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High-resolution HLA A∼B∼DRB1 haplotype frequencies from the Ezer Mizion Bone Marrow Donor Registry in Israel

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ABSTRACT

We have investigated HLA population alleles and haplotype frequencies for the ethnicities that comprise the contemporary population of Israel, using a large data set from the Ezer Mizion Bone Barrow Donor Registry. We genotyped 275,699 individuals at the HLA-A, -B and -DRB1 loci using HLA genotyping methods. HLA A∼B∼DRB1 haplotype frequencies were estimated from 19 sub-ethnic Jewish populations and other non-Jewish minorities using the maximum likelihood model, which accommodates typing ambiguities. We present overall and sub-ethnicity specific HLA diversity results of the registry, which will help guide a data-driven strategy for future registry expansion.

1. Introduction

Israel is home to the entire genetic spectrum of the Jewish Diaspora as well as for non-Jewish minorities, leading to marked ethnic diversity in a country of only eight million individuals. Before the founding of the modern state of Israel (1948), the Jewish Diaspora consisted of separate Jewish communities in Europe, North Africa, and Asia. Ancient communities of Jewish exiles formed in Iran and Iraq from the 7th to the 5th centuries BCE. From the 1st century BCE onward, Jewish communities spread westward through the north and south coasts of the Mediterranean basin, throughout the Levant and inland into the European continent. Subsequently, Jewish populations expanded in central and eastern Europe, along the North African coast and in the southern Arabian peninsula. Jews migrated eastwards from the Persian empire and reached as far as India and China. Toward the late 19th century through the 20th century, there was significant immigration of Jews from Europe to North and South America. Admixtures of Jewish migrants with indigenous host populations led to increasing genetic diversity between individual Diaspora communities, while cultural and religious forces maintained coherence of the Jewish people [1–3]. During the last 100 years, increasing immigration to Israel, together with the growth of Muslim and Druze populations within the boundaries of the State have resulted in a panoply of sub-ethnicities that make up the patchwork of modern Israeli society. As second and third generation Israelis start marrying outside of their ancestral subethnicities, an additional layer of allelic diversity has been introduced into the HLA landscape in Israel, leading to intergenerational immunogenetic differences within the Israeli population [4].

In the last decades, the successful use of highly matched unrelated volunteer donors for hematopoietic stem cell transplantation (HSCT) has stimulated the development of many national volunteer unrelated donor stem cell registries. This paper outlines analyses of HLA population haplotype frequencies in a large stem cell donor registry to characterize the genetic population profile of the contemporary Israeli population. In addition to the large extent of the population size analyzed, the high-resolution HLA profile presented in this study improves on data obtained in previous studies [2,5–8]. This analysis is the first phase of a project that seeks to guide strategic planning for donor recruitment and expansion of the Ezer Mizion Bone Marrow Donor Registry (EM BMDR) in Israel.

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2. Materials and methods

2.1. Study population

We examined all 754,135 unrelated volunteer donors registered in EM BMDR from its inception through June 2014 to gauge HLA haplotype diversity within the Israeli population. All subjects provided informed consent for registration at recruitment and self-reported their parents' country of origin, permitting us to assign sub-ethnicities. Each sub-ethnic population included only individuals who self-reported the same sub-ethnic population for both parents; multi- or mixed-ethnicity donors were excluded from this analysis. The study was approved by the Ethics Committee of Rabin Medical Center, and was conducted in accordance with the 2014 Ministry of Health (Israel) Guideline for Clinical Trials in Human Subjects.

