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Distribution of HLA-A, -B and -DRB1 antigenic groups and haplotypes from the Brazilian bone marrow donor registry (REDOME)

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ABSTRACT

To improve assistance for patients awaiting a bone marrow transplant from an unrelated donor, it is important to genetically characterize the Brazilian volunteer bone marrow donors registry (REDOME). Our objective was to describe the antigenic groups and haplotype frequencies of HLA-A, HLA-B and HLA-DRB1 in the five regions of Brazil and by self-reported ethnicity groups using the REDOME data. Our study included 3,038,286 individuals. HLA antigenic groups and haplotype frequencies were estimated using an Expectation-Maximization (EM) algorithm. All described HLA-A*, HLA-B* and HLA-DRB1* groups were identified in this study. A*02 (25.9%), B*35 (11.8%) and DRB1*13 (13.4%) are the most frequent antigenic groups in REDOME, and the A*01-B*08-DRB1*03 haplotype is the most frequent in the registry. The antigenic group and haplotype frequency data obtained in this study could be helpful for national donor recruitment strategies across the country.

1. Introduction

Allogeneic hematopoietic stem cell transplantation is an effective therapy for the treatment of a large number of high-risk blood disorders. The major limitation is finding a suitable match from the pool of healthy donors. Brazilian volunteer bone marrow donors registry (REDOME) is currently the world's 3rd largest Bone Marrow Donor Registry (BMDR), and it reached 4.2 million donors in December 2016, just behind the Zentrales Knochenmarkspender Register Deutschland (ZKRD) and the National Bone Marrow Program (NMDP), with more than 7.2 million and 8.2 million donors [1], respectively.

The huge size of the Brazilian territory, combined with the large genetic diversity observed in the Brazilian population, makes it difficult to develop a Registry that represents the entire pool of probable HLAs for their specific subpopulation. Reach this goal worldwide have been described in the literature: recruitment efforts targeting ethnic minorities [2,3], the selective recruitment of relatives of donors who have infrequent HLA phenotypes [4], and the use of regional differences in HLA phenotype or haplotype distributions [5].

Brazil is a continental country geopolitically divided into five regions by the Brazilian Institute of Geography and Statistics (IBGE) as follows: North, Northeast, Central-West, Southeast and South. All these regions have their own complex colonization histories that shaped and strengthened the region differences in the admixed proportions across the country. For instance, the first inhabitants of Brazil were Native Americans splitted in diverse tribes and villages since the Pre-Columbian Era until the arrival of the Europeans. The 16th century marks the arrival of the Portuguese in the Northeast coast region. Then came to Brazil, the French, Dutch, Sub Saharan African – as slaves, and in the 19th century Germans, Italians, Spanish and Japanese [6]. All these immigrants colonized different areas of Brazil at different times. This has resulted in a great variability of skin pigmentation. IBGE pre-established color/race categories based on self-reported classification: White, Brown (Mestizos), Black, Yellow (East Asian phenotype) and Indigenous (Native American). These categories are used as proxies for ancestry [7], and one problem in performing

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this is the possibility of spurious association with false-positive or false-negative results [8–14], even though they may be based on a complex phenotypic evaluation, skin pigmentation is the most relevant character [15]. Because it captures the continuous aspect of phenotypes [16], the use of this term rather than the term "race" is justified.

Colonization and interbreeding were the main cause of the Brazilian high admixed population over the past five hundred years among Native Americans, Europeans, Africans and Asians [17].

To improve assistance for patients awaiting a bone marrow transplant from an unrelated donor, it is important to genetically characterize the registry. Our objective was to describe the antigenic groups and haplotype frequencies of HLA-A, HLA-B and HLA-DRB1 in the five regions of Brazil and by self-reported ethnicity groups using the REDOME data.

2. Methods

2.1. Subjects

This study presents data from 3,038,286 individuals (Table 1) who volunteered as potential hematopoietic stem cell donors between January 2003 and July 2014 and who self-reported their ethnicity as defined by IBGE's classification [18].

Donors come from recruitment centers distributed throughout the country and their DNA was genotyped in Health Ministry accredited Brazilian laboratories. The dataset was subdivided according to the ethnicity and according to geographic criteria. We used the official geographic macro division defined by IBGE [19]. As parental populations, we used data from Portugal, Italy, Germany, France, Spain, Sub-Saharan Africa, Japan, Chile, Peru and Mexico populations. Data on all these parental populations are available in the Allele Frequencies database [20].

2.2. HLA typing

Donor's DNA were genotyped utilizing different polymerase chain reaction (PCR) techniques available over the years (PCR-SSOPH, PCR-SSP and PCR-SBT). We only considered HLA-A, -B and -DRB1 antigenic groups (1st field level) for this study. As an approximation, all individuals with only one antigenic group at a given locus were analyzed as homozygous at this locus.

2.3. Statistical analysis

ARLEQUIN 3.5 software [21] was used to estimate antigenic groups and haplotype frequencies, for testing of the Hardy-Weinberg equilibrium [22]. An Analysis of Variance (ANOVA) [21] was also used in order to determine whether the observed HLA genetic diversity was significantly structured in regard to geographic regions or ethnicity. Principal component analysis (PCA) was used for dimensionality reduction in a data set, identifying those elements that contribute most to its variance, and is particularly useful as an exploratory tool in a complex data set [23].

