HLA Nomenclature

Contents of the Nomenclature Section

- This brief introduction to HLA nomenclature
- Tables of all HLA-A,B,Cw,DR,DQ serological antigens and their splits
- Serological-DNA equivalents
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Where to Find the Latest Information

The latest nomenclature updates are published periodically in Tissue Antigens and Human Immunology.

A Brief Introduction

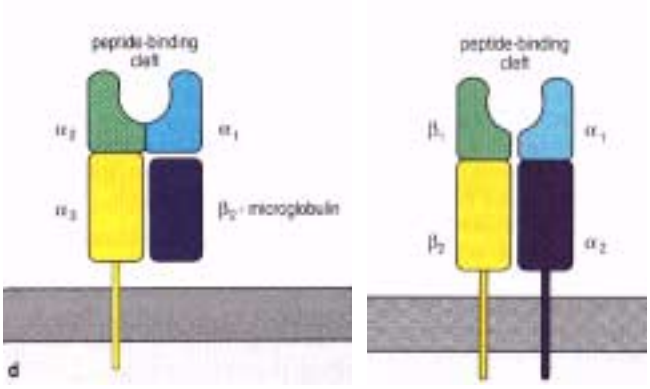
HLA nomenclature has developed historically from the original serological designations to modern molecular definitions. At first, only a few serological specificities could be defined. It quickly became apparent that that not only were there numerous serological specificities but that they fell into natural groups:

HLA-A HLA-B HLA-Cw (w=workshop)	Class I
HLA-DR (D-related) HLA-DQ HLA-DP (D-priming)	Class II

HLA-A,B,DR seemed to be the most important for solid organ and bone marrow transplantation. HLA-A,B played a major role in antibody-mediated rejection of kidney grafts while Class II seemed to play a role in cell-mediated graft rejection. All three loci are important in graft versus host disease in bone marrow transplants.

It turned out that Class I and Class II differed not only in their transplantation roles but also in their molecular makeup. Class I consisted of a polymorphic heavy chain associated with a nonpolymorphic beta-2-microglobulin (β_2M) molecule. Class II consisted of a sometimes polymorphic heavy alpha chain (34kDa) with a lighter polymorphic beta chain (29kDa):

Class I Class II



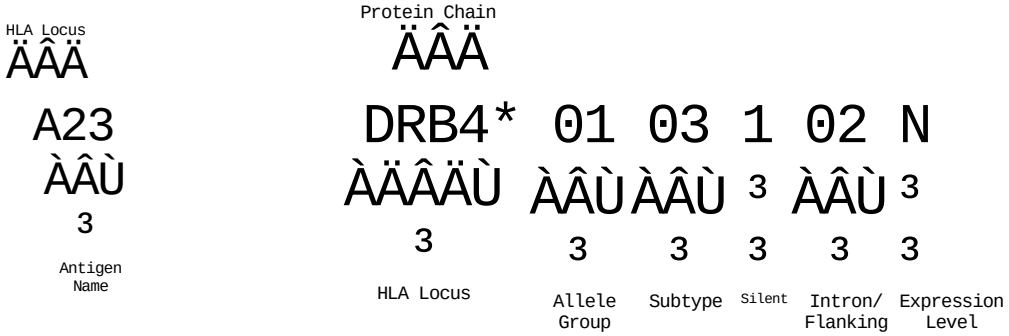
Throughout the 1970's and 1980's more and more serological antigens were defined. As serological techniques improved "splits" of the originally defined antigens were defined. For example HLA-A9 (parent antigen) was split into A23 and A24 and later A2304. The splitting of antigens makes HLA nomenclature difficult for the beginner.

Since the HLA-A and HLA-B loci were discovered first they do not share allele designations. Namely, while there is an HLA-A23 there is not B23; likewise, there is a B7 but no A7. All other HLA loci were numbered independently and sequentially. The early discovery of HLA-A,B also means that many temporary antigen designations had to be discarded later. For example, there is no HLA-A20 or HLA-B20.

