MOLECULAR AND EXPERIMENTAL BIOLOGY IN MEDICINE

HUMAN LEUKOCYTE ANTIGEN POLYMORPHISM IN SEARCH FOR A MATCHED UNRELATED DONOR IN HAEMATOPOIETIC STEM CELL TRANSPLANTATION

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Abstract: The importance of recipient and donor matching for genes of the Human Leukocyte Antigens (HLA) system for the outcome of hematopoietic stem cell transplantation (HSCT) is well-established and documented. This review gives a brief summary of the genetic complexity of the HLA system, a description of HLA class I and II genes, as well as an overview of HLA class I and II molecules and their function in immunological processes. The review then focuses on the main characteristics of the HLA system that play an important role in HSCT, the extensive polymorphism of HLA genes and linkage disequilibrium, by providing examples of HLA alleles and haplotypes distribution in various worldwide populations. The second part of the review gives a detailed explanation of why the knowledge about this distribution is of great importance in the HSCT program, especially in the search for a matched unrelated donor (MUD), with respect to the evaluation of probabilities for finding a suitable donor. The final part of the review discusses the impact of different HLA mismatches on HSCT outcome in terms of the risk for graft vs. host disease (GvHD), transplant-related mortality, graft failure and overall survival.

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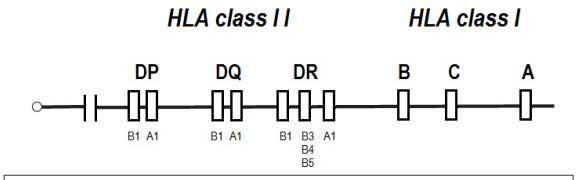
INTRODUCTION

The human leukocyte antigen (HLA) system is comprised of a group of highly polymorphic genes on the short arm of chromosome 6 (6p21.3), and spans around 4 Mbp. HLA molecules, encoded by HLA class I and HLA class II genes, are cell-surface glycoproteins that present intracellular and extracellular peptides to T cells and play a key role in the bodyôs immune protection.[1] They are involved in cellular and humoral adaptive immune response, and for that reason they are important as a barrier in protection against infections, but also act as an obstacle to transplantation.

HLA GENES AND MOLECULES

The HLA system is subdivided into three regions. The HLA class I region contains classical HLA class I genes (HLA-A, -B, and -C) and non-classical genes; the HLA class II region contains classical active genes (HLA-DRA1, -DRB1, -DRB3, -DRB4, -DRB5, -DQA1, -DQB1, -DPA1, and DPB1) and many other HLA class II pseudogenes (HLA-DRB2, -DRB6, -DRB7, -DRB8, -DRB9, -DQA2, -DQB2, -DQB3, -DPA2, -DPB2), while the HLA class III region does not include HLA genes, but contains genes for complement components, tumor necrosis factor, etc. (Figure 1). Classical HLA class I genes encode the heavy chain (α chain) of the HLA class I molecule, while classical HLA class II genes encode both chains (α and β chain) of the HLA class II molecule (Figure 2). The α1 and α2 domains, encoded by exons 2 and 3, contain variable amino acid sequences which



alleles	947	1,236	2,383	4,828	3,579	3,968
proteins	665	809	1,741	3,501	2,490	2,781
null alleles	22	34	65	146	128	181

IPD-IMGT/HLA Database, Version Report - 3.29.0.1 (2017-08)
http://www.ebi.ac.uk/ipd/imgt/hla/stats.html

Figure 1. Schematic map of the human leukocyte antigen (HLA) region and number of HLA alleles, proteins and null alleles

determine the antigenic specificity of HLA class I molecules.[2] The antigenic specificity of HLA class II molecules is determined by α1 and β1 domains, encoded by exon 2 of A and B genes, respectively. The majority of the polymorphisms found within HLA genes are located in the exons encoding the peptide-binding cleft of the HLA molecule, but polymorphisms are also located in other exons, as well as in introns [2].

HLA class I molecules are expressed on most nucleated cells and have the role of presenting intracellular peptides (usually comprised of 8-10 amino acids) to CD8+ cytotoxic T-lymphocytes. At the same time, HLA class II molecules are expressed on the antigen presenting cells (APC), such as B cells, activated T-cells, dendritic cells, and macrophages, and are responsible for the presentation of extracellular peptides (usually comprised of 10-30 amino acids) to CD4+ helper T cells.

