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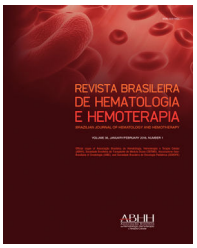

Original article

Human leukocyte antigen allele linkage disequilibrium and haplotype structure in volunteer bone marrow donors of Paraná State

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ABSTRACT

Background: Bone marrow transplantation has been used in the treatment of various diseases, especially hematologic diseases. The success of this treatment, among other factors, requires human leukocyte antigens (HLA) compatibility between patient and donor. Knowing the human leukocyte antigens allele group and haplotype frequencies as well as the linkage disequilibrium between alleles of different human leukocyte antigens loci can shorten the search time for a compatible bone marrow donor.
Objective: To assemble and analyze data on human leukocyte antigens frequencies available in the Laboratory of Immunogenetics and Histocompatibility (LIGH) database of the Universidade Federal do Paraná adding an estimation of the Hardy–Weinberg equilibrium and linkage disequilibrium.
Methods: The sample was composed of seven populations grouped by self-declared ancestry or inferred from the surname as follows: Laboratory of Immunogenetics and Histocompatibility database (all groups), descendants of Italians, Poles, and Asians, Afro-Brazilians, Mulattos (mixed ancestry) and Amerindians. Human leukocyte antigens genotyping was carried out using the polymerase chain reaction-sequence specific primers (PCR-SSP) and -sequence specific oligonucleotide (PCR-SSO) technologies.
Results: There were high frequencies of the *HLA-A*02*, *HLA-B*35* and *HLA-DRB1*13* allelic groups in all groups. The same was observed for the *HLA-A*01-B*08-DRB1*03* haplotype except for Asian descendants. It was observed that the human leukocyte antigens Laboratory of Immunogenetics and Histocompatibility database and the Asian group are not in Hardy–Weinberg equilibrium. The Italian, Polish, Asian, Mulatto and Amerindian descendants showed haplotypes in complete linkage disequilibrium. Our results were compared with data on the human leukocyte antigens in the Paraná population available from the Brazilian Voluntary Bone Marrow Donor Registry (REDOME) and data published on the population of Curitiba and the northern region of Paraná.

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Conclusions: Haplotypes frequent in the Asian group were not the most frequently observed in the Laboratory of Immunogenetics and Histocompatibility database and the National Bone Marrow Donor Registry for the state of Paraná. Linkage disequilibrium information may prove useful in the search for bone marrow donors for patients awaiting a suitable donor.

Introduction

Bone marrow transplantation is a treatment for various blood-related diseases, such as leukemias, lymphomas, and severe anemia. Among other factors, compatibility of human leukocyte antigens (HLA) between patient and donor is mandatory for a successful bone marrow transplantation. This lessens the chance of graft rejection and the occurrence of graft versus host disease (GVHD). Although immunosuppressive drugs reduce the possibility of rejection, HLA compatibility is the factor that provides the best prognosis for a successful procedure.[1] Currently *HLA-A, -B* and *-DRB1* are matched as one of the first phase criteria in the search of compatible donors for recipients on the waiting list.

HLA diversity reflects extraordinary polymorphism and polyallelism at multiple class I and class II loci that have co-dominant expressions. Recombination events between alleles in the major histocompatibility complex (MHC) regions occur with a frequency of 2–4%.[1] For this reason, HLA genes are inherited in a tight cluster of closely linked genes or haplotypes. They code for the most immunogenic proteins known to date and knowledge about the HLA profile of patient and donor is an important issue in the context of cell and tissue transplantation.[1]

According to Vogel & Motulsky, the genes in the HLA system present striking deviations from equilibrium.[2] Lewontin & Kojima created the term linkage disequilibrium (LD) that, similar to other terms, does not describe the true meaning, that is, the non-random association of alleles at two or more loci. The words LD can also refer to genes located on different chromosomes that segregate independently in a population with a recent past of panmictic breeding or genes located at adjacent genetic loci.[3] LD is characterized when the frequency of association between alleles is higher or lower than what would be expected considering the individual allele frequencies. The pattern of LD varies markedly between populations and depends on the evolutionary history. The more generations of panmixia, the closer the population will be to the equilibrium.

