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A Clinical and Epidemiological Study of Human Leukocyte Antigen-DPB Alleles in Hodgkin's Disease[1]

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ABSTRACT

An international study to investigate the role of human leukocyte antigen (HLA)-DPB alleles in Hodgkin's disease was conducted with 17 participating centers in 12 countries. A total of 741 patients and 686 controls were typed using polymerase chain reaction amplification of HLA-DPB alleles and subsequent sequence specific oligonucleotide hybridization. The frequency of HLA-DPB1*0301 was found to be significantly increased in white patients, compared with ethnically matched controls. In this population group, the DPB1*0301 allele is associated with a relative risk of 1.95 ($P < 0.01$). There was also a significant reduction in the frequency of HLA-DPB1*0401 in patients from Japan and Taiwan (relative risk, 0.15; $P < 0.01$). Clinical analysis from data on 551 patients demonstrated a significantly inferior remission duration in patients with HLA-DPB1*0901, overall ($P < 0.05$), and in the Japanese and Taiwanese populations ($P = 0.02$), where this allele is most prevalent. This analysis suggests an epidemiological as well as a possible prognostic association between HLA-DPB alleles and Hodgkin's disease.

INTRODUCTION

Immunological abnormalities in patients, conferring susceptibility to infections, have been recognized in Hodgkin's disease virtually from its initial description. The first case of Hodgkin's had evidence of concomitant tuberculosis at the time of death (1). Patients with Hodgkin's disease are also prone to other opportunistic infections (2). There is evidence for impaired immunity at presentation in Hodgkin's disease, and this may correlate adversely with survival (3).

The first association between human major histocompatibility complex and disease was in Hodgkin's disease (4), with an increased frequency of antigen 4c (a mosaic of specificities including HLA[4]-B15, -Bw35, -B5, and -B18) in patients. Since the initial study by Amiel (4), several other studies investigating the role of HLA in Hodgkin's disease have reaffirmed the initial observations (5–17). Some of these studies were performed on a heterogeneous collection of patients, with a wide distribution in age, stage, histology, and outcome to therapy. In addition, as a significant number of these studies were retrospective, for practical reasons, there was probable inadvertent positive selection for survivors; patients who succumbed early to disease were probably underrepresented in these analyses. Allowing for these reservations, a consistent trend emerges, with an increased frequency of HLA-A1 and B8 (4, 16). Prospective studies, conducted to assess the true relevance of these subtypes, also produced similar results, the most consistent feature being an excess of HLA-A1 (10, 15, 16). The increase in HLA-A1 was more significant when results were combined with retrospective studies (16). Pooling data from all these studies points to a weak increase in susceptibility to Hodgkin's disease, associated with HLA-A1, -B5, -B8, and -B18, increasing the relative risk of Hodgkin's disease between 1.3- and 1.5-fold (16).

The importance of HLA in Hodgkin's disease has also received independent confirmation from family studies, where there is more than one affected individual. In affected sibling studies, a significantly greater excess of HLA identity is observed, compared with the expected trend from Mendelian segregation (16). A greater degree of HLA concordance persists when cousins with Hodgkin's disease are typed (16).

A large number of studies have linked certain HLA antigens with susceptibility to and survival following Hodgkin's disease. The ability to accurately type class I antigens led to most of the initial studies focusing on HLA class I disease associations. A number of subsequent studies investigated the role of HLA-DR in Hodgkin's disease, with no significant association emerging (12, 15, 16). In 1989, Bodmer *et al.* (18) described a study using restriction fragment length polymorphism to type patients with Hodgkin's disease, comparing the results with an equal number of controls. A significant reduction in the restriction fragment length polymorphism fragment associated with DPw2 was observed in patients with Hodgkin's disease, as well as an increase in the fragment associated with DPw3, -5, and -6.

Against this background, a study was set up as part of the 11th International Histocompatibility Workshop to confirm these preliminary findings of an association between HLA-DPB alleles and Hodgkin's disease. It was also planned to correlate the HLA-DP typing with ethnic origin and clinical parameters.

