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• *BRIEF REPORTS* •

Genetic distinctions between autoimmune hepatitis in Italy and North America

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Abstract

AIM: Our goals were to analyze the known genetic predispositions for autoimmune hepatitis (AIH) in AIH Italian population and to compare them with North American counterparts.

METHODS: Human leukocyte antigens (HLA) B8, C7, DR3, DR4, DR7, DR11, DR13, DQ2 and the B8-DR3-DQ2 phenotype were determined by microlymphocytotoxicity and polymerase chain reaction in 74 Italian patients (57 with type 1 and 17 with type 2 AIH) and 149 North American patients with type 1 AIH, and in adequate controls.

RESULTS: B8-DR3-DQ2 occurred more frequently in Italian patients with type 1 AIH than in Italian controls (30% *vs* 7%, $P<0.0001$), but less frequently than in North American counterparts (30% *vs* 48%, $P = 0.02$). DR4 occurred less frequently in Italian patients with type 1 AIH (23% *vs* 43%, $P = 0.01$) and in controls (16% *vs* 34%, $P = 0.0003$) than in North American counterparts. No differences were found in alleles' frequency between type 1 and type 2 Italian AIH patients. DR11 had a frequency lower in type 1 Italian AIH patients than controls (17% *vs* 35%, $P = 0.01$).

CONCLUSION: HLA DR4 is not associated with AIH in Italy. The known HLA risk factors for AIH occur similarly in Italian patients with type 1 and type 2 AIH, and they are less frequent than in North American patients. B8-DR3-DQ2 is the predominant phenotype of type 1 AIH also in Italy, and HLA DR11 may be a regionally distinctive protective factor against type 1 AIH.

Key words: Type 1 autoimmune hepatitis; Type 2 autoimmune hepatitis; Human leukocyte antigen

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INTRODUCTION

Autoimmune hepatitis (AIH) is characterized by interface hepatitis, high serum gamma-globulin levels, and circulating autoantibodies[1]. Antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) characterize type 1 AIH, whereas liver/kidney microsomal antibody type 1 (LKM1) and liver cytosol antibody type 1 (LC1) are the markers of type 2 AIH[2].

AIH has a worldwide prevalence, and its occurrence varies in different geographical regions and ethnic groups. Several reports have described associations between type 1 AIH and class I and class II human leukocyte antigens (HLA). In North America and in northern Europe, a strong association between type 1 AIH and HLA A1-B8-DR3 and HLA DR4 has been observed[3-5], and *DRB1*0301* and *DRB1*0401* are the main susceptibility alleles for type 1 AIH in these regions[6]. In contrast, *DRB1*0405* is strongly associated with type 1 AIH in Argentina[7] and Japanese[8] adults, and *DRB1*0404* is the main susceptibility allele for type 1 AIH in Mestizo Mexicans[9]. Among South American children, HLA DR13 (*DRB1*1301*) is a risk factor for protracted infection with hepatitis A virus[10] and the development of type 1 AIH[11-13]. HLA DR5 can be split into HLA DR11 and HLA DR12 by DNA-based techniques; in particular, HLA DR11 has been associated with a lower frequency in primary biliary cirrhosis in Italian patients suggesting a possible protective role of this allele in Italian population[14]. From the clinical standpoint, the observation that patients with type 1 AIH and HLA DR3 have a more aggressive clinical course and a poor response to corticosteroid therapy than patients with HLA DR4 [5,15] suggests that the genetic background may affect disease expression and treatment outcome.

Only a few studies investigated the relationship between HLA and type 2 AIH: Czaja[16] and Bittencourt[17] found an increased prevalence of HLA DR7 in German and Brazilian patients, whereas Jurado[18] reported a significant association

with HLA DQ2 in a Spanish cohort.

In this study we determine for the first time the associations between AIH in a southern European country and the HLA risk factors that have been implicated elsewhere in the occurrence of the disease. We also identify genetic distinctions that may explain regional differences in disease susceptibility, clinical phenotype, and treatment outcome, by comparing patient and normal populations from Italy and a prototypic North American population.

