Associations between Human Leukocyte Antigen Type and Nasopharyngeal Carcinoma in Caucasians in the United States

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Abstract

A genetic component to nasopharyngeal carcinoma (NPC) has been suggested by associations of the malignancy with human leukocyte antigens (HLAs) in Southern Chinese populations, among which NPC is a major cancer. Data from other races are inconclusive. We have investigated associations between NPC and HLA antigens at the HLA-A, B, C, and DQ loci and alleles at the DRBI locus in a population-based, multicenter investigation in the United States. Data from 82 cases and 140 controls are presented, making this the largest study population analyzing data from Caucasians to date. HLA frequencies from study cases were also compared with external control groups from the 11th International Histocompatibility Workshop and the National Marrow Donor Program. Logistic regression methods were used to investigate the effects of the joint occurrence of multiple HLA types and to assay for differences in HLA-associated risk in different age groups. A meta-analysis was undertaken to compare and summarize our results with previously published findings. The meta-analysis found a protective association with A2 antigen in non-Chinese [odds ratio (OR), 0.63; P < 0.001], a protective association with A11 across all races (OR, 0.54; P < 0.001), and an increased risk associated with B5 in Caucasians (OR, 2.81; P < 0.001). The present study also found independent associations, in a logistic regression model, between NPC and DRBI*1501 (OR, 0.33), DRBI*0405 (OR, 7.57), and Cw3 (OR, 0.42), although these data must be interpreted cautiously due to multiple-testing considerations. Associations were found to be more pronounced in younger patients for A2, A11, A28, B8, and B51.

Introduction

NPC is a cancer with unusually variable incidence rates around the world. It is a major cancer in certain areas of South China, where an incidence rate of about 30 per 100,000 per year makes it the leading cause of cancer deaths in males. In the United States it is a rare tumor, with an incidence rate less than 1 per 100,000 per year (1). Other groups, including Alaskan Native Americans and North Africans, have intermediate levels of incidence, on the order of 2 per 100,000 per year (2).

Both environmental and genetic components of NPC etiology have been proposed. Among environmental risk factors, diet, and salted fish in particular (3, 4), appears to play a significant role in high-risk areas. There is also evidence that cigarette smoking, alcohol intake, and formaldehyde exposure may increase the risk of the disease (5–9). EBV, a nearly ubiquitous infection in all human populations, is associated with undifferentiated NPC tumors (10) and may also play a role in differentiated tumors (11).

There is good evidence of a genetic contribution to NPC in Chinese populations. A study of affected Chinese sib pairs found strong linkage of a disease susceptibility gene to the HLA region (12), and a series of reports from Singapore has found a significant association with certain HLA antigens among Chinese populations, most notably the joint A2, B46 phenotype and the B17 and A11 antigens (13).

In other races, there have been a number of investigations of the HLA and NPC association (14–21). Because the disease is uncommon in non-Chinese populations, the studies have had limited numbers of cases and have typically reported no statistically significant association with NPC after adjustment of P to control for multiple testing. Given the limited power of these studies and the conservative effect of such adjustments, this result is not surprising and offers little evidence to exclude an association in these groups.

We report the results in Caucasians of a population-based, multicenter study of the association between HLA type and NPC in the United States. A preliminary report of our findings for the A2 antigen has been published (22). In addition, we have...
combined our results with those of previously published studies in a meta-analysis in which we undertake a formal comparison and summary of our own and previous results.

Subjects and Methods
Cases were identified by three cancer registries participating in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. These included residents of a 13-county region of northwestern Washington State, the state of Connecticut, and the three counties of metropolitan Detroit. Eligible cases were persons diagnosed with carcinoma of the nasopharynx (International Classification of Diseases for Oncology code 147) who were between 18 and 74 years of age. Cases were diagnosed in the time interval starting April 1, 1987, and ending June 30, 1991, in Connecticut and Detroit; case eligibility continued until September 30, 1994, in Washington. Study subjects were interviewed by telephone to determine a number of behavioral, occupational, residential, and medical exposures of potential relevance to NPC etiology and, if willing, subsequently had blood drawn by a licensed phlebotomist. For cases, the mean time from diagnosis to draw was slightly less than 12 months; for both cases and controls the mean time from interview to draw was about 4 months.

