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A new strategy for systematically classifying HLA alleles into serological specificities

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HLA serological specificities were defined by the reactivity of HLA molecules with sets of sera and monoclonal antibodies. Many recently identified alleles defined by molecular typing lack their serotype assignment. We surveyed the literature describing the correlation of the reactivity of serologic reagents with AA residues. 20 - 25 AA residues determining epitopes (DEP) that correlated with 82 WHO serologic specificities were identified for HLA class I loci. Thirteen DEP each located in the beta-1 domains that correlated with 24 WHO serologic specificities were identified for HLA-DRB1 and -DQB1 loci. The designation of possible HLA-DPB1, -DQA1, -DPA1, and additional serological specificities that result from epitopes defined by residues located at both -DQA1 and -DQB1 subunits were also examined. HATS software was developed for automated serotype assignments to HLA alleles in one of the three hierarchical matching criteria: (1) all DEP (FULL); (2) selected DEP specific to each serological specificity (SEROTYPE); (3) one AA mismatch with one or more SEROTYPES (INCOMPLETE). Results were validated by evaluating the alleles whose serotypes do not correspond to the first field of the allele name listed in the HLA dictionary. Additional 85 and 21 DEP patterns that do not correspond to any WHO serologic specificities for common HLA class I and DRB1 alleles

Abbreviations: AA, amino acids; CDQS, combinatorial DQ serotypes; CIDW, common, intermediate and well-documented; CREG, cross reactive group; CWD, common and well-documented; DEP, determining Epitope; DSA, donor-specific antibodies; HATS, HLA allele to serotype; HSCT, hematopoietic stem cell transplantation; IHIW, International HLA and Immunogenetics Workshops; IHW, International Histocompatibility Workshops; IMGT, ImMunoGeneTics; IPD, ImmunoPolymorphism database; mAb, monoclonal antibody; NSD, novel split designation; SAB, single antigen bead; SS, serologic specificities; UNA, UNASSIGNED; UNOS, United Network for Organ Sharing; WD, well documented; WHO, World Health Organization.

were identified, respectively. A comprehensive antibody identification panel would allow for accurate unacceptable antigen listing and compatibility predictions in solid organ transplantation. We propose that antibody-screening panels should include all serologic specificities identified in this study.

KEYWORDS

antigen, common allele, epitope, eplet, residue, serotype

1 | INTRODUCTION

Identification of serological specificities is critical to assess whether anti-HLA humoral reactivity present in the patient's serum corresponds to donor-specific antibodies (DSA). Serological HLA specificities have been characterized during the International HLA and Immunogenetics Workshops (IHIW), previously known as Histocompatibility Workshops (IHW) through the correlation analyses of serological reactivity patterns defined by testing HLA typed cell panels with series of allo-antisera, monoclonal antibodies (mAbs), and specific amino acid (AA) residues of HLA alleles.[1–7] The HLA serologically defined antigens had been officially recognized by the WHO Nomenclature Committee for Factors of the HLA System[8] following the extensive serologic testing exercises performed at previous IHW.[2] The report from Milford et al.[2] illustrated how serologically defined specificities showed unique reactivity patterns as plotted in the so called "serograms." With the advent of molecular testing, serologic typing has virtually been discontinued and serologic exercises have been reduced or no longer performed after the 13th IHIW.[6] As a result, many of the recently identified alleles lack the corresponding serotype designation. At IHIW, each recognized specificity was defined by its unique reactivity pattern with distinct clusters of allo-antisera; each serum cluster showed distinctive inclusion of serologic HLA specificities.[1] The elegant early experiments pioneered by van Rood and van Leeuwen demonstrated that some sera included in the same reactivity cluster recognized the same epitopes that could be confidently adjudicated as such by the preservation of the reactivity after performing absorption/elution experiments. These tests were able to rule out that for some mono-specific sera, the positive reactions did not result from the occurrence of mixed populations of allo-antibodies.[9] These investigators described the codominant bi-allelic system with the antigens 4a/4b.[9] These mutually exclusive specificities are now officially designated as Bw4/Bw6 that behave as supertypic epitopes to nearly all currently named HLA-B antigens with a few exceptions in which the antigen/alleles are assigned neither as Bw4 nor Bw6. With the development of mAbs, the processes for recognition and assignment of HLA serologic determinants became more straightforward obviating the need of performing additional characterization steps.[10–12] The evaluation of protein structures of HLA class I alleles and their correlation between mAbs further allowed identification of critical AA residues determining the epitopes recognized by the latter[12–15]; this work allowed identification of the dimorphism at residues 82 and 83 of HLA-B alleles as a necessary determinant of the Bw4 and Bw6 reactivity. The elegant work performed by Lutz and coworkers[15] examining single residue variants of HLA-B7 allowed mapping the reactivity of anti-Bw6 mAbs to specific residues and showed that, despite some overlap in the determining residues, substitutions at additional residues appear to further determine the antibody reactivity (DEP). Further identification of critical residues determining HLA-A[16–18] and -B[19–29] serotypes and epitopes were readily identified by the direct comparison of the protein sequences of alleles that are structurally related that differ only by a few amino acids and have distinct serotypes. The evaluation of the reactivity of mAbs with different alleles allowed for the identification of residues possibly defining HLA class I epitopes to be mapped to residues shared by different alleles.[10–14,30–35] Critical residues defining serotypes or determining epitopes of HLA class II products were identified by similar approaches for HLA-DR,[36–43] DQ[43–45] and DP.[46–48] Many of the epitopes defined in early studies were identified by non-human mAbs; additional work confirmed that these same epitopes were also identified by both, allo-antisera and mAbs of human origin.[6,7,49,50]

The simultaneous application of molecular typing methods and serologic testing in IHIW exercises allowed inference of which amino acids at polymorphic positions in the HLA class I and class II proteins, may determine epitopes recognized by sets of mAbs or by clusters of allo-antibody reagents evaluated in the 12th[4,5] and 13th[6,7] IHIW. In the 13th IHIW the systematic computational analyses for examination of the mAbs and allo-antisera reactivity allowed mapping the putative epitopes recognized by serologic reagents.[6] These analyses appeared to identify AA at specific positions that defined distinct epitopes when combined with substitutions at other

AA positions. More recently, residues or eplets defining epitopes were further characterized or cataloged systematically.[51–59]

These studies identified residues that determine epitopes that in turn allow for the definition and distinction of the currently recognized WHO serological specificities. The majority of the residues mapped as defining serologic epitopes are located in the alpha-helical segments of the membrane distal domain, and these allo-antibodies react with HLA molecules regardless of peptide bound. However, some important residues defining epitopes, for example, those defining major DR serotypes and residue 45 of HLA-B, are located in positions that do not appear to be directly accessible to antibodies, and these are examples of allo-antibodies whose paratope may depend on the peptide bound.[60,61] Similarly, the serologic splits of B14 are B64 and B65; the corresponding prototype alleles HLA-B*14:01 and HLA-B*14:02 differ only by one AA replacement at residue 11 that is located at the bottom of the groove.[29] With the current knowledge of residues determining serotypes, it can be proposed that HLA serotypes can be defined by the examination of the residues located at the principal serotype defining positions.

Names of previously recognized serological specificities were closely associated with the HLA allele name. For example, the HLA-A2 specificity corresponding to the allele HLA-A*02:10 were named as the associated antigen HLA-A210. Three HLA-A (A203, A210, and A2403), six HLA-B (B703, B3901, B3902, B4005, B5102, and B5103) and three DRB1 (DR103, DR1403, and DR1404) serological specificities were officially named as associated antigens by the WHO Nomenclature Committee for Factors of the HLA System in 1991,[62] and B2708 was named in 1996.[63] The serologic exercises performed in various IHIW identified possible serologic splits of HLA-A34,[64,65] -A66[64] and -DR4,[66] however, these splits were not officially named. The examination of residues defining serotypes can, therefore, be used to name new splits corresponding to common prototype alleles. New serotypes of common alleles can also be assigned according to the AA substitutions in residues defining serologic epitopes.

All recently recognized HLA alleles are identified solely by molecular typing, and the number of alleles has been increasing in IPD-IMGT/HLA Database.[67] The most recent serologic information for some HLA alleles is available through HLA Dictionary 2008 in IPD-IMGT/HLA Database, however, it contains information on only 1262 HLA class I and 336 class II alleles.[68] Therefore, many HLA alleles defined by molecular typing lack their serotype assignment.

HLA alleles follow a heavy tail distribution across all population/racial groups.[69] A small fraction of HLA alleles have been characterized as belonging to "common," "intermediate," and "well-documented" (CIWD) categories,[70–73] with the majority of the HLA alleles in rare categories. It is not operationally feasible to have full representation of all HLA alleles in the antigen panel of solid phase antibody detection assays. In practice, it is valuable to have defined serotypes for all the common alleles that are often encountered in the routine clinical HLA tests, and to have common serotype representation in the antigen panel of solid phase assays.

Recently, serological specificities were predicted for HLA-B*15 alleles based on amino acid sequence patterns.[74] Using the information of the key AA residues that define serotypes, a computational tool that performs virtual serotype assignments for the HLA-A, -B, -C, -DRB1, -DRB3/4/5 and -DQB1 alleles that have little or no information about their serological specificities is designed in this study.

Serotypes for alleles at the HLA-DQA1, -DPA1, and -DPB1 loci have not been assigned with official WHO Nomenclature; there is a large body of evidence showing that serologic epitopes present in alleles at these loci can be identified using allo-antisera and mAbs.[53,75–78] We propose to assign serotypes to alleles of these loci by selecting residues that appear to correlate well with the main epitopes of these loci. For HLA-C alleles that have no serologic antigen counterpart (blank), we propose to assign serotypes to the various groups of alleles at this locus based on the knowledge of a number of epitopes[79–81] and including additional residue DEP that are important for the other homologous class I loci, HLA-A and -B. In this study, when HLA alleles that do not fit exactly in any existing serological groups were observed, new serological groups were created.

2 | MATERIALS AND METHODS

2.1 | IPD-IMGT/HLA database

IPD-IMGT/HLA Database release versions 3.38.0 and 3.44.0 were downloaded from GitHub (https://github.com/ANHIG/IMGTHLA.git).[67] hla_prot.fasta files were used to obtain the amino acid sequence for each allele. Nonitalicized two-field HLA allele name, e.g., HLA-B*14:01, is used to represent expressed protein product.[8]

2.2 | Residues for Public Epitopes, Bw4, Bw6, KIR C1, and KIR C2

WHO assigned HLA-B antigens are often distinguished using the differences in the presence of Bw4 and Bw6 epitopes, for example, B21 to B49 (Bw4) and B50 (Bw6), B12 to B44 (Bw4) and B45 (Bw6), B16 to B38 (Bw4) and B39

TABLE 1 Bw4, Bw6, Negative, KIR C1, and KIR C2 residues

	Residue position					Serotypes	
Associated to	**76**	**77**	**80**	**82**	**83**	**WHO assigned antigens**	**Proposed new serotypes**
Bw4				L	R	A23, A24, A2403, A25, A32, B13, B27, B37, B38, B44, B47, B49, B51, B5102, B5103, B52, B53, B57, B58, B59, B63, B77	A-2304, A-2405, A-2408, A-2423, A-2424, A-6836, A-3204, B-1523, B-1524, B-1809, B-0802, B-4404, B-4408, B-4047, B-0736, B-3702
Bw6	E			R	G	B7, B703, B8, B18, B2708, B35, B39, B3902, B4005, B41, B42, B45, B48, B50, B54, B55, B56, B60, B61, B62, B64, B65, B67, B71, B72, B75, B76, B78, B81, B82, B83	A-3002, A-3007, B-1537, B-1538, B-1540, B-1542, B-1552, B-3510, B-3515, B-3519, B-3910, B-2712, B-3705, B-4804, B-4016, B-4021, C-1212
Negative	V			R	G	B46, B73	B-1806, B-0713, B-0715, B-6702
KIR C1	V	S/G	N			Cw1, Cw9, Cw10, Cw7, Cw8, B46, B73	C-1202, C-1402, C-1602, C-0227, C-0702, C-0704, C-0802, C-0803, C-1507
Uncertain	V	N	N				C-1404[#]
KIR C2	V	N	K			Cw2, Cw4, Cw5, Cw6	C-1502, C-1701, C-1801, C-0114, C-0307, C-0403, C-0410, C-0509, C-0810, C-0608, C-0707, C-1204, C-1602
Uncertain	V	S	K				C-0310[#]

Note: Table shows residues used to define Bw4-associated, Bw6-associated, KIR C1 and KIR C2 epitopes. The "Negative" category was added based on the presence of V instead of E at residue 76 in HLA-B and HLA-C alleles. The presence or absence of Bw4 and Bw6-associated residues was assessed in HLA-A and HLA-C alleles. Residues 76, 77 and 80 were assessed to distinguish HLA-C antigens from most HLA-B alleles, and to determine the KIR C1 and KIR C2 ligands and associated serologic epitopes. The majority of HLA alleles that are recognized as KIR C1 and KIR C2 that carry residues 76V77S80N and 76V77N80K, respectively. HLA-B73 that carries 76V77G80N is classified as KIR C1. [#]Two uncertain KIR ligand categories that carry 76V77N80N (e.g., HLA-C*14:04) and 76V77S80K (e.g., HLA-C*03:10) are included, but serotypes for these alleles were not proposed in this study.

(Bw6), respectively.[8,26] Residues 82L83R, 76E82R83G and 76V82R83G are used to identify Bw4, Bw6 and Bw4/Bw6 negative status (Table 1),[82] respectively. We also included these residues to screen Bw4- or Bw6-associated status for HLA-A and HLA-C (Table 1). The residues 76 V77S80N and 76V77N80K are known to determine the KIR C1 and KIR C2 ligands, respectively,[83] and they display different serological specificities, for example, HLA-C*16:01 and HLA-C*16:02, respectively.[80,120] HLA-B*73:01 that carries 76V77G80N is classified as KIR C1.[84,85] Two "Uncertain" KIR ligand categories were created for the alleles that a carry different substitution (76V77N80N and 76V77S80K) at residue 77 (Table 1).

2.3 | Key amino acid (AA) residues determining serologic epitopes and specificities

Prototype alleles that correspond to the WHO assigned antigens[8] and logical key residue positions based on the previously recognized AA residues that define specific serotypes were selected for proteins encoded at HLA-A, -B, -C, -DRB1/3/4/5 and -DQB1 loci (Tables 2A–E, Supplemental Methods). Many key AA residues are shared across HLA class I antigens. Tables 3A–F show key AA residues for HLA-A, -B, -C, -DRB1/3/4/5 and -DQB1 loci. When HLA alleles that do not fit exactly in any existing serological groups corresponding to the WHO assigned antigens were observed, new serological groups were created and proposed (Tables 2A–E). Each proposed new serotype is associated to one of the WHO assigned antigens using the information described in the HLA Dictionary 2008 (Tables 2A–E).[68] With a few exceptions, the WHO antigen was systematically assigned to each allele based on the assigned serotype (Supplemental Tables 1–4). Supplemental Methods include detailed descriptions of the criteria applied to the identification and selection of key residues.