MATERIALS AND METHODS

Italian patients with type 1 AIH

Fifty-seven consecutive Italian patients with type 1 AIH referred to the Division of Internal Medicine (Department of Internal Medicine, Cardioangiology, Hepatology, Alma Mater University, Bologna) were enrolled in this study. According to the scoring system of the International Autoimmune Hepatitis Group[19], 38 patients (67%) received a diagnosis of "definite" AIH and 19 (33%) of "probable" AIH. Fifty patients were women (88%), and the median age was 38 years (range, 15-76 years). Serological characterization was performed as previously reported[20,21]; SMA were detected in 44 patients (77%), and ANA in 34 patients (60%). Twenty-three of the ANA-positive patients had a diffuse pattern of nuclear immunofluorescence (68%)[22,23]. Twenty-nine patients (51%) had both ANA and SMA; 15 patients (26%) had SMA as their sole serological finding, and 5 patients (9%) had ANA alone. Eight patients (14%) were negative for ANA and SMA, but they were retained in the analysis because of their diagnostic scores for AIH.

Liver biopsy was available in 54 patients (95%), and mild-moderate activity was present in 26 (48%), severe activity was present in 23 (43%), and cirrhosis was present in 5 (9%). Three patients did not undergo liver biopsy because clinical signs of cirrhosis (ascites and/or esophageal varices) were already documented at the time of the diagnosis. All patients were seronegative for any viral infection, and metabolic and genetic causes of liver disease had been excluded by appropriate tests.

Italian patients with type 2 AIH

Seventeen patients with type 2 AIH were enrolled in the study. According to the scoring system of the *International Autoimmune Hepatitis Group*[19], 15 (88%) reached a cumulative score consistent with the diagnosis of "definite" AIH, and 2 of "probable" AIH. Fifteen patients were women (88%), and the median age was 18 years (range, 8-34 years). Serological reactivities were as follows: LKM1 alone were detected in nine patients (53%); LKM and LC1 were detected in three patients (18%); LKM1 and SMA were present in three patients (18%); LKM and ANA were detected in one patient (6%), and LC1 alone were present in one patient (6%).

Liver biopsy was performed in 14 patients (82%), and mild-moderate activity was present in five patients (36%), severe activity in six (43%), and active cirrhosis in three (22%). All patients were seronegative for hepatitis B and C infection, and metabolic and genetic causes of liver disease had been excluded by appropriate tests.

North American patients with type 1 AIH

One hundred and forty-nine Caucasoid patients from North America who had been evaluated at the Mayo Clinic and who satisfied international criteria for the diagnosis of AIH[19] constituted the North American comparison population with type 1 AIH. One hundred and twenty-two patients (82%) were female, and the median age was 47 years (range, 13-81 years). Thirty-eight patients (26%) had ANA; 36 patients (24%) had SMA; and 75 patients (50%) had SMA and ANA at presentation. One hundred and thirty-five patients (91%) had been assessed for LKM1 by a previously reported assay[24], and each was seronegative for this marker. One hundred and forty-seven patients (99%) had undergone liver biopsy evaluation at accession, and 78 of the biopsied patients (52%) had interface hepatitis (mild-moderate activity), 15 patients (10%) had bridging necrosis (severe activity), 19 patients (13%) had multilobular necrosis (severe activity), and 35 patients (24%) had active cirrhosis. All patients were seronegative for hepatitis B and C infection, and other bases for their liver disease had been excluded by appropriate tests.

Clinical and laboratory features of all the Italian and North American patients at baseline are shown in Table 1.

Our study had been approved by the Institutional Review Boards of the University of Bologna and Mayo Clinic.

Table 1 Clinical and biochemical parameters of the studied groups at baseline

Features	Italian type 1 AIH (57 patients)	Italian type 2 AIH (17 patients)	North American type 1 AIH (149 patients)
Gender (m/f)	7/50	2/15	27/122
Age (yr)	38 (15–76)	18 (8–34)	47 (13–81)
AST (×UNL)	10.9 (0.5–56)	4.7 (1.5–5.1)	9.5 (0.5–66)
ALP (×UNL)	1.1 (0.2–4.56)	1.5 (0.6–4.4)	0.91 (0.6–6)
Bilirubin (mg/dL)	1.3 (0.2–26)	3.8 (0.9–4.3)	1.9 (0.3–29)
Albumin (g/L)	37 (24–46)	40 (19–48)	32 (15–42)
γ-Globulin (g/L)	23 (10–59)	22 (13–48)	29 (4–62)
IgG (mg/dL)	2 592 (1 260–6 948)	2 600 (1 530–4 212)	2 460 (248–7 200)
IgA (mg/dL)	301 (40–963)	346 (30–643)	290 (6–1 870)
IgM (mg/dL)	200 (75–597)	307 (150–577)	228 (28–1 400)
ANA positivity	34 (60%)	0	113 (76%)
SMA positivity	44 (77%)	0	111 (74%)
LKM1 positivity	0	16 (94%)	0
LC1 positivity	0	4 (23%)	Not tested

Data are shown as the median value (range). AST: serum aspartate aminotransferase level. ALP: serum alkaline phosphatase level. ANA: anti-nuclear antibodies. SMA: smooth muscle antibodies. LKM1: liver kidney microsome antibodies type 1. LC1: liver cytosol antibodies.

