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HLA nomenclature: a user-friendly system?

Scientists are frequently criticised for failing to explain their work clearly to others and the use of specialist terminology contributes significantly to this problem. Jargon can be a highly efficient means of communication between specialists but creates a barrier to those unfamiliar with the language; nowhere is this more apparent than in the complex field of immunogenetics. Even the most dedicated immunologist must periodically despair at the proliferation of novel HLA alleles or the redesignation of others previously familiar under other names. For the clinical rheumatologist, however, some knowledge of the nomenclature is desirable if only to open up new areas of interest in the journals.

The HLA (human leucocyte antigen) extravaganza began in the 1960s with the use of serological reagents to identify transplantation antigens. First, these reagents were used to identify the HLA class I antigens (A, B and C) present on all nucleated cells and, subsequently, HLA class II products (DR, DQ and DP) which are found only on selected cells, including macrophages and some lymphocytes. Many of the early antisera were non-specific, recognising antigenic determinants (epitopes) on several different molecules (public epitopes), for example, Bw4 and Bw6. Subsequently, more sensitive serological discrimination of specific determinants (private epitopes) on these molecules proved possible, resulting in the first revisions to the nomenclature. Thus some of the original classical serological specificities have been refined, for example, DR5 splits into DR11 and DR12; DR6 splits into DR13 and DR14; B15 splits into B62, B63, B75, B76 and B77, but still these reagents do not allow perfect discrimination. The complementary use of other techniques (mixed lymphocyte culture, primed lymphocyte typing, isoelectric focussing, 2D gel electrophoresis, and DNA based methods such as RFLP analysis, oligonucleotide probes and sequencing) has greatly improved the discriminatory powers of HLA typing but increased its complexity. This is nicely illustrated with respect to the HLA class II system in which many techniques have been used for HLA typing, some of which have had their own associated nomenclature. For example, the Dw series of antigens defined by the mixed lymphocyte reaction (MLR) is closely related but not identical to the serologically defined DR (D-related) series. MLR can discriminate several Dw subtypes within certain serologically defined specificities, for example, DR4 (Dw4, Dw10, Dw13, Dw14, Dw15) and DR2 (Dw2, Dw12, Dw21, Dw22). It should also be noted that the original 'w' (workshop) prefix has now been

dropped for most of the serologically defined specificities, for example, DR w 13 $\Rightarrow$ DR13 [NB HLA-C locus products retain the Cw prefix to distinguish them from complement components; the DP specificities defined by primed lymphocyte (DPw1–DPw6) also retain the w prefix].

In recent years traditional HLA typing has been increasingly superseded by methods based on the DNA sequence of the corresponding genes, initially restriction fragment length polymorphisms (RFLP) but subsequently and crucially, PCR-based methods of sequencing specific genes. The latter has been extremely effective in population studies of disease associations¹ and has greatly facilitated the rapid and precise definition of novel HLA alleles. It is therefore logical that the new World Health Organisation HLA Nomenclature should be based firmly on the nucleotide sequences of these alleles.^{2,3}

The main genetic loci corresponding to the polymorphic polypeptides of these HLA molecules are HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQA1, HLA-DQB1, HLA-DPA1 and HLA-DPB1 and for each of these there is a series of alleles based where possible on the pre-existing serological nomenclature.⁴ Thus for HLA-B27 the new name is HLA-B*27. However, to take account of the 7 allelic subtypes of B27 currently recognised at the DNA level these are designated HLA-B*2701–7. Likewise, for the 14 variants of DR4 (HLA-DRB1*04) there are 14 alleles (HLA-DRB1*0401–0414). In addition to the main HLA loci illustrated in the figure there are others, some of which are pseudogenes and some of which are expressed

Class I	B	*0701–*7901	B5–B78
	Cw	*0101–*1401	Cw1–Cw8
	A	*0101–*7401	A1–A74
Class II	DPB1	*0101–*3601	DPw1–DPw6
	DPA1	*0101–*0401	
	DQB1	*0201–*0608	DQ1–DQ9
	DQA1	*0101–*0601	
	DRB1	*0101–*1410	DR1–DR18 Dw1–Dw23
	DRB3	*0101–*0301	DR52 Dw24–Dw26
	DRB4	*0101	DR53
	DRB5	*0101–*0202	DR51
	DRA	*0101–*0102	

Schematic representation of the major HLA loci within the MHC on chromosome 6, indicating the range of HLA alleles at each locus and the corresponding serological or cellular specificities (defined by MLR or primed lymphocyte typing).

on certain haplotypes only (for example, DRB3 on the DR52 haplotype group, DRB5 on the DR51 haplotype group and DRB4 on the DR53 haplotype group). The nucleotide sequences of the alleles at these loci and their corresponding serological and cellularly defined specificities have been reported in detail elsewhere.²⁻⁴

A complete list of all the HLA class I and II alleles is beyond the scope of this editorial but may be found in reference 4, together with all the corresponding cellularly and serologically defined specificities by which they have been previously recognised. The new genetically based nomenclature does not preclude the use of the older serological or cellular specificities which continue to flourish. In future, however, the allocation of new serological names will be confined to those agents that identify specific epitopes rather than broad specificities such as HLA-A10 or Bw4 and the serological name should correspond as closely as possible with the allele sequence name. Of course, there are still problems: serological

specificities are not limited to single alleles (DR4 encompasses at least 14 alleles and B27 at least 7) and the genetic nomenclature can be cumbersome (the serological specificity DQ2 is certainly less of a mouthful than DQA1*0501, DQB1*0201). However, because of its precision the new system of nomenclature represents a considerable advance once the terminology has been mastered.

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