HLA POLYMORPHISM

Extremely high polymorphism is one of the main characteristics of the HLA system. As of August 2017, more than 17,000 HLA alleles have been assigned (www.ebi.ac.uk/ipd/imgt/hla), out of which 4,828 different alleles have so far been reported for the HLA-B locus, making it the most polymorphic HLA locus thus far.[3] These numbers are, however, definitely not final since, due to the usage of new technologies, as well as testing of new populations, the number of known HLA alleles is growing daily.[4]

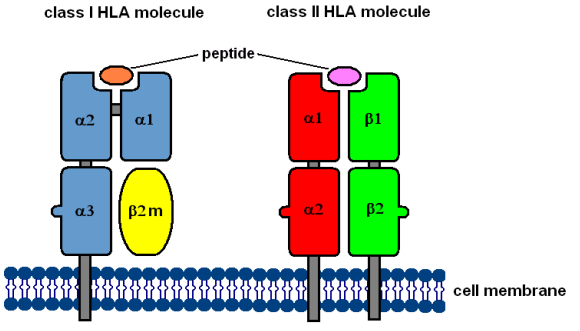
Despite the large number of reported HLA alleles in populations worldwide, a limited number of HLA alleles are found in any given population at a gene frequency of at least 0.1%.[5]

This exceedingly high polymorphism is the result of several genetic mechanisms, including gene conversion, point mutation, and recombination.[2, 6]

Approximately 25% of all HLA class I and II alleles differ by silent substitutions, while 3% are characterized as null-alleles (alleles without cell surface expression).[3]

Despite the wide diversity observed in different populations all over the world, a relatively low percentage of HLA alleles was observed with notable frequencies. For example, among individuals from the Croatian population who carry DRB1*11 alleles, 93% carry two (DRB1*11:01 or DRB1*11:04) out of eight detected alleles at the DRB1*11 gene, while the remaining six alleles (DRB1*11:02, DRB1*11:03, DRB1*11:06, DRB1*11:11, DRB1*11:15, and DRB1*11:28) are present with a frequency of less than 7%.[7, 8] HLA alleles differ in frequency within worldwide populations as well as between different regions in a given country.[5, 9, 10]

Examples of such variation in the distribution of several HLA alleles in different European populations are presented in Table 1. For example, the A*01:01 allele is one of the common HLA-A alleles in the European populations and demonstrates a higher frequency in Northern Europe in comparison to its presence in Southern Europe. On the other hand, the frequency of the B*27:02 allele in our population is similar to the frequency of this allele among South European populations (Bulgarians, Greeks, Romanians) and it ýts well in the pattern of B*27:02 allele frequency among European populations, which decreases from the Middle East and North Africa to Northern Europe.[5, 11] Another example is the distribution of the DRB1*16:01 allele which is less frequent among Northern European populations than among Southern Europeans. Population studies also established the distribution of the HLA-A~B~DRB1 haplotypes among Europeans in general.[12] Similarly to the variation in HLA allele frequency, differences regarding the HLA-A~B~DRB1 haplotype frequencies between various populations across Europe are documented. For instance, the HLA-A*02:01~B*18:01~DRB1*11:04 haplotype is ranked second in the Croatian population (Table 2), while at same time this haplotype is not among the fifteen most frequent haplotypes among populations of European origin reported by Gragert et al.[7, 12] It is apparent from Table 2 that differences in HLA haplotype frequencies between our population and other European



Legend: The HLA class I molecules are composed of a heavy chain (α chain) and β2-microglobulin (β2m). The domains α1 and α2 of HLA Class I molecule are encoded by exons 2 and 3, respectively, while domain α3, encoded by exon 3, interacts with β2-microglobulin (β2m). The HLA class II molecules are heterodimers composed of an α-chain and a β-chain. The α1 domain is encoded by exon 2 of A gene (e.g. DRA1), while β1 domain is encoded by exon 2 of B gene (e.g. DRB1).

