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ORIGINAL PAPER

HLA DRB1*13 as a Risk Factor for Type 1 Autoimmune Hepatitis in North American Patients

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Abstract Our goal was to determine if HLA DRB1*13 is associated with autoimmune hepatitis in North American patients. Two hundred and ten adults with definite type 1 autoimmune hepatitis were typed by DNA-based techniques, and the frequency of HLA DRB1*13 in patients without DRB1*03 and DRB1*04 was compared to that in 396 patients with eight other chronic liver diseases and 102 normal individuals. HLA DRB1*13 occurred more commonly in the autoimmune patients who lacked DRB1*03 and DRB1*04 than normal subjects who were similarly restricted (56% vs. 27%, $P = 0.007$). The frequency of HLA DRB1*13 was higher in autoimmune patients without DRB1*03 and DRB1*04 than in patients with other chronic liver diseases who were similarly restricted (59% vs. 32%, $P = 0.01$). Only patients with primary sclerosing cholangitis had a comparable occurrence of HLA DRB1*13. In conclusion, HLA DRB1*13 may be a genetic risk factor for some white North American patients with type 1 autoimmune hepatitis.

Keywords Genetic predisposition · Susceptibility factor · Distinctions

Introduction

HLA DRB1*13 is a risk factor for type 1 autoimmune hepatitis in South America [1–4], and HLA DRB1*03 and DRB1*04 are independent risk factors for the disease in white North Americans [5–7]. HLA DRB1*13 has been implicated in the clearance of viral infection [8] and in the immune response against viral proteins [9]. Its presence may select individuals for protracted exposure to viral and hepatic antigens that favor development of the disease. Previous studies have indicated that HLA DRB1*13 and DRB1*03 occur with similar frequencies in the normal populations of Brazil and the United States [10]. The predominance of HLA DRB1*13 over DRB1*03 in the Brazilian patients suggests that certain indigenous triggering antigens, possibly infectious agents, are selected for presentation by HLA DRB1*13 rather than HLA DRB1*03 because of their uniqueness or abundance.

North American patients with classical type 1 autoimmune hepatitis can lack HLA DRB1*03 and HLA DRB1*04, and many of these individuals have HLA DRB1*13 [11]. This finding suggests that a small subgroup of white North American adults with type 1 autoimmune hepatitis may have triggering antigens different from those with classical HLA markers, and that HLA DRB1*13 may influence susceptibility to these other etiologic factors [11]. This hypothesis requires that HLA DRB1*13 be associated with type 1 autoimmune hepatitis in the absence of HLA DRB1*03 and DRB1*04.

In this retrospective analysis of prospectively acquired data, we determine if HLA DRB1*13 is a risk factor for type 1 autoimmune hepatitis in white adult North American patients who lack HLA DRB1*03 and DRB1*04. The frequency of HLA DRB1*13 in these patients is compared to that in white adults from the same geographical region

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who have other chronic liver diseases and in similarly restricted white adult normal individuals. In this fashion, we determine if HLA DRB1*13 is a disease-specific risk factor for type 1 autoimmune hepatitis in white North American adults and if HLA DRB1*13 should be incorporated into hypotheses of pathogenesis.

Patients and methods

Patients with type 1 autoimmune hepatitis

Two hundred and ten white North American adult patients who had been fully characterized by one investigator (AJC) in accordance with a previously published clinical protocol constituted the study population [11, 12]. All patients had been referred to the autoimmune hepatitis treatment program of the Mayo Clinic, and had been evaluated between 1975 and 2005. Study patients were selected from 302 patients who had been seen during this same interval because they satisfied the following additional criteria. Patients had to be ≥18 years old at presentation to be considered adult and included in the study population. They had to satisfy the pre-treatment diagnostic criteria of the international autoimmune hepatitis group for definite autoimmune hepatitis, and the definite diagnosis had to be supported by the international scoring system [13]. All patients had to be white North Americans to evaluate the genetic predispositions associated with the disease, and each required HLA typing by DNA-based techniques. The mean diagnostic score prior to therapy was 18.6 ± 0.1 points (range, 16–24 points; median score, 19 points).

One hundred and seventy-four patients were women (83%), and the mean age was 48 ± 1 years (range, 18–88 years; median, 49 years). All patients had been assessed for antinuclear antibodies (ANA), smooth-muscle antibodies (SMA), antimitochondrial antibodies (AMA), and antibodies to liver/kidney microsome type 1 (anti-LKM1) by indirect immunofluorescence or enzyme-linked immunosorbent assays based on recombinant antigens, as described previously [14]. Each patient was seronegative for AMA and anti-LKM1, and they satisfied criteria for designation as type 1 autoimmune hepatitis [15].

Liver tissue examinations were performed at presentation in 205 of the 210 patients (98%), and the histological findings of autoimmune hepatitis were documented in each, including 54 patients (26%) who satisfied histological criteria for cirrhosis [16]. All patients were typed for HLA DRB1*03, DRB1*04, and DRB1*13 by restriction fragment-length polymorphism (79 patients) or polymerase chain reaction with sequence specific primers (131 patients) according to methods reported previously [6–18].

Our study had been approved by the Institutional Review Board of the Mayo Clinic.

Patients with other chronic liver diseases

Three hundred and ninety-six white adult North American patients with other chronic liver diseases constituted the disease-specific comparison groups. Their mean age was 51 ± 1 years (range, 19–81 years; median age, 49 years), and 228 patients (58%) were women. Each had undergone DNA-based HLA typing by restriction fragment-length polymorphism (179 patients) or polymerase chain reaction with sequence specific primers (217 patients). All patients satisfied conventional criteria for their diagnosis, and each had been evaluated by the same investigator at the time of presentation (AJC) [17, 18]. These patients had participated in our earlier studies evaluating the genetic bases of chronic liver disease outside autoimmune hepatitis, and they were not part of a liver transplantation registry, which may have skewed their disease severity.

