

HLA and Autoimmune Diseases

A. SVEJGAARD

Tissue-Typing Laboratory of the Blood Grouping Department, State University Hospital (Rigshospitalet) of Copenhagen, Denmark

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During the first years after the discovery of the HLA system (2), it was mainly of interest to a limited group of clinicians and scientists involved in transplantation, blood transfusion, and genetics. More recently, however, it has become clear that the biological function of this system makes it important for much larger groups of doctors and biologists. This became clear when it was realized that the HLA system is deeply involved in the susceptibility and resistance to a variety of diseases and when it was discovered that the HLA homologues in animals play a fundamental role in many immune responses. To-day, at least one (HLA-B27) of the more than 50 different HLA factors presently known is familiar to most clinicians working in the field of internal medicine. However, because the HLA system seems to have a central position in many immune responses involved in many disease processes, it is important that a more detailed knowledge of this system becomes available for larger groups of colleagues since such knowledge may aid in the clarification of several pathogenetic mechanisms. The purpose of this review is to survey the present knowledge of the HLA system with special reference to the associations which have been found between this system and susceptibility to some "auto-immune" disorders. The term "auto-immunity" will be used in a rather broad sense without assuming that autoimmune processes,

although present, are necessarily of pathogenetic importance.

The major histocompatibility complex (MHC)

The HLA system is the first (A) Human Leucocyte blood group system discovered. It controls the strongest transplantation antigens in man. A similar major histocompatibility complex (MHC) has also been found in all other vertebrates studied and there is pronounced homology between all these systems: when the MHC of one species has been observed to control a certain character, e.g. a complement component, investigations of the MHC's of other species have revealed that they control the same type of character, too. Most details are known about the MHC of mice, the H-2 system, because it has been the subject of many experiments with various inbred strains and crosses between them (7).

The MHC is unique mainly because it controls several quite different biological characters and because there are so many different MHC types in the population. The characters controlled by MHC comprise (i) antigens on cell surfaces; (ii) some components of the complement cascade, i.e. properdin factor Bf of the alternative and the second (C2) and fourth (C4) components of the classical pathway; (iii) various specific responses in thymus-dependent immunity; and (iv) the

cooperation between various sets of T lymphocytes, monocytes, and B lymphocytes. The MHC genes involved in thymus-dependent immunity are the so-called *Immune response* (Ir) genes which control in a dominant way the ability of the individual to respond well with specific IgG antibody production and cell-mediated immunity to certain antigens (3). In recent years, it has become increasingly likely that the Ir determinants are in fact identical to some of those controlling cellular cooperations which may perhaps in turn be identical to some of the cell surface antigens controlled by the MHC. In brief, it seems as if a T lymphocyte in order to respond to a foreign antigen must recognize not only the foreign antigen but also some of the "self" MHC antigens present on the surface of the cell, e.g. a macrophage, presenting the foreign antigen to the T cell. Some of the MHC antigens are involved as part of the target on virus-infected or hapten-conjugated cells when these are lysed by cytotoxic T killer lymphocytes. Recent evidence indicates that the ability of T lymphocytes to recognize self MHC antigens is acquired during maturation in the thymus. However, there are still quite a number of *i*'s to be dotted before the complete relationship between MHC antigens, Ir determinants, and cellular cooperation has been worked out.

The HLA System (1, 8)

The genes controlling HLA factors are located on a number of closely linked loci within a short distance of each other on the short arm of chromosome 6 (Fig. 1). Three of the loci control the so-called classical HLA antigens of the HLA-A, B, and C series. These antigens are present on most cells in the body except red cells. For HLA-ABC typing, viable lymphocytes from a blood sample are used, and the various antigens are recognized by means of specific antisera which are usually obtained from parous women. The HLA-D antigens are recognized by means of cell culture techniques (mixed leucocyte culture = MLC). They are only present on macrophages, B lymphocytes,