Study controls were recruited by RDD (23) and frequency matched to cases by registry, 5-year age group, and sex. Two additional comparison groups were also used; HLA phenotype frequencies in U.S. Caucasians were calculated from the gene frequencies published by the Eleventh International Histocompatibility Workshop (n = 246 for class I antigens; n = 286 for DRB1) (24) and from the NMDP registry of volunteer unrelated bone marrow donors. To better reflect our study population, only NMDP participants from centers in Seattle, Detroit, and Connecticut were used (n = 80,210 for A and B antigens; n = 12,632 for DR antigens). Only a subset of NMDP participants had DR typings. Of those, some were typed only after being selected as potential marrow donors on the basis of a match at A and B loci to a transplant recipient; others were typed independently of a such a match. Only the latter group was used to avoid possible problems of bias toward those DR types in linkage disequilibrium with A or B types associated with need for a marrow transplant or toward the common A, B, and DR haplotypes, which constitute the majority of unrelated marrow transplants to date.

Serological HLA typing for the HLA-A, -B, -C, and -DQ antigens was performed by microcytotoxicity methods (25); DNA-based, sequence-specific oligonucleotide probe typing methods (26) were used to type alleles at the DRB1 locus. This report analyzes data from 222 Caucasians (82 cases and 140 controls). The number successfully typed at each locus varies slightly, because the serological class I, class II, and DNA methods each have different requirements with respect to cell numbers and viability.

Univariate ORs, exact 95% CIs, and P values were calculated. Reported P values were not corrected for multiple comparisons, although their effects on the interpretation of the data will be addressed in "Discussion." Logistic regression methods were used to adjust the OR estimate of each of the HLA types with NPC for the presence of the others (27). HLA types were included in the regression model, which had a significance level of P = 0.10 or less in univariate analysis; in addition, A2, A11, B8, and B51 were included, because previous studies suggested a possible association with NPC. Terms controlling for Surveillance, Epidemiology, and End Results center and age (older than or younger than 50 years) were included in the regression models; a term for sex had little influence (P = 0.84) and was not included in the models presented. Maximum likelihood estimates of the OR and likelihood ratio tests for significance are reported (28).

Age at diagnosis was categorized into groups consisting of patients diagnosed at older or younger than 50 years of age. Interaction terms between this age variable and indicator variables for those HLA types selected for logistic regression analysis were used to test whether the association of HLA type with NPC varied with age. Also, interaction terms between all pairwise combinations of HLA variables were tested to investigate joint phenotypes, the association with NPC of which differed from what would be expected on the basis of the associations of the constituent HLA types alone; such a finding could imply a haplotype-specific influence on NPC risk.

For the meta-analysis, the summary OR across studies, a significance test for the OR and a test for P_{het} were calculated according to methods recommended by Breslow and Day (28) for stratified analysis, using exact CIs and P values except in the calculation of P_{het}. To minimize potential reporting bias, five studies that reported results only for selected antigens were excluded.

Results
Current Study. The response figures for the study subjects and the reasons for non-response are shown in Table 1. Because race was not able to be determined for those subjects who refused interview, information is given for subjects of all races, although only Caucasians are analyzed further in this report.

Overall, 51% of eligible study subjects (47% of cases and 55% of controls) were successfully HLA typed. Death accounted for a substantial proportion (42%) of nonresponders among the cases, and ill health played a role in many of their refusals. There was substantial variation in response rates among the different participating centers, with overall rates of 62, 46, and 38% for Washington, Detroit, and Connecticut, respectively.