Figure 2. Schematic structure of HLA class I and class II molecules

Table 1. The frequency of HLA-A*01:01, B*27:02 and DRB1*16:01 alleles in different European populations[#]

Population	HLA-		
	A*01:01	B*27:02	DRB1*16:01
Austria	0.146	0.008	0.025
Belgium	0.155	0.005	0.025
Bulgaria	0.073	0.046	0.155
Croatia	0.124	0.021	0.094
Czech Republic	0.127	0.019	0.024
England North West	0.208	-	0.008
Finland	0.089	0.017	0.007
France Southeast	0.150	-	0.035
Germany	0.151	0.007	0.026
Greece	0.114	0.009	0.135
Ireland Northern	0.202	0.001	0.002
Italy	0.102	0.006	0.049
Netherlands	0.175	0.003	0.022
Poland	0.133	0.019	0.048
Portugal	0.130	-	0.020
Romania	0.122	0.022	-
Slovenia	-	-	0.094
Switzerland	0.128	0.006	-

Legend: [#] reference 5

populations exist, and a similar situation is reported for many other populations. For that reason, it is important to conduct population studies for each individual population, as this approach is the only reliable way to obtain data about HLA polymorphism in Europe.

Population Genetics Working Group from the European Federation for Immunogenetics (EFI) published a catalogue including common and well-documented HLA alleles. Namely, on the base of reported frequencies of HLA alleles, the group classified HLA alleles into two sets: ñcommonò (COM) HLA alleles when more than 3 copies of them were observed in at least 3 different populations or ñwell-documentedò (WD) HLA alleles when at least 5 copies of them were found in the total set of populations.[13] At the same time, a third category of HLA alleles exists: alleles which have been observed fewer than five times in worldwide populations and are named ñrareò alleles.

HLA HAPLOTYPES AND LINKAGE DISEQUILIBRIUM

Because HLA loci are closely linked to each other, they are inherited as a block, the so-called HLA haplotype from each parent. Two siblings have a 25% chance of being genotypically HLA identical, and this probability increases with the number of siblings.

One of the most important features of the HLA system is linkage disequilibrium (LD), the fact that HLA alleles on different loci form HLA haplotypes more frequently than can be expected on the basis of the individual frequencies of these HLA alleles. For that reason, the number of HLA haplotypes observed in different populations is much smaller than it would be expected in theory.[14] One of the most frequently mentioned examples of strong LD is the HLA-A*01~B*08~C*07~DRB1*03~DQB1*02 haplotype, also known as the autoimmune haplotype, which is one of the most common haplotypes in Europe.[5]

LD is, on the other hand, the result of a small distance between HLA loci, but on the other hand, it is probably also the result of evolution and selection forces that induce specific combinations of HLA alleles into a haplotype. However, none of the explanations offered so far has given a complete answer to this phenomenon.[6]

Table 2. The frequency of the fifteen most common HLA-A~B~DRB1 haplotypes in populations of European origin[a] and Croatians[b]

Populations of European origin[a]			Croatians[b]		
RANK	HLA-A*~B*~DRB1*	HF	RANK	HLA-A*~B*~DRB1*	HF
1	01:01~08:01~03:01	0.06526	1	01:01~08:01~03:01	0.0415
2	03:01~07:02~15:01	0.03114	2	02:01~18:01~11:04	0.0148
3	02:01~07:02~15:01	0.01974	3	03:01~07:02~15:01	0.0120
4	02:01~44:02G~04:01	0.01852	4	02:01~27:05~01:01	0.0085
5	29:02~44:03~07:01	0.01567	5	02:01~51:01~11:01	0.0077
6	03:01~35:01~01:01	0.01121	6	02:01~13:02~07:01	0.0076
7	02:01~08:01~03:01	0.00864	7	02:01~27:02~16:01	0.0074
8	01:01~57:01~07:01	0.00828	8	02:01~44:02G~16:01	0.0072
9	02:01~40:01~13:02	0.00766	9	02:01~07:02~15:01	0.0068
10	24:02~07:02~15:01	0.00731	10	11:01~35:01~01:01	0.0067
11	02:01~15:01~04:01	0.00701	11	02:01~51:01~16:01	0.0063
12	30:01~13:02~07:01	0.00639	12	23:01~44:03~07:01	0.0062
13	23:01~44:03~07:01	0.00587	13	25:01~18:01~15:01	0.0053
14	11:01~35:01~01:01	0.00567	14	03:01~35:01~01:01	0.0049
15	33:01~14:02~01:02	0.00442	15	24:02~13:02~07:01	0.0046

Legend: HF ï haplotype frequency; B*44:02g ï B*44:02 or B*44:27; [a] reference 7; [b] reference 12