2.2. HLA genotyping

HLA typing analyses evolved during the building of the EM BMDR roster, starting with serologic determinations and evolving to DNA-based testing at low, intermediate, and allele resolution (SSO-, SSP-, or SBT based). Only data genotyped by DNA-methods was used in this analysis. The initial dataset included 67 sub-ethnicities, with an average sample size of 5200 (2–79,066) per population. However, only 19 populations, containing a total of 275,699 donors, were large enough for analysis, based on a minimum sample size per of >200 high-resolution typed samples at HLA-A, -B and -DRB1 loci per sub-ethnicity (Table 1 and Fig. 1). It should be noted that Argentina and USA population are derived from emigrants of European Jews; SEE sub-ethnic population include Jews from Romania, Bulgaria, Moldova, Greece, Yugoslavia, Albania, Serbia, Transylvania and Cyprus; USSR sub-ethnic population include Jews from Russia, Ukraine, Belarus, Lithuania, Latvia and East Europe.

Table 1
A list of all 19 analyzed Ezer Mizion populations and sample counts.

Ezer Mizion populations	Sample counts
Arab	12,300
Argentina[a]	4307
Ashkenazi	4625
Bukhara	2317
Druze	5914
Ethiopia	5928
Georgia	4471
Iran	8153
Iraq	13,270
Israel	69,716
Kavkaz	2840
Libya	3739
Morocco	36,718
Poland	13,871
SEE[b]	11,179
Tunisia	9070
USA[a]	6058
USSR[c]	45,681
Yemen	15,542
Total	275,699

[a] Argentina and USA population are derived from emigrants of European Jews.
[b] SEE include Romania, Bulgaria, Moldova, Greece, Yugoslavia, Albania, Serbia, Transylvania and Cyprus.
[c] USSR include Russia, Ukraine, Belarus, Lithuania, Latvia and East Europe.

Fig. 1. Hot spot map of the EM populations used for analysis.

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Table 2a
Top 10 HLA-A Alleles frequencies of all 19 analyzed populations.

Rank	HLA-A	ARAB	ARGENTINA	ASHKENAZ	BUKHARA	DRUZE	ETHIOPIA	GEORGIA	IRAN	IRAQ	ISRAEL
1	A*01:01	0.164	0.130	0.108	0.069	0.089	0.039	0.041	0.218	0.183	0.143
2	A*02:01	0.150	0.184	0.154	0.053	0.030	0.063	0.152	0.013	0.019	0.181
3	A*03:02	0.041	0.080	0.068	0.131	0.042	0.073	0.193	0.078	0.107	0.093
4	A*02:02	0.004	0.001	0.002	0.071	0.186	0.118	0.000	0.037	0.034	0.000
5	A*24:02	0.101	0.014	0.015	0.019	0.016	0.028	0.011	0.010	0.088	0.006
6	A*30:02	0.012	0.037	0.007	0.031	0.081	0.018	0.000	0.147	0.007	0.002
7	A*30:01	0.055	0.003	0.029	0.143	0.006	0.080	0.008	0.015	0.061	0.050
8	A*23:01	0.032	0.022	0.025	0.005	0.021	0.030	0.045	0.017	0.043	0.035
9	A*24:07	0.000	0.001	0.001	0.001	0.001	0.000	0.001	0.131	0.001	0.000
10	A*26:01	0.055	0.111	0.118	0.034	0.069	0.002	0.107	0.070	0.045	0.097

Rank	HLA-A	KAVKAZ	LIBYA	MOROCCO	POLAND	SEE	TUNISIA	USA	USSR	YEMEN
1	A*01:01	0.063	0.146	0.197	0.129	0.123	0.171	0.131	0.121	0.020
2	A*02:01	0.100	0.201	0.025	0.184	0.192	0.030	0.190	0.217	0.027
3	A*03:02	0.075	0.078	0.100	0.063	0.078	0.066	0.080	0.086	0.038
4	A*02:02	0.000	0.000	0.107	0.001	0.000	0.153	0.001	0.001	0.104
5	A*24:02	0.150	0.013	0.114	0.090	0.012	0.120	0.012	0.018	0.014
6	A*30:02	0.004	0.001	0.042	0.007	0.003	0.003	0.036	0.003	0.006
7	A*30:01	0.039	0.063	0.008	0.035	0.039	0.052	0.005	0.033	0.004
8	A*23:01	0.012	0.024	0.028	0.030	0.028	0.030	0.025	0.023	0.135
9	A*24:07	0.003	0.001	0.001	0.001	0.001	0.001	0.000	0.001	0.001
10	A*26:01	0.086	0.035	0.087	0.128	0.107	0.046	0.122	0.097	0.013

Table 2b
Top 10 HLA-B Alleles of all 19 analyzed populations.

