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HLA EPLET Frequencies Are Similar in Six Population Groups and Are Expressed by the Most Common HLA Alleles

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ABSTRACT

The degree of immunological compatibility between donors and recipients greatly impacts allograft survival. In the United States kidney allocation system, HLA antigen-level matching has been shown to cause ethnic disparities and thus, has been de-emphasised. However, priority points are still awarded for antigen-level zero-ABDR matching, zero-DR matching and one-DR matching. Recently, the degree of HLA molecular (eplet) mismatch has emerged as a more accurate measure of immunological risk, and eplet mismatch load has gained attention as a possible biomarker to improve HLA compatibility. However, little is known about the frequency of eplets in population groups, which is a necessary step to ensure that candidates from any ethnical background can have similar chances at a well-matched organ. Eplet frequencies were estimated using HLA alleles in the Common, Intermediate and Well-Documented (CIWD) 3.0.0 catalogue for six population groups: African-American (AFA), Asian-Pacific Islander (API), European/European descent (EURO), Middle East/North Coast of Africa (MENA), Hispanic/Latino (HIS) and Native-American (NAM). We determined that 98.6% (484 out of 491) of HLA eplets are expressed by the common HLA alleles in all population groups. Of the seven eplets that were expressed by less common HLA alleles, six were Class I eplets and one was expressed by HLA-DQB1 alleles and most were expressed by HLA alleles that were more commonly observed in European/European descent populations. Our observations indicate that HLA eplets will not cause any significant disparity if applied to HLA molecular compatibility, regardless of the ethnic origin of both recipients and donors.

1 | Introduction

The degree of HLA compatibility between recipients and donors is associated with post-transplant allograft survival [1–3]. In the United States, points for HLA-B antigen match were removed because of increased ethnic disparities while showing only a modest correlation with graft survival [4–6]. Currently, antigen-level zero-ABDR, zero-DR and one-DR mismatches are awarded points in the United States deceased-donor kidney allocation system [7]. However, a study found that zero-ABDR antigen mismatch donor offers to European/European-descent candidates will occur six times more often than for African Americans and nine times more frequently than for Asians [8]. Therefore, a newly proposed allocation policy would include priority points only for zero- and one-DR antigen mismatches [9]. Although recognising the benefit of HLA-DR matching, the American Society of Transplant Surgeons

(ASTS) has raised concerns about its fairness for ethnic minorities [10]. Recently, the Sensitization in Transplantation: Assessment of Risk (STAR) working group strongly suggested more studies be conducted to assess equity and the significance of molecular (eplet) mismatch in the context of organ allocation [11].

Next-generation sequencing (NGS) for HLA genotyping has enabled allele-level HLA compatibility assessment of patients and donors [12]. While antigen-level genotyping broadly identifies HLA molecules based on their serological reactivity, allele-level typing identifies a specific HLA protein. With allele-level typing, the amino-acid (molecular) differences between recipient and donor can be calculated and used to identify well-matched donors [13].

Polymorphic amino-acid residues exposed on the molecular surface of HLA antigens are known as HLA eplets [14, 15]. Non-self eplets can cause the generation of donor-specific antibody (DSA) and lead to allograft rejection [16]. Therefore, through the examination of critical amino-acid clusters involved in immune recognition, eplet-based molecular compatibility may lead to improved transplant outcomes by providing a more precise assessment of donor-recipient immunological compatibility [17]. Notably, the majority of post-transplant DSA are against Class II HLA molecules, especially HLA-DQ, and are associated with early allograft loss [18–23]. Several studies have demonstrated that the level of HLA-DR and -DQ eplet mismatch correlates with the generation of post-transplant de novo DSA (dnDSA) and allograft rejection [24–34]. Moreover, the significance of HLA-DQ mismatch in kidney transplantation and the notion that the vast majority of dnDSA target the donor HLA-DQ molecule, is supported by numerous literature reports [23, 35].

In recent years, eplet mismatch load has been embraced as a new prognostic biomarker for graft outcome [24]. Additionally, utilisation of eplet mismatch load in kidney allocation is gaining attention from the transplant community [13, 36]. Organisations such as the National Kidney Registry (NKR) [37, 38] and the Royal Children's Hospital of Melbourne [39] have already adopted eplet mismatch into their allocation systems [11]. However, although HLA eplet compatibility holds the promise to improve allograft outcomes, equity across ethnic groups is of foremost importance [12, 40].

In our study, we estimated the frequency of Class I and Class II HLA eplets from the frequencies of HLA alleles as described in the Common, Intermediate and Well-Documented (CIWD) 3.0.0 catalogue [41]. The CIWD catalogue includes the most common HLA alleles as observed in more than 8 million individuals from six major ethnic/geographic groups: African-American (AFA), Asian-Pacific Islander (API), European/European descent (EURO), Middle East/North Coast of Africa (MENA), Hispanic/Latino (HIS) and Native-American (NAM).

2 | Methods and Materials

2.1 | Data Sources and Population Groups

The HLA eplets used in the study were sourced from the HLAMatchmaker database version 3.0. HLAMatchmaker is a theoretical algorithm that allows users to view HLA molecules as patches of immunogenic amino acids in antibody-accessible positions [42]. The list of HLA alleles was obtained from the IPD-IMGT/HLA database version 3.39.0 (01/2021). As source of both CIWD HLA alleles and their frequencies, we used the CIWD 3.0.0 catalogue [41]. The following population groups were used in this paper: AFA, API, EURO, MENA, HIS, and NAM. The number of volunteer donors from each registry was described by Hurley et al. [41]. As the source of two HLA-haplotypes, the allele-level HLA genotypes of 1196 transplant candidates and 4000 potential donors were obtained from the NKR.

2.2 | Frequency in the IPD-IMGT/HLA Database

To determine the frequency of an eplet in the IPD-IMGT/HLA database, we counted the number of alleles containing the eplet and divided by the total number of alleles for the specific locus. For HLA-A/B/C and HLA-DRB1/3/4/5, frequencies were calculated for each locus and for the combination of loci. Because several eplets are shared between HLA-A/B/C or HLA-DRB1/3/4/5 alleles, frequency calculations for these shared eplets are based on the total number of alleles for these loci.