MATERIALS AND METHODS

Organization. Participating clinical centers were paired with HLA laboratories (Table 1). Hodgkin's disease patients who were on treatment or in follow-up at these centers, were typed. An ethnically matched control population was also typed at each participating laboratory.

Questionnaires with detailed clinical information about each typed patient were requested from participating centers (Table 2). The information obtained was used to construct a clinical database. All completed pro-formas were rechecked at St. Bartholomew's Hospital for any obvious inconsistency. Clinical information for analysis was available on 551 patients from 12 centers. The HLA-DP typing and clinical analysis of these data formed the basis of this report. The Cotswolds' recommendations were used for staging and response classification in this report (19).

Survival analyses were not performed on the data, as the HLA typing was on live patients only. Historical data from patients treated and followed up at St. Bartholomew's Hospital were used to illustrate the differences between the population studied for this workshop and an "unselected" population of newly diagnosed, previously untreated patients treated over a 25-year period.

Characteristics of the overall patient population are shown in Table 3.

Patients were recruited from Autumn 1989 to Autumn 1991. HLA-DP typing was performed during this period. Final data were collated and analyzed in October 1991.

Typing Methods. HLA-DP typing was performed using DNA extracted from EDTA blood samples. The detailed methodology was according to 11th International Histocompatibility Workshop protocol (20). The amplified product was dot-blotted on to nylon membranes and subsequently hybridized with

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[3] Collaborators are listed in Table 1.

[4] The abbreviations used are: HLA, human leukocyte antigen; ICRF, Imperial Cancer Research Fund; CR, complete remission; RR, relative risk.

Table 1 *Centers involved in the 11th Workshop Hodgkin's Disease Study*

Laboratories in collaboration with clinical centers	
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G. M. Taylor, D. Gokale St. Mary's Hospital, United Kingdom	D. Crowther, P. Woll Christie Hospital, United Kingdom
C. Loeliger, P. Kuehnl University Hospital Eppendorf, Germany	W. Zeller, D. K. Hossfeld University Hospital Eppendorf Hamburg, Germany W. Kuse St. Georg Hospital, Hamburg, Germany
G. Pellegris Istituto Nazionale Tumori, Italy	G. Bonadonna Instituto Nazionale Tumori, Italy
K. Takacs, G. Petranyi National Institute of Haematology and Blood Transfusion, Hungary	Z. Molnar, S. Eckhardt National Institute of Oncology, Hungary
E. Gazit, T. Klein The Chaim Sheba Medical Centre, Israel	I. Ben-Bassat The Chaim Sheba Medical Centre, Israel
E. du Toit, R. Martell Provincial Laboratory for Tissue Immunology, South Africa	P. Jacobs, C. Johnson University of Cape Town Medical School, South Africa
M. G. Hammond, S. V. van Tonder Natal Institute of Immunology, South Africa	D. J. Kenoyer University of Natal Medical School, South Africa
R. Liang, T. Wong, V. Chan Queen Mary Hospital, Hong Kong	R. Liang, D. Todd, T. K. Chan Queen Mary Hospital, Hong Kong
W. Klitz University of California A. Begovich Cetus Corporation, California	S. Horning, S. Rosenberg Stanford University School of Medicine, Stanford, CA
G. Woodfield, M. Roberts Auckland Regional Blood Center, New Zealand	V. Harvey, P. Thompson, P. Browett Auckland Hospital, New Zealand
J. D. Bignon, Centre de Transfusion Sanguine, France A. Mikata, T. Takenouchi Chiba University, Japan	J. L. Harousseau Centre de Transfusion Sanguine, France

a panel of 25 radiolabeled or biotinylated sequence-specific oligonucleotides. The hybridization pattern was visualized either by exposure on X-ray film or by development using streptavidin horseradish peroxidase conjugate. The hybridization patterns were initially analyzed at each individual laboratory and subsequently rechecked at ICRF Tissue Antigen Laboratory. HLA-DPB alleles were assigned using a computer program designed by A. Wasik and J. G. Bodmer (ICRF).