3. Results

3.1. Hardy-Weinberg equilibrium

The observed heterozygosity for the Regions ranged from 87.4% to 88.5% for HLA-A, 92.8% to 93.2% for HLA-B and 89% for HLA-DRB1, and for ethnicities of Brazil, they ranged from 87.4% to 89.1% for HLA-A, 92.8% to 93.4% for HLA-B and 89% for HLA-DRB1. The observed heterozygosity for the entire registry was 87.9% for HLA-A, 93.1% for HLA-B and 89.2% for HLA-DRB1. Deviations from Hardy-Weinberg equilibrium ($P < 0.05$) were found in all population categories, either analyzed separately or when considering the entire registry. Exceptions for deviations ($P > 0.05$) were found for Browns, Northeast populations and REDOME registry for DRB1 locus. Heterozygosity and P-values for all subpopulations are available in Supplementary File S1.

3.2. Antigenic groups frequencies for REDOME

Table 2 shows HLA-A, HLA-B and HLA-DRB1 antigenic groups frequencies for REDOME. The most frequent HLA-A is A*02 (25.9%), followed by A*24 (10.0%) and A*03 (9.2%). For HLA-B, B*35 (11.8%), B*44 (10.8%) and B*15 (9.1%) are the most frequent. Lastly, for HLA-DRB1, the most frequent are DRB1*13 (13.4%), DRB1*07 (12.9%) and DRB1*04 (12.5%).

3.3. Antigenic groups frequencies for the regions

In each region, A*02 as the most frequent antigenic group ranged from 25.2% (Northeast) to 27.0% (South). For HLA-B, B*35 as the most frequent ranged from 10.7% (North) to 12.8% (Northeast)

Table 1
Total number of individuals by Region and Ethnicity that are present in this study.

REDOME			North Region			Northeast Region		
Ethnicity	N° of donors	%	Ethnicity	N° of donors	%	Ethnicity	N° of donors	%
Yellows	117,884	3.88%	Yellows	2928	1.32%	Yellows	42,143	9.12%
Whites	1,660,759	54.66%	Whites	69,555	31.35%	Whites	160,580	34.76%
Indigenous	19,038	0.63%	Indigenous	2035	0.92%	Indigenous	7779	1.68%
Browns	520,060	17.12%	Browns	91,346	41.17%	Browns	135,982	29.43%
Blacks	214,653	7.06%	Blacks	18,244	8.22%	Blacks	38,359	8.30%
NI*	505,892	16.65%	NI*	37,789	17.03%	NI*	77,148	16.70%
Total	3,038,286	100.00%	Total	221,897	100.00%	Total	461,991	100.00%
Central West Region			Southeast Region			South Region		
Ethnicity	N° of donors	%	Ethnicity	N° of donors	%	Ethnicity	N° of donors	%
Yellows	13,644	5.10%	Yellows	46,103	3.42%	Yellows	13,066	1.77%
Whites	127,006	47.50%	Whites	735,170	54.50%	Whites	568,448	77.01%
Indigenous	1116	0.42%	Indigenous	6063	0.45%	Indigenous	2045	0.28%
Browns	52,817	19.75%	Browns	203,594	15.09%	Browns	36,321	4.92%
Blacks	20,893	7.81%	Blacks	108,595	8.05%	Blacks	28,562	3.87%
NI*	51,909	19.41%	NI*	249,352	18.49%	NI*	89,694	12.15%
Total	26,0.385	100.00%	Total	1,348,877	100.00%	Total	738,136	100.00%

NI* = not informed.

Table 2
Antigenic groups frequencies in a sample of 3,038,286 volunteer bone marrow donors from Brazil that were REDOME registered in the period from 2003 to Jun 2014.

HLA-A	Frequency (%)	HLA-B	Frequency (%)	HLA-DRB1	Frequency (%)
01	0.0918	**07**	0.0691	**01**	0.0995
02	0.2590	**80**	0.0511	**03**	0.0974
03	0.0924	**13**	0.0159	**04**	0.1253
11	0.0532	**14**	0.0527	**07**	0.1290
23	0.0503	**15**	0.0910	**08**	0.0620
24	0.1004	**18**	0.0476	**09**	0.0172
25	0.0126	**27**	0.0223	**10**	0.0197
26	0.0334	**35**	0.1183	**11**	0.1214
29	0.0451	**37**	0.0107	**12**	0.0165
30	0.0524	**38**	0.0214	**13**	0.1340
31	0.0476	**39**	0.0346	**14**	0.0422
32	0.0321	**40**	0.0480	**15**	0.0974
33	0.0303	**41**	0.0129	**16**	0.0385
34	0.0076	**42**	0.0140		
36	0.0051	**44**	0.1081		
43	0.0001	**45**	0.0174		
66	0.0097	**46**	0.0004		
68	0.0614	**47**	0.0022		
69	0.0018	**48**	0.0072		
74	0.0119	**49**	0.0278		
80	0.0019	**50**	0.0239		
		51	0.0834		
		52	0.0194		
		53	0.0238		
		54	0.0007		
		55	0.0109		
		56	0.0037		
		57	0.0280		
		58	0.0265		
		59	0.0002		
		67	0.0003		
		73	0.0010		
		78	0.0009		
		81	0.0042		
		82	0.0005		
		83	<0.0001		

and for HLA-DRB1, DRB1*04 as the most frequent ranged from 11.8% (Southeast) to 14.6% (North). All antigenic groups frequencies for HLA-A, -B and -DRB1 in each Region of Brazil is available as Supplementary File S2.

