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Letter to the Editor

Bone marrow transplant donor recruitment strategies to maximize, optimize, and equalize recipient chances of an acceptable match

Dear Editor,

The number of named alleles of the human leukocyte antigen (HLA) genes, HLA-A, HLA-B and DRB1 are 3399, 4242 and 1883,[1,2] respectively. Owing to analyses of the frequencies and distributions of these alleles worldwide, 246 HLA-A alleles, 367 HLA-B alleles and 226 HLA-DRB1 alleles are now common or well documented.[3] As the first step in finding a bone marrow match for a new patient, an algorithm scans the entire registry every day and displays possible donors that match the recipient's genotype. Then, new and complementary HLA typings are requested for loci DQB1 and C and allelic level for Class II, and if the donor is in good health, a confirmatory high-resolution HLA test is performed.

When no compatible donor can be found, the family and friends of the patient engage themselves in campaigns to recruit possible donors, hoping that a match will be found among the new volunteers. These recruitments have sensitized many to the need for bone marrow donation, and approximately 25% of the entries ($n = 956{,}330$) in the Brazilian Bone Marrow Donor Registry (REDOME) were obtained from 1431 campaigns to recruit bone marrow donors in 593 Brazilian cities. In 2010, more than 270 such campaigns accounted for 30.1% of new donors. The Health Ministry has limited the annual reimbursement for HLA typings to 300,000 new entrants in the REDOME since 2012 and increased, proportionally, financial resources to improve hematopoietic cell transplantation (HCT). Although REDOME entries cover 97.4% of Brazilian Municipalities, the proportion of entries per city according to population varies greatly, ranging from 0.002% to 23.543% (median: 0.584%).

Two main factors must guide recruitment: (1) the probability of finding a match based on the frequency distribution of the alleles in the population, and (2) the HLA allele frequency in diseases that could benefit from HCT. In a more simplified model, an equal chance to find a donor match should be based on the Brazilian distribution of HLA haplotypes. As haplotypes have a genetic background, cities with well-defined ethnic colonization or a low migration index will have a smaller number of haplotypes with less diversity. The HLA diversity among the volunteers recruited during 18 of these campaigns was compared with the diversity in random samples (consisting of 350, 1250, and 2250 entries) generated from the REDOME. The results showed that the number of haplotypes was directly proportional to the number of new donors (Figure 1). The number of haplotypes also decreases as a function of linked disequilibrium. This loss in diversity due to imbalanced recruitment increases the costs to the Health Ministry in terms of reimbursements for HLA typing to laboratories. It also reduces the chances of finding a bone marrow match for some individuals who share haplotypes that are more common in the REDOME. Moreover, additional costs will also be incurred related to complementary tests to define possible donors among these new entries.

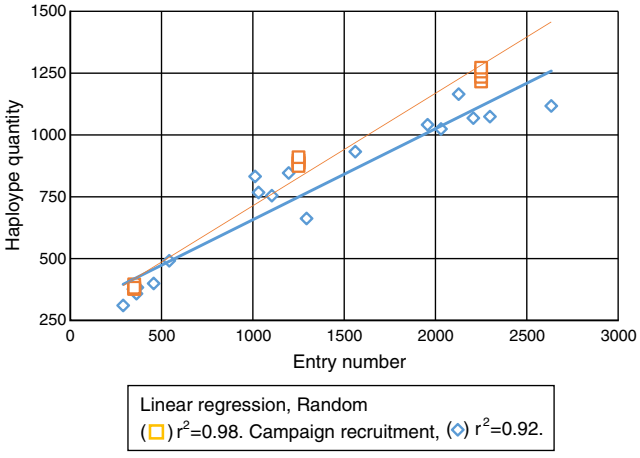

Figure 1 – Haplotype quantity and number of recruits in campaigns or randomly selected entries ($n = 350$, 1250, and 2250). Number of haplotypes calculated with Arlequin.[8]

A new recruitment protocol that considers the experiences of other large registries,[4,5] including the recruitment and maintenance of donors, is proposed. Campaigns should be followed by complementary steps before initial laboratory typing of the samples. A phone call should be made to the potential recruit to confirm the proposal to adhere to the

Table 1 – State-estimated population, number of municipalities, actual number of entries (donors), number of municipalities without donors in the state and percentage of the population not represented in the Brazilian Bone Marrow Donor Registry (REDOME).

