Diseases associated with specific HL-A antigens

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Summary: Significantly increased prevalences of particular HL-A antigens have been reported for many human diseases. The correlation is particularly striking in ankylosing spondylitis, Reiter's syndrome, psoriasis and some immunopathic disorders, so that HL-A typing may be of great value in diagnosis. The possible mechanisms whereby these associations may occur suggest the cause of certain disorders, and further investigation will likely help in the understanding of the pathogenesis of many diseases.

Résumé: *Présence d'antigènes spécifiques du système HL-A dans de nombreuses pathologies humaines*

On retrouve de plus en plus d'antigènes particuliers du système HL-A dans de nombreuses maladies chez l'homme. La corrélation est singulièrement frappante dans la spondylarthrite ankylosante, le syndrome de Reiter, le psoriasis et certains troubles immunologiques. Il ressort de cette constatation que le typage de l'antigène HL-A peut avoir une grande valeur diagnostique. La découverte des mécanismes par lesquels ces associations peuvent survenir permettrait de trouver la cause de certaines maladies, et des études plus approfondies dans ce domaine aideront probablement à mieux comprendre la pathogénie de nombreuses maladies.

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The HL-A (human leukocyte-locus A) system is now regarded as the main leukocyte isoantigen system in man. Recognition of HL-A antigens began in the early 1950s with the detection of leukoagglutinating antibodies in multitransfused patients, the antibodies developing as an immunologic response directed against foreign isoantigens present on leukocytes in transfused blood. A similar immunization was found to occur in pregnant women, the antibodies being directed against isoantigens of the husband's leukocytes. With the use of these immune sera a number of different isoantigens were identified on human leukocytes, and through family studies the leukocyte isoantigens of each individual were found to be products of a single locus (HL-A) on each member of one specific pair of chromosomes.[1] It is presently accepted that the HL-A locus consists of two subloci, each responsible for one antigen. Thus, in general, four different types of HL-A antgiens can be detected on leukocytes of one individual. The nomenclature of presently known HL-A antigens is shown in Table I. In vitro studies have shown that the same HL-A antigens are present on most nucleated cells of an individual, and it is now generally agreed that the HL-A system is most probably a major histocompatibility system in man.[2]

Recently another aspect of biologic significance of the HL-A system in man has emerged: that is, a possible association of particular HL-A antigens with certain disease states.[3] Correlation of histocompatibility antigens with certain pathologic conditions has been established in mice and other animal species,[4] and similar studies in man have become available because of advances in serologic typing of leukocyte antigens. The findings from these studies are of more than academic interest and possibly of diagnostic value in certain diseases. The purpose of this paper is to review the published data on this subject and to cite some possible clinical applications.

Reported studies

Data concerning the association of HL-A antigens with disease states are based on statistical analysis of the prevalence of a particular antigen in a group of patients with a specific disease in comparison with the prevalence in a control population. Various diseases in which a significant association with HL-A antigens has been found are listed in Table II. These diseases may be grouped into two broad categories: (a) lymphomas and leukemias, and (b) immunopathic or rheumatic diseases. There have also been reports of a few other diseases, such as sarcoidosis, multiple sclerosis, malignant melanoma and breast cancer, in which such an association may exist.

Table I—HL-A antigen nomenclature*

First series	Second series
HL-A1	HL-A
HL-A2	HL-A7
HL-A3	HL-A8
HL-A9	HL-A12
HL-A10	HL-A13
HL-A11	W5
W23	W10
W24	W14
W25	W15
W26	W16
W28	W17
W29	W18
W30	W21
W31	W22
W32	W27

*Amos *et al* [42]

Lymphomas and leukemias

Hodgkin's disease: While HL-A typing was still in a relatively new and developing stage, Amiel[5] in 1967 reported data showing an increased prevalence of one HL-A specificity (then called 4c) in 41 patients with Hodgkin's disease compared with 44 controls (51% *v.* 27%). This finding was later confirmed by Zervas, Delamore and Israels,[6] and Thorsby and colleagues,[7] who found an increased prevalence of HL-A5 (now known to be included in the designation 4c) in patients with this disease. In the study of Zervas *et al*[6] HL-A5 was found in 63% of 27 patients and in 19% of 68 controls. Thorsby *et al*[7] noted HL-A5 in 24% of 78 patients and in 9% of 65 controls. Subsequently there have been reports of a significantly increased prevalence of W5 (another 4c-related antigen) in patients with this disease; Morris and Forbes[8] found W5 in 32% of 127 patients, compared with 12% of 273 controls; and Van Rood and Van Leeuwen[9] found W5 in 33% of 98 patients, compared with 18% of 400 controls.