3.4. Antigenic groups frequencies for the ethnicity groups

In each ethnicity category, A*02 as the most frequent antigenic group ranged from 23.4% (Blacks) to 26.5% (Whites). For HLA-B, B*35 as the most frequent ranged from 10.5% (Blacks) to 12.4% (Whites) and for HLA-DRB1, DRB1*13 is the most frequent ranged from 13% (Yellows) to 13.8% (Blacks). All antigenic groups frequencies for HLA-A, -B and -DRB1 in each ethnicity in REDOME is available as Supplementary File S3.

3.5. Haplotype frequencies

The most frequent haplotypes in REDOME are: A*01-B*08-DRB1*03 with 2.1%, A*29-B*44-DRB1*07 with 1.4% and A*03-B*07-DRB1*15 with 1.0%. Fig. 1 shows the top-30 haplotypes in REDOME. As a reflection of the overall A-B-DRB1 haplotype similarity among the five regions and ethnicity groups, we present the rank order of haplotypes from the perspective of the 10 most common haplotypes in each population tested: Regions (Table 3) and Ethnicity (Table 4). A complete list of haplotypes for each subpopulations is available as a Supplementary File S4.

The main haplotype in REDOME (HLA-A*01-B*08-DRB1*03) is very representative in Portugal, with frequencies reaching up to 3.9%. Besides, countries like Sweden, Croatia, Russia, United States, Ireland and Wales feature frequencies range from 3.9% to 10.1% showing that this haplotype has a Caucasoid origin. Other haplotypes that are quite representative in Portugal are also present in the registry such as: HLA-A*29-B*44-DRB1*07, HLA-A*03-B*07-DRB1*15 and HLA-A*02-B*44-DRB1*04. As might be expected, we also identified haplotypes seen only or mainly in African and Afro-descendant populations in our registry, confirming that these haplotypes (HLA-A*23-B*15-DRB1*11, HLA-A*02-B*58-DRB1*11 and HLA-A*30-B*42-DRB1*03) were inherited from generation to generation. Over the past two centuries, Brazil received countless Asians immigrants and some haplotypes can also be identified in our registry such as: HLA-A*01-B*37-DRB1*10, HLA-A*01-B*07-DRB1*15 and HLA-A*01-B*37-DRB1*01. Haplotype A*01-B*08-DRB1*03 is also the most frequent haplotype in Yellow population sample suggesting substantial admixture with non-Asian populations. Indigenous tribes still populate the continent keeping their cultures and some remain 'unexploited' by modern civilization. However, we were able to identify in REDOME some haplotypes that are present in other indigenous populations in Latin America [24–27] such as: HLA-A*02-B*48-DRB1*08, HLA-A*02-B*35-DRB1*08 and HLA-A*02-B*40-DRB1*04.

3.6. Genetic structure and diversity

An ANOVA was performed to evaluate whether the observed HLA genetic diversity was significantly structured in relation to a given geographic or ethnicity partition (Supplementary File S5) of Brazil. A geographic partition into 5 predefined groups – North versus Northeast versus Central-West versus Southeast versus South – is not a real group structure because the proportion of genetic variation observed among the groups (F_{CT} of 0.00048%) is

