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Research article

HLA major allele group frequencies in a diverse population of the Free State Province, South Africa

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ABSTRACT

Background: Human Leucocyte Antigens (HLA) play a vital role in disease pathogenesis and transplant rejection. HLA-typing is a useful tool in predicting disease progression and to identify potential organ donors. Due to human migration and known ethnic variation, frequent targeted HLA sequencing of specific populations is crucial to increase their representation in global reference panels.
Materials and methods: We performed a retrospective file audit of all HLA-typings done in our setting from 2005-2019. We discuss data for the major HLA-A, HLA-B, HLA-C, and HLA-DRB1 allele groups.
Results: Overall, the most common allele groups were HLA-A*02, HLA-B*15, HLA-C*07 and HLA-DRB1*03. For the African descent group, the most common alleles were HLA-A*30, HLA-B*15, HLA-C*07 and HLA-DRB1*03. For the European descent group, the most common alleles were HLA-A*02, HLA-B*07, HLA-C*07 and HLA-DRB1*15. For the mixed ancestry group, the most common allele groups were HLA-A*02, HLA-B*15, HLA-C*02 and HLA-DRB1*13. HLA-B*44 was identified as the most common allele group in patients with renal failure.
Discussion and conclusion: The significant variation within the HLA frequencies between the different ethnic groups highlights the value of population-specific HLA-typing. Furthermore, the identification of HLA-B*44 as a prominent HLA in our renal failure population warrants in-depth investigation of this group.

1. Introduction

The major histocompatibility complex (MHC) are highly polymorphic cell surface molecules involved in foreign organ rejection. In humans, the MHC is called the human leukocyte antigens (HLA) system, as they were first identified and characterised using alloantibodies against leukocytes [1]. Genes encoding HLA are located on the short arm of chromosome 6 (6p21) and contains roughly 3,600-kilobases of DNA [2]. The HLA system consists of class I and class II antigens. Class I has HLA-A, HLA-B and HLA-C, and class II contains HLA-DR, HLA-DQ and HLA-DP [3].

The HLA complex is one of the most polymorphic genetic regions in the human genome [4] and is encoded by more than 220 genes, with 21 core genes of interest [5]. The high level of polymorphism is evident with over 3,000 variants reported of the HLA-B subtype alone [6]. Since the 1960s, the association between HLA genotypes and disease has been extensively researched, with several hundred conditions reported to occur more commonly in people with specific HLA genotypes [7]. HLA typing may also greatly assist in raising awareness of the possible underdiagnosis of particular disorders, especially in resource-constrained developing countries. This is illustrated by two studies from Kazakhstan, where disease-associated HLA genotypes were found to be much more common in the population than their associated disorders, probably highlighting some impairment to diagnosis [8, 9]. Therefore, we can use HLA data to assess potentially underscored diseases in our population. Furthermore, the frequency distribution of HLA alleles in different human ethnic groups can contribute to determining the heritage, human migrations and admixtures amongst diverse human populations [10].

Due to the limited number of organ and stem cell donors available, country-specific donor registries have attempted to make their registries globally available to increase the possibility to find suitable matches for patients awaiting transplants. However, searching each database for a match can become a very arduous task. Therefore, by determining the allele and haplotype frequencies in specific countries and regions, it can be established if some patients would benefit from being on the transplant list of another country [11].

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Limited HLA frequency data is available for the South African population. Due to this under-representation of southern African genetic data, the current global reference panels (particularly disease association studies) have limited value for these populations. Therefore, targeted HLA sequencing of the diverse southern African populations is essential to increase their representation in global reference panels [12]. According to a 2018 South African Bone Marrow Registry (SABMR) study, determining HLA alleles and haplotypes will contribute to the development of a resource for disease association, anthropology, and evolutionary studies, support models for population-specific vaccine development and advance donor enrolment in South African populations [13]. The last formal study on people residing in our local Free State Province, South Africa, was published in 1997 [14]. Taking human migration and a steady increase in urbanisation in South Africa into consideration [15], it can be hypothesised that a possible change in HLA-allele frequencies may have occurred since the previous publication. Furthermore, the majority of the South African HLA studies focus mainly on healthy individuals [13, 14, 16, 17]. Therefore, determining HLA-frequencies in specific disorders may significantly contribute to establishing disease-specific reference panels for our population.