2.4 | Rules for novel split designation (NSD)

The serologic specificities for HLA-A, -B, -C and -DRB1 were designated using the locus name followed by the corresponding two-field allele name without colon (:) of the most common or lowest-digit prototype separated by

TABLE 2 New serotypes, WHO assigned antigens and critical residue positions

A: HLA-A proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Bw4/Bw6 associated	Prototype	Critical residue positions
	Associated	Split	Broad			
			A1		A*01:01	44,67,76,163,166,167
A-0201			A2		A*02:01	43,62,73,107,144,145,149
A-0202					A*02:02	
	A203				A*02:03	
	A210				A*02:10	43,62,73,76,107,145,149
A-0211					A*02:11	43,62,73,107,144,145,149
A-0219					A*02:19	62,65,82,83,144,145,151,161,163,166,167
A-0244					A*02:44	
A-0246					A*02:46	62,65,82,83,144,151,166,167
A-0256					A*02:56	43,62,73,107,144,145,149
A-0265					A*02:65	45,56,62,63,73,76,144,161,163
A-0285					A*02:85	43,62,73,107,144,145,149
A-0301			A3		A*03:01	62,76,144,161,163
A-0305					A*03:05	62,76,144,145,161,163
A-0323					A*03:23	62,65,82,83,144,145,151,161,163,166,167
A-2301		A23	A9	Bw4 associated	A*23:01	62,65,82,83,144,151,166,167
A-2304				Bw4 associated	A*23:04	
A-2424				Bw4 associated	A*24:24	
A-2402		A24		Bw4 associated	A*24:02	
	A2403			Bw4 associated	A*24:03	
A-2404					A*24:04	
A-2405				Bw4 associated	A*24:05	
A-2408				Bw4 associated	A*24:08	
A-2423				Bw4 associated	A*24:23	
		A25	A10	Bw4 associated	A*25:01	76,82,83,144,149,163,166,167
A-2601		A26			A*26:01	62,63,74,76,144,149,163,166
A-2603					A*26:03	
A-2607					A*26:07	
A-2614					A*26:14	
A-3401		A34			A*34:01	62,66,67,144,149,163
A-3402					A*34:02	
A-6601		A66			A*66:01	62,66,74,76,149,163
A-6602					A*66:02	
			A11		A*11:01	62,76,144,161,163,167
		A29	A19		A*29:01	44,62,63,144,151
A-3001		A30			A*30:01	56,62,73,76,82,83,144
A-3002				Bw6 associated	A*30:02	
A-3007				Bw6 associated	A*30:07	
		A31			A*31:01	56,73,76,82,83,144
A-3201		A32		Bw4 associated	A*32:01	62,82,83,144,161,163,167

(Continues)

TABLE 2 (Continued)

A: HLA-A proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Bw4/Bw6 associated	Prototype	Critical residue positions
	Associated	Split	Broad			
A-3204				Bw4 associated	A*32:04	
A-3301		A33			A*33:01	62,63,73,76,144,151,171
A-3303					A*33:03	
A-3313					A*33:13	62,63,73,76,144,151,163,171
A-3308					A*33:08	45,56,62,63,73,76,144,161,163
		A74			A*74:01	
A-6801		A68	A28		A*68:01	62,76,107,144,145
A-6810					A*68:10	
A-6836				Bw4 associated	A*68:36	62,76,82,83,107,144,145
		A69			A*69:01	62,76,107,144,145
			A36		A*36:01	44,67,76,166,167
			A43		A*43:01	62,63,74,76,144,149,163,166
			A80		A*80:01	62,66,144,145,151,166,167

B: HLA-B proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Bw4/Bw6	Prototype allele	Critical residue positions
	Associated	Split	Broad			
B-5101		B51	B5	Bw4	B*51:01	45,62,63,82,83,103,163,167,171
	B5102			Bw4	B*51:02	
	B5103			Bw4	B*51:03	
		B52		Bw4	B*52:01	
B-0702			B7	Bw6	B*07:02	45,63,69,70,71,76,82,83,147,163,171,178
	B703			Bw6	B*07:03	
B-0715				Negative	B*07:15	
B-0736				Bw4	B*07:36	
B-0713				Negative	B*07:13	45,63,69,70,71,76,82,83,103,147,163,171,178
B-0801			B8	Bw6	B*08:01	45,63,69,71,76,82,83,163,177,180
B-0802				Bw4	B*08:02	
B-4402		B44	B12	Bw4	B*44:02	45,62,63,82,83,163,167
B-4404				Bw4	B*44:04	
B-4408				Bw4	B*44:08	
B-4406				Bw4	B*44:06	45,62,63,82,83,103,163,167,171
		B45		Bw6	B*45:01	45,63,76,82,83,163,167
			B13	Bw4	B*13:02	45,63,82,83,145,163,178
		B64	B14	Bw6	B*14:01	45,67,76,82,83,158,163,171
		B65		Bw6	B*14:02	
B-1501		B62	B15	Bw6	B*15:01	45,46,62,63,69,70,76,82,83,163,167,171,178,180
B-1524				Bw4	B*15:24	
B-1538				Bw6	B*15:38	
B-1540				Bw6	B*15:40	

TABLE 2 (Continued)

B: HLA-B proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Bw4/Bw6	Prototype allele	Critical residue positions
	Associated	Split	Broad			
B-1542				Bw6	B*15:42	
B-1516		B63		Bw4	B*15:16	45,46,62,63,69,70,76,82,83,103,163,167,171,178,180
B-1517				Bw4	B*15:17	
		B75		Bw6	B*15:02	45,46,62,63,69,70,76,82,83,163,167,171,178,180
		B76		Bw6	B*15:12/ B*15:14	
		B77		Bw4	B*15:13	
B-3801		B38	B16	Bw4	B*38:01	45,63,67,71,82,83,158,163,171
B-3803					B*38:03	
B-3806					B*38:06	
	B3901	B39		Bw6	B*39:01/B*39:06	45,63,67,71,76,82,83,158,163
	B3902			Bw6	B*39:02	
B-3910				Bw6	B*39:10	
		B57	B17	Bw4	B*57:01	45,46,62,63,69,70,83,163
		B58		Bw4	B*58:01	
B-1801			B18	Bw6	B*18:01	45,63,76,82,83,163,171
B-1806				Negative	B*18:06	
B-1809				Bw4	B*18:09	45,63,82,83,163,171
		B49	B21	Bw4	B*49:01	45,46,63,82,83,103,163,167,178
		B50		Bw6	B*50:01	45,46,63,76,82,83,103,163,167,178
		B54	B22	Bw6	B*54:01	45,63,67,69,76,83,158,163,167,177,178,180
		B55		Bw6	B*55:01	
		B56		Bw6	B*56:01	
B-2705			B27	Bw4	B*27:05	45,63,70,71,82,83,178
	B2708			Bw6	B*27:08	45,63,70,71,76,82,83,143,163,178
B-2712				Bw6	B*27:12	
B-3501			B35	Bw6	B*35:01	45,63,70,71,76,82,83,163,171
B-3510				Bw6	B*35:10	
B-3515				Bw6	B*35:15	
B-3519				Bw6	B*35:19	
B-3701			B37	Bw4	B*37:01	45,62,63,70,76,82,83,163
B-3702				Bw4	B*37:02	
B-3705				Bw6	B*37:05	
B-4001		B60	B40	Bw6	B*40:01	45,46,76,82,83,143,163,178
B-4047				Bw4	B*40:47	45,63,70,71,82,83,143,163,177
B-4002		B61		Bw6	B*40:02	45,46,76,82,83,143,163,178
B-4016				Bw6	B*40:16	
B-4021				Bw6	B*40:21	
	B4005			Bw6	B*40:05	45,46,63,76,82,83,103,163,167,178
			B41	Bw6	B*41:01	45,63,70,71,76,83,163,167,177,178,180

(Continues)

TABLE 2 (Continued)

B: HLA-B proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Bw4/Bw6	Prototype allele	Critical residue positions
	Associated	Split	Broad			
			B42	Bw6	B*42:01	45,67,69,70,71,76,82,83,163,177,178,180
			B46	Negative	B*46:01	45,46,62,63,69,76,82,83,163,167
			B47	Bw4	B*47:01	45,63,70,71,82,83,143,163,177
B-4801			B48	Bw6	B*48:01	45,63,70,71,76,82,83,143,163,167,177,178,180
B-4804				Bw6	B*48:04	
B-4805				Bw6	B*48:05	
			B53	Bw4	B*53:01	45,63,70,71,82,83,103,163,171
			B59	Bw4	B*59:01	45,63,67,71,82,83,163,171,177
B-6701			B67	Bw6	B*67:01	45,67,71,76,82,83,103,158,163
B-6702				Negative	B*67:02	45,67,71,76,82,83,103,158,163
B-1510		B71	B70	Bw6	B*15:10	45,46,62,63,69,70,76,82,83,163,167,171,178,180
B-1523				Bw4	B*15:23	45,46,62,63,67,69,70,76,82,83,163,167,178
B-1537				Bw6	B*15:37	45,46,62,63,69,70,76,82,83,163,167,171,178,180
B-1552				Bw6	B*15:52	
		B72		Bw6	B*15:03	
			B73	Negative	B*73:01	45,63,67,70,76,82,83,163,178
			B78	Bw6	B*78:01	45,76,82,83,163,171
			B81	Bw6	B*81:01	45,69,70,71,76,82,83,147,163,178
			B82	Bw6	B*82:01	45,63,67,69,70,71,76,82,83,167,178

C: HLA-C proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Bw4/Bw6	Prototype allele	Critical residue positions
	Associated	Split	Broad			
C-0102			Cw1		C*01:02	66,73,76,77,80,82,83,99,163,177
C-0114					C*01:14	
C-0202			Cw2		C*02:02	45,66,73,76,77,80,82,83,143,163,177
C-0227					C*02:27	
		Cw9	Cw3		C*03:03	45,49,66,76,77,80,82,83,91,147,163,173
		Cw10			C*03:04	
C-0307					C*03:07	
C-0401			Cw4		C*04:01	24,49,66,73,76,77,80,99,163
C-0403					C*04:03	
C-0408					C*04:08	
C-0410					C*04:10	
C-0501			Cw5		C*05:01	49,73,76,77,80,138,163,177
C-0509					C*05:09	
C-0810					C*08:10	
C-0602			Cw6		C*06:02	24,49,66,73,76,77,80,82,83,99,143,163
C-0608					C*06:08	
C-0701			Cw7		C*07:01	66,73,76,77,80,147,177
C-0702					C*07:02	

TABLE 2 (Continued)

C: HLA-C proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Bw4/Bw6	Prototype allele	Critical residue positions
	Associated	Split	Broad			
C-0704					C*07:04	
C-0707					C*07:07	
C-0801			Cw8		C*08:01	73,76,77,80,138,173,175,177
C-0802					C*08:02	
C-0803					C*08:03	
C-1202					C*12:02	73,76,77,80,82,83,147,158,163,173,177
C-1204					C*12:04	24,49,66,73,76,77,80,82,83,99,147,158,163,173
C-1212				Bw6 associated	C*12:12	45,73,76,77,80,82,83,147,158,163,173
C-1402					C*14:02	73,76,77,80,99,163,177
C-1502					C*15:02	66,73,76,77,80,82,83,177
C-1507					C*15:07	
C-1601					C*16:01	45,66,73,76,77,80,99,138,163,173,177
C-1602					C*16:02	
C-1701					C*17:01	76,77,80,143,147,163
C-1801					C*18:01	24,49,73,76,77,80,99

D: HLA-DRB1/3/4/5 proposed new serotypes, WHO assigned antigens

Proposed new serotype	WHO assigned antigen			Prototype allele	Critical residue positions
	Associated	Split	Broad		
DR-0101			DR1	DRB1*01:01	9,10,11,12,13,70,71
	DR103			DRB1*01:03	
		DR15	DR2	DRB1*15:01	9,10,11,12,13,70
		DR16		DRB1*16:01	
		DR17	DR3	DRB1*03:01	9,10,11,12,13,47,58,71,74
		DR18		DRB1*03:02	
DR-0401			DR4	DRB1*04:01/DRB1*04:04	9,10,11,12,13,58,70,71,74
DR-0402				DRB1*04:02	
DR-0403				DRB1*04:03	
DR-0412				DRB1*04:12	
DR-0415				DRB1*04:15	
DR-1410				DRB1*14:10	
DR-1101		DR11	DR5	DRB1*11:01	9,10,11,12,13,58,70,71
DR-1102				DRB1*11:02	
DR-1105				DRB1*11:05	
DR-1107				DRB1*11:07	
DR-1117				DRB1*11:17	
		DR12		DRB1*12:01	9,10,11,12,13,47,58,60,71,74
DR-1301		DR13	DR6	DRB1*13:01	9,10,11,12,13,58,60,70,71,74
DR-1303				DRB1*13:03/DRB1*13:05	
DR-1317				DRB1*13:17	

(Continues)

TABLE 2 (Continued)

D: HLA-DRB1/3/4/5 proposed new serotypes, WHO assigned antigens

	WHO assigned antigen				
Proposed new serotype	**Associated**	**Split**	**Broad**	**Prototype allele**	**Critical residue positions**
DR-1339				DRB1*13:39	
DR-1343				DRB1*13:43	
DR-1454		DR14		DRB1*14:54	9,10,11,12,13,16,58,60,70,71,74
DR-1402				DRB1*14:02/DRB1*14:19	
	DR1403			DRB1*14:03	9,10,11,12,13,58,60,70,71,74
	DR1404			DRB1*14:04	9,10,11,12,13,16,58,60,70,71,74
DR-1405				DRB1*14:05	
DR-1411				DRB1*14:11	
DR-1414				DRB1*14:14	
DR-1422				DRB1*14:22	
DR-1424				DRB1*14:24	9,10,11,12,13,58,60,70,71,74
DR-1448				DRB1*14:48	
			DR7	DRB1*07:01	9,10,11,12,13,14,60,74
DR-0801			DR8	DRB1*08:01	9,10,11,12,13,58,74
DR-0818				DRB1*08:18	9,10,11,12,13,47,58,60,71,74
			DR9	DRB1*09:01	9,10,11,12,13,60,74
			DR10	DRB1*10:01	9,10,11,12,13
DR-5101			DR51	DRB5*01:01	9,10,11,12,13,71
DR-5102				DRB5*02:02	
DR-5103				DRB5*01:03	
DR-5201			DR52	DRB3*01:01	9,10,12,13,60
DR-5202				DRB3*02:02	
			DR53	DRB4*01:01	9,10,11,12,13

E: HLA-DQB1 proposed new serotypes, WHO assigned antigens

WHO assigned antigen			
Split	**Broad**	**Prototype allele**	**Critical residue positions**
DQ5	DQ1	DQB1*05:01	84,85,86,87,89,90
DQ6	DQ1	DQB1*06:02/DQB1*06:04	
	DQ2	DQB1*02:01	46,47,71,74,85,86,87
DQ7	DQ3	DQB1*03:01/DQB1*03:04	45,57,74,84,85
DQ8		DQB1*03:02	
DQ9		DQB1*03:03	
	DQ4	DQB1*04:01	57,70,71,84,85,87

Note: Tables 2A–E show "Proposed new serotype", "WHO assigned antigen", "Bw4/Bw6 associated" status, "Prototype" and "Critical residue positions" to define SEROTYPE assignments of HLA-A, -B, -C, -DRB1/3/4/5 and -DQB1. The "Associated", "Split," and "Broad" column indicates currently accepted antigens for HLA-A, -B, -C, -DRB1, -DRB3/4/5 and -DQB1 by WHO Nomenclature Committee for HLA factors, and the "Prototype" column shows the prototype two-field HLA alleles corresponding to the new proposed serotypes or WHO assigned antigens. The majority of the proposed new serotypes were assigned to one of the WHO-assigned Antigens according to the first field allele name, but some of these serotypes have not been experimentally confirmed yet. The serotype DR-1410 was assigned to DR4 based on residues 9–13. The alleles HLA-B*07:13 and HLA-B*67:02 with the proposed new serotypes B-0713 and B-6702, were not assigned to WHO-accepted antigens. These antigens may show a distinct serological reactivity, because the amino acid sequence in the alpha 1 domains are identical to those of some HLA-C alleles.