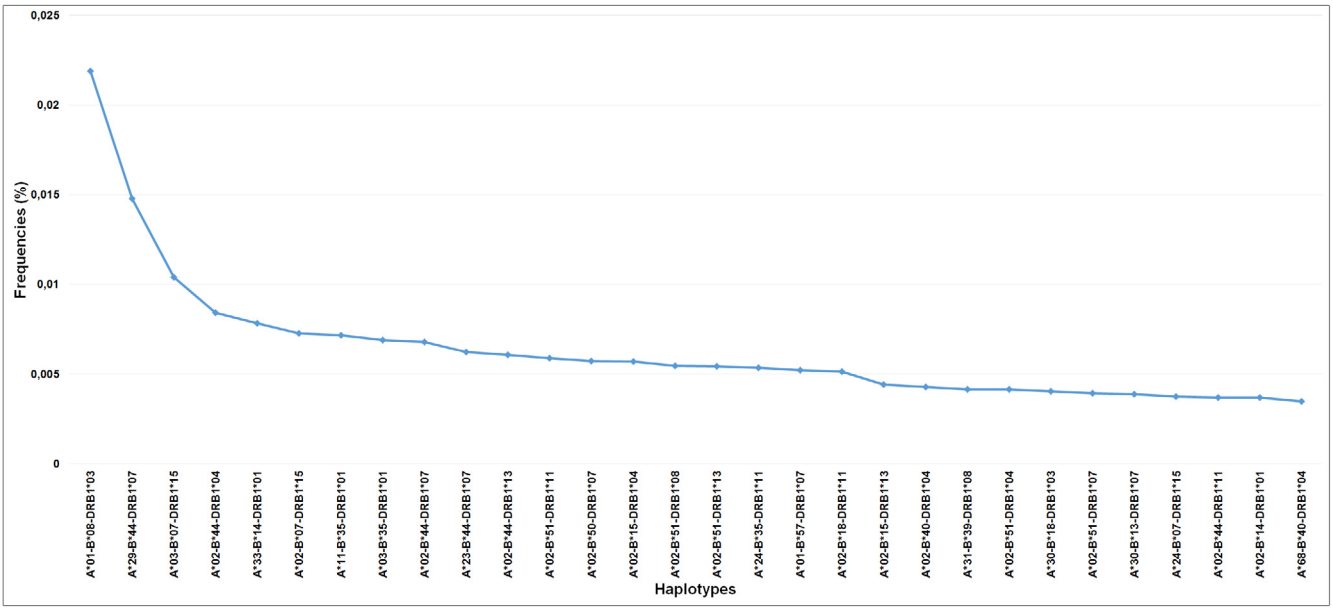

Fig. 1. Top-30 Haplotypes in REDOME.

lesser than the proportion of genetic variation observed within those groups (F_{SC} of 0.00073%). For the ethnicity partition into 5 groups – Blacks versus Browns versus Whites versus Yellows versus Indigenous, the F_{CT} index is significant ($P < 0.0001$) and its value is greater than the F_{SC} value (0.00086% versus 0.00062%, respectively). Individual analysis per locus indicates that HLA-A and HLA-B loci present lesser genetic variation proportion among groups than within those groups and HLA-DRB1 locus is the opposite.

3.7. Principal component analysis

Fig. 2 shows the PCA results for the Regions of Brazil and for ethnicity groups. Clearly, we can observe, in the first analysis of PCA (regions), the formation of a triangle formed by the vertices: North, Northeast and South (Fig. 2A). This shows us that these regions present unusual characteristics in the haplotypes. The Central-west region near the Southeast region was not expected and the Southeast region is more correlated with the Southern region than the North and Northeast regions. The present sample of the South region population was most similar to the populations of Spain and Portugal, followed by those of Italy and Germany (Fig. 2B), which agrees with the historical data on the initial settlement of southern Brazil. This result is in concordance with another study from Rio Grande do Sul [15]. The largest parental contributions came from these 4 countries, either through direct immigration from Europe or because of the proximity to the borders of Hispanic countries, such as Argentina and Uruguay. South region itself was part of the Hispanic colonization from the 16th to 17th centuries [28].

In the second analysis (ethnicity), we can also observe the formation of a triangle: Whites, Blacks, Yellows (Fig. 2C). This shows us, also distinct characteristics in these populations. On the other hand, we observed that the Browns present are more correlated with Blacks. Browns and Indigenous individuals are very close on the graph, intermediate between Blacks and Whites (Fig. 2D). This result may lead to the confusion of the perception of ancestry with that of skin color, because both Brown and Indigenous tend to be intermediate skin color phenotypes, between Blacks and Whites. This result is in concordance from the same study mentioned above.

4. Discussion

This study analyzes antigenic groups data for HLA-A, -B, and -DRB1 from REDOME data with more than 3 million potential hematopoietic stem cell donors and investigates the genetic variation between the different regions of Brazil and self-reported ethnicity.

Social and political considerations influenced the creation of the Brazilian census categories for the regions of Brazil and ethnicity that are used here. The African population that came forced, as slaves, to Brazil trace their history to the many diverse peoples native to Sub-Saharan Africa (Angola, Guinea, Benin, Nigeria, Mozambique, Bantu and Congo) [29,30]. The category "Yellow" is actually an agglomeration of immigrants from the Asian continent (mainly from Japan) from the beginning of the 20th century [31]. The Whites or Caucasians (Portugal, France, Italy, Spain, Netherlands) includes individuals of European ancestry [32]. Europe itself represents many populations having greater or lesser degrees of HLA differentiation among its inhabitants [33]. The indigenous peoples of Brazil comprise a large number of different ethnic groups inhabiting the country since millennia before the beginning of Portuguese colonization, and is part of the largest group of Amerindian population [34].

Admixture among the five ethnicity groups is a prominent and ongoing feature of the Brazilian population. Despite this diversity of origins and admixture, the two main groups (Regions and Ethnicity) exhibit considerable uniqueness in terms of HLA variation in each category. The exploration of these differences in Tables 3 and 4 is an initial characterization of the HLA divergence and similarity between the groups and it also underlines the importance of keeping HLA divergence in mind when utilizing HLA information for the design and use of transplant registries.

The basic assumptions, which are of great importance for the haplotype reconstruction method (EM algorithm), are the lack of departures from the Hardy-Weinberg equilibrium and occurrences of free recombination events. However, Hardy-Weinberg departures were found in this study and may be due to one of the following alternatives or combined effects: a) over- and underestimates of particular haplotype frequencies [35], even for common haplotypes, especially when the loci involved deviate significantly from Hardy-Weinberg; b) as Fig. 2B-D suggest, REDOME samples diverged from others parental samples and we observed a

Table 3
Occurrences of the first 10 A-B-DRB1 frequency-ranked haplotypes for each census group in each of the other four groups.

