Proc. Natl. Acad. Sci. USA
Vol. 81, pp. 3539–3542, June 1984
Medical Sciences

Inherited predisposition to iridocyclitis with juvenile rheumatoid arthritis: Selectivity among *HLA-DR5* haplotypes

(early-onset pauciarticular/linkage/*HLA-Bw44*, *HLA-Bw35*)

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Communicated by K. Frank Austen, February 21, 1984

ABSTRACT ***HLA-DR5* is associated with a chronic iridocyclitis and juvenile rheumatoid arthritis with onset in early childhood. Previously published data provided indirect evidence for selective linkage between two *HLA-B* alleles and *HLA-DR5*. To test this observation further, 38 families, the probands of which have chronic iridocyclitis and juvenile rheumatoid arthritis, were *HLA* typed so that haplotypes associated with disease could be established. *HLA-DR5* was linked to *HLA-Bw44* or to *HLA-Bw35* and to *HLA-Cw4* in the majority of haplotypes obtained in the probands. Both *HLA-Bw44*, *-DR5* and *HLA-Bw35*, *-Cw4*, *-DR5* occurred more commonly in the proband haplotypes than in the control haplotypes. The frequency of the haplotype *HLA-Bw44*, *-DR5* was 0.133 compared with 0.007 ($\chi^2 = 27.04$, $P < 10^{-6}$) and for *HLA-Bw35*, *-Cw4*, *-DR5*, it was 0.093 compared with 0.11 ($\chi^2 = 13.83$, $P = 0.0002$). The relative risks were 20.77 and 9.23, respectively, versus 3.52 for *HLA-DR5* alone. *HLA-Bw44* occurred much more commonly in proband *HLA-DR5* haplotypes (0.455) compared with control *HLA-DR5* haplotypes (0.067) ($\chi^2 = 8.26$, $P < 0.01$). Not all *HLA-DR5*-bearing haplotypes predisposed equally to chronic iridocyclitis and early-onset pauciarticular juvenile rheumatoid arthritis.**

Juvenile rheumatoid arthritis (JRA) is associated with a range of HLA antigens that are in part distinct from those found in chronic arthropathies in adults (1, 2). These HLA associations include antigens HLA-DR5, HLA-DRw8, and HLA-B27 and reflect the different forms of JRA that can be distinguished clinically. HLA-DR5 is associated with one form that occurs in children, predominantly females, with limited joint disease at onset (pauciarticular). This form develops in early childhood and is associated with antinuclear antibody in serum (3–7). In at least half of the instances, these children have a chronic iridocyclitis from which the long-term morbidity is often substantially greater than that from arthritis alone (8, 9). In an initial report of the association between the disease and HLA-DR5, indirect evidence for selective linkage between two HLA-B series antigens, HLA-B12 and HLA-Bw35, and HLA-DR5 was obtained (3). These data, obtained through study of probands alone, were based on estimates of linkage disequilibrium, the excess of observed over expected numbers of individuals sharing particular HLA antigens.

In the present investigation the necessary family studies were performed to examine directly the linkage between *HLA-A*, *-B*, and *-C* genes and *HLA-DR5* in a group of patients with JRA and chronic iridocyclitis.[||]

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METHODS

Subjects. Thirty-eight North American Caucasian patients (35 females and 3 males) with early-onset pauciarticular JRA with iridocyclitis and 239 family members were studied. All were drawn from communities throughout the New England area and reflect the ethnic variation of the region. Patients of both Northern and Southern European extraction were included. Eighteen of the probands were included in a previous study (3). All children met the criteria for pauciarticular onset JRA as defined by the Criteria Committee of the American Rheumatism Association (10). Additional study criteria included onset of arthritis before the age of 8 yr and the presence of iridocyclitis observed by either of two ophthalmologists experienced with the eye disease associated with JRA. Evidence either of active inflammation or of previous inflammatory eye disease, including synechiae or band keratopathy in the absence of active inflammation, was acceptable. Patients with posterior uveitis were not studied. Finally, the availability and consent of sufficient family members to establish genotypes for the *HLA* region in the probands was required.

Probands and family members were typed for HLA-A, -B, -C, -DR, DC(MB), and MT antigens in the Tissue Typing Laboratory of the Department of Rheumatology and Immunology, The Brigham and Women's Hospital.

Family trees were constructed and haplotype assignments were made for each locus when an informative assortment of alleles was demonstrated. If an assignment could not be made for a particular polymorphism, that haplotype was not considered in calculating the gene frequencies for the locus.

