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Brief report

HLA-DR, HLA-DQ, and TAP genes in familial Hodgkin disease

Lea C. Harty, Albert Y. Lin, Alisa M. Goldstein, Elaine S. Jaffe, Mary Carrington, Margaret A. Tucker, and William S. Modi

The HLA region has long been implicated in sporadic and familial Hodgkin disease (HD), with recent case-control studies suggesting that HLA class II loci predispose to sporadic nodular sclerosis HD (NSHD). To determine whether this predisposition extends to familial HD, HLA class II loci (DRB1, DQA1, DQB1, DRB3, DRB4, and DRB5) and transporter associated

with antigen processing (TAP) loci (TAP1, TAP2) were investigated in 100 members of 16 families with at least 2 confirmed cases of HD. With the use of the transmission disequilibrium test, evidence for linkage disequilibrium with familial HD and, in particular, familial NSHD was obtained for the DRB1*1501-DQA1*0102-DQB1*0602 haplotype, the TAP1 allele encoding Ile at resi-

due 333, and the DRB5-0101 allele. These 3 markers were in linkage disequilibrium and may not represent independent susceptibility regions. Use of a family-based approach excludes population stratification as an explanation for these findings. (Blood. 2002; 99:690-693)

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Introduction

The etiology of Hodgkin disease (HD) is largely unknown and probably involves both environmental and genetic factors. Ferraris et al¹ estimate that 4.5% of HD cases occur as familial HD.² Although considerable evidence exists supporting a chronic infectious process due to Epstein-Barr virus (EBV) in HD,³ EBV-encoded RNA has been detected in only approximately 27% of tumors from familial HD cases,^{4,5} and the association is weakest with nodular sclerosis HD (NSHD), the HD subtype overrepresented among young adults and familial cases.^{6,7} More importantly, within families there is no excess concordance of the EBV status of tumors.^{4,5} In contrast, an elevated risk of HD among monozygotic twins compared with dizygotic twins of HD patients⁸ suggests a role for shared genetic factors in familial HD.

The HLA class I region on chromosome 6 (particularly the B5, B8, B18, and A1 alleles) has been weakly but consistently associated with both sporadic and familial HD.⁹⁻¹¹ In familial HD, 60% to 70% of cases of which may be linked to this region,¹² there is significant HLA class I haplotype sharing among affected individuals.^{11,13} More recent evidence suggests a role of HLA class II antigens. The DPB1*0301 allele was implicated in HD,^{14,15} but an analysis of multiple HLA class II loci (eg, DRB1, DQA1, DQB1, and DPB1) discounted an independent role of DPB1.¹⁶ Klitz et al¹⁶ conducted a case-unrelated control study and reported that NSHD (but not other histologic subtypes) is positively associated with the DRB1*1501, DQB1*0602, and DRB1*1104 alleles and negatively associated with the DRB1*1601, DRB1*0404, and DQB1*0303 alleles. They concluded that susceptibility to NSHD was probably due to several HLA class II loci, including DRB1, DQB1, and perhaps other, yet-to-be-identified loci.

We investigated whether alleles at HLA class II loci (DQA1, DQB1, DRB1, DRB3, DRB4, DRB5) and transporter associated with antigen processing (TAP) loci (TAP1 and TAP2) play a role in

familial HD. We tested for linkage disequilibrium with familial HD and, in particular, with familial NSHD.

