Advances in Rheumatology

RESEARCH

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HLA-B27 positivity in a large miscegenated population of 5,389,143 healthy blood marrow donors in Brazil

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Abstract

Background The prevalence of HLA-B27 gene positivity in healthy Caucasian communities varies between 8 and 14%. However, there is a lack of information in countries with a high rate of miscegenation, such as Brazil.

Aim To estimate the frequency of HLA-B27 in the Brazilian general population using a large national registry database.

Methods This is a cross-sectional ecological study using the Brazilian Registry of Volunteer Bone Marrow Donors (REDOME) database on HLA-B27 allelic frequency and proportion of positives of healthy donors (18–60 years old). Data were analyzed according to sex, age, race **(**by self-reported skin color recommended by the Brazilian Institute of Geography and Statistics **-** IBGE), and geographic region of residence.

Results From 1994 to 2022, a total of 5,389,143 healthy bone marrow donors were included. The overall positivity for HLA-B27 was 4.35% (CI 95% 4.32–4.37%), regardless of sex and age (57.2% were women, mean age was 41.7yo). However, there was a difference between races: 4.85% in Whites; 2.92% in Blacks; 3.76% in *Pardos* (Browns i.e. mixed races); 3.95% in *Amarelos* (Yellows i.e. Asian Brazilians); and 3.18% in Indigenous. There was also a difference regarding geographic region of residence (North: 3.62%; Northeast: 3.63%; Southeast: 4.29%; Midwest: 4.5% and 5.25% in South). The homozygosity rate for the HLA-B27 was 1.32% of all the positives and only 0.06% in the general population.

Conclusions Our findings provide the first Brazilian national prevalence for HLA-B27 in 4.35%. There is a gradient gene positivity from North to South, suggesting that the genetic background related to the miscegenation due to colonization, slavery, and some later waves of immigration together with internal migratory flows, could explain our findings.

Keywords HLA-B27, Brazil, Ankylosing spondylitis, Bone-marrow donors, Epidemiology

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Table 1 Studies published with HLA-B27 positivity in Brazilian healthy population

Author, Year	Sample size	Race	HLA-B27 positivity
Rosales, 1985 [15]	247	White	7.3%
Trachtenberg, 1988 [16]	977	White	5.8%
Braun-Prado, 2000 [18]	151	White	3.6%
	157	Brown	0.6%
	40	Black	1.3%
Dalalio, 2002 [17]	1399	White	5.2%

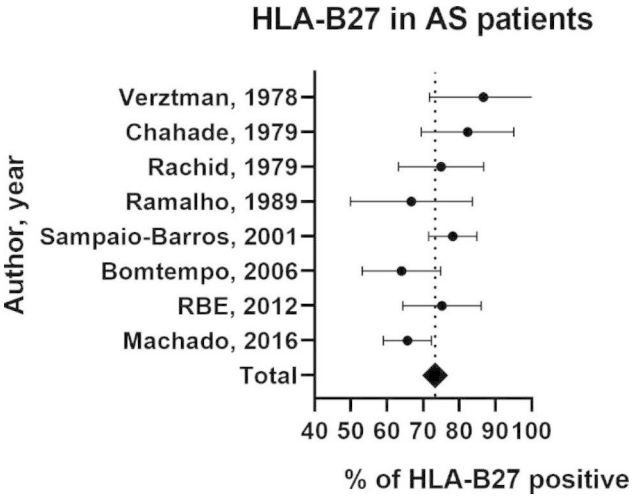

Fig. 1 Brazilian epidemiological studies with HLA-B27 frequency in AS patients. Data were adapted from the published references [19–24]

Introduction

Since the initial description of the close relationship between ankylosing spondylitis (AS) and HLA-B27 in 1973 [1, 2], several studies have confirmed this association with variable strength, predominantly linked to racial variability among populations around the world [3, 4]. In this context, HLA-B27 is also considered one of the main factors associated with the heterogeneity of the clinical presentation of axial spondyloarthritis (AxSpA) [5]. After 50 years, HLA-B27 test order has become routine in the clinical practice of rheumatologists, mainly for diagnostic and prognostic purposes [6].