The denominator used to calculate gene frequencies varied therefore between polymorphisms being lower for some, especially the *DC(MB)* and *MT* genes, than for *HLA-A*, *-B*, *-C*, and *-DR*.

Control data consisted of 314 haplotypes established in members of the probands' families but excluded haplotypes inherited by a proband. Inclusion of all available family members ensured adequate numbers of control haplotypes. No haplotype was counted twice and one potential control haplotype in recombination with a proband's haplotype was excluded. This method of establishing control gene frequency and control haplotype frequencies by using the proband's family's has been compared with haplotype frequencies derived from families without an affected member. Very comparable results have been obtained between the two methods (11). The control gene frequencies were, in addition, com-

Abbreviations: JRA, juvenile rheumatoid arthritis; MNL, mononuclear leukocyte(s); CDC, complement-dependent cytotoxicity.

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[||]Alternative terms to describe the same population include juvenile arthritis and juvenile chronic polyarthritis.

pared with data for North American Caucasians from the Eighth International Histocompatibility Workshop (Table 2).

Cells. Peripheral blood mononuclear leukocytes (MNL) were obtained by density gradient centrifugation through Ficoll-Paque (Pharmacia).

HLA-A, -B, -C Typing. HLA-A, -B, -C typing for 39 specificities was carried out by microdroplet complement-dependent cytotoxicity (CDC) (12). HLA-A, -B, -C antisera were kindly supplied by the National Institute of Allergy and Infectious Diseases (Bethesda, MD).

HLA-DR Typing. HLA-DR specificities were typed by CDC on a nylon wool B-cell-enriched MNL population (13).

All preparations studied were evaluated in CDC with a polyvalent rabbit antiserum Ia serum kindly supplied by J. Strominger (Biological Laboratories, Harvard University, Boston) and were found to contain 70% Ia-bearing MNL.

The CDC assays were performed as follows: MNL with antisera were incubated at room temperature for 1 hr and then incubated for a further 2 hr (14) with rabbit complement (Pel-Freez).

Typing antisera, including sera defined by the Eighth Histocompatibility Workshop (15), covered 9 *DR* specificities, were obtained locally, or were gifts from other laboratories.

DC(MB)/MT Typing. The MNL population was collected and the CDC assay was performed as for the *HLA-DR* specificities. Typing antisera defined a DC(MB)1/MT1 specificity and 4 additional specificities, 2 for DC(MB) and 2 for MT (16, 17).

Statistical Methods. *HLA* gene frequencies and selected *HLA* haplotypes were compared to controls by χ^2 analysis. Relative risks were calculated as in Woolf (18).

The *HLA* haplotype data, in addition to direct χ^2 testing, were analyzed by multivariate techniques (19) similar to methods recently applied to *HLA* data (20). This allows one to control for observed differences in gene frequencies between probands and controls, after which the data were retested by χ^2 analysis for differential linkage between probands and controls.

Corrections of *P* values (Table 4) for the numbers of statistical tests run have not been made in view of the data suggesting linkage disequilibrium between *HLA-DR5* and both *HLA-Bw35* and *HLA-Bw44* in independently conducted population studies (21, 22).

RESULTS

The mean age of onset of joint disease in the 38 probands was 2.5 yr (range, 10 months to 6 yr). The mean age at first detection of eye disease was 5.0 yr (range, 11 months to 17 yr). Antinuclear antibody is present in serum in 76% of those tested (19/25). The mean length of follow-up from first presentation was 8.6 yr (range, 10 months to 24 yr).

Gene frequencies of the *HLA-A*, *-B*, *-C*, *-DR*, *DC(MB)*, and *MT* polymorphisms for the locally established control haplotypes did not differ significantly from the gene frequencies reported from the Eighth Histocompatibility Workshop (15) (χ^2 = 8.78, 9 *df*, P = 0.46 for the *HLA-DR* gene frequencies). Thirty of the 314 control haplotypes were shown to include *HLA-DR5*.

Gene Frequencies. HLA-A, -B, *and* -C *loci*. The frequencies of *HLA-A2*, *HLA-Bw44*,** *HLA-Bw16*, *HLA-Bw35*, and *HLA-Cw4* were found to be increased in the proband compared with control haplotypes (Table 1).