Region	Haplotype	North		Northeast		Central-West		Southeast		South	
Rank	A-B-DRB1	Rank	Freq. (%)	Rank	Freq. (%)	Rank	Freq. (%)	Rank	Freq. (%)	Rank	Freq. (%)
North											
1	A*01-B*08-DRB1*03	1	0.0156	1	0.0156	1	0.0208	1	0.0213	1	0.0291
2	A*29-B*44-DRB1*07	2	0.0132	2	0.0137	2	0.0152	2	0.0150	2	0.0153
3	A*31-B*39-DRB1*08	3	0.0084	32	0.0034	26	0.0040	30	0.0033	21	0.0050
4	A*03-B*07-DRB1*15	4	0.0079	3	0.0092	3	0.0091	3	0.0094	3	0.0141
5	A*24-B*35-DRB1*08	5	0.0078	320	0.0007	263	0.0009	410	0.0006	246	0.0009
6	A*02-B*44-DRB1*04	6	0.0077	4	0.0086	4	0.0088	5	0.0081	6	0.0090
7	A*33-B*14-DRB1*01	7	0.0069	5	0.0081	5	0.0077	4	0.0083	10	0.0071
8	A*02-B*44-DRB1*07	8	0.0066	11	0.0058	7	0.0069	7	0.0069	9	0.0072
9	A*02-B*40-DRB1*04	9	0.0065	10	0.0060	20	0.0043	35	0.0032	24	0.0045
10	A*11-B*35-DRB1*01	10	0.0063	6	0.0066	6	0.0073	6	0.0071	7	0.0078
Northeast											
1	A*01-B*08-DRB1*03	1	0.0156	1	0.0156	1	0.0208	1	0.0213	1	0.0291
2	A*29-B*44-DRB1*07	2	0.0132	2	0.0137	2	0.0152	2	0.0150	2	0.0153
3	A*03-B*07-DRB1*15	4	0.0079	3	0.0092	3	0.0091	3	0.0094	3	0.0141
4	A*02-B*44-DRB1*04	6	0.0077	4	0.0086	4	0.0088	5	0.0081	6	0.0090
5	A*33-B*14-DRB1*01	7	0.0069	5	0.0081	5	0.0077	4	0.0083	10	0.0071
6	A*11-B*35-DRB1*01	10	0.0063	6	0.0066	6	0.0073	6	0.0071	7	0.0078
7	A*02-B*07-DRB1*15	14	0.0055	7	0.0064	8	0.0067	8	0.0067	4	0.0096
8	A*02-B*44-DRB1*13	13	0.0055	8	0.0061	10	0.0063	11	0.0063	16	0.0057
9	A*23-B*44-DRB1*07	20	0.0051	9	0.0061	12	0.0059	15	0.0059	8	0.0074
10	A*02-B*40-DRB1*04	9	0.0065	10	0.0060	20	0.0043	35	0.0032	24	0.0045
Central-West											
1	A*01-B*08-DRB1*03	1	0.0156	1	0.0156	1	0.0208	1	0.0213	1	0.0291
2	A*29-B*44-DRB1*07	2	0.0132	2	0.0137	2	0.0152	2	0.0150	2	0.0153
3	A*03-B*07-DRB1*15	4	0.0079	3	0.0092	3	0.0091	3	0.0094	3	0.0141
4	A*02-B*44-DRB1*04	6	0.0077	4	0.0086	4	0.0088	5	0.0081	6	0.0090
5	A*33-B*14-DRB1*01	7	0.0069	5	0.0081	5	0.0077	4	0.0083	10	0.0071
6	A*11-B*35-DRB1*01	10	0.0063	6	0.0066	6	0.0073	6	0.0071	7	0.0078
7	A*02-B*44-DRB1*07	8	0.0066	11	0.0058	7	0.0069	7	0.0069	9	0.0072
8	A*02-B*07-DRB1*15	14	0.0055	7	0.0064	8	0.0067	8	0.0067	4	0.0096
9	A*02-B*50-DRB1*07	21	0.0051	15	0.0052	9	0.0064	14	0.0060	19	0.0055
10	A*02-B*44-DRB1*13	13	0.0055	8	0.0061	10	0.0063	11	0.0063	16	0.0057
Southeast											
1	A*01-B*08-DRB1*03	1	0.0156	1	0.0156	1	0.0208	1	0.0213	1	0.0291
2	A*29-B*44-DRB1*07	2	0.0132	2	0.0137	2	0.0152	2	0.0150	2	0.0153
3	A*03-B*07-DRB1*15	4	0.0079	3	0.0092	3	0.0091	3	0.0094	3	0.0141
4	A*33-B*14-DRB1*01	7	0.0069	5	0.0081	5	0.0077	4	0.0083	10	0.0071
5	A*02-B*44-DRB1*04	6	0.0077	4	0.0086	4	0.0088	5	0.0081	6	0.0090
6	A*11-B*35-DRB1*01	10	0.0063	6	0.0066	6	0.0073	6	0.0071	7	0.0078
7	A*02-B*44-DRB1*07	8	0.0066	11	0.0058	7	0.0069	7	0.0069	9	0.0072
8	A*02-B*07-DRB1*15	14	0.0055	7	0.0064	8	0.0067	8	0.0067	4	0.0096
9	A*02-B*51-DRB1*11	27	0.0045	28	0.0036	16	0.0048	9	0.0067	12	0.0066
10	A*03-B*35-DRB1*01	18	0.0052	14	0.0052	13	0.0059	10	0.0066	5	0.0094
South											
1	A*01-B*08-DRB1*03	1	0.0156	1	0.0156	1	0.0208	1	0.0213	1	0.0291
2	A*29-B*44-DRB1*07	2	0.0132	2	0.0137	2	0.0152	2	0.0150	2	0.0153
3	A*03-B*07-DRB1*15	4	0.0079	3	0.0092	3	0.0091	3	0.0094	3	0.0141
4	A*02-B*07-DRB1*15	14	0.0055	7	0.0064	8	0.0067	8	0.0067	4	0.0096
5	A*03-B*35-DRB1*01	18	0.0052	14	0.0052	13	0.0059	10	0.0066	5	0.0094
6	A*02-B*44-DRB1*04	6	0.0077	4	0.0086	4	0.0088	5	0.0081	6	0.0090
7	A*11-B*35-DRB1*01	10	0.0063	6	0.0066	6	0.0073	6	0.0071	7	0.0078
8	A*23-B*44-DRB1*07	20	0.0051	9	0.0061	12	0.0059	15	0.0059	8	0.0074
9	A*02-B*44-DRB1*07	8	0.0066	11	0.0058	7	0.0069	7	0.0069	9	0.0072
10	A*33-B*14-DRB1*01	7	0.0069	5	0.0081	5	0.0077	4	0.0083	10	0.0071

