SHORT REPORT

HLA antigens in chronic inflammatory demyelinating polyneuropathy

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Abstract

HLA typing of 71 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) showed an overall increase in frequencies of HLA-A3, -B7, -DR2 as well as concomitantly decreased frequencies of HLA-44 and DR7. The strongest associations were seen with HLA-DR2, -DR7 and -B44 in CIDP overall, although they did not reach statistical significance.

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It is generally considered that acute inflammatory neuropathy (Guillain-Barré syndrome, GBS) and chronic inflammatory neuropathy (CIDP) are variants of the same disease[1-4] and it has been proposed that genetically determined host factors may govern the chronicity of the pathological process.[4-6] The hypothesis has received some support from the reported association of HLA-B8, -Dw3,[5,6] -AW30 and -AW31 antigens[5] with CIDP. By contrast no association of GBS has been demonstrated with HLA antigens.[7-8] Further evidence for genetic factors in the pathogenesis of CIDP include the demonstration of an association with the M3 allele of the alpha-1-antitrypsin system (PiM3)[9] and possibly Gm haplotypes[10] on chromosome 14

As the earlier studies of HLA antigens and CIDP were performed on small numbers of patients, we have examined the HLA class I and II antigen frequencies on a larger group of 71 patients.

Patients and methods

HLA-A and -B antigens were determined in 71 patients who satisfied the diagnostic criteria for CIDP.[4,11,12] Fifty six of these were also investigated for HLA-DR /-DRw and -DQ. CIDP patients were further divided into chronic relapsing (CR) and non-relapsing (CNR) subgroups.[12] Most of the patients have been described earlier[4,12] and this study includes those reported in the earlier, smaller series.[5]

Control populations consisted of 2,516 normal healthy blood donors and hospital staff typed for HLA-A and -B locus antigens. One thousand and fifty eight of these were also typed for HLA-D. Three hundred and fifteen and 322 were satisfactorily typed for DRw and DQ respectively.

Typing for HLA-A and -B antigens was carried out by the standard NIH microlymphocytotoxicity test. HLA-DR/DRw/DQ antigens were typed by the standard procedure of the Seventh International Histocompatibility workshop. All typing sera were standardised against International Histocompatibility Workshop sera. Phenotype frequencies were compared by the chi-square test using Yates' correction factor for continuity. Correction for multiple comparisons was applied where appropriate.

Results

Results are summarised in tables 1-3.

HLA typing revealed non-significant frequency increases of HLA-A3 ($p = 0.239$) -B7 ($p = 0.150$), -DR2 ($p = 0.104$) and an overall decrease of -B44(B12) ($p = 0.069$) and -DR7 ($p = 0.060$) frequencies in both chronic relapsing (CR) and non-relapsing (CNR) subgroups of CIDP. No change was seen in the frequencies of HLA-A30/31 or -B8 in either group. The frequency of HLA-DR2 was raised in both subgroups although it fell short of statistical significance ($p = 0.104$).

It is well recognised that HLA-B7 and -DR2 are in linkage disequilibrium in the normal population. We have observed a non statistically significant increase in the frequency of HLA-B7 and -DR2 in this patient cohort and would therefore expect a corresponding increase in the co-incidence of the B7-DR2 supratype. In the current data, this co-occurrence of B7 and DR2 appears to be much greater than would be seen normally (table 3).

Discussion

This report represents the largest number of patients so far studied for HLA associations in CIDP. It does not confirm earlier observations of a borderline increase in frequency of HLA-B8/-Dw3 or -Aw 30/31.[5,6] This work suggests that there may be an association with -DR2, although the findings do not reach statistical significance after applying the correction for multiple comparisons and would need to be confirmed in another cohort. The difference between our findings and those of the earlier studies are probably explained by the smaller number of patients in the first reports.