Genes for the *HLA-A* locus could be assigned for 75 proband haplotypes and 291 control haplotypes. The frequency of *HLA-A2* was 0.453 versus 0.278, and the χ^2 comparing the frequencies of *HLA-A2* equaled 6.14 ($P < 0.01$). Assignments for *HLA-B* alleles were possible for 75 proband haplotypes and 293 control haplotypes. The *HLA-Bw44* frequency was 0.280 (21/75) compared with 0.130 (38/293), for which the χ^2 was 8.43, yielding $P < 0.01$. *HLA-Bw16* was found with a frequency of 0.120 (9/75) compared with 0.020 (6/293); the χ^2 was 14.49 ($P < 0.001$). Additionally, the frequency of *HLA-Bw35* was 0.200 (15/75) versus 0.102 (30/293). The χ^2 from the comparison of *HLA-Bw35* frequencies equaled 4.66 ($P < 0.02$).

Chromosomal assignment of *HLA-C* alleles could be made for 69 proband haplotypes, of which 0.261 (18/69) were *HLA-Cw4*, and for 245 control haplotypes, with 0.106 (26/245) being *HLA-Cw4*. The difference was significant (χ^2 = 10.70, $P < 0.005$).

HLA-DR *locus*. Seventy-six *HLA-DR* alleles could be assigned to the proband haplotypes and 273 were in the control haplotypes. The frequencies of two genes were increased: *HLA-DR5*, 23/76 compared with 30/273 (χ^2 = 14.55, $P < 0.001$), and *HLA-DRw8*, 9/76 compared with 9/273 (χ^2 = 8.42, $P < 0.01$), whereas the frequencies of three genes were decreased: *HLA-DR1* (χ^2 = 5.30, $P < 0.02$), *HLA-DR4* (χ^2 = 7.05, $P < 0.01$), and *HLA-DR7* (χ^2 = 5.56, $P < 0.02$) (Table 2).

DC(MB)/MT. The *DC(MB)/MT* polymorphisms were informative for 54 alleles in proband haplotypes and 216 in control haplotypes (Table 3). Proband and control haplotypes had similar frequency distributions with regard to the *DC(MB)* genes but differed with regard to the *MT* genes. In particular, *MT2* was more frequent (χ^2 = 8.71, $P < 0.01$) and *MT3* was less frequent (χ^2 = 6.45, $P < 0.02$).

***HLA-DR5* Haplotypes.** The distribution of 3 alleles, *HLA-Bw44*, *HLA-Bw35*, and *HLA-Cw4*, observed to be in linkage

Table 1. Frequency of *HLA-A*, *-B*, and *-C* genes in iridocyclitis and early-onset pauciarticular JRA

Locus	Haplotype: Proband	Haplotype: Control	χ^2	Relative risk
HLA-A	(n = 75)	(n = 291)		
A2	0.453	0.278	6.14	2.20
HLA-B	(n = 75)	(n = 293)		
Bw16	0.120	0.020	14.49	6.35
Bw35	0.200	0.102	4.66	2.19
Bw44	0.280	0.130	8.43	2.61
HLA-C	(n = 69)	(n = 245)		
Cw4	0.261	0.106	9.20	2.97

For each HLA locus gene frequencies were compared by analyzing $R \times 2$ tables, where R is the number of genes considered. χ^2 contributions of deviations from expected values in each row are shown in Tables 1–3 and are treated as χ^2 statistics with 1 degree of freedom.

Table 2. Frequency of *HLA-DR* genes in iridocyclitis and early-onset pauciarticular JRA

HLA specificity	Haplotype: Proband (n = 76)	Haplotype: Control (n = 273)	Workshop*	χ^2
DR1	0.026	0.121	0.106	5.30
DR2	0.105	0.161	0.136	1.25
DR3	0.145	0.117	0.118	0.36
DR4	0.039	0.168	0.148	7.05
DR5	0.303	0.110	0.102	14.55†
DRw6	0.079	0.033	0.037	2.92
DR7	0.026	0.125	0.126	5.56
DRw8	0.118	0.033	0.027	8.42‡
DRw9	0.013	0.004	0.015	0.94
DRX§	0.145	0.128	0.185	0.12

*Eighth International Histocompatibility Workshop.
†Relative risk, 3.52.
‡Relative risk, 3.94.
§Not detected by presently available serology.