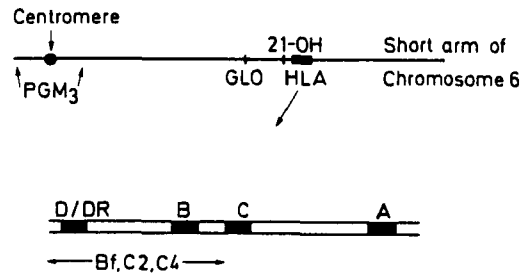


Fig. 1. Arrangement of HLA genes on the short arm of chromosome 6. The locations of the HLA-A, B, C, D, and DR loci are shown as are the possible positions of the complement components, Bf, C2, and C4. PGM₃, GLO, and 21-OH are the loci for the enzymes phosphoglucomutase, glyoxylase, and 21-hydroxylase.

and a few other cell types. The same is true of the HLA-DR (D-related) antigens, but these are recognized by serological techniques on B lymphocyte-enriched cell suspensions. At least some of the HLA-DR antigens are probably identical to some of the HLA-D antigens. At the time of writing, typing for HLA-D and DR is much more difficult and less reliable than HLA-ABC typing.

Table 1 shows the most well-known of the HLA-A, B, C, D, and DR antigens. The striking point to note is the impressive number of different antigens within each series. Because the antigens of a given series, say HLA-A, are controlled by alleles, each individual can have no more than two antigens from each series. However, at the population level, all the different combinations between the various antigens can be seen and this is the basis for the extreme genetic polymorphism of the HLA system: it is rare to find unrelated individuals carrying the same HLA-A, B, C, D, and DR antigens. In siblings, however, HLA identity is quite common—about a quarter of all sibpairs are HLA identical. This is so because the HLA loci are so closely linked that crossing-over only happens in about 1–2% of meiotic divisions. Accordingly, a parent usually hands on one of his two sets of HLA genes to each of his children. Such a set of HLA genes on one and the same chromosome is called an HLA haplotype.

Table 1
HLA antigens

<i>HLA-A Series</i>	<i>HLA-B Series</i>	<i>HLA-C Series</i>
HLA-A1	HLA-B5	HLA-Cw1
HLA-A2	HLA-B7	HLA-Cw2
HLA-A3	HLA-B8	HLA-Cw3
HLA-A9	HLA-B12	HLA-Cw4
HLA-A10	HLA-B13	HLA-Cw5
HLA-A11	HLA-B14	HLA-Cw6
HLA-A25 } A10	HLA-B15	<i>HLA-D Series</i>
HLA-A26 }	HLA-B17	
HLA-A28	HLA-B18	HLA-Dw1
HLA-A29	HLA-B27	
HLA-Aw19	HLA-B37	HLA-Dw2
HLA-Aw23 } A9	HLA-B40	HLA-Dw3
HLA-Aw24 }	HLA-Bw4	HLA-Dw4
HLA-Aw30	HLA-Bw6	HLA-Dw5
HLA-Aw31	HLA-Bw16	HLA-Dw6
HLA-Aw32	HLA-Bw21	HLA-Dw7
HLA-Aw33	HLA-Bw22	HLA-Dw8
HLA-Aw34	HLA-Bw35	HLA-Dw9
HLA-Aw36	HLA-Bw38 } BW16	HLA-Dw10
HLA-Aw43	HLA-Bw39 }	HLA-Dw11
	HLA-Bw41	<i>HLA-DR Series</i>
	HLA-Bw42	
	HLA-Bw44 }	HLA-DRw1
	HLA-Bw45 }	
	HLA-Bw46	HLA-DRw2
	HLA-Bw47	HLA-DRw3
	HLA-Bw48	HLA-DRw4
	HLA-Bw49	HLA-DRw5
	HLA-Bw50	HLA-DRw6
	HLA-Bw51	HLA-DRw7
	HLA-Bw52	
	HLA-Bw53	
	HLA-Bw54	

HLA-A1 and the B8 antigen, whereas only 7% would do so if there was no association between A1 and B8, i.e. no linkage disequilibrium. This phenomenon holds for all known HLA factors (including the complement components mentioned below) and it is most probably true also for as yet unknown HLA factors. This is why it is occasionally difficult to decide whether a disease is more strongly associated with, say HLA-Dw3, than with HLA-B8 which is strongly associated with HLA-Dw3 in the general population. And it is for the same reason that it is difficult—often impossible—to know whether an observed association is secondary to a primary, causative association with an as yet unknown HLA factor, e.g. an immune response determinant.

