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HLA-Matched Unrelated Donors for Patients with Sickle Cell Disease: Results of International Donor Searches

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A B S T R A C T

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy. Hematopoietic stem cell transplantation (HCT) is the sole curative therapy for SCD, but few patients will have a matched sibling donor. Patients with SCD are mostly of African origin and thus are less likely to find a matched unrelated donor in international registries. Using HaploStats, we estimated HLA haplotypes for 185 patients with SCD (116 from a Brazilian center and 69 from European Society for Blood and Marrow Transplantation [EBMT] centers) and classified the ethnic origin of haplotypes. Then we assessed the probability of finding an HLA-matched unrelated adult donor (MUD), considering loci A, B, and DRB1 (6/6), in international registries. Most haplotypes were African, but Brazilians showed a greater ethnic admixture than EBMT patients. Nevertheless, the chance of finding at least one 6/6 potential allelic donor was 47% for both groups. Most potential allelic donors were from the US National Marrow Donor Program registry and from the Brazilian REDOME donor registry. Although the probability of finding a donor is higher than previously reported, strategies are needed to improve ethnic diversity in registries. Moreover, predicting the likelihood of having an MUD might influence SCD management.

INTRODUCTION

The most common inherited hemoglobinopathy worldwide [1], sickle cell disease (SCD) is caused by a single nucleotide substitution in the beta globin chain, determining the production of the mutant hemoglobin S (HbS), which polymerizes under stress conditions [2-4]. HbS polymerization determines hemolysis and vaso-occlusion, the key elements in SCD complications [1]. SCD can affect all organs, and some of its associated complications, such as cerebral vasculopathy, renal failure, and acute chest syndrome, have high morbidity and mortality. Although hydroxyurea and red blood cell (RBC) transfusions have improved SCD management, these therapies are not curative and do not prevent some severe complications [5]. Patients with SCD still face a decreased life span and quality of life.

Hematopoietic stem cell transplantation (HCT) is the sole currently available curative therapy for SCD [5-8]. The largest series reported to date, with 1000 patients who underwent HCT from an HLA-identical sibling donor, showed good overall

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survival (OS) and event-free survival (EFS) [6]. Nevertheless, few patients will have an identical sibling donor, and thus most patients will not benefit from an HLA-identical sibling HCT, justifying the development of matched unrelated donor (MUD) HCT to treat SCD. Some studies have reported high overall survival after MUD HCT, but a high rate of rejection and graft-versus-host disease (GVHD) are major obstacles for long-term cure. In addition to the difficulty of finding an MUD in this ethnic minority population, improvements in patient selection, conditioning, and GVHD prophylaxis are needed [9,10].

The donor search remains a major concern for these patients. SCD originated in sub-Saharan Africa, the Middle East, and India [11,12], and patients are mainly from African origin. These populations are underrepresented in registries worldwide [13-15]. It has been reported that patients of African origin have only ow as 16% of finding an unrelated donor, whereas at least one can be identified for up to 75% of Caucasian patients [16]. In another recent study, patients with an African background had the lowest chance of finding an 8/8 MUD [15]. To date, few studies have been performed in SCD populations to evaluate their likelihood of finding a matched unrelated donor in local registries [17-19].

Because of the importance of HCT in SCD, and considering the difficulty in identifying donors for ethnic minorities, we estimated the HLA haplotypes of 2 SCD populations of different ethnic backgrounds and calculated their probability of finding an allele-matched unrelated donor in international donor searches.

METHODS

Study Population

The study population was composed of 185 patients with SCD divided into 2 subcohorts: Brazilian patients who underwent HCT from an identical sibling donor or were not submitted to HCT and patients who underwent related or unrelated HCT from an HLA- identical or -nonidentical donor in transplantation centers reporting to the European Society for Blood and Marrow Transplantation (EBMT). In Brazil, all patients were followed at the University Hospital of Ribeirão Preto and had HLA data available or DNA samples stored for performing HLA typing. One patient had 2 siblings and another patient had 1 sibling in the same cohort. Siblings were excluded from HLA allele frequency estimation. In the EBMT cohort, all patients had HLA typing available, in intermediate or high resolution.

HLA Typing

For the Brazilian patients, HLA typing was performed by real-time polymerase chain reaction (RT-PCR) using sequence-specific oligonucleotides (SSO) in intermediate resolution. For the EBMT patients, HLA typing was performed by PCR-SSO, sequence-based typing, or next-generation sequencing in high resolution. We collected data on loci A, B and DRB1.

