencies of 24.68% for C\*03, 19.82% for C\*07, and 18.89% for C\*01, respectively, comparable to our results.<sup>16</sup>

Our results of alleles and their frequencies are similar to those in domestic studies. For the class II HLA locus HLA-DRB1, DRB1\*12 was the most common allele in the patients (23.77%), followed by DRB1\*03 (11.07%) and DRB1\*15 (10.25%). B.K. Hoa et al. commented similarly on the most common allele, DRB1\*12 (35.5%), followed by DRB1\*15 and DRB1\*09.<sup>7</sup> V.T. An's study on Vietnamese Muong people in Vietnam showed clear differences in results. The allele distribution of this gene locus in the Vietnamese Muong people significantly differed from the Vietnamese Kinh, although the geographical distance between the two populations is insignificant. Specifically, the allele with the most predominance in this study was HLA-DRB1\*14 (19%); in our research, it had the 8th (6.85%). The second highest was DRB1\*16 (18%); in our study, it was rare and

accounted for only 3.23%.<sup>17</sup> Common alleles of other populations notably differ from those in our study. Gourraud et al. (2003) showed that DRB1\*07 (15.9%) was the most common in the French population.<sup>0</sup> While in our study, DRB1\*07 only accounted for about 7.7%. This is also found in the survey of the Chinese people; the DRB1\*09 allele was the most common, while in our study, this allele ranked 4th - 8.08%.<sup>12</sup>

All four loci, HLA-A, HLA-B, and HLA-DRB1, are significant for hematopoietic stem cell transplantation. According to stem cell transplant guidelines worldwide, these are the primary loci for selecting blood units for transplant patients with the requirement of a minimum match rate to be 6/8 alleles.<sup>18,19</sup> If the patient has common haplotypes, the chance of finding a successful donor is very high.<sup>20-22</sup> Therefore, the research team determined to identify a common HLA haplotype of these four loci in a total of 122 blood samples of patients at the Department of Hematology, Vietnam National Children's Hospital. We obtained 1984 haplotypes in 122 patients. The results showed that the most common haplotype was also formed from the HLA alleles with the highest frequencies in each locus, which was the haplotype A\*11/B\*15/C\*08/DRB1\*12 with a frequency of 1.21%. Other possible haplotypes were A\*33/B\*58/C\*03/DRB1\*03 and A\*11/B\*15/C\*04/DRB1\*12 (1.06% and 0.76%); A\*11/B\*15/C\*03/DRB1\*12 and A\*02/B\*15/C\*08/DRB1\*12 (0.71% and 0.66%) (Table 5). Although most often made up of high-frequency alleles, these haplotypes were also selective in combination. Our results are equivalent to the study of B.K. Hoa as haplotype A\*11/B\*15/C\*08/DRB1\*12 accounted for the highest frequency.<sup>7</sup> However, the second-highest occurrence of haplotype A\*29/B\*07/C\*15/DRB1\*10 in the study of B.K.

HoA ranked very low in our patients (0.25%). The reason for this difference may be related to the method of implementation, selection of subjects, number of samples, or whether these haplotypes affect blood disease. A recent study by M.D. Do et al. (2020), when identifying 28 HLA-A, 41 HLA-B, 21 HLA-C, and 26 HLA-DRB1 alleles from 101 unrelated healthy Vietnamese Kinh individuals from southern Vietnam, also showed the two most predominant haplotypes to be A\*29/B\*07/C\*15/DRB1\*10 (4.46%) and A\*33/B\*58/C\*03/DRB1\*03 (4.46%). The latter haplotype accounted for 1.06% of our study, the second-most occurrence. A\*11/B\*15/C\*08/DRB1\*12 only ranked third with 3.84%. These values differ from our study with frequencies of 1.21%.<sup>13</sup> These results had some differences with studies in other communities worldwide. Pédrón et al (2003) in France showed that the most common haplotype HLA-A, -B, -C, -DRB1 is: A\*01/B\*08/C\*07/DRB1\*03 while it did not appear in our results.<sup>22</sup> Different populations presented diverse HLA haplotypes such as A\*01/B\*08/C\*07/DRB1\*03 common in Macedonia and Serbia.<sup>15,23</sup> A\*24/B\*08/C\*07/DRB1\*03 in Saudis, A\*02/B\*46/C\*01/DRB1\*09 in Zhejiang Han, China.<sup>14,16</sup> As a result, we see that the Vietnamese Kinh population in Vietnam also has characteristics for the haplotypes in HLA loci that are different from other populations in the world.

## V. CONCLUSION

Research results on HLA characteristics of 122 samples of HSCT patients at Vietnam National Children's Hospital showed that the HLA-A locus has 12 alleles of which the highest frequency alleles are A\*11 (24.18%), A\*02 (23.36%), A\*33 (20.90%), and A\*24 (14.34%). HLA-B locus has 24 alleles -of which the highest frequency alleles are B\*15 (24.59%), B\*58 (12.30%), B\*07 (9.02%), and B\*46 (8.20%).

HLA-C locus has ten alleles of which the highest frequency alleles are C\*03 (24.59%), C\*07 (22.12%), and C\*04 (13.52%). HLA-DRB1 locus has 13 alleles of which the highest frequency alleles are DRB1\*12 (23.77%), DRB1\*03 (11.07%), DRB1\*15 (10.25%), and DRB1\*09 & DRB1\*07 (8.20%). There are 1984 haplotypes combined from 4 loci HLA-A, HLA-B, HLA-C, and HLA-DRB1, of which the highest frequency haplotypes are A\*11/B\*15/C\*08/DRB1\*12 (1.21%); A\*33/B\*58/C\*03/DRB1\*03 (1.06%); A\*11/B\*15/C\*04/DRB1\*12 (0.76%); A\*11/B\*15/C\*04/DRB1\*12 (0.71%), and A\*11/B\*15/C\*03/DRB1\*12 (0.71%).

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