HLA and eye disease

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SUMMARY This review article discusses the evolution and function of the histocompatibility system, the nature of the HLA antigens and their classification, the phenomenon of linkage disequilibrium, and the mechanisms of HLA and disease susceptibility. The reported associations between HLA antigens and various eye diseases are analysed and their significance is discussed. Problems in designing studies on HLA and disease associations are highlighted and suitable statistical procedures for the analysis of the results are outlined.

When first introduced by an international committee sponsored by the World Health Organisation the term HLA stood for antigens associated with *human leucocytes* at the genetic locus *A* (that is, first locus). Since this antigenic system has now been found to consist of more than one locus of interconnected sets of genes, HLA is now used to cover the entire group of histocompatibility or transplantation antigens. These antigens are surface glycoproteins which occur not only on leucocytes but also on other nucleated cells, platelets, and reticulocytes. If these antigens are removed by enzymes *in vitro* the cell can reconstitute them within 6 hours, which indicates their rapid turnover. It is not surprising, therefore, that small amounts are continuously released into the plasma. Embryological studies have shown that these antigens can be detected in fetal tissues as early as the sixth to eighth week of gestation. Every individual possesses these cell membrane antigens as a direct expression of his or her genotype, and it is therefore not surprising that they differ from one person to another, the differences being greatest between members of unrelated families.

Classification

Much of our understanding of the human HLA system comes from studies in mice in which the major histocompatibility system known as H-2 evokes a particularly strong response in an allogeneic host, that is, members of the same species, and outweighs all other systems in promoting graft rejection. HLA, the comparable major histocompatibility system in man, probably comprises

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Fig. 1 Genetic determinants of the major histocompatibility antigens. Each of a pair of autosomal chromosome 6 possess 5 adjacent loci which carry the genes responsible for the formation of HLA antigens

more than 70 different antigens (Table 1). Those which have not been unequivocally demonstrated and whose separate identity is still debatable are called *w* (workshop) antigens. The development of this group of transplantation antigens appears to be controlled by 5 adjacent loci on the major histocompatibility region of each of the pair of autosomal chromosome 6 (Fig. 1). Consequently each cell

Table 1   *Classification of HLA antigens*

Locus A		Locus B		Locus C		Locus DR		Locus D		
HLA A1		HLA Bw4		HLA Cw1		HLA DRw1		HLA Dw1		
A2		B5	{	Bw51		Cw2		DRw2		Dw2
A3				Bw52		Cw3		DRw3		Dw3
A9	{	Aw23		Bw6		Cw4		DRw4		Dw4
		Aw24		B12	{	Bw44		Cw5		DRw5
A10	{	Aw25				Bw45		Cw6		DRw6
		Aw26		B14				DRw7		Dw7
A11		B15								Dw8
Aw19	{	A29		Bw16	{	Bw38				Dw9
		Aw30				Bw39				Dw10
		Aw31		B17						Dw11
		Aw32		Bw21	{	Bw49				
		Aw33				Bw50				
		Aw34		Bw22						
		A28		B27						
Aw36*		Bw35								
Aw43*		B37								
		B40								
		Bw41								
		Bw42*								
		Bw46†								
		Bw47								
		Bw48								
		Bw53								
		Bw54†								

*Found only in black population. †Found only in mongoloid population

membrane in a heterozygous individual may contain a maximum of 10 different antigens (Bodmer, 1978; Gill *et al.*, 1978). The HLA antigens most commonly associated with the first, that is, A, locus include HLA A1, A2, A3, A9 (which is now divisible into Aw23 and Aw24), and HLA A10 (which has been split into A25 and A26), while prominent among the antigens controlled by the second (or B) locus are HLA B5 (comprising Bw51 and Bw52), HLA B7, B8, and B27. The third serologically determined locus codes provisionally for about 6 different antigens designated HLA Cw1 . . . HLA Cw6.

Grafts bearing various HLA antigens give rise to humoral antibodies in an allogeneic host and can therefore be detected by serological methods using sera derived from such sources as multiparous

women who have developed antibodies to their offsprings' paternally derived antigens, from recipients of multiple blood transfusion, from immunised volunteers, and from patients who have previously rejected an incompatible graft. Categorisation of HLA antigens at loci A, B, and C is usually performed by exposing suspensions of patients' lymphocytes to a battery of specific antisera in the presence of rabbit complement and looking for evidence of cell lysis.

In addition to these histocompatibility antigens detected by serological methods (that is, serologically determined 'SD' antigen) there are other HLA antigens which can be detected only by incubating donor lymphocytes with lymphocytes of the proposed recipient (mixed lymphocyte culture) and

examining for evidence of blastic transformation and division. More recently a panel of homozygous typing cells (HTC) have been used to detect these lymphocyte-defined (LD) antigens, which are controlled by the locus D on the major histocompatibility region and are designated HLA D. These consist of about 11 different provisional antigens (HLA Dw1...Dw11).

There is considerable evidence indicating the existence of another HLA locus which is closely linked with the D locus antigens and is therefore called HLA DR (that is, D related). The corresponding antigens can be detected, however, by serological methods and have been designated HLA DRw1...DRw7. It is of interest that, although HLA A, B, and C antigens are expressed on the surfaces of almost all cells except erythrocytes, spermatozoa, and placental trophoblasts, the HLA DRw antigens have a restricted tissue distribution, being present only in B lymphocytes, in monocytes, and in the Langerhans cells of the skin. The biological implications of this restricted expression are discussed later.