At the Universitas Academic Hospital in Bloemfontein, Free State, South Africa, HLA typing has been performed for many years for various reasons, but mostly related to pre-transplantation work-up. Thus, genotypic HLA data to calculate HLA allele frequency is readily available. Therefore, we aimed to determine the HLA allele frequencies in this setting for a 15-year period (2005–2019).

2. Methods and materials

We performed a retrospective file audit of all HLA-typings done at the National Health Laboratory Service (NHLS) Tissue Typing laboratory at Universitas Academic Hospital from 2005 to 2019. This laboratory uses commercially available HLA SSP kits (Bio-Rad Medical Diagnostics GmbH, Germany) to perform HLA typings. The Bio-Rad kits were evaluated by the manufacturer by comparing these kits to another SSP kit and an SSO typing system using 167 transplant recipient and potential donor samples from two geographically distinct locations and found a 100% concordance [18]. Unfortunately, the specific geographical areas are not specified. Ethics approval (FS-HSD2020/0139/2502) was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State. Due to the study's retrospective nature, the requirement for informed consent was waived with the express provision that all results be de-identified. Further permission was given by the NHLS to access their patient result files. A total of 1,151 HLA profiles were analysed for this study. Individuals tested included (but not limited to) healthy possible donors, patients with end-stage renal failure awaiting kidney transplants and patients with haematological malignancies awaiting stem-cell transplantation. Together with the HLA data, the result files also contained data regarding the gender, ethnicity, the reason for HLA-typing, and the diagnosis. The manuscript was prepared according to the STrengthening the REporting of Immunogenomic Studies (STREIS) guidelines.

Results from the physical files were de-identified and placed into a single Microsoft® Excel® spreadsheet for analysis. The frequencies for each of the alleles were calculated by a direct counting method (total number of copies of the allele divided by 2n) [10] using Excel functions. Deviations from Hardy-Weinberg equilibrium (HWE) at allele level were analysed using a chi-squared test [19]. Pairwise linkage disequilibrium (LD) was calculated for all loci pairs using the Arlequin v3.5.2 software [20]. The empirical P-values were obtained by permutation testing (10,000 randomisations).

3. Results

3.1. Demographics and clinical details

The total population (n = 1,151) consisted of 661 (55.69%) people from African descent, 380 (33.01%) people from European descent, 107 (9.3%) people with mixed ancestry, 10 (0.9%) people from Asian descent, and 13 (1.13%) individuals with unclassified descendancy. Males comprised 54.2% and females 43.2% of the population, with 2.6% of the population with unknown genders (Table 1). We evaluated 406 (35.27%) healthy potential donors and 745 (64.73%) patients with varying diagnoses. The most common diagnoses were renal failure (n = 237), acute leukaemia (n = 77), aplastic anaemia (n = 36), Fanconi anaemia (n = 26) and chronic leukaemia (n = 19). A total of 233 (31.3%) HLA-typing requests were made without any clinical details reported for the patients.

3.2. HLA-allele group frequencies

3.2.1. HLA-allele group frequencies – total population (n = 1,151)

Out of the total population, twenty-six (26) HLA-A allele groups, fifty (50) HLA-B allele groups, fifteen (15) HLA-C allele groups, and fourteen (14) HLA-DRB1 allele groups were detected. In some cases, the healthcare providers requested not all HLA-subtypes; therefore, we postulate that there are probably more allele groups in our population, with our data having a slight underrepresentation. All HLA allele group subsets deviated from the expected HWE ($p < 0.05$), even within the different reported ethnic groups. This finding was expected based on our population's diverse heterogenous genetic makeup and is comparable to results reported from similarly diverse populations [13, 21]. We determined the three most common allele groups for each subtype for the total population, the various ethnic groups, and the donor populations (Table 2). We further determined the three most common allele groups in common disorder populations (Table 3). Due to the relatively low numbers (n < 40) of patients with other recorded disorders, HLA frequencies in these population groups are not discussed.

