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HLA Allele Distribution in Romanian People: Clinical Significance and Utility Related to Population Genetic Background

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Abstract

Knowledge of allele frequencies of the human leukocyte antigen (HLA) system is essentially important in the search for unrelated kidney and bone marrow donors. The Romanian Caucasian population is heterogeneous and the HLA genotyping of the most common alleles brings information on HLA polymorphisms. We have characterized the HLA genetic profile of regional populations in Romania. By this we have targeted the HLA allele frequencies of our Romanian people in order to make possible several clinical applications: the search for best match donors, disease associations, genetic background of rare diseases and disease susceptibility. Our study was carried out on 8252 people typed for the HLA-A, B and DRB1 loci, belonging to four main regions of Romania. The alleles were characterized by the polymerase chain reaction sequence-specific oligonucleotides (SSO) method using the LabType SSO kit, sequence-specific primers (SSP) INNO-TRAIN SSP low resolution kit and INVITROGEN SSP high resolution kit. The most common alleles found in the Romanian population are: HLA-A*01, A*02, A*03, A*11, A*24; HLA-B*18, B*35, B*44, B*51 and HLA-DRB1*01, DRB1*03, DRB1*07, DRB1*11, DRB1*13, DRB1*15, DRB1*16. More than half of them are non-homogeneously spread in Romania. Based on our HLA alleles analysis we think this study provide useful information and the results can serve as a starting point for future research. In order to obtain reliable results concerning factor analysis in the area of allele frequencies, the number of regions included in the study needs to be increased.

Keywords: HLA allele frequencies; Polymorphism; HLA allele distribution; Genetic background

Opinion Article

The HLA complex is defined by the genes of the Major Histocompatibility Complex (MHC). These loci play a key role in the immune system response and are among the most polymorphic in humans, comprising more than 20 genes, but only six loci are routinely typed by laboratories, i.e. HLA-A, -B, -C for class I and HLA-DRB1, -DQB1 and -DPB1 for class II. According to the IPD-IMGT/HLA Database (Release 3.28.0, April 2017), at present more than 16,000 alleles (12,351 for HLA class I and 4,404 for HLA class II) have been reported.

These loci have been studied extensively for at least four reasons: (i) for donor-recipient matching in organ and stem cell transplantation success [1,2] (ii) due to associations between polymorphisms and response to infectious diseases [3] or susceptibility to autoimmune diseases [4,5] (iii) due to associations between particular HLA polymorphisms and increased risk for adverse drug reactions [6,7] (iv) the HLA region is also commonly analyzed in anthropology studies [8].

In Romania, during the last decade, through both National Transplant Agency and the Volunteer Bone Marrow Donors National Registry, the solid organ and bone marrow transplantation program has been greatly developed. The number of transplant procedures increased year by year. It is well known that an appropriate HLA matching between recipient and donor is the key to a successful transplant outcome, especially when we talk about the bone marrow transplantation. Well known HLA genetic profile of the population it is very helpful for disease associations, genetic basis of rare diseases and disease susceptibility.

In this context, it becomes very important to know the HLA allele frequencies and their distribution in different regions of the country. Romania's population includes, besides Romanians, other ethnic groups such as Germans, Hungarians, Tatars, Turks, Russians and Gypsies.

A first study on HLA polymorphism in Romania was performed by Prof. Nicole Suciu-Foca and the results were published in 1992 in the Tissue Antigens Journal [9]. This study was carried out on a small group of people (83 Romanians). The HLA typing was done using conventional serology combined with PCR amplification of HLA-class II genes.

By contrast, in our study [10] there were analyzed more than 6000 HLA alleles (6760-A, 6415-B and 6066-DRB1) and moreover, the samples were collected from all over the four main regions of Romania: Wallachia, Moldavia, Transylvania and Banat.

The results showed that, in terms of HLA allele frequencies, nationwide distribution in Romania is much closer to countries located in the Western part of Europe (France, Germany and Italy) than to Eastern and South-Eastern countries. However, it was revealed that in Banat and Wallachia there are some influences from Bulgaria, Turkey and Serbia.

The study represents our first approach of HLA genotype characterization. In the future, we aim to extend our analysis of Romanian population on C, DQB1 and DPB1 loci at high resolution level. Taking into account the increasing number of bone marrow transplants in our country and the initiation of the HLA-haploidentical bone marrow transplantation, we believe that it would be extremely beneficial to analyze the HLA haplotypes frequencies and distribution.