HLA-B27 belongs to a family with several closely related cell surface proteins encoded in the HLA-B locus. There are more than 200 alleles at nucleotide level and around 160 subtypes at protein level, with at least one amino acid in a different sequence [7]. Although it has heterogeneous prevalence according to the population (0.1–15% of healthy individuals), it has been more documented and with greater interest in AS patients (from 50% to more than 90%, according to genetic background), particularly the following five subtypes: B*2701, B*2702 (Mediterranean people), B*2704 (Chinese), B*2705 (Caucasians), or B*2707. Two subtypes, HLA-B27*06 and HLA-B27*09, seem to have no disease association [8, 9]. A Brazilian study showed an increased prevalence of B*2705 and B*2702 in patients with AS [10]. Other MHC and non-MHC genes are also related to AS pathogenesis [11, 12].

Brazil, in addition to being a nation of continental dimensions, is one of the countries with greatest racial miscegenation [13, 14], which makes it extremely difficult to carry out broad studies on the prevalence of HLA-B27 and AS (Table 1) [15–18]. The few studies evaluating the prevalence of HLA-B27 in Brazilians were carried out in white populations; the only study that evaluated racial differences showed a clear predominance of HLA-B27 in whites when compared to blacks [18]. The average frequency of HLA-B27 in Brazilian studies with AS patients is around 75% (Fig. 1), with some variability between different geographic regions [19–22].

Based on these difficulties in accessing all segments of the Brazilian population, this study aimed to analyze the frequency of positivity for the HLA-B27 gene from the Brazilian Registry of Volunteer Bone Marrow Donors (REDOME) database, analyzing the importance of sex, race, and geographic region. **Knowing the frequency of HLA-B27 positivity in a huge sample consisting of healthy individuals allows estimating its specificity for the diagnosis of AS and its role in the characterization of the other SpA. Similarly, knowing its frequency in AS patients allows estimating its sensitivity, as also shown in** Fig. 1.

Methods

This is a cross-sectional ecological study using REDOME database (https://redome.inca.gov.br/). Data regarding the HLA-B27 allelic frequency (AF – the total number of copies of the allele in the population sample), percentage of positivity (PP – the percentage of the individuals carrying at least a copy of the allele), and homozygosity rate were extracted in September 2022.

REDOME has more than 5 million registered donors submitted to HLA typing with identification of HLA-A, HLA-B, and HLA-DRB1 alleles. Different methodologies were used for HLA typing: PCR-SSO (Sequence-Specific Oligonucleotide), PCR-SSP (Sequence-specific amplification), Sanger sequencing and RT-PCR. REDOME is currently the third largest bone marrow donor's registry of the world and the largest registry with exclusively public funding, supported by the Brazilian Ministry of Health and coordinated by the National Cancer Institute (INCA) since 1998 [25].

All data are completely anonymous and distributed according to sex, race, and state/region of residence. Race was defined as self-reported skin color according to the Brazilian Institute of Geography and Statistics (IBGE) recommendations [26]. Potential donors must be

between 18 and 60 years of age, in good general health, with no comorbidities, no infectious or disabling disease, cancer, hematological or immune system disease, including rheumatoid arthritis and ankylosing spondylitis.

An overall type-I error (2-sided) probability of 5% was used. A logistic regression was employed to analyze the association between HLA-B27 positivity (dependent variable) and age, sex, race, and state/region of residence (independent variables). The R program version 4.2.2 (https://www.r-project.org/) was used for statistical analyses.

According to Resolution No. 510 of the National Health Council (CNS), research with databases, whose information is aggregated, without the possibility of individual identification, are exempt from registration and evaluation by the CEP/CONEP system (ethical analysis) [27]. All patients read and signed the informed consent form before inclusion, according to the REDOME rules and policies.

