Human Immunology 80 (2019) 823–827

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

High resolution HLA allele and haplotype frequencies for Arab donors in the Hadassah bone marrow donor registry

Amal Bishara[a], Michael Halagan[b], Chaim Brautbar[a], Shoshana Israel[a], Martin Maiers[b], Abeer Madbouly[b,*]

[a] *Hadassah Medical Center, Tissue Typing and Immunogenetics, Jerusalem, Israel*
[b] *Bioinformatics Research, Center for International Blood and Marrow Transplant Research, Minneapolis, MN, USA*

ABSTRACT

Five locus allele-level HLA-A, -B, -C, -DRB1, -DQB1 allele and haplotype frequencies have been calculated for almost 29,000 people from three Arab populations that live in Israel and were recruited as donors to the Hadassah bone marrow donor registry. These groups are of Muslim, Christian and Bedouin Arab descent which represent more than 90% of the Arabs that live in Israel. The goal of the study was to describe the HLA genetic profiles of the Hadassah Arab registry donors and investigate the utility of these donors for the local and international hematopoietic stem-cell transplant community.

The results demonstrate that the analyzed Arab populations share at least seven of the top ten most frequent alleles. Comparison with other populations confirmed the proximity of the three Arab populations to each other and to the Be The Match® Middle Eastern population. Despite these similarities, some alleles are private to each of the three groups, possibly because of historical, environmental or societal events. Clinical data showed that Arab donors were HLA matched with Arab and international patients. This analysis indicates the value added by the Hadassah Arab donors to the local and global transplant community.

1. Introduction

Hematopoietic stem cell transplantation (HSCT) from an HLA-matched unrelated donor is currently the best therapeutic option for eligible patients without an HLA identical sibling donor [1–4]. Volunteer unrelated donor registries have been established worldwide to help facilitate this process. However, the chance of finding a matched unrelated donor (MUD) is dependent on several factors such as the HLA and ancestral representation of different patient ethnic groups in world registries [2,5]. The Hadassah unrelated donor registry was established in 1987 with the bulk of the donors joining from various Jewish communities in Israel. Even though Arabs form more than 20% of the Israeli population, the representation of Arabs in the Hadassah registry was negligible, resulting in poor donor allocation for Arab patients locally and in the international registries. Unrelated donors were found for only 10% of Arab patients in need of HSCT in Israel (personal communication with Dr. Amal Bishara). This was the main motivation for a project started in 2008 with the goal of increasing the representation of Israeli Arabs in the Hadassah registry. Arab donors were recruited through more than 150 drives in cities and villages of the Arab community, including universities and colleges. By April 2018, more than 37,000 Arab donors had been recruited. Arabs represent about 21% of the population in Israel, dispersed in three main groups. The largest group are people of Muslim descent at 17.5% (85% of total Israeli Arab population). The remainder is formed of individuals of Christian, Druze and other religious descents (source: Statistical Abstract of Israel, Central Bureau of Statistics, 2016, Table 2). The group of people of Muslim descent includes the Bedouin subpopulation who migrated from the Arabian, Jordanian and Syrian regions and live in two principal areas in the north and south of Israel. Although it may be unusual to categorize different populations due to their religion, it is not unique. Population genetic similarities in this geographic region have often been associated with genealogies defined by religion [6]. Most populations in this region have lived separately for generations. Even in mixed communities there are no intermarriages between groups of different religious and ethnic descents. Once these groups were settled in the region their religions tended to keep them as closed communities.

The aim of this study is to assess the needs of HSCT patients in Israel by studying the HLA genetic profile of different local Arab groups. Allele and haplotype frequencies were estimated for groups of Muslim, Christian, and Bedouin descent and compared to other global populations. This is an initial step to strategically plan for the expansion of the Hadassah registry to better serve populations that are underrepresented in the registry.

---

[*] Corresponding author.
E-mail address: amadboul@nmdp.org (A. Madbouly).

https://doi.org/10.1016/j.humimm.2019.05.003
Received 30 December 2018; Received in revised form 29 April 2019; Accepted 10 May 2019
Available online 22 May 2019
0198-8859/ © 2019 American Society for Histocompatibility and Immunogenetics. Published by Elsevier Inc. All rights reserved.