Study design

Subjects

Sixteen white families with at least 2 members with histologically confirmed HD (9 sibling pairs; 4 parent-child pairs; 1 sibling-sibling-parent trio; 1 sibling-sibling-cousin trio; and 1 cousin-cousin-uncle trio) were ascertained through self-referral or physician referral to the National Cancer Institute between 1978 and 1993. Thirteen of these families had been studied previously in relation to HLA class I haplotypes¹³ or EBV.⁵ Four patients were excluded because they did not provide a blood sample for genetic analysis. The present analysis included 28 affected members (23 NSHD, 5 non-NSHD) with at least one parent available for genotyping; 3 affected family members (all non-NSHD) with both parental genotypes unknown; and 69 unaffected family members (27 parents, 33 full siblings, 7 half-siblings, and 2 parents of half-siblings). The 28 affected members with known parental genotypes (17 male, 11 female) were first diagnosed with HD at a mean age of 24 years (range: 6-40 years). HD diagnoses were confirmed by review of histologic specimens (20 of 35 patients, 57.1%) or original pathology reports if histologic material was unavailable. The study protocol was approved by the National Institutes of Health Institutional Review Board, and subjects or their parent/guardian gave informed consent to participate.

HLA class II and TAP genotyping

DNA was isolated from frozen lymphocytes by proteinase K digestion and phenol-chloroform extraction, followed by ethanol precipitation. The single-strand conformational polymorphism assays used to determine subjects' genotypes have been described for DQA1,¹⁷ DQB1,¹⁷ DRB1,¹⁸ DRD3,¹⁸ DRB4,¹⁸ DRB5,¹⁸ TAP1,¹⁹ and TAP2.¹⁹ The individual DRB1

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alleles within the DR13 and DR14 groups (serogroups or lineages) were not subtyped at the allele level.

Statistical analysis

Linkage disequilibrium between alleles or haplotypes and HD and, in particular, NSHD was assessed by means of the transmission-disequilibrium test (TDT).^{20,21} DRB3, DRB4, and DRB5 data were treated as a single variable, called DRB3-5. Candidate alleles (ie, those with statistically significant associations with HD in the only previous study of these factors¹⁶) at multiallelic loci were evaluated against all other alleles combined, without adjustment for multiple comparisons. Certain noncandidate alleles (ie, those that either were not significantly associated with HD¹⁶ or were not investigated previously) were evaluated with the use of adjusted significance points²¹ if the number of informative transmissions was large enough to achieve a statistically significant result ($P < .05$). Meiotic segregation distortion was evaluated by examining transmission to the unaffected siblings and half-siblings of the affected members with known parental genotypes.

It was necessary to exclude one family from analysis for one locus (TAP2 Ile379Val) because one parent was unavailable, the other parent and the offspring were heterozygous, and the transmitted allele could not be determined. Because such exclusion can produce bias,²² we determined the range of its potential effect by including this family in the analysis assuming that the heterozygous parent transmitted (1) the Ile allele to all offspring or (2) the Val allele to all offspring. The results were essentially unchanged and are not presented. For all other loci, the transmissions within this family were unambiguous. There were 5 other families in which one parent of affected member(s) was unavailable, and the transmitted alleles were unambiguous for all loci in these families.

To control for potential confounding by other alleles at the locus under investigation, the TDT was also performed with the exclusion of candidate alleles at the locus from the analysis. The results were similar to those obtained without exclusions and are not presented.

Results and discussion

This study provides evidence that the DRB1*1501-DQA1*0102-DQB1*0602 haplotype is related to the development of familial HD ($P = .03$), particularly, familial NSHD ($P = .02$) (Table 1). This haplotype was transmitted 72.7% of the time (16 of 22) to an affected offspring, while it was transmitted 44% of the time (12 of 27) to unaffected siblings. At individual loci, evidence for linkage was obtained for DRB1*1501, DQB1*0602, and, for familial NSHD only, DQA1*0102 (Tables 1 and 2). The DRB1, DQB1, and

DQA1 loci are in tight linkage disequilibrium,²³ and the observed effect could not be localized to a single gene. All cases with the DRB1*1501 and DQB1*0602 alleles had the DRB1*1501-DQA1*0102-DQB1*0602 haplotype; 3 cases (2 NSHD, 1 non-NSHD) had the DQA1*0102 allele in a different haplotype (DRB1*1600-DQA1*0102-DQB1*0502). Our findings are in agreement with those from a case-control study involving 196 nonfamilial HD patients, in which a significantly increased risk of NSHD was associated with the DRB1*1501-DQA1*0102-DQB1*0602 haplotype but could not be attributed to a single locus within the haplotype.¹⁶ Unlike case-control analyses, the TDT is insensitive to population stratification; thus, the significant findings obtained in our study provide important new evidence of linkage and association.