2.3 | Frequency in the CIWD 3.0.0 Catalogue

The frequencies of the observed HLA alleles were obtained from the CIWD 3.0.0 catalogue [41]. The frequencies of HLA eplets were calculated for the entire catalogue and for each population group. To calculate the frequency of an eplet, the frequencies of the alleles expressing that eplet were summed together. For eplets shared by HLA-A/B/C or HLA-DRB1/3/4/5 alleles, we calculated the average frequency across the loci. All frequency calculations were performed in R statistical software.

2.4 | Assignment of Common, Intermediate, Well-Documented, and Rare Status

To assign Common, Intermediate, Well-Documented, and Rare Status (CIWDR) status to HLA eplets, we mirrored the strategy from Hurley et al. [41]. HLA eplets were given the designation of 'Common' (C) when present with a frequency of ≥ 0.0001 in the entire catalogue and in each population group. Eplets were designated as 'Intermediate' (I) when their frequency was < 0.0001 but ≥ 0.00001 and 'Well-Documented' (WD) when the eplet had a frequency < 0.00001 but occurred over five times. HLA eplets that occurred five times or fewer or expressed exclusively by HLA alleles not observed in the CIWD 3.0.0 were designated as 'Rare' (R).

2.5 | HLA Eplets Frequency in the NKR Two HLA-Haplotypes Database

To confirm that the HLA eplets defined in our eplet CIWD (ep-CIWD) catalogue still met the criteria for 'Common' in a real-world patient data set, their frequencies were calculated using the NKR two HLA-haplotypes candidate and donor databases. For each eplet observed in the candidate's, we compared its

frequency in the donor data set. To ensure that the results were not biased by relatedness, the frequency expression of candidate's eplets was also determined for the unrelated donor's cohort only.

2.6 | Statistical Analysis

Descriptive statistics were performed in GraphPad Prism 9 using standard methods. All other calculations and data visualisations were generated using R Studio 2023.06.1 Build 524 running R version 4.3.1. Base R functions were used for all calculations, and reshape2 and ggplot2 packages were used for data visualisation [43–46].

3 | Results

3.1 | HLA Eplets Frequency in the IPD-IMGT/HLA Database

Out of 11,952 alleles in the IPD-IMGT/HLA 3.39.0 version, 6485 (54.3%) were observed in the CIWD 3.0.0 data set and 3055 of these (47.1%) were included in the CIWD categories [41]. Within this group, only 545 HLA-A/B/C/DRB1/DQB1/DPB1 alleles (17.83%) were designated as 'Common'. Another 513 alleles (16.79%) were considered 'Intermediate', while 57 (1.87%) DRB3/4/5 alleles were designated as 'Well-Documented'. Therefore, a majority ($n = 1940$, 63.51%) of HLA alleles observed in the CIWD 3.0.0 catalogue were rare as they fell outside of these classifications [41].

In contrast, HLA eplets are co-expressed by many HLA alleles (see Table S1 for the number of HLA alleles expressing each eplet). Figure 1 shows the frequency distribution of HLA eplets in the IPD-IMGT/HLA database version 3.39.0. The median expression of the HLA-A/B/C eplets was 1113 alleles, with a 25th percentile of 427 alleles. The HLA-DR eplets had a median expression of 436 alleles and a 25th percentile of 168 alleles. The HLA-DQB1 eplets had a median expression of 356 alleles and a 25th percentile of 190. The HLA-DQA1 eplets were expressed by a median of 30 alleles and the 25th percentile was 12. The HLA-DPB1 eplets had a median expression of 303 alleles and a 25th percentile of 148, and the HLA-DPA1 eplets were expressed by a median of 27 alleles and had a 25th percentile of 19. Out of 11,952 alleles in the 3.39.0 IPD-IMGT/HLA database, the HLA eplets (total 491) were expressed by an average of 516 alleles and had a 25th percentile of 164 alleles. Altogether, these data clearly demonstrate that HLA eplets are expressed by many alleles and suggest that HLA eplets may be more common than HLA alleles in the data sets used in this study (see Table S2 for the frequencies of individual eplets in the IPD-IMGT/HLA database).

3.2 | HLA Eplets Are More Common Than HLA Alleles

Because HLA eplets are highly co-expressed in the HLA alleles, we postulated that the vast majority will also be expressed in common alleles and in all population groups. To confirm our hypothesis, we compared the number of CIWD alleles (Figure 2A) with the number of HLA eplets that are expressed by CIWD alleles (Figure 2B).