Rank	HLA-B	ARAB	ARGENTINA	ASHKENAZ	BUKHARA	DRUZE	ETHIOPIA	GEORGIA	IRAN	IRAQ	ISRAEL
1	B*35:08	0.061	0.154	0.088	0.000	0.120	0.012	0.188	0.143	0.130	0.160
2	B*49:01	0.049	0.013	0.011	0.027	0.056	0.187	0.068	0.018	0.051	0.024
3	B*38:01	0.044	0.135	0.167	0.142	0.027	0.000	0.096	0.055	0.042	0.120
4	B*44:03	0.019	0.058	0.047	0.099	0.004	0.016	0.033	0.039	0.003	0.074
5	B*35:01	0.050	0.013	0.021	0.034	0.016	0.003	0.075	0.013	0.017	0.005
6	B*53:01	0.021	0.003	0.002	0.008	0.024	0.038	0.001	0.133	0.030	0.015
7	B*07:05	0.010	0.003	0.030	0.122	0.004	0.008	0.007	0.035	0.073	0.001
8	B*18:01	0.066	0.040	0.034	0.019	0.066	0.023	0.042	0.112	0.058	0.051
9	B*14:02	0.032	0.105	0.104	0.044	0.053	0.076	0.005	0.011	0.013	0.081
10	B*50:02	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Rank	HLA-B	KAVKAZ	LIBYA	MOROCCO	POLAND	SEE	TUNISIA	USA	USSR	YEMEN
1	B*35:08	0.144	0.142	0.071	0.116	0.150	0.123	0.144	0.003	0.070
2	B*49:01	0.017	0.011	0.046	0.015	0.015	0.023	0.011	0.015	0.044
3	B*38:01	0.052	0.013	0.091	0.166	0.145	0.041	0.152	0.116	0.046
4	B*44:03	0.020	0.097	0.089	0.049	0.062	0.099	0.062	0.058	0.157
5	B*35:01	0.111	0.013	0.012	0.025	0.011	0.014	0.014	0.135	0.023
6	B*53:01	0.004	0.001	0.009	0.002	0.002	0.010	0.003	0.002	0.071
7	B*07:05	0.084	0.027	0.003	0.007	0.003	0.025	0.004	0.005	0.028
8	B*18:01	0.071	0.065	0.074	0.038	0.042	0.069	0.037	0.055	0.031
9	B*14:02	0.075	0.018	0.036	0.101	0.101	0.040	0.100	0.076	0.062
10	B*50:02	0.000	0.102	0.003	0.000	0.000	0.002	0.000	0.000	0.000

2.3. HLA allele and haplotypes frequency analysis

Three-locus haplotype frequencies (A∼B∼DRB1) were estimated for each of the 19 populations, resolving phase and allelic ambiguity using the expectation–maximization (EM) algorithm [9,10]. The applied EM algorithm was designed to handle mixed resolution data [11,12]. Allele frequencies were calculated by summing across the haplotype frequencies. Deviations from Hardy–Weinberg equilibrium (HWE) were assessed at the allele-family level (first nomenclature field) using a chi-squared test as implemented in the software PyPop [13].

2.4. Clustering analysis

HLA haplotype frequency visualizations on the study populations were created using the CLUTO software [14] by clustering the top 100 haplotypes (rows) in the 19 studied populations, and separating them into eight clusters of haplotypes based on haplotype similarity across populations (columns). It should be noted that since CLUTO examines only the top 100 haplotypes in each sub-ethnicity, this analysis may highlight the dominant themes of a population's composition as compared with other tools such as principal components analysis or neighbor-joining (NJ).