Among the 64 patients where HLA-DQB1 typing was done, six (6) allele groups were identified, with DQB1*03 (26.2%) being the most common allele group. However, because of the low numbers of patients, HLA-DQB1 results do not reach the minimum required statistical power to warrant further discussion.

The rarest allele groups in the total population, with a frequency of ≤0.1%, where HLA-A*10, HLA-A*21, HLA-A*28, HLA-A*73, HLA-B*16, HLA-B*17, HLA-B*21, HLA-B*22, HLA-B*28, HLA-B*43, HLA-B*54, HLA-B*61, HLA-B*64, HLA-B*75, HLA-B*76, HLA-C*09 and HLA-DRB1*02.

3.3. HLA-haplotype frequencies

Given that loci are out of HWE, and the haplotype estimation method we aimed to use assumes that they are, we were unable to determine HLA-haplotype frequencies for our population group.

3.4. Pairwise global linkage disequilibrium (LD)

Strong linkage was confirmed within HLA class 1 loci and between HLA class 1 and 2 loci. The LD was found to be $p < 0.05$ in the total population, as well as within the different ethnic groups investigated.

Table 1. Total population distribution as reported in the test request files (N = 1,151).

Ethnicity	Male	Female	Unknown Gender	Total
African descent (N = 641)	31.19%	23.02%	1.48%	55.69%
European descent (N = 380)	16.33%	15.73%	0.96%	33.01%
Mixed ancestry (N = 107)	5.56%	3.65%	0.09%	9.30%
Asian descent (N = 10)	0.52%	0.35%	0%	0.9%
Unknown ethnicity (N = 13)	0.61%	0.43%	0.09%	1.13%
Total	54.2%	43.2%	2.6%	

Table 2. The three most common HLA-allele group frequencies for the total population, specific ethnic groups, and donor groups.

	Total (N = 1,151)	African descent (N = 641)	European descent (N = 380)	Mixed Ancestry (N = 107)	All Donors (N = 406)	African descent donors (N = 189)	European descent donors (N = 165)
HLA-A	HLA-A*02 (15.3%), HLA-A*03 (9.1%), HLA-A*68 (9.1%)	HLA-A*30 (13.1%), HLA-A*68 (12.8%), HLA-A*02 (12.3%)	HLA-A*02 (22.4%), HLA-A*03 (15.7%), HLA-A*24 (9.4%)	HLA-A*02 (11.7%), HLA-A*30 (11.2%), HLA-A*68 (9.6%)	HLA-A*02 (17.6%), HLA-A*68 (11.8%), HLA-A*03 (9.3%)	HLA-A*68 (15.2%), HLA-A*02 (12.8%), HLA-A*30 (11.8%)	HLA-A*02 (22.5%), HLA-A*03 (14.6%), HLA-A*24 (11.4%)
HLA-B	HLA-B*15 (11.1%), HLA-B*44 (10.1%), HLA-B*07 (10%)	HLA-B*15 (12.6%), HLA-B*58 (11.7%), HLA-B*44 (9.9%)	HLA-B*07 (14.6%), HLA-B*44 (10.6%), HLA-B*51 (7.3%)	HLA-B*15 (17%), HLA-B*07 (10.3%), HLA-B*44 (9.3%), HLA-B*58 (9.3%)	HLA-B*07 (11.3%), HLA-B*15 (10.3%), HLA-B*44 (9.7%)	HLA-B*15 (11.9%), HLA-B*58 (11.4%), HLA-B*44 (9.5%)	HLA-B*07 (15.5%), HLA-B*44 (9.5%), HLA-B*51 (7.9%)
HLA-C	HLA-C*07 (19.3%), HLA-C*06 (14.6%), HLA-C*04 (11.5%)	HLA-C*07 (16.8%), HLA-C*06 (16.4%), HLA-C*04 (12.8%)	HLA-C*07 (24.6%), HLA-C*03 (12.6%), HLA-C*06 (11.5%)	HLA-C*02 (14.5%), HLA-C*06 (14.5%), HLA-C*07 (13.4%)	HLA-C*07 (20%), HLA-C*06 (14.7%), HLA-C*04 (11%)	HLA-C*06 (18.8%), HLA-C*07 (18%), HLA-C*04 (10.5%)	HLA-C*07 (25.3%), HLA-C*03 (12.7%), HLA-C*04 (11%)
HLA-DRB1	HLA-DRB1*03 (15.2%), HLA-DRB1*13 (14.2%), HLA-DRB1*15 (13.9%)	HLA-DRB1*03 (17.2%), HLA-DRB1*13 (16.1%), HLA-DRB1*11 (16%)	HLA-DRB1*15 (15.2%), HLA-DRB1*04 (14.3%), HLA-DRB1*03 (11.5%)	HLA-DRB1*13 (16.1%), HLA-DRB1*03 (15.5%), HLA-DRB1*15 (14.3%)	HLA-DRB1*15 (17.9%), HLA-DRB1*03 (14.7%), HLA-DRB1*13 (12%)	HLA-DRB1*03 (19.8%), HLA-DRB1*15 (16.7%), HLA-DRB1*11 (14.2%)	HLA-DRB1*15 (19.4%), HLA-DRB1*04 (12.4%), HLA-DRB1*13 (12.4%)