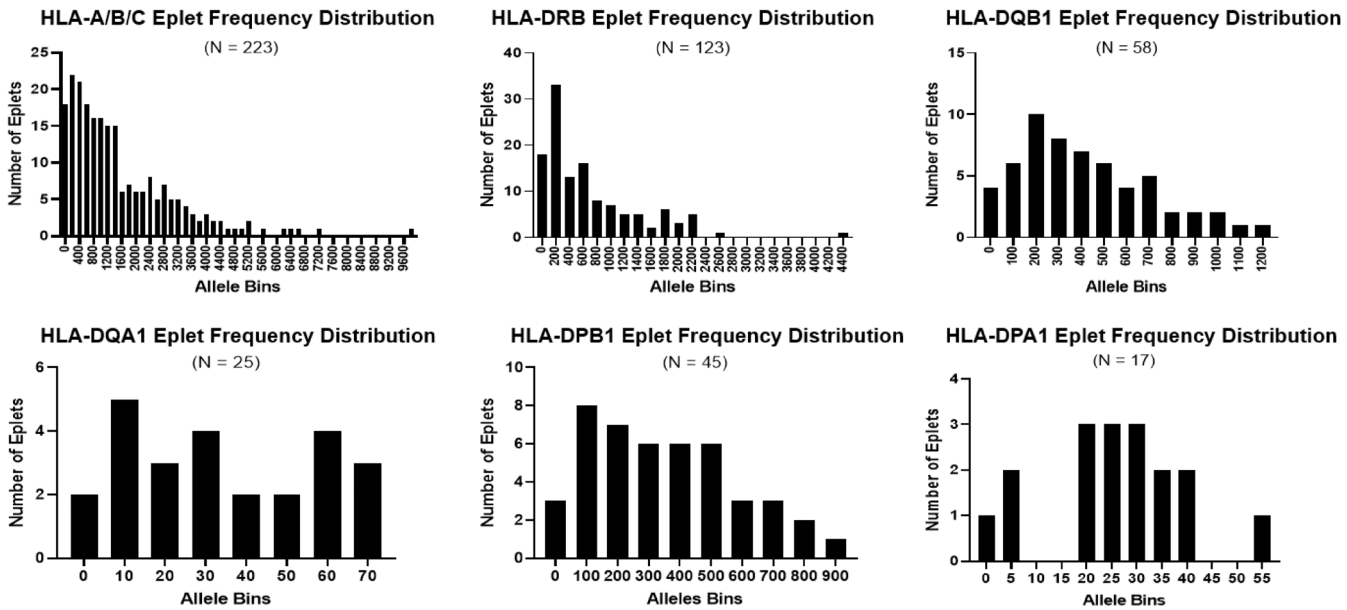


FIGURE 1 | Distribution of HLA Eplets (HLAMatchmaker version 3.0) in the IMGT/HLA database (version 3.39.0). The eplets expression in IMGT alleles was stratified in bins of 400 alleles for HLA-A/B/C, 200 alleles for HLA-DRB, 100 alleles for HLA-DQB1 and DPB1, 10 alleles for HLA-DQA1 and 5 alleles for HLA-DPA1. HLA-A/B/C eplets were expressed by a median of 1113 alleles, HLA-DR eplets by 436 alleles, HLA-DQB1 eplets by 356 alleles, HLA-DQA1 eplets by 30 alleles, HLA-DPB1 eplets by 303 and HLA-DPA1 by 27. Out of 11,952 alleles in the IMGT/HLA database, HLA eplets were expressed by an average of 516 alleles and had a 25th percentile of 164 alleles. AFA, African-American; API, Asian-Pacific Islander; C, common; EURO, European/European descent; HIS, Hispanic/Latino; I, intermediate; MENA, Middle East/North Coast of Africa; NAM, Native-American; R, rare; WD, well-documented.

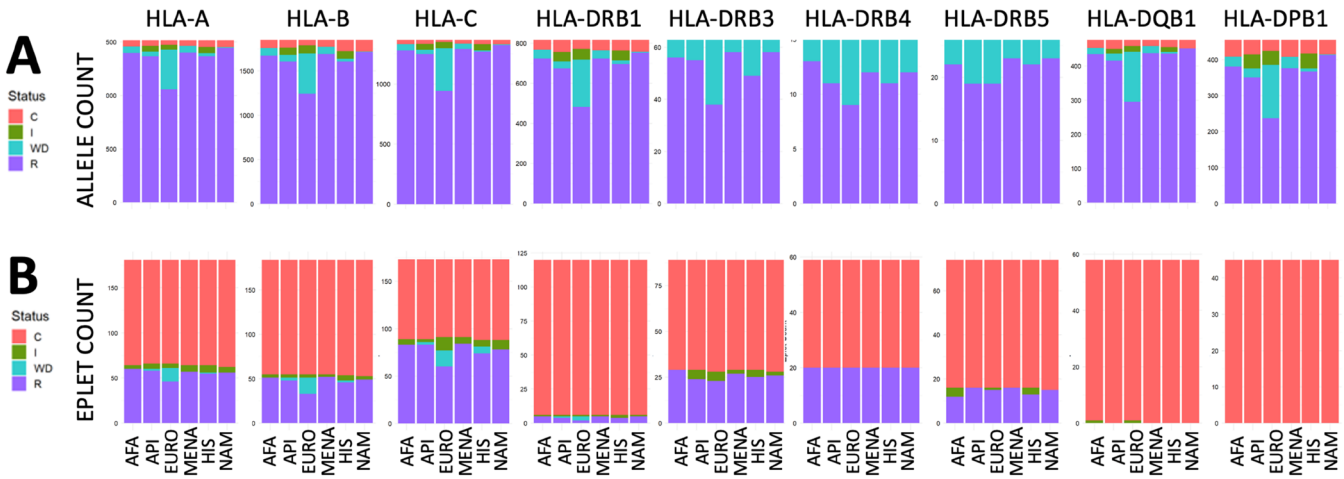


FIGURE 2 | Population expression of IMGT/HLA alleles and HLA eplets compared by their CIWD assignment. When the alleles of the IMGT/HLA (version 3.39.0) were categorised by their CIWD status (CIWD 3.0.0), the percentage of Common alleles in each population ranged from 2.25% to 10.75%, and the vast majority are rare (A). However, when the HLA eplets (HLA Matchmaker version 3.0) were classified according to the CIWD 3.0.0 categories, the vast majority were common in all populations (B). AFA, African-American; API, Asian-Pacific Islander; C, common; EURO, European/European descent; HIS, Hispanic/Latino; I, intermediate; MENA, Middle East/North Coast of Africa; NAM, Native-American; R, rare; WD, well-documented.

As documented in the CIWD version 3.0.0, most of the HLA alleles included in the catalogue are either well-documented (WD) or rare (R) (Figure 2A) [41]. Out of 2388 two-field HLA-A/B/C/DRB1/DQB1/DPB1 alleles included in the CIWD catalogue, only 15.6% of HLA-A alleles (105 out of 673), 22.6% of HLA-B alleles (195 out of 864), 12% of HLA-C alleles (72 out of 602), 20.4% HLA-DRB1 alleles (86 out of 422), 16.2% of HLA-DQB1 alleles (29 out of 179) and 22.5% of HLA-DPB1 alleles (58 out of 258) are common. When the alleles of the IPD-IMGT/HLA database are categorised according to the CIWD designation, the percentage of common alleles in each population group ranges from 2.25% to 10.75% (see Table S3) and the vast majority of HLA alleles are rare in all population groups.

However, given the promiscuity of the HLA eplets, most are expressed by common alleles, especially at HLA-DRB1, HLA-DQB1 and HLA-DPB1 (Figure 2B). A total of 64.5% of HLA-A eplets, 70.4% of HLA-B eplets and 48.4% of HLA-C eplets are expressed by common HLA alleles in all population groups (see Table S3). Among Class II eplets, the percentage of eplets expressed by common alleles in all population groups is 95% for HLA-DRB1, 67.8% for HLA-DRB3, 66.1% for HLA-DRB4, 78.6% for HLA-DRB5, 99.4% for HLA-DQB1 and 100% HLA-DPB1, respectively (see Table S3). In Figure 2, the HLA Class I and HLA-DRB alleles were divided for comparison with the CIWD status of the HLA alleles. However, the eplets of both Class I and HLA-DRB have a significant co-expression among HLA-A/B/C and HLA-DRB1/3/4/5 loci and eplets that are well-documented or rare for one locus can be very common for another. As shown in Figure 3, when HLA-A/B/C and HLA-DRB1/3/4/5 are considered together, 99.73% of Class I eplets and 100% of HLA-DRB eplets are defined as common in all population groups (see Table S3).