3. Results

3.1. HLA allele frequency

HLA alleles frequency data are presented for 19 ethnic groups containing a total of 275,699 subjects from the EM BMDR. A summary of the 10 most common HLA-A, HLA-B and HLA-DRB1 alleles and their respective estimated frequencies are presented in Table 2. Top 100 alleles frequencies of HLA-A, HLA-B and HLA–DRB1 loci are provided in Supplementary Table S1. The most frequent alleles for the HLA-A locus were A*01:01, A*02:01 and A*03:02. The most frequent alleles for the locus HLA-B were B*35:08, B*49:01 and B*38:01. The most frequent alleles for the locus HLA-DRB1 were

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Table 2c
Top 10 HLA-DRB1 Alleles of all 19 analyzed populations.

Rank	HLA-DRB1	ARAB	ARGENTINA	ASHKENAZ	BUKHARA	DRUZE	ETHIOPIA	GEORGIA	IRAN	IRAQ
1	DRB1*11:04	0.186	0.167	0.175	0.201	0.231	0.000	0.242	0.298	0.339
2	DRB1*07:01	0.087	0.123	0.133	0.214	0.094	0.141	0.050	0.089	0.093
3	DRB1*13:02	0.048	0.060	0.062	0.009	0.074	0.172	0.138	0.172	0.080
4	DRB1*04:02	0.024	0.108	0.115	0.051	0.011	0.000	0.007	0.021	0.044
5	DRB1*03:01	0.092	0.062	0.063	0.041	0.100	0.125	0.045	0.093	0.058
6	DRB1*14:01	0.044	0.026	0.019	0.116	0.026	0.003	0.078	0.048	0.023
7	DRB1*01:02	0.044	0.108	0.106	0.048	0.035	0.100	0.020	0.016	0.014
8	DRB1*15:03	0.015	0.000	0.000	0.000	0.000	0.099	0.000	0.000	0.000
9	DRB1*04:03	0.093	0.034	0.036	0.020	0.093	0.017	0.051	0.047	0.026
10	DRB1*13:03	0.052	0.019	0.015	0.047	0.026	0.049	0.038	0.048	0.036

Rank	HLA-DRB1	KAVKAZ	LIBYA	MOROCCO	POLAND	SEE	TUNISIA	USA	USSR	YEMEN
1	DRB1*11:04	0.215	0.174	0.164	0.178	0.201	0.232	0.176	0.163	0.057
2	DRB1*07:01	0.083	0.233	0.239	0.126	0.120	0.180	0.133	0.128	0.178
3	DRB1*13:02	0.035	0.049	0.054	0.072	0.058	0.055	0.071	0.058	0.055
4	DRB1*04:02	0.127	0.037	0.052	0.134	0.122	0.041	0.128	0.092	0.080
5	DRB1*03:01	0.049	0.043	0.046	0.060	0.061	0.064	0.062	0.063	0.115
6	DRB1*14:01	0.082	0.005	0.049	0.019	0.030	0.010	0.018	0.026	0.019
7	DRB1*01:02	0.074	0.023	0.038	0.106	0.105	0.038	0.109	0.098	0.008
8	DRB1*15:03	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.001
9	DRB1*04:03	0.021	0.056	0.059	0.030	0.023	0.054	0.024	0.021	0.090
10	DRB1*13:03	0.022	0.087	0.015	0.010	0.019	0.050	0.002	0.024	0.024

Table 3
Top 10 A∼B∼DRB1 Haplotype frequencies of all 19 analyzed populations.