TABLE 3 Serotypes and residues used to define FULL and SEROTYPE assignments

A: HLA-A Serotypes and selected AA residues

Serotype	43[6,86]	44[51]	45	56[87]	62[51,87–90]	63[21,74]	65[51]	66[91]	67[92]	73[86,87,91]	74	76[51]	82[51]	83[51]	107[51]	127[51,93]	144[51,94,121,122]	145[95]	149[51,64,87,96]	151[94,121,122]	161[51]	163[6,51,56]	166[97]	167[74]	171[98]
A1	Q	K	M	G	Q	E	R	N	M	T	D	A	R	G	G	N	K	R	A	H	E	R	D	G	Y
A-0201	Q	R	M	G	G	E	R	K	V	T	H	V	R	G	W	K	K	H	A	H	E	T	E	W	Y
A-0202	R	R	M	G	G	E	R	K	V	T	H	V	R	G	W	K	K	H	A	H	E	T	E	W	Y
A203	Q	R	M	G	G	E	R	K	V	T	H	V	R	G	W	K	K	H	T	H	E	T	E	W	Y
A210	Q	R	M	G	G	E	R	K	V	T	H	V	R	G	G	K	K	H	A	H	E	T	E	W	Y
A-0211	Q	R	M	G	G	E	R	K	V	I	D	V	R	G	W	K	K	H	A	H	E	T	E	W	Y
A-0219	Q	R	M	G	G	E	R	K	V	T	H	V	R	G	W	K	K	R	A	H	E	T	D	G	Y
A-0244	Q	R	M	G	G	E	R	K	V	T	H	V	R	G	W	K	K	R	A	H	E	T	E	W	Y
A-0246	Q	R	M	G	E	E	G	K	V	T	H	V	R	G	W	K	K	H	A	H	E	T	E	W	Y
A-0256	Q	R	M	G	Q	E	R	N	V	T	H	V	R	G	W	K	K	H	A	H	E	T	E	W	Y
A-0265	Q	R	M	G	G	E	R	K	V	T	H	V	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-0285	Q	R	M	G	G	E	R	K	V	T	H	V	R	G	W	K	K	H	V	H	E	T	E	W	Y
A-0301	Q	R	M	G	Q	E	R	N	V	T	D	V	R	G	G	N	K	R	A	H	D	T	E	W	Y
A-0305	Q	R	M	G	Q	E	R	N	V	T	D	V	R	G	G	N	K	R	A	H	E	T	E	W	Y
A-0323	Q	R	M	G	G	E	R	K	V	T	D	V	R	G	G	N	K	R	A	H	D	T	E	W	Y
A-2301	Q	R	M	G	E	E	G	K	V	T	D	E	L	R	G	K	Q	R	A	R	E	T	D	G	Y
A-2304	Q	R	M	G	E	E	G	K	V	T	D	E	L	R	G	K	Q	R	A	R	E	T	E	W	Y
A-2402	Q	R	M	G	E	E	G	K	V	T	D	E	L	R	G	K	K	R	A	H	E	T	D	G	Y
A2403	Q	R	M	G	E	E	G	K	V	T	D	E	L	R	G	K	K	R	A	H	E	T	E	W	Y
A-2404	Q	R	M	G	E	E	G	K	V	T	D	A	R	G	G	K	K	R	A	H	E	T	D	G	Y
A-2405	Q	R	M	G	E	E	G	K	V	T	D	E	L	R	G	K	Q	R	A	H	E	T	D	G	Y
A-2408	Q	R	M	G	G	E	R	K	V	T	D	E	L	R	G	K	K	R	A	H	E	T	D	G	Y
A-2423	Q	R	M	G	E	E	G	K	V	T	D	E	L	R	G	K	K	R	A	H	E	T	D	W	Y
A-2424	Q	R	M	G	R	N	R	N	V	T	D	E	L	R	G	K	Q	R	A	R	E	T	D	G	Y
A25	Q	R	M	G	R	N	R	N	V	T	D	E	L	R	G	N	Q	R	T	H	E	R	E	W	Y
A-2601	Q	R	M	G	R	N	R	N	V	T	D	A	R	G	G	N	Q	R	T	H	E	R	E	W	Y
A-2603	Q	R	M	G	R	N	R	N	V	T	H	V	R	G	G	N	Q	R	T	H	E	R	E	W	Y
A-2607	Q	R	M	G	G	E	R	K	V	T	D	A	R	G	G	N	Q	R	T	H	E	R	E	W	Y
A-2614	Q	R	M	G	R	N	R	N	V	T	D	A	R	G	G	N	Q	R	A	H	E	R	E	W	Y
A-3401	Q	R	M	G	R	N	R	K	V	T	D	V	R	G	G	N	Q	R	T	H	E	T	E	W	Y
A-3402	Q	R	M	G	R	N	R	N	V	T	D	V	R	G	G	N	Q	R	T	H	E	T	E	W	Y
A-6601	Q	R	M	G	R	N	R	N	V	T	D	V	R	G	G	N	Q	R	T	H	E	R	E	W	Y
A-6602	Q	R	M	G	R	N	R	N	V	T	D	V	R	G	G	N	Q	R	T	H	E	E	E	W	Y
A11	Q	R	M	G	Q	E	R	N	V	T	D	V	R	G	G	N	K	R	A	H	E	R	E	W	Y

(Continues)

TABLE 3 (Continued)

A: HLA-A Serotypes and selected AA residues

Serotype	43[6,86]	44[51]	45	56[87]	62[51,87–90]	63[21,74]	65[51]	66[91]	67[92]	73[86,87,91]	74	76[51]	82[51]	83[51]	107[51]	127[51,93]	144[51,94,121,122]	145[95]	149[51,64,87,96]	151[94,121,122]	161[51]	163[6,51,56]	166[97]	167[74]	171[98]
A29	Q	R	M	G	L	Q	R	N	V	T	D	A	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-3001	Q	R	M	R	Q	E	R	N	V	T	D	V	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-3002	Q	R	M	R	Q	E	R	N	V	T	D	E	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-3007	Q	R	M	R	E	E	G	K	V	T	D	E	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A31	Q	R	M	R	Q	E	R	N	V	I	D	V	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-3201	Q	R	M	G	Q	E	R	N	V	T	D	E	L	R	G	N	Q	R	A	R	E	T	E	W	Y
A-3204	Q	R	M	G	Q	E	R	N	V	T	D	E	L	R	G	N	K	R	A	H	D	T	E	W	Y
A-3301	Q	R	M	G	R	N	R	N	V	I	D	V	R	G	G	N	Q	R	A	R	E	T	E	W	H
A-3303	Q	R	M	G	R	N	R	N	V	I	D	V	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-3308	Q	R	M	G	G	E	R	K	V	I	D	V	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-3313	Q	R	M	G	R	N	R	N	V	T	D	A	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A74	Q	R	M	G	Q	E	R	N	V	T	D	V	R	G	G	N	Q	R	A	R	E	T	E	W	Y
A-6801	Q	R	M	G	R	N	R	N	V	T	D	V	R	G	G	K	K	H	A	H	E	T	E	W	Y
A-6810	Q	R	M	G	E	E	R	N	V	T	D	V	R	G	G	K	K	H	A	H	E	T	E	W	Y
A-6836	Q	R	M	G	R	N	R	N	V	T	D	E	L	R	G	K	K	H	A	H	E	T	E	W	Y
A69	Q	R	M	G	R	N	R	N	V	T	D	V	R	G	W	K	K	H	A	H	E	T	E	W	Y
A36	Q	K	M	G	Q	E	R	N	M	T	D	A	R	G	G	N	K	R	A	H	E	T	E	W	Y
A43	Q	R	M	G	L	Q	R	N	V	T	D	A	R	G	G	N	Q	R	T	H	E	R	E	W	Y
A80	Q	R	M	E	E	E	R	N	V	T	N	A	R	G	G	N	K	R	A	R	E	E	D	G	Y

B: HLA-B Serotypes and selected AA residues

Serotype	11[29]	45[74,87,96]	46[74,87,96]	62[88,89]	63[21,74]	67[87]	69[51,54,111]	70[74,111]	71[111]	76[51]	82[51]	83[51]	103	127[51,93]	143[59]	145[6]	147[54]	158[112]	163[51,56]	167[74]	171[98,113]	177[11]	178[11]	180[11]
B-5101	A	T	E	R	N	F	T	N	T	E	L	R	V	N	T	R	W	A	L	W	H	E	T	Q
B5102	A	T	E	R	N	F	T	N	T	E	L	R	V	N	T	R	W	A	L	W	Y	E	T	Q
B5103	A	T	E	R	N	F	T	N	T	E	L	R	V	N	T	R	W	A	L	G	H	E	T	Q
B52	A	T	E	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	L	W	H	E	T	Q
B-0702	S	E	E	R	N	Y	A	Q	A	E	R	G	V	N	T	R	W	A	E	W	Y	D	K	E
B703	S	E	E	R	N	Y	T	N	T	E	R	G	V	N	T	R	W	A	E	W	Y	D	K	E
B-0715	S	E	E	R	N	Y	A	Q	A	V	R	G	V	N	T	R	W	A	E	W	Y	D	K	E
B-0736	S	E	E	R	N	Y	A	Q	A	E	L	R	V	N	T	R	W	A	E	W	Y	D	K	E
B-0713	S	G	E	R	E	Y	R	Q	A	V	R	G	V	N	T	R	W	A	E	W	Y	D	K	E
B-0801	A	E	E	R	N	F	T	N	T	E	R	G	V	N	T	R	W	A	T	W	Y	D	T	E
B-0802	A	E	E	R	N	F	T	N	T	E	L	R	V	N	T	R	W	A	T	W	Y	D	T	E
B-4402	A	K	E	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	L	S	Y	E	T	Q
B-4404	A	K	E	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	T	S	Y	E	T	Q

TABLE 3 (Continued)

B: HLA-B Serotypes and selected AA residues

Serotype	11[29]	45[74,87,96]	46[74,87,96]	62[88,89]	63[21,74]	67[87]	69[51,54,111]	70[74,111]	71[111]	76[51]	82[51]	83[51]	103	127[51,93]	143[59]	145[6]	147[54]	158[112]	163[51,56]	167[74]	171[98,113]	177[11]	178[11]	180[11]
B-4408	A	M	A	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	L	S	Y	E	T	Q
B-4406	A	T	E	R	N	F	T	N	T	E	L	R	V	N	T	R	W	A	L	S	Y	E	T	Q
B45	A	K	E	R	E	S	T	N	T	E	R	G	L	N	T	R	W	A	L	S	Y	E	T	Q
B13	A	M	A	R	E	S	T	N	T	E	L	R	L	N	T	L	W	A	E	W	Y	E	T	Q
B64	S	E	E	R	N	C	T	N	T	E	R	G	V	N	T	R	W	A	T	W	H	E	T	Q
B65	A	E	E	R	N	C	T	N	T	E	R	G	V	N	T	R	W	A	T	W	H	E	T	Q
B1501	A	M	A	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	L	W	Y	E	T	Q
B-1524	A	M	A	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	L	W	Y	E	T	Q
B-1538	A	M	A	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	L	W	H	E	T	Q
B-1540	A	M	A	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	E	W	Y	E	T	Q
B-1542	A	M	A	R	E	S	T	N	T	E	R	G	L	N	T	R	W	A	T	W	Y	E	T	Q
B-1516	A	M	A	R	E	M	A	S	A	E	L	R	L	N	T	R	W	A	L	W	Y	E	T	Q
B-1517	A	M	A	R	E	M	A	S	A	E	L	R	V	N	T	R	W	A	L	W	Y	E	T	Q
B75	A	M	A	R	N	S	T	N	T	E	R	G	V	N	T	R	W	A	L	W	Y	E	T	Q
B76	A	M	A	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	L	G/S	Y	E	T	Q
B77	A	M	A	R	N	S	T	N	T	E	L	R	V	N	T	R	W	A	L	W	Y	E	T	Q
B-3801	S	E	E	R	N	C	T	N	T	E	L	R	V	N	T	R	W	T	T	W	Y	E	T	Q
B-3803	S	E	E	R	E	S	T	N	T	E	L	R	V	N	T	R	W	T	T	W	Y	E	T	Q
B-3806	S	T	E	R	N	F	T	N	T	E	L	R	V	N	T	R	W	T	T	W	Y	E	T	Q
B3901	S	E	E	R	N	C	T	N	T	E	R	G	V	N	T	R	W	T	T	W	Y	E	T	Q
B3902	S	E	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	T	T	W	Y	E	T	Q
B-3910	S	E	E	R	N	Y	T	N	T	E	R	G	V	N	T	R	W	T	T	W	Y	E	T	Q
B57	A	M	A	G	E	M	A	S	A	E	L	R	V	N	T	R	W	A	L	W	Y	E	T	Q
B58	A	T	E	G	E	M	A	S	A	E	L	R	L	N	T	R	W	A	L	W	Y	E	T	Q
B-1801	S	T	E	R	N	S	T	N	T	E	R	G	V	N	T	R	W	A	T	W	H	E	T	Q
B-1806	S	T	E	R	N	S	T	N	T	V	R	G	V	N	T	R	W	A	T	W	H	E	T	Q
B-1809	S	T	E	R	N	S	T	N	T	E	L	R	V	N	T	R	W	A	T	W	H	E	T	Q
B49	A	K	E	R	E	S	T	N	T	E	L	R	L	N	T	R	W	A	L	W	Y	E	T	Q
B50	A	K	E	R	E	S	T	N	T	E	R	G	L	N	T	R	W	A	L	W	Y	E	T	Q
B54	A	G	E	R	N	Y	A	Q	A	E	R	G	L	N	T	R	W	A	T	W	Y	E	T	Q
B55	A	E	E	R	N	Y	A	Q	A	E	R	G	L	N	T	R	W	A	T	W	Y	E	T	Q
B56	A	E	E	R	N	Y	A	Q	A	E	R	G	L	N	T	R	W	A	L	W	Y	E	T	Q
B-2705	S	E	E	R	E	C	A	K	A	E	L	R	V	N	T	R	W	A	E	W	Y	E	T	Q
B2708	S	E	E	R	E	C	A	K	A	E	R	G	V	N	T	R	W	A	E	W	Y	E	T	Q
B-2712	S	E	E	R	E	C	T	N	T	E	R	G	V	N	T	R	W	A	E	W	Y	E	T	Q

(Continues)

TABLE 3 (Continued)