3.3 | HLA Eplets Are Expressed by Common HLA Alleles in All Population Groups

To assign CIWDR status to the HLA eplets, we used the 3055 two-field HLA alleles included in the CIWD 3.0.0 catalogue [41]. Because the CIWD HLA alleles catalogue does not include HLA-DQA1 and HLA-DPA1 alleles, we determined the frequency of only HLA-A/B/C/DRB/DQB1/DPB1 eplets ($n = 491$). As indicated in Section 2, the status assignment mirrors that of the CIWD 3.0.0 catalogue [41]. The frequency expression of all HLA eplets in each population group is available in Table S5. The CIWD designation for all HLA eplets in each population group is available in Table S6. As shown in Table 1, on average, 222 out of 223 (99.6%) HLA-A/B/C eplets were expressed by common alleles in all population groups. On Class II, 100% of HLA-DR eplets ($n = 123$), 99.7% of HLA-DQB1 ($n = 58$) and 100% of HLA-DPB1 ($n = 45$) eplets were expressed by common alleles in all population groups. When we considered the CIWD alleles as a 'whole' and assessed the probability of any given HLA eplet to occur at a frequency ≥ 0.0001 (thus to be commonly expressed), we were able to determine that 100% of HLA-A/B/C/DQB/DPB and 92.68% of HLA-DRB eplets are expressed by the most common (CIWD) alleles in the World (Table S7). The nine HLA-DRB eplets (7.32%) that did not have a frequency ≥ 0.0001 were expressed by DRB3/4/5 alleles, which were automatically assigned as WD in the CIWD catalogue (Table S7).

3.4 | Less Common HLA Eplets

Out of 491 HLA eplets, 484 (98.6%) were common in all population groups and 7 (1.4%) were assigned as intermediate (5 eplets) or well-documented/rare (2 eplets). Figure 4 shows the distribution of the 7 HLA eplets with a non-common status. As shown in Table 2, six were Class I eplets (56E, 59H, 103M, 145HT, 162DLS and 163LG) and one was an HLA-DQB1 eplet (23L). In addition, Table 2 summarises the description, allele expression and frequencies for these non-common HLA eplets.

3.4.1 | Intermediate Eplet 56E

The eplet 56E is a provisional eplet (not verified with a monospecific alloserum or monoclonal antibody) expressed exclusively

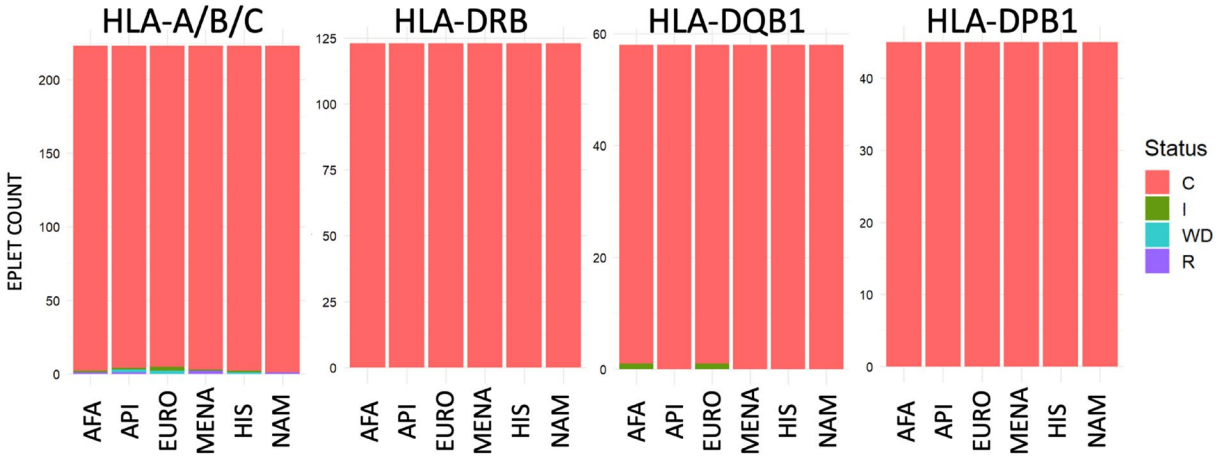


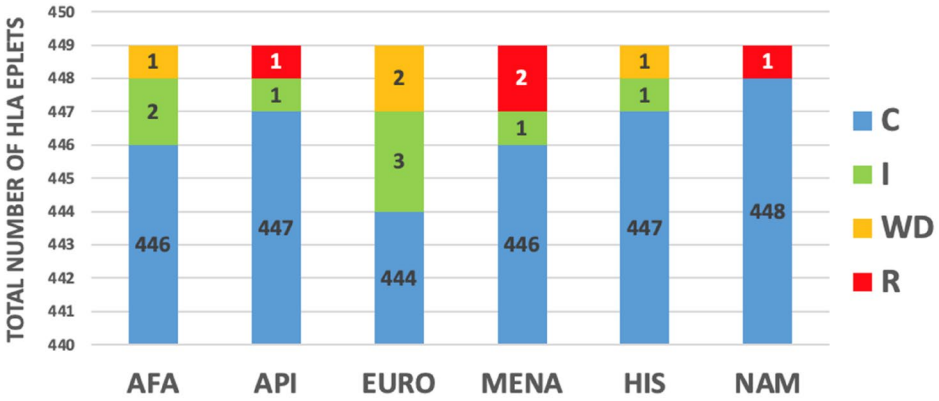
FIGURE 3 | Most HLA eplets are expressed by common HLA alleles in every population. Because eplets are shared across multiple HLA-A/B/C or HLA-DRB1/3/4/5 alleles, the expression frequency in the population should not be divided by each locus (as in Figure 2) but summed together. When HLA-A/B/C and HLA-DRB1/3/4/5 are considered together, 99.73% of Class I eplets and 100% of HLA-DRB eplets are defined as common in all populations. AFA, African-American; API, Asian-Pacific Islander; C, common; EURO, European/European descent; HIS, Hispanic/Latino; I, intermediate; MENA, Middle East/North Coast of Africa; NAM, Native-American; R, rare; WD, well-documented.

TABLE 1 | HLA eplets (HLAMatchmaker version 3.0) status in the world population.