Table 1
Sample size and available typing stratified by population and HLA locus.

	ALL	Muslim Descent	Christian Descent	Bedouin Descent
HLA-A	28,966	23,544	4601	821
HLA-B	28,966	23,544	4601	821
HLA-C	5989	4644	724	621
HLA-DRB1	28,966	23,544	4601	821
HLA-DQB1	1482	814	308	360

Table 2
P-values associated with the locus-level tests run to estimate deviation from HWE proportions at the allele-family resolution. Values less than 0.05 indicate deviation from HWE proportions. Values in **bold** indicate loci that did not exhibit deviation from HWE proportions. MD: Arabs of Muslim Descent, CD: Arabs of Christian Descent, BD: Arabs of Bedouin Descent, HWE: Hardy-Weinberg equilibrium.

	HLA-A p-value	HLA-B p-value	HLA-C p-value	HLA-DRB1 p-value	HLA-DQB1 p-value
MD	< 0.0001	< 0.0001	0.0002	< 0.0001	**0.4739**
CD	0.0068	0.0066	0.0066	0.0063	**0.7125**
BD	< 0.0001	< 0.0001	**0.1240**	0.0006	**0.2042**

2. Materials and methods

2.1. Study population

Between 2008 and the end of 2014, 28,966 Arab donors have been added to the Hadassah Registry. The ethnic and religious affiliations were collected for most of them. This cohort consists of people from the three main Israeli Arab communities: Arabs of Muslim descent (MD) from the center and north of Israel; Arabs of Christian descent (CD) mainly from the north of Israel, and Arabs of Bedouin descent (BD) mainly from the north of Israel. These three communities represent more than 90% of Arabs in Israel.

2.2. HLA genotyping of donors

All donors were genotyped for HLA-A, -B and -DRB1, 21% were typed for HLA-C and 5% for HLA-DQB1 (Table 1). Donors were typed by sequence methods; exon 2 and 3 for HLA-A, B, C genes and exon 2 for DRB1 and DQB1 genes were amplified. The Amplicons were sequenced using Sanger and single molecular sequencing method (Next Generation Sequencing). For more details on genotyping please refer to Cereb et al. [7]

2.3. Statistical analysis

Five locus allele-level HLA A ~ C ~ B ~ DRB1 ~ DQB1 haplotype frequencies were estimated using an implementation of the Expectation Maximization (EM) algorithm that resolves phase, allelic and missing allele ambiguities [8]. The applied EM algorithm was shown to cope with varying levels of typing resolution, even if the level of typing resolution is not independent of the HLA type (for example higher rate of missing typing at particular loci like HLA-C and HLA-DQB1). This allows the use of intermediate and high-resolution data from patient-directed registry typing (i.e. from subjects who were selected for testing on behalf of a specific patient) to extend haplotype frequency estimates to the allele level for alleles with higher rates of missing data like HLA-C and HLA-DQB1. More details are described elsewhere [8].

Once all ambiguities were resolved, allele frequencies were generated from the EM-estimated haplotypes. Deviations from Hardy–Weinberg equilibrium (HWE) were assessed at the allele-family level using a modified version of the Guo & Thompson algorithm [9] as implemented in the software Pypop [10].

Comparisons were performed between the different Hadassah Arab populations, and also with other populations from the US Be The Match® Registry. A clustering analysis was performed using Principal Components Analysis (PCA) of different population haplotype frequencies. PCA was performed using MATLAB (MATLAB and statistics Toolbox release 2017b, MathWorks, Inc. Natick, Massachusetts, United States).

3. Results

3.1. HLA alleles

Allele frequencies for HLA-A, -B, -C, -DRB1 and -DQB1 are listed in Supplementary Table 1 for all three studied Arab populations: MD, CD and BD. The table also provides ranks for the listed alleles and comparison of ranks and frequencies among the three studied groups. For most loci, at least seven of the most frequent alleles are shared by all three Hadassah Arab populations. For example, with HLA-DRB1, all the top 10 alleles are shared by both CD and MD while only seven are shared by BD.