4. Discussion

HLA-typing is a useful tool to assist in identifying suitable potential tissue donors, as pre-transplantation HLA matching greatly improves graft survival in transplant recipients [22]. In our setting, we only perform SSP low-resolution HLA-typing, producing two-digit level results. This is in contrast to most of the prospective studies that were performed in South Africa over the last couple of years that mostly used high-resolution sequence-based technologies (SBT) [12]. However, due to our large study population, we believe that our results may greatly contribute to understanding the HLA diversity within our country.

One major challenge we encountered in our study was the classification of ethnicity in our region. The South African national census only reports on four broad ethnic population groups, namely Black African, Coloured (mixed ancestry), Indian/Asian, and White (European-decent). The Free State Province is located in the centre of South Africa, consequently resulting in a complex cultural diversity [23]. Our hospital is the main academic hospital in the Free State Province and the only hospital providing transplantation services in our region. Therefore, we serve a vast geographic area, complicating the establishment of specific ethnic origins. The traditional ethnic classification in South Africa is broadly based on the home language of the different population groups. Therefore, the Black African population is broadly divided into Pedi, Sotho, Tswana, Swati, Venda, Tsonga, Ndebele, Xhosa, and Zulu. With the white population broadly being divided into Afrikaans and English speaking [24]. However, the traditionally white populations in South Africa are mainly descendants of Dutch, German, French, English, and other European settlers [25]. Furthermore, the South African Constitution (1996) contains reference to eleven official and 14 other commonly used languages in South Africa [24]. It is reported that the most common language in the Free State Province is Sesotho (71.9%) and that the majority of the European-descent population are Afrikaans speaking [23]. However, it is evident that these self-reported language preferences are not an accurate indicator to determine ethnic origin. Therefore, taken this massive genetic diversity within our region, it is apparent why all HLA allele groups deviated from HWE, even within the different population groups.

The demographic distribution of our study does not reflect the reported demographics of the Free State province. People with African descent ethnicity are under-represented (55.69% vs 88.7%), where both European descent and mixed ancestry ethnicities are over-represented (33.01% vs 8.5% and 9.3% vs 2.5%, respectively). People with Asian ethnicity remained consistently low (0.9% vs 0.3%) [23].