	Total # eplets	Category	AFA [*n* (%)]	API [*n* (%)]	EURO [*n* (%)]	MENA [*n* (%)]	HIS [*n* (%)]	NAM [*n* (%)]
HLA-ABC	223	C	221 (99)	219 (98)	218 (98)	220 (99)	221 (99)	222 (99.6)
		I	1 (0.45)	1 (0.45)	3 (1.35)	1 (0.45)	1 (0.45)	0 (0.00)
		WD	0 (0.00)	2 (0.9)	2 (0.9)	0 (0.00)	1 (0.45)	0 (0.00)
		R	1 (0.45)	1 (0.45)	0 (0.00)	2 (0.9)	0 (0.00)	1 (0.45)
HLA-DRB	123	C	123 (100)	123 (100)	123 (100)	123 (100)	123 (100)	123 (100)
		I	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		WD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		R	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
HLA-DQB1	58	C	57 (99)	58 (100)	57 (99)	58 (100)	58 (100)	58 (100)
		I	1 (1.72)	0 (0.00)	1 (1.72)	0 (0.00)	0 (0.00)	0 (0.00)
		WD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		R	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
HLA-DPB1	45	C	45 (100)	45 (100)	45 (100)	45 (100)	45 (100)	45 (100)
		I	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		WD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
		R	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Note: On average, 222 out of 223 (99.6%) HLA-A/B/C eplets, 100% of HLA-DR eplets ($n=123$), 99.7% of HLA-DQB1 eplets ($n=58$) and 100% of HLA-DPB1 eplets ($n=45$) are Common and expressed by Common alleles in all populations.
Abbreviations: AFA, African-American; API, Asian-Pacific Islander; C, common; EURO, European/European descent; HIS, Hispanic/Latino; I, intermediate; MENA, Middle East/North Coast of Africa; NAM, Native-American; R, rare; WD, well-documented.

by A*03:93, A*24:169, A*32:37, A*68:70, A*80:01, B*07:176, B*15:277, B*15:278, B*35:122, B*40:145, B*56:29, C*04:81 and C*06:25. The glutamic acid (E) at Position 56 maps at the margin of the antigen-binding site (ABS) of the Class I molecule. A*80:01 was the only allele observed in the CIWD catalogue and was more frequently expressed by AFA ($f=0.00712$), followed by NAM ($f=0.00223$), HIS ($f=0.00168$), MENA ($f=0.00056$), EURO ($f=0.00015$) and API ($f=0.00002$).



Locus	Population	INTERMEDIATE	WELL-DOCUMENTED	RARE
HLA-ABC	AFA	145HT		163LG
	API	103M		162DLS
	EURO	145HT 56E 59H	162DLS 163LG	
	MENA	145HT		162DLS 163LG
	HIS	145HT	163LG	
	NAM			163LG
HLA-DQB1	AFA	23L		
	API			
	EURO	23L		
	MENA			
	HIS			
	NAM			

FIGURE 4 | Distribution of HLA eplets (HLAMatchmaker version 3.0) in the population by CIWDR classification (epCIWDR). Out of 491 HLA eplets included in the HLA Matchmaker version 3.0, 484 (98.6%) were common in all populations and 7 (1.4%) were assigned as intermediate (5 eplets) or well-documented/rare (2 eplets). The table identifies the eplet, HLA locus, population and ICWDR status for the seven non-common HLA eplets. AFA, African-American; API, Asian-Pacific Islander; C, common; EURO, European/European descent; HIS, Hispanic/Latino; I, intermediate; MENA, Middle East/North Coast of Africa; NAM, Native-American; R, rare; WD, well-documented.

3.4.2 | Intermediate Eplet 59H

The eplet 59H is a provisional eplet expressed exclusively by A*11:95, B*07:264, B*08:137, B*15:160, B*27:03, B*27:139 and B*27:151. The histidine (H) at Position 59 maps at the margin of the ABS of the Class I molecule. B*15:160 has been observed only in EURO ($f=0.0000168$). B*27:03 is more frequently expressed by AFA ($f=0.00367$), followed by MENA ($f=0.00102$), HIS ($f=0.00062$), NAM ($f=0.00060$), EURO ($f=0.00012$) and API ($f=0.00002$). The other alleles were not observed in the CIWD catalogue.

3.4.3 | Intermediate Eplet 103M

The eplet 103M is a provisional eplet expressed exclusively by B*07:158, B*08:58, B*40:288, B*73:01 and C*05:82. The methionine (M) at Position 103 maps under the ABS of the Class I molecule and thus, the true nature of this eplet is equivocal. The only allele sharing this eplet observed in the CIWD catalogue was B*73:01, which was more frequently expressed by MENA ($f=0.00387$), followed by NAM ($f=0.00087$), HIS ($f=0.00075$), AFA ($f=0.00066$), EURO ($f=0.00057$) and API ($f=0.00018$).

3.4.4 | Intermediate Eplet 145HT

The eplet 145HT (144K-145H-149T) is a provisional eplet expressed exclusively by the A*02:03, A*02:25, A*02:38, A*02:171, A*02:280, A*02:281, A*02:315, A*02:345, A*02:355, A*02:431, A*02:529, A*02:568, A*02:595 and A*02:612. The complex lysine (K) 144, histidine (H) 145 and threonine (T) 149 maps at the margin of the ABS of the Class I molecule. Of the 59 alleles expressing this eplet, A*02:25 has only been observed in EURO ($f=0.00000168$) and A*02:38 in AFA/API/EURO/HIS/NAM but at a frequency not greater than 0.0000149. The more common A*02:03 allele is primarily expressed by API ($f=0.01994$), followed by NAM ($f=0.00067$), MENA ($f=0.00030$), AFA ($f=0.00020$), HIS ($f=0.00012$) and EURO ($f=0.00004$).

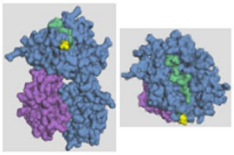
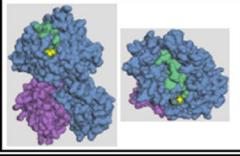
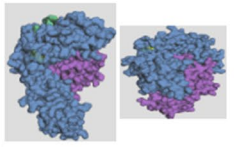
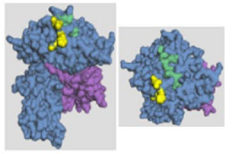
3.4.5 | Well-Documented/Rare Eplet 162DLS

The eplet 162DLS (162D-163L-167S) is a provisional eplet expressed exclusively by the B*82:01 and B*82:03 alleles. The complex aspartic acid (D) 162, leucine (L) 163 and serine (S) 167 maps at the ABS of the Class I molecule and are in close contact with the peptide. The B*82:01 is more frequently expressed by AFA ($f=0.00238$), followed by NAM ($f=0.00051$), HIS ($f=0.00031$), EURO ($f=0.00000377$), API ($f=0.00000308$) and MENA ($f=0.00000249$).