Rank	Haplotype	ARAB	ARGENTINA	ASHKENAZ	BUKHARA	DRUZE	ETHIOPIA	GEORGIA	IRAN	IRAQ
1	A*03:02∼B*44:03∼DRB1*07:01	0.0003	0.0000	0.0001	0.0837	0.0000	0.0001	0.0002	0.0006	0.0001
2	A*23:01∼B*44:03∼DRB1*07:01	0.0011	0.0025	0.0021	0.0004	0.0002	0.0006	0.0005	0.0014	0.0006
3	A*26:01∼B*38:01∼DRB1*04:02	0.0012	0.0519	0.0606	0.0022	0.0012	0.0000	0.0019	0.0013	0.0032
4	A*33:01∼B*14:02∼DRB1*01:02	0.0124	0.0267	0.0236	0.0009	0.0101	0.0002	0.0016	0.0048	0.0039
5	A*02:01∼B*50:02∼DRB1*07:01	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
6	A*30:01∼B*13:02∼DRB1*07:01	0.0072	0.0011	0.0113	0.0538	0.0001	0.0030	0.0008	0.0028	0.0124
7	A*29:01∼B*07:05∼DRB1*14:01	0.0003	0.0002	0.0000	0.0533	0.0000	0.0000	0.0012	0.0021	0.0015
8	A*30:02∼B*53:01∼DRB1*03:01	0.0000	0.0000	0.0002	0.0004	0.0000	0.0001	0.0000	0.0392	0.0031
9	A*30:01∼B*38:01∼DRB1*11:04	0.0000	0.0000	0.0003	0.0392	0.0000	0.0000	0.0000	0.0000	0.0000
10	A*24:07∼B*18:01∼DRB1*11:04	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0383	0.0000
No. of haplotypes with freq > 0.0001	1579	1449	1506	692	699	1117	948	719	877	

Rank	Haplotype	ISRAEL	KAVKAZ	LIBYA	MOROCCO	POLAND	SEE	TUNISIA	USA[a]	USSR	YEMEN
1	A*03:02∼B*44:03∼DRB1*07:01	0.0008	0.0024	0.0000	0.0011	0.0003	0.0005	0.0005	0.0003	0.0027	0.0004
2	A*23:01∼B*44:03∼DRB1*07:01	0.0074	0.0010	0.0000	0.0009	0.0018	0.0029	0.0013	0.0020	0.0041	0.0793
3	A*26:01∼B*38:01∼DRB1*04:02	0.0423	0.0020	0.0022	0.0199	0.0677	0.0579	0.0129	0.0637	0.0416	0.0006
4	A*33:01∼B*14:02∼DRB1*01:02	0.0174	0.0574	0.0026	0.0043	0.0218	0.0249	0.0048	0.0215	0.0211	0.0004
5	A*02:01∼B*50:02∼DRB1*07:01	0.0000	0.0000	0.0554	0.0000	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000
6	A*30:01∼B*13:02∼DRB1*07:01	0.0115	0.0198	0.0078	0.0049	0.0139	0.0120	0.0099	0.0026	0.0141	0.0003
7	A*29:01∼B*07:05∼DRB1*14:01	0.0001	0.0314	0.0000	0.0001	0.0001	0.0000	0.0001	0.0001	0.0006	0.0000
8	A*30:02∼B*53:01∼DRB1*03:01	0.0002	0.0019	0.0001	0.0002	0.0000	0.0001	0.0003	0.0002	0.0000	0.0001
9	A*30:01∼B*38:01∼DRB1*11:04	0.0003	0.0000	0.0000	0.0000	0.0003	0.0001	0.0001	0.0000	0.0011	0.0000
10	A*24:07∼B*18:01∼DRB1*11:04	0.0000	0.0008	0.0000	0.0002	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000
No. of haplotypes with freq > 0.0001	1012	922	814	943	967	1035	1061	936	1215	984	

DRB1*11:04, DRB1*07:01 and DRB1*13:02. HLA-DRB1*11:04 was observed with a frequency greater than 15% in all populations except Yemen and Ethiopia. Locus level deviations from HWE were detected at HLA-A, -B, and -DRB1 in 11 of the 19 analyzed populations. The most significant HWE deviation was detected at HLA-B among those donors who self-designated themselves as "Israeli" between the homozygous expected and observed counts (5326 expected, 5922 observed, $p = 4 \times 10^{-16}$). This result was expected since the "Israel" group comprises of donors who reported that their parents were born in Israel, however their specific ethnic origin was not indicated. Thus, the "Israel" group is likely to be of mixed ethnicity with parents who do not necessarily share the same ethnic origin. Data results of HWE analysis are provided in Supplementary Table S2.