B: HLA-B Serotypes and selected AA residues

Serotype	11[29]	45[74,87,96]	46[74,87,96]	62[88,89]	63[21,74]	67[87]	69[51,54,111]	70[74,111]	71[111]	76[51]	82[51]	83[51]	103	127[51,93]	143[59]	145[6]	147[54]	158[112]	163[51,56]	167[74]	171[98,113]	177[11]	178[11]	180[11]
B-3501	A	T	E	R	N	F	T	N	T	E	R	G	L	N	T	R	W	A	L	W	Y	E	T	Q
B-3510	A	T	E	R	E	F	T	N	T	E	R	G	L	N	T	R	W	A	L	W	Y	E	T	Q
B-3515	A	T	E	R	N	F	T	N	T	E	R	G	L	N	T	R	W	A	E	W	Y	E	T	Q
B-3519	A	K	E	R	N	F	T	N	T	E	R	G	L	N	T	R	W	A	L	W	Y	E	T	Q
B-3701	S	T	E	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	T	W	Y	E	T	Q
B-3702	S	T	E	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	E	W	Y	E	T	Q
B-3705	S	T	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	T	W	Y	E	T	Q
B60	A	K	E	R	E	S	T	N	T	E	R	G	V	N	S	R	L	A	E	W	Y	D	K	E
B-4016	A	K	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	E	W	Y	D	K	E
B-4021	A	M	A	R	E	S	T	N	T	E	R	G	V	N	S	R	L	A	E	W	Y	D	K	E
B-4047	A	K	E	R	E	S	T	N	T	E	L	R	V	N	S	R	L	A	E	W	Y	D	K	E
B61	S	K	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	E	W	Y	E	T	Q
B4005	S	K	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	L	W	Y	E	T	Q
B41	A	K	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	T	W	Y	D	T	E
B42	S	E	E	R	N	Y	A	Q	A	E	R	G	V	N	T	R	W	A	T	W	Y	D	T	E
B46	A	M	A	R	E	Y	R	Q	A	V	R	G	V	N	T	R	W	A	L	W	Y	E	T	Q
B47	A	K	E	R	E	S	T	N	T	E	L	R	V	N	T	R	W	A	E	W	Y	E	T	Q
B-4801	S	E	E	R	E	S	T	N	T	E	R	G	V	N	S	R	L	A	E	W	Y	D	K	E
B-4804	S	E	E	R	E	S	T	N	T	E	R	G	V	N	S	R	L	A	E	W	Y	E	T	Q
B-4805	S	E	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	E	W	Y	D	K	E
B53	A	T	E	R	N	F	T	N	T	E	L	R	L	N	T	R	W	A	L	W	Y	E	T	Q
B59	A	E	E	R	N	F	T	N	T	E	L	R	L	N	T	R	W	A	T	W	Y	E	T	Q
B67	S	E	E	R	N	Y	A	Q	A	E	R	G	V	N	T	R	W	T	T	W	Y	E	T	Q
B-6702	S	G	E	R	E	Y	R	Q	A	V	R	G	V	N	T	R	W	T	T	W	Y	E	T	Q
B-1510	A	E	E	R	N	C	T	N	T	E	R	G	V	N	T	R	W	A	L	W	Y	E	T	Q
B-1523	A	E	E	R	N	C	T	N	T	E	L	R	V	N	T	R	W	A	L	W	Y	E	T	Q
B-1537	A	E	E	R	N	C	T	N	T	E	R	G	V	N	T	R	W	A	L	W	H	E	T	Q
B-1552	A	E	E	R	N	C	T	N	T	E	R	G	V	N	T	R	W	A	E	W	Y	E	T	Q
B72	A	E	E	R	E	S	T	N	T	E	R	G	V	N	T	R	W	A	L	W	Y	E	T	Q
B73	S	E	E	R	N	C	A	K	A	V	R	G	M	N	T	R	W	A	E	W	H	E	T	Q
B78	A	T	E	R	N	F	T	N	T	E	R	G	V	N	T	R	W	A	L	W	H	E	T	Q
B81	S	E	E	R	N	Y	A	Q	A	E	R	G	V	N	S	R	L	A	E	W	Y	D	K	E
B82	A	E	E	R	N	Y	A	Q	A	E	R	G	L	N	T	R	W	A	L	S	Y	E	T	Q

TABLE 3 (Continued)

C: HLA-C serotypes and selected AA residues

Serotype	24	45	49[114]	66[91]	73[87]	76[51,80]	77[80]	80[80]	82[51]	83[51]	91[114–117]	99[114]	138[118]	143[59]	147[54,118]	158	163[51,56]	173[118]	175[114]	177[87,118]
C-0102	S	G	A	K	T	V	S	N	R	G	G	C	T	T	W	A	T	E	G	E
C-0114	S	G	A	K	T	V	N	K	R	G	G	C	T	T	W	A	T	E	G	E
C-0202	A	G	A	K	T	V	N	K	R	G	G	Y	T	T	W	A	E	E	G	E
C-0227	A	G	A	K	T	V	S	N	R	G	G	Y	T	T	W	A	E	E	G	E
Cw9	A	G	A	K	T	V	S	N	R	G	R	Y	T	T	W	A	L	K	G	E
Cw10	A	G	A	K	T	V	S	N	R	G	G	Y	T	T	W	A	L	K	G	E
C-0307	A	G	A	K	T	V	N	K	R	G	G	Y	T	T	W	A	L	K	G	E
C-0401	A	G	E	K	A	V	N	K	R	G	G	F	T	T	W	A	T	E	G	E
C-0403	A	G	A	K	A	V	N	K	R	G	G	F	T	T	W	A	T	E	G	E
C-0408	A	G	E	K	A	V	N	K	R	G	G	F	T	T	W	A	L	E	G	E
C-0410	A	G	E	K	T	V	N	K	R	G	G	F	T	T	W	A	T	E	G	E
C-0501	A	G	A	K	T	V	N	K	R	G	G	Y	K	T	W	A	T	E	G	K
C-0509	A	G	A	K	T	V	N	K	R	G	G	Y	K	T	W	A	T	E	G	E
C-0810	A	G	A	K	T	V	N	K	R	G	G	Y	T	T	W	A	T	E	G	K
C-0602	S	G	A	K	A	V	N	K	R	G	G	Y	T	T	W	A	T	E	G	E
C-0608	S	G	A	K	A	V	N	K	R	G	G	Y	T	T	W	A	E	E	G	E
C-0701	S	G	A	N	A	V	S	N	R	G	G	Y	T	T	L	A	T	E	G	E
C-0702	S	G	A	K	A	V	S	N	R	G	G	S	T	T	L	A	T	E	G	E
C-0704	S	G	A	K	A	V	S	N	R	G	G	Y	T	T	L	A	T	E	G	K
C-0707	S	G	A	N	A	V	N	K	R	G	G	Y	T	T	L	A	T	E	G	E
C-0801	A	G	A	K	T	V	S	N	R	G	G	Y	T	T	W	A	T	E	G	K
C-0802	A	G	A	K	T	V	S	N	R	G	G	Y	K	T	W	A	T	E	G	K
C-0803	A	G	A	K	T	V	S	N	R	G	G	Y	T	T	W	A	T	E	R	K
C-1202	A	G	A	K	A	V	S	N	R	G	G	Y	T	T	W	A	T	E	G	E
C-1204	A	G	A	K	A	V	N	K	R	G	G	Y	T	T	W	A	T	E	G	E
C-1212	A	G	A	K	A	E	S	N	R	G	G	Y	T	T	W	A	T	E	G	E
C-1402	A	G	A	K	T	V	S	N	R	G	G	F	T	T	W	A	T	E	G	E
C-1502	A	G	A	N	T	V	N	K	R	G	G	Y	T	T	W	A	T	E	G	E
C-1507	A	G	A	N	T	V	S	N	R	G	G	Y	T	T	W	A	T	E	G	E
C-1601	A	G	A	K	T	V	S	N	R	G	G	Y	T	T	W	A	T	E	G	E
C-1602	A	G	A	K	T	V	N	K	R	G	G	Y	T	T	W	A	T	E	G	E
C-1701	A	G	A	K	A	V	N	K	R	G	G	Y	T	S	L	A	E	E	G	E
C-1801	S	G	A	K	A	V	N	K	R	G	G	F	T	T	W	A	T	E	G	E

(Continues)

TABLE 3 (Continued)

D: HLA-DRB1 related Serotypes and selected AA residues													
Serotype	**9**[43]	**10**[43]	**11**[43]	**12**[43]	**13**[43]	**14**[43]	**16**[5,55]	**47**[54]	**58**[39,43]	**60**[43]	**70**[54]	**71**[99]	**74**[5]
DR-0101	W	Q	L	K	F	E	H	Y	A	Y	Q	R	A
DR103	W	Q	L	K	F	E	H	Y	A	Y	D	E	A
DR15	W	Q	P	K	R	E	H	F	A	Y	Q	A	A
DR16	W	Q	P	K	R	E	H	Y	A	Y	D	R	A
DR17	E	Y	S	T	S	E	H	F	A	Y	Q	K	R
DR18	E	Y	S	T	S	E	H	Y	A	Y	Q	K	R
DR-0401	E	Q	V	K	H	E	H	Y	A	Y	Q	K/R	A
DR-0402	E	Q	V	K	H	E	H	Y	A	Y	D	E	A
DR-0403	E	Q	V	K	H	E	H	Y	A	Y	Q	R	E
DR-0412	E	Q	V	K	H	E	H	Y	A	Y	D	R	L
DR-0415	E	Q	V	K	H	E	H	Y	E	Y	D	R	A
DR-1410	E	Q	V	K	H	E	H	Y	A	H	R	R	E
DR-1101	E	Y	S	T	S	E	H	F	E	Y	D	R	A
DR-1102	E	Y	S	T	S	E	H	F	E	Y	D	E	A
DR-1105	E	Y	S	T	G	E	H	F	E	Y	D	R	A
DR-1107	E	Y	S	T	S	E	H	F	E	Y	Q	K	R
DR-1117	E	Y	S	T	S	E	H	Y	E	Y	R	R	E
DR12	E	Y	S	T	G	E	Y	F	A	S	D	R	A
DR-1301	E	Y	S	T	S	E	H	F	A	Y	D	E	A
DR-1303	E	Y	S	T	S	E	H	Y	A	Y	D	K/R	A
DR-1317	E	Y	S	T	G	E	Y	F	A	Y	D	E	A
DR-1339	E	Y	S	T	S	E	H	F	A	S	D	E	A
DR-1343	E	Y	S	T	S	E	H	F	A	H	D	E	A
DR-1454	E	Y	S	T	S	E	H	Y	A	H	R	R	E
DR-1402	E	Y	S	T	S	E	H	Y	A	Y	Q	R/K	A
DR1403	E	Y	S	T	S	E	H	Y	A	Y	D	R	L
DR1404	E	Y	S	T	G	E	Y	Y	A	H	R	R	E
DR-1405	E	Y	S	T	S	E	Q	Y	A	Y	R	R	E
DR-1411	E	Y	S	T	G	E	Y	Y	E	Y	R	R	E
DR-1414	E	Y	S	T	S	E	H	Y	A	Y	R	R	E
DR-1422	E	Y	S	T	S	E	H	Y	A	H	D	R	A
DR-1424	E	Y	S	T	S	E	H	Y	A	Y	Q	A	A
DR-1448	E	Y	S	T	S	E	H	Y	A	S	Q	R	A
DR7	W	Q	G	K	Y	K	H	Y	A	S	D	R	Q

DR-0801	E	Y	S	T	G	E	Y	Y	A	Y	D	R	L
DR-0818	E	Y	S	T	G	E	Y	Y	A	Y	D	R	A
DR9	K	Q	D	K	F	E	H	Y	A	S	R	R	E
DR10	E	E	V	K	F	E	H	Y	A	Y	R	R	A

E: HLA-DRB3/4/5 related Serotypes and selected AA residues

Serotype	9[43]	10[43]	11[43]	12[43]	13[43]	60[43]	71[99]
DR-5101	Q	Q	D	K	Y		R
DR-5102	Q	Q	D	K	Y		A
DR-5103	Q	Q	D	K	Y		T
DR-5201	E	L		K	S	S	
DR-5202	E	L		K	S	Y	
DR53	E	Q	A	K	C		

F: HLA-DQB1 related serotypes and selected AA residues

WHO accepted antigen	45[119]	46[43]	47[43]	57	70[43]	71[43]	74[43]	84[43]	85[43]	86	87	89[43]	90[43]
DQ5	G	V	Y	V	G	A	S	E	V	A	Y	G	I
DQ6	G	V	Y	D	G	T	E	E	V	A/G	F/Y	G	I
DQ2	G	E	F	A	R	K	A	Q	L	E	L	T	T
DQ7	E	V	Y	D/A	R	T	E	Q	L	E	L	T	T
DQ8	G	V	Y	A	R	T	E	Q	L	E	L	T	T
DQ9	G	V	Y	D	R	T	E	Q	L	E	L	T	T
DQ4	G	V	Y	D	E	D	S	Q	L	E	L	T	T

G: HLA-DQA1 related Serotypes, reference HLA-DQA1 proteins and AA residues at each position

Serotype	Protein	25	51	52	53	56	74	75	76
DQA-01	DQA1*01:01	Y	F	S	K	G	N	I	M
DQA-03	DQA1*03:01	Y	F	R	R	R	N	I	V
Serotype	Protein	25	51	52	53	56 (57)	74 (75)	75 (76)	76 (77)
DQA-02	DQA1*02:01	F	F	H	R	F	I	L	I
DQA-04	DQA1*04:01	Y	L	R	Q	F	I	L	I
DQA-05	DQA1*05:01	Y	L	R	Q	F	S	L	I
DQA-06	DQA1*06:01	F	L	R	Q	F	I	L	I

H: HLA-DPB1 related serotypes, reference HLA-DPB1 proteins and AA residues at each position

Serotype	Protein	56[75,77,78]	57[75,77,78]	69[99]	82	84[75,77,78]	85[75,77,78]
DP-01	DPB1*01:01/DPB1*11:01	A	E	K/R	E	D	E
DP-0201	DPB1*02:01	E	E	E	E	G	G
DP-0202	DPB1*02:02	A	E	E	E	G	G

(Continues)

TABLE 3 (Continued)

H: HLA-DPB1 related serotypes, reference HLA-DPB1 proteins and AA residues at each position							
Serotype	**Protein**	**56**[75,77,78]	**57**[75,77,78]	**69**[99]	**82**	**84**[75,77,78]	**85**[75,77,78]
DP-03	DPB1*03:01/DPB1*69:01	E	D	K/R	E	D	E
DP-06	DPB1*06:01	E	D	E	E	D	E
DP-0401	DPB1*04:01	A	E	K	E	G	G
DP-0402	DPB1*04:02	E	E	K	E	G	G
DP-10	DPB1*10:01	E	E	E	E	D	E
DP-13	DPB1*13:01	A	E	E	E	D	E
DP-15	DPB1*15:01/DPB1*34:01	A	E	R/K	E	V	G
DP-18	DPB1*18:01	E	E	K	E	V	G
DP-45	DPB1*45:01/DPB1*136:01	E	E	K/R	E	D	E
DP-46	DPB1*46:01	E	D	E	E	G	G
DP-80	DPB1*80:01	E	D	K	E	G	G

I: HLA-DPA1 related Serotypes, reference HLA-DPA1 proteins and AA residues at each position						
Serotype	**Protein**	**50**	**55**	**58**	**59**	**60**
DPA-01	DPA1*01:03	Q	E	G	G	L
DPA-02	DPA1*02:01	R	E	G	G	L

Note: Tables 3A–I show Amino Acid (AA) residues used to define FULL and SEROTYPE assignments of HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1 and -DPA1. The "Serotype" column shows serotypes for each HLA locus, the numbers indicate residue positions, and the alphabetical characters indicates amino acids at each residue position. Combination of AA residues in the gray shaded cells define "SEROTYPE" assignments. Combined AA residues in the white, gray and black cells in each row define FULL assignments. The black shaded cells indicate AA residues that likely display different serological specificities from those of the prototype serotypes. For HLA-A in Table 3A, residue 45 was included to eliminate HLA-C alleles. For HLA-B in Table 3B, residue 103V was used for the serotype B-713 to eliminate HLA-C proteins, e.g., HLA-C*02:23 and HLA-C*04:77. For HLA-A and HLA-B, residue 127 was included only to define FULL assignments. For HLA-C in Table 3C, residue 158 was used to distinguish C-1202 from B-6702. For HLA-DQA1 in Table 3G, the serotypes DQA-02, DQA-04, DQA-05, and DQA-06 carry a single AA deletion at residue position 56 in the AA alignment view in the IPD-IMGT/HLA Database. The numbers in row 1 and 4 reflect the actual AA residue position, and the numbers in the parenthesis in row 4 reflect the residue positions including the deletion in the AA alignment view. References were shown in superscript numbers for each residue position.

dash (−), for example, A-0201 for the HLA-A*02:01. The classical naming of the splits of B14, Cw3, DR3 and DQ3 are maintained in NSD to be consistent with previous naming of the broad antigens; their serologic split names differ from the first field of the corresponding prototype allele, for example, HLA-B*14:01 to be B64 and HLA-B*14:02 to be B65 (Tables 2B and 3B).