Non-Hodgkin's lymphomas: Morris and Forbes[10] reported a significantly increased prevalence of HL-A12 in 56 patients with follicular lymphomas compared with 273 controls (63% *v.* 32%). They also reported a considerably, but not significantly, greater prevalence of HL-A7 in 50 patients with lymphosarcoma compared with 273 controls (40% *v.* 25%), and of HL-A12 in 28 patients with reticulum cell sarcoma compared with the same controls (50% *v.* 32%).

Infectious mononucleosis: A significant association of infectious mononucleosis with antigen W5 was found by Morris and Forbes:[10] the antigen was noted in 33% of 40 patients, compared with 12% of 273 controls. Noting the similar association of W5 with Hodgkin's disease, these authors suggested a possible viral cause for Hodgkin's disease, as for infectious mononucleosis.

Leukemias: Walford and colleagues[11] found a significantly increased prevalence of HL-A12 in 16 patients with acute lymphocytic leukemia of childhood compared with 100 controls (75% *v.* 29%). Degos, Drolet and Dausset[12] reported no significant association of chronic lymphocytic leukemia with any of the HL-A antigens; however, they found a significantly decreased prevalence (an inverse correlation) of HL-A12 in 47 patients with chronic myeloid leukemia compared with 450 controls (96% *v.* 31%). Jeannet and Magnin[13] found no significant association of acute myeloid leukemia with HL-A type.

Jeannet and Magnin[13] also studied HL-A antigens in 147 patients with various malignant diseases (lymphomas, leukemias and cancers of breast and lung). The only striking finding was an almost complete absence (2%) of HL-A11 in this group of patients compared with a 16% prevalence in 305 controls.

Immunopathic and rheumatic diseases

Chronic glomerulonephritis: In view of the application of HL-A typing in kidney transplantation, chronic glomerulonephritis was one of the earliest diseases studied for a possible association with HL-A antigens. Patel, Mickey and Terasaki[14] in 1969 reported their study on HL-A typing of 485 patients with chronic glomerulonephritis of a variety of diagnostic categories in comparison with 428 controls. They found a relatively less striking but significant difference in the prevalence of HL-A2 between the patient and control groups (52% *v.* 42%). There has been no subsequent report concerning this disease, probably because a large number of patients have to be studied in order to obtain a meaningful result.

Systemic lupus erythematosus: A significantly increased prevalence of HL-A8 and W15 in patients with systemic lupus erythematosus was reported by Grumet and colleagues:[15] they found HL-A8 in 33% of 40 patients, compared with 16% of 82 controls; and W15 in 40% of the same patients, compared with 11% of the same controls. Waters, Konrad and Walford[16] also reported an increased prevalence of W15-related antigens in a group of patients with this disease.

Adult celiac disease: Stokes and colleagues[17] reported a significantly increased prevalence of HL-A1 in 49 patients with adult celiac disease compared with 159 controls (78% *v.* 33%), and a similarly increased prevalence of HL-A8 in the same patients compared with the controls (80% *v.* 30%). The prevalence of a combination of HL-A1 and HL-A8 was also found to be significantly higher in the patients compared with the controls (75% *v.* 20%). Another study, by Falchuk, Rogetine

Table II—Diseases and associated HL-A antigens

Disease	HL-A antigens associated	Patients: No. tested (% positive)	Controls: No. tested (% positive)	Reference no.
Lymphomas and leukemias				
Hodgkin's disease	W5	127 (32)	273 (12)	8
"	W5	38 (33)	400 (18)	9
Follicular lymphoma	12	56 (63)	273 (32)	10
Lymphosarcoma	—	50	273	10
Reticulum cell sarcoma	—	28	273	10
Acute lymphoid leukemia	12	16 (75)	100 (29)	11
Chronic lymphoid leukemia	—	44	450	12
Acute myeloid leukemia	—	25	305	13
Chronic myeloid leukemia	—12*	47 (6)	450 (31)	12
Immunopathic or rheumatic diseases				
Chronic glomerulonephritis	2	485 (52)	428 (42)	14
Systemic lupus erythematosus	8	40 (33)	82 (16)	15
"	W15	40 (40)	82 (11)	15
Adult celiac disease	1	49 (78)	159 (33)	17
"	8	44 (88)	159 (30)	17
"	1 & 8	49 (75)	159 (20)	17
Chronic active hepatitis	1	33 (60)	350 (31)	19
"	8	33 (68)	350 (18)	19
Childhood asthma	1	35 (43)	891 (29)	20
Myasthenia gravis	8	100 (59)	533 (19)	22
Psoriasis	13	44 (27)	89 (3)	23
"	13	156 (15)	386 (5)	24
"	W17	44 (23)	89 (9)	23
"	W17	156 (26)	386 (8)	24
Ankylosing spondylitis	W27	40 (88)	906 (8)	25
"	W27	75 (96)	75 (4)	26
Reiter's syndrome	W27	33 (76)	33 (6)	29
"	W27	24 (96)	1863 (8)	30
Juvenile rheumatoid arthritis	W27	26 (42)	267 (6)	31
Rheumatoid arthritis	—	104	102	32
"	—	119	906	25
Gout	—	66	906	25
Rheumatic fever	—3*	76 (15)	177 (28)	33
Other diseases				
Infectious mononucleosis	W5	40 (33)	273 (12)	10
Sarcoidosis	—	132	60	32
Multiple sclerosis	3	94 (40)	871 (24)	34
"	7	107 (39)	800 (26)	35
Malignant melanoma	—	29	20	36
Breast cancer	—	200	—	37