The Brazilian population, whose roots are based on an ethnic matrix of European, African and Amerindian origins, has been pluralized and increased with the diversity and genetic composition of various migratory flows of populations with different backgrounds. Each Brazilian region has its own ethnic particularity. In Paraná State, located in southern Brazil, there is a prevalence of Europeans, mainly Germans, Italians and Poles. Currently, the HLA diversity of the Paraná population is related to the ancient populations that arrived in the state at the end of the 19th century. According to ethnic self-classification in the 2010 census, 70.06% of the population stated they were White, 25.35% Mulattos, 3.15% Black, 1.19% Asians and 0.25% were Indigenous.[4]

For patients on the waiting list for whom there is no HLA-identical sibling donor, a search for an unrelated hematopoietic stem cell (HSC) donor can be initiated using the Brazilian Voluntary Bone Marrow Donor Register (REDOME). Currently, more than 4,000,000 potential HSC donors are registered on REDOME nationwide with 3858 patients on the Brazilian Bone Marrow Recipient Register (REREME) waiting for a compatible HLA match. Despite the increase in the number of HLA-typed volunteer donors, a significant percentage of patients will still not be transplanted in Brazil or internationally.[5]

The search can be performed first in the group that shares the same ancestry where, theoretically, there is a greater chance to find a HLA-compatible donor; haplotype differences are found between different ethnic groups. Haplotypes that are rare in some populations are common in others.

The primary goal of the current study was to bring together previous studies on HLA frequencies [6–10] and to add estimations of the Hardy–Weinberg equilibrium and LD to understand the allele and haplotype structures better in a representative sample of bone marrow volunteer donors in Paraná State.

Methods

A total of 121,305 volunteer bone marrow donors in the Laboratory of Immunogenetics and Histocompatibility (LIGH) database of the Universidade Federal do Paraná were used in this study. In Brazil, the REDOME guidelines recommend that transplants should have high-resolution matches for *HLA-A, -B, -C, -DRB1* and *-DQB1* (10/10 matches) between donor and recipient by DNA-based methods. In the present study the low/medium resolution typing for *HLA-A, -B* and *-DRB1* requirements for registering in the REDOME were used. Informed written consent was obtained from all participants.[5]

Self-classification and classification of ancestry by surnames

The Instituto Brasileiro de Geografia e Estatística (IBGE) is the official census taking institution in Brazil. Five skin color categories based on self-classification have been used since 1991: White, Brown, Black, Yellow and Indigenous. According to Pena et al. the term 'color' results from a phenotypic

evaluation that considers skin and hair pigmentation, eye melanization and facial features such as nose and lip shape. The term 'Brown' is an attempt to synthetize a variety of classifications that emerges from the extensive miscegenation that exists in the Brazilian population.[11]

The ancestry or racial background was obtained by self-assessment in the Brazilian census of the IBGE. Aiming to add efficiency to sampling strategies, surnames were also included, mainly for Italians and Poles as proxies for ethnic origin. In the context of population genetics, certain surnames are unique to a particular ethnic group and may contain information related to family groups or ancestry of their bearers. Several researchers used surnames as tools to evaluate average consanguinity, to assess population isolation and structure, and to estimate the intensity and directionality of migrations.[12]

This study sample was grouped according to self-classification or inferred ancestry according to surname as follows: LIGH database (all groups: $n = 121{,}305$), Italian ($n = 212$), Polish ($n = 277$), Asian ($n = 1681$), Afro-Brazilian descendants ($n = 3822$), Mulatto (Brazilian mixed ancestry; $n = 14{,}553$) and Amerindians ($n = 704$). Ancestry inferred by surnames was especially helpful for the classification of Italian and Polish people.

The allele and haplotype frequencies of all groups were compared with HLA frequencies for Paraná State available in the REDOME database.[5]

Blood was collected in 4-mL tubes containing ethylenediaminetetraacetic acid (EDTA) anticoagulant in blood banks of the Centro de Hematologia e Hemoterapia do Paraná (Hemepar) or in the blood bank of Erasto Gaertner Hospital (Curitiba, PR). The collected material was transported to the LIGH where DNA extraction was performed by one of the following techniques: salting-out, EZ-DNA kit (Biometrix), iPREP® Purelink® gDNA Blood Kit (Life Technologies) or Biopur kit (Biometrix). *HLA-A*, *HLA-B* and *HLA-DRB1* typing was performed by the polymerase chain reaction-sequence specific primers (PCR-SSP) method using the Micro-SSP-ABDR Low/Medium Resolution kit (One Lambda) or the polymerase chain reaction-sequence specific oligonucleotide (PCR-SSO) method using Labtype SSO kits (One Lambda) for low/medium resolution according to the manufacturer's instructions. Samples were read on a Luminex Labscan 100 apparatus (One Lambda). The analysis was performed using the HLA Visual (One Lambda) or HLA Fusion software (One Lambda).