Results

From 1994 to 2022, a total of 5,389,143 healthy donors were included in this study, of whom 57.2% were females, mean age was 41.7 years old. **This sample represents 2.6% of the current Brazilian population, with its distribution among the five most important racial groups 60.1% in Whites, 7.8% in Blacks, 28.2% in*Pardos*(Browns i.e., mixed races), 3.5% in*Amarelos*(Yellows i.e., Asian Brazilians), and 0.4% in Indigenous** (Fig. 2). Regarding region of residence, 7.2% of the individuals included were from the North; 18.8% from the Northeast; 42.8% from the Southeast; 10% from Midwest; and 21.2% from the South.

The general HLA-B27 AF was 2.20%. The PP of HLA-B27 in this sample was 4.35% (CI95% 4.32–4.37%), **as expected**, regardless of gender (4.3% in males and 4.4% in females) and age. Homozygosity rate for the HLA-B27 was 1.3% of all the positives and only 0.06% for the general population.

Regarding racial groups, HLA-B27 PP was 4.85% in Whites; 2.92% in Blacks; 3.76% in Browns; 3.95% in Asian Brazilians; and 3.18% in Indigenous. Figure 3 shows the stratified by region HLA-B27 positivity on the three major racial groups in Brazil. Among the regions of residence, the PP was as follows: 3.62% in the North (N); 3.63% in the Northeast (NE); 4.29% in the Southeast (SE); 4.50% in the Midwest (MW); and 5.25% in the South (S) (Fig. 4). When the 27 Brazilian federal units were analyzed individually, the highest PP was seen in Santa Catarina (5.52%) in the South region, while the lowest PP (2.72%) was seen in Sergipe, located in the Northeast region (Table 2).

Discussion

Our data showed that the overall prevalence of HLA-B27 gene positivity in a representative national sample was 4.35% in Brazil. Furthermore, we observed a peculiar distribution along a latitude-dependent gradient with a significant increase from North (around 3.7%) to South (around 5.3%). The genetic inheritance formed by the miscegenation between the major parent populations since the beginning of colonization, slavery period, and other settlement processes with some later waves of immigration and internal migratory flows, could explain our findings. Within this context, the Brazilian Registry on Spondyloarthritis (RBE) demonstrated that ethnic background seems to be associated with different disease

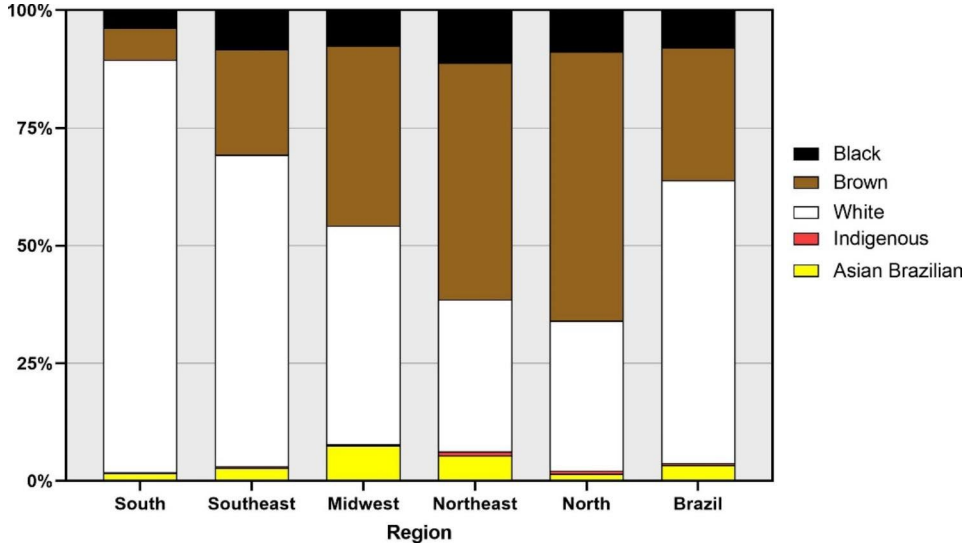

Fig. 2 The racial composition of the population samples of each region and of the total, by self-reported skin color, according to the REDOME database