The Class I HLA-A and HLA-B antigens were readily defined by serological techniques. However, HLA-Cw and HLA-DR proved more troublesome. This was an impetus for the development of molecular typing techniques. By the early 1990's molecular typing techniques became available for typing Class II alleles. This means that there were now two related nomenclatures:

> Serological Nomenclature: Defined proteins, not alleles. Antigen families defined by antibody reaction patterns.
>
> Molecular Nomenclature: Types alleles, not proteins. Allele families defined by sequence similarity as influenced by serological reactivities (if known) of expressed proteins.

The molecular nomenclature and serological nomenclatures are compared below:



HLA Locus:	Defines a location on chromosome six
Protein Chain:	Alpha or Beta chain (Class II only)
Allele Group:	A group of closely-related alleles at a locus. Usually equivalent to a serological group
Subtype:	Specific allele
Silent:	Known silent (i.e., no amino acid sequence change) mutations are numbered consecutively
Intron/Flanking:	Known intron or flanking region mutations are numbered consecutively
Expression Level:	N=No expression, L=Low expression, while no letter indicates a normal level of expression

Low Resolution: Samples typed at the allele group level: DRB1*15, A*11, DRB4*01

Intermediate Resolution: Samples typed to a subset of alleles: DRB1*15(01,03,06), A*11(01,04)

High Resolution: Samples typed to the allele level: DRB1*1501, DRB1*15011, A*1101

Tables of Serological-DNA Equivalents from:

Bodmer, JG, et al. Nomenclature for factors of the HLA system 1998. Tissue Antigens 53:407-446. 1999.

Schreuder GMT, Hurley CK, Marsh SGE, Lau M, Maiers M, Kollman C, Noreen H. The HLA dictionary 1999: A summary of HLA-A,-B,-C,DRB1/3/4/5,=DQB1 alleles and their association with serologically defined HLA-A,-B,-C,-DR,-DQ antigens. Tissue Antigens 54:407-437. 1999.

Notes:

- ✓ **Alleles without known serological specificity are not individually listed**
- ✓ **Null alleles, not listed, are assumed to be serological blanks**
- ✓ **Statements such as A*02=A2 are generalizations with exceptions listed below**
- ✓ **There will be no further serology-DNA updates of this table from November 1999 forward. The details of serology-DNA equivalents can be found in Shreuder, et al.**

HLA-A

Broad Sero Name	Splits	No Bw4/Bw6	Weak Bw4
A1	A*01=A1	A1	
A2	A*02=A2 A*0203=A203 A*0210=A210	A2, A203, A210	
A3	A*03=A3	A3	
A9	A*23=A23 A*24=A24 A*2403=A2403 A*2410=A9		A23, A24, A2403
A10	A*2502=A10 A*2501=A25 A*26=A26 A*66(01,02)=A66 A*6603=A10	A26, A66	A25
A11	A*11=A11	A11	
A19	A*29=A29 A*30=A30 A*31=A31 A*32=A32 A*33=A33 A*74=A74 A*7403=A19	A29, A30, A31, A33, A74	A32
A28	A*68=A68	A68, A69	

	A*6803=A28 A*69=A69		
A36	A*36=A36	A36	
A43	A*43=A43	A43	
A80	A*80=A80	A80	

HLA-B

Broad Sero Name	Splits	Bw4	Bw6
B5	B*51=B51 B*5102=B5102 B*5103=B5103 B*5106=B5 B*5116=B52 B*52=B52		B51, B5102, B5103, B52
B7	B*07=B7 B*0703=B703		B7, B703
B8	B*08=B8		B8
B12	B*44=B44 B*4409=B12 B*45=B45	B44	B45
B13	B*13=B13	B13	
B14	B*1401=B64 B*1402=B65		B64, B65
B15 See also B70	B*15(28,29,33-35)=B15 B*1522=B35 B*15(01,04-07, 15,20,24,25,27,30,32,45,48)=B62 B*15(16,17)=B63 B*15(02,08,11,21,31)=B75 B*15(12,14)=B76 B*1513=B77	B63, B77	B62, B75, B76
B16	B*38=B38 B*3803=16 B*39=B39 B*3901=B3901 B*3902=B3902 B*3905=B16	B38	B39, B3901, B3902