When compared to the initial study of De Kock et al. [14], HLA-A*30 remained the most common HLA-A allele group in the African descent population (13.1% vs 12.2%), and HLA-A*02 remained the most common HLA-A allele group in the European descent and mixed ancestry populations (22.4% vs 23.8% and 11.7% vs 11.23%, respectively). Our results correlate with other studies that reported HLA-A*30 as the most common HLA-A allele group in southern African descent populations, and HLA-A*02 as most common in South African-European and American-European, and European populations [12]. Even though HLA-A*02 was the most common allele group in the mixed ancestry population, it was closely followed by HLA-A*30 (11.2%). In the 1997 study, HLA-A*02 and HLA-A*30 were jointly the most common HLA-A allele groups in the mixed ancestry population (both 11.23%) [14]. Therefore, we can postulate that these two allele groups have a similar probability of occurring and passed on to this group's progeny.

For the HLA-B antigen, HLA-B*15 was the most common allele group for both the African descent and mixed ancestry populations (12.6% and 17%, respectively). It is in contrast to the original study, where HLA-B*15 was not reported, and HLA-B*17 was the most common allele group in both these populations (17.8% and 14.8%, respectively) [14]. However, HLA-B*17 was almost entirely absent in our current study, with only two individuals from the total population showing this allele. In 1997, HLA-B*57 and HLA-B*58 were seen as split antigens and designated as

Table 3. The three most common HLA-allele group frequencies per disorder group.

	All patients with renal failure (N = 237)	African descent patients with renal failure (N = 166)	European descent patients with renal failure (N = 60)	All patients with acute leukaemia (N = 77)
HLA-A	HLA-A*02 (14.6%), HLA-A*23 (9.7%), HLA-A*68 (9%)	HLA-A*23 (12%), HLA-A*68 (11%), HLA-A*02 (10.1%)	HLA-A*02 (27.2%), HLA-A*03 (14.9%), HLA-A*01 (7%), HLA-A*11 (7%)	HLA-A*02 (16.2%), HLA-A*30 (13%), HLA-A*29 (7.8%)
HLA-B	HLA-B*44 (12%), HLA-B*58 (9.5%), HLA-B*07 (8.4%)	HLA-B*58 (11.1%), HLA-B*44 (10.5%), HLA-B*07 (7.5%)	HLA-B*44 (16.7%), HLA-B*07 (10.5%), HLA-B*51 (8.8%)	HLA-B*15 (9.7%), HLA-B*07 (9.1%), HLA-B*58 (9.1%)
HLA-C	HLA-C*07 (17.5%), HLA-C*06 (17.3%), HLA-C*04 (13.9%)	HLA-C*06 (17.3%), HLA-C*07 (17.3%), HLA-C*02 (15.7%)	HLA-C*07 (18.8%), HLA-C*06 (17%), HLA-C*03 (13.4%)	HLA-C*07 (21.4%), HLA-C*02 (14.3%), HLA-C*04 (11.7%), HLA-C*06 (11.7%)
HLA-DRB1	HLA-DRB1*13 (15.2%), HLA-DRB1*03 (14.8%), HLA-DRB1*11 (12.4%)	HLA-DRB1*13 (17.1%), HLA-DRB1*03 (16.5%), HLA-DRB1*11 (14.9%)	HLA-DRB1*04 (19%), HLA-DRB1*15 (12.9%), HLA-DRB1*01 (12.1%)	HLA-DRB1*13 (17.8), HLA-DRB1*03 (15.8%), HLA-DRB1*11 (15.8%)

HLA-B*17. Therefore, with the improved sensitivity of modern detection methods, our current study was more sensitive in correctly identifying HLA-B*15 as the most common allele group, as HLA-B*57 and HLA-B*58 could be separated. HLA-B*15 has also been identified as the most common allele group in African descent Mozambican and African descent South African Zulu populations. HLA-B*07 remained the most common HLA-B allele group in the European descent population (14.6% vs 12.03%), which is also similar to the findings of other South African studies [12].