The distribution of HLA-A, B, C, DRB1, and DQ types among the cases and RDD controls is shown in Table 2 along with the associated univariate ORs, 95% CIs, and P values, which are unadjusted for multiple comparisons. In instances in which the serological typing could resolve a broader specificity into its splits for only some subjects, as, for example, with A10, the data from the splits are combined with the broader specificities, which are then shown beneath the splits in parentheses.
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| HLA-C [n (cases) = 78; n (controls) = 137] |
| w1    | 2     | 3        | 11 | 8       | 0.30  | 0.08-1.44 | 0.18 |
| w2    | 14    | 18       | 13 | 9       | 2.09  | 0.85-5.13 | 0.12 |
| w3    | 10    | 13       | 32 | 23      | 0.48  | 0.20-1.09 | 0.09 |
| w4    | 16    | 21       | 34 | 25      | 0.78  | 0.37-1.60 | 0.39 |
| 1 blank | 26    | 33       | 64 | 47      | 0.57  | 0.31-1.05 | 0.08 |
| 2 blank | 39    | 50       | 59 | 43      | 1.32  | 0.91-3.03 | 0.10 |
The strongest NPC association in these data is with DRB1*1501 (OR, 0.42; CI, 0.19–0.87). There are suggestions of association with A28 (OR, 2.54; CI, 0.97–6.82), DRB1*0405 (OR, 5.41; CI, 0.93–54.63), and Cw3 (OR, 0.48; CI, 0.20–1.09). HLA-A2, A11, B51, and B8 showed weaker associations, with P values ranging from 0.11 to 0.17, but are included in subsequent analyses, because previous results suggest that investigation of their association with NPC is of interest.

Although an increased OR for B17 was one of the stronger findings among the Singapore Chinese population (13), in our data the component splits of B17 showed little association with NPC: B57 (OR, 1.03) or B58 (OR, 0.88). Because there have been reports that B17 is associated with poor survival with NPC (29), we examined whether B57 showed an elevated OR among cases from whom blood was drawn within 12 months of diagnosis. Of the 78 cases, 53 had blood drawn within 1 year of diagnosis, including 5 of the 8 positive for B17; the OR was 0.92.

To test for possible anomalies in the RDD controls, we compared the HLA distributions in cases with those in two external control groups: from the 11th Histocompatibility International Workshop and from the NMDP (Table 3). A2, A11, A28, B8, and Cw2 show quite similar associations with NPC whether compared with our RDD controls or with the external controls. B51 is somewhat more common in the NMDP controls than in the other groups. On the hand, there is considerable disparity in the findings for Cw3 and DRB1*1501 between the 11th Workshop and the RDD controls. For DR2, the broad specificity of which DRB1*1501 is the most common allele in Caucasians, the NMDP data report a prevalence intermediate between that of the RDD and 11th Workshop groups. It is difficult to judge whether these disparities are the product of biases in the external populations, in which subject recruit-
Because data for DRB1*1501 were not available from the NMDP, the broader specificity DR2 is used.

\[ P = DRBJ*1501, \]

For Cw3 and age group. The difference between age groups was of low significance for each individual HLA type (\( P = 0.14 - 0.76 \)). For Cw3 and DRB1*1501, little difference was noted between age groups.

Pairwise interaction terms were used to evaluate whether the joint occurrence of pairs of these HLA types was associated with a risk for NPC substantially different from what would be expected on the basis of the individual types alone. We found a suggestion that B8 was associated with an increased risk for NPC only among persons without an A2 antigen (\( P = 0.09 \) for the interaction term). Also, because A1 and B8 are in substantial linkage disequilibrium, regression models were used to test whether the association of B8 with NPC was independent of the presence of A1. As the addition of a term for A1 had little influence on the risk estimates for B8, the model indicated that the excess NPC risk was associated with B8.

**Meta-Analysis.** A meta-analysis was undertaken to facilitate an overview and summary of existing evidence of HLA associations with NPC combining the data from the present study with previous reports (Table 5). To compare results from the present study with previous reports, the B51 and B52 antigens have been combined into the B5 specificity, and the DRB1*1501, 1502, 1601, and 1602 alleles are represented by the DR2 antigen.

For A2, a summary OR of 0.63 (CI, 0.48–0.82; \( P < 0.001 \)) is found in non-Chinese populations. All studies in Chinese populations, on the other hand, show an increased risk associated with A2. Because the present analysis excludes studies that report results only for selected HLA antigens, this comparison excludes two studies included in a preliminary report from our data on HLA-A2 (22). Their inclusion in the present analysis would yield a summary OR of 0.71 (\( P = 0.004 \)).