HLA IN HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

It is an established fact that, among many factors that influence the outcome of HSCT, HLA polymorphism represents the most important barrier. The above-mentioned characteristics of the HLA system are essential, but also limiting factors in the search for the best matched donor.[15-18]

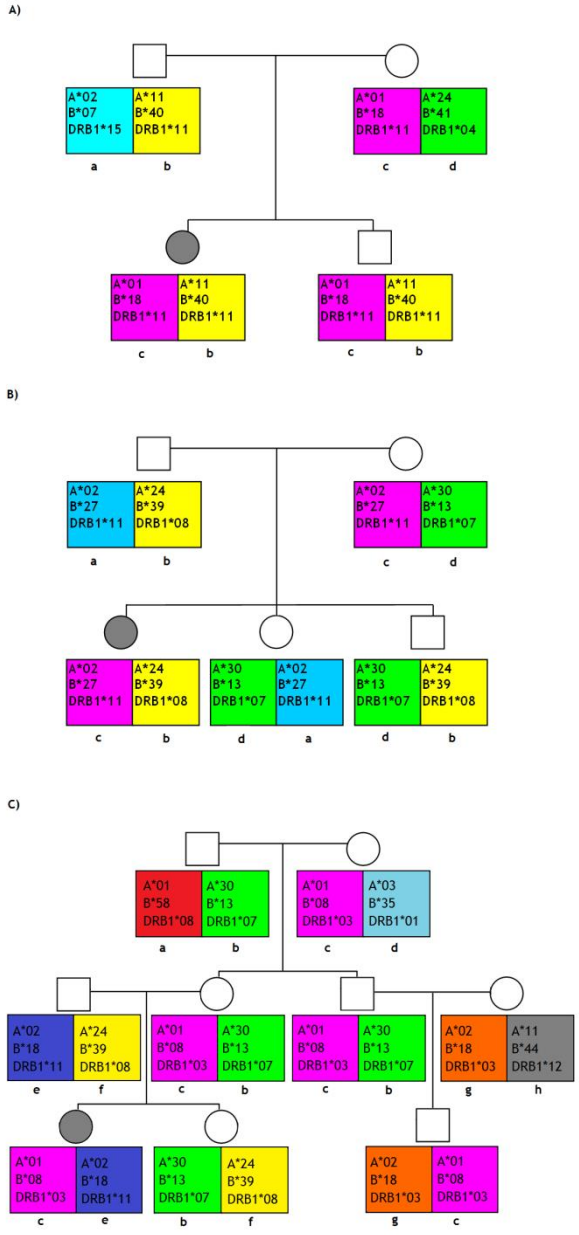
The undisputedly best donor in HSCT is a genotypically HLA-matched sibling. This is the case when the patient and sibling donor share the same paternal and maternal haplotype. Namely, it is possible to determine the inherited HLA haplotypes in most cases by typing for HLA-A, -B, and -DRB1 loci of family members at the low-resolution level (2-digit DNA typing; typing at specificity/gene level). The probability of having a genotypically HLA-identical sibling donor is 25% for each sibling, whereas the probability of having an HLA-haploidentical donor is 50%. In some cases, when patient does not have a genotypically HLA-identical donor, it is possible to find a phenotypically HLA-identical donor in blood-related members of the extended family (for example patients' aunts/uncles on the paternal side married to aunts/uncles on the maternal side). At the same time, in cases when the patient carries a very frequent HLA-A~B~DRB1 haplotype, it might be possible that one of the parents is a phenotypically HLA-identical donor (Figure 3).

For the remaining patients, there is an opportunity to find a well-matched unrelated donor (MUD) through a national registry or through a worldwide registry of volunteer donors (Bone Marrow Donors Worldwide, BMDW). The BMDW is the world's largest database of volunteer hematopoietic stem cell donors and cord blood units, listing more than 29.5 million donors and over 730,000 cord blood units (October, 2017). BMDW coordinates a collection of data from 75 hematopoietic cell donor registries from 53 countries, and 53 cord blood banks from 36 countries.[19]

The European Bone Marrow Transplantation (EMBT) and The National Marrow Donor Program (NMDP) protocols base their search protocols on compatibility at HLA-A, -B, -C, and -DRB1 loci (8/8 MUD) or HLA-A, -B, -C, -DRB1, and -DQB1 loci (10/10 MUD) at high-resolution level.[20, 21] The term "high resolution" is defined by HLA typing at the level of alleles (four digits, e.g., HLA-A*02:01, B*27:02).