Locus-level deviations from HWE proportions were detected at HLA-A, -B, -C and -DRB1 in all three populations except for HLA-C in the BD population ($p = 0.124$). HLA-DQB1 was not shown to deviate from HWE proportions in any of the analyzed groups (MD: $p = 0.474$, CD: $p = 0.71$, BD: $p = 0.2$). Detailed results are depicted in Table 2. More significant deviations were observed in the MD population than the other two. Genetic drift can be a possible cause of deviation in the smaller CD and BD populations where heterozygosity is lost as gamete sampling causes allele frequencies to drift towards zero or one. Such random genetic drift of allele frequencies is of negligible importance in very large populations, but the level of allele homozygosity can nevertheless be inflated by consanguineous mating [11]. This is likely the cause of deviations from HWE in the larger MD population.

A total of 43 novel alleles were identified in Hadassah Arab donors and reported to the IMGT database between the years 2010 and 2015; these were comprised of 12 HLA-A, 18 HLA-B, 6 HLA-C and 7 HLA-DRB1 alleles. Fourteen of these Alleles were reported in three or more donors (Table 3). Only 6 of the 43 novel alleles reported in the Arab donors were later found in updated frequencies of other populations as listed in Table 3. None of these alleles were reported in Jewish donors in the Hadassah Registry, indicating that these novel alleles probably originated in the local Arab communities.

We observed similarities in allele frequencies between the Hadassah Arab populations and the Arab populations reported in Manor et al. [12] in the Ezer-Mizion bone marrow registry, where they reported population allele and haplotype frequencies for HLA-A, HLA-B and HLA-DRB1 for multiple populations in Israel. The authors in Manor et al. report the most frequent Arab HLA-A, HLA-B and HLA-DRB1 alleles as HLA-A*01:01, HLA-A*02:01, HLA-A*03:02, HLA-B*35:08, HLA-B 49:01, HLA-B 38:01 and HLA-DRB1*11:04, HLA-DRB1*04:03, HLA-DRB1*03:01 and HLA-DRB1*07:01. All of the reported common alleles overlap with the most frequent alleles reported in the three Arab groups presented here. Particularly, six of the 10 most frequent HLA-A and B alleles and eight of the 10 HLA-DRB1 alleles are shared by the Arab donors in both registries.

Some overlap was also observed with alleles or allele families reported at neighboring populations, for example, some of the common HLA-DRB1 alleles observed here (HLA-DRB1*03:01, HLA-DRB1*07:01, HLA-DRB1*13:02, HLA-DRB1*11:04, and HLA-DRB1*15:02) overlapped with the most-common low-resolution DR specificities reported in a Kuwaiti population of Schizophrenic patients and healthy controls [13].

Other similarities were observed with Mediterranean populations, such as the Greek population reported in a cohort of German donors with Greek parentage [14]. There were multiple alleles reported common in both the Greek and Hadassah Arabs at HLA-A, B, C and

Table 3
Fourteen novel HLA alleles identified in three or more donors in the analyzed Arab populations between the years 2010 and 2015. Some alleles were reported in other populations after 2010 as shown in the last column.

Novel Allele	Year reported	Population	Donor count	Later found in other groups
A*02:242	2010	MD	16	Reported in US African Black*
A*02:286	2010	MD	3	None
A*03:01:30	2010	MD	4	None
A*24:02:19	2010	MD	5	Reported in Morocco Settat Craoya**
A*26:01:19	2010	MD	34	None
A*25:52	2009	BD	7	None
B*13:48	2009	MD	3	None
B*15:64	2009	MD	3	Reported in multiple US populations*
B*15:229	2009	BD	7	None
B*35:158	2010	MD	15	Reported in US African Americans*
B*39:63	2010	MD	3	Reported in US European Caucasians*
B*57:39	2009	MD	49	Reported in US European Caucasians*
C*07:429	2015	BD	11	None
C*15:114	2015	BD	3	None

*Gragert et al., Human Immunology, 2013.
**Allele Frequencies.net Database.

DRB1, including: HLA-A*02:01, HLA-A*01:01, HLA-A*11:01, HLA-A*26:01, HLA-A*03:01, HLA-A*24:02, and HLA-A*32:01, HLA-B*51:01, HLA-B*35:01, HLA-B*18:01, HLA-B*35:03, and HLA-B*08:01, HLA-C*07:01, HLA-C*04:01, and HLA-C*12:03, HLA-DRB1*11:04, HLA-DRB1*11:01, HLA-DRB1*16:01, HLA-DRB1*07:01 and HLA-DRB1*03:01.