The DRB1*1501-DQA1*0102-DQB1*0602 haplotype was observed in 16 of 28 HD cases (57.1%) (11 heterozygotes, 5 homozygotes) and in 14 of the 23 cases (60.9%) with NSHD (9 heterozygotes, 5 homozygotes). Nine of 16 families presented as sibling pairs with HD, which may indicate a recessive pattern of inheritance or a dominant gene with moderate to low penetrance. However, 6 families had HD cases in successive generations, suggesting a dominant gene with decreased penetrance in at least a subset of the families or a frequent recessive gene. The TDT provides valid results regardless of the mode of inheritance. There was no evidence that affected individuals within families were more likely to share the same HD subtype than unrelated affected individuals ($P > .99$). The affected individuals analyzed in this study were those living at the time the family was referred to the National Cancer Institute and therefore may represent a subset of patients with better survival. Approximately 80% of cases had NSHD, slightly higher than the rate seen (70%) among whites overall.⁶

We observed nonsignificant excesses of the DRB1*1104 allele and the DRB1*1104-DQA1*0501-DQB1*0301 haplotype and nonsignificant deficits of the DRB1*0701 and DQA1*0201 alleles among all familial HD cases and among the subset of familial NSHD cases (Table 1). Although the number of informative transmissions was limited for these comparisons, our results are consistent with the statistically significant associations found for these genetic markers by Klitz et al.¹⁶

Among noncandidate alleles, the DQB1*0201 allele was under-represented among familial HD cases ($P = .13$); the TAP1 allele encoding Ile at residue 333 predisposed to familial HD, particularly

Table 1. Transmission-disequilibrium test results for linkage between familial Hodgkin disease and candidate alleles at HLA class II and transporter associated with antigen processing loci, National Cancer Institute, Bethesda, MD, 1978-1993

| | All familial HD (n = 28) | | | | Familial NSHD only (n = 23) | | | | Unaffected siblings (n = 40)† | | | |
|-------------------|--------------------------|----|----------|-----|-----------------------------|----|----------|------|-------------------------------|----|----------|-----|
| | T | NT | χ^2 | P | T | NT | χ^2 | P | T | NT | χ^2 | P |
| DRB1 | | | | | | | | | | | | |
| *1501 | 16 | 6 | 4.55 | .03 | 15 | 5 | 5.00 | .03 | 12 | 15 | 0.33 | .57 |
| *1104 | 6 | 2 | 2.00 | .16 | 6 | 2 | 2.00 | .16 | 3 | 2 | 0.20 | .65 |
| *0701 | 2 | 6 | 2.00 | .16 | 2 | 6 | 2.00 | .16 | 5 | 7 | 0.33 | .57 |
| DQA1 | | | | | | | | | | | | |
| *0201 | 2 | 6 | 2.00 | .16 | 2 | 6 | 2.00 | .16 | 5 | 7 | 0.33 | .57 |
| DQB1 | | | | | | | | | | | | |
| *0602 | 16 | 6 | 4.55 | .03 | 16 | 5 | 5.76 | .02 | 12 | 15 | 0.33 | .57 |
| DRB1-DQA1-DQB1 | | | | | | | | | | | | |
| *1501-*0102-*0602 | 16 | 6 | 4.55 | .03 | 16 | 5 | 5.76 | .02 | 12 | 15 | 0.33 | .57 |
| *1104-*0501-*0301 | 6 | 2 | 2.00 | .16 | 6 | 2 | 2.00 | .16 | 3 | 2 | 0.20 | .65 |
| *1400-*0101-*0503 | 3 | 1 | 1.00 | .32 | 1 | 1 | 0.00 | 1.00 | 2 | 5 | 1.29 | .26 |

Candidate alleles are those for which statistically significant associations with sporadic Hodgkin disease were reported by Klitz et al.¹⁶

T indicates number of transmitted alleles; NT, number of nontransmitted alleles; HD, Hodgkin disease; and NSHD, nodular sclerosis Hodgkin disease.