Italian control population

Three hundred and seventy-two Italian blood donors were tested for class I HLA (A and B loci), and 250 were tested for class II HLA (DR and DQ loci) by standard microlymphocytotoxicity and polymerase chain reaction, as previously described[25]. Class I HLA within the C locus were determined in 350 blood donors by standard microlymphocytotoxicity[26]. All Italian patients and controls were tested at Laboratory of Genetics, S.Orsola-Malpighi, University of Bologna, Bologna, Italy.

North American control population

One hundred and two Caucasoid blood donors at the Mayo Clinic constituted the control population from North America. Ninety-eight subjects (96%) were tested for class I HLA (A and B loci) by standard microlymphocytotoxicity, and 102 subjects were tested for class II HLA (DR and DQ loci) by polymerase chain reaction and sequence specific primers (PCR-SSP), as reported previously[5,6]. The normal subjects resided in Olmsted County, MN, and their ethnicity was similar to that of the North American patient populations with type 1 AIH. All North American patients and controls were tested at the Centre for Liver Research, University of Newcastle, Newcastle, UK.

Class I and II HLA determinations in patient groups

Class I HLA (A, B and C loci) were determined in all Italian patients by the standard microlymphocytotoxicity assay[26] using a panel of antisera from the 11th International Histocompatibility Workshop and several commercial antisera (Onelambda Inc., Los Angeles, CA). Class I HLA (A and B loci) were determined in 147 of the 149 North American patients with type 1 AIH (99%) by this standard technique[26,27].

Class II HLA (DR and DQ loci) were determined in all Italian patients by the standard microlymphocytotoxicity assay[26]. All samples positive for HLA DR5 and DR6 by the serological technique underwent DNA typing by PCR-SSP to split them into DR11 and DR12 (DR5) and DR13 and DR14 (DR6).

Class II HLA were determined in all 149 North American patients with type 1 AIH by PCR-SSP[5].

Statistical analysis

The Fisher's exact probability test was used to compare dichomotous variables. HLA B8, C7, DR3, DR4, DR7, DR11, DR13, DQ2 and the B8-DR3-DQ2 phenotype are known risk factors for AIH, and only the frequencies of these markers were analyzed in our study populations. Because the variables for comparison had been formulated a priori and then assessed systematically in our study groups, an uncorrected P value of 0.05 was used to determine statistical significance. The t-test with Welch's correction was used for the comparison of continuous variables.

RESULTS

Class I and II HLA in Italian patients with AIH and Italian normal subjects

HLA B8 (32% *vs* 10%, $P<0.0001$) and HLA C7 (51% *vs* 20%, $P<0.0001$) were significantly more frequent in Italian patients with type 1 AIH than in the Italian control population. HLA B8 and HLA C7, however, were similarly detected in Italian patients with type 1 and type 2 AIH (Table 2).

HLA DR3 occurred more commonly in Italian patients with type 1 AIH (30% *vs* 13%, $P = 0.004$) and type 2 AIH (29% *vs* 13%, $P = 0.07$) than in the Italian control subjects. In patients with type 2 AIH, however, this difference was not statistically significant.

HLA DR4 occurred as commonly in Italian patients with type 1 AIH (23%) or type 2 AIH (23%) as in Italian control subjects (16%). Furthermore, the frequency of HLA DR4 did not differ significantly in all three groups when only the patients and control subjects who were negative for HLA DR3 were analyzed.

HLA DR7 was detected more frequently in Italian patients with type 2 (35%) than in those with type 1 AIH (16%) and in the Italian control subjects (29%), but the small number of patients with type 2 AIH limited the statistical analysis.