3.2. HLA haplotypes

Five-locus HLA-A ~ C ~ B ~ DRB1 ~ DQB1 haplotype frequencies for all three Arab populations: MD, CD and BD are presented in Supplementary Table 2. The most common haplotype observed in all populations is HLA-A*33:01 ~ HLA-C*08:02 ~ HLA-B*14:02 ~ HLA-DRB1*01:02 ~ HLA-DQB1*05:01; ranking first in CD and BD and second in MD with frequencies 1.73%, 1.88% and 1.01% respectively. This haplotype is also common in Jewish, US Middle Eastern and Lebanese populations [12,15,16]. Another common haplotype is HLA-A*02:05 ~ HLA-C*06:02 ~ HLA-B*50:01 ~ HLA-DRB1*07:01 ~ HLA-DQB1*02:01 ranking second in CD, BD, and ninth in MD. This haplotype is one of the most common ancestral haplotypes observed at multiple typing resolutions in Jewish and Arab populations [12,15,17,18].

Comparing our results to haplotypes reported from Ezer-Mizion [12] at the three locus HLA-A ~ HLA-B ~ HLA-DRB1, we found significant overlap of the most common haplotypes in both Hadassah and Ezer-Mizion Arab populations. Seven of the top ten three-locus haplotypes in the Ezer-Mizion Arab population overlap with common haplotypes in the Hadassah populations studied here.

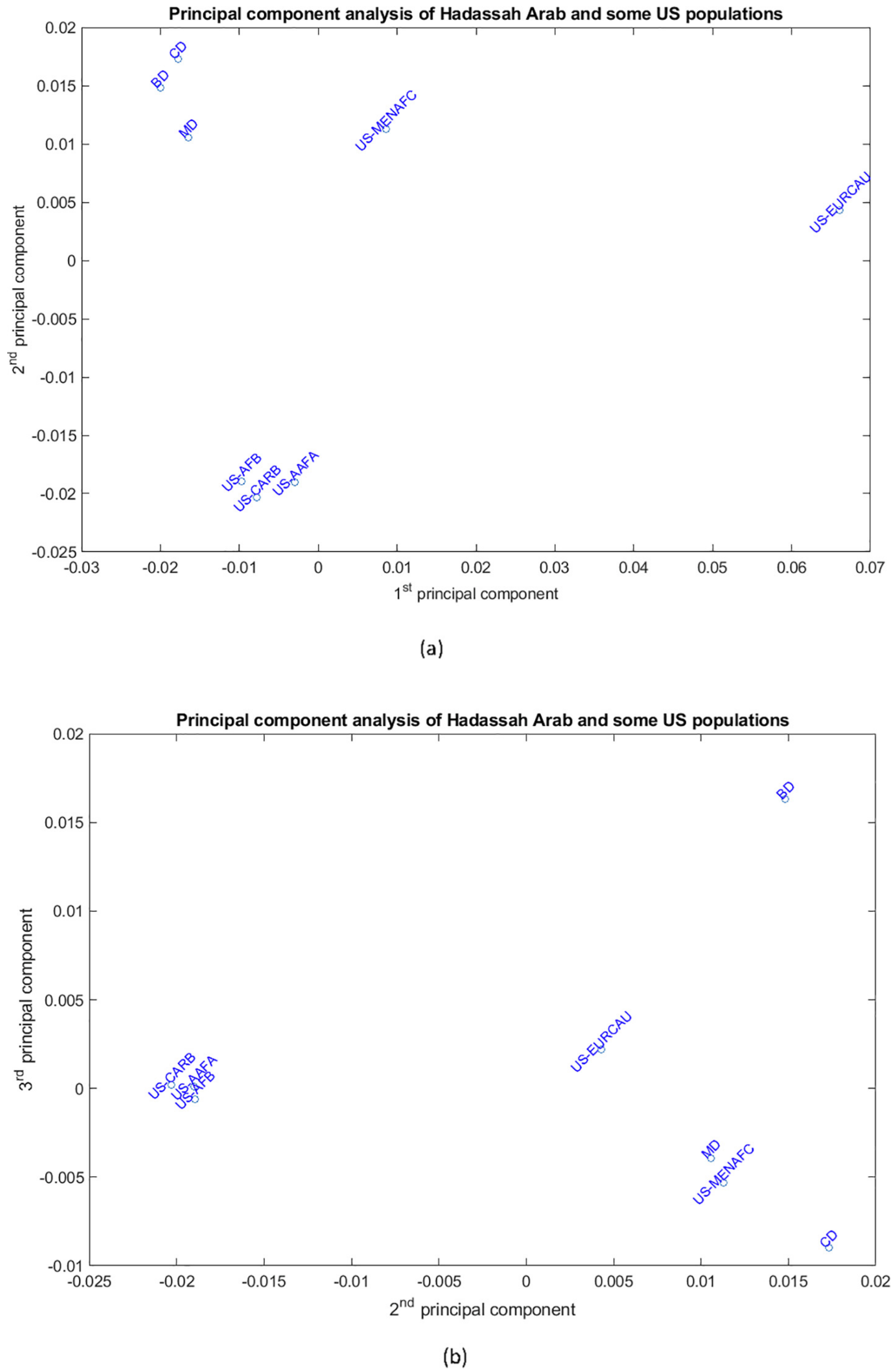
Fig. 1 depicts a comparison of the three Arab populations to some US groups from the Be The Match bone marrow registry based on geographical proximity of the ethnic origin of these populations with the studied groups. Comparison was performed using Principal Component Analysis (PCA) of the haplotype frequencies of each population [15]. The results show tight clustering of all three Arab populations indicating genetic similarity. Expectedly, the closest US population to all three Hadassah Arab groups was the Middle East/North African coast (MENAFC) population along the combined main principal components (PCs), with more genetic proximity to the MD in particular along the 2nd and 3rd PCs (Fig. 1b). Multiple African groups were close to the Hadassah populations along the first and second PCs, including African-American (AAFA), African (AFB) and Black Caribbean (CARB). Of interest, the African populations were closer to the Arab groups along the first PC than the US European Caucasian population (EURCAU). The first thee PCs accounted for over 96% of the total variance with the breakdown of the variance of the 1st through 3rd PCs as follows: 68.5%, 23.4%, and 4.85%