****HLA-Bw44* is a serological split of *HLA-B12*.

Table 3. Frequency of *DC(MB)/MT* genes in iridocyclitis and early-onset pauciarticular JRA

DC(MB)/MT specificity	Haplotype: Proband (n = 54)	Haplotype: Control (n = 216)	χ^2
MB2	0.259	0.241	0.06
MB3	0.259	0.245	0.03
MT2	0.556*	0.292	8.71
MT3	0.074	0.255	6.45

*Relative risk, 3.04.

disequilibrium with *HLA-DR5* in earlier studies of phenotypes (3), was compared in proband and in control haplotypes (Table 4). *HLA-Bw44, -DR5* was present with a frequency of 0.133 (10/75) compared with 0.007 (2/273) (χ^2 = 27.04, $P < 10^{-6}$). The *HLA-Bw35, -Cw4, -DR5* haplotype also differed, 0.093 (7/75) versus 0.011 (3/273), the χ^2 being 13.83 (P = 0.0002).

The observed differences in *HLA-DR5* haplotypes were not simply a consequence of the difference in frequency of the *HLA-DR5* genes between the two groups. *HLA-B* alleles linked to *HLA-DR5* had different frequencies in the 22 proband *HLA-DR5* (+) haplotypes compared to the 30 control *HLA-DR5* (+) haplotypes (Table 5). *HLA-Bw44* was linked to *HLA-DR5* much more frequently in proband haplotypes compared with control haplotypes, 0.455 (10/22) versus 0.067 (2/30) (χ^2 = 8.26, $P < 0.01$). The frequency of *HLA-Bw35, -Cw4* linked to *HLA-DR5* was 0.318 (7/22) versus 0.100 (3/30) (χ^2 = 3.15, $P < 0.1$). Proband and control *HLA-DR5* (−) haplotypes differed in *HLA-Bw35, -Cw4* genes (χ^2 = 4.92, $P < 0.05$).

Multivariate analysis of the data given in Table 5 indicated some difference in the relative frequencies of *HLA-B*-locus genes, between probands and controls, depending on the presence or absence of *HLA-DR5* in the haplotype. The χ^2 statistic for an excess of *Bw44* in *DR5* (+) haplotypes was 4.18 ($P < 0.05$).

Twelve of the proband's *HLA-DR5* haplotypes were also informative for the *DC(MB)* and *MT* polymorphisms; 11 carried the *MB3* and 10 carried the *MT2* alleles. The remaining alleles, 1 at the *MB* locus and 2 at the *MT* locus, were not serologically defined (*MBX* or *MTX*). Of the 30 control *HLA-DR5* haplotypes, 16 were informative at the *MB* and 20 were informative at the *MT* loci. Fifteen of the *MB* alleles were *MB3* and 1 was *MBX*. Eighteen of the *MT* alleles were *MT2*, 1 was *MT1*, and 1 was *MTX*.

DISCUSSION

The gene frequencies of 8 *HLA* alleles from 5 loci have been shown to be increased in 38 patients with chronic iridocyclitis and early-onset pauciarticular JRA. The alleles *HLA-A2, HLA-Bw44, HLA-Bw35, HLA-Bw16, HLA-Cw4, HLA-DR5, HLA-DRw8*, and *MT2* were found more frequently than expected in the disease group. This increased risk, albeit of a fairly modest degree, was greater for the *HLA-DR* alleles than for those of other loci, a finding common to many diseases with an immunologic component in their pathogenesis.

Table 4. Frequency of selected *HLA-B, -DR5* haplotypes

HLA allele	Haplotype: Proband (n = 75)	Haplotype: Control (n = 273)	Relative risk	χ^2
Bw44, DR5	0.133	0.007	20.77	27.04
Bw35, Cw4, DR5	0.093	0.011	9.23	13.83
Other	0.773	0.982	0.06	2.65

Table 5. *HLA-B* alleles linked to *HLA-DR* alleles

HLA allele	Haplotype: Proband	Haplotype: Control	Relative risk	χ^2
DR5				
Bw44	0.455 (10)	0.067 (2)	11.67	8.26
Bw35, Cw4	0.318 (7)	0.100 (3)	4.20	3.15
B other	0.227 (5)	0.833 (25)	0.06	8.09
Non-*DR5*				
Bw44	0.170 (9)	0.128 (31)	1.39	0.56
Bw35, Cw4	0.113 (6)	0.037 (9)	3.30	4.92
B other	0.717 (38)	0.835 (202)	0.50	0.76

n values are given in parentheses.

Four of these observations, those relating to *HLA-Bw35, -Cw4, -Dw5*, and *-DRw8*, agree with earlier findings of increased antigen frequencies in several studies of probands alone (2, 3). In an earlier investigation, although *HLA-Bw44* was not increased in frequency overall, it was observed to be in linkage disequilibrium with *HLA-DR5* in the study population (3). *HLA-A2* has been reported to be associated with JRA in two independent investigations (23, 24). To the best of our knowledge, the associations of *HLA-Bw16* and *MT2* with the disease have not been documented hitherto. That with *MT2* is predictable given the established relationship between *HLA-DR5, HLA-DRw8*, and *MT2* (17).