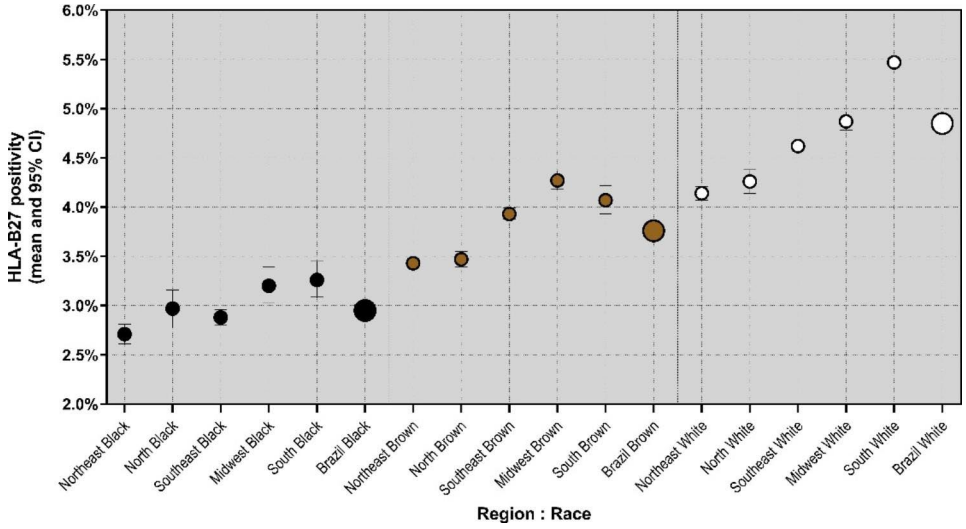

Fig. 3 HLA-B27% of positivity in the general healthy population, specified by region and race in Brazil (from the REDOME database)

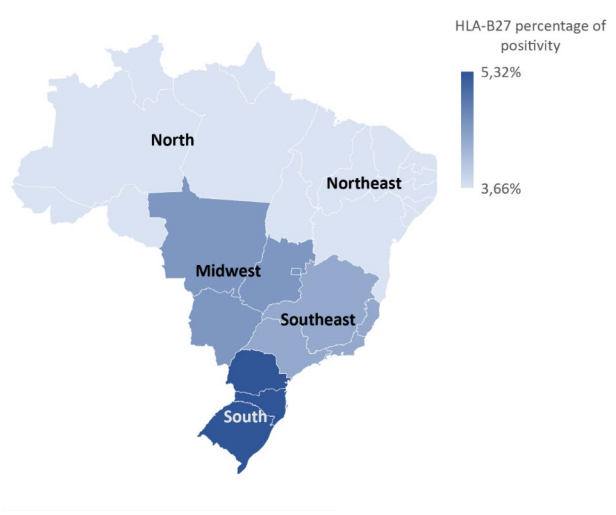

Fig. 4 HLA-B27% of positivity in the general healthy population, according to region of residence in Brazil (from REDOME database)

Table 2 HLA-B27% of positivity, according to each federal unit (FU) and region in Brazil

FU (Region)	HLA-B27 positivity	FU (Region)	HLA-B27 positivity
Acre (N)	3.54%	Paraíba (NE)	4.05%
Alagoas (NE)	4.21%	Paraná (S)	5.06%
Amapá (N)	3.17%	Pernambuco (NE)	3.54%
Amazonas (N)	3.01%	Piauí (NE)	3.62%
Bahia (NE)	3.13%	Rio De Janeiro (SE)	4.06%
Ceará (NE)	3.70%	Rio Grande Do Norte (NE)	4.41%
Distrito Federal (MW)	4.49%	Rio Grande Do Sul (S)	5.39%
Espírito Santo (SE)	3.84%	Rondônia (N)	3.95%
Goiás (MW)	4.96%	Roraima (N)	3.29%
Maranhão (NE)	3.88%	Santa Catarina (S)	5.52%
Mato Grosso (MW)	4.21%	São Paulo (SE)	4.23%
Mato Grosso Do Sul (MW)	3.97%	Sergipe (NE)	2.72%
Minas Gerais (SE)	4.75%	Tocantins (MW)	4.02%
Pará (N)	3.46%		