4. Discussion

This article reports five locus HLA allele and haplotype frequencies for three Arab populations recruited from various parts of Israel as a part of the Hadassah bone marrow donor registry. Frequencies are estimated at the allele level from a sample of approximately 29,000 individuals. To our knowledge, this is the largest sample and highest typing resolution reported to date from any Arab population in the East Mediterranean region reporting HLA haplotype frequencies at five-locus, allele-level resolution.

Some deviations from HWE were found in the studied populations (Table 2). Major deviations were reported for all loci, except for HLA-DQB1 in the MD population, and for HLA-A and B in the BD population, while minor deviations were reported in the CD groups, except for HLA-DQB1 that was not found to deviate from HWE proportions. While substantial efforts were made to diversify recruitment drive locations and donor communities, inbreeding caused by family marriages remains a significant cultural factor in this region which leads to excess homozygosity and deviation from HWE proportions. Additionally, genetic drift could have influenced some of the smaller populations like BD. To estimate haplotype frequencies for the studied groups, we used an EM algorithm built to accommodate missing loci, mixed resolution HLA genotypes and deviations from HWE proportions [8]. Additionally, other researchers have shown the robustness of the EM algorithm results in the presence of deviations from HWE proportions [19]. The main findings indicated robustness of the estimated frequencies, especially with minor deviations from HWE or with large sample sizes. The authors also found that excess heterozygosity led to loss of accuracy for the estimated frequencies, while excess homozygosity had little effect on the estimation accuracy. Given these findings, we suspect that deviations from HWE proportions in our data had a negligible effect on the quality of the estimated haplotype frequencies.