B17	B*57=B57 B*58=B58	B57, B58	
B18	B*18=B18		B18
B21	B*49=B49 B*5001=B50 B*5002=B45	B49	B50
B22	B*54=B54 B*55=B55 B*5505=B22 B*56=B56 B*5603=B22		B54, B55, B56
B27	B*27=B27 B*2708=B2708	B27, B2708	
B35	B*35=B35		B35
B37	B*37=B37	B37	
B40	B*40(03,04)=B40 B*4005=B4005 or B50 B*40(01,10)=B60 B*40(02,06,09)=B61		B4005,B60, B61
B41	B*41=B41		B41
B42	B*42=B42		B42
B46	B*46=B46		B46
B47	B*47=B47	B47	
B48	B*48=B48		B48
B53	B*53=B53	B53	
B59	B*59=B59	B59	
B67	B*67=B67		B67
B70	B*1509=B70 B*15(10,18)=B71 B*15(03,46)=B72		B71, B72
B73	B*73=B73		B73
B78	B*78=B78		B78
B81	B*81=B81		B81
No serological Equivalent	B*82		B*82

HLA-Cw	
Broad Sero Name	Splits
Cw1	Cw*01=Cw1
Cw2	Cw*02=Cw2
Cw3	Cw*03(02,04)=Cw10 Cw*0303=Cw9 Cw*0307=Cw3
Cw4	Cw*04(01,02)=Cw4
Cw5	Cw*05=Cw5
Cw6	Cw*06=Cw6
Cw7	Cw*07(01-04,06)=Cw7
Cw8	Cw*08=Cw8
No Serological Equivalent	Cw*12,Cw*13,Cw*14,Cw*15, Cw*16,Cw*17,Cw*18

HLA-DR		
Broad Sero Name	Splits	DR51/52/53 Linkage
DR1	DRB1*01=DR1 DRB1*0103=DR103	None
DR2	DRB1*15=DR15 DRB1*1508=DR2 DRB1*16= DR16 DRB1*16(03,05)=DR2	DR51
DR3	DRB1*0306=DR3 DRB1*03(01,04,05)=DR17 DRB1*03(02,03)=DR18	DR52
DR4	DRB1*04=DR4	DR53
DR5	DRB1*11=DR11 DRB1*1107=DR3/DR11 DRB1*1117=DR14 DRB1*12=DR12	DR52
DR6	DRB1*13=DR13 DRB1*13(12,29)=DR6 DRB1*14=DR14 DRB1*14(17,18)=DR6 DRB1*1403=DR1403 DRB1*1404=DR1404 DRB1*1415=DR8 DRB1*1421=DR13	DR52

DR7	DR7	DR53
DR8	DR8	None
DR9	DR9	DR53
DR10	DR10	None
DR51	DRB5*01=DR51 DRB5*02=DR51	
DR52	DRB3*01=DR52 DRB3*02=DR52 DRB3*03=DR52	
DR53	DRB4*01=DR53	

HLA-DQ	
Broad Sero Name	Splits
DQ1	DQB1*05=DQ5 DQB1*06=DQ6 DQB1*06(11,12)=DQ1
DQ2	DQB1*02
DQ3	DQB1*03(01,04)=DQ7 DQB1*03(02,05)=DQ8 DQB1*0303=DQ9
DQ4	DQB1*04

A Simpler Serological Version of the Above Split Charts:

HLA-A	Split
A1	A1
A2	A2
A3	A3
A9	A23,A24
A10	A25,A26, A34,A66
A11	A11
A19	A29,A30, A31,A32, A33,A74
A28	A68,A69
A36	A36
A43	A43
A80	A80