Statistical analysis

The Arlequin software version 3.11[13] was used to calculate the allelic groups and haplotypes frequencies, the Hardy–Weinberg equilibrium and LD.

Results

The ten most common allelic groups and haplotypes in the LIGH database are shown in Figures 1–4.

The three HLA loci studied were in Hardy–Weinberg equilibrium for all groups except for the LIGH database: *HLA-A* (p-value = 0.000), *HLA-B* (p-value = 0.000) and *HLA-DRB1* (p-value = 0.000); and Asian: *HLA-A* (p-value = 0.000), *HLA-B* (p-value = 0.000) and *HLA-DRB1* (p-value = 0.001); Hardy–Weinberg equilibrium was set for p-values >0.05 (Table 1).

As for the LIGH database, the strongest LD was observed for *HLA-B*08-DRB1*03* ($D' = 0.540$: $r^2 = 0.170$: p-value = 0.000). Several haplotypes in the Italian group were in complete LD, e.g. *HLA-A*69-B*39* ($D' = 1.000$: $r^2 = 0.075$: p-value = 0.000) as well as for Polish descendants: *HLA-A*80-B*50* ($D' = 1.000$: $r^2 = 0.082$:

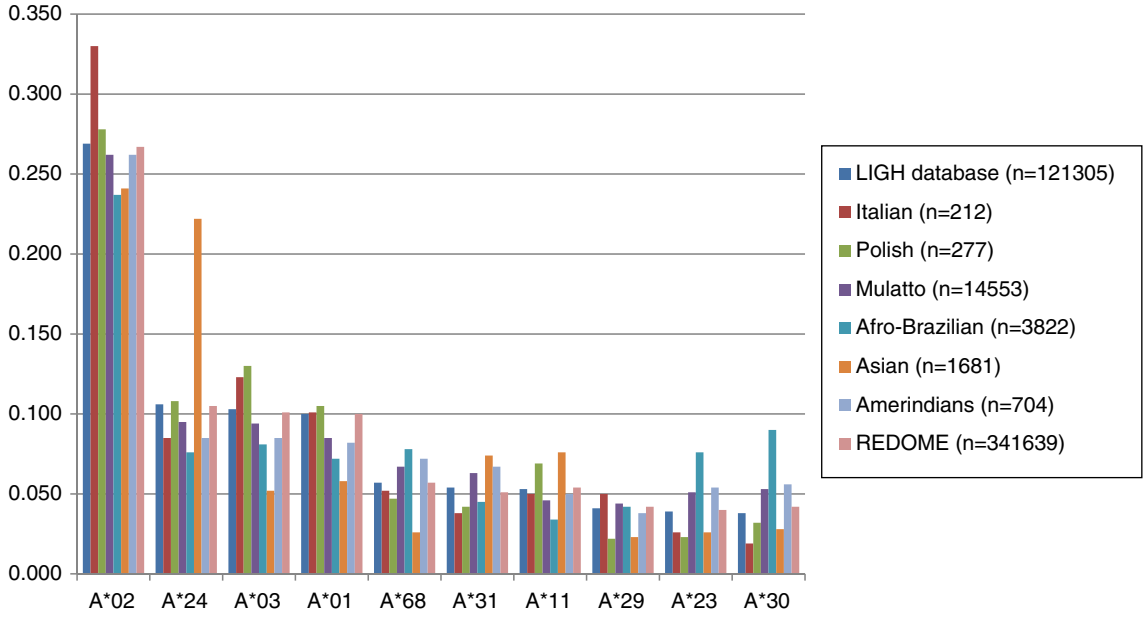

Figure 1 – *HLA-A* ten most frequent allelic groups in the Laboratory of Immunogenetics and Histocompatibility database compared with ethnic groups as well as Brazilian Voluntary Bone Marrow Donor Register (REDOME) data for the state of Paraná.