†Includes full siblings and half siblings of HD patients.

Table 2. Transmission-disequilibrium test results for linkage between familial Hodgkin disease and noncandidate alleles at HLA class II and transporter associated with antigen processing loci, National Cancer Institute, Bethesda, MD, 1978-1993

| | All familial HD (n = 28) | | | | Familial NSHD only (n = 23) | | | | Unaffected siblings (n = 40)¶ | | | |
|-----------------------|--------------------------|----|----------|-------|-----------------------------|----|----------|-------|-------------------------------|----|----------|-------|
| | T | NT | χ^2 | P† | T | NT | χ^2 | P† | T | NT | χ^2 | P† |
| DRB1 | | | | | | | | | | | | |
| *0301 | 1 | 6 | 3.57 | .24 | — | — | — | — | 7 | 9 | 0.25 | — |
| *0401 | 5 | 4 | 0.11 | — | 3 | 4 | 0.14 | > .99 | 11 | 5 | 2.25 | .53 |
| *1300 | 3 | 6 | 1.00 | — | 3 | 4 | 0.14 | > .99 | 5 | 3 | 0.50 | — |
| All others‡ | 36 | 29 | — | — | 32 | 30 | — | — | 13 | 14 | — | — |
| Total | 45 | 45 | 4.07 | .25 | 38 | 38 | 0.23 | .97 | 64 | 64 | 2.27 | .52 |
| DQA1 | | | | | | | | | | | | |
| *0101 | 5 | 7 | 0.33 | — | 1 | 7 | 4.50 | — | 7 | 8 | 0.07 | — |
| *0102 | 19 | 9 | 3.57 | .29 | 19 | 5 | 8.17 | .02 | 18 | 20 | 0.11 | — |
| *0301 | 5 | 5 | 0.00 | — | 3 | 5 | 0.50 | — | 8 | 6 | 0.29 | > .99 |
| *0501 | 11 | 12 | 0.04 | — | 10 | 9 | 0.05 | — | 14 | 13 | 0.04 | — |
| All others‡ | 3 | 10 | — | — | 3 | 10 | — | — | 9 | 9 | — | — |
| Total | 43 | 43 | 6.17 | .19 | 36 | 36 | 13.59 | .01 | 56 | 56 | 0.41 | .98 |
| DQB1 | | | | | | | | | | | | |
| *201 | 3 | 11 | 4.57 | .13 | 3 | 8 | 2.27 | .53 | 9 | 13 | 0.73 | — |
| *0301 | 10 | 6 | 1.00 | — | 7 | 6 | 0.08 | — | 11 | 6 | 1.47 | .90 |
| *0302 | 2 | 5 | 1.29 | — | 2 | 5 | 1.29 | — | 7 | 4 | 0.82 | — |
| All others‡ | 25 | 18 | — | — | 21 | 14 | — | — | 26 | 30 | — | — |
| Total | 40 | 40 | 6.00 | .11 | 33 | 33 | 3.78 | .29 | 53 | 53 | 2.48 | .48 |
| DRB1-DQA1-DQB1 | | | | | | | | | | | | |
| *0301-*0501-*0201 | 1 | 6 | 3.57 | .18 | — | — | — | — | 7 | 9 | 0.25 | — |
| *0701-*0201-*0201 | 2 | 5 | 1.29 | — | 2 | 5 | 1.29 | .77 | 4 | 6 | 0.40 | > .99 |
| All others‡ | 42 | 34 | — | — | 36 | 33 | — | — | 46 | 42 | — | — |
| Total | 45 | 45 | 3.80 | .15 | 38 | 38 | 0.71 | .70 | 57 | 57 | 0.55 | .76 |
| DRB3-5 | | | | | | | | | | | | |
| DRB3*0101 | 2 | 6 | 2.00 | — | — | — | — | — | 4 | 10 | 2.57 | .54 |
| DRB3*0202 | 7 | 5 | 0.33 | — | 5 | 5 | 0.00 | — | 8 | 5 | 0.69 | — |
| DRB4*0101 | 7 | 13 | 1.80 | — | 5 | 13 | 3.56 | — | 16 | 13 | 0.31 | — |
| DRB5*0101 | 16 | 6 | 4.55 | .16 | 16 | 5 | 5.76 | .08 | 12 | 15 | 0.33 | — |
| All others‡ | 5 | 7 | — | — | 5 | 8 | — | — | 11 | 8 | — | — |
| Total | 37 | 37 | 7.20 | .13 | 31 | 31 | 7.51 | .11 | 51 | 51 | 3.50 | .48 |
| TAP1 Ile333Val | | | | | | | | | | | | |
| Ile | 14 | 6 | 3.20 | .07 | 12 | 3 | 5.40 | .02 | 15 | 13 | 0.14 | .71 |
| TAP1 Asp637Gly | | | | | | | | | | | | |
| Asp | 7 | 6 | 0.08 | .78 | 5 | 4 | 0.11 | .74 | 14 | 7 | 2.33 | .13 |
| TAP2 Ile379Val | | | | | | | | | | | | |
| Ile | 5 | 5 | 0.00 | > .99 | 3 | 5 | 0.50 | .48 | 9 | 3 | 3.00 | .08 |
| TAP2 Ala665Thr | | | | | | | | | | | | |
| Ala | 5 | 4 | 0.11 | .74 | 3 | 4 | 0.14 | .71 | 5 | 7 | 0.33 | .57 |