As an additional quality control measure, a test of the accuracy of HLA-DPB typing in the different laboratories was performed by sending DNA samples from 8 homozygous cell lines blind to each collaborating laboratory for typing. The results were collated and verified at the ICRF Tissue Antigen Laboratory, London, United Kingdom.

The frequency of HLA-DPB alleles in patients was compared to the distribution in ethnically matched controls. Individual groups from ethnically similar populations were merged if, statistically, the degree of heterogeneity between them was shown to be small. There were only 8 patients from Brazil and, in the absence of another similar ethnic group in the study, these patients were not included in the individual frequency comparisons or remission duration analysis.

Statistical Analysis. Relative risks and χ^2 were calculated on data from patients and controls to whom alleles had been assigned. The data from each center were analyzed against their matched controls and subsequently by ethnic grouping.

Proportions of patients achieving CR in different prognostic groups were compared using the χ^2 test with Yates' correction (21). Duration of remission curves was plotted using standard life table methods (22) and compared using the log rank method (23). The significance of prognostic factors in determining the achievement of CR was evaluated by logistic regression analysis, whereas duration of CR differences was determined using a stepwise linear regression method based on Cox's proportional hazards model (24).

RESULTS

Overall Analysis. Seventeen centers from 12 countries participated in this study, with HLA-DPB typing data available on 741 patients and 686 controls. Of these, clinical correlation was possible in 551 patients and 574 controls from 14 centers. Three major ethnic groups were represented—white, Asian, and African black. The overall frequency distribution of HLA-DPB alleles in patients and controls is shown in Fig. 1. The overall distribution is similar in both groups, apart from a statistically significant increase in HLA-DPB1*0301 in patients. This profile, however, merges different ethnic populations with very diverse HLA genotypes. Thus, the frequencies of HLA-DPB alleles in patients and controls were analyzed separately according to center and ethnic group.

Comparing HLA-DPB allele frequencies by center, the increase in HLA-DPB1*0301 in patients compared with controls was seen in all centers (Fig. 2), and was statistically highly significant in white patients (Britain, France, Germany, Italy, and Hungary), merged on the basis of small heterogeneity between them. In this population, the allele DPB1*0301 is associated with an increased RR of 1.95 ($P < 0.01$).

Table 2 *Clinical information collected on patients*

Age
Ethnic origin
Family history (Hodgkin's, non-Hodgkin's or other malignancy)
History of infectious mononucleosis
Histology
Date of diagnosis
Stage, clinical/pathological
Number of sites of disease
Therapy details
Outcome—CR, PR, FAIL, PD[a]
Recurrence details
Pretreatment:
Erythrocyte sedimentation rate
Serum albumin
Full blood count with differential
Blood group

[a] CR, complete remission; PR, partial remission; PD, progressive disease.

Table 3 *Patient population*

	No. of patients
Total	551
Histology	
Nodular sclerosis	281
Lymphocyte predominant	62
Mixed cellularity	136
Lymphocyte deplete	21
Unspecified	
Stage	
I	88
II	203
III	152
IV	73
?	35
B symptoms	212
Outcome	
Complete remission	400
Complete remission (u)	46
Partial remisson	47
Fail	8
Early death	2
Not specified	48
Recurrence	78
Clincal history of infectious mononucleosis	
Yes	36
No	392

The only other statistically significant difference was seen in the distribution of HLA-DPB1*0401, with a lower frequency in patients from Japan and Taiwan, compared with local controls (Fig. 3). A similar trend was seen in the South African and United Kingdom populations, but this did not reach statistical significance. In the Asian populations, this allele was associated with a significantly reduced RR of 0.15 ($P < 0.01$). Paradoxically, the reverse was seen in the groups from Israel and United States, with RRs of 3.0 and 1.8, respectively ($P < 0.05$).

