BRIEF REPORT

HLA ANTIGENS IN WHIPPLE'S DISEASE

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The prevalence of HLA–A and B antigen loci in patients with Whipple's disease was determined from data obtained in a review of the literature and from personal communications. Data on the HLA–A and B locus typing of 30 patients were available (with the exception that 1 of the patients was not typed for the HLA–B locus), and for an additional 18 patients, HLA–B27 data were available. Of the 47 patients typed for B27, 13 (28%) were B27 positive. Twelve of the 48 patients had sacroiliitis, and 2 (17%) of them were B27 positive. These data suggest that Whipple's disease may be associated with HLA–B27, even in the absence of concomitant sacroiliitis.

In 1979, Feurle and colleagues reported a possible association between Whipple's disease and an increased frequency of HLA–B27 antigen (1); 4 of their 9 patients (44%) expressed the B27 antigen. It is difficult, however, to draw conclusions from such a short series. There are now published and unpublished data on 48 patients (1–29): HLA antigen typing has been done on 30 individuals, and the presence or absence of HLA–B27 antigen has been determined in 18 individuals. Much of this data is not readily available in English-language publications; therefore, it seems worthwhile to make it available in a single brief paper.

Methods. During the past 21 years, I have compiled a complete bibliography of all English and foreign-language reports of Whipple's disease. My information was drawn from the *Cumulated Index Medicus*, Excerpta Medica Database, and Medlars II, and consists of 671 original papers, reviews, and letters. Six hundred twenty-six of these reports have been obtained and, when necessary, translated. Of these 626 papers, 29 report results of HLA typing in 1 or more patients with Whipple's disease. Duplicate reporting of these patients was excluded.

There are unpublished data available on HLA typing of 1 patient from this medical center (courtesy of Dr. Jane Schultz and Dr. Armin Good), 1 patient from the Allen Park VA Medical Center (Detroit, MI; courtesy of Dr. Pat Kuzma-Sell), 1 patient from the VA Medical Center (Durham, NC; courtesy of Dr. Charles Mansbach), and 1 patient from Royal Liverpool Hospital (Liverpool, UK; courtesy of Dr. J. C. Woodrow and Dr. Armin Good). In addition, data on 3 patients who had been typed for HLA–B27 antigen alone were supplied by Dr. Alvin Zfass (Richmond, VA), Dr. Stephen Kingsley (Danbury, CT), and Dr. R. B. Lorenzo (VA Medical Center, Roseburg, OR), respectively. The HLA typing data obtained from personal communications were not solicited, but were obtained incidental to communications regarding diagnosis or management of the patients.

Data are available only for class I antigens (HLA–A, B, and C). There are no data concerning class II (HLA–DR) antigen expression.

Results. Table 1 gives the reported results of typing of 30 patients in whom HLA–A, B, and some-

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Supported by Merit Review Funds from the Veterans Administration.

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Submitted for publication April 28, 1986; accepted in revised form June 18, 1986.

Table 1. HLA antigen frequency in 30 patients with Whipple's disease*

Patient (reference no.)	Year, country of origin	HLA type
1 (3)	1978, South Africa	A1,A2, B7
2 (4)	1983, UK	A2,A29, B7,Bw62
3 (5)	1980, France	A2,A9, B5,B17
4 (7)	1976, France	A2,Aw32, Bw15,Bw35
5 (1)	1979, FRG	A11,A28, Bw35
6 (1)	1979, FRG	A1,A2, B15,Bw21
7 (1)	1979, FRG	A2,A9, Bw22,B27
8 (1)	1979, FRG	A3, B7,B14
9 (1)	1979, FRG	A2,A9, B5
10 (1)	1979, FRG	A2, B12,B27, Cw3
11 (1)	1979, FRG	A1,A29, B8,B17, Cw6
12 (1)	1979, FRG	A1,Aw24, B8,B27, Cw2
13 (1)	1979, FRG	A1,A2, B17,B27
14 (11)	1972, Canada	A1,A2, Te51μ,Te57
15 (13)	1982, USA	A1,A3, B5,B7
16 (13)	1982, USA	A26, B14,Bw16
17 (14)	1978, USA	A2, Bw21,B27, Cw2
18 (15)	1983, France	A1,A11, B7,B35
19 (18)	1982, Italy	A2,A29, B13,Bw21
20 (21)	1984, USA	A2, Bw40,Bw62
21 (22)	1983, FRG	A2,A9, B13,Bw37
22 (26)	1984, Bulgaria	A2,A24, B5,B17, C4
23 (26)	1984, Bulgaria	A2,A24, B12,B16
24 (27)	1981, Portugal	A1,A11, B12,Bw40
25 (28)	1981, France	A2,A3, B7,B17
26 (29)	1979, UK	A2,A9(A23), B5,B7
27 (pc)	–, USA	A3, B7,Bw35
28 (pc)	–, USA	A31,A33, B18,B27
29 (pc)	–, USA	Aw23,Aw33, Bw44, Cw4
30 (pc)	–, UK	A1,A11, B7,Bw22

* Patients 1–26 were described in the literature, patient 27 was seen at the author's institution, and data on patients 28–30 were from personal communications (pc).

times C loci were determined. Eighteen patients were typed for only HLA–B27. Of these 18, 7 were B27 positive (personal communication and refs. 6, 8, 23, and 25), and 11 were B27 negative (2,9,10,12,13,16, 17,19,20,24). B locus typing was not done by Groll et al (11). Thus, 13 of the 47 patients (28%) typed for B locus were B27 positive. Forty-five patients were men and 3 were women. Forty-seven were white, and there was 1 black man who was B27 negative (patient 29, Table 1).