Biochemistry of HLA antigens

The HLA A, B, C, and DRw antigens are insoluble in traditional aqueous solvents owing to the presence of a small hydrophobic domain in the molecule which is inserted in the lipid bilayer of the cell membrane. The HLA A, B, and C antigens consist of a single glycosylated polypeptide of 43 000 molecular weight which is non-covalently linked to another distinct polypeptide β 2 microglobulin. The HLA DRw antigens on the other hand comprise two distinct glycosylated polypeptides of molecular weights 28 000 and 33 000. The human DRw antigens thus resemble mouse and guinea-pig Ia (immune associated) antigens. The precise biochemical nature of HLA D antigens is not clear.

It has been calculated that more than 300 million genetically different individuals can be formed by the known alleles of the HLA A, B, C, and D loci, and of these more than 30 million will have distinguishable combinations of antigens. Sometimes alleles at different loci occur together on the same chromosome more often than is expected by chance. This tendency is called 'linkage disequilibrium' and is of importance in studies on mechanisms underlying HLA and disease association. Thus, A1 often exists with B8, A3 with B7, B7 with Dw2 and DRw2, B8 with Dw3 and DRw3, B12 with Dw2, and B15 with Dw4. Furthermore, in any study on HLA and disease association it is important to realise that, although certain antigens, for example, HLA A2, are present at a relatively high frequency in popula-

tions all over the world, some may have a restricted distribution probably related to evolution and survival of the fittest. Thus, A1, A3, A28, A29, Aw30, and Aw32 are absent in Japanese, whereas A11 is not found in African blacks, who have Aw43 and Bw42, which is not found in other races.

Biological role of HLA antigens

It seems unlikely that HLA antigens were developed to outmanoeuvre the transplantation surgeon, and, although it has been speculated for some time that they facilitate immune surveillance and consequent destruction of mutant tumour cells having a different set of such antigens, it has only recently been possible to show that they play an important role in the normal immune response. It has also been postulated that a large number of antigenic receptors shared by different classes of lymphocytes might be the outcome of lymphoid cells in early embryogenesis responding to host transplantation antigens by undergoing division and somatic mutation. The major histocompatibility region in mice incorporates loci concerned with immunological responsiveness—the so-called Ir genes—and if similarly true of the human species such a relationship could help to explain the concomitance of several diseases such as ankylosing spondylitis and acute anterior uveitis in which there may be an intrinsic immunological dysfunction with the presence of specific HLA antigens.

It is known that an immune response to most of the antigens requires co-operation between macrophages, helper T cells, and B lymphocytes before differentiation of the latter into plasma cells. For a successful interaction it is essential that the helper T cells react simultaneously with the antigen as well as the HLA DR antigens (Ia in mice) on the surface of a macrophage or a B lymphocyte. T cells with suppressor activity are essential for the regulation of immune response, and studies have shown that HLA compatibility is essential for this effect.

Furthermore, it is inferred from studies in mice that cytotoxic T cells in man appear to use antigens determined by HLA A and B loci for recognition and subsequent killing of their targets. It would appear that, although the biological role of HLA in immune functions is largely inferred from evidences obtained in animals, there is no doubt that histocompatibility gene products modulate lymphoid cell interactions and are responsible for recognition and handling of antigen.

HLA and disease susceptibility

It is well established that over 90% of patients with ankylosing spondylitis show the presence of HLA

B27, and a normal person who is positive for this antigen is about 100 times more at risk of developing this disease than a B27-negative person. At the same time it is also true that, although nearly all patients with ankylosing spondylitis may have B27, only a relatively small proportion of people with B27 ever suffer from the disease. The question therefore arises how a particular HLA antigen increases the susceptibility of an individual to a particular disease and what other factors act in concert to determine the final outcome. Although the precise mechanism of HLA and disease susceptibility is still enigmatic the following hypotheses may explain some of the possibilities.

(i) There is a molecular mimicry between some components of the infecting organism and one of the HLA antigens. This would lead individuals having the relevant antigen being unable to mount an immune response to the pathogen, as indeed to self antigens. This would allow infection to occur and might encourage persistent infection with organisms that will otherwise be eliminated. Evidence has been presented in favour of this form of cross tolerance, and it has been shown that antibodies raised against klebsiella react only with HLA B27+ve lymphocytes. This supports the idea that ankylosing spondylitis and acute anterior uveitis develop as a result of infection with this group of organisms in individuals who do not recognise klebsiella antigens (Seager *et al.*, 1979).

(ii) It has been suggested that certain HLA antigens may act as cell-membrane receptors for pathogens, thus allowing them a strong foothold. There is as yet little experimental evidence to support this view. It is possible that the relevant HLA antigens are later modified by the organism and mount an autoimmune inflammatory reaction.

(iii) It has also been proposed that in some diseases certain HLA antigens may in some way play a limiting role on the efficiency with which T lymphocytes and macrophages recognise determinants on a particular pathogen.