3.2. Frequent HLA-A, HLA-B and HLA-DRB1 haplotypes

Table 3 illustrates the top 10 ranked A∼B∼DRB1 haplotypes for all 19 analyzed populations. Results of the complete haplotype frequencies are provided in Supplementary Table S3. The number of haplotypes with a minimum frequency of 10^{-4} ranged from 692 to 1579 depending on sub-ethnicity groups. Several haplotypes were shared among sub-ethnic populations while others remained private. The haplotype A*26:01∼B*38:01∼DRB1*04:02 was shared among Ashkenazi populations with a frequency of 2.3–6.7%. The haplotypes A*33:01∼B*14:02∼DRB1*01:02 and A*30:01∼B*13:02∼DRB1*07:01, common in the US Middle Eastern/North African coast population, were common in most sub-ethnicities with frequencies 0.02–5.3%. Also, A*02:05∼B*50:01∼DRB1*07:01,

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common to most Arab populations, was among the top 100 haplotypes in the Ezer Mizion data with frequencies ranging from 0.02% to 1.29%.

3.3. Classification of populations and haplotypes

Fig. 2 shows the clustering of the Top 100 haplotypes (rows) in the 19 studied sub-ethnicities, which could be resolved into eight haplotype clusters based on similarities across populations (columns). Several inferences can be drawn from the generated clusters. As expected, the largest cluster of haplotypes (cluster 4) includes the Ashkenazi populations. These populations cluster more tightly together than the non-Ashkenazi groups. Other clusters correlate with geographic proximity, such as Iran and Iraq (cluster 3), Bukhara and Iraq (cluster 2, although Bukhara also contained some private haplotypes) and Libya and Tunisia (cluster 5). Other clustering trends were noted. As expected, populations related by immigration patterns form clusters such as Morocco and Tunisia, and Ashkenaz, Poland and USSR. In general, HLA haplotypes of most Ashkenazi populations cluster together while those of non-Ashkenazi populations are more divergent.

4. Discussion

We described allele and haplotype frequency distribution based on data obtained from 275,699 hematopoietic stem cell donors, representing 19 different ethnic groups contained in the Ezer Mizion Bone Marrow Donor Registry using a maximum likelihood model that can resolve genotyping ambiguities. The large sample size of this study population validates the findings of previously published haplotype frequencies that relied on a smaller sample size with a less stringent HLA-typing resolution [2,5–8]. Additionally, we present information regarding unique sub-ethnicities that have not previously been reported (Bukhara) or have been reported with limited number of subjects (Ethiopia and Druze) [7]. The sub-ethnic populations of the donors included in this study were stratified according to the donors' self-reporting of their parents' origin. It should be mentioned that the extent to which self-reporting ethnicity or geographic ancestry will correspond to genetic ancestry is likely to vary as previously discussed by Hollenbach et al. [15]. This fact is specifically observed in one of our large, but undistinguished, self-reported population that is composed of donors who listed themselves as "Israel". This heterogeneous group likely consists of many mixed sub-ethnicity donors for whom sub-ethnic assignations cannot be made.

The cross-sectional nature of our registry permits a detailed view of the contemporary Israeli genetic profile. We compared our results to a previously published study by the Hadassah registry (HD) in Israel [2] which in some ways were similar to our data and in other divergent, most likely due to differing sample sizes, resolution level and recruitment strategies. In order to compare both registries we rolled up the EM BMDR data to the 2-digit level, which could introduce a source of discrepancy between the results. As expected, we have observed that populations of geographic proximity in both studies share common haplotype. Examples are (to name a few) Iran, Libya and Israeli in the data sets from both registries, Algeria and Morocco in the data set of HD vs. Morocco in EM BMDR data set, Argentina in the HD data set vs. Argentina and Uruguay in EM BMDR, Germany and Poland in the HD study vs. Poland in EM BMDR donors. Some haplotypes emerged as common across different geographic areas, for example, the haplotype A*26:01∼B*38:01∼DRB1*04:02 and A*24:02∼B*35:02∼DRB1*11:04 are common in most Ashkenazi populations while the haplotype A*02:05∼B*50:01∼DRB1*07:01

