# Human leukocyte antigen matched unrelated donors for patients with sickle cell disease according to geographic origin: results of international donor searches.

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## Background

Hematopoietic stem cell transplantation (HSCT), the only currently largely available curative therapy for sickle cell disease (SCD), remains hampered by the lack of histocompatibility between patients and stem cell donors. Most patients will not have a suitable human leukocyte antigen (HLA) matched sibling donor. In addition, SCD affects ethnic groups that are under-represented in stem cell donor registries worldwide.

## Objective

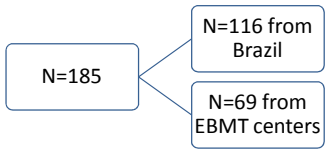
To assess the probability of having a potential allelic HLA matched unrelated donor (MUD) for *HLA-A,HLA-B* and HLA-*DRB1* loci in international donor registries for patients with SCD.

## Methods

All patients had HLA typing available at intermediate or high resolution. For intermediate resolution, using the National Marrow Donor Program (NMDP) code, we assigned alleles based on allele frequencies.

HLA haplotype estimation using HaploStats (https://haplostats.org), which describes HLA haplotype frequency from the NMDP registry for the following ethnic groups: Caucasian, African-American, Asian, Hispanic and Native American. Because Hispanic is not a primary ethnicity, we did not consider this group in our analyses. Based on haplotype frequency of each ethnic group, we defined the most likely ethnicity for each estimated haplotype.

Unrelated donor search was done using the World Marrow Donor Association (WMDA) algorithm, which is based on haplotype matching. A potential allelic donor was defined as a full match high resolution 6/6 donor. Because it is described that testing at least 5 potential allelic donors simultaneously increases the chances of having a real donor, we assessed the probability of finding at least 1 and at least 5 potential allelic donors. Patients who received HSCT from MUD were excluded from donor searches (n=10). Comparisons of probabilities of having potential allelic donors between Brazilian and EBMT cohorts were performed by chi-square.




## Results

### Demography

| | Brazil, n=116 (%) | EBMT, n=69 (%) |
|---|---|---|
| SCD genotype | | |
| SS | 96 (83) | 47 (82) |
| Sβ | 15 (13) | 10 (18) |
| SC | 5 (4) | |
| Gender | | |
| Female | 64 (55) | 36 (52) |
| Male | 52 (45) | 33 (48) |
| Underwent HSCT | | |
| HLA identical sibling | 23 | 69 |
| HLA identical unrelated | 23 | 59 |
| | 0 | 10 |

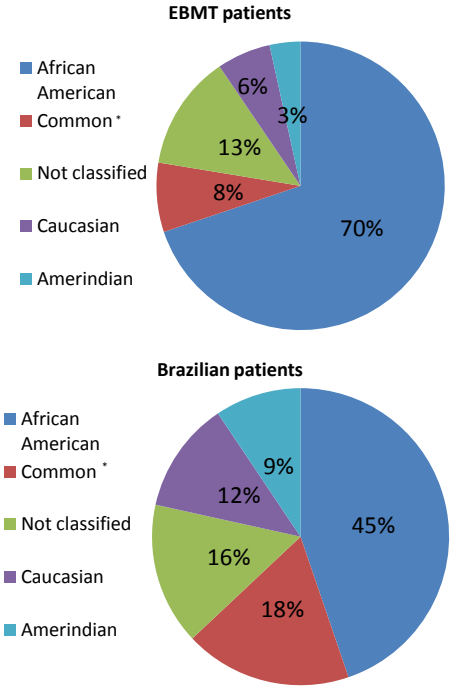
Abbreviations: HLA: histocompatibility leukocyte antigen; HSCT: Hematopietic stem cell transplantation; SCD: sickle cell disease

### Probability of finding a donor in international donor search, overall and by population

| | 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 |

* EBMT patients who received HSCT from a HLA identical unrelated donor were excluded from donor searches (n=10)

### Frequency of haplotypes by ethnicity (NMDP classification) in each population




* Haplotypes with frequency ≥1:1000 in all ethnic groups were named common

## Conclusions

Migration from Africa to Brazil started at the colonial period, and inter-ethnic admixture has been occurring since then, explaining the higher diversity observed in the Brazilian cohort. Despite differences in ethnic composition, chances of having at least one potential allelic MUD are identical, probably because carrying at least one African or Amerindian haplotype decreases the chances of a full HLA matching. Although we demonstrated higher probabilities of finding a potential allelic MUD in SCD than previous studies, the chances are still low, therefore further strategies are required to increase donor representativeness for SCD. In this setting, alternative sources, such as haploidentical HSCT and cord blood, should be considered. Also, our study might help to predict the probabilities of finding a MUD for patients with SCD. This is important because, given that HSCT in SCD has better results if performed at earlier age, knowing which patients are less likely to find a MUD might influence therapy management.

There are no conflicts of interest to disclose.
This work was supported by the Centre Scientifique de Monaco and by CAPES.
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