Alleles and Haplotype Estimation

For the Brazilian patients, because HLA typing was in intermediate resolution, we decodified National Marrow Donor Program (NMDP) codes using the multiple allele code (MAC) service from the NMDP (https://hml.nmdp.org/MacUI/) and estimated alleles based on previously described allele frequencies [16,20]. In some cases, the allele was estimated together with haplotype estimation. Hardy-Weinberg equilibrium (HWE) for loci and allele frequencies was assessed using PyPOP software [21]. We compared allele frequencies found in our population with the African American population described in the NMDP [16]. Haplotype estimation (HLA-A, -B and -DRB1 loci) was done using HaploStats (https://www.haplostats.org/haplostats?execution=e2s1).

Haplostats performs haplotype estimation based on the expectation-maximization (EM) algorithm [22]. In brief, the EM algorithm contains 2 phases: expectation (E), in which the probability of each haplotype is calculated based on the current haplotype estimates, and maximization (M), in which the results of the E phase are used to update the haplotype frequency estimates, yielding a new estimate. The E and M phases are repeated until they meet a convergence criterion [22,23]. The HaploStats database contains information from the NMDP registry on HLA haplotype frequency for the following ethnic groups: Caucasian, African American, Asian, Hispanic, and Native American. Based on the described haplotype frequency for each ethnic group, we defined the most likely ethnicity of each estimated haplotype as described elsewhere [24]; some haplotypes are described at high frequencies, defined as $\geq 1/1000$[22], in all populations and were defined as "common." Because "Hispanic" is not a primary ethnicity, it was not considered for haplotype classification. In 17 cases, family typing was available, and the family study agreed with the HaploStats estimation in all cases. In 33 cases, it was not possible to define the haplotype because the probabilities of estimation were very similar. The distribution of haplotypes according to ethnicity was compared between the Brazilian and EBMT cohorts using the chi-square test.

Donor Search

We performed donor searches using the World Marrow Donor Association algorithm for adult donors. The matching algorithm was set to match by haplotype. A potential donor was defined as a fully matched donor in HLA-A, -B, and -DRB1 loci (6/6 HLA match) in low resolution. A potential allelic donor was defined as a fully matched donor for the same loci in high resolution. For each patient, we assessed the probability of finding at least 1 potential donor and 1 potential allelic donor. Because registered donors are sometimes unavailable for cell donation, performing confirmatory typing from at least 5 potential allelic donors simultaneously is recommended [25]. For this reason, we also calculated the probability of having at least 5 potential allelic donors. Patients who underwent an MUD HCT were excluded from our donor searches. We did not include mismatched donors in our searches.

Ethical Considerations

This study was approved by the EBMT Paediatric Diseases Working Party, by the Ethics Committee of the Clinics Hospital of Ribeirão Preto, and by the Eurocord Scientific Committee.

RESULTS

Demography

A total of 185 patients were included in the study. The Brazilian cohort comprised 116 Brazilian patients, including 64 females (55%) and 52 males (45%). The SCD genotype was SS in 96 patients (83%), Sβ in 15 patients (13%) and SC in 5 patients (4%). Twenty-three patients underwent HLA-identical related HCT at the Ribeirão Preto Clinics Hospital. The EBMT cohort comprised 69 patients, including 36 females (52%) and 33 males (48%). The SCD genotype was SS in 47 patients (82%) and Sβ in 10 patients (18%). Patients underwent transplantation in 24 EBMT centers, mainly in France (n = 18), The Netherlands (n = 10), Belgium (n = 10), and Italy (n = 8). HCT was from an identical sibling donor in 54 patients, from an MUD in 10 patients, and from a mismatched unrelated donor in 5 patients.

HLA Allele and Haplotype Frequencies

Thirty-three different alleles were described in HLA-A, 67 in HLA-B, and 43 in HLA-DRB1. In both populations, HWE was neutral for loci A and DBR1 and deviated in locus B. Main HLA allele frequencies found in the whole cohort, in the Brazilian patients, and in the EBMT patients, and comparisons with the African American population described in the NMDP are summarized in Supplementary Table S1.