All1 shows a protective association across four studies in Chinese populations (OR, 0.48; CI, 0.37–0.62; \( P < 0.001 \)). In populations at intermediate incidence, there is a weak suggestion of a protective association, whereas in Caucasians there are mixed findings. A summary across all populations yields a protective association (OR, 0.54; CI, 0.43–0.67; \( P < 0.001 \)); the fluctuations between the studies are consistent with a single common OR (\( P_{het} = 0.41 \)).

The A28 antigen shows considerable variation in each
### Table 5  
**HLA associations with NPC: comparisons across different studies**

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<th>P</th>
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<td>0.84-1.62</td>
<td>0.71</td>
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<td>Betuel et al. (17)</td>
<td>Tunisia</td>
<td>109</td>
<td>0.58</td>
<td>0.31-1.11</td>
<td>0.75</td>
<td>0.23-2.42</td>
<td>0.98</td>
<td>0.39-2.53</td>
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<td>Herait et al. (30)</td>
<td>N. Africa</td>
<td>76</td>
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<td>0.27-1.01</td>
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<td>0.24-2.55</td>
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<td>Chan et al. (18)</td>
<td>Malaysia</td>
<td>45</td>
<td>0.81</td>
<td>0.36-1.73</td>
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<td>Hall et al. (19)</td>
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<td>0.43-0.87</td>
<td>0.006</td>
<td>0.70</td>
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<td>Jing et al. (14)</td>
<td>United States</td>
<td>37</td>
<td>4.36</td>
<td>1.55-12.07</td>
<td>0.46</td>
<td>0.17-1.21</td>
<td>1.25</td>
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<td>Chan et al. (13)</td>
<td>Singapore</td>
<td>366</td>
<td>1.50</td>
<td>1.09-2.02</td>
<td>0.51</td>
<td>0.37-0.69</td>
<td>0.50</td>
<td>0.01-9.68</td>
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<td>Yuan et al. (31)</td>
<td>Sichuan</td>
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<td>0.17-0.70</td>
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<td>0.15-10.25</td>
</tr>
<tr>
<td>Cui and Lin (32)</td>
<td>N. China</td>
<td>33</td>
<td>1.63</td>
<td>0.55-4.82</td>
<td>0.73</td>
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<td>1.28-2.13</td>
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<td>0.48</td>
<td>0.37-0.62</td>
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<td><strong>Overall summary</strong></td>
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<td>1.03</td>
<td>0.86-1.23</td>
<td>0.80</td>
<td>0.54</td>
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<td>0.48-0.82</td>
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</table>

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Population analyzed, and the summary offers little evidence of an overall association with NPC.

Four studies reporting B5 associations with NPC in Caucasians yield a consistent and significantly elevated OR (OR, 2.81; CI, 1.76-5.12; P < 0.001) but with strong indications of heterogeneity among the studies (P<sub>het</sub> = 0.02). The report by Krüger et al. (16) shows an OR markedly higher than the others; its exclusion would result in an OR of 1.98 (P = 0.03;
eign antigens for immune recognition. The most common A2

Analyses exist to adjust

procedures, which suggests increased risk, although the statistical

significance of this estimate is low (OR, 1.43; \( P = 0.15 \); CI,

0.89–2.32; \( P_{\text{het}} = 0.80 \)). The two studies of DR2 in Caucasians

show contradictory results, and no consistent pattern is evident

among the other populations.

Discussion

We have conducted measurements of HLA type frequencies in

a population-based study of 82 U.S. Caucasian NPC cases and

140 controls identified by RDD. This represents the largest
group of Caucasians in whom an HLA-NPC association has

been investigated. Although several HLA associations with

NPC were observed in our data, because of the multiple testing

inherent in the investigation, several significant associations

would be expected to emerge by chance alone. Although pro-

cedures exist to adjust \( P \) values to correct for such multiple
testing, they are conservative and do not take into account
the existence of previous results. We have evaluated HLA-NPC
associations in our data by considering first those HLA types
for which our meta-analysis indicates a consistent pattern of
association in independent data sets. Then, for those HLA types
associated with NPC in our data for which previous reports
were unavailable, or too sparse to form a coherent meta-anal-

ysis, we interpret our findings primarily as an indication that
these specificities should be candidates for scrutiny in further
studies of HLA-NPC association. HLA-NPC associations are
also interpreted in light of what is known about the HLA types
involved in presenting EBV peptides for recognition by the
immune system, which represents a potential mechanism to
account for HLA-NPC associations.