Since CIDP has been regarded as the peri-

Table 1 Antigen frequencies

HLA-A Locus *Antigen*	*CIDP Total*	*CIDP-CR*	*CIDP-CNR*	*Controls*
A1	0·3622	0·3542	0·3913	0·3373
A2	0·4507	0·4583	0·4348	0·4901
A3	0·3380[a]	0·3333	0·3478	0·2677
A11	0·1127	0·1250	0·0870	0·1269
A23(9)	0·0000	0·0000	0·0000	0·0259
A24(9)	0·2113	0·2083	0·2174	0·1480
A26(10)	0·0425	0·0208	0·0870	0·0601
A28	0·0425	0·0208	0·0870	0·0680
A29(19)	0·0563	0·0832	0·0000	0·0772
A30(19)	0·0704	0·0832	0·0435	0·0434
A31(19)	0·0425	0·0208	0·0870	0·0354
A32(19)	0·0563	0·0624	0·0435	0·0632
Aw33(19)	0·0000	0·0000	0·0000	0·0115
Aw34(10)	0·0000	0·0000	0·0000	0·0004
Aw36	0·0000	0·0000	0·0000	0·0004
Aw43	0·0000	0·0000	0·0000	0·0000
	n = 71	n = 48	n = 23	n = 2516
HLA-B Locus				
Antigen	*CIDP total*	*CIDP-CR*	*CIDP-CNR*	*Controls*
B7	0·3521[b]	0·3333	0·3913	0·2679
B8	0·2535	0·2500	0·2609	0·2691
B13	0·0704	0·0624	0·0870	0·0366
B14	0·1408	0·1664	0·0870	0·0783
B18	0·0282	0·0208	0·0435	0·0731
B27	0·0425	0·0416	0·0435	0·0870
B35	0·1408	0·1040	0·2174	0·1343
B37	0·0425	0·0624	0·0000	0·0203
B38(16)	0·0563	0·0624	0·0435	0·0262
B39(16)	0·0000	0·0000	0·0000	0·0330
Bw41	0·0141	0·0208	0·0000	0·0095
Bw42	0·0000	0·0000	0·0000	0·0000
B44(12)	0·1833[c]	0·2083	0·1305	0·2893
B45(12)	0·0000	0·0000	0·0000	0·0123
Bw46	0·0000	0·0000	0·0000	0·0000
Bw47	0·0000	0·0000	0·0000	0·0103
Bw48	0·0000	0·0000	0·0000	0·0000
B49(21)	0·0282	0·0416	0·0000	0·0207
Bw50	0·0000	0·0000	0·0000	0·0155
B51(5)	0·1275	0·1458	0·0870	0·0765
Bw52(5)	0·0141	0·0000	0·0435	0·0251
Bw53	0·0141	0·0208	0·0000	0·0014
Bw54(22)	0·0000	0·0000	0·0000	0·0001
Bw55(22)	0·0141	0·0000	0·0435	0·0208
Bw56(22)	0·0141	0·0000	0·0435	0·0186
Bw57	0·0850	0·1040	0·0435	0·0701
Bw58(17)	0·0000	0·0000	0·0000	0·0175
Bw60(40)	0·0991	0·0624	0·1740	0·1085
Bw61(40)	0·0141	0·0000	0·0435	0·0175
Bw62(15)	0·1275	0·1040	0·1740	0·1165
Bw63	0·0000	0·0000	0·0000	0·0024
Bw71(70)	0·0000	0·0000	0·0000	0·0009
Bw72(70)	0·0000	0·0000	0·0000	0·0006
Bw73	0·0000	0·0000	0·0000	0·0000
	n = 71	n = 48	n = 23	n = 2516

[a]:p = 0·239
[b]:p = 0·150
[c]:p = 0·069

pheral nervous system analogue of multiple sclerosis,[3, 12, 13] it is interesting that the HLA antigen frequency changes seen in this study, though modest, are similar to those seen in some Caucasian patients with multiple sclerosis. Early studies in Northern Europe, the United States and later in Australia, reported an increased frequency of HLA -A3 and -B7 and decreased frequency of -B12 in Caucasians with MS.[14–16]

Table 2 Antigen frequencies

HLA-DR, DRw, DQ LOCI *Antigen*	*CIDP Total*	*CIDP-CR*	*CIDP-CNR*	*Controls*
DR1	0·1607	0·1579	0·1667	0·1730
DR2	0·4107[d]	0·4211[e]	0·3889	0·2987
DR3	0·3214	0·2895	0·3889[f]	0·2892
DR4	0·2321	0·2368	0·2222	0·3176
DR7	0·1429[g]	0·1579	0·1111	0·2552
DRw8	0·0357	0·0000	0·1111	0·0435
DRw9	0·0179	0·0263	0·0000	0·0123
DRw10	0·0000	0·0000	0·0000	0·0019
DRw(11)	0·0893	0·1316	0·0000	0·1115
DRw12(5)	0·0000	0·0000	0·0000	0·0217
DRw13(w6)	0·2500	0·2105	0·3333	0·1957
DRw14(w6)	0·0179	0·0263	0·0000	0·0473
	n = 56	n = 38	n = 18	n = 1058
DRw52	0·5536	0·4474	0·7777	0·6667
DRw53	0·3929	0·4211	0·3333	0·5841
	n = 56	n = 38	n = 18	n = 315
DQw1	0·7140	0·7368	0·6667	0·6304
DQw2	0·3929	0·3947	0·3889	0·4627
DQw3	0·4107	0·4474	0·3333	0·5621
	n = 56	n = 38	n = 18	n = 322

d: p = 0·104; e: p = 0·152; f: p = 0·508; g: p = 0·060.

Table 3 Co-occurrence of HLA Antigens

	CIDP	Controls*
Frequency of DR2 in B7 individuals	80%	48·3%
Frequency of B7 in DR2 individuals	62%	31·7%

*Ninth Histocompatibility Workshop 1984.

In the current study, both clinical subgroups of CIDP displayed a tendency for raised frequencies of HLA-B7 and -DR2 and decreased frequencies of HLA-44 (B12).

These results suggest that there may be genetic similarities between peripheral and central demyelinating disorders mapping to chromosome 6 genes, or linked genes. Involvement of common HLA alleles in CIDP and MS would support our earlier observation[9] in the alpha-1-antitrypsin (Pi) system, but clearly, large multicentre studies are required to resolve this issue.

Alpha-1-antitrypsin genes are known to be in linkage with genes that code for constant regions of IgG heavy chains (Gm),[17] and in turn, these Gm genes interact with HLA genes to influence the immune response[18] to disease.[19–22] It is therefore appropriate to examine the possibility that HLA, Pi and Gm gene system interactions may be involved in CIDP and these studies are now planned.

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