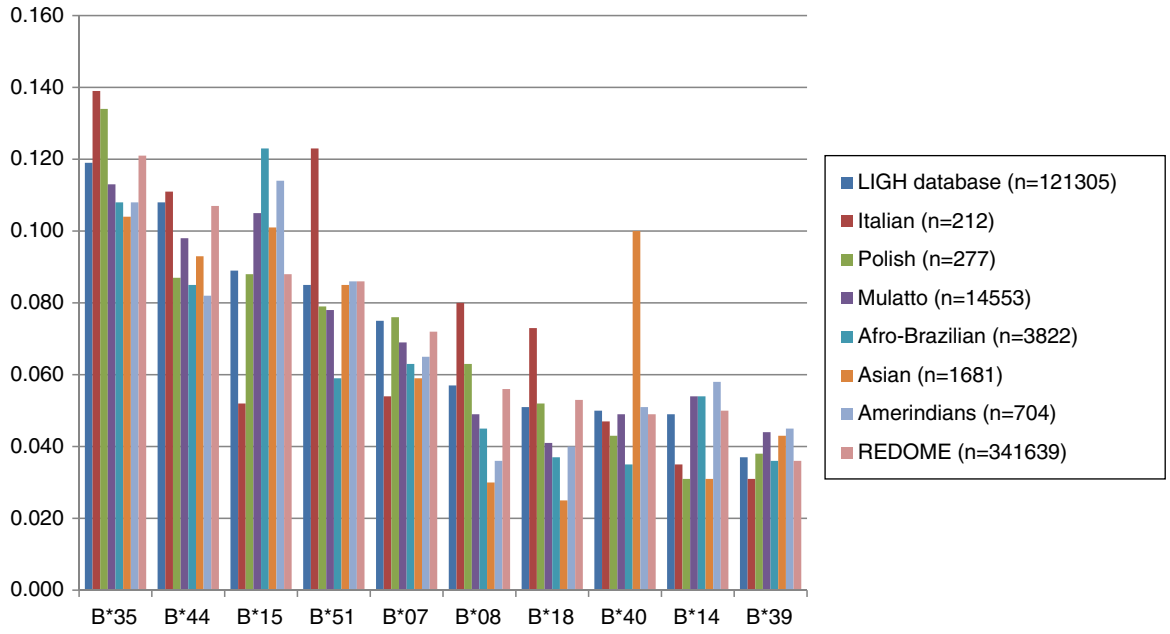

Figure 2 – *HLA-B* ten most frequent allelic groups of Laboratory of Immunogenetics and Histocompatibility database compared with ethnic groups as well as Brazilian Voluntary Bone Marrow Donor Register (REDOME) data for the state of Paraná.

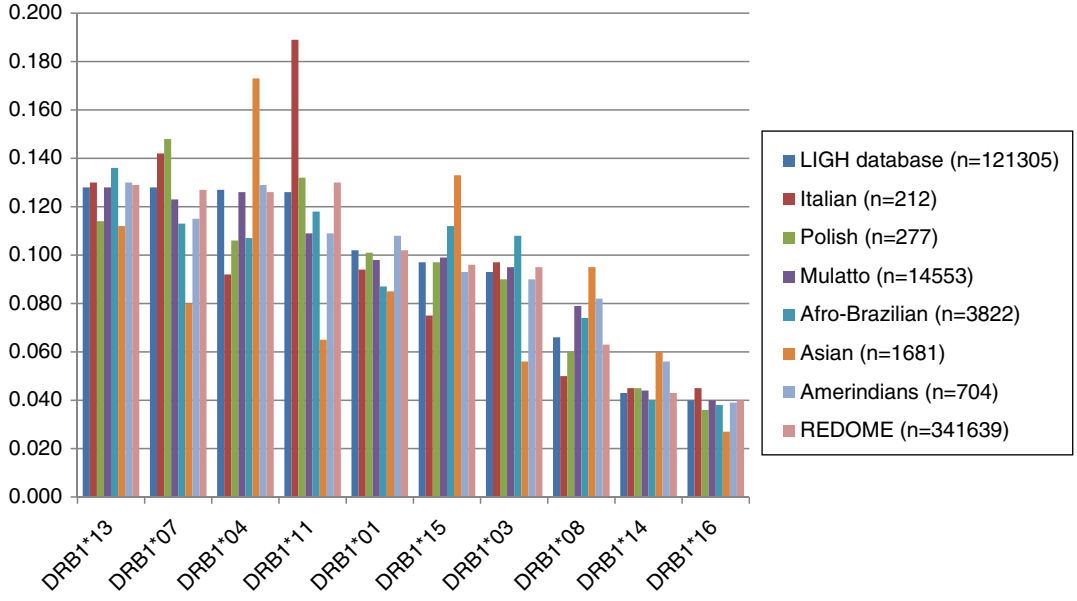

Figure 3 – *HLA-DRB1* ten most frequent allelic groups of Laboratory of Immunogenetics and Histocompatibility database compared with ethnic groups as well as Brazilian Voluntary Bone Marrow Donor Register (REDOME) data for the state of Paraná.