Because there is an increased prevalence of ankylosing spondylitis (AS) in B27 positive individuals, and because there may be an association of AS with Whipple's disease, the reports were analyzed in this regard (Table 2). Radiologic evidence of sacroiliitis was present in 12 individuals who had been typed for B27, and 2 (17%) of these were B27 positive. Of the total of 13 patients with Whipple's disease who were

Table 2. Prevalence of HLA–B27 in patients with Whipple's disease and with sacroiliitis*

Reference no.	Year	Sacroiliitis	B27
3	1978	Unilateral	–
5	1980	Bilateral	–
6	1978	Bilateral	+
7	1976	Unilateral	–
8	1983	Bilateral	+
10	1983	Bilateral	–
13	1982	Bilateral	–
15	1983	Bilateral	–
16	1985	Bilateral	–
17	1982	Bilateral	–
19	1985	Unilateral	–
24	1978	Bilateral	–

* Sacroiliitis was confirmed by radiographic studies in each case cited.

B27 positive, only 2 (15%) were reported to have radiologically demonstrable sacroiliitis.

Discussion. The frequency of B27 in European and North American white populations is 8% (30). The gene frequency of HLA–B27 in those ethnic groups which are most likely to develop Whipple's disease ranges from 0.3–6.9% (Table 3). Eighty-three white control subjects, i.e., persons who were without rheumatic diseases or other significant illnesses, were typed in our VA Hospital. Of these, 8.4% were B27 positive. Thus, the 27% incidence (13 of 47 patients) of B27 in this retrospective analysis clearly suggests an increased prevalence of B27 in patients with Whipple's disease ($P < 0.01$ by chi-square test and by comparison of reported data [13 of 47 patients] with our control data [7 of 83 subjects]). Sacroiliitis appears to be more frequent in Whipple's disease (12 of 48 patients), but it is associated with a minimal increase in B27 (2 of 12 patients).

Table 3. HLA–B27 gene frequency in control subjects*

Population	Gene frequency
American	2.8
English	6.0
French	1.6
German	2.9
Canadian	6.9
Italian	0.3

* Control subjects in this study were selected white populations. Frequency of occurrence of B27 was compared with occurrence of Whipple's disease. Modified from Albert ED, Baur MP, Mayr WR: Histocompatibility Testing 1984. New York, Springer-Verlag, 1984, pp 333–341.

There are 4 B locus antigens that cross-react with B27: B7, Bw22, Bw40, and Bw42. Of the 29 patients who had complete B locus typing (Table 1), 6 (21%) had B27 alone, 9 (31%) had B7, 2 (7%) had Bw22, and 2 (7%) had Bw40, while none were Bw42 positive. Thus, 17 of 29 patients (59%) possessed B27 and/or 1 of its cross-reacting antigens (1 had both Bw22 and B27, while another had B7 and Bw22). Thirty-one (37%) of our 83 control subjects possessed B27 and/or 1 of the cross-reacting antigens.

A retrospective analysis such as this has many problems. It would be far better to obtain the data in a prospective fashion, for the typing to be done in a single laboratory, and for all patients to have routine roentgenogram studies of the sacroiliac joints. Because of the rarity of Whipple's disease, such an ideal study is not possible. I have tabulated clinical data on 594 cases reported in the literature and have carefully corrected for the 62 instances in which a single patient was described more than once. Also, I have included unpublished clinical data on 79 patients. These precautions having been taken, it is reasonable to conclude that Whipple's disease may be associated with HLA–B27, even in the absence of concomitant sacroiliitis. The increased prevalence of sacroiliitis may be more suspect than that of B27, i.e., patients with Whipple's disease and with sacroiliitis are more likely to be described than those without sacroiliitis. Further, interpretations of radiographs of sacroiliac joints may vary. In the study by d'Eshougues and colleagues (7) of 36 Whipple's disease patients who were seen in rheumatology and gastroenterology clinics in France, 5 patients (14%) demonstrated sacroiliitis radiologically, and 11 (31%) had clinical and/or radiologic changes of sacroiliitis.

One may argue that B27 positive patients with Whipple's disease are more likely to be described than are B27 negative individuals. The significance of the difference between HLA antigen frequencies in Whipple's disease patients compared with those in control subjects cannot be determined. If valid, this difference is genetically determined, and may play a role in the likely immunologic tolerance (11) or subtle cellular immune deficiency that appears to be present in Whipple's disease (31).

Acknowledgments. The author is grateful to Dr. Armin Good and to Dr. Jane Schultz for reviewing the manuscript and making many helpful suggestions.

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