2.5 | Serologic specificities for DQA1, DPA1, and DPB1

The serologic specificities for HLA-DQA1 and -DPA1 were designated using DQA and DPA followed by the common first-field allele name separated by dash (−). Six serotypes, DQA-01, DQA-02, DQA-03, DQA-04, DQA-05, and DQA-06, were created for HLA-DQA1, and two serotypes, DPA-01 and DPA-02, were created for HLA-DPA1. For HLA-DPB1, analogous to DQ splits, the first field of the allele name is used to designate the serologic specificity separated by dash (−). Initially eight serotypes DP-01, DP-0201, DP-03, DP-0401, DP-10, DP-15, DP-18, and DP-46 were defined using the residues 56–57 and 84–85 (Table 3H).[75,77,78] Serotypes were further split using residue 69,[99] therefore, additional six serotypes DP-13, DP-0402, DP-06, DP-0202, DP-18, and DP-80 were defined. Tables 3G–I show AA residues that define specific serotypes for HLA-DQA1, HLA-DPB1, and HLA-DPA1.

2.6 | HLA allele to serotype (HATS) software and antigen assignments

A computational tool (HLA allele to serotype: HATS) was developed using Perl Programming Language to translate an HLA allele to a serotype. To create reference DEP patterns, HATS captures AA residues at predefined DEP positions (Table 3A–I) from full-length protein sequences of the prototype alleles in one hla_prot.fasta file. When leader peptide sequence that corresponds to exon 1 was missing for a certain HLA allele, the leader peptide sequences were filled with "X" to adjust these alleles to be full-length. HATS was originally optimized using IPD-IMGT/HLA Database release version 3.38.0, and tested using release version 3.44.0. HATS assigns HLA alleles to the predefined HLA serotypes in one of the following two criteria: key AA residues matched to a specific serotype either at (1) all positions defined in Table 3A–I (FULL) or (2) at only positions defining a serotype (SEROTYPE), (residues highlighted in gray in Table 3A–I).

In addition to the FULL and SEROTYPE assignments, the software defines INCOMPLETE assignments that implies alleles that carry a single mismatch with one or more SEROTYPES and UNASSIGNED (UNA). The INCOMPLETE assignments were further classified as SHORT that carries a single mismatch with a SEROTYPE, and SHORT-CROSSREACTIVE assignment that implies alleles that carry a single mismatch with two or more SEROTYPES. HATS is available at https://github.com/kosoegawa/HATS.

TABLE 4 Proposed serologic Antigens defined by combinations of polymorphic subunits (DQ) observed in *cis* in the most common DQA1∼DQB1 blocks

Cis encoded Prototype protein combination	CDQS
DQA1*02:01∼DQB1*02:02	DQA-02∼DQ2
DQA1*02:01∼DQB1*03:03	DQA-02∼DQ9
DQA1*03:03∼DQB1*02:02	DQA-03∼DQ2
DQA1*03:03∼DQB1*04:01	DQA-03∼DQ4
DQA1*03:03∼DQB1*03:01	DQA-03∼DQ7
DQA1*03:01∼DQB1*03:02	DQA-03∼DQ8
DQA1*03:02∼DQB1*03:03	DQA-03∼DQ9
DQA1*04:01∼DQB1*04:02	DQA-04∼DQ4
DQA1*04:01∼DQB1*03:19	DQA-04∼DQ7
DQA1*05:01∼DQB1*02:01	DQA-05∼DQ2
DQA1*05:05∼DQB1*03:01	DQA-05∼DQ7
DQA1*05:05∼DQB1*03:03	DQA-05∼DQ9
DQA1*06:01∼DQB1*03:01	DQA-06∼DQ7

Note: "Prototype *cis* combination" column shows combinations of two-field HLA-DQA1 and HLA-DQB1 alleles separated by tilde (∼). The column represents the common *HLA-DQA1∼HLA-DQ1* haplotypes containing the common alleles. CDQS column shows proposed combinational serotypes defined by DQA subunit, DQA02/03/04/05/06, and DQB1 subunit, DQ2/4/7/8/9.

2.7 | Serologic DQA1∼DQB1 antigens defined by combinatorial DQ serotypes (CDQS)

Additional DQ serologic specificities were identified by mAbs and allo-antisera recognizing combinatorial epitopes defined by variations at the DQA1 and DQB1 subunits.[100] Allele-specific constraints were reported for formation of heterodimeric DQα and DQβ on cell surface.[101] In this report, *cis* combinatorial HLA-DQA1 (DQA-02/03/04/05/06) and HLA-DQB1 (DQ2/4/7/8/9) serotypes using common *HLA-DQA1∼HLA-DQB1* haplotypes containing the common alleles were proposed (Table 4).

2.8 | Common, intermediate, and well-documented HLA alleles

The common and well-documented (CWD) and common, intermediate, and well-documented (CIWD) allele

TABLE 5 Observed new serotypes that likely show different serological specificities than those of the WHO-accepted antigens

Allele	CIWD	Expert assigned	WHO Assigned	NN assigned	Comments	Serotype	Note
A*02:02	C	A2	A2	Training - A2	13th IHW: variant serum pattern	A-0202	43R
A*02:11	C	A2	A2	A2	13th IHW: short A2	A-0211	73I74D
A*02:19	I	A2	-	A2		A-0219	145R166D167G
A*02:44	I	A2/blank	-	A2		A-0244	145R
A*02:46	WD	A2	A2	A2		A-0246	62E65G
A*02:56	I	A2		A2	Short A2	A-0256	62Q
A*02:65		A2/A19	A2/A19	Not assigned	NN: A74	A-0265	A2/A74 hybrid
A*02:85	C	A2				A-0285	149 V
A*03:05	I	A3/blank	A3	A3	13th IHW: only reactive with some A3 + 11 and A3 + 19 + 34 sera; normal A3	A-0305	161E
A*03:23	WD	A3	-	A3		A-0323	62G + 161D A2/A3 hybrid
A*23:04	WD	A23	A23(A9)	A23	13th IHW: short A23, negative with A9 + 80(+1) sera	A-2304	166E167 W
A*24:04	I	A24	A24 (9)			A-2404	Negative[102]
A*24:05	C	A9	A9	A24		A-2405	144Q151H123
A*24:08	I	A24	A24 (9)	A24	short A24, similar to A2403	A-2408	62G
A*24:23	C	A24	A2403	A24	A2403	A-2423	166D167 W
A*24:24	WD	A9		A9f	NN: A23	A-2424	A6836/A23 hybrid
A*26:03	C	A26	A26 (10)	Training - A10 A26	13th IHW: short A26	A-2603	74H77D
A*26:07	I	A26	A26 (10)	Not assigned	NN: A43, A10, A26	A-2607	62G[31]
A*26:14	I	A26	-	A26		A-2614	149A
A*30:02	C	A30	A30 (19)	Training - A30		A-3002	Bw6-associated[18]
A*30:07	C	A30				A-3007	Bw6-associated+62E
A*32:04	I	A32/A3	-	Not assigned	A3 with most A32 sera reactive (13th IHW); NN: A32 A3	A-3204	144K161D
A*33:03	C	A33	A33 (19)	Training - A33		A-3303	171Y; A33(171H)
A*33:08	WD	Undefined	A33 (19)	Not assigned	NN: A31, A33	A-3308	62G63E
A*33:13	WD	Undefined	-	Not assigned	NN: A33	A-3313	73 T76A171Y
A*34:02	C	A34	A34 (10)	Training - A10 A34	13th IHW: distinct pattern from A*3401	A-3402	66 N
A*66:02	C	A66	A66 (10)	A66	13th IHW: A'6602', short A66	A-6602	163E[51]
A*68:10	C	A68	A28	A68	13th IHW: possibly A68, but cell also A2 pos.	A-6810	62E
A*68:36	WD	A68	A68 (28)	A28	NN: A68	A-6836	76E77N-Bw4

TABLE 5 (Continued)

Allele	CIWD	Expert assigned	WHO Assigned	NN assigned	Comments	Serotype	Note
B*07:13	WD	B7/blank		B7		B-0713	HLA-C*12 + B7
B*07:15	I	B7	B7	B7	B7var, some Bw6 sera negative	B-0715	Negative
B*07:36	WD	B7		B7	Bw4 pos	B-0736	Bw4
B*08:02	WD	B8	B8	Not assigned	B8 Bw4; 13th IHW: B8Bw4 with extra reactions; NN: B8	B-0802	Bw4
B*15:16	C	B63	B63 (15)	Training - B15 B63		B-1516	103 L, African B63[21]
B*15:23	I	B70/B5/blank		Not assigned	B5x70-Bw4, B5/53/77var; NM5; 13th IHW: new pattern, short B71-Bw4; NN: B70 B71	B-1523	B71-Bw4[74]
B*15:24	C	B62	B62 (15)	B15	B62 Bw4	B-1524	B62-Bw4[74]
B*15:37	C	B70	B70	B71		B-1537	171H
B*15:38	C	B62	–	B62	B62var, also reactive with B52 sera	B-1538	171H
B*15:40	C	B62/blank		B62	Short B62	B-1540	163E
B*15:42	WD	B15	–	B62	Short B15; reactive with some B22 sera	B-1542	163 T
B*15:52	C	Undefined	B15	B71	B15	B-1552	163E
B*18:06	I	B18	B18	B18	B18var, negative with Bw4 and Bw6 sera	B-1806	Negative
B*18:09	WD	B18	B18	Not assigned	B18 Bw4; NN: B18 B38	B-1809	Bw4
B*27:12	C	Undefined	B27	Not assigned	blank Bw6; B27 sera neg, B7 + 27(+40) sera pos; 13th IHW: blank, B61 B27-Bw6; NN: B27	B-2712	Similar to B2708/B61
B*35:10	C	B35	B35	B35	13th IHW: short B35	B-3510	63E
B*35:15	I	B35	B35	B35	Short B35, B75 CREG sera reactive.	B-3515	163E
B*35:19	C	B35/ blank	B35	B35	13th IHW: new pattern, blank, very short B35	B-3519	45 K
B*37:02	C	B37/B27		Not assigned	B37x27 or blank; few B37 and few B27 sera reactive. NN: B37	B-3702	163E
B*37:05	WD	blank		Not assigned	blank Bw6, B37 and Bw4 sera negative, Korean. NN: B37	B-3705	Bw6
B*38:03	I	B38	B16	Not assigned	B16 Bw4, B38 and B39 sera negative, NN: B16 B38	B-3803	63E67S: same as B3902 split
B*38:06	WD	B38	-	B38		B-3806	45T67F
B*39:10	C	B39	B39 (16)	B39		B-3910	67Y
B*40:16	C	B61	B61 (40)	Not assigned	NN: B40 B-4101	B-4016	143 T178K
B*40:21	WD	B40/B15	-	Not assigned	B40x15, reactive with B40 + 48, B15 + 57 sera, not with B40 + 13 sera; NN: B15 B48	B-4021	45M46A
B*40:47	WD	B40	B40	Not assigned	B40 Bw4; short B60, Bw4pos: NN: B40 B60	B-4047	Bw4

(Continues)

TABLE 5 (Continued)

Allele	CIWD	Expert assigned	WHO Assigned	NN assigned	Comments	Serotype	Note
B*44:04	C	B44	B44 (12)	B44	13th IHW: short B44	B-4404	163 T
B*44:06	I	B44	B44 (12)	B44	Short B44 or blank; ihw13: blank, short B44: NN: B44 B12	B-4406	45T63N
B*44:08	I	B44	B44 (12)	B44	Short B44; also reactive with B62 + 63 + 57 sera, in Welsh, but very rare; 13th IHWC: new pattern,	B-4408	45M46A
B*48:04	C	B48	B48	B48	Normal B48	B-4804	177E178T180Q
B*48:05	WD	B48	B48	Not assigned	NN: B48 B7	B-4805	143 T
B*67:02	WD	Undefined	-	Not assigned	NN: B67	B-6702	HLA-C*12 + B67 hybrid
C*01:14	WD	Cw1		Cw1		C-0114	KIR C2
C*02:27	I					C-0227	KIR C1
C*03:07	C	Cw3	Cw3	Cw10		C-0307	KIR C2
C*04:03	C	Cw4/Cw6		Not assigned	NN: Cw4; Cw4/6var; 13th IHW: Cw6 or blank, only Cw4 + 6 sera reactive	C-0403	49A99F
C*04:08	C	Cw4				C-0408	163 L
C*04:10	C	Cw4	Cw4	Cw4	Normal Cw4	C-0410	73 T
C*05:09	C	Cw5		Cw5		C-0509	177E
C*08:10	C	Undefined		Cw5		C-0810	77N80K – KIR C2
C*06:08	C	Cw6		Cw6		C-0608	163E
C*07:02	C	Cw7	Cw7	Training - Cw7		C-0702	66K177E
C*07:04	C	Cw7	Cw7	Cw7		C-0704	66K177K
C*07:07	I	Cw7		Cw7		C-0707	KIR C2
C*08:02	C	Cw8	Cw8	Training - Cw8		C-0802	138K175G
C*08:03	C	Cw8	Cw8	Cw8		C-0803	138T175R
C*12:04	C	Blank		Cw6		C-1204	KIR C2
C*12:12	C	Undefined		Not assigned		C-1212	Bw6
C*15:07	C	Cw3		Cw3		C-1507	KIR C1
C*16:02	C	Undefined		Not assigned	NN: Cw2 Cw6	C-1602	KIR C2[80]
DRB1*14:10	C	DR14	DR14 (6)	Not assigned	NN: DR4 DR14 DR6	DR-1410	9–13: DR4
DRB1*04:02	C	DR4	DR4	Training - DR4		DR-0402	70D71E
DRB1*04:03	C	DR4	DR4	Training - DR4		DR-0403	74E
DRB1*04:12	WD	DR4		DR4		DR-0412	70D74L

TABLE 5 (Continued)

Allele	CIWD	Expert assigned	WHO Assigned	NN assigned	Comments	Serotype	Note
DRB1*04:15	WD	DR4	DR4	DR4	DR4x11	DR-0415	58E70D
DRB1*08:18	I	DR8	DR8	DR8		DR-0818	74A
DRB1*11:02	C	DR11	DR11 (5)	Training - DR11		DR-1102	71E
DRB1*11:05	I	DR11	DR11 (5)	DR11		DR-1105	13G
DRB1*11:07	I	DR11	DR11 (5)	Not assigned	DR11x3; NN: DR17 DR3 DR11	DR-1107	70Q71K74R
DRB1*11:17	C	DR14		DR14	NN: DR6	DR-1117	70R74E
DRB1*13:03/ DRB1*13:05	C	DR13	DR13 (6)	Training - DR6 DR13		DR-1303	71 K/71R
DRB1*13:17	WD	DR13	DR13 (6)	Not assigned	DR13x8; NN: DR8	DR-1317	13G
DRB1*13:39	WD	DR13		DR13		DR-1339	60S
DRB1*13:43		DR13		DR13		DR-1343	60H
DRB1*14:02/ DRB1*14:19	C	DR14	DR14 (6)	Training - DR6 DR14		DR-1402	70Q71R/K74A
DRB1*14:05	C	DR14	DR14 (6)	DR14		DR-1405	16Q60Y
DRB1*14:14	WD	DR14	DR14 (6)	DR14		DR-1414	16H60Y
DRB1*14:11	C	DR14	DR14 (6)	Not assigned	DR14x11; NN: DR14	DR-1411	58E60Y
DRB1*14:22	I	DR14	DR14 (6)	DR14		DR-1422	60H70D
DRB1*14:24	C	DR14		DR14		DR-1424	60Y70Q
DRB1*14:48	C	DR14		DR14		DR-1448	60S70Q
DRB5*02:02	C	DR51	DR51	Not tested		DR-5102	71A
DRB5*01:03	C	Undefined	-			DR-5103	71 T
DRB3*02:01	C	DR52	DR52	Not tested		DR-5202	60Y

Note: The "Allele" column shows two-field HLA allele name used to created new serotypes. The columns "Expert assigned," "WHO Assigned," "NN assigned," and "Comments" shows information listed in the HLA Dictionary 2008. The "Serotype" column shows new proposed serotype name, and "Note" column includes brief description why the new serotype was proposed. The "C (Common)" category was assigned for the proposed new serotypes DR-5102, DR-5103 and DR-5202 using CWD2.0 catalogue, because only WD category was assigned for HLA-DRB3/4/5 loci in the CIWD3.0.[71]

TABLE 6 Number of AA residue positions selected to define HLA serotypes, WHO assigned antigens and proposed new serotypes

Locus	Residues	WHO Assigned Antigens	Proposed new serotypes	Total
HLA-A	25	24	29	53
HLA-B	24	49	32	81
HLA-C	20	9 (15 Cw)	18	33
HLA-DRB1	13	17	21	38
HLA-DRB3	5	1	1	2
HLA-DRB4	5	1	0	1
HLA-DRB5	6	1	2	3
HLA-DQB1	13	7	0	7
HLA-DQA1	8	0	6	6
HLA-DPB1	6	0	14	14
HLA-DPA1	5	0	2	2

Note: Locus column shows 11 HLA loci. "Residues" column shows the number of AA residues used to define FULL serotypes for each locus. "WHO Assigned Antigens" column shows the number of currently WHO assigned antigens. "Proposed New Serotypes" column shows the number of proposed new serotypes. "Total" column shows the total number of serotypes recognized in this study.

catalogs were published and became publicly available.[70–73] The CIWD3.0 catalogue was generated using HLA typing data originating from bone marrow registries around the world, but the CWD2.0 catalogue was not considered.[71] Both CIWD3.0 and CWD2.0 allele catalogs were referenced to be comprehensive, and two-field allele name was used to represent protein level. All CWD HLA alleles identified in Europe and within European sub-regions were examined[73]; the CIWD3.0 catalogue included all these alleles. It is clinically valuable if all common alleles are associated with specific serotypes. When common HLA alleles that fell INCOMPLETE or UNA categories, new serotypes were created. Table 5 shows a list of new serotypes proposed in this study and includes information from the HLA Dictionary 2008[68] and a brief descriptions why these serotypes were proposed in this study.