Different studies demonstrated that for approximately 50% of all patients, a 10/10 MUD can be identified, and for an additional 20-30% patients, a 9/10 MUD or 8/10 MUD can be found, while for the remaining patients an alternative source of HSC, such as an haploidentical donor or a cord blood unit, can be used.[22] In one study from Croatia, a 10/10 MUD donor was found for approximately 68% of patients, a 9/10 MUD was identified for around 28% of patients, while an 8/10 MUD was available in 4% of cases. These percentages are consistent with the results of similar studies from other authors.[23, 24]

Strong LD helps to identify matched donors, but at the same time presents a limiting factor which needs to be taken into account due to the established fact that patients carrying a haplotype which is not in LD have a lower chance of ýnding a compatible donor. For example, the probability of finding a 10/10 MUD is greatly decreased for those patients who carry the HLA-A*01:01~B*08:01~DRB1*01:01 haplotype in comparison to those who carry the HLA-A*01:01~B*08:01~DRB1*03:01 haplotype.



Legend: A ï example of a genotypically identical sibling donor; B ï example of a parent identified as a phenotypically identical donor; C ï example of a phenotypically identical donor identified in a member of an extended family; a-g ï different HLA haplotypes

Figure 3. Different type of family donors for haematopoietic stem cell transplantation

A further example of the important role of LD in a search for a MUD is the strong LD between HLA-B and -C alleles on finding a suitable donor. Namely, numerous recent studies have demonstrated that unrelated individuals are rather frequently mismatched (MM) for one or both HLA-C alleles.[25, 26] Moreover, even in the context of frequent haplotypes, HLA-C MMs were often present if those haplotypes included B*18, B*44 or B*51 alleles.[27, 28] More precisely, the HLA-B*51:01 allele is an example of an HLA-B allele which forms haplotypes with various HLA-C alleles, although haplotypes with C*15:02, C*14:02, and C*01:02 are the most common ones (Table 3). In this particular case, such a linkage pattern means that a patient with the HLA-B*51:01~C*16:02 haplotype has a very low probability (>1%) of finding a 10/10 MUD.[29] A similar situation can also occur because of a strong LD between HLA-DRB1 and -DQB1 alleles. For example, for patients who carry the unusual HLA-DRB1*15:01~DQB1*05:02 combination, the chance of obtaining a MUD matched at the HLA-DQB1 locus is extremely low because the common combination is HLA-DRB1*15:01~DQB1*06:02.

Table 3. The HLA-B*51:01~C haplotypes among Croatians and the European population in general

	Croatians (N=600)[1] %	Europeans[2]
51:01~01:02	20.83	intermediate
51:01~02:02	7.83	intermediate/rare
51:01~03:03	1.83	rare
51:01~03:04	0.50	rare
51:01~04:01	2.50	intermediate/rare
51:01~05:01	1.67	rare
51:01~06:02	1.17	extremely rare
51:01~07:01	1.83	rare
51:01~07:02	0.50	extremely rare
51:01~12:03	3.68	rare
51:01~14:02	21.00	common
51:01~15:02	31.83	common
51:01~15:04	0.17	intermediate/rare
51:01~15:05	0	extremely rare
51:01~15:06	0	extremely rare
51:01~16:01	1.83	rare
51:01~16:02	2.83	intermediate/rare

Legend: [1] reference 12; [2] reference 29

One of the essential factors for a successful search for a suitable donor is the knowledge of the distribution of HLA alleles in worldwide populations, as this enables the prediction of the probability of finding a 10/10 MUD. The estimation of the likelihood of identifying a 10/10 MUD also depends on the determination of risk HLA alleles/haplotypes carried by the patient.[30] Some national registries have developed software for the calculation of the probability of identifying 10/10 MUD or 9/10.[31-33] At the same time, some countries have also established a search algorithm on a national basis with search probabilities being assigned as high, intermediate, or low based on the patientôs HLA-A, -B, -C, -DRB1, -DQB1 haplotypes and the examination of the BMDW database. These types of algorithms are very helpful for optimizing a MUD search.[32, 34]