(iv) However, it is possible that HLA antigens themselves play an insignificant role in disease susceptibility, but they may be linked to several putative immune-response genes which are responsible for variations in specific immune responses to pathogenic micro-organisms.

HLA studies: design and evaluation

When conducting studies on HLA and eye disease it is important to recognise the problems that can arise both in the designing of studies and in the analysis of the results. Disregard of these ground rules may, and in fact has, led to a series of reports

on HLA association with glaucoma, retinoblastoma, and other eye diseases which have later been invalidated by more careful studies (Damgaard-Jensen and Kissmeyer-Nielsen, 1978).

It is important, for example, to give due attention to proper selection of controls, which must include consideration of age, sex, race, exposure to environmental factors, and possible triggering events. A disease of multifactorial aetiology might not show clear HLA and disease inheritance patterns, because coexistence of several genes might be prerequisite for the manifestation of the disease state. This may be the case in some of the negative reports in those eye diseases such as retinitis pigmentosa in which there is otherwise evidence of a genetic linkage.

Problems may arise both with the sera and the cells used for HLA typing. A very potent antiserum, for example, may in fact be multispecific, and some of the antibodies may thus be detecting non-HLA antigens. Furthermore, lack of sufficient sera for some allelic specificities can bias results if it leads to false assignment of antigens.

In the analysis of the results some of the statistical errors and shortcomings deserve emphasis because of their great importance (Edwards, 1974; Svejgaard *et al.*, 1974; Dick, 1978).

(i) Linkage disequilibrium may provide spurious associations unless recognised. Thus, HLA A1, which is often found in association with HLA B8, may be spuriously associated with some diseases in which in fact the frequency only of HLA B8 is increased. Multiple comparisons will dilute the significance of such associations.

(ii) If an HLA association is sought, with significance around the 5% value, then if 20 or more HLA antigens are tested there is a purely random chance that one of the antigens may be altered in frequency (1 in 20 = 5%). It has been suggested that the statistical significance in such situations can be corrected by multiplying the P value with the number of separate specificities tested (Woolf, 1955). Thus in one study (Zimmerman *et al.*, 1977), in which increased frequency of HLA B5 was reported in association with herpetic keratitis ($P < 0.01$), the P value after correction (P_c) appears to be insignificant ($P < 0.3$).

(iii) Since HLA antigen prevalences, unlike many other histochemical data, are not independent events, many statisticians believe that the method recommended by Woolf is too conservative and may not be strictly correct. It has been recommended, therefore, that either the findings should be compared with another published report or a second series of cases should be evaluated in the light of the results from the first series.

(iv) Once the association of a particular HLA

Table 2 HLA association with diseases of ophthalmic importance

Disease	Antigen	Frequency percentage		Relative risk
		Patients	Controls	
Behçet's disease	HLA B5	60	28	3.86
Vogt-Koyanagi-Harada syndrome	HLA Bw54	45	13	5.4
	HLA Dwa	67	16	10.5
Malignant melanoma of the choroid	HLA Aw32	11	3	4
Acute anterior uveitis	HLA B27	43	7	10
Diabetic retinopathy (juvenile)	B8 (without A1)	56	4	30*
Recurrent herpetic keratitis	B5	26	11	3
Cicatricial ocular pemphigoid	B12	45	20	3.2
Myasthenia gravis	HLA DRw3	32	17	2.3
	HLA B8	39	17	3.1
Thyrotoxicosis	HLA DW3	53	18	5.1
	HLA B8	44	18	3.6
Type I diabetes (juvenile)	HLA DRw3	27	17	1.8
	HLA DRw4	39	15	3.6
	HLA B8	32	16	2.5
Multiple sclerosis	HLA DRw2	41	22	2.5
	HLA Dw2	47	15	5
Ankylosing spondylitis	HLA B27	90	8	103.5
Reiter's disease	HLA B27	80	9	40.4
Rheumatoid arthritis	HLA DRw4	56	15	7.2
	HLA Dw4	60	12	11

*Normally B8 is in linkage disequilibrium with A1. Presence of B8 alone in juvenile diabetes increases the risk of retinopathy. Data on systemic diseases are from Bodmer and Bodmer (1978)

with a disease state is suspected, it is important to know the relative risk for normal persons in the general populations carrying the same antigen. This can be calculated with the help of the following simple formula:

Relative risk

$$= \frac{\text{HLA +ve patients}}{\text{HLA +ve control}} \times \frac{\text{HLA - ve control}}{\text{HLA - ve patients}}$$

Thus in ankylosing spondylitis, in which 90% of the patients are +ve for HLA B27 as compared to 8% in the control population, the relative risk is 103 (Table 2).

(v) Sometimes HLA association may not be obvious in those diseases where other modifying influences such as incomplete penetrance of the disease gene, varying exposure to external agents, or the presence of modifying genes may affect the expression of the disease. Sometimes genetic factors not connected with the HLA system may contribute to disease susceptibility. This, for example, may be operative in atopy, where genetic factors controlling the level of IgE interact with HLA-linked effects. It is also possible that the disease being studied is heterogeneous and the HLA association is only

with a particular group of individuals having the disease. This is applicable to myasthenia gravis, where definite HLA association is found only in those patients who do not have thymoma.