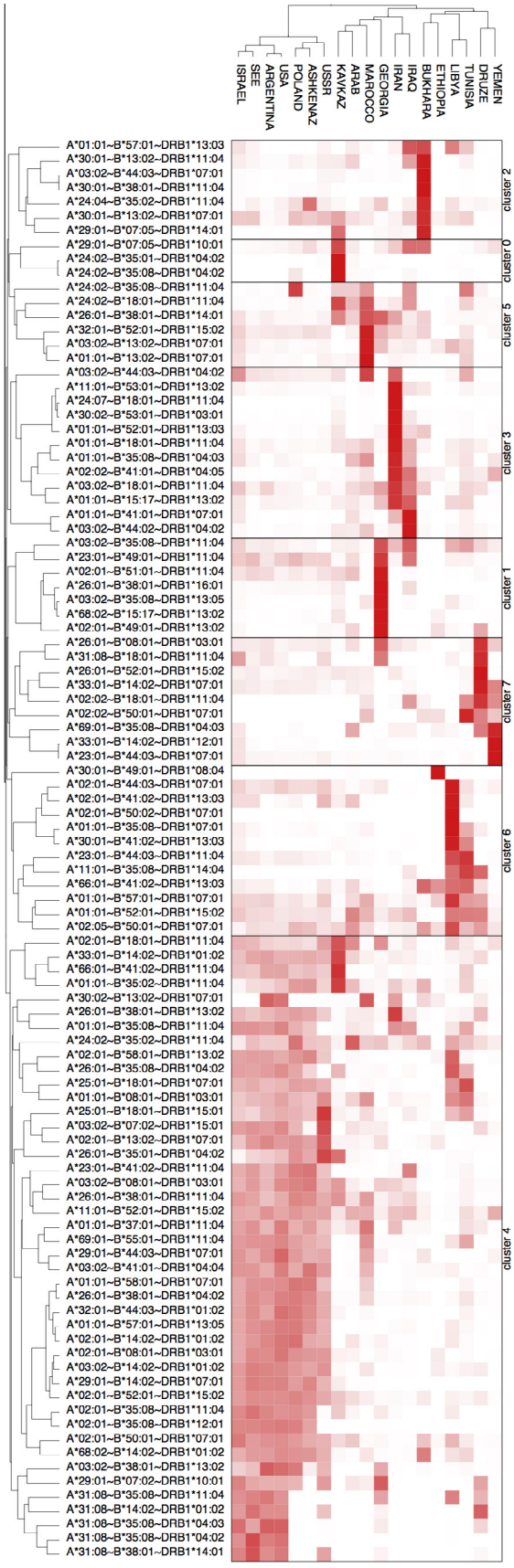

Fig. 2. Clustering of the top 100 haplotypes on 19 sub-ethnic populations defined by country of origin.

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and A*02:01∼B*50:01∼DRB1*07:01 were shared in Middle Eastern populations in both studies. Some Jewish sub-ethnicities in both the Hadassah and EM BMDR registries share some common haplotypes such as: A*26∼B*38∼DRB1*04, A*24∼B*35∼DRB1*04 and A*24∼B*35∼DRB1*11. It also should be noted that some allele families appear to be shared among most populations (e.g. A*02, 24 and 26; B*35, 38 and 50 and DRB1*04, 07 and 11).