One striking finding is that HLA-B*44 is the most common HLA-B allele group in patients with renal failure. It is especially true in the European descent population, where HLA-B*44 represents 16.7% of the renal failure population. It signifies a substantial 57.5% relative increase in frequency when compared to all European descents in the population (10.6%) and an even more noteworthy 75.8% relative increase in frequency when compared to the European descent donor population (9.5%) in our study. The presence of HLA-B*44 has been implicated as a contributory factor in recurrent sinopulmonary infections [26], as well as in Crohn's disease-associated ankylosing spondylitis [27], and recurrent aphthous stomatitis [28]. However, an increased frequency in renal failure has not been previously described.

Another interesting observation was made regarding the ankylosing spondylitis-associated HLA allele, HLA-B*27 [29]. HLA-B*27 was only seen in roughly 0.6% of the African descent population, while it was much more common in the European descent (5.2%) and mixed ancestry (3.6%) populations. This distribution is reflected in an old study on a South African population of African descent that showed that ankylosing spondylitis is encountered in less than 1% of that population [30], as well as the fact that ankylosing spondylitis is reportedly much more prevalent in European populations (23.8 per 10,000) than in African populations (7.4 cases per 10,000) [31].

For the HLA-C antigen, HLA-C*07 was still the most common allele group in the European descent group (24.6% vs 17.5%), which correlated with another South African study [16]. However, for the African descent group, HLA-C*07 (16.8%) overtook HLA-C*02 (12.3%) as the most common HLA-C allele group in our study population. Nevertheless, HLA-C*07 (13.33%) was also a common allele group in the 1997 African descent population [14], and HLA-C*02 remained one of the most common allele groups in the current study. Interestingly, none of the other South African studies identified either as the most common allele group [12]. Conversely, HLA-C*06 was reported as the most common HLA-C allele group in African descent South Africans [16]. However, HLA-C*06 (16.4%) was the second most common allele group in our African descent population. HLA-C*02 remained the most common HLA-C allele group in the mixed ancestry population when compared to the original study (14.5% vs 15.42%). However, HLA-C*06 (14.5%) was jointly the most common, with the same frequency as HLA-C*02 in the mixed ancestry population [14].

HLA-DRB1 proved to be the most diverse among the ethnic groups. For the African descent population, HLA-DRB1*03 (17.2%) was the most common; HLA-DRB1*15 (15.2%) was the most common in the European descent population; and HLA-DRB1*13 (16.1%) was found to be the most common in the mixed ancestry population. Our findings are in contrast with other studies where HLA-DRB1*11 was the most common in the African descent populations of southern Africa, and HLA-DRB1*03 was the most common allele group in European descent South Africans [12]. However, both these alleles are still some of the more common allele groups in the African descent and European descent populations in our study (HLA-DRB1*11 = 16% and HLA-DRB1*03 = 11.5%, respectively).

One limitation of our data set is that only low-resolution typing data is available for the whole time-period. Performing high-resolution (allelic) HLA typing can be prohibitively costly and, in most cases, requires access to advanced next-generation technologies [12]. Therefore, being located in a resource-scarce developing country, the NHLS Tissue Typing laboratory at Universitas Academic Hospital only performed DNA-based sequence-specific primer (SSP) low-resolution (generic) typing as a screening tool (Bio-Rad Medical Diagnostics GmbH, Germany) for HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3, HLA-DRB4, HLA-DRB5 and HLA-DQB1. HLA-DQB1 was added to the testing repertoire in 2019; therefore, limited profiles (n = 64) contained HLA-DQB1 results. Thus, the HLA-DQB1 results have limited statistical power and should be interpreted with caution. The SSP low-resolution typing method only indicates the presence or absence of the HLA-DRB3, HLA-DRB4, HLA-DRB5 alleles and consequently, these allele groups were excluded from the data analysis.

With the identification of these limitations, we intend to expand our laboratory's capacity to perform high-resolution HLA typing and perform prospective disease-association studies in our population.