N = North; NE = Northeast; MW = Midwest; SE = Southeast; S = South

patterns, including more axial involvement in patients from the South region and more peripheral joint involvement in those from the North region, suggesting a possible relevant role of HLA-B27 in this conundrum of spectra and gradient [28, 29].

The HLA-B27 is an ancestral gene related to the common evolutionary history of mankind and it is present worldwide with higher positivity among Caucasians, the genetically unmixed native populations of North America (Eskimos) and the aborigines of Australia. On the other hand, it is less frequent among the Japanese and there is a lack of information about African and South American countries [30]. Furthermore, it is significantly higher in Western countries, especially among Caucasians (up to 15–16%), than in Middle Eastern, Asian, and Arab countries (0.3–6.8%) [8, 31, 32]. North Americans have a national prevalence of 6.1% (95% CI 4.6–8.2), according to the NHANES (National Health and Nutrition Examination Survey). Similar to our data, prevalence varied when data were analyzed according to race [7.5% (95% CI 5.3–10.4) among non-Hispanic Whites and 3.5% (95% CI 2.5–4.8) among all other US races combined. In Mexican Americans, the prevalence was lower [4.6% (95% CI 3.4–6.1)] [33].

Considering that the HLA-B27 plays a key role in SpA classification [34] and is of pivotal importance in referral strategies and early diagnosis [35], knowing the percentage of its positivity in the general healthy population is an important strategy to establish public health policies. In

addition to being an important diagnostic tool, it is associated with higher susceptibility to develop AS in first-degree relatives, with a 16-fold greater risk in HLA-B27 positive family members compared to HLA-B27 positive individuals in the general population (21% versus 1.3%, respectively) [36]. The presence of this allele was also associated with different AxSpA-related spectra and outcomes [37–39].

In North American patients with low back pain, the prevalence of HLA-B27 is quite similar to that of the general US population [40], but these data cannot be extrapolated to all different populations. Thus, the referral strategy for early recognition of axial SpA in primary care needs to consider each population specificity to avoiding system errors, diagnostic delays and providing better support and accuracy for clinicians [41, 42].

The prevalence of HLA-B27 is also important for other specialties that participate in the **multi-professional** management of AxSpA. From the ophthalmologist's perspective, the HLA-B27 is frequently associated with recurrent acute anterior uveitis (AAU), the most common extra-articular manifestation of AxSpA. It is associated with a five-fold increase in the 10-year cumulative incidence (0.2% in the general population and 1% in those HLA-B27-positive) [43]. In patients with AS, the prevalence of AAU was 0.4% in the HLA-B27-positive and 0.02% in the HLA-B27-negative [44]. Furthermore, Oliveira et al. showed that patients with AAU can present sacroiliitis by MRI regardless of axial symptoms [45]; however, further studies are necessary to prove AAU as an early marker of AxSpA. As for infectologists, the positivity for HLA-B27 can confer a more pronounced immune/inflammatory response leading to an effective clearance of some pathogens and lower probability of progression of some infections, such as influenza, HIV and HCV [46].