3.4.6 | Well-Documented/Rare Eplet 163LG

The eplet 163LG (163L-167G) is a provisional eplet expressed exclusively by A*24:143, B*15:12, B*15:19 and B*51:03, with B*15:12 and B*51:03 being the only alleles observed in the CIWD

TABLE 2 | Description, allele expression and population frequency of non-common HLA eplets.

HLA Eplet	pHLA3D	HLA Allele	Allele Count by Population Group								Allele Frequency by Population Group							
			AFA	API	EURO	MENA	HIS	NAM	UNK	Total	AFA	API	EURO	MENA	HIS	NAM	UNK	Total
56E		A*03:93	0	0	19	0	0	0	2	21	0	0	1.59E-06	0	0	0	1.51E-06	1.3E-06
		A*24:169	0	3	5	0	0	0	2	10	0	2.32E-06	4.19E-07	0	0	0	1.51E-06	6.21E-07
		A*32:37	0	0	4	0	0	0	0	4	0	0	3.35E-07	0	0	0	0	2.48E-07
		A*68:70	0	0	3	0	0	0	0	3	0	0	2.51E-07	0	0	0	0	1.86E-07
		A*80:01	**2764**	**25**	**1778**	**225**	**1176**	**149**	**1164**	**7281**	**0.007115**	**1.94E-05**	**0.000149**	**0.000559**	**0.001678**	**0.002225**	**0.000881**	**0.000452**
		B*07:176	0	0	0	1	0	0	2	3	0	0	0	2.49E-06	0	0	1.51E-06	1.86E-07
		B*15:277	0	2	0	0	0	0	0	2	0	1.54E-06	0	0	0	0	0	1.24E-07
		B*15:278	0	2	0	0	0	0	0	2	0	1.54E-06	0	0	0	0	0	1.24E-07
		B*35:122	0	0	1	0	1	0	1	3	0	0	8.37E-08	0	1.43E-06	0	7.57E-07	1.86E-07
		B*40:145	0	0	1	0	0	0	0	1	0	0	8.37E-08	0	0	0	0	6.2E-08
		B*56:29	0	0	1	0	0	0	0	1	0	0	8.37E-08	0	0	0	0	6.2E-08
		C*04:81	0	3	0	0	0	0	0	3	0	2.39E-06	0	0	0	0	0	1.88E-07
		C*06:25	0	0	2	0	0	0	0	2	0	0	1.69E-07	0	0	0	0	1.26E-07
59H		A*11:95	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		B*07:264	0	0	2	0	0	0	0	2	0	0	1.67E-07	0	0	0	0	1.24E-07
		B*08:137	0	0	3	0	0	0	0	3	0	0	2.51E-07	0	0	0	0	1.86E-07
		B*15:160	0	0	22	0	0	0	0	22	0	0	1.84E-06	0	0	0	0	1.36E-06
		B*27:03	**1386**	**29**	**1432**	**410**	**432**	**40**	**507**	**4236**	**0.003567**	**2.23E-05**	**0.00012**	**0.001019**	**0.000616**	**0.000597**	**0.000384**	**0.000263**
		B*27:139	1	0	0	0	0	0	0	1	2.57E-06	0	0	0	0	0	0	6.2E-08
		B*27:151	0	0	0	0	0	0	2	2	0	0	0	0	0	0	1.51E-06	1.24E-07
103M		B*07:158	0	0	3	0	2	0	0	5	0	0	2.51E-07	0	2.85E-06	0	0	3.1E-07
		B*08:58	0	0	2	0	0	0	0	2	0	0	1.67E-07	0	0	0	0	1.24E-07
		B*40:288	0	0	1	0	0	0	0	1	0	0	8.37E-08	0	0	0	0	6.2E-08
		B*73:01	256	231	6845	1558	524	58	1054	10526	0.000659	0.000178	0.000573	0.003874	0.000748	0.000866	0.000798	0.000653
		C*05:82	0	0	2	0	0	0	0	2	0	0	1.69E-07	0	0	0	0	1.26E-07
145HT		**A*02:03**	**78**	**25743**	**499**	**119**	**80**	**45**	**1512**	**28076**	**0.000201**	**0.019938**	**4.18E-05**	**0.000296**	**0.000114**	**0.000672**	**0.001145**	**0.001744**
		A*02:25	0	0	2	0	0	0	0	2	0	0	1.68E-07	0	0	0	0	1.24E-07
		A*02:38	4	1	163	0	3	1	12	184	1.03E-05	7.75E-07	1.37E-05	0	4.28E-06	1.49E-05	9.09E-06	1.14E-05
		A*02:171	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		A*02:280	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		A*02:281	0	2	0	0	0	0	0	2	0	1.55E-06	0	0	0	0	0	1.24E-07
		A*02:315	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		A*02:345	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		A*02:355	0	0	0	1	0	0	0	1	0	0	0	2.48E-06	0	0	0	6.21E-08
		A*02:431	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		A*02:529	0	2	0	0	0	0	0	2	0	1.55E-06	0	0	0	0	0	1.24E-07
		A*02:568	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		A*02:595	0	3	0	0	0	0	0	3	0	2.32E-06	0	0	0	0	0	1.86E-07
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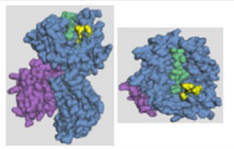
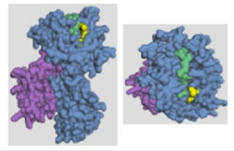
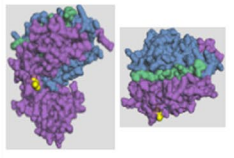
162DLS		A*82:01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		A*82:03	1	0	0	0	0	0	0	1	2.57E-06	0	0	0	0	0	0	6.2E-08
163LG		A*24:143	0	1	0	0	0	0	0	1	0	7.75E-07	0	0	0	0	0	6.21E-08
		B*15:12	**1**	**1973**	**66**	**3**	**17**	**0**	**143**	**2203**	**2.57E-06**	**0.00152**	**5.53E-06**	**7.46E-06**	**2.43E-05**	**0**	**0.000108**	**0.000137**
		B*15:19	0	21	0	0	2	0	9	32	0	1.62E-05	0	0	2.85E-06	0	6.81E-06	1.99E-06
		B*51:03	0	0	2	0	0	0	0	2	0	0	1.67E-07	0	0	0	0	1.24E-07
23L		DQB1*02:172	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*03:100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*03:126	0	0	3	0	0	0	2	5	0	0	2.56E-07	0	0	0	1.63E-06	3.16E-07
		DQB1*03:308	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:01	**19**	**18612**	**865**	**357**	**83**	**16**	**3161**	**23113**	**5.02E-05**	**0.014158**	**7.37E-05**	**0.000886**	**0.000122**	**0.000241**	**0.002574**	**0.001462**
		DQB1*04:05	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:08	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:61	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:62	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:69	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:71	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:74	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:92	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:93	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:94	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		DQB1*04:95	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Note: Out of 491 HLA eplets, 484 (98.6%) were common in all populations and 7 (1.4%) were assigned as intermediate (5 eplets) or well-documented/rare (2 eplets). Six were Class I eplets (56E, 59H, 103M, 145HT, 162DLS and 163LG) and one was an HLA-DQB1 eplet (23L). Out of 70 HLA alleles expressing these less-common HLA eplets, 24 (34.3%) were not observed in the CIWD 3.0.0 catalogue. 3D rendering of HLA molecules from pHLA3D (https://www.phla3d.com.br/).
Abbreviations: AFA, African-American; API, Asian-Pacific Islander; C, common; EURO, European/European descent; HIS, Hispanic/Latino; I, intermediate; MENA, Middle East/North Coast of Africa; NAM, Native-American; R, rare; WD, well-documented.

