P1352 THE INTRA-POPULATION HLA DIVERSITY IN CRETE AND THE IMPORTANCE OF THE REGIONAL PUBLIC UMBILICAL CORD BLOOD BANK IN HLA-BASED DONOR SELECTION FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Topic: 22. Stem cell transplantation - Clinical

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Background: Allogeneic hematopoietic stem cell transplantation is the elective treatment for several life-threatening hematologic diseases. The high genetic diversity of HLA across populations, combined with the complexity of its molecular variation and the limitations of traditional HLA typing, confines the effectiveness of matched unrelated donor registries and public umbilical cord blood banks (UCBB), particularly in populations with ethnic minorities.

Aims: Prompted by our recent study describing a considerable HLA diversity between a representative Cretan cohort and the donors of DKMS, we set out to unravel the effect of potential intra-population diversity on HLA distribution. We used samples stratified by a specific Prefecture of origin aiming to signify the possible existence of a severe shortage of genetically HLA compatible samples and to justify the importance of the regional UCBB for an HLA-based donor selection in Crete.

Methods: A combined cohort of 1,744 representative samples from the four Prefectures of Crete (Heraklion, Lasithi, Rethymno, Chania) were typed for HLA Class I (-A, -C, -B) and Class II (-DRB1, -DQB1) loci using 2nd field NGS. Fisher’s exact test was used for the comparison of g-grouped alleles with frequencies corrected by Bonferroni and of haplotypes estimated by Hapl-o-Mat with frequencies f≥1/2n. The average probability of finding a >6/10 compatible donor within and across the four Prefectures was also estimated using custom scripts in R.

Results: In the combined cohort, HLA-B exhibited the highest allelic variability (n=74) and number of unique alleles (n=21/39). While the diversity of all loci, except for HLA-C, was attributed to the largest Prefecture, Heraklion, the high number of unique HLA-C alleles in Chania (n=4/8) contributed to both intra- and inter-population diversity. While the distribution of the most frequent common alleles across the 5 loci were similar between all Prefectures, significant differences (n=27 alleles) were revealed when each Prefecture was compared to the remaining pooled Cretan cohort. Such analyses substantiated the diversity of Chania (37.04%) mostly versus the geographically and genetically isolated Prefectures of Lasithi and Rethymno. Significant diversity was also observed among the 1,406 inferred haplotypes, with 80.2% being unique. The distribution of the top 10 out of the 21 common haplotypes in the combined cohort was 0.63%-1.38%. However, the most common haplotypes A*24:02~B*35:02~C*04:01~DRB1*11:04~DQB1*03:01 (1.38%) and A*33:01g~B*14:02g~C*08:02g~DRB1*01:02g~DQB1*05:01g (1.38%) were mainly attributed to Rethymno with frequencies of 3.35% and 1.96%, respectively. The low frequency of A*24:02~B*35:02~C*04:01~DRB1*11:04~DQB1*03:01 in Heraklion (0.97%) and Chania (0.73%) resulted in a significant difference (p=5.8e-05) when both were compared to Rethymno. The diversity of Chania may underlie the higher probability of not finding a compatible donor in Lasithi and Rethymno (i.e. >30%) or Heraklion (i.e. >20%). Besides the lower distribution of the most common haplotypes, Heraklion seems a good pool for finding potential donors since 46.8-49.1% of common HLA haplotype needs are met between the former and each Prefecture.

Summary/Conclusion:

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The in-depth immunogenetic profile of the Cretan population justifies the reported HLA diversity compared to the European populations of DKMS. The significant differences in the estimated haplotype frequencies between the Cretan Prefectures substantiates the importance of geographically or genetically isolated population clusters in the regional UCB banking and donor selection.