The significance of regional HLA heterogeneity in determining the optimal donor recruitment strategy in Greece.

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Purpose of the study: The geographic diversity of Human Leukocyte Antigens (HLA) is a major hurdle during patient-matched donor selection in allogeneic hematopoietic stem cell transplantation. Our previous work [1] revealed the importance of demographic history in the evolution of HLA variants, i.e. influenced by allelic heterogeneity, balancing selection, etc. Also, subsequent analyses (unpublished data) using donors, i.e. Cord Blood Units (CBUs) and Bone Marrow Donors (BMDs), from the Greek public donor banks and registries highlighted the importance of diversity over quantity in HLA donor banking.
To this end we aim to a) assess, by using state of the art statistical methods, that the efficacy of a donor registry is dependent not only on the size but also the diversity of HLA haplotypes, and b) test whether the estimated cumulative HLA matching coverage is improved by using geographically-oriented donors within a highly HLA-heterogeneous Greek population.
Methodology: We used 5-loci HLA data (4-digit resolution) of 38,940 donors (1,087 CBUs and 37,853 BMDs) from the 3 Public CB Banks and the Center of BMDs of Greece, all under the auspices of the Hellenic Transplant Organization. Haplotypes were estimated using the EM algorithm both for the total and the stratified by the 5, geographically-defined, Greek Health Regions groups of donors. Given their frequencies, the estimated subsequent 5-loci genotypes and their frequencies were calculated according to the frequencies of the combined haplotypes.
In order to adjust for limitations of the EM algorithm that may lead to loss of regional diversity all clusters were merged and analyses were performed by taking into account the percentage of each cluster to the real Greek population as weight.

Finally, the probability for a random patient to find at least one matching donor from a given cluster was calculated as:

$$p(N) = 1 - \sum_{i=1}^{G} p_{r_i}(1 - p_{d_i})^N$$

Where N is the size of the donor population and p_{r_i} and p_{d_i} the genotype i frequencies in the recipients and donor populations, respectively.

Results: The highest probability of finding a compatible donor was achieved when donors and patients were from the same cluster, reflecting a similar genetic architecture (Figure). This advantage was pronounced as matching criteria became more stringent, especially when requiring 10/10 compatibility.
Searching for a donor using the total Greek cohort represented the second highest probability, reflecting the importance of diversity in large registries. In contrast, the worst probabilities were observed between clusters characterised by increased HLA heterogeneity due to population structure effects (e.g. Crete).

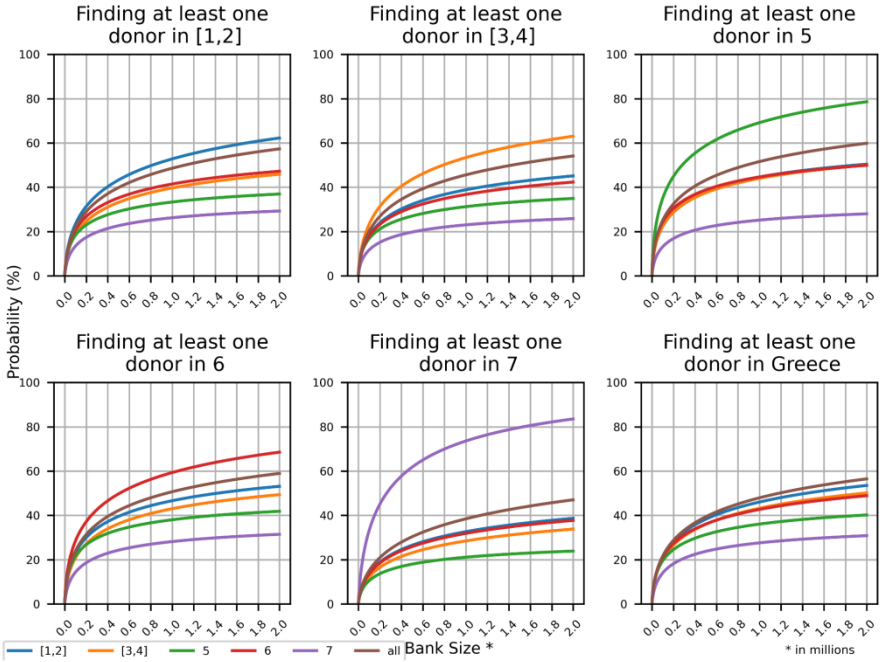

Figure. Probability of finding at least one donor between the Health Region Clusters.
Patient-donor matching compatibility used 10/10 for 5-HLA loci (HLA-A, -B, -C, -DRB1, DQB1). Health Region Cluster (1): Attica; (2): Peiraius, North & South Aegean; (3):Central & Western Macedonia; (4):Eastern Macedonia & Thrace; (5): Thessaly & Central Greece; (6): Peloponesse, Ionian Islands, West Greece, Epirus; (7) Crete.

Conclusion: Our results unravel the importance of regional donor banks and verify that increasing diversity over quantity of HLA donors may improve the probability of finding a MUD in populations with high HLA diversity, and, thus, the cost-effectiveness of a HLA donor registry required to cover the transplantation needs of the Greek population.

Reference

Latsoudis H., Stylianakis E, Mavroudi I, et al. Significance of regional population HLA immunogenetic datasets in the efficacy of umbilical cord blood banks and marrow donor registries: a study of Cretan HLA genetic diversity. *Cytotherapy* 2022; 24(2): 183-192, doi.10.1016/j.jcyt.2021.07.010.