A total of 297 HLA-A, -B, and -DRB1 haplotypes were found. Because of the size of the cohort, we did not assess HWE and linkage disequilibrium. The most frequent haplotypes in the entire population (n = 297) were *A*01:01 B*08:01 DRB1*03:01* (n = 5; 2%), *A*36:01 B*53:01 DRB1*11:01* (n = 4; 1%), and *A*23:01 B*44:03 DRB1*07:01* (n = 4; 1%). In the Brazilian population, the most common haplotypes were *A*01:01 B*08:01 DRB1*03:01* (n = 5; 3%), *A*23:01 B*44:03 DRB1*07:01* (n = 3; 2%), *A*02:01 B*27:05 DRB1*01:01* (n = 3; 2%), and *A*03:01 B*58:02 DRB1*15:03* (n = 3; 2%). In the EBMT population, the most frequent haplotypes were *A*36:01 B*53:01 DRB1*11:01* (n = 3; 3%), *A*68:02 B*15:10 DRB1*03:01* (n = 2; 2%), and *A*23:01 B*07:05 DRB1*11:01* (n = 2; 2%). Two haplotypes were not described previously: *A*23:03 B*08:01 DRB1*03:01* and *A*24:03 B*35:43 DRB1*15:01*; both patients carrying these haplotypes underwent HCT from an identical sibling donor.

HLA Haplotype Ethnicity

Most HLA haplotypes from the entire population were classified as African American haplotypes (n/N = 162/297; 55%); 43 (14%) haplotypes were classified as common, 29 (10%) were classified as Caucasian, 21 (7%) were classified as Amerindian, and 43 (14%) could not be classified. The distribution of haplotypes was significantly different between the 2 cohorts (P = .006), with Brazilian patients showing a greater admixture compared with the EBMT population. In the Brazilian cohort (n = 181), the ethnic distribution was 45% African American (n = 81), 18% common (n = 33), 12% Caucasian (n = 22), and 9% Amerindian (n = 17); 28 haplotypes (15%) could not be classified. In the EBMT cohort (n = 116), 81 haplotypes (70%) were African American, 9 (8%) were common, 7 (6%) were Caucasian, 4 (3%) were Amerindian, and 15 (13%) could not be classified. Figure 1 shows the distribution of haplotype ethnicities among the 2 populations.

Donor Search

To assess the probability of finding an MUD in an international donor search, we excluded 10 patients from the EBMT cohort who underwent MUD HCT. Overall (n = 175), 141 (80%) patients had at least 1 potential donor; of these, 83 (47%) had at least 1 potential allelic donor, and 37 (21%) had at least 5 potential allelic donors.

In the Brazilian population (n = 116), 99 patients (85%) had at least 1 potential donor. Fifty-five of these patients (47%) had at least 1 potential allelic donor, of whom 28 (24%) had at least 5 potential allelic donors. The probability of finding at least 1 potential allelic donor was 68% in REDOME, 62% in the NMDP, 34% in European registries, and 21% in other registries. In the EBMT cohort, 42 of 59 patients (71%) had a potential donor. Twenty-eight patients (47%) had a least 1 potential allelic donor, and 9 (15%) had 5 or more potential allelic donors. The probability of finding at least 1 potential allelic donor was 33% in REDOME, 66% in the NMDP, 37% in European registries, and 26% in other registries. Table 1 summarizes donor search probabilities.

Haplotype Ethnicity and Donor Search

Among the 27 Brazilian patients with 5 or more potential allelic donors, 17 patients had at least 1 common haplotype, 8