HLA and eye disease

Following reports 6 years ago (Brewerton *et al.*, 1973a, 1973b) of a close association between HLA B27 and ankylosing spondylitis and acute anterior uveitis there has been almost a rush for the 'gold mine', and there is no dearth of reports in the ophthalmic literature incriminating an HLA antigen in a variety of ocular disorders of unknown aetiology (Tables 2 and 3). Some of the studies are based on logic and reasoning while others originate from sheer enthusiasm to explore new avenues. Consequently, the rules of statistics have been ignored by some and only partially obeyed by others. This has inevitably created chaos and has bewildered those who are desperately trying to keep up with this difficult and new concept of immunological modulation in a variety of histocompatibility-gene-related hereditary, degenerative, and inflammatory diseases of the eye. Unless the study is based on a large series

Table 3 HLA and eye disease

Disease	Reference	Antigens tested	Observed increase in frequency
Ocular cicatricial pemphigoid	Mondino <i>et al.</i> , 1978	A and B loci	A3, B12
Cogan's syndrome	Char <i>et al.</i> , 1975 Kaiser-Kupfer <i>et al.</i> , 1978	A and B loci A and B loci	B17 None
Keratoconus	Gasset <i>et al.</i> , 1977	A and B loci	B27 (only 3 patients studied)
Recurrent herpetic keratitis	Zimmerman <i>et al.</i> , 1977	A and B loci	B5
Primary open-angle glaucoma	Aviner <i>et al.</i> , 1976 Shin and Becker, 1977 Grabner <i>et al.</i> , 1977 Damgaard <i>et al.</i> , 1978 Kass <i>et al.</i> , 1978 Ritch <i>et al.</i> , 1978 David <i>et al.</i> , 1979	A and B loci A and B loci A, B, and C loci A, B, and C loci A and B loci A and B loci A, B, and C loci	Bw35 B7, B12 None None None None None
Pigment dispersion syndrome	Becker <i>et al.</i> , 1977 Kaiser-Kupfer and Mittal, 1978	A and B loci A, B, and C loci	B13 and B17 None
Acute anterior uveitis	Brewerton <i>et al.</i> , 1973 Ehlers <i>et al.</i> , 1974 Woodrow <i>et al.</i> , 1975	A and B loci A and B loci A and B loci	B27 B27 B27
Chronic iridocyclitis (adults)	Ohno <i>et al.</i> , 1977b	A and B loci	B27
Chronic iridocyclitis (juvenile)	Ohno <i>et al.</i> , 1977a	A and B loci	None
Behçet's disease	Ohno <i>et al.</i> , 1978 Ohno <i>et al.</i> , 1978 Jung <i>et al.</i> , 1976	A and B loci A and B loci A and B loci	B5 (Japanese patients) B5 infrequent in American and British patients
Vogt-Koyanagi-Harada syndrome	Tagawa <i>et al.</i> , 1977	A, B, and D loci	Bw54 and LD-wa (Both antigens are exclusive to Japanese)
Chorioretinitis	Bertrams <i>et al.</i> , 1978a	A and B loci	None
Toxoplasmic retinochoroiditis	Ohno <i>et al.</i> , 1977c	A and B loci	None
Malignant melanoma (choroid)	Bertrams <i>et al.</i> , 1978a	A and B loci	Aw32
Retinoblastoma	Bertrams <i>et al.</i> , 1973 Gallie <i>et al.</i> , 1977	A and B loci A, B, and D loci	Bw35 None
Eales's disease	Bertrams <i>et al.</i> , 1978a	A, B, and D loci	None
Presumed ocular histoplasmosis	Godfrey <i>et al.</i> , 1978 Braley <i>et al.</i> , 1978	A, B, and D loci A, B, and D loci	B7 B7
Diabetic retinopathy	Larkin <i>et al.</i> , 1978 Moller <i>et al.</i> , 1978	A, B, and D loci A, B, C, and D loci	B8 (without A1) Juvenile-onset diabetes None (Adult-onset diabetes)
Central serous retinopathy	Bertram <i>et al.</i> , 1978a	A, B, C, and D loci	None
Haemorrhagic maculopathy	Flage <i>et al.</i> , 1977	A, B, and C loci	None
Rhegmatogenous retinal detachment	Bertrams <i>et al.</i> , 1978b	A, B, and C loci	B12
Retinitis pigmentosa (recessive)	Chen <i>et al.</i> , 1978	A, B, and C loci	None
Sjögren's syndrome	Chused <i>et al.</i> , 1977	A, B, and D loci	Dw3

and the results meet all the requirements of statistical significance already outlined, any report on HLA association and eye disease should be treated with reserve. Those who have patience and time should correct the P value if necessary, and calculate the relative risk, because although both of these statistical parameters are important they are often ignored by contributors to ophthalmic journals. Furthermore, it often pays to wait for independent confirmation of a reported finding.