2.9 | Validation

HLA alleles whose serologic specificities were described to be discordant with the first field molecular designation in the previously published HLA Dictionary[68] were used for the validation of the serologic assignments. In addition, the AA sequences of the selected alleles were aligned with those of the prototype alleles corresponding to the assigned serotype using the Sequence Alignment Tool in IPD-IMGT/HLA Web site (https://www.ebi.ac.uk/ipd/imgt/hla/alignment/). The AA sequence alignments were visually inspected for concordance with the HATS assignment.

3 | RESULTS

3.1 | HLA class I antigen assignments

3.1.1 | HLA-A

For the 24 WHO assigned HLA-A antigens, 5–9 AA residues were selected for SEROTYPE assignments (Table 2A). The use of these residues resulted in the recognition of 29 additional serotypes (Tables 5 and 6). Up to 11 AA residues were used to define the proposed new serotypes containing hybrid AA residue pattern, for example, A-0219, A-0244 and A-0323 (Table 2A). When all residue positions were considered, 25 polymorphic residue positions were recognized for HLA-A (Table 3A and Figure 1A), and these were used to make the new designate FULL assignments (Table 6). Supplemental Table 1 contains HLA-A two-field alleles and their serotypes. Thirty HLA-A proteins (two-field alleles) in which their first-field molecular designation does not correspond to the predicted WHO assigned HLA-A antigens were identified (Table 7), for example, HLA-A*02:55 was designated to A69 serologic specificity (Table 8). In addition, 26 HLA-A proteins for which first-field molecular designation does not correspond to the newly defined HLA-A serotypes were identified (Table 7), for example, HLA-A*26:09 was assigned to A-3402 serologic specificity (Table 8). Only 2 HLA-A alleles (HLA-A*11:271 and HLA-A*29:51) could not be assigned to specific antigens (marked as UNA in Supplemental Table 1), because these alleles had two or more mismatches to the DEP residues in any given serotypes.

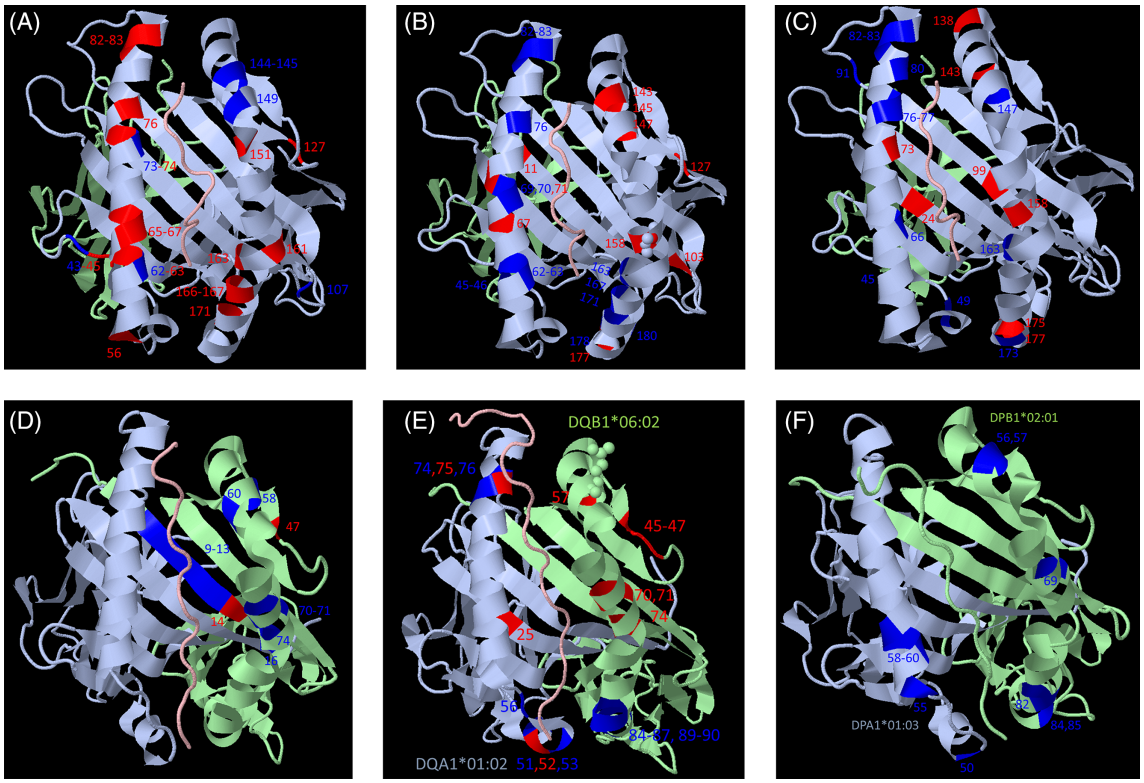

FIGURE 1 Ribbon-taped crystal protein structures for HLA-A, HLA-B, HLA-C, HLA-DRA1∼HLA-DRB1, HLA-DQA1∼HLA-DQB1, and HLA-DPA1∼HLA-DPB1 molecules. (A) HLA-A*02:01 molecule (PDB DOI: 10.2210/pdb7RTD/pdb)[124] and residues representing FULL (RED+BLUE) and SEROTYPE (BLUE) for the serotype A-0201. (B) HLA-B*15:01 molecule (PDB DOI: 10.2210/pdb1XR8/pdb)[103] and residues representing FULL (RED+BLUE) and SEROTYPE (BLUE) for the serotype B-1501. (C) HLA-C molecule and residues representing FULL (RED+BLUE) and SEROTYPE (BLUE) for the WHO assigned antigen Cw9. HLA-C*06:02 (PDB DOI: 10.2210/pdb5W67/pdb)[125] is used to represent HLA-C molecule. (D) HLA-DRB1 molecule (light green) and residues representing FULL (RED+BLUE) and SEROTYPE (BLUE) for the serotype DR-1454. HLA-DRB1*04:01 (PDB DOI: 10.2210/pdb5NI9/pdb)[104] is used to represent HLA-DRB1 molecule. (E) HLA-DQA1*01:02∼HLA-DQB1*06:02 molecule (PDB DOI: 10.2210/pdb1UVQ/pdb)[105] and residues representing FULL (RED+BLUE) and SEROTYPE (BLUE) for the serotypes DQA-01, DQ6 and combinatorial DQA-01∼DQ6. (F) HLA-DPA1*01:03∼HLA-DPB1*02:01 molecule (PDB DOI: 10.2210/pdb3LQZ/pdb)[106] and critical residues defining the serotypes for DPA-01, DP-0201 and combinatorial DPA-01∼DP-0201.[104-106]

TABLE 7 HLA alleles whose first field designation is discrepant with the predicted HLA Antigen Assignments

	WHO assigned antigens		Proposed new serotypes	
HLA loci	**Alleles**	**Proteins**	**Alleles**	**Proteins**
HLA-A	34	30	26	26
HLA-B	155	145	52	50
HLA-C	93	78	69	56
HLA-DRB1/3/5	29	29	28	28
HLA-DQB1	12	10	0	0

Note: Table shows the number of HLA alleles and proteins (two-field) with first-field names that are discrepant with the predicted WHO assigned antigens and proposed new serotypes.

3.1.2 | HLA-B

Currently, there are 49 WHO assigned HLA-B antigens not counting 10 broad specificities (B5, B12, B14, B15, B16, B17, B21, B22, B40, and B70). In all, 6–15 residues were selected to define WHO assigned HLA-B antigens for SEROTYPE assignments (Table 2B). When these residues were considered, 32 additional HLA-B antigens were defined (Table 6). When all residue positions were combined, 24 polymorphic positions were used to make

TABLE 8 Two-field HLA alleles included in the HLA Dictionary 2008 used to validate the criteria for definition of HLA Antigens

Allele	Expert assigned	WHO Assigned	NN assigned	Comments	Serotype	Note
A*02:55	A2/A28		Not assigned	NN: A2 A28 A69	A69	62R
A*02:48	A2	-	A2	A2x9, few A23 + 24 sera reactive	A-0246	62E65G
A*26:09	A26	A26 (10)	A26	13th IHW: short A26	A-3402	163 T
A*31:07	Undefined		Not assigned	NN: A32 A23 A9	A-3201	Bw4, carries 56R, but lacks 73I => likely shows A30 + A32
A*31:08	A31/A24		Not assigned	A31x24; previously A*2416; NN: A23 A9 A32	A-2304	62E,Bw4
A*31:10	A31	A31 (19)	Not assigned	NN: A32	A-3201	Bw4, carries 56R, but lacks 73I => likely shows A30 + A32
B*13:03	B49/B15		B13	B15x21-Bw4; B21 variant with some B15 sera reactive	B-1524	
B*13:04	B49/B15	B15/B21	B13	B15x21-Bw4, similar to B*1303; 13th IHW: new pattern, also B49, B63 and B77 reactivity	B-1524	
B*15:46	Undefined	B72 (70)	Not assigned	NN: B15 B62	B4005	
B*15:47	B70/blank		B72	B48, all B15 sera negative	B-2712	
B*35:21	B35/B78		B35	13th IHW B35/78 var	B78	
B*40:12	B60/B48		Not assigned	B48x70, some reactivity with B40 + 48 and B15 + 70 CREG sera NN: B48	B-4801	
B*40:13	Undefined		Not assigned	B40 Bw4 NN: B61 B40	B47	Bw4
B*40:19	B61		Not assigned	B40 Bw4, B*4002 with Bw4 epitope; 13th IHW: new pattern short B61 Bw4 pos; NN: B61 B40	B47	Bw4
B*42:07	Undefined		Not assigned	NN: B42 B8	B-0801	
B*44:09	B45	B45 (12)	B12	B44 Bw6, will be typed as B45 or B12; most B44 and B45 specific sera negative	B45	Bw6
B*44:16	B47/B44	B47	B44	B44x47, reactive with most B47 and few B44/12 sera	B47	
B*44:31	B44	B44 (12)	Not assigned	Almost normal B44; NN: B60 B40 B12	B-4047	
B*44:42	Undefined	B21	B44		B49	167 W
B*44:46	B12		B12		B45	Bw6
B*45:04	B21		B21	NN: B50	B50	167 W
B*48:02	B48/B70	B48	Not assigned	B71-like; 13th IHW: pattern identical to *B*1510; NN: B35*	B72	
B*50:02	B45	B45 (12)	Training B12 B45		B45	167S
B*52:23	B51	–	B51		B-4406	167S
B*51:42	Undefined	?B44 (12)	Not assigned	NN: B44 B12 B53	B-4406	167S
B*55:07	B54	B54 (22)	B22	NN: B54	B54	45G
B*55:08	B56	B56 (22)	B56		B56	163 L
B*56:06	B78	B78	B22	B78var, some B35 and B15 CREG sera positive, all B22 sera negative	B78	

TABLE 8 (Continued)

Allele	Expert assigned	WHO Assigned	NN assigned	Comments	Serotype	Note
B*56:07	B56	B56 (22)	Not assigned	B-5601 Bw4, some B7 sera pos; 13th IHW: B-5601 Bw4; NN: B-5601 B22	B56	Bw4
B*56:10	B55	B55 (22)	B55	short B22, reactive with B54 + 55 sera, negative with B55 + 7 sera	B55	163 T
B*56:12	B22	B55 (22)	B22		B55	163 T
B*57:08	B57	B57 (17)	B57	Bw4 sera neg, only strongly reactive with B15 + 57 sera	B57	83P
B*78:04	B35		Not assigned	NN B35	B-3501	171Y
*DRB1*08:31*	DR8 /DR11	DR11 (5)	Not assigned	NN: DR8 DR11	DR-1105	
*DRB1*14:15*	DR8	DR8	DR8	DR8 + DR52	DR-0801	
*DRB1*14:16*	DR6	DR6	DR13	DR14x13	DR-1343	
*DRB1*15:21*	DR2	–	DR2	NN: DR15 DR16	DR16	

Note: The "Allele" column shows two-field HLA allele with first field numbers that are discrepant with the predicted serotype. The columns "Expert assigned," "WHO assigned," "NN assigned," and "Comments" shows information listed in the HLA Dictionary 2008. The "Serotype" column shows assigned serotype using HATS.

FULL assignments (Figure 1B and Table 6). Supplemental Table 2 contains two-field HLA-B alleles and their serotypes. 145 HLA-B proteins (two-field alleles) in which their first-field molecular designation does not correspond to the WHO assigned HLA-B antigens were identified (Table 7), for example, HLA-B*15:46 was assigned as HLA-B4005 serologic designation (Table 8). In addition, 50 HLA-B proteins in which their first-field molecular designation does not correspond to the newly defined HLA-B serotypes were identified (Table 6), for example, HLA-B*13:03 was designated to the proposed new B-1524 serologic specificity (Table 8). Only 10 HLA-B proteins (two-field alleles), HLA-B*07:219, HLA-B*15:101, HLA-B*15:592, HLA-B*35:186, HLA-B*38:26, HLA-B*39:170, HLA-B*46:40, HLA-B*46:77, HLA-B*46:86, and HLA-B*55:34, were not assigned to specific serotypes, because these had two or more mismatches in the DEP residues that were used to define any given serotypes.

3.1.3 | HLA-C

Excluding HLA-Cw3, there are 9 WHO assigned HLA-C antigens including the splits Cw9 and Cw10. In addition, 6 possible HLA-C antigens corresponding HLA-C alleles with a blank HLA-C antigen were recognized when taking sequence homology into account (C-1202, C-1402, C-1502, C-1601, C-1701, and C-1801). These 15 possible HLA-C antigens account for the serologic specificities used in clinical practice. Additional 18 HLA-C antigens were recognized when examining 20 DEP residue positions for FULL assignments (Figure 1C and Table 6). A range of 6–14 selected residues were used for SEROTYPE assignments (Table 2C). Supplemental Table 3 contains HLA-C alleles and their antigens. Three HLA-C alleles (HLA-C*02:12, HLA-C*07:238, and HLA-C*16:85) were not assigned to specific serotypes.