— = No significantly associated HL-A antigen found.
*Significantly lower incidence (inverse correlation).

and Stober,[18] also showed a significantly increased prevalence of HL-A8 in this disease.

Chronic active hepatitis: A significantly increased prevalence of HL-A1 in 37 patients with chronic active hepatitis compared with 350 controls (60% *v.* 31%), and a similarly increased prevalence of HL-A8 in the same patients compared with the controls (68% *v.* 18%) was reported by Mackay and Morris.[19] They also noted a close correlation between a positive LE cell test and the presence of the two antigens. Citing the reported high prevalence of HL-A8 in systemic lupus erythematosus[15] and celiac disease,[17] Mackay and Morris speculated that HL-A8 is probably associated with an enhanced immune response to certain autoantigens, thereby predisposing to the development of autoimmune diseases.

Allergic diseases: Thorsby and Lee[20] reported a significantly increased prevalence of HL-A1 in 35 patients with childhood asthma compared with 891 controls (43% *v.* 29%). They also noted a considerably increased prevalence of the haplotype HL-A1,8 in these patients compared with the controls (15% *v.* 8%), but the difference was not significant.

Marsh and colleagues[21] found a greater prevalence of HL-A7 and its crossreacting antigens (W10, W22 and W27) in 18 allergic patients responsive to a minor ragweed pollen allergen, Ra5, compared with 77 nonresponsive controls.

Myasthenia gravis: A significantly increased prevalence of HL-A8 in 100 patients with myasthenia gravis compared with 533 controls (59% *v.* 19%) was reported by Feltkamp and colleagues.[22] They noted that the association with HL-A8 was more striking in the female patients.

Psoriasis: Russell, Schulters and Kuban[23] reported a significantly increased prevalence of HL-A13 in 44 patients with psoriasis compared with 89 controls (27% *v.* 3%), and a considerably greater prevalence of W17 in the same patients (23%) compared with the controls (23% *v.* 9%). A simultaneous study by White and colleagues[24] also revealed that both of these antigens were present in a significantly larger proportion of their patients than in their controls: HL-A13 was found in 15% of 156 patients, compared with 5% of 386 controls; and W17 in 26% of the patients, compared with 8% of the controls. In the patient group there was also a significantly decreased prevalence of HL-A12, but this finding was not confirmed in their later study of an additional 300 patients.

Ankylosing spondylitis: A significantly increased prevalence of antigen W27 in 40 patients with ankylosing spondylitis compared with 906 controls (88% *v.* 8%) was reported by Schlosstein and colleagues.[25] A simultaneous study by Brewerton and colleagues[26] showed a similarly increased incidence of W27 in 75 patients compared with 75 controls (96% *v.* 40%). In a study by Russell and colleagues,[27] of 60 patients with Crohn's disease 7 were found to have ankylosing spondylitis and W27 was present in only these 7 patients. Among 31 patients with inflammatory bowel disease studied by Morris and colleagues[28] there were 8 patients with ankylosing spondylitis; W27 was found in 6 of these 8 but in none of the patients with spondylitis.

Reiter's syndrome: Brewerton and colleagues[29] reported a significantly increased prevalence of W27 in patients with Reiter's syndrome: 76% of 33 patients, compared with 6% of 33 controls, were found to have this antigen. A subsequent study by Morris and associates[30] showed an even more striking association of W27 with this syndrome: 96% of 24 patients, compared with 8% of 1863 controls, were found to have this antigen. Morris and associates proposed that W27 may be a useful marker in the differentiation of Reiter's syndrome from gonococcal arthritis.