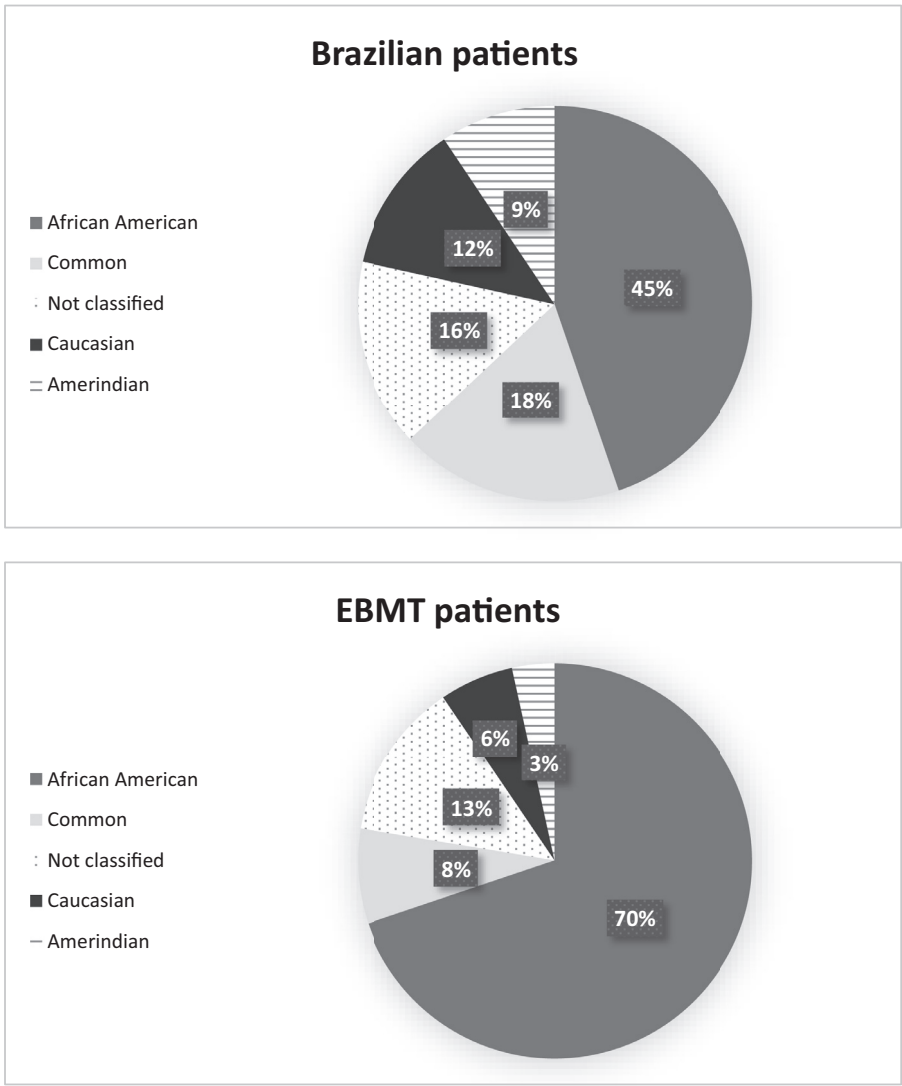

Figure 1. Frequency of haplotypes by ethnicity in each population.

Table 1

	Overall	Brazilian patients (n=116)	EBMT patients (n=59)	P-value
Potential donor (%)	141 (80)	99 (85)	42 (71)	
Allelic donor (%)	83 (47)	55 (47)	28 (47)	NS
≥ 5 allelic donors (%)	37 (21)	28 (24)	9 (15)	NS

had an African American haplotype, 3 had a Caucasian haplotype, and 4 had an Amerindian haplotype. Conversely, among the 57 patients with no donors available, 37 patients had at least 1 African American haplotype, 9 had an Amerindian haplotype, 8 had a Caucasian haplotype, and only 5 had a common haplotype.

In the EBMT cohort, among the 9 patients with 5 or more potential allelic donors, 3 had an African American haplotype, 3 had a Caucasian haplotype, 2 had a common haplotype, and 2 had an Amerindian haplotype. Interestingly, the 2 patients with an Amerindian haplotype had 32 and 12 potential allelic donors in the REDOME database, respectively; 1 patient had a donor in the NMDP, and none had donors in other registries. Among the patients without a donor (n = 34), 22 carried at least 1 African American haplotype; 20 of these patients had 2 African American haplotypes. Two patients had an Amerindian haplotype. The 2 patients who carried the never-described haplotypes were also in the group with no donors. Furthermore, considering the 10 patients who underwent matched unrelated HCT, 9 had exclusively African American haplotypes; however, in all these cases, the haplotypes were frequently described in the HaploStats database.

DISCUSSION

We have shown the differences in allele and haplotype frequencies between 2 SCD cohorts and in the likelihood of patients with SCD of finding an unrelated donor. This is the largest report on HLA allele frequencies in SCD and the largest donor search reported in these settings published to date.

The HbS mutation appeared first in Africa and India. The original distribution of the β^S allele coincides with the main areas affected by malaria, because HbS is protective against infection by the plasmodium parasite [11,26]. SCD originally was not seen in Northern European and Amerindian populations [27]; however, SCD spread to the Americas and Europe via the slave-trading routes from Africa to North, Central and South America.