For three of the HLA types with NPC associations in our
data, HLA-A2, A11, and B5, the meta-analysis offers substan-
tial support for an influence on disease risk, although important
qualifications must be noted in each instance. HLA-A2 was
found to be associated with a decreased risk of NPC in non-

Chinese populations (OR, 0.63) and a high level of significance
(\( P < 0.001 \)), and there was little evidence of heterogeneity
among the different studies (\( P_{\text{het}} = 0.94 \)). The OR for A2 in
the current study is in better agreement with the meta-analysis than
that reported in a preliminary publication, which was based on
considerably smaller numbers of subjects (22). As was noted in
that report, the consistently elevated OR for A2 in Chinese is
likely to result from the influence of an A2/B46 haplotype, and
there are indications that this involves a specific A2 allele rare
in Caucasian populations. In the absence of B46, A2 was also
found in Chinese populations to be protectively associated with
NPC (13).

Arguments of biological plausibility also support an etio-

logical role for A2 in NPC. EBV has long been associated with
the undifferentiated form of NPC (10) and may play a role in
differentiated NPC as well (11). HLA molecules present for-
eign antigens for immune recognition. The most common A2
allele, \( A^*0201 \), presents a peptide from the EBV LMP-2 protein
(37). LMP-2 is one of the few EBV gene products detected in
NPC tumors (38). Individuals expressing A2 may thus be at an
advantage in mounting an immune response to EBV-infected
cells.

The protective association of HLA-A11 with NPC (OR,
0.26 in logistic regression model) is among the stronger asso-
ciations in our data. The meta-analysis for A11, however,
introduces complications. Two studies in Caucasians found
elevated risk, whereas two, including the present report, found
a protective association. All studies in non-Caucasians show a
protective association. The overall summary shows that the data
are consistent with a common protective association across the
different studies (\( P_{\text{het}} = 0.41 \)). Nonetheless, the varying results in
Caucasians leave open the issue of whether these represent
statistical fluctuation or are evidence of a true difference in
association in different racial groups.

Interestingly, A11 has been reported to present the EBV

EBNA-4 and, to a lesser extent, EBNA-6 proteins to the im-

mune system (39). These EBV proteins have not been detected
in NPC tumors. It seems possible, however, that at earlier
points in the evolution of an EBV-infected cell into a NPC
tumor, a broader pattern of EBV expression is manifested than
has been reported from the final malignancy. EBNA-4 or -6
could thus represent a target for immune surveillance at such
stages.

We found an elevated risk for NPC among individuals
with the B51 antigen (OR, 2.09). The meta-analysis showed
that risk measurements for B5, the broader specificity encom-

passing the B51 antigen, are consistently elevated in studies in
Caucasians, even allowing for a possibly anomalous result in
the report by Krüger et al. (16). Little association is evident in
non-Caucasians; conceivably, the distribution of the alleles
underlying the B5 antigen varies in different races.

Although little evidence has been reported implicating
B51 in EBV immune presentation, it is of interest that B5 has
also been observed to be associated with increases in risk for
Hodgkin’s disease. Modest, although highly significant, in-
creases in risk for Hodgkin’s disease for B5 (OR, 1.63; \( P < 0.001 \))
have been noted in a comprehensive meta-analysis of
published reports (40). These findings are of particular moment,
because EBV has been detected in the malignant cells of a
substantial proportion of Hodgkin’s disease tumors (41), is
clonal within a tumor (42), and may play a role in the devel-

opment of the malignancy. We speculate that a common, EBV-
mediated mechanism may underlie the association of the B5
antigen with both Hodgkin’s disease and NPC.

Our data contain only a suggestion of an increased risk
associated with B8 (\( P = 0.11 \)). Likewise, the meta-analysis
offers no more than equivocal support for an association in
Caucasians (\( P = 0.15 \)). It warrants mention, however, that B8,
like B5, has been implicated in Hodgkin’s disease with high
significance in a meta-analysis (OR, 1.27; \( P < 0.001 \); Ref. 40).