Juvenile rheumatoid arthritis: Rachelefsky and associates[31] reported a significantly increased prevalence of W27 in patients with juvenile rheumatoid arthritis: 42% of 26 patients, compared with 6% of 267 controls, were found to have this antigen. These authors also noted a decreased prevalence of HL-A1 in the same patients: 11% of patients compared with 35% of controls had this antigen. This difference was not significant.

Rheumatoid arthritis: In two studies no distinct association was found between HL-A antigens and rheumatoid arthritis. Keuppers, Brackertz and Mueller-Eckhardt[32] compared 104 patients with 102 control subjects and Schlosstein and colleagues[25] studied 119 patients and 906 controls.

Gout: Schlosstein and colleagues[25] found no association of gout with HL-A antigens in a study of 66 patients.

Rheumatic fever: Falk and colleagues[33] reported a significantly decreased prevalence of HL-A3 in 76 patients with rheumatic fever or rheumatic heart disease compared with 177 healthy controls (15% *v.* 28%). The total number of HL-A antigens detected was significantly less among the patients than the controls.

Other diseases

Sarcoidosis: No association of sarcoidosis with HL-A type was found by Kueppers and colleagues[32] in a study of 132 patients and 600 controls.

Multiple sclerosis: Naito and associates[34] reported a significantly increased prevalence of HL-A3 in 93 patients with multiple sclerosis compared with 871 controls (40% *v.* 24%) in the Los Angeles area. Jersild and Fog,[35] on the other hand, found a significantly increased prevalence of HL-A7 in 107 patients compared with 800 controls (39% *v.* 26%) in Denmark. The prevalence of HL-A7 did not differ between the patient and control groups in the study by Naito *et al.*[34] Presumably the geographic or ethnic background accounts for this discrepancy.

Malignant melanoma: None of 29 patients with malignant melanoma in a study by Clark and colleagues[36] had HL-A5 but 6% of 20 healthy controls did. This inverse correlation, however, was not significant.

Breast cancer: In a study by Van Rood[37] of over 200 patients with breast cancer no distinct association with HL-A type was revealed. Van Rood, however, suggested further extended studies in this disease.

Discussion

McDevitt and Bodmet[38] in 1972, citing several reported associations of HL-A antigens with some diseases (Hodgkin's disease, lymphocytic leukemia, chronic glomerulonephritis and systemic lupus erythematosus), suggested that the available clinical evidence must be regarded as fragmentary and inconclusive, although the correlations clearly justified further studies.

More convincing data of an association of HL-A type with disease have been reported from several more recent studies on patients with certain diseases of immunopathic or rheumatic nature with familial occurrence. With most of these diseases more than one confirmatory report has appeared. Evidence now seems to be strong for the following associations: (a) W27 with ankylosing spondylitis and Reiter's syndrome; (b) HL-A13 and W17 with psoriasis; (c) HL-A8 with certain autoimmune-type diseases such as adult celiac disease, chronic active hepatitis and systemic lupus erythematosus; and (d) probably W5 with Hodgkin's disease.

These associations of HL-A antigens with certain diseases suggest that a particular antigen might influence an individual's susceptibility to a particular disease. Although the mechanism for this in man is unknown, at least three models have been proposed from animal studies.[38] The first is that the histocompatibility antigens represent specific receptor sites for the attachment of a pathogenic agent such as a virus;

the cells having such a surface configuration might be unusually susceptible to that particular pathogen. The second possible mechanism involves the phenomenon of crosstolerance (or molecular mimicry), whereby pathogenic antigens mimic certain histocompatibility antigens; susceptible hosts would mistake viral or tumour antigens for self-antigens and therefore fail to react adequately to control the pathologic process. The third possibility is the existence of "immune response genes", which are closely linked to the histocompatibility genes and control the ability of a host to react to a particular antigen;[39] such genes may also be linked to or strongly influenced by the HL-A genes in man.[40] Thus, in families with a high prevalence of a single disease it may be possible to find an association between the disease susceptibility and one HL-A locus irrespective of individual HL-A antigenic specificities.

Whatever the mechanism, all the reported correlations between HL-A antigens and specific diseases are not absolute but only statistical, which suggests multifactorial control of an individual's susceptibility to a disease.

In addition to the possible diagnostic value of HL-A typing, there also seems to be a prognostic value. Falk and Osoba[41] reported a significantly greater prevalence of HL-A8 in a subgroup of long-term (more than 5 years) survivors of Hodgkin's disease, compared with patients with recent onset of the same disease or a control population, suggesting a possible association of HL-A8 with relative resistance to the disease. A similar analysis may prove useful in predicting the course for patients with some other diseases.

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