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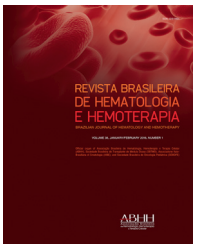

Scientific Comment

Understanding population-wide haplotype frequencies of human leukocyte antigen (HLA) alleles in linkage disequilibrium is important for hematopoietic stem cell transplantation☆

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Linkage disequilibrium (LD) refers to the non-random association of alleles at different gene loci. Alleles that always randomly sort independent of others at surrounding foci are said to be in linkage equilibrium. For two alleles, say A and B, the probability of an individual having one haplotype AB is a function of the population frequency of A (pA) and B (pB). If these two alleles are in complete linkage equilibrium and so are independently sorted, the true population frequency of the haplotype AB would equal the product of pA and pB. So $pAB - (pA \times pB) = 0$.

When allele A and allele B do not independently sort, or are linked together despite being on different loci, the true population frequency of the haplotype AB exceeds the product of their individual frequencies. So $pAB - (pA \times pB) > 0$. The value of this difference represents the co-efficient of linkage disequilibrium. The higher this positive value, the stronger the linkage between these alleles, i.e. the higher the LD.

Of course, the coefficient of LD calculation gets more complicated the more alleles being studied in defining haplotypes of interest in various diseases. In particular, the major histocompatibility system has a significant number of genes exhibiting strong linkage disequilibrium.[1] This has an important bearing on ideal donor identification for hematopoietic stem cell transplantation (HSCT) as it is related to risk of graft versus host disease (GVHD) and immunogenicity for graft versus tumor effect.

Coefficients of linkage disequilibrium determined from human leukocyte antigen (HLA) allele frequencies can help predict probability of allele/haplotype matches when only low-resolution donor HLA typing is available

In the context of HSCT, current selection of ideal unrelated donors is based on allele level matching of human leukocyte antigen (HLA)-A, -B, -C, -DRB1, -DQB1 and more recently -DPB1 (permissive or non-permissive mismatches). Diseases requiring allogeneic HSCT particularly in adults are most often of an acute nature and delays to HSCT often result in disease progression, significant morbidity and debilitation, precluding HSCT as a curative option. This implies that once a patient in need of HSCT is identified, and found to have no available matched sibling donor, the search for a matched unrelated donor (MUD) has to proceed rapidly. If a MUD cannot be identified, having this knowledge in a timely manner facilitates early clinical decision-making whether to transplant with an

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alternative donor (cord blood or haploidentical donor) or proceed with a non-transplant strategy. In the era prior to having search algorithms based on haplotype frequencies, searches for 10/10 MUDs in different European populations ranged from four to 11 weeks.[2] This is where an understanding of the distribution of the abundant HLA-alleles in the donor pool population is crucial.

The probability of an allele level match can be inferred from HLA serologic typing when population frequencies of each allele are known. Transplant centers in the United States, Europe and Japan now use search algorithms developed from frequencies of common/well-documented HLA alleles seen in their regional/national donor registries.[2–4] Haplogic was developed based on US haplotype frequency data and has, since 2006, facilitated searches by rapidly determining the probability of MUD availability.[5,6] Similar haplotype frequencies have been studied in other populations resulting in search algorithms such as Optimatch (Germany) and EasyMatch (France). Most of these donor populations are significantly homogeneous including the US registry where Caucasians are over-represented therefore probability estimates are limited for application to non-Caucasian patients.[6,7] Large databases are needed for ethnically diverse populations. The study by Costantino et al.[8] reviewing donors in a regional yet ethnically diverse database (LIGH) in Brazil is an example of one from which search algorithms could be constructed to facilitate timely donor identification.

Human leukocyte antigen (HLA) haplotype frequencies calculated for alleles in high linkage disequilibrium may predict for non-HLA antigen match versus mismatch

There is increasing evidence that patients with one or two frequently occurring haplotypes (FH) encompassing both HLA and some non-HLA antigens in high linkage disequilibrium experience less acute GVHD.[9–11] These non-HLA genes include genes that could regulate the immune response [e.g. tumor necrosis factor (TNF)-block genes, major histocompatibility complex class I polypeptide-related sequence A/B (MICA/B) and microsatellite markers].[9] The association with less acute GVHD may also be explained by the increased probability that patients with these frequent haplotypes will also match at minor histocompatibility antigens that are not routinely included in both donor and patient HLA typing.

Presence of FH also predicts probability of finding HLA-matched donors. Patients with at least two frequent HLA haplotypes in a Dutch registry of leukemia patients were most likely to find a 10/10 matched unrelated donor in a significantly shorter time than those without FH (35 versus 59 days).[9]

To summarize, population based studies of both HLA allele level and haplotype frequencies and the resulting estimates of LD facilitate the development of algorithms to speedily target stem cell donor searches. These studies also enhance our ability to recognize frequent haplotypes of both HLA and non-HLA antigens in high LD that could affect post-transplantation outcomes.

Conflicts of interest

The author declares no conflicts of interest.

REFERENCES

1. Nowak J. Role of HLA in hematopoietic SCT. Bone Marrow Transpl. 2008;42 Suppl. 2:S71–6.
2. Tiercy JM. Unrelated hematopoietic stem cell donor matching probability and search algorithm. Bone Marrow Res. 2012;2012:695018.
3. Cano P, Klitz W, Mack SJ, Maiers M, Marsh SG, Noreen H, et al. Common and well-documented HLA alleles: report of the ad-hoc committee of the American society for histocompatiblity and immunogenetics. Hum Immunol. 2007;68(5):392–417.
4. Mack SJ, Cano P, Hollenbach JA, He J, Hurley CK, Middleton D, et al. Common and well-documented HLA alleles: 2012 update to the CWD catalogue. Tissue Antigens. 2013;81(4):194–203.
5. Dehn J, Setterholm M, Buck K, Kempenich J, Beduhn B, Gragert L, et al. HapLogic: a predictive human leukocyte antigen-matching algorithm to enhance rapid identification of the optimal unrelated hematopoietic stem cell sources for transplantation. Biol Blood Marrow Transpl. 2016;22(11):2038–46.
6. Maiers M, Gragert L, Klitz W. High-resolution HLA alleles and haplotypes in the United States population. Hum Immunol. 2007;68(9):779–88.
7. Pidala J, Kim J, Schell M, Lee SJ, Hillgruber R, Nye V, et al. Race/ethnicity affects the probability of finding an HLA-A, -B, -C and -DRB1 allele-matched unrelated donor and likelihood of subsequent transplant utilization. Bone Marrow Transpl. 2013;48(3):346–50.
8. Costantino PR, Zeck SC, da Silva WA, Bicalho MG. Human leukocyte antigen allele linkage disequilibrium and haplotype structure in volunteer bone marrow donors of Paraná State. Rev Bras Hematol Hemoter. 2017;39:229–36.
9. Joris MM, Lankester AC, von dem Borne PA, Kuball J, Bierings M, Cornelissen JJ, et al. Bone Marrow Transpl. 2013;48(4):483–90.
10. Joris MM, Lankester AC, von dem Borne PA, Kuball J, Bierings M, Cornelissen JJ, et al. The impact of frequent HLA haplotypes in high linkage disequilibrium on donor search and clinical outcome after unrelated haematopoietic SCT. Bone Marrow Transpl. 2013;48(4):483–90.
11. Morishima S, Ogawa S, Matsubara A, Kawase T, Nannya Y, Kashiwase K, et al. Impact of highly conserved HLA haplotype on acute graft-versus-host disease. Blood. 2010;115(23):4664–70.