3.2 | HLA class II antigen assignments

3.2.1 | HLA-DRB1 and -DRB3/4/5

For the assignment of all currently WHO assigned DR antigens, 5–11 HLA-DRB1/3/4/5 residues were selected to make SEROTYPE assignments (Table 2D); taking these residues into consideration, 21, 1 and 2 additional antigens were defined for HLA-DRB1, HLA-DRB3 and HLA-DRB5 alleles, respectively (Table 6). When all polymorphic residue positions are combined, 13 positions were identified for making FULL assignments for HLA-DRB1 alleles (Figure 1D). Table 3D and E show the residues selected to designate FULL and SEROTYPE

antigens corresponding to the products of HLA-DRB1/3/4/5 genes. Supplemental Table 4 shows DR serotype information. Thirty DR proteins (two-field HLA-DRB1/3/5 alleles) for which their first-field allele name does not correspond to the currently WHO assigned HLA-DR antigens were identified (Table 7). Of these, eight two-field HLA-DRB1 alleles (HLA-DRB1*03:42, HLA-DRB1*03:87, HLA-DRB1*11:30, HLA-DRB1*12:57, HLA-DRB1*13:67, HLA-DRB1*13:195, HLA-DRB1*14:46, and HLA-DRB1*14:141) were recognized carrying polymorphic residues associated with HLA-DR52 specificity corresponding to HLA-DRB3 alleles, and one HLA-DRB1 allele (HLA-DRB1*09:07) was recognized carrying residues associated with HLA-DR51 specificity corresponding to HLA-DRB5 alleles. The allele HLA-DRB3*01:14 was recognized carrying polymorphic residues associated with DR18 specificity (Supplemental Table 4). The proposed new serotype DR-0403 for the two-field allele HLA-DRB1*04:20 was assigned *in silico*, since the reference AA sequence of this allele does not include residues 9–13. Three HLA-DRB alleles (HLA-DRB1*04:66, HLA-DRB1*04:229, and HLA-DRB4*01:97) were not assigned to any of the currently known or newly proposed specific serotypes.

3.2.2 | HLA-DQB1

Table 3F shows residue positions used to define FULL or SEROTYPE assignment of HLA-DQB1 (Figure 1E), and Supplemental Table 5 shows DQ serotype information for each HLA-DQB1 allele. Ten two-field HLA-DQB1 alleles in which their first-field allele name does not correspond to the WHO assigned HLA-DQ antigens were identified (Table 7).

3.2.3 | HLA-DQA1

Table 3G shows residue positions used to define FULL or SEROTYPE assignment of HLA-DQA1 (Figure 1E), and Supplemental Table 6 shows DQA serotype information for each HLA-DQA1 allele identified to present. No discrepant assignments were identified when correlating the first field designation and the proposed DQA serotypes.

3.3 | Serologic DQA1/DQB1 antigens defined by combinations of polymorphic subunits

Table 4 includes the serologic specificities defined by both subunits that are encoded in *cis* by common DQ haplotype blocks.

3.4 | HLA-DPB1 and HLA-DPA1

Table 3H shows residue positions used to make FULL assignment of HLA-DPB1 antigens (Figure 1F), and Supplemental Table 7 shows the proposed DP serotype information for each HLA-DPB1 allele. Residue 82 that is specific to HLA-DPB1 was included among the residues that define HLA-DP specificities. All 1653 expressed HLA-DPB1 alleles were assigned to the newly proposed HLA-DP serotypes (Supplemental Table 7).

Table 3I shows residue positions used to make FULL or SEROTYPE assignment corresponding to the product of the HLA-DPA1 alleles (Figure 1F); Supplemental Table 8 shows DPA serotype information for each HLA-DPA1 allele. We assigned all 247 expressed HLA-DPA1 alleles to two serotypes (Supplemental Table 8).

3.5 | Distribution of FULL, SEROTYPE, SHORT (S), SHORT AND CROSS-REACTIVE (SC) serologic specificities among common, intermediate, well-documented and rare alleles

Among the proposed 103 new serotypes for alleles at HLA-A, -B, -C, -DRB1, -DRB5 and -DRB3 loci, 55 were found among Common alleles, 22 were found in the group of Intermediate alleles, 24 of these serotypes were in the well-documented (WD) group. Only 2 alleles (HLA-A*02:65 and HLA-DRB1*13:43) of the proposed new serotypes were found in the rare allele category (Table 5). The creation of serotypes for the rare alleles is an artifact using the lowest-digit allele names to represent the serotypes, because five WD group alleles (HLA-A*02:135, -A*02:149, -A*02:174, -A*02:190, and -A*29:48) were assigned to the serotype A-0265, and one Intermediate HLA-DRB1*14:16 allele was assigned to the serotype DR-1343. Therefore, these serotypes are virtually considered as WD and Intermediate group, respectively. Of 15,999 two-field alleles at five loci HLA (HLA-A, HLA-B, HLA-C, HLA-DQB1, and HLA-DRB1) that are assigned in one of the four categories, 3.3% (525) were common, 3.0% (474) were intermediate, 11.4% (1823) were WD and 82.3% (13,177) were rare categories in the CIWD 3.0. All common alleles were assigned in one of the serotypes as either FULL (84%) or SEROTYPE (16%) assignment. Figure 2A–D show the percentage of "C," "I," "WD," and "Rare" alleles assigned as either FULL, SEROTYPE, S or SC categories for each locus.

3.6 | Serotype validation

Table 7 shows the number of HLA alleles and proteins with first-field names that are discrepant with the predicted serotype. Supplemental Table 9 contains list of HLA-A, -B, -C, -DRB1/3/5 and -DQB1 alleles in which their first-field allele name does not correspond to the WHO assigned antigens and proposed new serotypes. These outlier HLA alleles were used to validate the results if serotype information of HLA alleles is available in the HLA Dictionary 2008. Table 8 summarizes the validation results. For example, HLA-A*02:55, HLA-B*78:04 and HLA-DRB1*14:15 were assigned to A69, B35 and DR8 being consistent with the report in the HLA Dictionary 2008, respectively. The proposed new serotypes were associated with WHO assigned antigens based on the information described in the HLA Dictionary as shown in Table 5. Some discrepancies in WHO antigen assignments were found between the information provided in Supplemental Tables 1–5 and the information described in the HLA Dictionary for the alleles that were not used as prototype. For example, the alleles HLA-B*13:03 and -B*13:04 are reported in the present study as having the serotype B-1524, these were WHO assigned to the antigen B62 and Broad antigen B15 in Supplemental Table 2B. These alleles were, however, described as B49/B15 or B15x21-Bw4 in the HLA Dictionary (Table 8). The WHO assigned antigen B62 was associated with these alleles, because the prototype allele HLA-B*15:24 was described as B62 in the Dictionary.

3.7 | Bw4- and Bw6-associated residues

Table 9 includes HLA alleles that most likely show different Bw4 or Bw6 reactivity from those of the prototype HLA alleles. The WHO assigned antigens A23, A24, A25, and A32 carry Bw4-associated residues. In addition to HLA-B alleles, Bw6-associated residues are found in the proposed new antigens A-3002, A-3007, and C-1212, Bw4-associated residues are found in A-6836. Of 6622 HLA-C alleles, we identified 16 HLA-C alleles carrying the Bw6-associated residues (Table 9). The HLA class I alleles are noted as Bw4 or Bw6 in Supplemental Tables 1–3. Table 9 includes HLA-B alleles that most likely lack Bw4 or Bw6 reactivity because of the substitutions at the key residue positions; these are noted as "Negative". For example, the allele HLA-B*57:08 carries residues 82L83P (Table 9), and the HLA Dictionary 2008 describes "Bw4 sera negative" (Table 7).

4 | DISCUSSION

With a few exceptions, the currently recognized antigens were defined by serum cluster analyses and reactivity patterns. Only a few studies correlating serologic testing with molecular typing have been performed to present.[68,74] In addition, a small number of the serologic typing reagents have been characterized with novel and refined antibody screening technologies that include testing cells expressing a single expressed HLA antigen[107] or solid phase assays with single antigen preparations.[108] Therefore, the currently recognized HLA antigens do not identify the full extent of possible serotypes that can be defined by reagents detecting the most common immunogenic HLA epitopes, and do not include all specificities corresponding to some loci. In the solid organ transplantation setting, the assessment of humoral compatibility with a given donor is based on the evaluation of the patient's sensitization status and anti-HLA antibody reactivity and the precise knowledge of the donor's HLA mismatched alleles. The HLA allele to serotype conversion tables provided in this manuscript (Supplemental Tables 1–8) may prove to be clinically valuable in defining DSA. Informative antibody screening can be achieved by testing the patient's serum with a panel of antigen preparations that include the most common serotypes in a given population. The present study aimed to obtain a refined and likely more accurate characterization of serotypes defined *in silico* and to identify the common serotypes that can be found in most donors of allogeneic transplants based on the knowledge of the distribution of common alleles in world populations. Additional serotypes, which have been recognized in the course of several IHIW, but were not named officially, are proposed in the present study. The current study focused on well-recognized residues located at the distal membrane domains that define common epitopes; all these residues are included in eplets located at these domains (Tables 3A–I). Supplemental Table 10 contains a list of these critical residues. Some residues that may determine less-recognized serologic splits and may not likely define distinct serologic epitopes in HLA antigens expressed on living cells were not considered as being relevant DEP in the present study; namely, residue 9 (distinguishing HLA-A*02:01 from HLA-A*02:06), residue 156 (distinguishing pairs of common alleles HLA-B*44:02/HLA-B*44:03[109] and HLA-B*35:01/HLA-B*35:08) of class I; residues 86 of HLA-DRB1 (distinguishing pairs of common alleles HLA-DRB1*11:01/HLA-DRB1*11:04 and HLA-DRB1*15:01/HLA-DRB1*15:02) and 112 (distinguishing a pair of HLA-DRB1*14:01/HLA-DRB1*14:54) and residue 160 of HLA-DQA1 (distinguishing pairs of

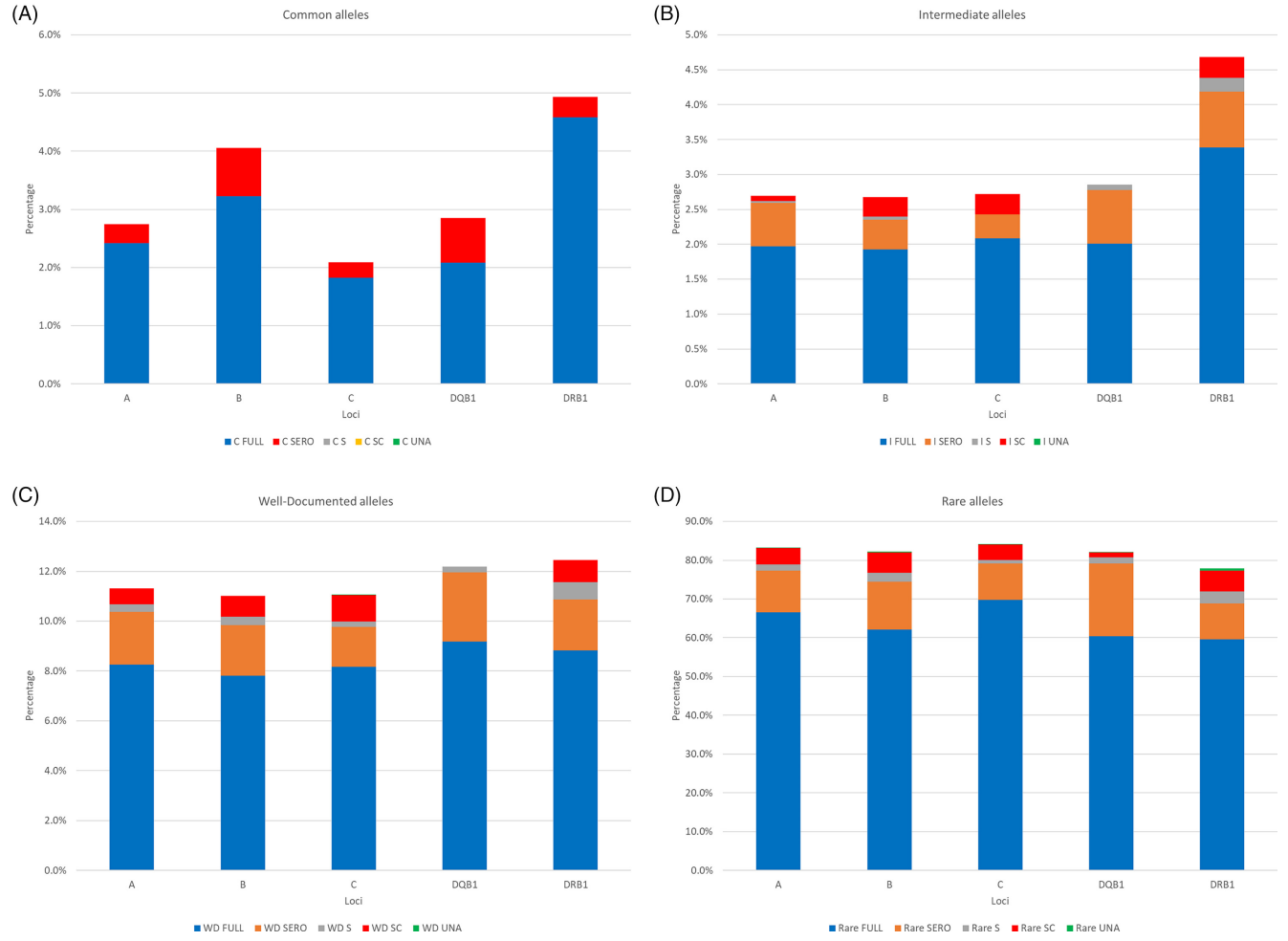

FIGURE 2 Representation of CIWD and Rare alleles in FULL, SEROTYPE, S, SC or UNA categories. (A) Common alleles. (B) Intermediate alleles. (C) Well-documented alleles. (D) Rare alleles. Each HLA-A, -B, -C, -DQB1 and -DRB1 two-field allele (protein level) was classified as "Common (C)," "Intermediate (I)," "Well-Documented (WD)," and "Rare" categories. HATS assigned serotypes for 4010 HLA-A, 4932 HLA-B, 3786 HLA-C, 1296 HLA-DQB1 and 2006 HLA-DRB1 two-field HLA alleles in one of the five (FULL, SEROTYPE, S, SC and UNA) categories. Null (N), Questionable (Q) alleles are excluded in these analyses. Figures 2A–D show the percentage of "C," "I," "WD," and "Rare" alleles assigned as either FULL, SEROTYPE, S, SC, or UNA categories. HLA-A, -B, -C, -DQB1, and -DRB1 loci are represented as A, B, C, DQB1, and DRB1 in these figures, respectively

HLA-DQA1*03:01/HLA-DQA1*03:03 and HLA-DQA1*05:03/HLA-DQA1*05:05) were not included among DEP. Residue 57 was not used to define HLA-DRB1 splits while this residue was conditionally considered in DQB1; the residues 57A (HLA-DQB1*03:04) and 57D (HLA-DQB1*03:01) do not split DQ7, but historically they are used to distinguish DQ8 (HLA-DQB1*03:02) from DQ9 (HLA-DQB1*03:03).

The classification of HLA alleles into previously assigned and proposed novel specificities is likely to enhance and increase precision in the assessment of DSA in allogeneic transplantation; for example, for the donor alleles assigned to the FULL category that carry identical replacements at common DEP residues, it is possible to use the prototype as surrogate in virtually all instances. For instance, a donor who carries the HLA-B*35:03 allele may not be represented in the panel of single antigen beads, but the HLA-B*35:01 allele that is a prototype for the serotype B-3501 is represented. The HLA-B*35:01/B*35:03 alleles share all residues defining major epitopes/eplets for B-3501, therefore, the reactivity with B-3501 antigen preparation may serve as a precise surrogate to HLA-B*35:03. In this case, the donor's allele and the prototype differ by a single AA substitution at residue 116 (Phe for HLA-B*35:03 and Ser for HLA-B*35:01) located at the bottom of the groove, and this difference is not likely to determine major immunogenic serologic epitopes.