Based on homologies between HLA and homologous systems in animals, it is believed that the human Ir genes are located close to the HLA-D and DR loci and there is circumstantial evidence that this is indeed the case. Moreover, there is even some evidence that the HLA-D and DR antigens may themselves be Ir determinants.

The complement components controlled by HLA (Bf, C2, and C4) are probably controlled by genes located between the HLA-B and D/DR loci. The polymorphism at these complement loci is much more limited than that for the antigens: there are only two major alleles at each of the complement loci.

When crossing-over does not occur, the four different parental haplotypes, say *a* and *b* in the father, and *c* and *d* in the mother, can only be combined in four different ways in the offspring: *a/c*, *a/d*, *b/c*, and *b/d*.

One characteristic of the HLA system which must be borne in mind when discussing disease associations, is the so-called linkage disequilibrium phenomenon. This means that genes from neighbouring loci are not randomly distributed on the haplotypes, and it is reflected in the population by associations between some of the HLA antigens. For example, about 20% of Danes carry both the

Associations between HLA and autoimmune disorders

Table 2 shows a list of the definite associations which exist between HLA and diseases which may be considered "autoimmune". These data have been extracted from a recent report from the HLA and Disease Registry (5). The most well known are, of course, those involving HLA-B27: ankylosing spondylitis, Reiter's disease and several other post-infectious arthropathies, psoriatic arthritis, juvenile rheumatoid arthritis, and acute anterior uveitis. In contrast, classical rheumatoid arthritis shows a quite strong association with HLA-Dw4 and DRw4. Then follows a list of

Table 2

Associations between HLA and autoimmune diseases

Disease	Antigen	Frequency (%) of antigen		Relative risk	Significance <i>P</i>
		Controls	Patients		
<i>Arthropathies</i>					
Ankylosing spondylitis	B27	9.4	90	87.4	< 10 ⁻¹⁰
Reiter's syndrome	B27	9.4	79	37.0	< 10 ⁻¹⁰
Reactive arthritis	B27	increased in yersinia, salmonella, and shigella arthritis			
Psoriatic arthritis	B27	9.4	29	4.0	< 10 ⁻¹⁰
Psoriatic arthritis	B16	5.9	15	2.8	< 10 ⁻³
Juvenile arthritis	B27	9.4	32	4.5	< 10 ⁻¹⁰
Rheumatoid arthritis	Dw4	19.4	50	4.2	< 10 ⁻⁹
	DRw4	28.4	70	5.8	< 10 ⁻³
<i>Eye diseases</i>					
Acute anterior uveitis	B27	9.4	52	10.4	< 10 ⁻¹⁰
<i>Skin diseases</i>					
Dermatitis herpetiformis	Dw3	26.3	85	15.4	< 10 ⁻¹⁰
Dermatitis herpetiformis	DRw3	25	97	56.4	< 10 ⁻¹⁰
<i>Intestinal diseases</i>					
Coeliac disease	Dw3	26.3	79	10.8	< 10 ⁻⁸
<i>Liver diseases</i>					
Chronic autoimmune hepatitis	B8	24.6	75	9.0	< 10 ⁻¹⁰
	DRw3	19	78	13.9	< 10 ⁻⁶
<i>'Systemic' diseases</i>					
Bürger's disease	B12	24.4	3	0.1	< 10 ⁻⁴
Myasthenia gravis	B8	24.6	57	4.1	< 10 ⁻¹⁰
Sicca syndrome	Dw3	26.3	78	9.7	< 10 ⁻⁹
S.l.e.	B8	24.6	41	2.1	< 10 ⁻¹⁰
C2 deficiency	A recessive trait closely linked to HLA and strongly associated with B18 and Dw2.				
<i>Endocrine diseases</i>					
Juvenile and/or insulin dependent diabetes	Dw2	25.8	0	0.0	< 10 ⁻⁶
	Dw3	26.3	44	2.2	< 10 ⁻³
	Dw4	19.4	49	4.0	< 10 ⁻¹⁰
Graves' disease	Dw3	26.3	57	3.7	< 10 ⁻⁹
Idiopathic Addison's disease	Dw3	26.3	69	6.3	< 10 ⁻³

These data are from Ryder et al. (5) and based on calculations from all available studies. Control antigen frequencies refer to a Danish population. The relative risk indicates how many times more frequently the disease develops in individuals carrying the antigen in question compared with individuals lacking it. Only supposedly primary associations are given.