Table 1 – Hardy–Weinberg equilibrium (p-value > 0.05) per locus in each of the ethnic groups analyzed.

HLA-	LIGH database (n = 121,305)	Italian (n = 212)	Polish (n = 277)	Mulatto (n = 14,553)	Afro-Brazilian (n = 3822)	Asian (n = 1681)	Amerindians (n = 704)
A	0.000	0.240	0.204	0.143	0.658	0.000	0.320
B	0.000	0.837	0.169	0.134	0.846	0.000	0.405
DRB1	0.000	0.364	0.693	0.075	0.167	0.001	0.384

LIGH: Laboratory of Immunogenetics and Histocompatibility.

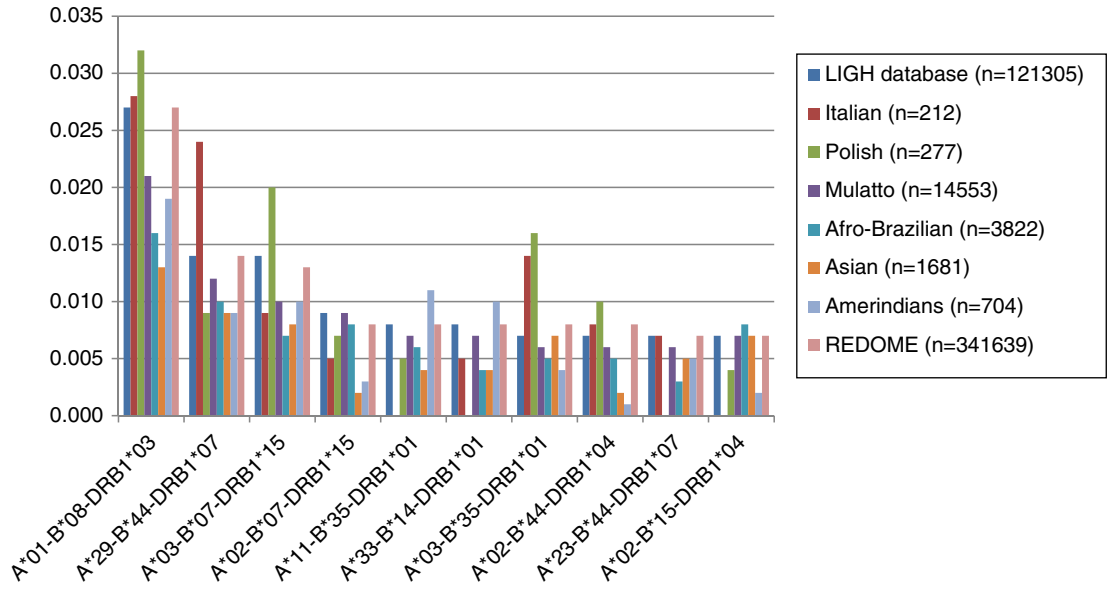

Figure 4 – *HLA-A-B-DRB1* ten most frequent haplotypes of Laboratory of Immunogenetics and Histocompatibility database compared with ethnic groups and with the available Brazilian Voluntary Bone Marrow Donor Register (REDOME) data for the state of Paraná.

p-value = 0.000). Concerning to Mulatto group, the strongest LD values were observed for haplotypes *HLA-A*01-B*59* ($D' = 1.000$: $r^2 = 0.000$: *p*-value = 0.001) and *HLA-B*59-DRB1*03* ($D' = 1.000$: $r^2 = 0.000$: *p*-value = 0.000) that were in complete LD. As for Afro-Brazilians, the haplotype *HLA-B*82-DRB1*11* ($D' = 0.870$: $r^2 = 0.010$: *p*-value = 0.000) showed the strongest LD. Asian descendants presented different haplotypes in complete LD, including *HLA-A*69-B*35* ($D' = 1.000$: $r^2 = 0.003$: *p*-value = 0.003). The Amerindians group also showed haplotypes in complete LD such as *HLA-A*80-B*15* ($D' = 1.000$: $r^2 = 0.006$: *p*-value = 0.005); LD was set for *p*-values >0.05 (Table 2).