State	Estimated population	Number of municipalities	Number of donors	Donors per estimated population	Municipalities without REDOME entries	Sum of the populations of these municipalities	Population without REDOME volunteers (%)
Acre	803,513	22	2948	0.0037	4	32,718	4.1
Amazonas	3,938,336	62	30,588	0.0078	19	404,793	10.3
Roraima	505,665	15	7105	0.0141	1	9488	1.9
Pará	8,165,436	144	83,988	0.0103	1	15,446	0.2
Tocantins	1,515,126	139	29,260	0.0193	1	1814	0.1
Maranhão	6,904,241	217	14,913	0.0022	33	425,475	6.2
Piauí	3,204,028	224	67,281	0.0210	14	50,528	1.6
Rio Grande do Norte	3,442,175	167	62,565	0.0182	5	16,570	0.5
Paraíba	3,972,202	223	54,982	0.0138	8	26,823	0.7
Alagoas	3,340,932	102	34,001	0.0102	2	12,340	0.4
Sergipe	2,242,937	75	22,355	0.0100	1	3170	0.1
Bahia	15,203,934	417	105,402	0.0069	14	157,819	1.0
Minas Gerais	20,869,101	853	428,704	0.0205	16	90,721	0.4
Santa Catarina	6,819,190	295	156,741	0.0230	2	21,853	0.3
Rio Grande do Sul	11,247,972	497	301,651	0.0268	7	16,758	0.1
Mato Grosso do Sul	2,651,235	79	119,715	0.0452	1	5150	0.2
Mato Grosso	3,265,486	141	51,041	0.0156	4	11,538	0.4
Goiás	6,610,681	246	129,948	0.0197	8	30,461	0.5
Total	104,702,190	3918	1,703,188	0.0163	141	1,333,465	1.3

In AC (Acre), AM (Amazonas), RR (Roraima), MA (Maranhão), and PI (Piaui), >1.5% of the population do not have entries in the REDOME. Every municipality of the states of Amapá, Ceará, Espírito Santo, Paraná, Pernambuco, Rio de Janeiro, Rondônia, São Paulo and the Federal District have volunteers registered in the REDOME.

registry, so that he or she can rethink the decision. This measure will permit us to ascertain whether or not the individual will actively participate in the search for bone marrow compatibility. Another measure is to limit the number of new donors in campaigns in cities with less than 20,000 citizens and a low migration index. These measures could result in the following: (1) great fidelity and improved availability of donors, as their contact information will be checked via the phone call, (2) savings for the Health Ministry and society, as the costs of typing samples of people who do not give their consent at the moment of donation will diminish, and (3) a better representation of haplotypes in cities, reducing duplicates related to family background.

Specific recruitment should also be implemented to reduce differences among self-declared race/color.[6] Our preliminary results show significant differences related to race/color with compatibility in 9 of 10 and 10 of 10 loci in the REDOME.[7] The rational use of public resources to increase HCT since 2012 may be guided by technical information to define recruitment campaigns for the REDOME. New donors are still needed, but their recruitment should not be adjusted according to the wishes of the patient's family neither defined by the Justice system in reimbursement campaigns for HLA typing based on family plea. Moreover, some cities and even states are underrepresented in the REDOME (Table 1).

Finally, the size (number of entries) of the REDOME should be augmented to provide a reasonable chance of HCT for patients and complement the availability of samples in Brazilian cord and placenta blood banks (BRASILCORD) as well as internationally.

Conflicts of interest

The author declares no conflicts of interest.

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