Clinical Analysis. The overall complete remission rate was high (80%). If patients in equivocal complete remission (19) are included, the remission rate is 89%. The duration of remission is long, being significantly better in comparison with previously untreated patients treated at St. Bartholomew's Hospital over a 24-year period. This, coupled with the fact that virtually all patients in this study are alive, demonstrates the significant, albeit inadvertent, positive selection bias of patients in this study. The distribution of patients is skewed with a preponderance of survivors, in a good prognostic category.

The duration of remission in patients with different HLA-DPB alleles was compared. HLA-DPB1*0901 was associated with inferior remission duration overall ($P = 0.04$), and in the Japanese population, where this allele is most prevalent ($P < 0.05$). There was no significant correlation between other HLA-DPB alleles and remission duration ($P = 0.9$). Comparison of remission duration by center demonstrated shorter duration of remission for Asian patients, compared with other centers ($P = 0.02$).

The distribution of HLA-DPB alleles in patients who had a positive family history of Hodgkin's disease was identical to the overall distribution (data not shown). There was no correlation between HLA-DPB type and stage, histology, history of infectious mononucleosis, response to initial therapy, presentation blood count, serum albumin, or erythrocyte sedimentation rate. There was no significant influence of age, stage, histology, erythrocyte sedimentation rate, serum albumin, or lymphocyte count on remission duration. This absence of correlation with traditionally defined prognostic indicators implies a preponderance of patients in a favorable prognostic group in continued remission.

DISCUSSION

This study confirms the previously reported significant association between HLA-DP and Hodgkin's disease. The increased frequency of HLA-DPB1*0301 in patients with Hodgkin's disease, compared with controls, verifies the reported association with HLA-DPw3 (18). The previously noted association with HLA-DPw2 could not be confirmed. The reason may have been due to inadvertent bias due to a smaller size of patients and controls in the first study, or a statistical fluke.

The increased frequency of HLA-DPB1*0301 may imply susceptibility to Hodgkin's disease associated with this allele, or due to a

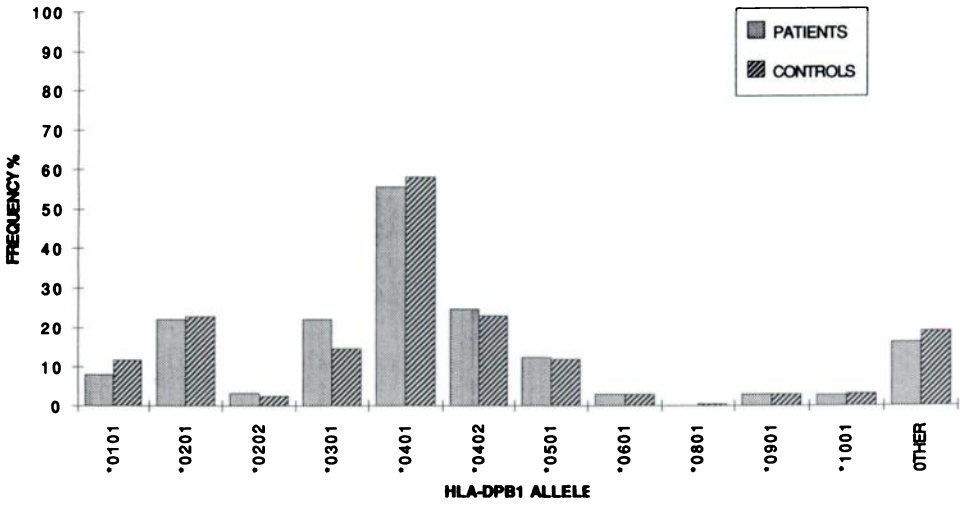

Fig. 1. Overall HLA-DPB allele frequency distribution of patients and controls.