Considering the HLA-B27 heterogeneity throughout the world, it is worth investigating this gene positivity in a country with a huge continental geographic area (8.514.876 km^2) and highly mixed population (213.3 million inhabitants in 2022). Brazilian people have their genetic inheritance formed by a fusion of racial nuances in just over 520 years of history. Three Major parental populations merged in the genetic background: the original Tupi-Guarani Indians (Brazilian Native Amerindians); the European Caucasian Whites, especially of Portuguese and Dutch origin, during the colonization era after the navigations; and the Africans brought from the east coast of Atlantic Africa during the slavery period, when around 5 million enslaved Africans were brought to Brazil between the 16th and 19th centuries. The miscegenation intensified later, by the flow of immigration from other European or Asian communities after the industrial revolution and World War II, mainly Italians, Spanish, Germans, and Japanese. Approximately 6 million Europeans immigrate to Brazil in the 19th and 20th centuries [47]. Therefore, currently, a greater contribution of European ancestry can be found (0.66–0.77) followed by African (0.14–0.21) and Amerindian (0.08 to 0.17) contributions [48–51]. In the Latin American context, Brazil has the 5th largest European contribution, the 12th for the African component and the 10th for the Amerindian ancestry.

In addition, it is worth addressing the flow of internal migrations in Brazil. It was also quite heterogeneous in the 19th and 20th centuries, promoting the construction of the urban and rural society that we have nowadays. The search for better living conditions, economic stability, and job prospects, especially with industrialization, made many inhabitants of the North and Northeast regions migrate to the Southeast and South regions in the 60 and 80 s, while the search for agribusiness and livestock made the flow from the South to the Midwest of the country [52–56], explaining the HLA-B27 positivity increasing gradient that we found in our country as observed in Fig. 4. According to our results, there was significant interaction between race and region with HLA-B27 positivity, suggesting a two-way hand regarding these two demographic denominators (Fig. 3). This divergence between ancestry proportions of the same race categories (by self-declaration of skin color) from different regions of Brazil had already been demonstrated, proposing regional semantic differences in self-classification as white, brown, or black as one of its sources [47, 57]. Interestingly, in the federal capital (Brasília) and two Brazilian states (São Paulo and Minas Gerais), the HLA-B27 positivity were very close to the national mean demonstrating this dynamic migratory flow throughout the Brazilian regions as economic, political, and cultural catalysts for our country [58–60].

Our study has several strengths, such as a representative national data with a large sample size that involved healthy individuals without rheumatic complaints. However, it is important to point out some limitations, such as different lab methodologies for HLA-B27 typing, lack of lab centralization and the fact that we were unable to subtype the alleles. Another downside is the divergence between racial composition of the study sample and the estimated for the current Brazilian population, according to data from the last National Household Sample Survey (PNAD), 2021 [61], with an overrepresentation of Whites (60% vs. 43%, respectively), an underrepresentation of Browns (28% vs. 47%, respectively) and quite similar proportions of Blacks (8% vs. 9%, respectively).

Conclusions

Our findings provide the first national prevalence estimates of HLA-B27 in Brazil, a peculiar country characterized by immense ethnic diversity where cultures that are so different from each other coexist, originating a unique people and society. A nation with many accents, skin colors and multicultural backgrounds, but which are linked by language, flag, cuisine, and the spirit of being Brazilian, with its cordiality and "Brazilianness".

In the 50th anniversary edition since Schlosstein and Brewerton, our study highlights that HLA-B27 gene positivity in Brazil is around 4.35% with an increasing gradient from North to South regions and provides a framework for future research with higher external validity power to calculate the HLA-B27 sensitivity and specificity values and estimate the prevalence of AS in Brazil.

List of abbreviations

AAU	Acute anterior uveitis
AF	Allelic frequency
AxSpA	Ankylosing spondylitis
AxSpA	Axial spondyloarthritis
IBGE	Brazilian Institute of Geography and Statistics
PP	Proportion of positivity
REDOME	Brazilian Registry of Volunteer Bone Marrow Donors

Acknowledgements

Not applicable.

Authors' contributions

GGR and JSSBF were responsible for the statistical analyses. All authors interpreted the results. MMP, GGR and PDSB were the main contributors in writing the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

According to Resolution No. 510 of the National Health Council (CNS), research with databases, whose information is aggregated, without the possibility of individual identification, are exempt from registration and evaluation by the CEP/CONEP system (ethical analysis). All patients read and signed the informed consent form before inclusion, according to the REDOME rules and policies.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 15 February 2023 / Accepted: 13 April 2023
Published online: 20 April 2023

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