We have compared the studied Arab populations to select US groups, where the selection was driven by possible ancient or recent genetic ties with these populations due to historic bottleneck and/or migration events over multiple generations either directly to Israel or to neighboring countries. Population genetics analysis shows similarities among the three analyzed Arab populations: Arabs of Muslim Descent, Arabs of Christian Descent and Arabs of Bedouin Descent as well as the US Middle Eastern/North African coast populations. Genetic similarities were also seen with some African groups. Other researchers have shown similar genetic proximities between Arabs in this region and some African groups; similarities mainly attributed to ancient historic



(a)

(b)

Fig. 1. Comparison of Hadassah Arab populations with some US populations by Principal Component Analysis (PCA) a) first and second PCs, b) second and third PCs. MD: Arabs of Muslim Descent, CD: Arabs of Christian Descent, BD: Arabs of Bedouin Descent, AAFA: African-American, AFB: African, CARB: Black Caribbean, MENAFC: Middle East/North African coast, EURCAU: European Caucasian.

migration, the slave trade across the Indian ocean, procreation patterns across many generations, and to proximity of the Arabian Peninsula to the African black nations [16,20,21]. Due to the paucity of allele-level, five-locus data published from the region, we could not directly compare our results with other neighboring populations. However, we detected some significant allele and haplotype overlap with lower resolutions or three-locus frequencies reported from populations of close geographical proximity like the Ezer-Mizion Arab population [12], Greece [14] and Kuwait [13].

Even though we report similarities with other world populations, the studied Arab groups have some unique aspects, as indicated by multiple new HLA class I alleles typed and reported to the IMGT database (Table 3). Most of the common alleles and haplotypes are shared among the three Arab group. However, some private alleles were unique to each studied population, possibly caused by the lack of mixing between these three groups and the neighboring communities. It is worth noting that the Hadassah Arab donors do not cluster with the US European Caucasian population which could explain why patients from this region are underserved by the larger bone marrow registries in Europe and the US.

Fig. 2. Geographical locations of patients who found matched donors in the Hadassah Arab registry.

By studying the genetic HLA profiles of the Arab donors in the Hadassah registry, we have demonstrated how these donors could enrich the genetic diversity of the international donor pool. By the end of 2017 a total of 300 Arab donors were matched with Arab (n = 90) and non-Arab (n = 210) patients locally and worldwide. Most of these donors were 10/10 HLA matched (85%) while the remaining 15% were single allele mismatched (9/10). Fig. 2 demonstrates the geographic distribution of patients who found an HLA-matched donor in the studied pool. As of April 2018, 81 Arab donors proceeded to donate bone marrow (n = 19) and peripheral blood stem cells (n-62) evenly distributed between patients of Arab descent and other ethnicities.

Acknowledgments

This publication marks lifetime achievements of the coauthor Prof. Chaim Brautbar in the establishment of the Hadassah Unrelated Bone Marrow Donor Registry and the Arab Donor Project Outreach.

We thank the Kahane Foundation (KKF) and Mrs. Susanne Shaked and Hadassah Austria for generous support of the Arab Donor Project through the years. Without their contribution, we could not establish this life saving project.

Finally, the authors thank Dr. Michael Wright for his useful input and advice on the content and format of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.05.003.

References

[1] S. Spellman, M. Setterholm, M. Maiers, H. Noreen, M. Oudshoorn, M. Fernandez-Viña, et al., Advances in the selection of HLA-compatible donors: refinements in HLA typing and matching over the first 20 years of the National Marrow Donor Program Registry, Biol. Blood Marrow Transplant. 14 (2008) 37.

[2] L. Gragert, M. Eapen, E. Williams, J. Freeman, S. Spellman, R. Baitty, et al., HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry, N. Engl. J. Med. 371 (2014) 339.

[3] S.J. Lee, J. Klein, M. Haagenson, L.A. Baxter-Lowe, D.L. Confer, M. Eapen, et al., High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation, Blood 110 (2007) 4576.

[4] D.S. Serna, S.J. Lee, M.J. Zhang, K. Baker, M. Eapen, M.M. Horowitz, et al., Trends in survival rates after allogeneic hematopoietic stem-cell transplantation for acute and chronic leukemia by ethnicity in the United States and Canada, J. Clin. Oncol. 21 (2003) 3754.

[5] M. Maiers, M. Halagan, S. Joshi, H.S. Ballal, L. Jagannathan, S. Damodar, et al., HLA match likelihoods for Indian patients seeking unrelated donor transplantation grafts: a population-based study, Lancet Haematol. 1 (2014) e57.