deficiency of heterozygotes and this is known as the Wahlund effect [36] but this study has not shown that this is really the case; c) as an approximation, since all individuals with only one antigenic group at a given locus were analyzed as homozygous at this locus. We highlight that the frequencies estimated at the Brazilian registry level were not in equilibrium and should not be relied on as characteristics of a "Brazilian population."

Several antigenic groups (A*43, B*56, B*59, B*67, B*83) are considered rare worldwide [37–43], and these antigenic groups certainly contribute to be part of a rare haplotype thus making difficult the chances of finding an initial 6/6 match or even a 10/10 match for a patient. The continuous evaluation of this analysis will allow us to chart where these rare haplotypes are and in which ethnicity. Also, it would be interesting to consider what is rare in REDOME may not be, necessarily, rare for another registry thus allowing these donors to be provided to other registries facilitating bone marrow transplants around de world enriching global cooperation.

A disparity between the self-reported and genetic ancestries of the admixed Brazilian populations is known [7]. A recent study from Brazil observed that individuals self-reported as Blacks had around 40% of European genetic ancestry, whereas those self-reported as Browns had around 70% of European genetic ancestry [44]. Other studies with ancestry informative markers on different populations in Brazil have also shown a discrepancy between self-declared information and genetic ancestry [8,45–47].

Table 4
Occurrences of the 1st 10 A-B-DRB1 frequency-ranked haplotypes for each census group in each of the other four groups.