HLA-Dw3 associated disease belonging to the group of so-called organ-specific autoimmune diseases: insulin-dependent diabetes, Graves' disease, idiopathic Addison's disease, chronic autoimmune hepatitis, the sicca syndrome, dermatitis herpetiformis, and coeliac disease, whereas myasthenia gravis may be more

strongly associated with HLA-B8 than with Dw3. Systemic lupus erythematosus is also associated with B8 but has not been sufficiently studied for HLA-D or DR antigens, which is particularly difficult in this disorder because the lymphocytes of the patients are often extraordinarily susceptible to the action of

antibodies and because an impaired responsiveness in MLC may be seen in severe cases.

It is questionable whether subacute thyroiditis may be considered autoimmune—the association with HLA-B35 may also be explained by a purely infectious pathogenesis. The negative association between HLA-B12 and Bürger's disease still needs confirmation, but has been included in the Table because it indicates that this much debated disease may in fact exist.

Finally, C2-deficiency is not a disease as such but it may increase the susceptibility to glomerulonephritis, lupoid-like syndromes, and severe infections. It is very strongly associated with HLA-Dw2 and B18 because of linkage disequilibrium between the *C2-deficiency* gene and *Dw2* and *B18*.

Applications

HLA typing is now widely used in cases of suspected ankylosing spondylitis or Reiter's disease where the demonstration of HLA-B27 supports these diagnoses whilst its absence makes it less likely, but it should be kept in mind that both of these disorders can develop in individuals lacking B27. In psoriatic arthritis, the diagnostic value of B27 is much less, but it is worth noting that the presence of B16 (or one of its "splits", Bw38 and Bw39) may also support this diagnosis. For most other HLA associated diseases, HLA typing is not of real diagnostic value, either because the associations are too weak or because the diagnoses are firmly based on other criteria.

The problem whether HLA typing may have prognostic implications has not been solved. Thus, the evidence that rheumatoid arthritis may run a more severe course in DRw4-positive patients is conflicting, and there are no solid studies allowing reliable estimates of the risk of subsequent development of ankylosing spondylitis in B27-positive patients with Reiter's disease. Investigations of apparently healthy B27-positive individuals have revealed a strikingly high (about 20%)

prevalence of non-symptomatic sacroiliitis and/or ankylosing spondylitis in most but not all studies. This obviously makes it difficult to evaluate the prognostic role of B27 also in relatives of patients.

Dw3-positive patients with Graves' disease seem to have higher risk than Dw3-negative ones to recurrence of the disease after treatment with antithyroid drugs, but it is questionable whether this has practical value.

In general, it would appear that the major importance of the HLA and disease associations should be seen in the light they may throw on the subdivisions of diseases, their mode of inheritance, and their pathology, i.e. in research.

The associations have already given important nosological information. For example, the concept of juvenile and maturity onset diabetes as separate entities has now been strongly supported by the observation that only the former shows HLA associations. In analogy, the finding that the association between HLA-B8 and myasthenia gravis seems mainly to hold for early-onset (before the age of 35) disease in patients without thymoma helps to distinguish the two types of this disease. In contrast, the HLA-B27 antigen helps to tie together the diverse disorders associated with this antigen, and it is plausible—but not certain—that all the Dw3-associated organ specific autoimmune diseases listed in Table 2 have a common genetic background, although extra associations exist for juvenile diabetes (with Dw4) and coeliac disease (with Dw7). In this context, it is interesting that two "classical" organ-specific autoimmune diseases, Hashimoto's thyroiditis and pernicious anaemia, do not seem to be associated with HLA, although more studies—in particular of HLA-D and/or DR antigens—are needed to exclude this possibility.