The most frequent alleles (>10%) in Romania are: HLA-A*02 (29%), A*01 (14.3%) and A*24 (11.2%); HLA-B*35 (16%), B*18 (11%); HLA-DRB1*11 (18.5%), DRB1*03 (11.3%) and DRB1*13 (10.5%) (Figures 1-3).

In the main four regions of the country the situation is different due to migration influences during history. In Transylvania, A*01 is the most frequent allele (21.2%) and DRB1*04 has the lowest frequency (3.3%). This aspect is statistically significant ($p<0.05$) in comparison to other Romanian regions and European countries. In particular, B*52 allele has a high frequency in Banat (6.2%) and also compared to other European countries [10].

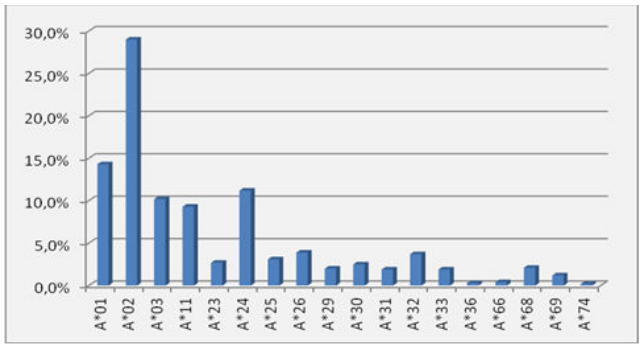

Figure 1: HLA-A allele frequencies (%) in Romania

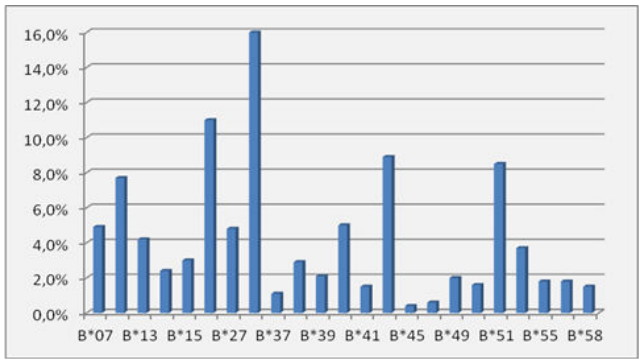

Figure 2: HLA-B allele frequencies (%) in Romania

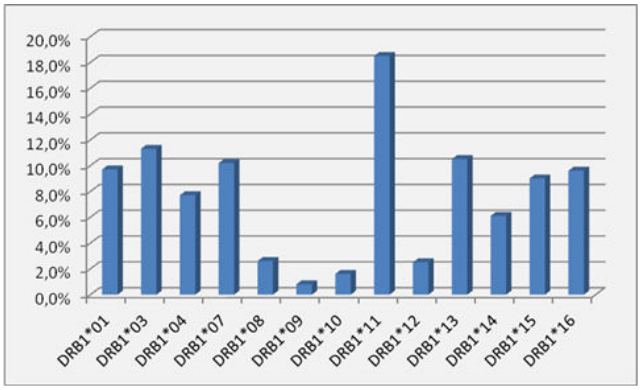

Figure 3: HLA-DRB1 allele frequencies (%) in Romania

Italy, France, Germany, Serbia and Romania form a homogenous HLA allele cluster which is significantly different than the one from Turkey and Bulgaria. Analyzing Romania's regions, two clusters could be distinguished: Wallachia & Moldavia versus Transylvania & Banat [10].

Analysis of genetic differences between distinct Romanian population groups and European Caucasian population leads to the conclusion that Romanian people is of European origin. Massive population migration could increase the possibility of more polymorphic HLA allele distribution over all European regions. It would be very interesting to look at HLA allele polymorphisms in different regions of European countries in order to be able to design an HLA allele distribution map.

This work is valuable in establishing HLA typing strategies within the Volunteer Bone Marrow Donors National Registries in Europe, sustaining the efforts of finding the best matched donor for the patients in need. Last but not least, HLA disease associations could be implemented in many diagnostic algorithms revealing specific genetic information for many conditions. Furthermore, other clinical applications of HLA allele's assessment could be relevant for the genetic background of rare diseases and disease susceptibility.

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