HLA-B	Split
B5	B51,B52
B7	B7
B8	B8
B12	B44,B45
B13	B13
B14	B64,B65
B15 See also B70	B62,B63, B75,B76, B77
B16	B38,B39
B17	B57,B58
B18	B18
B21	B49,B50
B22	B54,B55, B56
B27	B27
B35	B35
B37	B37
B40	B60,B61
B41	B41
B42	B42
B46	B46
B47	B47
B48	B48
B53	B53
B59	B59
B67	B67
B70	B71,B72
B73	B73
B78	B78
B81	B81

HLA-Cw	Split
Cw1	Cw1
Cw2	Cw2
Cw3	Cw9,Cw10
Cw4	Cw4
Cw5	Cw5
Cw6	Cw6
Cw7	Cw7
Cw8	Cw8
No Cw11	

<u>Bw6:</u>

- All HLA-B that are not Bw4
- No HLA-A

<u>Bw4:</u>

A9,A25,A32,B5,B13,B17,B27,B37,B38
B44,B47,B49,B53,B59,B63,B77

HLA Allele Listing Order:
Lists of HLA allele sequences are often ordered counterintuitively. DRB1*1101 is often listed before DRB1*0701. This is in deference to the order of the older, unsplit serological nomenclature.

Serological Splits:
Serological splits are sometimes written as B14(B64) or B64(B14). This is meant as an explicit reminder of the parent-split relationship.

HLA Allele Nucleotide Numbering:
HLA allele nucleotides are numbered based upon an archetypal cDNA (intronless) sequence. For DRB1/3/4/5 the archetype is DRB1*0101. In essence, that means new alleles are aligned with the archetype even if they have small insertions are deletions. The table below provides the ending nucleotide positions for each exon for some of the HLA genes:

Locus	DRB1/3/4/5	DPB1	DQA1	DQB1	A	B	Cw
Arche-type	DRB1*0101	DPB1*01011	DQA1*0101	DQB1*0501	Class I Cons.	Class I Cons.	Class I Cons.
Start	1	1	-69	1	1	1	1
Exon 1	13	13	13	13	73	73	73
Exon 2	283	277	262	283	343	343	343
Exon 3	565	559	544	565	619	619	619
Exon 4	676	670	699(end)	676	895	895	895
Exon 5	700	690(end)		703	1015	1015	1015
Exon 6	714(end)			714(end)	1057	1057	1057
Exon 7					1096	1096	1096
Exon 8					1101(end)	1101(end)	1101(end)

Linkage Disequilibrium
The HLA alleles are ordered on chromosome 6 as DP-DQ-DR-B-C-A. Those alleles that are physically closest to each other usually have the highest linkage disequilibrium, i.e., they are inherited together. In common parlance two alleles are said to be “tightly linked”. The strongest linkages are B-Cw, DRB1-DRB3/4/5, and DRB1-DQB1. Remember that Bw4 and Bw6 cannot be “linked” to an antigen since they are a physical epitope of that antigen.

The 6 Critical Antigens
In discussing a donor-recipient pairing the degree of matching will often be summarized as a fraction of the number 6: 2/6 or 6/6, for example. This fraction refers to the HLA-A,B,DR (DRB1) antigens only. Of course, these three antigens are inherited in maternal/paternal pairs resulting in 6 total antigens for comparison.

CREG

A CREG (cross-reactive group) is a group of class I HLA proteins that share public antigenic specificities. When these proteins are assayed serologically they appear to fall naturally into groups that crossreact because of these shared epitopes.

CREG Name	Private Proteins Sharing Public Epitope
1C (A1)	A1,A36,A3,A11
28C (A28)	A10,A11,A28,A30,A31,A33
2C (A2)	A2,A28
5C (B5)	B5,B35,B53,B15,B17,B18,B70
7C (B7)	B7,B42,B41,B60
22C (B22)	B7,B22,B27,B17(some),B46(some)
27C (B27)	B7,B27,B13,B40,B47
8C (B8)	B8,B14,B18,B39,B38(some),B51(some)
12C (B12)	B12,B21,B13,B41,B47,B60,B37(some),B61(some)
21C (B21)	B21,B5,B35,B15
Bw4	>14 B Alleles
Bw6	>23 B Alleles
Interlocus	A2,B17
Interlocus	Bw4,A9,A32
Interlocus	Bw6,Cw3,A11(some)