Ethnicity	Haplotype	Blacks		Browns		Whites		Yellows		Indigenous	
Rank	A-B-DRB1	Rank	Freq. (%)	Rank	Freq. (%)	Rank	Freq. (%)	Rank	Freq. (%)	Rank	Freq. (%)
Blacks											
1	A*01-B*08-DRB1*03	1	0.0147	1	0.0172	1	0.0251	1	0.0181	1	0.0153
2	A*29-B*44-DRB1*07	2	0.0109	2	0.0133	2	0.0159	2	0.0135	2	0.0116
3	A*03-B*07-DRB1*15	4	0.0070	3	0.0084	3	0.0117	4	0.0086	3	0.0083
4	A*02-B*44-DRB1*04	5	0.0066	4	0.0080	4	0.0089	5	0.0080	4	0.0072
5	A*30-B*42-DRB1*03	3	0.0075	18	0.0050	70	0.0021	42	0.0030	8	0.0066
6	A*33-B*14-DRB1*01	7	0.0061	5	0.0075	5	0.0081	6	0.0075	5	0.0072
7	A*02-B*07-DRB1*15	6	0.0061	8	0.0061	6	0.0079	11	0.0059	7	0.0068
8	A*11-B*35-DRB1*01	9	0.0055	7	0.0065	8	0.0077	7	0.0066	10	0.0057
9	A*02-B*44-DRB1*07	8	0.0055	6	0.0065	9	0.0071	12	0.0056	6	0.0072
10	A*02-B*44-DRB1*13	10	0.0051	9	0.0060	12	0.0062	10	0.0059	12	0.0056
Browns											
1	A*01-B*08-DRB1*03	1	0.0147	1	0.0172	1	0.0251	1	0.0181	1	0.0153
2	A*29-B*44-DRB1*07	2	0.0109	2	0.0133	2	0.0159	2	0.0135	2	0.0116
3	A*03-B*07-DRB1*15	4	0.0070	3	0.0084	3	0.0117	4	0.0086	3	0.0083
4	A*02-B*44-DRB1*04	5	0.0066	4	0.0080	4	0.0089	5	0.0080	4	0.0072
5	A*33-B*14-DRB1*01	7	0.0061	5	0.0075	5	0.0081	6	0.0075	5	0.0072
6	A*02-B*44-DRB1*07	8	0.0055	6	0.0065	9	0.0071	12	0.0056	6	0.0072
7	A*11-B*35-DRB1*01	9	0.0055	7	0.0065	8	0.0077	7	0.0066	10	0.0057
8	A*02-B*44-DRB1*13	10	0.0051	9	0.0060	12	0.0062	10	0.0059	12	0.0056
9	A*02-B*07-DRB1*15	6	0.0061	8	0.0061	6	0.0079	11	0.0059	7	0.0068
10	A*23-B*44-DRB1*07	12	0.0048	10	0.0058	11	0.0067	17	0.0053	9	0.0058
Whites											
1	A*01-B*08-DRB1*03	1	0.0147	1	0.0172	1	0.0251	1	0.0181	1	0.0153
2	A*29-B*44-DRB1*07	2	0.0109	2	0.0133	2	0.0159	2	0.0135	2	0.0116
3	A*03-B*07-DRB1*15	4	0.0070	3	0.0084	3	0.0117	4	0.0086	3	0.0083
4	A*02-B*44-DRB1*04	5	0.0066	4	0.0080	4	0.0089	5	0.0080	4	0.0072
5	A*33-B*14-DRB1*01	7	0.0061	5	0.0075	5	0.0081	6	0.0075	5	0.0072
6	A*03-B*35-DRB1*01	14	0.0047	13	0.0053	7	0.0079	14	0.0055	15	0.0050
7	A*02-B*07-DRB1*15	6	0.0061	8	0.0061	6	0.0079	11	0.0059	7	0.0068
8	A*11-B*35-DRB1*01	9	0.0055	7	0.0065	8	0.0077	7	0.0066	10	0.0057
9	A*02-B*44-DRB1*07	8	0.0055	6	0.0065	9	0.0071	12	0.0056	6	0.0072
10	A*02-B*51-DRB1*11	21	0.0037	19	0.0045	10	0.0068	21	0.0046	24	0.0039
Yellows											
1	A*01-B*08-DRB1*03	1	0.0147	1	0.0172	1	0.0251	1	0.0181	1	0.0153
2	A*29-B*44-DRB1*07	2	0.0109	2	0.0133	2	0.0159	2	0.0135	2	0.0116
3	A*03-B*07-DRB1*15	4	0.0070	3	0.0084	3	0.0117	4	0.0086	3	0.0083
4	A*33-B*14-DRB1*01	7	0.0061	5	0.0075	5	0.0081	6	0.0075	5	0.0072
5	A*02-B*44-DRB1*04	5	0.0066	4	0.0080	4	0.0089	5	0.0080	4	0.0072
6	A*02-B*51-DRB1*11	21	0.0037	19	0.0045	10	0.0068	21	0.0046	24	0.0039
7	A*11-B*35-DRB1*01	9	0.0055	7	0.0065	8	0.0077	7	0.0066	10	0.0057
8	A*03-B*35-DRB1*01	14	0.0047	13	0.0053	7	0.0079	14	0.0055	15	0.0050
9	A*24-B*35-DRB1*11	24	0.0037	22	0.0043	16	0.0060	16	0.0054	31	0.0036
10	A*02-B*44-DRB1*13	10	0.0051	9	0.0060	12	0.0062	10	0.0059	12	0.0056
Indigenous											
1	A*01-B*08-DRB1*03	1	0.0147	1	0.0172	1	0.0251	1	0.0181	1	0.0153
2	A*29-B*44-DRB1*07	2	0.0109	2	0.0133	2	0.0159	2	0.0135	2	0.0116
3	A*03-B*07-DRB1*15	4	0.0070	3	0.0084	3	0.0117	4	0.0086	3	0.0083
4	A*02-B*44-DRB1*04	5	0.0066	4	0.0080	4	0.0089	5	0.0080	4	0.0072
5	A*33-B*14-DRB1*01	7	0.0061	5	0.0075	5	0.0081	6	0.0075	5	0.0072
6	A*02-B*07-DRB1*15	6	0.0061	8	0.0061	6	0.0079	11	0.0059	7	0.0068
7	A*03-B*35-DRB1*01	14	0.0047	13	0.0053	7	0.0079	14	0.0055	15	0.0050
8	A*11-B*35-DRB1*01	9	0.0055	7	0.0065	8	0.0077	7	0.0066	10	0.0057
9	A*02-B*44-DRB1*07	8	0.0055	6	0.0065	9	0.0071	12	0.0056	6	0.0072
10	A*23-B*44-DRB1*07	12	0.0048	10	0.0058	11	0.0067	17	0.0053	9	0.0058

The current ethnicity categories in the recruitment questionnaire may not be adequate to capture the individual's ancestry because multi-race individuals are complex to analyze due to the number of different population combinations that reduce sample size and high proportions of first generation admixture leads to divergence from Hardy-Weinberg equilibrium assumed by the EM algorithm. The same applies to the regionality that is high in our country due to the strong immigration and migration process between regions. Thus, we must look out for new aspects while studying our current donors so that we may in the near future recruit new donors more adequately and always keeping in mind that the patients are the reference.