5. Conclusion

This study correlates well with other studies on a similar population and may contribute to improved donor recruitment strategies in our region. The substantial variation in HLA frequencies between the ethnic groups in our region highlights the value of population-specific HLA sequencing studies. The change in HLA-B*15 and HLA-B*17 frequencies between the original study done in our region over 20 years ago and our current study demonstrates how advanced technologies can improve diagnostic tests' accuracy. Therefore, it is another reminder that regular studies of this nature should be done to keep region-specific statistics up-to-date. Furthermore, HLA-allele and haplotype frequencies are vital to perform HLA-associated disease studies; thus, keeping population-specific data current remains paramount for this purpose. It is illustrated in this study through the observation of HLA-B*44 as a prominent HLA in our renal failure population, which warrants further in-depth investigation of this allele group within this patient cohort.

Declarations

Author contribution statement

Walter J. Janse van Rensburg: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

André de Kock: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Chené Bester: Performed the experiments.

Jean F. Kloppers: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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References

[1] P.I. Terasaki, History of HLA: Ten Recollections, UCLA Tissue Typing Laboratory, Los Angeles, 1990.
[2] S. Beck, J. Trowsdale, The human major histocompatibility complex: lessons from the DNA sequence, Annu. Rev. Genom. Hum. Genet. 1 (1) (2000) 117–137.
[3] S.G.E. Marsh, E.D. Albert, W.F. Bodmer, et al., Nomenclature for factors of the HLA system, 2004, Tissue Antigens 65 (4) (2005) 301–369.
[4] L.P. Wong, R.T.H. Ong, W.T. Poh, et al., Deep whole genome sequencing of 100 southeast Asian Malays, Am. J. Hum. Genet. 92 (1) (2013) 52–66.
[5] R. Horton, L. Wilming, V. Rand, et al., Gene map of the extended human MHC, Nat. Rev. Genet. 5 (2004) 889–899.
[6] J. Robinson, J.A. Halliwell, J.D. Hayhurst, et al., The IPD and IMGT/HLA database: allele variant databases, Nucleic Acids Res. 43 (Database issue) (2015) D423–D431.
[7] W.M. Howell, HLA and disease: guilt by association, Int. J. Immunogenet. 41 (2014) 1–12.
[8] D. Poddighe, A. Turganbekova, D. Baymukasheva, Z. Saduakas, Z. Zhanzakova, S. Abdrakhmanova, Genetic predisposition to celiac disease in Kazakhstan: potential impact on the clinical practice in Central Asia, PloS One 15 (1) (2020), e0226546.
[9] D. Poddighe, A. Turganbekova, Z. Mukusheva, A. Abdirakhmanova, M. Assylbekova, S. Adbrakhmanova, HLA-B*51 allelic and carrier frequency in Kazakhstan: insights into Behçet's disease prevalence in Central Asia, Int. Emerg. Med. (2020).
[10] A.M. Ikhtiar, B. Jazairi, I. Khansa, A. Othman, HLA class I alleles frequencies in the Syrian population, BMC Res. Notes 11 (2018) 324.
[11] L.Y.C. Takeshita, A.R. Jones, F.F. Gonzalez-Galarza, D. Middleton, Allele frequencies database, Transfus. Med. Hemotherapy 41 (2014) 352–355.
[12] M. Tshabalala, J. Mellet, M.S. Pepper, Human leukocyte antigen diversity: a southern African perspective, J. Immunol. Res. (2015) 1–11.
[13] M. Tshabalala, C. Ingram, T. Schlaphoff, V. Borrill, A. Christoffels, M.S. Pepper, Human leukocyte antigen-A, B, C, DRB1, and DQB1 allele and haplotype frequencies in a subset of 237 donors in the South African Bone Marrow Registry, J. Immunol. Res. (2018) 1–8.