For alleles belonging to the same SEROTYPE category, it is possible to use the prototype as surrogate in

TABLE 9 HLA class I alleles whose proteins will likely show differences in the serologic assessments associated with Bw4 or Bw6 serological specificities than those of the prototype serotypes

Allele	Serotype	COMMENT	Bw4/Bw6	Prototype	Note
A*01:95	A-0101	SC	Bw4-associated	Negative	82L83R
A*01:289	A-0101	SC	Bw4-associated	Negative	82L83R
A*01:298	A-0101	SC	Bw4-associated	Negative	82L83R
A*02:81	A-0201	SEROTYPE	Bw4-associated	Negative	82L83R
A*02:87	A-0201	SEROTYPE	Bw4-associated	Negative	82L83R
A*02:112	A-0201	SEROTYPE	Bw4-associated	Negative	82L83R
A*02:124	A-0201	SEROTYPE	Bw4-associated	Negative	82L83R
A*02:136	A-0201	SEROTYPE	Bw4-associated	Negative	82L83R
A*02:184	A-0201	SEROTYPE	Bw6-associated	Negative	76E
A*02:247	A-0201	SEROTYPE	Bw6-associated	Negative	76E
A*03:173	A-0301	S	Bw6-associated	Negative	76E
A*03:273	A-0246	SEROTYPE	Bw6-associated	Negative	76E
A*11:111	A11	S	Bw6-associated	Negative	76E
A*11:178	A11	S	Bw4-associated	Negative	82L83R
A*11:190	A11	S	Bw4-associated	Negative	82L83R
A*24:373	A-2404	SEROTYPE	Bw6-associated	Negative	76E
A*26:05	A-2601	SC	Bw6-associated	Negative	76E
A*29:13	A29	SEROTYPE	Bw4-associated	Negative	82L83R
A*29:98	A29	SEROTYPE	Bw6-associated	Negative	76E
A*30:22	A-0265	S	Bw6-associated	Negative	76E
A*68:109	A-6801	S	Bw6-associated	Negative	76E
A*68:136	A-6801	S	Bw6-associated	Negative	76E
A*80:04	A80	SEROTYPE	Bw6-associated	Negative	76E
B*38:26	B55	S	Bw4	Bw6	
B*41:46	B41	SC	Bw4	Bw6	
B*41:60	B41	SC	Bw4	Bw6	
B*44:166	B41	S	Bw4	Bw6	
B*54:12	B54	S	Bw4	Bw6	
B*55:90	B55	S	Bw4	Bw6	
B*55:103	B55	S	Bw4	Bw6	
B*56:07	B56	S	Bw4	Bw6	
B*56:21	B56	SC	Bw4	Bw6	
B*56:46	B56	S	Bw4	Bw6	
B*56:65	B56	S	Bw4	Bw6	
B*46:72	B46	S	Bw6	Negative	76E
B*55:34	None	UNA	Bw6	Bw4	
B*57:12	B57	S	Bw6	Bw4	
B*58:64	B58	SC	Bw6	Bw4	
B*07:79	B-0702	SC	Negative	Bw6	83R
B*07:185	B-0702	SC	Negative	Bw6	76D
B*07:195	B-0702	S	Negative	Bw6	82H
B*07:211	B-0702	S	Negative	Bw6	83V

(Continues)

TABLE 9 (Continued)

Allele	Serotype	COMMENT	Bw4/Bw6	Prototype	Note
B*07:244	B-0702	S	Negative	Bw6	83S
B*07:299	B-0702	SC	Negative	Bw6	76Q
B*08:15	B-0801	S	Negative	Bw6	76V
B*08:29	B-0801	S	Negative	Bw6	82H
B*08:34	B-0801	S	Negative	Bw6	83C
B*08:157	B-0801	S	Negative	Bw6	82S
B*08:174	B-0801	S	Negative	Bw6	82P
B*08:199	B-0801	S	Negative	Bw6	83V
B*08:216	B-0801	SC	Negative	Bw6	83R
B*14:63	B65	SC	Negative	Bw6	76V
B*14:97	B64	SC	Negative	Bw6	76V
B*15:57	B62	SC	Negative	Bw6	76V
B*15:289	B62	SC	Negative	Bw6	76V
B*15:318	B62	SC	Negative	Bw6	76V
B*15:397	B72	S	Negative	Bw6	76V
B*15:403	B-1517	SC	Negative	Bw4	83P
B*15:481	B-1501	SC	Negative	Bw6	82L
B*15:526	B71	S	Negative	Bw6	76V
B*15:579	B-1501	SC	Negative	Bw6	76V
B*18:147	B-1801	S	Negative	Bw6	82H
B*18:190	B-1801	S	Negative	Bw6	83S
B*27:49	B-2705	S	Negative	Bw4	82F
B*27:116	B-2705	S	Negative	Bw4	83H
B*27:169	B-2705	S	Negative	Bw4	83L
B*35:36	B-3501	S	Negative	Bw6	83D
B*35:74	B-3501	S	Negative	Bw6	76V
B*35:160	B-3501	S	Negative	Bw6	83V
B*35:186	None	UNA	Negative	Bw6	76V
B*35:313	B-3501	S	Negative	Bw6	76K
B*35:338	B-3501	SC	Negative	Bw6	82L
B*35:351	B-3501	S	Negative	Bw6	76Q
B*35:356	B-3501	S	Negative	Bw6	76V
B*35:424	B-3501	S	Negative	Bw6	82C
B*37:58	B-3701	S	Negative	Bw4	83H
B*38:61	B38	S	Negative	Bw4	83H
B*39:27	B3901	S	Negative	Bw6	76V
B*39:143	B-3910	S	Negative	Bw6	76V
B*39:164	B3902	S	Negative	Bw6	76V
B*39:166	B3901	S	Negative	Bw6	76V
B*39:170	None	UNA	Negative	Bw6	76V
B*40:73	B60	S	Negative	Bw6	76V
B*40:119	B61	S	Negative	Bw6	76D
B*40:207	B-4001	S	Negative	Bw6	83D

TABLE 9 (Continued)

Allele	Serotype	COMMENT	Bw4/Bw6	Prototype	Note
B*40:246	B61	S	Negative	Bw6	83D
B*40:281	B-4001	S	Negative	Bw6	82H
B*40:465	B61	S	Negative	Bw6	76V
B*41:68	B41	S	Negative	Bw6	76D
B*44:127	B-4402	S	Negative	Bw4	83H
B*44:458	B-4402	S	Negative	Bw4	83L
B*45:16	B45	S	Negative	Bw6	82S
B*49:21	B49	S	Negative	Bw4	83C
B*55:03	B55	S	Negative	Bw6	76V
B*55:49	B55	S	Negative	Bw6	76V
B*55:69	B55	S	Negative	Bw6	76V
B*55:73	B55	S	Negative	Bw6	83S
B*57:08	B57	S	Negative	Bw4	83P
C*01:95	C-0102	SC	Bw6-associated	Negative	76E
C*01:157	C-1212	SEROTYPE	Bw6-associated	Negative	76E
C*02:131	C-0227	S	Bw6-associated	Negative	76E
C*03:70	Cw10	S	Bw6-associated	Negative	76E
C*03:127	Cw9	S	Bw6-associated	Negative	76E
C*03:179	Cw10	S	Bw6-associated	Negative	76E
C*03:274	Cw9	S	Bw6-associated	Negative	76E
C*06:69	C-0602	S	Bw6-associated	Negative	76E
C*06:147	C-1212	S	Bw6-associated	Negative	76E
C*07:124	C-0701	SC	Bw6-associated	Negative	76E
C*07:155	C-0702	SC	Bw6-associated	Negative	76E
C*08:73	C-0802	SC	Bw6-associated	Negative	76E
C*12:12	C-1212	FULL	Bw6-associated	Negative	76E
C*12:301	C-1212	S	Bw6-associated	Negative	76E
C*12:325	C-1212	FULL	Bw6-associated	Negative	76E
C*15:45	C-1502	S	Bw6-associated	Negative	76E

Note: The column "Allele" shows HLA class I two-field alleles. The "Serotype" column shows assigned serotypes for each allele by HATS, and the "COMMENT" column indicates the assignment category: FULL, SEROTYPE, S and SC. The column "Bw4/Bw6" shows expected Bw4 and Bw6 reactivity or Negative for these alleles. The "Prototype" column shows Bw4, Bw6 or Negative status of the corresponding prototype HLA serotypes. The "Note" column indicates substituted AA residues that affect the different Bw4 or Bw6 specificities from the prototype serotypes.

most instances, however, in order to perform more accurate DSA assessment, further epitope analyses in the corresponding serum antibody pattern may be needed to assign DSA. For example, the alleles HLA-A*24:373, HLA-A*29:98 and HLA-A*80:04 are assigned as serotypes A-2404, A29, and A80, respectively, in SEROTYPE category (Supplemental Table 1). Residue 76 is not required to assign these serotypes, thus an AA substitution at this position does not change the serotype assignment. However, these proteins carry the Bw6-associated residues, therefore, these may show reactivity with all sera that define the SEROTYPE assignments and likely display additional reactivity with anti-Bw6 allo-antisera (Table 9). The allele HLA-B*44:31 is assigned as the proposed new serotype B-4047 that resembles HLA-B60 being Bw4 positive in the SEROTYPE category but carries 167S that is an important residue to define the broad antigen HLA-B12 that includes both HLA-B44 and HLA-B45 (Tables 3B and 8). These cases exemplify the need of performing further epitope analyses to assess DSA when the donor carries an allele whose serologic assignment falls in the SEROTYPE category.

With a few exceptions, designating new serotypes for the alleles that were not in CIWD categories in CWD2.0, CIWD3.0 or European CWD was avoided, and INCOMPLETE (SHORT and SHORT-CROSS-REACTIVE) category was used to classify the serotype of rare HLA alleles that present a single AA difference in the residues that define SEROTYPES. There are a few alleles whose serotype fall in the UNA category; these alleles present two or more AA differences in the residues that define any of the proposed SEROTYPES described in this study. Like the SEROTYPE category, performing the epitope analyses would be required to assess possible DSA for the alleles in INCOMPLETE and UNA categories.

A comprehensive evaluation of the splits corresponding to the HLA-B*15 alleles was performed in the present study; the results were concordant with those reported in a recent publication from Duygu and collaborators.[74] In both studies, similar sets of residues were used to define the broad HLA-B15 and -B70 serotypes except for residues 24 and 77 that were used for HLA-C serotypes in the present study, and residue 163 that was not used by Duygu and collaborators (Table 3C). Supplemental Table 11 contains 41 HLA-B*15 alleles that were discussed by Duygu and collaborators[74] and the serotype assignments in this study. The minor differences were because of the differences in these residues (Supplemental Table 11). The other differences were observed in outlier alleles. For example, the alleles HLA-B*15:46, -B*15:53, -B*15:106, -B*15:212, and -B*15:525 were not previously assigned to any broad HLA-B15 serotypes,[74] on the other hand, these alleles were assigned as B4005 in the present study. The allele HLA-B*15:46 was assigned as HLA-B72 in the HLA Dictionary 2008, but carries a mismatch at residue 45 K compared with the serotype HLA-B72 (45E). It has been described to show serological reactivity with allo-antisera specific for both HLA-B50 and -B72.[110]

The serologic splits of HLA-DR4 that correlated well with HLA-D types were identified as early as 1984,[1,66] and subsequently HLA-D types were correlated with alleles defined at the molecular level. Therefore, the residues determining serologic specificities identified readily, and the extended analyses of the substitutions at DEP led to identifying and proposing additional HLA-DR splits. These extensions were validated by the occurrence of previously defined splits in families of other HLA-DRB1 alleles (e.g., HLA-DR103 as an associated antigen of HLA-DR1) or hinted in other studies (e.g., HLA-DRB1*11:02 determining a split of HLA-DR11[99]). The present study also defines several splits of the ill-defined HLA-DR14 serologic specificity; it is likely that the new definition of these splits will allow for precise assessment of DSA directed against some HLA-DR14 associated specificities and not to others.

The present study defines serotypes for all loci assessed routinely for humoral compatibility in solid organ transplantation and HSCT; these loci include the products of HLA-DQA1, -DPA1 and -DPB1 (Supplemental Tables 6–8). It is important to note that the first field of HLA-DPB1 does not reflect the serotype. In addition to the serotypes of HLA-DQA1, -DPA1 and -DPB1 serotypes resulting from the combination of proteins encoded by HLA-DQA1 and -DQB1 are presented (Table 4). Although additional splitting of HLA-DQA1, -DPA1, -DQB1 and -DPB1 encoded proteins has been suggested, no additional higher resolution specificities are proposed at this time. In the future, additional serologic specificities could be accepted by the general community, if significant evidence for further splitting the serological specificities corresponding to the products of these loci were to be demonstrated using cell-based assays. The combinatorial specificities associated with HLA-DQA1*01 alleles are not included in this study, because their proteins combine only with the product of *HLA-DQB1*05* or *-DQB1*06* alleles to form heterodimers because of restrictions in pairing, and splits of HLA-DQA01, -DQ5 and -DQ6 are not proposed yet.

A set of 240 serotypes (167 for HLA class I and 73 for HLA class II) representing all common alleles in all human populations has been presented in this report. Some of the newly proposed serotypes are virtually predicted *in silico* in this study; therefore, it will be valuable to conduct follow-up validation studies of the newly proposed serotypes with sera and/or mAbs in future studies. The information may be used in a rational design and antigen composition of anti-HLA antibody single antigen screening panels. The inclusion of at least one antigen preparation corresponding to the prototype alleles of each serotype will result in the representation of virtually all serotypes likely to be present in a given donor. The evaluation of the reactivity of the patient's serum with this panel and the patient's and donor's HLA genotypes obtained at a resolution that allows discriminating between alleles of the common serotypes will allow for precise predictions of cross-match results *in silico*. The use of antigen preparations including the proposed extended serotype coverage will result in a simple process for performing virtual cross-matches with enhanced resolution and increase prediction of physical cross-matches. In the United States, virtual cross-matching has become even more important given the new UNOS Kidney allocation system which has resulted in broader sharing of organs across larger geographical regions. Many transplant centers and HLA labs have been reticent to adopt virtual cross-matching or compatibility assessment in lieu of a physical

one because of the present limitations of coverage of the single antigen bead assays. The HATS tables provided as Supplemental 1–8 will allow for more accurate antibody profiling translating into better risk assessment of patients.

In summary, we developed logics for serotype assignments, and a computational tool (HATS) for systematically classifying HLA alleles into serological specificities. HATS can be implemented for systematic serotype assignment of all HLA alleles for every release of IPD-IMGT/HLA database version in the future. This manuscript proposes the designation of novel serological specificities presented in an organized manner that includes an addition to the previously recognized HLA antigens and an expansion to antigens of HLA loci that can be recognized at the serologic level. The lists of prototype and newly defined serotypes may serve for improvement of allele composition of single antigen panels for antibody screening. In order to facilitate their implementation in clinical Histocompatibility practice, we would like to propose to the WHO Nomenclature Committee for Factors of the HLA System that these newly defined serotypes become officially accepted having a new Antigen or Associated Antigen status.

AUTHOR CONTRIBUTIONS

This study was initially designed by Kazutoyo Osoegawa and Marcelo A. Fernández Viña. Kazutoyo Osoegawa developed HATS, performed data validation. Kazutoyo Osoegawa and Marcelo A. Fernández Viña were also involved in data interpretation and drafting the manuscript. Steven GE Marsh, Rhonda Holdsworth, Sebastiaan Heidt, Gottfried Fischer, Cathi Murphey, Martin Maiers contributed significantly to the refinement of the initial design and were responsible for reviewing HLA nomenclature including serotypes. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declared no conflicting interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Supporting Information of this article and will also be posted on the web site of the 18th International HLA & Immunogenetics Workshop (https://www.ihiw18.org/serology-2022/).

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