Although an increased risk for A28 is evident in our data,
the association is weaker after adjustment for the occurrence
with other HLA types associated with NPC risk. There is little
evidence from other studies of an association with NPC. In the
absence of evidence that our study population is different from
other populations of Caucasians with respect to distribution of
A28 or its measurement, we would judge a causal association
unlikely.

For Cw2, Cw3, \( DRB1*0405 \), and \( DRB1*1501 \), data from
previous studies are insufficient to form a coherent meta-anal-

ysis, and we regard our findings for these HLA types as ex-

plosory. The association in our data for \( DRB1*1501 \), the most
common allele of the DR2 family in Caucasians, is at variance
with the only other report in Caucasians (15). A number of
studies in Chinese populations and one in North Africans like-
wise fail to confirm the protective association observed in
the present study, although the allelic distribution of DR2 varies
in different racial groups (24). It should be noted that \( DRB1*1501 \)
was not observed to be more strongly associated with NPC in
younger patients. In Caucasians, except for the rare association
with \( DRB1*0101 \), the HLA \( DRB5 \) locus is present only on

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chromosomes bearing a DR2 allele at the DRB1 locus (24). Thus, an association of DRB5 with NPC would be expected to produce an association of DR2 with NPC, and our data are consistent with such a DRB5-NPC association. Finally, the discrepancies in proportions of controls positive for DR2 in the random digit-dialed controls and the two external control groups should be noted.

We observed a protective association between Cw3 and NPC (OR, 0.42). The two studies that to our knowledge reported measurements of for the Cw3 antigen in NPC cases, one in an East African population (19) and the other in Prague (20), fail to confirm our findings, although the numbers involved are small, and racial and ethnic diversity may play a role. C locus antigens are generally considered more poorly defined than other serological specificities. Because errors in exposure classification will in general bias risk estimates toward an OR of 1.00, a positive finding in the face of such error likely represents a conservative estimate of association.

Other studies of cancer etiology have found that a genetic component is most pronounced in that group of malignancies with a comparatively young age at onset; for instance, focusing on breast cancer patients with early disease was instrumental in devising the strategy that led to the localization of the BRCA1 gene. We found that for six of the eight HLA types with the strongest independent association with NPC, the association was stronger in patients younger than 50 years than those older than 50 years. Although the statistical significance of these findings is low for each individual HLA type, the consistency of the relationship and its biological plausibility are noteworthy. In other analyses from the current study, we found that cigarette smoke and alcohol intake were associated with increased risk of NPC only among persons older than 50 years (6).

The low response rates in our study, 47% for cases and 55% for controls, must be considered in the interpretation of all of our findings. Because death and ill health were factors that influenced response in cases, we would expect any HLA types associated with poor prognosis (29) to be underrepresented in our case population and our estimates for their ORs to be lowered. Furthermore, our study population would suffer a bias difficult to evaluate if subjects from different ethnic groups with distinctive HLA frequencies were subject to differential response rates.

The existence of a genetic predisposition to NPC in Caucasians would be of considerable interest; identification of a gene influencing cancer risk would enhance our understanding of cancer etiology and open possibilities to prevent and treat the disease. We have investigated measures of NPC association to HLA type and found a number of associations. The evaluation of the significance of these findings, however, requires consideration of the strength and consistency of the association across different studies, the potential for differing associations to persist to different populations, potential biases in the constitution of our case and control populations, and the role of chance. As in all HLA association studies, the possibility must be entertained that an observed disease association is a product of linkage disequilibrium of the implicated HLA locus with the gene truly associated with NPC. DNA-based HLA typing would more precisely define which HLA alleles most strongly associated with NPC and, therefore, would help focus attention on the most likely area of the genome to harbor a gene influencing disease susceptibility. Investigation of the natural history of EBV involvement in NPC and the human immune response to EBV infection could help establish the biological basis for the HLA-NPC associations we have noted.

Acknowledgments

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References


Associations between human leukocyte antigen type and nasopharyngeal carcinoma in Caucasians in the United States.

R D Burt, T L Vaughan, B McKnight, et al.