HLA DR11 was less frequently present in Italian patients with type 1 AIH (17% *vs* 35%, $P = 0.01$) than in Italian control subjects, whereas B8-DR3-DQ2 occurred more commonly in Italian patients with type 1 AIH than in the Italian control population (30% *vs* 7%, $P<0.0001$). B8-DR3-DQ2 was detected more often in Italian patients with type 1 AIH than in those with type 2 AIH (30% *vs* 12%, $P = 0.2$), but the difference did not reach statistical significance.

The only biochemical feature characteristic of the Italian patients with type 1 AIH and HLA DR3 was the higher serum levels of alanine aminotransferase at baseline (764±580 UI/L *vs* 440±376 UI/L, $P = 0.03$), whereas all the other biochemical and clinical parameters were indistinguishable.

Comparison of Italian and North American patients with AIH and normal populations

Patients with type 1 AIH from North America had a significantly higher frequency of HLA B8 (49% *vs* 32%, $P = 0.02$), HLA DR3 (52% *vs* 30%, $P = 0.005$) and HLA DR4 (43% *vs* 23%, $P = 0.01$) than those from Italy, and the B8-DR3-DQ2 phenotype was more commonly present (48% *vs* 30%, $P = 0.03$); in contrast patients with type 1 AIH from Italy significantly more often had the HLA DR11 allele (18% *vs* 7%, $P = 0.01$) than those from North America (Table 3).

The normal subjects from North America, in contrast with the Italian normal subjects, had a significantly greater frequency of the HLA B8 (20% *vs* 10%, $P = 0.009$), HLA DR4 (34% *vs* 16%, $P = 0.0003$) and B8-DR3-DQ2 phenotype (15% *vs* 7%, $P = 0.01$). In contrast, the Italian control population more commonly had HLA DR11 (35% *vs* 12%, $P = 0.000007$). No differences were found in HLA DR3, DR7, DR13, DQ2 frequencies between Italian and North American controls.

Table 2 Comparison of class I and class II HLA in Italian patients and controls (*n*, %)

HLA	Type 1 AIH (57 cases)	Type 2 AIH (17 cases)	Controls (250 BD)	P_I	P_{II}	P_{III}
B8	18 (32)	3 (18)	[1]38 (10)	<0.0001	NS	NS
C7	29 (51)	7 (41)	[2]70 (20)	<0.0001	NS	NS
DR3	17 (30)	5 (29)	32 (13)	0.004	NS	NS
DR4	13 (23)	4 (23)	41 (16)	NS	NS	NS
DR7	9 (16)	6 (35)	72 (29)	NS	NS	NS
DR11	10 (17)	7 (41)	87 (35)	0.01	NS	NS
DR13	15 (26)	1 (6)	65 (23)	NS	NS	NS
DQ2	30 (53)	9 (53)	75 (30)	<0.0001	NS	NS
B8–DR3–DQ2	17/57 (30)	2 (12)	[3]23 (7)	<0.0001	NS	NS

Test used: Fisher's exact test. AIH: autoimmune hepatitis. BD: blood donors. P_I: type 1 AIH *vs* controls, P_{II}: type 2 AIH *vs* controls, P_{III}: type 1 AIH *vs* type 2 AIH. [1]Evaluated on a sample of 372 controls. [2]Evaluated on a sample of 350 controls. [3]Evaluated on a sample of 337 controls.

Table 3 Comparison between Italian and North American AIH patients

HLA	Italian type 1 AIH (57 cases)	North American type 1 AIH (n = 149)	Italian type 2 AIH (17 cases)
B8	18 (32)[a]	73 (49)[a]	3 (18)[a]
DR3	17 (30)[a]	77 (52)[a]	5 (29)
DR4	13 (23)[a]	64 (43)[a]	4 (23)
DR7	9 (16)	23 (15)	6 (35)
DR11	10 (18)[a]	11 (7)[a,c]	7 (41)[c]
DR13	15 (26)	24 (16)	1 (6)
DQ2	30 (53)	84 (57)	9 (53)
B8–DR3–DQ2	17 (30)[a]	70 (48)[a,c]	2 (12)[c]

[a]P<0.05, [c]P<0.005. Evaluation on a sample of 146 patients.