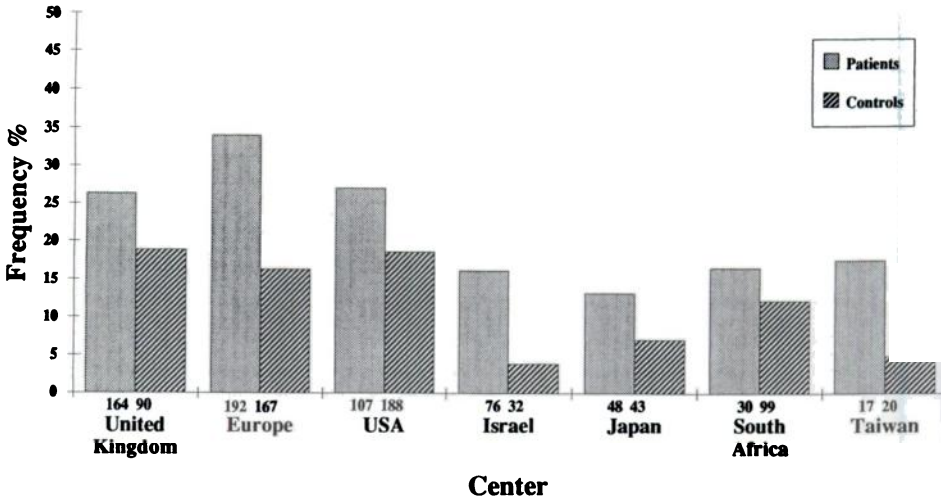

Fig. 2. Frequency distribution of HLA-DPB1*0301 by center. Values on x-axis indicate total numbers of patients/controls typed at each center.

gene closely linked or in linkage disequilibrium with this allele. Similarly, the reduction in frequency of HLA-DPB1*0401 would suggest protection associated with this gene, or linked to this gene in Asians. In both these scenarios, one would have to postulate differing influence of genetic and environmental susceptibility to explain the different associations. Epidemiologically, there is a great deal of variability in the pattern of Hodgkin's disease in different populations and countries (25).

The differing influence of HLA in different populations was also apparent with the demonstration of a significantly reduced frequency of HLA-DPB1*0401 in Asians. This association was not apparent in white subjects and underscores the value of conducting HLA association studies in well defined, relatively homogenous populations, to avoid minor differences in gene frequency being missed (or gaining false emphasis) when 2 or 3 different ethnic populations are mixed in a single study.

The documented inadvertent selection of survivors may either mask or give place undue emphasis on these associations. Ideally, a truly representative cohort of individuals with Hodgkin's disease would be typed prospectively, at the time of initial diagnosis. This approach has practical limitations because of the rarity of the disease and long time course, the latter being a direct consequence of successful therapy in the majority. Thus, a study to assess the epidemiological and prognostic significance of HLA would be slow to accrue patients and take years to demonstrate any possible survival advantage. An alternative approach is to retrospectively type a cohort of patients, using stored material.

The role of HLA in immunomodulation is well established, and this could make the HLA system a possible factor in determining survival in patients with Hodgkin's disease. Some of the initial studies analyzed HLA results according to survival; HLA A1 and B8 were found in increased frequency in long term survivors. The HLA types in long term survivors have to be compared with patients who died shortly after the onset of disease to explore the role of HLA in resistance to progression of the disease. The role of HLA in influencing survival in Hodgkin's disease has been reported previously. Falk and Osoba (6) found an increase in antigens A1, A5 (now B5), and A8 (now B8) in patients with Hodgkin's disease as a whole, with A8 (B8) being particularly prevalent in patients who had survived more than 5 years. In addition, the frequency of HLA-A3 was increased in patients with recent onset, suggesting that this could be of adverse prognostic significance. Osoba and Falk (6) prospectively studied 79 previously untreated patients who were diagnosed between 1972 and 1973 at The Princess Margaret Hospital, Toronto, Ontario, Canada. HLA phenotype Aw19[Aw29, Aw30, Aw31, Aw32, Aw33, and Aw74] was found to be a highly significant prognostic factor, on univariate as well as multivariate analyses, and was independent of stage, age, histology, or sex (14). The significance of HLA-Aw19 was also confirmed by comparing the frequency of this antigen between patients in good and bad survival groups. Another recent study reported