Sub-ethnic and genetic heterogeneity within the Israeli population necessitates a population specific unrelated bone marrow donor registry that reflects the commonalities and diversities of the overall population. Enhanced representation of both common and uncommon alleles increases the likelihood of HLA-matching between Israeli donors and Israeli patients (including Jewish patients in the Diaspora) of all sub-ethnicities. The results or our analysis have implications on cross-population matching and can help in donor searches and population-based recruitment strategies. Gragert et al. published a recent study regarding the likelihood of finding a suitably matched adult donor or cord-blood unit in the NMDP registry that included projections that account for future registry growth [16]. The development of accurate models for prediction of optimal registry size and expansion require the determination of high-resolution HLA haplotype frequencies within the target population that includes cross-sectional coverage of sub-ethnicities within said population. The haplotype frequencies of the major sub-ethnic groups in the EM BMDR presented in this current study are part of a strategic effort to guide recruitment goals and expansion of the Ezer Mizion volunteer adult unrelated donor registry.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.humimm.2016.09.004.

References

[1] H.H. Ben-Sasson (Ed.), A History of the Jewish People, Harvard University Press, Cambridge, MA, 1976, pp. 570–573.
[2] W. Klitz, L. Gragert, M. Maiers, M. Fernandez-Viña, Y. Ben-Naeh, G. Benedek, et al., Genetic differentiation of the Jewish population, Tissue Antigens 76 (2010) 442–458.
[3] R. Mahler, A History of Modern Jewry, Schocken, 1971.
[4] M. Israeli, M. Oudshoorn, G.W. Haasnoot, T. Klein, B. Zisser, G. Bach, et al., Age-dependent HLA profiles of the Israeli population: impact on hematopoietic cell donor recruitment and availability, Immunogenetics 66 (9–10) (2014) 525–533.
[5] B. Bonné-Tamir, J.G. Bodmer, W.F. Bodmer, P. Pickbourne, C. Brautbar, E. Gazit, et al., HLA polymorphism in Israel. 9. An overall comparative analysis, Tissue Antigens 11 (1978) 235–250.
[6] C. Brautbar, S. Battat, L. Sherman, R. Benhamu, O. Cohen, HLA antigens in Israeli Ashkenazi and non-Ashkenazi Jews, in: M. Aizawa (Ed.), HLA in Asia-Oceania, Proceedings of the Third Asia Oceania Histocompatibility Workshop Conference, University Press, Sapporo, Hokkaido, 1986, pp. 324–327.
[7] A. Amar, O.J. Kwon, U. Motro, C.S. Witt, B. Bonne-Tamir, R. Gabison, et al., Molecular analysis of HLA class II polymorphisms among different ethnic groups in Israel, Hum. Immunol. 60 (8) (1999) 723–730.
[8] A. Roitberg-Tambur, A. Friedmann, C.S. Witt, et al., HLA polymorphism in Moroccan Jewry, Hum. Immunol. 40 (1) (1994) 61–67.
[9] L. Excoffier, M. Slatkin, Maximum-likelihood estimation of molecular haplotype frequencies in a diploid population, Mol. Biol. Evol. 12 (5) (1995) 921–927.
[10] A.P. Dempster, N.M. Laird, D.B. Rubin, Maximum likelihood from incomplete data via the EM algorithm, J. R. Stat. Soc. Ser. B (Methodological) 39 (1) (1977) 1–38.
[11] C. Kollman, M. Maiers, L. Gragert, C. Müller, M. Setterholm, M. Oudshoorn, 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) 950–958.
[12] 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 (10) (2013) 1313–1320.
[13] 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 4 (Suppl. 1) (2007) 192–197.
[14] G. Karypis, CLUTO: A Clustering Toolkit Technical Report 02-017, University of Minnesota, 2002.
[15] J.A. Hollenbach, A. Saperstein, M. Albrecht, C. Vierra-Green, P. Parham, P.J. Norman, et al., Race, ethnicity and ancestry in unrelated transplant matching for the national marrow donor program: a comparison of multiple forms of self-identification with genetics, PLoS One 10 (8) (2015) e0135960.
[16] 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) 339–348.