Noncandidate alleles either were not significantly associated with sporadic Hodgkin disease or were not evaluated in the study by Klitz et al.¹⁶

TAP indicates transporter associated with antigen processing. Other abbreviations are explained in Table 1.

¶Includes full siblings and half siblings of HD patients.

†Significance points for χ^2_{n-1} distribution for all alleles ("Total") at a locus tested simultaneously, and for a χ^2_1 distribution for the largest component with the use of *P* values adjusted by the method of Bonferroni.

‡All others include candidate alleles, alleles without power to test, and uninformative typings, which were grouped into a single category.

familial NSHD ($P = .02$); and the DRB5*0101 allele was transmitted more often than expected, particularly in familial NSHD ($P = .08$) (Table 2). However, the DRB5*0101 allele always cosegregated with the DRB1*1501-DQA1*0102-DQB1*0602 haplotype. Also, evidence for linkage disequilibrium between familial NSHD and TAP1 Ile333Val was limited to the subset of transmissions in which the TAP1 Ile allele cosegregated with the DRB1*1501-DQA1*0102-DQB1*0602 haplotype and the DRB5*0101 allele. Thus, we cannot resolve whether the 3 markers that demonstrated linkage disequilibrium with familial NSHD (ie, the DRB1*1501-DQA1*0102-DQB1*0602 haplotype, the TAP1 Ile allele, and the DRB5*0101 allele) represent more than one independent susceptibility locus.

There was no evidence for preferential transmission of particular alleles or haplotypes to the unaffected siblings and half siblings

of HD patients (Tables 1, 2). Taken together, the results of this study and those of Klitz et al¹⁶ provide evidence that the DRB1*1501 and DQB1*0602 alleles, or loci in linkage disequilibrium with them, confer risk for the development or, perhaps, survival of both sporadic and familial HD.

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