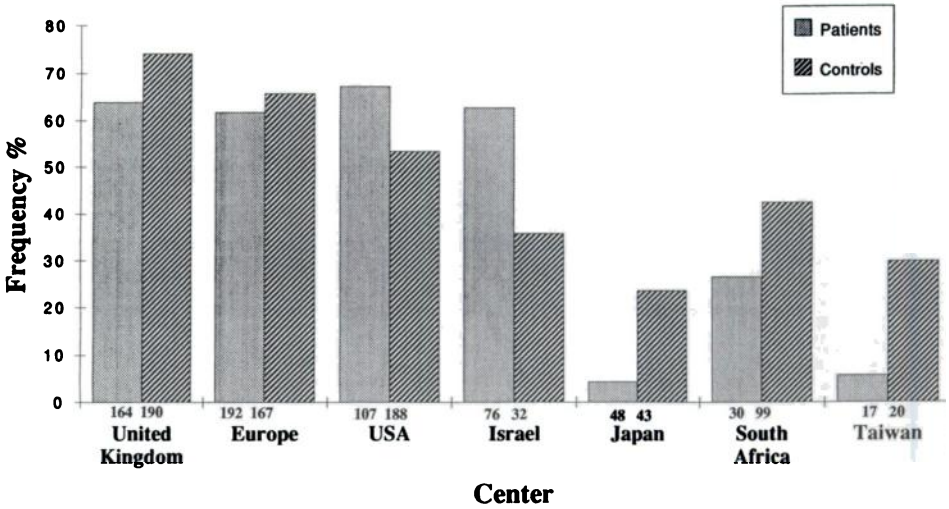

Fig. 3. Frequency distribution of HLA-DPB1*0401 by center. Values on x-axis indicate total numbers of patients/controls typed at each center.

a significant increase in HLA-B5 in patients who relapsed (17). This is of interest, as a preliminary analysis of the patients reported by Osoba *et al.* (14) had also linked this antigen with poor survival, being present in high numbers in patients who had died within 3 years of diagnosis (8).

This study suggests that the HLA association with Hodgkin's disease is closer to the HLA-DPB locus than to other loci studied previously. This was confirmed by the analysis of linkage disequilibria of HLA-DPB1*0301 and DPB1*0401 in random donors from the population studies. Significant linkage disequilibria were seen between DPB1*0301 and both DRB1*0301 and DRB1*1302 in white subjects and between DPB1*0401 and DRB1*1302 in Japanese subjects (26, 27). The possibility remains, however, that a candidate gene may be in strong linkage disequilibrium with both DPB and HLA class I, but is not part of the known HLA. This would explain the well described association with HLA-A, -B, and -DP. However, apparent linkage between an allele and a disease may be observed if the group sampled is not representative of the total population (28). The inadvertent selection bias favoring patients in remission may therefore be of obvious importance. This selection bias can be overcome by either typing a cohort preferably prospectively, or by typing patients who were underrepresented in the cohort already typed.

These results demonstrate that in Hodgkin's disease, the HLA system may have an epidemiological association influencing host resistance/susceptibility and perhaps be prognostic. It is a matter of speculation as to whether the observed epidemiological variability in the incidence and pattern of Hodgkin's disease in different populations is inherently related to the ethnic variability in HLA patterns, and consequent host defenses. Epstein-Barr virus has been linked etiologically to Hodgkin's disease in numerous epidemiological and molecular studies. However, there are no studies which have directly addressed the question of HLA based immunity, Epstein-Barr virus infection, and Hodgkin's disease.

There is now a substantial body of information, past and present, linking HLA alleles with Hodgkin's disease. However, the molecular mechanisms which are responsible for this association remain obscure and present a continuing challenge.

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