DISCUSSION

Several studies analyzed the predisposing role of class I and class II HLA in the development of AIH, especially in North America and northern Europe[3-6,13,28,29], but only a few focused on AIH patients born in the Mediterranean area. Our study is the first to assess the possible role of known susceptibility factors for AIH in Italian patients, who are compared with a well-defined pathological and normal population from North America. We are therefore in the unique position to assess the regional/geographical basis for differences in disease susceptibility. In keeping with previous reports[3,6,29], our study shows that the B8-DR3-DQ2 phenotype is significantly more frequent in Italian patients with type 1 AIH, while HLA DR4, a secondary but independent risk factor for AIH in North America and northern Europe, was not associated with type 1 or type 2 AIH in Italy; interestingly, in Italy it is detected less often than in North American patients with type 1 AIH. In Italy the association between AIH and HLA DR4 is absent even if the analysis is restricted to HLA DR3-negative AIH patients. Furthermore, HLA DR4 occurred less commonly in the Italian control subjects than in North American normal population. This finding marks the most important HLA/genetic difference between Italian and North American patients with type 1 AIH, and it suggests that susceptibility to AIH in Italy is associated with etiologic factors or triggering events that may be region-specific, possibly favored by the HLA DR3 allele. The Italian genetic background appears to be the opposite to that described in Japan, where the HLA DR4, but not the HLA DR3, is the main susceptibility factor for AIH[8,30].

North American patients with type 1 AIH are different from Italian patients with type 1 AIH due to their higher frequencies of HLA DR3 and B8-DR3-DQ2 phenotype; these differences were also evident when North American controls were compared to Italian normal subjects. These findings indicate that HLA DR3 and B8-DR3-DQ2, the main genetic risk factors for AIH in North America, are less common in Italy. This finding suggests that the susceptibility to AIH in Italy is genetically different than in North America, and that other genetic or etiologic factors are possibly involved.

Among Italian patients the finding of a significant association between HLA C7 and type 1 AIH is not surprising, since HLA C7 is in linkage disequilibrium with B8-DR3, and Strettell and co-workers[31] have already described such an association in Caucasoid patients with AIH. HLA C7 helps natural killer cells in target recognition[32,33], therefore its potential role in the pathogenesis of AIH requires further studies.

Our findings support the notion that B8-C7-DR3-DQ2 is the extended haplotype of Italian patients with type 1 AIH.

Furthermore, the HLA DR11 allele was found than in controls in Italiar type 1 AIH patients, an observation consistent with a recent report by Invernizzi *et al*[14], in a series of Italian patients with PBC, where a possible protective role of HLA DR11 has been hypothesized; given the same origin and genetic background of patients and controls, it is tempting to extend the possible protective significance of HLA DR11 to the full spectrum of autoimmune liver diseases, including AIH, at least in the Italian population.

From the clinical standpoint, the observation that HLA DR3-positive Italian patients with type 1 AIH had higher ALT serum levels supports the notion that genetic factors could affect not only the occurrence of the disease, but also its clinical severity/expression[5,15].

Italian patients with type 1 and type 2 AIH had a similar HLA profile: HLA DR3, DQ2 and DR7 occurred with the same frequency in both groups. Such an observation suggests that type 1 and type 2 AIH are one and the same disease, even if marked by different serological findings. The significance of the statistical comparisons, however, is limited by the small number of Italian patients with type 2 AIH. Lenzi and colleagues reported an increased frequency of HLA DR3 in a mixed population of Italian and British patients with type 2 AIH, and Jurado and co-workers[18] showed higher frequencies of HLA DR3 and DQ2 (with only the latter frequency being statistically significant) in Spanish patients with type 2 AIH. Other reports from Germany[16] and Brazil[17] pointed to HLA DR7 as a risk factor. The intriguing hypothesis of a common genetic background for both types of AIH in Italian patients should be tested with a larger series of patients.

In summary, HLA B8-DR3-DQ2 is associated with type 1 AIH in Italian and North American patients, but this phenotype occurs less commonly in Italian patients and Italian normal subjects than in North American counterparts. HLA DR4 is not associated with type 1 AIH in Italian patients, since this also occurs less commonly in the Italian than in the North American normal population. This finding represents the main difference in the HLA profile between Italian and North American patients and normal controls. HLA DR11 appears to be a specific protective factor against autoimmune liver disease, and particularly type 1 AIH, at least in Italy. Italian patients with type 1 and type 2 AIH seem to have a similar genetic background, but a larger number of patients should be analyzed to reach firm conclusions. Differences in the occurrence of HLA alleles between Italian and North American patients and normal subjects may affect the frequency of the disease.

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