Uveitis

The number of occasions when a specific aetiology of uveitis can be demonstrated or reasonably assumed is rarely more than about 50% and is frequently less, despite thorough investigations. Of all the arthritic conditions ankylosing spondylitis is the one most consistently associated with uveitis. It affects about a quarter of these patients, HLA B27 being present in 85 to 95% of patients with ankylos-

ing spondylitis. In one study (Brewerton *et al.*, 1973a) 52% of 50 patients with anterior uveitis possessed B27, compared with 4% of the control group, and even in the absence of sacroiliitis 8 of 29 (28%) patients with acute anterior uveitis were B27 positive. The very close association of the disease with HLA B27 in Caucasian, Asian, and Japanese populations, suggests a disease susceptibility gene very closely linked to the HLA B locus. It is of interest that although the frequency of B27 is low in Negroes and ankylosing spondylitis may develop in the absence of this antigen, acute anterior uveitis in these B27-negative American Negroes is extremely rare (Khan *et al.*, 1977). Recent studies suggest that the frequency of HLA A2 is also increased in ankylosing spondylitis, but although there is associated increased frequency of HLA Cw1, Cw2, and Dw1 in B27-positive individuals, there is no difference in the distribution of these antigens in healthy persons and patients with ankylosing spondylitis (Sachs and Brewerton, 1978).

Uveitis with ulcers of the buccal mucosa and external genitalia form the triad of Behçet's disease, which is associated with several immunological changes, including the presence of immune complexes in patients' sera (Rahi *et al.*, 1976; Rahi *et al.*, 1979). Although the aetiology of the disease is still unknown, recent studies have shown that a large number of Japanese and Turkish patients possess HLA B5 antigen (Ohno *et al.*, 1978b); this, however, does not appear to be the case in Caucasian populations (Jung *et al.*, 1976; Ohno *et al.*, 1978a).

No HLA association has been found, however, in chronic anterior uveitis of childhood, choroidoretinitis and chronic cyclitis (Table 3).

The Vogt-Koyanagi-Harada syndrome is characterised by bilateral granulomatous uveitis in conjunction with variable degrees of skin and hair depigmentation, hair loss, and meningeal irritation. While the aetiology of this disease is obscure, evidence in favour of an autoimmune component is provided by the demonstration of antibodies to uveal pigment and cell-mediated allergy in the form of delayed skin hypersensitivity, lymphocyte transformation, and leucocyte migration inhibition. A close association with HLA Bw54 and LDwa (a Japanese D locus antigen) suggests the presence of uveitis susceptibility genes in the major histocompatibility system (Tagawa *et al.*, 1977).

Optic neuritis

Multiple sclerosis is much the most important cause of optic neuritis, and over half of the patients presenting with acute optic neuritis as an isolated sign later develop other features of multiple sclerosis.

Although the aetiology of this disease is still unknown, and a virus infection is a strong possibility, it appears that multiple sclerosis is the only disease recognised to be strongly associated with HLA DRw2 and HLA Dw2 antigens in Caucasians. Recently, the syndrome of nephritis and lung haemorrhage (Goodpasture's syndrome), in which Bruch's membrane along with glomerular and other basement membranes is involved (Jampol *et al.*, 1975), in an antibody mediated type II reaction, has been shown to have the same association. Other HLA antigens, such as A3 and B7, also appear to be associated with optic neuritis. It has recently been shown that in patients with isolated optic neuritis the presence of BT101, which is closely related to HLA DRw2, is significantly associated with an increased risk of developing multiple sclerosis, especially in those individuals who develop ocular signs in the winter (Batchelor *et al.*, 1978).

Retinal diseases

Retinal involvement is a well-known complication of diabetes in which genetic, environmental, immunological, metabolic, and hormonal influences interact to produce the clinical picture of the disease. There is increasing evidence of a possible role of virus infection in the juvenile-onset (that is, type I) diabetes, which is often associated with islet cell and other organ-specific autoantibodies. Population studies have shown that there is an increased relative risk of developing type I diabetes in persons who are HLA Dw3 and DRw3 positive, with secondary association with HLA A1, B8, or B18, and in subjects who are Dw4 and DRw4 positive with secondary association with A2, B15, B40, and Cw3 (Cudworth and Festenstein, 1978). Owing to linkage disequilibrium HLA A1 is often associated with HLA B8, and therefore in only about 4% of the control population is B8 present in the absence of A1, as opposed to 56% of patients with juvenile diabetes with retinopathy. It has been concluded, therefore, that the presence of HLA B8 singly in patients with type I diabetes carries a bad prognosis (Larkins *et al.*, 1978). There is no evidence of HLA association, however, in retinopathy due to type II adult-onset diabetes (Moller *et al.*, 1978).

Studies on HLA association with a variety of other retinal diseases such as choroidoretinitis, toxoplasmic retinochoroiditis, Eales's disease, retinal detachment, haemorrhagic maculopathy, central serous retinopathy, and retinitis pigmentosa have been so far negative except in choroidoretinitis due to presumed histoplasmosis, in which increased frequency of HLA B7 has been reported (see Table 3 for references).

Glaucoma

The association of primary open-angle glaucoma with HLA antigens appears to be spurious, and although the increased incidence of antinuclear antibody in these patients is still controversial (Felberg *et al.*, 1977; Nagasubramanian *et al.*, 1978) recent reports from several countries (see Table 3) clearly show that there is no association between histocompatibility antigens and the propensity to develop a raised intraocular pressure with consequent loss of vision.