Blanks versus Nulls versus Homozygotes

A blank allele is the *absence of detection* of a second allele at a given locus. The possible causes for a blank allele are listed below:

1. There is no second allele because the gene is absent in that haplotype. For example, the DR10-DQ5 class II haplotype lacks a DRB3/4/5.
2. A gene deletion has deleted the second allele. Extremely rare.
3. A second allele is present but cannot be detected by the current methodology. For example, some Cw antigens cannot be detected serologically
4. There are two copies of the same allele at the locus (a true **homozygote**)
5. There are two closely related alleles at the locus, but the technology used is unable to split them (an apparent **homozygote**)
6. The second allele fails to create a cell surface protein product that can be detected serologically. This is a true **null** allele. Null alleles can be detected using molecular techniques

How to Write a Blank

A blank than cannot be definitively shown to consist of two alleles is always written as "-" on our reports. If family studies prove the presence of a true homozygote the allele/protein designation may be written twice. Blanks are sometimes written as Ax, Cwx, et cetera.

Example 1: DRB1*0403 detected in a cord blood. No other DRB1 detected. No parents are siblings were typed. Write this type as:

DRB1*0403, -

Example 2: DRB1*0403 detected in a bone marrow patient. No other DRB1 detected. The mother is typed as DRB1*0403,DRB1*1401. The father is typed as DRB1*0102,DRB1*0403. Write this type as:

DRB1*0403, DRB1*0403

Example 3: DRB1*0403/DRB1*0404 detected in a bone marrow patient. To translate this type into a serological equivalent write:

DR4,DR4

Example 4: DRB4*0101 or DRB4*0101/DRB4*01032 detected in a bone marrow patient. No other DRB3/4/5 detected. Write this type as:

DRB4*01(01,032),-

or

DRB4*0101,DRB4*01(01,032)

Responsibilities:

Every technologist in the tissue typing laboratory has a responsibility to learn the HLA nomenclature. The following is a list of those topics that every worker should be familiar with:

- Serological nomenclature for HLA-A,B,DR including offhand familiarity with the most common splits
- Ability to lookup and understand CREG's
- Ability to lookup Bw4 and Bw6 associations for HLA-B alleles
- Ability to lookup common HLA haplotypes and linkages
- Structure of the molecular designations and the ability to read any molecular designation and all its subparts
- For molecular technologists familiarity with alleles deleted from the nomenclature is important

Other HLA Genes

Gene	Class	Comments
HLA-E	I	Not expressed on cell surface. Expressed in all cells.
HLA-F	I	Not expressed on cell surface
HLA-G	I	Expressed on cell surface. Expressed during development. May be involved in tolerance to fetus.
HLA-H	I	Very similar to HLA-A. RNA expressed in all tissues except brain. Mutations in HLA-H associated with hemochromatosis
HLA-J	I	Very similar to HLA-A. Pseudogene.
HLA-DMA HLA-DMB	II	Directs loading of peptide onto other Class II molecules. Not expressed at cell surface
HLA-DNA	II	Old name for HLA-DOA
HLA-DOA HLA-DOB	II	Associate to form HLA-DO protein. Found in B-cell lysosomes in association with HLA-DM
HLA-DPA HLA-DPB	II	Numerous studies indicate that the cell-surface product from these genes does not play a significant role in solid organ or bone marrow transplantation
HLA-DQA	II	The DQα component of the HLA-DQ molecule is not detectable serologically. It is used in certain forensic applications and population studies. It is generally not considered for transplantation purposes.
HLA-DQA2	II	Pseudogene
HLA-DQB2 HLA-DQB3	II	Pseudogenes
HLA-DRB2 HLA-DRB6 HLA-DRB7 HLA-DRB8 HLA-DRB9	II	Pseudogenes

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