Brazil received the largest number of African slaves in the Americas (http://www.slavevoyages.org/assessment/estimates), and interethnic relationships have been occurring since then. This is in line with our observations that despite the African origin of the SCD population, almost one-half of the HLA haplotypes in Brazilian patients were classified as common, Caucasian, or Amerindian. Previous studies analyzing the HLA haplotypes of donors registered in REDOME also showed a significant admixture in that population, and haplotype frequency was similar among the different ethnic groups [28,29]. Furthermore, the Brazilian SCD cohorts showed a high genetic admixture based on low-resolution HLA typing and other ancestry markers [17,30]. In contrast, although migratory movements from Africa to Europe have always existed, migration increased in the last century. Therefore, the ethnic admixture is less marked in the SCD population that underwent HCT in EBMT centers, explaining the higher rate of African haplotypes and the lower rate of haplotypes from other ethnicities seen in these centers.

Despite the differences in the HLA composition between the 2 populations, the chance of finding an unrelated 6/6 potential allele-matched donor in international donor search was similar in the 2 groups. Moreover, the probability of having 5 or more potential allelic donors was lower in the EBMT group but was low in both groups. This is worrisome because potential donors might be unavailable for various reasons, and most patients with few potential allelic donors end up having no donors at all. Although Brazilian patients had more Caucasian and common HLA haplotypes, most had at least 1 African haplotype, and most EBMT patients had 2 African haplotypes.

African donors are underrepresented in donor registries [13-15]. In 2014, a study assessing the probability of finding a matched donor in the NMDP registry according to ethnicity reported that African groups had a 16% to 19% chance of finding an 8/8 allele- matched adult donor, the lowest rate among the 21 racial/ethnic groups analyzed [16]. Another study reported that patients with previously undescribed HLA haplotypes, mostly nonwhite, had a 1.2% probability of finding an MUD in the NMDP [31]. More recently, Barker et al [15] analyzed the access to HLA MUD HCT in a racially distinct population of patients with hematologic disease; of 78 African American patients, only 17 received a 8/8-matched MUD [15]. In SCD settings, it was shown that patients had a 60% chance of having a potential 6/6-matched donor or an umbilical cord blood unit and a 20% chance of having a potential 8/8-matched donor in the NMDP registry [18,19]. Moreover, a Brazilian study comprising 126 patients with SCD who underwent HLA typing in low resolution showed that only 8% had a 6/6-matched potential donor in a subset of the REDOME [17]. Comparing these results with ours is difficult because of differing levels level of resolution and numbers of loci tested. Nevertheless, the probabilities were higher in our study, likely because of the international search, which is more realistic than single-registry searches, and because of the effective measures to improve donor representativeness, considering ethnic background, implemented by the NMDP, REDOME, and other registries around the world.

In our study, the probability of finding a donor was highest in the NMDP registry. The NMDP is the largest donor registry worldwide, with a wide diversity of ethnicities represented. As expected, the REDOME accounted for most matches in the Brazilian SCD population. In 2012, REDOME implemented strategies to improve the representativeness of all ethnic groups that compose the Brazilian population [28]. Moreover, one-third of the patients found donors in European registries, notably in the German registry, also reflecting the results of strategies aimed at ameliorating ethnic diversity throughout international registries. However, although higher than previously reported, the probability of having an MUD remains lower in patients with SCD than in those of other ethnic backgrounds, and most patients lack a matched unrelated donor. In addition, Africans show a high degree of genetic diversity [32] and a greater frequency of different HLA haplotypes [16], which might hamper representativeness. In this population, in the absence of an identical donor, alternative donor sources, such as cord blood and haploidentical HCT, might be considered.

The main limitation of our study is the size of the cohort, which precluded further HLA analyses. In addition, because it was not possible to estimate alleles and haplotypes from low-

resolution HLA typing, only patients typed in intermediate or high resolution could be included. Another limitation of the study was that because of data availability, our comparisons were performed at the 6/6 level rather than the current recommendation of 8/8 HLA typing for MUD HSCT [33]. We cannot exclude the possibility that the probability of finding a donor reported in this study would be lower if the HLA C locus were considered. Nonetheless, this study involves the largest donor search for HCT in patients with SCD in an international setting reported to date.

Although our results show a higher probability of finding donors for patients with SCD compared with previous reports, the overall likelihoods of having at least 1 allelic donor and at least 5 donors remain low. Further efforts are needed to keep improving donor availability in this population. Furthermore, our study might contribute to establishing specific algorithms for donor searches in patients with SCD. This is particularly important, because performing HCT at earlier age is associated with better outcomes in SCD [34], and knowing which patients are less likely to find an MUD might influence therapy management and even the indications for new treatments, such as gene therapy.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.07.015.

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