Patients with at least one common HLA haplotype have a very high probability of finding a 10/10 MUD, but the presence of a common HLA haplotype which is specific for a limited number of populations (or regions) not well-represented in BMDW changes the odds, and the probability of finding a 10/10 MUD for that particular patient decreases. The explanation for this lies in fact that the majority of donors registered in the BMDW currently come from Western European countries (Germany≈7,640,00, UK≈1,400,000, France≈275,000, etc.), or the USA (≈8,450,000). This further emphasises the necessity of enlarging national registers in Southern and Eastern parts of Europe.[18] It is also well-documented that patients with non-European ancestry or from isolated populations have a lower chance of finding a 10/10 MUD.[32] To be precise, a study from the USA reported that 31-75% of patients, depending on their ethnic origin, are able to ýnd an 8/8 MUD.[35]

Unsurprisingly, searches for patients with a rare allele or a non-frequent allele (e.g., B*27:30) have a low probability of success; however, searches for patients with alleles that represent 5-10% of all alleles within a group of alleles, such as B*35:08 among the B*35 group of alleles or DRB1*11:03 among the DRB1*11 group of alleles, also have a low rate of success. This is corroborated by data from studies which reported that the presence of HLA-B*35:02/*35:03/*35:08 confers a higher risk of a B*35 allele MM, or that as much as 61.7% of HLA-B allelic incompatibilities were due to the HLA-B*35 allelic group.[22, 34] It is also worth mentioning that there are patients who carry unique HLA phenotypes which are not represented in the BMDW. For example, studies from the Swiss population reported that around 5% of patients had such a unique HLA phenotype, while authors from Germany informed about approximately 3% of patients carrying unique combinations of HLA alleles.[36, 37]

The impact of a single HLA mismatch between patients and unrelated donors on HSCT has been documented in different studies, but it remains controversial as to which of the six major HLA genes are most important and which MMs result in an acceptable outcome in the context of the patientôs disease status.[38-41] HLA matching is a critical factor in reducing the risk of post-transplant complications such as graft failure and graft versus host disease (GvHD). It is an established fact that the incidence of GVHD as well as graft failure in HSCT from a MUD is significantly higher than in HSCT from an HLA-identical sibling donor.[42-44] A study performed in 2007 among patients who had undergone HSCT with myeloablative conditioning suggested that a single MM at the HLA-A or -DRB1 locus appeared to be more harmful than a single MM at the HLA-B or -C locus.[41] In contrast, the study evaluating the effect of HLA mismatches in a group of patients who had been transplanted with peripheral

blood stem cells reported higher risks of mortality for patients receiving transplants presenting one antigen MM at the HLA-B or -C locus.[45] Based on all those studies, Fernandez-Vina et al. reasoned that different MMs have distinct effects on the outcome of each individual transplant and presented evidence that C*03:03/C*03:04 MM was better-tolerated and resulted in superior outcomes compared with other single HLA mismatches.[26] At the same time, a study which included single nucleotide polymorphisms (SNPs) found that the clinical outcome after HLA-mismatched transplantation depends on undetected haplotype-linked SNPs that have synergistic effects with HLA mismatching.[46]

An interesting investigation from Japan demonstrated that a genetic difference derived from a HLA haplotype itself is associated with acute GvHD (aGvHD) in allogeneic HSCT.[47] Research from Kawase et al. gave information about a total of 15 significant high-risk HLA allele mismatch combinations and one HLA-DRB1-DQB1 linked mismatch combination (high-risk mismatch) associated with severe aGVHD; more precisely, 6 specific amino acid substitution positions in HLA class I were identified as those responsible for severe aGVHD.[48] More insight into this matter came from a report from the Japan Marrow Donor Program which offered evidence that those patients with mismatched HLA-C*14:02 had the most potent risk factor of severe aGvHD and mortality. Furthermore, the authors of this study concluded that an increased risk for developing severe aGvHD is not attributed only to the HLA-C*14:02 with the HLA-B*51:01 alleleôs involvement being only due to its genetic linkage with HLA-C*14:02, but that HLA-B*51:01 itself has a role in increasing the risk for aGvHD.[45]