The study was done on 1st field of the nomenclature, because many of the Brazilian patients that are in the search process have a minimal initial typing (A-B/low resolution and DRB1/intermediate resolution) as well as the donors that are in the registry since the beginning (A-B-DRB1 serology/low or intermediate resolution). Only in the last 4 years, REDOME has managed to get all new donors registered with intermediate resolution (A-B-DRB1) by default. REDOME has been working hard to change this aspect with the Government since it is a public registry. Although 9/10 or 10/10 compatibility is determined by the 2nd field of the nomenclature, REDOME has been developing other strategies, such as its own predictive algorithm, to help the searching

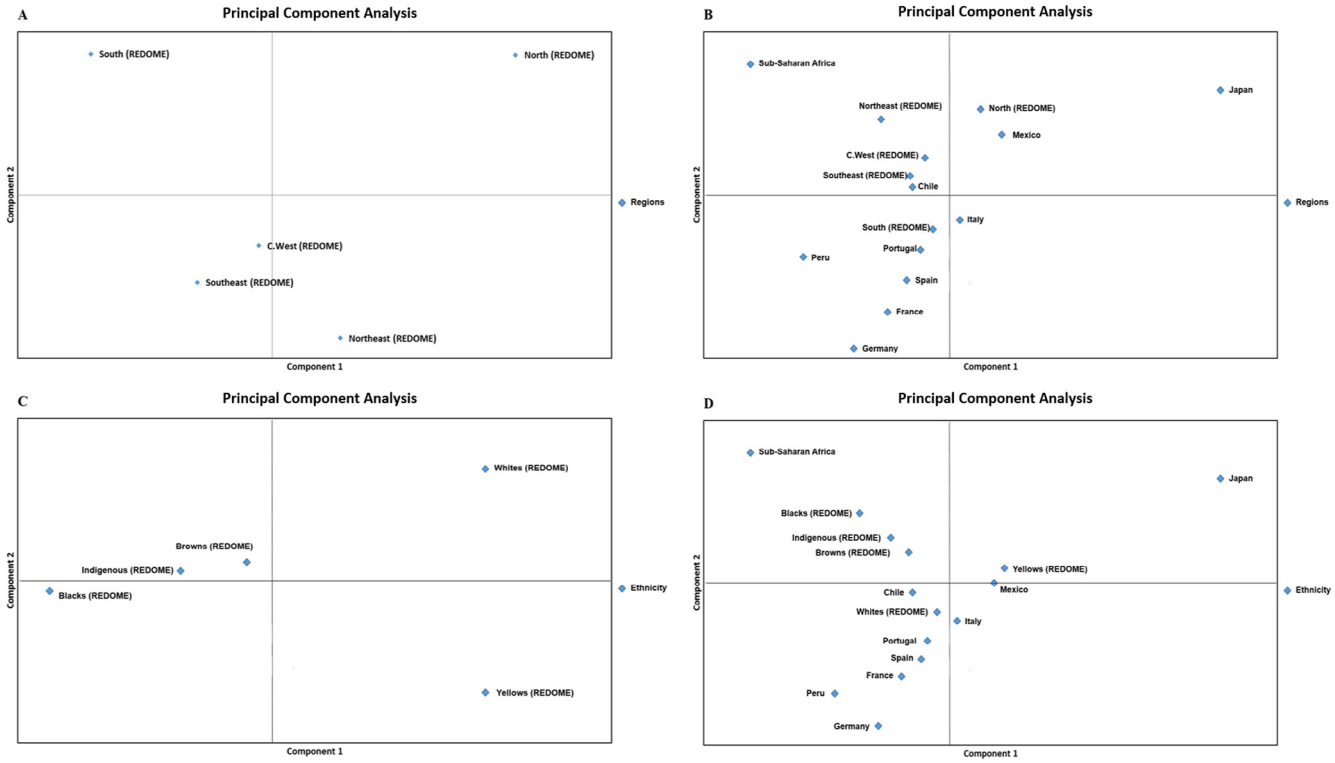

Fig. 2. Components 1 and 2 explains for the 97.8%, 76.4%, 96.9% and 77.1% of variation for A, B, C and D, respectively.

process of those patients and donors who have an inadequate HLA typing quality.

Nationally, the chances of identifying a compatible donor can reach 88% in the preliminary phase of the search (i.e. a 6/6 match at low resolution level) and 64% of the patients are assigned a compatible donor by the end of the process (i.e. 10/10 match at high resolution, with available donor [48]. As more than 2.400 patients (National and International) a year are registered for a donor search in Brazil, this study becomes an important object for the development of new search tools that can improve the search process for hematopoietic stem cell donors.

The present work did not investigate more specific and complex interactions of sampling effects with the properties of maximum likelihood methods implemented in EM algorithms used for registry data estimation [49]. However, as demonstrated in previous work on haplotype and linkage disequilibrium (LD) estimation [50,51], the influence of sampling errors on estimations based on the maximum likelihood model may be amplified.

The need to know the frequencies of HLA alleles and haplotypes has led to several genetic diversity studies over the decades and those have helped to optimize the recruitment and selection of hematopoietic stem cell donors by other registries and also for the REDOME [17,38,52–61]. Results presented in this study not only help to provide a better comprehension of the Brazilian registry, but also contribute to a better efficiency in the strategies of attracting new volunteer donors across the country.

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Conflict of interest

The authors have declared that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.humimm.2017.08.002.

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