The tissue typing of family members allowed us to make chromosomal assignments and thereby establish haplotypes for the *HLA* region. Comparisons could be made between haplotypes in probands and controls. Sufficient *HLA-DR5* haplotypes were documented among the 314 control haplotypes to allow this comparison for *HLA-DR5* but not for the other relevant but less common *HLA-DR* allele, *HLA-DRw8*. *HLA-DR5* was linked to *HLA-Bw44* or to *HLA-Bw35* and *HLA-Cw4* more commonly in the probands than *HLA-DR5* in the control haplotypes (Table 5). *HLA-DR5* was shown to be linked to either *HLA-Bw44* or *HLA-Bw35* and *HLA-Cw4* in 77% of instances in the probands compared with 16.6% of the control *HLA-DR5* haplotypes. There was little evidence for an effect of the *HLA-Bw44* gene independent of that from *HLA-DR5*, although *HLA-Bw44* was commoner in the haplotypes established among the *HLA-DR5* (−) probands; this increase did not reach a level of statistical significance. In contrast, the increase in the *HLA-Bw35, -Cw4* haplotype in the *HLA DR5* (+) probands may not be dependent entirely on the *HLA-DR5* linkage, as *HLA-Bw35, -Cw4* haplotypes did occur more commonly than expected in the *HLA-DR5* (−) probands. These data demonstrate that two haplotypes, *HLA-Bw44, -DR5, MT2, MB3* and *HLA-Bw35, -Cw4, -DR5, MT2, MB3*, predispose an individual to early-onset pauciarticular JRA with iridocyclitis more strongly than does the inheritance of chromosomes bearing the *HLA-DR5* gene with other linkages.

The relative risks for these haplotypes were 20.77 for the *HLA-DR5, HLA-Bw44* haplotype and 9.23 for the *HLA-DR5, HLA-Bw35*, and *HLA-Cw4* haplotype. Both are higher than the relative risk for single *HLA* allele and disease associations, even of the *HLA-D* locus.

The two *HLA-DR5* haplotypes associated with JRA and chronic iridocyclitis are not unique to the disease population. Both occurred in the control population, albeit infrequently. In addition, there is some evidence that *HLA-Bw44, HLA-Bw35* with *HLA-Cw4* and *HLA-DR5* are in linkage disequilibrium in unselected populations (21, 22) as well as in this disease situation.

Why an HLA disease association should be stronger for a haplotype that shows linkage disequilibrium rather than one without a characteristic linkage group is not known. Other disease associations with haplotypes have been reported, in-

cluding juvenile-onset diabetes mellitus, 21-hydroxalase deficiency, and drug toxicity (25, 26).†† Studies limited to probands suggest yet other diseases will have strong haplotypic associations when the appropriate family studies are done (27–29).

Some 20–30% of all *HLA* haplotypes show linkage disequilibrium that generally extends between *HLA*-B and *-DR* and includes alleles of the four *HLA*-linked complement loci (22, 29, 30). Occasionally, the linkage group involves an *HLA-A* allele and a glyoxalase allele,†† the latter being mapped centromeric to *HLA-D*. Several mechanisms have been suggested to account for the phenomenon of linkage disequilibrium. These include a relatively recent mutation, natural selection, and migration. Evidence for yet another mechanism has been recently presented. This mechanism would involve *t*-loci equivalents, loci concerned with organogenesis, which are likely to be linked to *HLA* (22). If these loci in man have the property of suppressing chromosomal recombination, as is the case in the mouse model, the trapping of disease-associated genes on a chromosome coding for characteristic linkage groups could occur (31). This explanation is consistent with the data presented above and is likely to be applicable to other HLA-associated diseases.

††Raum, D., Awdeh, Z., Gabbay, K., Yunis, E. J. & Alper, C. A., Fourth International Workshop for the Genetics of Complement, Boston, July 13–15, 1982, Abstr. 38.

The assistance of Agnes Maier in the preparation of this manuscript is gratefully acknowledged. This research was supported by the Easter Seals, the Gebbie and the Leeder Foundations, the Lions Clubs of Massachusetts, the New England Peabody Home for Crippled Children, the National Institutes of Health (AM30486 and AM05577), and the Multipurpose Arthritis Center (AM 20580 P16).

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