Discussion

HLA genes code for cell surface proteins that act as biochemical signatures. These HLA markers are classified as six types labeled *HLA-A, -B, -C, -DR, -DQ*, and *-DP*. A total of at least ten genes code for the HLA system giving each person an immune signature displaying peptides (foreign or self) for T lymphocytes. There are more than hundred variants for each of these genes resulting in billions of combinations or individual HLA types that pose a challenge for cell and tissue transplantation.[14]

However, HLA diversity is a key factor of the adaptive immune response directed toward a pathogen and an effective immune response, among other factors, depends on the HLA alleles a person carries. HLA alleles differ mainly at exons 2 and 3 for class I genes, and exon 2 for class II genes. These exons code for the peptide-binding region of HLA molecules. It has been assumed that polymorphisms of HLA alleles are functional as different HLA molecules bind different sets of related pathogen-derived peptides to present them to T-cell receptors. It has also been observed that HLA alleles that have a higher binding affinity to a particular pathogenic peptide are better at clearing infections. According to Sanchez-Mazas, the distribution of HLA alleles in different populations may be a consequence of this functional polymorphism.[15] As to HLA alleles, heterozygous individuals have a wider peptide-binding region repertoire and hence they may mount a better immune response to a specific peptide epitope of a pathogen compared to homozygous individuals.

From the biological point of view, to know which alleles are present in a population and their frequencies could be informative about the evolution of HLA polymorphisms and the population's genetic susceptibility to disease. For clinical transplantation purposes, however, this knowledge provides a more realistic overview of a population concerning their most frequent HLA alleles and haplotypes with this information being very useful in estimating the chances of finding a compatible donor for a patient on the waiting list for a hematopoietic stem cell transplantation (HSCT). It is well known that a significant degree of HLA matches between donor and recipient improves overall transplant survival, rates of engraftment and reduces the incidence of acute and chronic GVHD.

The three most common allelic groups, *HLA-A (-A*02, -A*24 and -A*03)* and *HLA-B (-B*35, -B*44 and -B*15)*, found in the LIGH database corroborate the overall frequency of the data available in the REDOME for the state of Paraná.[5] These findings are in agreement with a previous study for the population of the northern region of Paraná State [16] as well as with a previous survey conducted in the population of Curitiba.[1]

The *HLA-A (-A*02, -A*24 and -A*03)* and *HLA-B (-B*35, -B*44 and -B*15)* allelic groups were also the most common for Polish (0.278, 0.108, 0.130), Mulatto (0.262, 0.095, 0.094) and Amerindian (0.262, 0.085, 0.085) groups and Polish (0.134, 0.087, 0.088), Mulatto (0.113, 0.098, 0.105) and Afro-Brazilian (0.108, 0.085, 0.123) groups, respectively.

Table 2 – Description of the strongest linkage disequilibrium values for the haplotypes *HLA-A/-B*, *HLA-A/-DRB1* and *HLA-B/-DRB1* in each of the analyzed groups.