Data published by Tiercy et al. in an article from 2007 compared survival rates of transplanted patients in high vs. low/intermediate probability groups (groups are characterized based on the patientôs HLA profile) and reported a signiýcant difference. Probable explanations of this result were a higher rate of mismatched HSCT in the low/intermediate group and possibly an earlier decision to transplant in the high-probability group. Authors also pointed out that patients from the high-probability group showed a better HSCT outcome compared to the patients from intermediate and low-probability groups. The cause for such a difference probably lies in the fact that a higher compatibility for non-HLA polymorphisms encoded in the MHC should be expected for patients in the high-probability group, attributable to an increased frequency of conserved haplotypes carried by those patients.[22] Even though various reports have been presented on the issue of the cumulative impact of mismatches of HLA loci with lower expression (e.g. DRB3, DRB4, DRB5, DQB1, and DPB1), the fact remains that there is a lack of conclusive data about this matter. A paper from Fernandez-Vina et al. concluded that a single locus mismatch at low expression HLA loci has no influence on the clinical outcome of HSCT, while three or more mismatches at those loci are associated with a lower survival rate in cases of HSCT with a 7/8 MUD.[49] Some other studies showed that an isolated mismatch at HLA-DQB1 and -DPB1 loci was not associated with the mortality rate.[20, 37] One study showed that in case of a HSCT with multiple HLA mismatches, a mismatch at HLA-DQB1 locus should be avoided because patients with such a combination of HLA MMs showed worse survival rates.[50] As for the role of HLA-DPB1 mismatching, it has been proven that an HLA-DPB1 MM is associated with a higher risk of aGvHD and a decreased risk of relapse, without a signiýcant effect on overall survival.[51, 52] In contrast to that study, an investigation by van Balen et al. showed that mismatches for the HLA-DPB1 locus, but also mismatches for the HLA-DRB3 locus, may induce a severe GVHD.[53] Similar evidence was provided in a paper from 2009 in which the authors informed about four HLA-Cw and six HLA-DPB1 MM combinations responsible for a decreased risk of relaps,e and eight out of ten observed combinations were different from those responsible for severe aGVHD, including all six of the HLA-DPB1 combinations.[54] A retrospective study published two years ago showed a significant impact of DRB4 mismatching on survival, aGvHD and transplant-related mortality, while DRB3 and DRB5 mismatching did not show a negative impact on transplantation outcome.[55] The authors suggested that a multicentre prospective study is needed for a confirmation of the possible impact of DRB4 incompatibilities on the transplantation outcome. Finally, despite all of the above-mentioned reports, most transplant centres do not take into account a matching for HLA-DRB3, -DRB4, and -DRB5 loci in the choice of a MUD because their importance remains poorly documented and is still questionable.

On the other hand, it is well-documented that each HLA allele mismatch reduces the overall survival at 1 year by 9-10%. For that reason, it is important to determine how homozygosity at an HLA locus should be handled in defining the degree of acceptable mismatch between a patient and a potential donor. For that purpose, a group of authors from different transplantation centres proposed that, for unrelated donor selection, unidirectional HLA mismatches in the graft versus host (GVH) direction should be considered as the same level of risk as 7/8 bidirectional HLA mismatches. Namely, the authors suggested that for HLA homozygous recipients, a mismatch at the homozygous locus is preferred over a mismatch at the heterozygous locus.[41] This suggestion is contrary to the conclusions reached by the Seattle Transplant Group who suggested that the risk of graft failure was increased if the recipient was HLA homozygous at the mismatched HLA class I locus.[56]

The majority of studies discussed above were focused on patients with hematologic malignancies. The number of studies which analyse the impact of HLA matching on HSCT outcome among patients with non-malignant diseases (NMD) is much smaller. The data

from one large retrospective study clearly demonstrated that a transplantation from a donor mismatched at the HLA-A, -B, -C, or -DRB1, but not -DQB1 or -DPB1 loci was associated with higher mortality, strongly associated with graft failure, but not associated with GvHD.[45] The authors of this study concluded that, contrary to HSCT for malignancies where GVHD is the primary immunologic consequence of HLA mismatching, graft failure is the main concern in HSCT for NMD.[41, 46] They also suggested that the association between HLA mismatching and mortality may not be as strong as it is in malignant diseases.[45]

In conclusion, this review clearly presents that high HLA polymorphism, which plays a crucial role in our defence from infections, is one of the most important factor in the selection of an optimal donor in the HSCT program. The knowledge about HLA allele and haplotype distribution in different populations worldwide will enable the selection of the best MUD for patients in need of a treatment with HSCT.

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