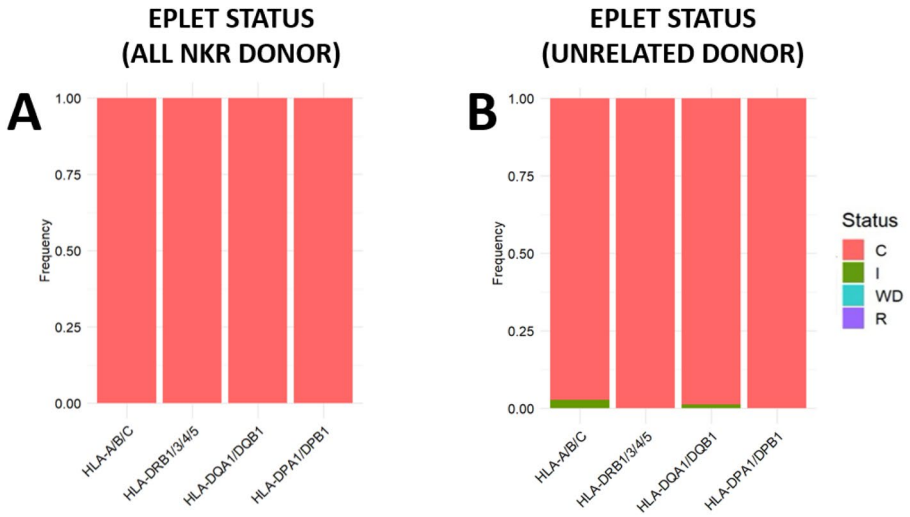


FIGURE 5 | epCIWDR status of HLA eplets (HLAMatchmaker version 3.0) in the NKR population. The frequency expression and CIWDR status of HLA eplets in real-life, allele-level two HLA-haplotype candidates ($n=1196$) and donors ($n=4000$) cohorts were compared. All but one HLA-A/B eplet (163LG) were commonly expressed in both cohorts (A). To rule-out the effect of relationship, the frequency of the eplet expressed by the candidate cohort ($n=1106$) was compared only to the unrelated donor cohort ($n=540$). The vast majority of HLA eplets had similar frequency also when only unrelated donors were considered (B). AFA, African-American; API, Asian-Pacific Islander; C, common; EURO, European/European descent; HIS, Hispanic/Latino; I, intermediate; MENA, Middle East/North Coast of Africa; NAM, Native-American; R, rare; WD, well-documented.

3.0.0. The complex leucine (L) 163 and glycine (G) 167 maps at the ABS of the Class I molecule and are in close contact with the peptide. Although B*51:03 has only been observed in EURO and at a very low frequency ($f=0.00000167$), the more common B*15:12 allele is primarily expressed by API ($f=0.00152$), followed by HIS ($f=0.0000243$), MENA ($f=0.00000746$), EURO ($f=0.0000553$) and AFA ($f=0.0000257$). B*15:12 was not observed in NAM.

3.4.7 | Intermediate Eplet 23L

The eplet 23L is a provisional eplet expressed exclusively by the DQB1*02:172, DQB1*03:100, DQB1*03:126, DQB1*03:308, DQB1*04:01, DQB1*04:05, DQB1*04:06, DQB1*04:07, DQB1*04:08, DQB1*04:14, DQB1*04:15, DQB1*04:16, DQB1*04:17, DQB1*04:38, DQB1*04:42, DQB1*04:61, DQB1*04:62, DQB1*04:69, DQB1*04:71, DQB1*04:74, DQB1*04:90, DQB1*04:92, DQB1*04:93, DQB1*04:94 and DQB1*04:95. The leucine (L) at Position 23 maps at the margin of the ABS of the beta-unit of the Class II molecule. Of the 25 alleles expressing this eplet, DQB1*04:01 was observed in the CIWD catalogue and was more frequently expressed by API ($f=0.00526$), followed by MENA ($f=0.00072$), HIS ($f=0.0000634$), NAM ($f=0.0000603$), EURO ($f=0.0000512$) and AFA ($f=0.0000238$).