HLA- LIGH database ($n = 121,305$)	A*24-B*59 $D' = 0.441$ $r^2 = 0.001$ $p = 0.000$	A*29-DRB1*07 $D' = 0.220$ $r^2 = 0.010$ $p = 0.000$	B*08-DRB1*03 $D' = 0.540$ $r^2 = 0.170$ $p = 0.000$								
HLA- Italian ($n = 212$)	A*69-B*39 $D' = 1.000$ $r^2 = 0.075$ $p = 0.000$	A*34-B*08 $D' = 1.000$ $r^2 = 0.027$ $p = 0.001$	A*02-B*45 $D' = 1.000$ $r^2 = 0.010$ $p = 0.044$	A*33-B*58 $D' = 1.000$ $r^2 = 0.282$ $p = 0.000$	A*03-B*47 $D' = 1.000$ $r^2 = 0.017$ $p = 0.007$	A*02-B*56 $D' = 1.000$ $r^2 = 0.010$ $p = 0.044$	A*69-DRB1*01 $D' = 1.000$ $r^2 = 0.023$ $p = 0.002$	A*34-DRB1*04 $D' = 1.000$ $r^2 = 0.023$ $p = 0.002$	B*45-DRB1*11 $D' = 1.000$ $r^2 = 0.020$ $p = 0.003$	B*47-DRB1*15 $D' = 1.000$ $r^2 = 0.029$ $p = 0.001$	B*48-DRB1*09 $D' = 1.000$ $r^2 = 0.665$ $p = 0.000$
HLA- Polish ($n = 277$)	A*80-B*50 $D' = 1.000$ $r^2 = 0.082$ $p = 0.000$	A*36-B*53 $D' = 1.000$ $r^2 = 0.199$ $p = 0.000$	A*25-B*56 $D' = 1.000$ $r^2 = 0.034$ $p = 0.000$	A*31-B*47 $D' = 1.000$ $r^2 = 0.042$ $p = 0.000$	A*36-DRB1*11 $D' = 1.000$ $r^2 = 0.010$ $p = 0.010$	A*80-DRB1*14 $D' = 1.000$ $r^2 = 0.040$ $p = 0.000$	B*47-DRB1*13 $D' = 1.000$ $r^2 = 0.010$ $p = 0.010$	B*81-DRB1*12 $D' = 1.000$ $r^2 = 0.160$ $p = 0.000$	B*56-DRB1*12 $D' = 1.000$ $r^2 = 0.080$ $p = 0.000$		
HLA- Mulatto ($n = 14,553$)	A*01-B*59 $D' = 1.000$ $r^2 = 0.000$ $p = 0.001$	A*43-DRB1*07 $D' = 0.430$ $r^2 = 0.000$ $p = 0.020$	B*59-DRB1*03 $D' = 1.000$ $r^2 = 0.000$ $p = 0.000$								
HLA- Afro-Brazilian ($n = 3822$)	A*69-B*55 $D' = 0.817$ $r^2 = 0.116$ $p = 0.000$	A*69-DRB1*11 $D' = 0.590$ $r^2 = 0.000$ $p = 0.000$	B*82-DRB1*11 $D' = 0.870$ $r^2 = 0.010$ $p = 0.000$								
HLA- Asian ($n = 1681$)	A*69-B*35 $D' = 1.000$ $r^2 = 0.003$ $p = 0.003$	A*11-B*67 $D' = 1.000$ $r^2 = 0.036$ $p = 0.000$	A*68-B*78 $D' = 1.000$ $r^2 = 0.011$ $p = 0.000$	A*69-DRB1*04 $D' = 1.000$ $r^2 = 0.001$ $p = 0.029$	B*78-DRB1*13 $D' = 1.000$ $r^2 = 0.002$ $p = 0.005$	B*73-DRB1*04 $D' = 1.000$ $r^2 = 0.006$ $p = 0.000$					
HLA- Amerindians ($n = 704$)	A*80-B*15 $D' = 1.000$ $r^2 = 0.006$ $p = 0.005$	A*02-B*56 $D' = 1.000$ $r^2 = 0.004$ $p = 0.018$	A*02-B*47 $D' = 1.000$ $r^2 = 0.004$ $p = 0.018$	A*03-B*54 $D' = 1.000$ $r^2 = 0.008$ $p = 0.001$	A*74-B*78 $D' = 1.000$ $r^2 = 0.028$ $p = 0.000$	A*80-DRB1*16 $D' = 1.000$ $r^2 = 0.020$ $p = 0.000$	B*54-DRB1*15 $D' = 1.000$ $r^2 = 0.010$ $p = 0.000$	B*78-DRB1*07 $D' = 1.000$ $r^2 = 0.010$ $p = 0.010$			

LIGH: Laboratory of Immunogenetics and Histocompatibility.
Linkage equilibrium for $p > 0.05$.

*HLA-A*11* and *HLA-B*40* were the third most common allelic groups in the Asian group, thus disagreeing with the findings of Bardi et al.[16] who reported *HLA-B*40* as the most prevalent in this group.