Several of the diseases listed in Table 2 have previously been shown by family studies to have a genetic element, but the modes of inheritance have not been known (4). HLA studies in ankylosing spondylitis have now shown that HLA-B27, or an unknown HLA

factor closely associated with this antigen, confers a dominant susceptibility to this disease. The situation for juvenile diabetes is less clear. Here the HLA-linked susceptibility may be recessive and due to only one HLA gene, or it may be dominant and due to two different HLA genes which may interact to increase the risk even more for individuals carrying both genes. This problem is likely to be solved in a few years when more HLA data become available. It is worth noting that HLA-Dw2 is associated with a remarkable resistance to juvenile diabetes. For the other disorders listed in Table 2 (apart from C2-deficiency which is clearly recessive) genetic elements seem not to be major factors in the development of the diseases, although the HLA associations clearly show that genetic susceptibility is involved. However, it may be assumed that environmental factors play a larger role, for example in rheumatoid arthritis and myasthenia gravis.

Mechanisms which may explain the associations

The mechanisms bringing about HLA-associated susceptibility to disease are almost totally unknown although several hypotheses have been advanced. Accordingly, the associations have not yet led to any definite breakthroughs in our knowledge of the pathogenetic mechanisms. However, with the increasing knowledge of the biological function of the MHC, this situation is likely to change.

At the present time, it seems most reasonable to assume that the associations primarily involving one or more HLA-D/DR antigens are due to the action of specific immune response (or immune suppressor) determinants, and these associations may thus be considered additional evidence that "aberrant" immunity plays a role in these "autoimmune" disorders. An association between HLA and the presence of organ-specific autoantibodies has been shown for HLA-Dw3 and anti-adrenal antibodies in Addison's disease and smooth muscle antibodies in chronic autoimmune hepatitis. These observ-

ations further support the hypothesis of Ir gene involvement in autoimmune diseases.

Primary associations with HLA-B antigens (e.g. ankylosing spondylitis) may also be explained by Ir determinants some of which might be more closely linked to the HLA-B than the D and DR loci. However, because the HLA-ABC antigens—and particularly their homologues in mice—have been shown to be involved in the lysis of virus-infected or hapten-conjugated target cells, these associations may also be due to this phenomenon. For example, it is possible that the HLA-B35 antigen may be particularly effective in presenting a hypothetical infectious agent to T lymphocytes in subacute thyroiditis.

Among other hypotheses which have been advanced to explain the associations, we may mention "molecular mimicry" which covers the possibility that a microorganism possessing an antigen resembling a certain HLA antigen may give rise to "abnormal" infections in individuals carrying the HLA antigen in question. For example, evidence has recently been presented that some *Klebsiella* bacteria possess antigens cross-reacting with the HLA-B27 antigen (6).

Still another possibility is that genetically determined variations in HLA-controlled complement components may cause differences in disease susceptibility. Thus, individuals with C2 deficiency seem to have an increased susceptibility to certain autoimmune disorders. However, this deficiency does not always lead to disease and it does not seem likely that it accounts for a larger fraction of these disorders. It is still uncertain whether the polymorphism at these complement loci is sufficiently pronounced to explain some of the associations in Table 2.

Concluding remarks

An impressive number of autoimmune conditions appear to be associated with certain HLA factors. Most of them concern primarily HLA-D antigens which are supposed to be closely related to the human immune response

determinants, and it is tempting to suggest that such determinants are responsible for many of the associations, but other explanations are also possible. These relationships have already contributed significantly to our knowledge of the inheritance of disease susceptibility and resistance and of disease heterogeneity. In some cases, they may have diagnostic and perhaps prognostic applications, but the real benefit may not be seen until more becomes known about the biological function of the HLA system, which may help in elucidating the pathogenesis and aetiologies of the disorders involved. Finally, it should be noted that studies of HLA in autoimmune disease are not yet exhausted—in particular, HLA-D and/or DR typing is indicated in a number of cases.

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Address:

A. Svejgaard

Tissue-Typing Laboratory of the

Blood Grouping Department

Rigshospitalet

DK-2200 Copenhagen N

Denmark