3.5 | HLA Eplets Frequency Comparison in the NKR Candidate/Donor Cohort

According to our observations, HLA eplets are expressed by most HLA alleles in the IPD-IMGT/HLA database and 98.6% (484 out of 491) are expressed by common alleles included in the CIWD 3.0.0 catalogue. To determine if the HLA eplets are still common in an actual candidate/donor data set, we obtained the two-field HLA genotype of 1196 candidates and 4000 donors enrolled in the NKR and determined if the frequency of the HLA eplets observed in the candidate data set was similar to that in the donor data set. As expected, we found that all but one HLA eplet (163LG) are common in both candidate and donor cohorts (Figure 5). As shown in Table 2, the only alleles expressing 163LG that were observed in the CIWD catalogue (B*15:12 and B*51:03) were primarily expressed in API and CAU. Because the NKR cohort is composed 62% of unrelated donors and 38% of related donors (32% first-degree, 3% second-degree and 3% third-degree), we also calculated the frequency of eplets between candidates ($n=1196$) to unrelated donors ($n=934$). As expected, 99.6% of HLA eplets were common in both candidates and unrelated donors with only eplets 59H and 163LG being less common.

4 | Conclusions

In this paper, we have attempted to address the concern of ethical fairness when HLA eplet mismatch load is used to compare a transplant candidate and a potential donor. Ethnic minorities face disadvantages in getting a well-matched kidney transplant in the current United States deceased donor allocation system due to demographic disparities and variations in HLA frequencies across population groups [47, 48]. Non-European/European-descent candidates have fewer opportunities to receive a low antigen-level mismatch kidney [8, 49]. The current prioritisation of antigen matching is ethnically disparate, but the impact of prioritising molecular matching on ethnic disparities in deceased donor kidney allocation is still unknown. If HLA eplets segregate ethnically, transplant candidates expressing uncommon eplets could be disadvantaged if matching algorithms use HLA eplets as one of the allocation scores.

Therefore, to address this concern, we investigated the expression of known HLA eplets in the IPD-IMGT/HLA database

[50] (version 3.39.0) and the CIWD 3.0.0 catalogue [41]. First, we used the CIWD catalogue to determine the classification of the HLA alleles in the IPD-IMGT/HLA database. Based on the current CIWD classification, most HLA alleles are uncommon. Only 54.3% of HLA alleles were observed in the CIWD catalogue and only 47.1% were included in one of the CIWD 3.0.0 classifications. Moreover, out of 3055 HLA alleles observed in the CIWD catalogue, 64.7% were not common. Based on the CIWD designation [41], the percentage of common HLA alleles in each population group ranges from 2.25% to 10.75%. Therefore, matching organs based on allele-level HLA genotype is likely to increase the ethnical disparity, especially in the unbalanced US donor population. However, when we investigated the expression of HLA eplets in the CIWD catalogue, we were able to demonstrate that 98.6% of eplets are common in all population groups. As shown in the results and Table 1, on average, 99.83% of HLA-A/B/C/DRB/DQB/DPB eplets are expressed by common alleles. Out of 491 HLA eplets studied, six Class I eplets (56E, 59H, 103M, 145HT, 162DLS and 163LG) and one HLA-DQB1 eplet (23L) were found to be less common. Therefore, our data suggest that HLA eplets do not impact equity since almost all (484 out of 491) are expressed by the most common HLA alleles in six population groups.

While we have shown that most individual eplets are commonly found in the various population groups in the CIWD catalogue, the question remains whether the same observation holds true when looking at the distribution of eplets within HLA haplotypes of candidates and donors, which are composed of combinations of up to 18 HLA alleles possessing a large number of eplets. Furthermore, the number of possible eplet haplotypes is greatly increased because of the large number of different HLA haplotypes observed in world populations. Not unexpectedly, our evaluation of the NKR candidate/donor cohorts has demonstrated that all but one (163LG) HLA eplets are common. This was also true when the frequency of HLA eplets in the candidates' cohort was compared to their frequency in only the unrelated donors. This observation suggests that, at least in the living donation setting, HLA eplets would not cause disparity.

A recent report from the STAR Working Group called for studies on equity and utility of molecular mismatch in the context of allocation [11]. To improve equity and to increase molecular compatibility of donated organs, several studies are underway to determine the feasibility and fairness of the eplet mismatch load in the US allocation system. Although several important questions remain, in this paper, we have addressed the question of HLA eplets expression across population groups and the concern with their impact on ethnical minorities. Our results show that, as compared to antigen or allele-level, HLA eplets seem to be more equitable when trying to identify a well-matched organ, regardless of ethnic background. To the best of our knowledge, this is the first observation of Class I and Class II HLA eplet frequency and the first CIWD classification of HLA eplets. More work needs to be done to address the concern of eplet immunogenicity; however, when considering using eplets for allocation this is the first step towards improving HLA compatibility while maintaining equity.

Potential limitations of our study are the total P-group two-field HLA assignments (tab. 3 of reference [41]) and the lack of data for DQA1 and DPA1 in the CIWD v3.0.0 data set, as well as the continual updates performed by IPD-IMGT/HLA on the HLA allele databases used for our calculations. However, we have clearly stated the versions used and explained our methodology so that others can reproduce the results with updated versions. Additionally, since the most seminal papers on the clinical implications of mismatched eplets [24, 25] used HLAMatchmaker to determine the mismatch load, our paper is based on the HLAMatchmaker eplet data set 3.0 and not that of the HLA Eplet Registry (https://www.epregistry.com.br). Another important limitation to mention is that about 68% of the volunteers in the CIWD catalogue are from the German and USA registries and can influence the frequency of HLA alleles in the catalogue, so it may not match the world population. Determination of the HLA eplet frequencies from a much more ethnically diverse population, such as the one from the Allele Frequency Net Database (https://www.allelefrequencies.net/), would probably result in more accurate data. We are addressing this issue, and we hope to include this data set in future updates of the HLA eplets CIWD catalogue.

In conclusion, we have shown a relatively uniform distribution of HLA eplets frequencies across various population groups and that these eplets are commonly expressed by the most common HLA alleles. This finding has potential implications for organ transplantation, as it could help reduce ethnic disparities in transplant outcomes. Our findings provide a basis for further exploration of the impact of eplet matching prioritisation on equity in kidney allocation.

Author Contributions

Massimo Mangiola designed the study, assisted with data analysis, prepared figures and assisted with manuscript preparation. Mitchell Ellison II performed data analysis, prepared tables and assisted with manuscript preparation. Marilyn Marrari and Michał Mankowski reviewed data results, tables, figures and assisted with manuscript preparation. Qingyong Xu, Doreen Sese, Bonnie E. Lonze, Robert A. Montgomery and Adriana Zeevi equally contributed to the review of results, tables, figures, manuscript and revisions.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.