Class II *HLA-DRB1*13, -DRB1*07* and *-DRB1*04* were the most frequent allelic groups in the LIGH database, thus agreeing, in part, with data available in REDOME for the state of Paraná[5] that reported *HLA-DRB1*11* as the most common. They were also the most common allelic groups of Mulattos and Amerindians. However in Asians the *HLA-DRB1*15* allelic group was the second most common, in agreement with a previous study carried out in the population of northern Paraná state.[16]

The three most frequent haplotypes (*HLA-A*01-B*08-DRB1*03, HLA-A*29-B*44-DRB1*07, HLA-A*03-B*07-DRB1*15*) found in the LIGH database are in line with the three most common haplotypes found in REDOME for the state of Paraná.[5] Bicalho et al.[1] and Ruiz et al.[17] reported similar results. These haplotypes were also the most frequent among Mulattos. The most common haplotype in Asians (*HLA-A*24-B*52-DRB1*15* – data not shown) was also the most frequent in the study by Bardi et al. for this ethnic group.[16]

Table 1 shows that all groups are in Hardy–Weinberg equilibrium for the *HLA-A*, *-B* and *-DRB1* loci except for the LIGH database and the Asian group where the number of observed heterozygotes is smaller than expected. This fact possibly occurs because the LIGH database is composed of donors from different parts of Paraná State or living in cities with high concentrations of people sharing the same ancestral background (Asian) that determine regional differences in the population. Additionally, the condition of strictly random marriages, which is fundamental to the accuracy of the Hardy–Weinberg equilibrium, may not occur.

The observed LD between HLA alleles provides valuable information about the structure of the population. It may cast some light on how evolutionary forces, such as natural selection, gene conversion, mutations, affect *HLA* gene frequencies. Further, it can pave the way for a better comprehension of allelic interactions that generate the allelic combinations, or haplotypes, in different populations because of their abilities to bind to peptides of pathogens in the environment. Hence, certain haplotype combinations are more likely to be found together than others. These associations of alleles can arise through their co-evolutionary interaction with pathogens. In clinical settings, individual conserved haplotypes within ethnic groups could be a key factor to increase the odds of finding a compatible HLA donor.

The haplotypes in LD *HLA-A*34-B*08* ($D' = 1.000$) and *HLA-A*03-B*47* ($D' = 1.000$) for the Italian group and *HLA-A*36-B*53* ($D' = 1.000$) and *HLA-A*36-DRB1*11* ($D' = 1.000$) for the Polish group are in agreement with the results obtained by Santos for Caucasians. Moreover, the *HLA-A*11-B*67* ($D' = 1.000$) haplotype in the Asian group is in line with the results of Santos.[18]

Complete LD ($D' = 1.000$) was widely found between the analyzed ethnic groups, indicating the existence of linkage between one allelic group and another thereby characterizing a particular haplotype. What is striking is the correlation (r^2) between allelic groups with complete LD which is 0.000 or very close to this. This fact indicates that these particular allelic groups are present at completely different frequencies, for example, the Mulatto group showed *HLA-A*01-B*59* ($D' = 1.000$ and $r^2 = 0.000$) with the respective *HLA-A*01* (0.085) and *HLA-B*59* (0.000034) frequencies. So, among Mulattos in the population of Paraná state, *HLA-B*59* is almost always associated with *HLA-A*01*. Nevertheless, the contrary is not true for *HLA-A*01*. This type of analysis is of utmost importance in the search for bone marrow volunteer donors, especially for the HLA laboratory team when facing genotyping ambiguities.

LD, the non-random association of alleles at different loci, can provide valuable information on the structure of haplotypes. This is often the basis for evaluating the association of genetic variations with human traits in unrelated subjects.[19] The knowledge of HLA genes and haplotypes in the population structure is relevant not only for genetic studies but in disease susceptibility and organ transplantation. In regards to a mixed population like Brazilians, the size and genetic diversity of REDOME should accomplish the requirement that the number of donors registered in the national database can ensure that each patient on the waiting list finds a compatible donor as early as possible. HLA frequencies can be used to estimate the probability of finding identical unrelated volunteer bone marrow donors. As alleles at closely linked HLA loci tend to be associated at the population level (e.g. in LD) it is common sense that patients with HLA haplotypes in strong LD have a higher probability of finding HLA-identical unrelated donors than others.[20]

Conclusions

All studied groups were in accordance with the HLA genetic profile of the Paraná population data found in REDOME in respect to the allelic groups and haplotype frequencies except for the Asian group. Regional genetic differences may influence the Hardy-Weinberg equilibrium[21] as seen in the Asian group and the LIGH database. The analysis of LD of HLA haplotypes is of the utmost importance to find compatible bone marrow volunteer donors and should be carefully conducted considering the group ancestry and regional peculiarities. These results contribute to the study of the population genetics of the Paraná State. The information on LD between HLA allelic groups may show its value and practical use in transplantation genetics when the purpose is to find compatible bone marrow donors.

Conflict of interest

The authors declare no conflicts of interest.

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