Intraocular tumours

The HLA system does not appear to exert any strong influence on the susceptibility of an individual to develop malignant disease. It is not surprising, therefore, that an earlier report of a possible HLA association with retinoblastoma (Bertrams *et al.*, 1973) has not been confirmed by other workers (Gallie *et al.*, 1977). There is some evidence, however, that malignant melanoma of the choroid may be associated with HLA Aw32, but this awaits confirmation.

Sjögren's syndrome

This condition predominates among women and in its fully developed form is characterised by keratoconjunctivitis sicca, xerostomia, and arthritis. Many patients have demonstrable rheumatoid factor in their sera, and Sjögren's syndrome specific (SS A and SS B) and non-specific antinuclear and anti-salivary duct antibodies are also demonstrable in a proportion of these patients (Alspaugh *et al.*, 1976). The aetiology of Sjögren's syndrome is unknown, but a T-lymphocyte-mediated autoimmunity to a cellular component of salivary gland is strongly suspected. It is of interest, therefore, that increased frequency of HLA Dw3 has been reported in these patients (Chused *et al.*, 1977).

Myasthenia gravis

Ocular symptoms in myasthenia gravis include ophthalmoplegia, paresis of accommodation, inadequate convergence, and diplopia, though occasionally the disturbance may be limited to a degree of ptosis. Autoantibodies and T cell sensitisation to acetylcholine receptors are believed to play a pathogenetic role. About 30% of such patients show the presence of HLA B8 and HLA Dw3. It is of interest that HLA B8 is present in increased frequency in a number of autoimmune diseases, and it has been postulated that HLA B8 gene is closely

concerned with T cell activity, especially suppressor T cell function, and this could account for the presence of several other unrelated autoantibodies in the sera of patients with myasthenia gravis.

Endocrine exophthalmos

At least half of thyrotoxic individuals develop signs of ocular involvement in the form of exophthalmos. The disease is often associated with a recently recognised autoantibody known as human specific thyroid stimulator; which, apart from stimulating the thyroid directly, facilitates binding of the exophthalmos-producing substance (a fragment of thyroid stimulating hormone) to the orbital tissues. As in other autoimmune disease there is a strong association between thyrotoxicosis and HLA B8 and HLA Dw3.

External disease of the eye

A high incidence of HLA A3 and B12 has been reported in ocular cicatricial pemphigoid (Mondino *et al.*, 1978), and HLA B5 is found in increased frequency in patients with recurrent herpetic keratitis. (Zimmerman *et al.*, 1977), but these claims await confirmation. Similarly, in a family study of keratoconus the mother and her 2 children were HLA B27 positive (Gassett *et al.*, 1977). It is of interest that a proportion of patients with keratoconus (which is a noninflammatory disease) are atopic and produce high levels of IgE (Rahi *et al.*, 1977). A high incidence of HLA B17 has been reported in Cogan's syndrome (Char *et al.*, 1975), but a recent report has failed to confirm this claim (Kaiser-Kupfer *et al.*, 1978).

In conclusion it may be said that apart from acute anterior uveitis, optic neuritis, and certain other autoimmune diseases such as myasthenia gravis and thyrotoxicosis, in which the eye is invariably involved, there is very little evidence of HLA association with other diseases of the eye. It is important not to be overenthusiastic about an apparently complex association with different antigens in studies based on a limited number of cases. Furthermore, strong positive association with one HLA antigen will necessarily entail negative association with other antigens, which may lead us to believe that the latter play a protective role. Such negative associations are difficult to establish, although one has been claimed for glaucoma (Shin and Becker, 1977), because the frequency of most antigens is already low and a further decrease is often unlikely to be judged as significant. Finally, so far, none of the HLA associations with disease is absolute. Even in the case of ankylosing spondylitis,

although over 90% of persons with the disease may be positive for HLA B27, only a relatively small proportion of the population with B27 ever suffer from the disease.