[14] A. De Kock, AdP. Heyns, P.N. Badenhorst, M.J. Coetzee, Human leucocyte antigen frequencies of the Free State population, South Africa, South Afr. J. Sci. 93 (1997) 335–337.
[15] P. Kok, M. Collinson, Migration and Urbanisation in South Africa. Report 03-04-02, Statistics South Africa, 2006.
[16] M. Paximadis, T.Y. Mathebula, N.L. Gentle, E. Vardas, M. Colvin, C.M. Gray, C.T. Tiemessen, A. Puren, Human leukocyte antigen class I (A, B, C) and II (DRB1) diversity in the black and Caucasian South African population, Hum. Immunol. 73 (2012) 80–92.
[17] S. Loubser, M. Paximadis, N.L. Gentle, A. Puren, C.T. Tiemessen, Human leukocyte antigen class I (A, B, C) and class II (DPB1, DQB1, DRB1) allele and haplotype variation in Black South African individuals, Hum. Immunol. 81 (1) (2020) 6–7.
[18] HLA SSP Kits Package Insert, Bio-Rad Medical Diagnostics GmbH, Germany, 2021. Available from, http://bmd.cdi.ch/PDF/TP-SSP/826201/MAN-189738-UK.PDF. (Accessed 10 February 2021).
[19] S.W. Guo, E.A. Thompson, Performing the exact test of Hardy-Weinberg proportion for multiple alleles, Biometrics 48 (2) (1992) 361–372.
[20] L. Excoffier, H.E.L. Lischer, Arlequin suite ver 3.5: a new series of programs to perform population genetics analyses under Linux and Windows, Mol. Ecol. Resour. 10 (3) (2010) 564–567.
[21] S. Buhler, J.M. Nunes, G. Nicoloso, J.M. Tiercy, A. Sanchez-Mazas, The heterogenous HLA genetic makeup of the Swiss population, PloS One 7 (7) (2012), e41400.
[22] R.A. Montgomery, V.S. Tatapudi, M.S. Leffell, A.A. Zachary, HLA in transplantation, Nat. Rev. Nephrol. 14 (2018) 558–570.
[23] Provincial Profile: Free State, Community Survey 2016, 2018. Report number 03-01-12. Statistics South Africa.
[24] K. Henrad, Minority Protection in Post-apartheid South Africa: Human Rights, Minority Rights, and Self-Determination, Greenwood Publishing Group, 2002, p. 43.
[25] J.L. Gibson, A. Gouws, Overcoming Intolerance in South Africa: Experiments in Democratic Persuasion, Cambridge University Press, 2005, p. 36.
[26] D.T. Johnson, G. Mehaffy, J. Thomas, K.R. Young Jr., H. Wiener, J. Li, R.C.P. Go, H.W. Schroeder Jr., Increased frequency of HLA-B44 in recurrent sinopulmonary infections (RESPI), Clin. Immunol. 119 (2006) 346–350.
[27] J. Purrmann, H. Zeidler, J. Bertrams, E. Juli, S. Cleveland, W. Berges, R. Gemsa, C. Specker, H.E. Reis, HLA antigens in ankylosing spondylitis associated with Crohn's disease. Increased frequency of the HLA phenotype B27, B44, J. Rheumatol. 15 (11) (1988) 1658–1661.
[28] L. Jaber, A. Weinberger, T. Klein, Close association of HLA-B52 and HLA-B44 antigens in Israeli Arab Adolescents with recurrent aphthous stomatitis, Arch. Otolaryngol. Head Neck Surg. 127 (2) (2001) 184–187.
[29] B. Chen, J. Li, C. He, D. Li, W. Tong, Y. Zou, W. Xu, Role of HLA-B27 in the pathogenesis of ankylosing spondylitis (Review), Mol. Med. Rep. 15 (2017) 1943–1951.
[30] L. Solomon, P. Beighton, H.A. Valkenburg, G. Robin, C.L. Soskolne, Rheumatic disorders in the South African Negro Part I. Rheumatoid Arthritis and Ankylosing Spondylitis, SA Med. J. 49 (1975) 1292–1296.
[31] L.E. Dean, G.T. Jones, A.G. MacDonald, C. Downham, R.D. Sturrock, G.J. Macfarlane, Global prevalence of ankylosing spondylitis, Rheumatology 53 (4) (2014) 650–657.