[6] A. Nebel, D. Filon, B. Brinkmann, P.P. Majumder, M. Faerman, A. Oppenheim, The Y-chromosome pool of Jews as part of the genetic landscape of the Middle East, Am. J. Human Genet. 69 (2001) 1095.

[7] N. Cereb, H.R. Kim, J. Ryu, S.Y. Yang, Advances in DNA sequencing technologies for high resolution HLA typing, Hum. Immunol. 75 (2015) 923.

[8] C.M.M. Kollman, L. Gragert, et al., Estimation of HLA-A, -B, -DRB1 haplotype frequencies using mixed resolution data from a National Registry with selective retyping of volunteers, Hum. Immunol. 68 (2007) 950.

[9] S.W. Guo, E.A. Thompson, Performing the exact test of Hardy-Weinberg proportion for multiple alleles, Biometrics 48 (1992) 361.

[10] A.K. Lancaster, R.M. Single, O.D. Solberg, M.P. Nelson, G. Thomson, PyPop update–a software pipeline for large-scale multilocus population genomics, Tissue Antigens 69 (Suppl 1) (2007) 192.

[11] M. Lynch, B. Walsh, Genetics and Analysis of Quantitative Traits, Sinauer, Sunderland, Mass, 1998.

[12] S. Manor, M. Halagan, N. Shriki, I. Yaniv, B. Zisser, M. Maiers, et al., High-resolution HLA A ~ B ~ DRB1 haplotype frequencies from the Ezer Mizion Bone Marrow Donor Registry in Israel, Hum. Immunol. 77 (2016) 1114.

[13] M.Z. Haider, M.A. Zahid, H.N. Dalal, M.A. Razik, Human leukocyte antigen HLA-DRB1 alleles in Kuwaiti Arabs with schizophrenia, Am. J. Med. Genet. 96 (2002) 870.

[14] J. Pingel, U.V. Solloch, J.A. Hofmann, V. Lange, G. Ehninger, A.H. Schmidt, High-resolution HLA haplotype frequencies of stem cell donors in Germany with foreign parentage: how can they be used to improve unrelated donor searches? Hum. Immunol. 74 (2013) 330.

[15] L. Gragert, A. Madbouly, J. Freeman, M. Maiers, Six-locus high resolution HLA haplotype frequencies derived from mixed-resolution DNA typing for the entire US donor registry, Hum. Immunol. 74 (2013) 1313.

[16] P. Cano, M. Testi, M. Andreani, E. Khoriaty, J. Bou Monsef, T. Galluccio, et al., HLA population genetics: a Lebanese population, Tissue Antigens 80 (2012) 341.

[17] M.A. Moheeb Al-Awwami, Hind Al-Humidan, et al., HLA haplotype frequencies in Saudi Arabia for design of a Saudi stem-cell registry, Hum. Immunol. 73 (2012) 106.

[18] A.H. Hajeer, M.A. Al Balwi, F. Aytül Uyar, Y. Alhaidan, A. Alabdulrahman, I. Al Abdulkareem, et al., HLA-A, -B, -C, -DRB1 and -DQB1 allele and haplotype frequencies in Saudis using next generation sequencing technique, Tissue Antigens 82 (2013) 252.

[19] R.M. Single, D. Meyer, J.A. Hollenbach, M.P. Nelson, J.A. Noble, H.A. Erlich, et al., Haplotype frequency estimation in patient populations: the effect of departures from Hardy-Weinberg proportions and collapsing over a locus in the HLA region, Genet. Epidemiol. 22 (2002) 186.

[20] J.L. Rodriguez-Flores, K. Fakhro, F. Agosto-Perez, M.D. Ramstetter, L. Arbiza, T.L. Vincent, et al., Indigenous Arabs are descendants of the earliest split from ancient Eurasian populations, Genome Res. 26 (2016) 151.

[21] R. Laso-Jadart, C. Harmant, H. Quach, N. Zidane, C. Tyler-Smith, Q. Mehdi, et al., The genetic legacy of the indian ocean slave trade: recent admixture and post-admixture selection in the Makranis of Pakistan, Am. J. Hum. Genet. 101 (2017) 977.