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References

- Alspaugh, M. A., Talal, D., and Tan, E. M. (1976). Differentiation and characterization of autoantibodies and their antigens in Sjögren's syndrome. *Arthritis and Rheumatism*, **19**, 216–222.
- Aviner, Z., Henley, W. L., Fotino, M., and Leopold, I. H. (1976). Histocompatibility (HLA) antigens and primary open-angle glaucoma. *Tissue Antigens*, **7**, 193–200.
- Batchelor, J. R., Compston, A., and McDonald, W. I. (1978). HLA and multiple sclerosis. *British Medical Bulletin*, **34**, 279–284.
- Becker, B., Shin, D., Cooper, D. G., and Kass, M. A. (1977). The pigment dispersion syndrome. *American Journal of Ophthalmology*, **83**, 161–166.
- Bertrams, J., Schildberg, P., Höpping, W., Böhme, W., and Albert, E. (1973). HLA—antigens in retinoblastoma. *Tissue Antigens*, **3**, 78–87.
- Bertrams, J., Spitznas, M., Rommel-Fanger, M. (1978a). Missing evidence for HLA antigens association with Eales' disease, chorioretinitis, central serous retinopathy and malignant choroidal melanoma. *Investigative Ophthalmology*, **17**, 918–920.
- Bertrams, J., Spitznas, M., and de Souza, N. V. (1978b). HLA—antigens in patients with rhegmatogenous retinal detachment. *Klinische Monatsblätter für Augenheilkunde*, **173**, 786–790.
- Bodmer, W. F. (1978). The HLA system: Introduction. *British Medical Bulletin*, **34**, 213–216.
- Bodmer, W. F., and Bodmer, J. G. (1978). Evolution and function of the HLA system. *British Medical Bulletin*, **34**, 309–316.
- Brale, R. E., Meridith, T. A., Aaberg, T. M., Koethe, S. M., and Witkowski, J. A. (1978). The prevalence of HLA-B7 in presumed ocular histoplasmosis. *American Journal of Ophthalmology*, **85**, 859–861.
- Brewerton, D. A., Caffrey, M., Hart, F. D., James, D. C. O., Nicholls, A., and Sturrock, R. D. (1973a). Ankylosing spondylitis and HLA 27. *Lancet*, **1**, 904–907.
- Brewerton, D. A., Caffrey, M., Nicholls, A., Walters, D., and James, D. C. O. (1973b). Acute anterior uveitis and HLA-27. *Lancet*, **2**, 994–996.
- Char, D. H., Cogan, D. G., and Sullivan, W. R. (1975). Immunologic study of nonsyphilitic interstitial keratitis with vestibulo-auditory symptoms. *American Journal of Ophthalmology*, **80**, 491–494.
- Chen, M. C., Marak, G. E., and Pilkerton, A. R. (1978). The incidence of HLA-SD antigens in recessive retinitis pigmentosa. *British Journal of Ophthalmology*, **62**, 172–173.
- Chused, T. M., Kassan, S. S., Opelz, G., Moutsopoulos, H. M., and Terasaki, P. I. (1977). Sjögren's syndrome associated with HLA-Dw3. *New England Journal of Medicine*, **296**, 895–897.
- Cudworth, A. G., and Festenstein, H. (1978). HLA genetic heterogeneity in diabetes mellitus. *British Medical Bulletin*, **34**, 285–289.
- Damgaard-Jensen, L., and Kissmeyer-Nielsen, F. (1978). HLA histocompatibility antigen in open angle glaucoma. *Acta Ophthalmologica*, **56**, 384–388.
- David, R., Maier, G., Baumarten, I., and Abrahams, C. (1979). HLA antigens in glaucoma and ocular hypertension. *British Journal of Ophthalmology*, **63**, 293–296.
- Dick, H. M. (1978). HLA and Disease: introductory review. *British Medical Bulletin*, **34**, 271–274.
- Edwards, J. H. (1974). HLA and disease: the detection of association. *Journal of Immunogenetics*, **1**, 249–257.
- Ehlers, N., Kissmeyer-Nielsen, F., Kjerbye, K. E., and Lamm, L. U. (1974). HLA-27 in acute and chronic uveitis. *Lancet*, **1**, 99.
- Felberg, N. T., Leon, S. A., Gasparini, J., and Spaeth, G. L. (1977). A comparison of antinuclear antibodies and DNA-binding antibodies in chronic open-angle glaucoma. *Investigative Ophthalmology*, **16**, 757–760.
- Flage, T., Bratberg, A., and Syrdalen, P. (1977). Haemorrhagic maculopathy in young adults. *Acta Ophthalmologica*, **55**, 489–496.
- Gallie, B. L., Dupont, B., Whitsett, G., Kitchen, F. D., Ellsworth, R. M., and Good, R. A. (1977). Histocompatibility typing in spontaneous regression of retinoblastoma. In *HLA and Malignancy*. Edited by G. P. Murphy. *Progress in Clinical and Biological Research*, **16**, 229–237.
- Gasset, A. R., Richman, A. V., and Frias, J. L. (1977). HLA antigens in keratoconus. *Annals of Ophthalmology*, **9**, 767–768.
- Gill, T. J., Cramer, D. V., and Kunz, H. W. (1978). The major histocompatibility complex—comparison in the mouse, man and the rat. *American Journal of Pathology*, **90**, 735–778.
- Godfrey, W. A., Sabates, R., and Cross, D. E. (1978). Association of presumed ocular histoplasmosis with HLA-B7. *American Journal of Ophthalmology*, **85**, 854–858.
- Grabner, G., and Mayr, W. R. (1977). Histokompatibilitäts antigene (HLA-Antigene) und offen winkel-glaukom. *Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie*, **202**, 75–79.
- Jampol, L. E., Lahav, M., Albert, D. M., and Craft, J. (1975). Ocular findings and basement membrane changes in Goodpasture's syndrome. *American Journal of Ophthalmology*, **79**, 452–463.
- Jung, R. T., Chalmers, T. M., and Joysey, V. C. (1976). HLA in Behçet's disease. *Lancet*, **1**, 694.
- Kaiser-Kupfer, M. I., and Mittal, K. K. (1978). The HLA and ABO antigens in pigment dispersion syndrome. *American Journal of Ophthalmology*, **85**, 368–372.
- Kaiser-Kupfer, M. I., Del Valle, L. A., Mittal, K. K., and Haynes, B. F. (1978). HLA and Cogan's syndrome. *New England Journal of Medicine*, **298**, 1094–1095.
- Kass, M. A., Palmberg, P., Becker, B., and Miller, J. P. (1978). Histocompatibility antigens and primary open-angle glaucoma: A reassessment. *Archives of Ophthalmology*, **96**, 2207–2208.
- Khan, M. A., Kushner, I., and Braun, W. E. (1977). Comparison of clinical features in HLA-B27 positive and negative patients with ankylosing spondylitis. *Arthritis and Rheumatism*, **20**, 909–912.
- Larkins, R. G., Martin, F. I. R., and Tait, B. D. (1978). HLA patterns and diabetic retinopathy. *British Medical Journal*, **1**, 1111.
- Moller, E., Persson, B., and Sterky, G. (1978). HLA phenotypes and Diabetic retinopathy. *Diabetologia*, **14**, 155–158.
- Mondino, B. J., Brown, S. I., and Rabin, B. S. (1978). HLA-antigens in ocular cicatricial pemphigoid. *British Journal of Ophthalmology*, **62**, 265–267.
- Nagasubramanian, S., Rahi, A. H. S., and Gloster, J. (1978). Immunological investigations in chronic simple glaucoma. *Transactions of the Ophthalmological Societies of the United Kingdom*, **98**, 22–27.
- Ohno, S., Char, D. H., Kimura, S. J., and O'Connor, G. R. (1977a). HLA antigens and antinuclear antibody titres in juvenile chronic iridocyclitis. *British Journal of Ophthalmology*, **61**, 59–61.

- Ohno, S., Char, D. H., Kimura, S. J., and O'Connor, G. R. (1978a). Studies on HLA antigens in American patients with Behçet's disease. *Japanese Journal of Ophthalmology*, **22**, 58–61.
- Ohno, S., Kimura, S. J., O'Connor, G. R., and Char, D. H. (1977b). HLA antigens and uveitis. *British Journal of Ophthalmology*, **61**, 62–64.
- Ohno, S., O'Connor, G. R., and Kimura, S. J. (1977c). HLA antigens and toxoplasmic retinochoroiditis. *Tohoku Journal of Experimental Medicine*, **123**, 91–94.
- Ohno, S., Sugiura, S., Itakura, K., and Aizawa, M. (1978b). Further studies on HLA antigens in Behçet's disease. *Japanese Journal of Ophthalmology*, **22**, 62–67.
- Rahi, A., Davies, P., Ruben, M., Lobascher, D., and Menon, J. (1977). Keratoconus and coexisting atopic disease. *British Journal of Ophthalmology*, **61**, 761–764.
- Rahi, A. H. S., Hoborow, E. J., Perkins, E. S., and Dinning, W. J. (1979). What is endogenous uveitis? In *Immunology and Immunopathology of the Eye*. Edited by A. M. Silverstein and G. R. O'Connor. Masson Publishing Inc.: New York (In press).
- Rahi, A. H. S., Holborow, E. J., Perkins, E. S., Gungen, Y. Y., and Dinning, W. J. (1976). Immunological investigations in uveitis. *Transaction of the Ophthalmological Societies of the United Kingdom*, **96**, 113–122.
- Ritch, R., Podos, S. M., Henley, W., Moss, A., Southren, A. L., and Fotino, M. (1978). Lack of association of histocompatibility antigens with primary open-angle glaucoma. *Archives of Ophthalmology*, **96**, 2204–2206.
- Sachs, J. A., and Brewerton, S. A. (1978). HLA, ankylosing spondylitis and rheumatoid arthritis. *British Medical Bulletin*, **34**, 275–278.
- Seager, K., Bashir, H. V., Geczy, A. F., Edmonds, J., and de Vere-Tyndall, A. (1979). Evidence for a specific B27 associated cell surface marker on lymphocytes of patients with ankylosing spondylitis. *Nature*, **277**, 68–70.
- Shin, D. H., and Becker, B. (1977). HLA-A11 and HLA-Bw35 and resistance to glaucoma in white patients with ocular hypertension. *Archives of Ophthalmology*, **95**, 423–424.
- Shin, D. H., Becker, B., Waltman, S. R., Palmberg, P. F., and Bell, C. E. (1977). The prevalence of HLA-B12 and HLA-B7 antigens in primary open-angle glaucoma. *Archives of Ophthalmology*, **95**, 224–225.
- Svejgaard, A., Jersild, C., Nielsen, L. S., and Bodmer, W. F. (1974). HLA antigens and disease of statistical and genetical considerations. *Tissue Antigens*, **4**, 95–105.
- Tagawa, Y., Sugiura, S., Yakura, H., Wakisaka, A., Aizawa, M., and Itakura, K. (1977). HLA and Vogt-Koyanagi-Harada syndrome. *Japanese Journal of Ophthalmology*, **21**, 22–27.
- Woodrow, J. C., Mapstone, R., Anderson, J., and Usher, N. (1975). HLA-27 and anterior uveitis. *Tissue Antigens*, **6**, 116–120.
- Woolf, B. (1955). On estimating the relation between blood group and disease. *Annals of Human Genetics*, **19**, 251–253.
- Zimmerman, T. J., McNeill, J. I., Richman, A., Kaufman, H. E., and Waltman, S. R. (1977). HLA types and recurrent corneal herpes simplex infection. *Investigative Ophthalmology*, **16**, 756–757.