One hundred and sixty-seven patients (42%) were classified as chronic hepatitis C; 21 patients (5%) had chronic hepatitis B; 52 patients (13%) had primary biliary cirrhosis (PBC); 35 patients (9%) had primary sclerosing cholangitis (PSC); 23 patients (6%) had autoimmune cholangitis or AMA-negative PBC; 29 patients (7%) had chronic alcoholic liver disease; 19 patients (5%) had cryptogenic chronic hepatitis; and 50 patients (13%) had non-alcoholic fatty liver disease (NAFLD).

All patients had been evaluated similarly at presentation by standard laboratory indices of liver inflammation and function, viral markers for hepatitis B and C infection; and serologic assays for ANA, SMA, AMA and anti-LKM1. Additional studies were performed that were appropriate to secure the specific diagnosis. All patients with PSC had undergone biliary imaging either by endoscopic cholangiography, magnetic resonance cholangiography or both, and the diagnosis of NAFLD required liver biopsy confirmation. Patients with cryptogenic chronic hepatitis had been screened for iron overload, alpha 1 antitrypsin deficiency, Wilson disease, viral or drug induced disease, and conventional immune markers [19].

Normal population

One hundred and two healthy white North American adults constituted the normal population. Each normal subject was a volunteer blood donor at the Mayo Clinic, and each had indicated the absence of major illness on a standard questionnaire. The mean age was 40 ± 1 years (range, 26–68 years; median, 39.5 years), and 59 were women (58%). All normal subjects resided in Olmsted County, Minnesota

and their ethnic backgrounds included varying mixtures of German, French, English, Norwegian, Irish, Polish, Bohemian, Dutch, Swiss, Danish, Scottish and Swedish.

Statistical analyses

The frequency of HLA DRB1*13 in patients with type 1 autoimmune hepatitis who lacked HLA DRB1*03 and DRB1*04 was determined, and the occurrence of this marker in these individuals was compared to that in the patients with other chronic liver diseases and to that in the normal adults. Comparisons were made with the patient and normal populations after restriction for HLA DRB1*03 and DRB1*04.

The Fisher exact test was used to compare dichotomous variables, and the unpaired *t*-test was used to compare differences in the means of continuous variables. Associations were sought only between HLA DRB1*03, DRB1*04, and DRB1*13. Since the variables for comparison were known risk factors for autoimmune hepatitis and had been formulated a priori and then assessed systematically in each study group, an unadjusted *P*-value of 0.05 was used to determine statistical significance. Data are presented as the mean ± standard error of the mean in the tables and text.

Results

Frequency of HLA DRB1*13 in type 1 autoimmune hepatitis

Thirty-eight of the 210 patients with definite type 1 autoimmune hepatitis (18%) had HLA DRB1*13, including three who were homozygous for this marker (Table 1). One hundred and eighty-three patients had the conventional HLA phenotypes for type 1 autoimmune hepatitis (87%), including 88 patients with HLA DRB1*03 (42%), 64 patients with HLA DRB1*04 (30%), and 31 patients with both HLA DRB1*03 and DRB1*04 (15%). Twenty-two of the 38 patients with HLA DRB1*13 (58%) had either HLA DRB1*03 (14 patients) or DRB1*04 (eight patients).

Twenty-seven patients (13%) lacked HLA DRB1*03 and DRB1*04, and 16 of these patients (59%) had HLA DRB1*13, including three patients who were homozygous for HLA DRB1*13 (Table 1). Whereas HLA DRB1*13 occurred as commonly in the patients with definite type 1 autoimmune hepatitis as in normal subjects (18% vs. 22%, $P = 0.5$), it was significantly more common in the patients with type 1 autoimmune hepatitis who lacked HLA DRB1*03 and DRB1*04 than in normal subjects (59% vs. 22%, $P = 0.0003$), including those normal individuals who lacked HLA DRB1*03 and DRB1*04 (59% vs. 27%, $P = 0.007$) (Table 1).

Frequency of HLA DRB1*13 in other chronic liver diseases

One hundred and one of the 396 patients with other chronic liver diseases had HLA DRB1*13 (26%), including 40 patients (10%) who had HLA DRB1*13 and either HLA DRB1*03 (25 patients) or DRB1*04 (15 patients) and 61 patients (15%) who lacked HLA DRB1*03 and DRB1*04 (Table 2). HLA DRB1*13 occurred significantly more frequently in the 27 patients with type 1 autoimmune hepatitis who lacked HLA DRB1*03 and DRB1*04 than in the 396 patients with other chronic liver diseases (59% vs. 26%, $P = 0.0005$), including the 188 patients who lacked HLA DRB1*03 and DRB1*04 (59% vs. 32%, $P = 0.01$). Homozygosity for HLA DRB1*13 also occurred more commonly in the patients with type 1 autoimmune hepatitis who lacked HLA DRB1*03 and DRB1*04 than the patients with other chronic liver diseases (11% vs. 1%, $P = 0.01$), but this difference was not statistically significant when the patients with other chronic liver diseases were restricted by HLA DRB1*03 and DRB1*04 (11% vs. 3%, $P = 0.06$) (Table 2).

Frequency of HLA DRB1*13 in individual liver diseases

Patients with type 1 autoimmune hepatitis who lacked HLA DRB1*03 and DRB1*04 had HLA DRB1*13 more commonly that patients with chronic hepatitis B (59% vs.

Table 1 Frequency of HLA DRB1*13 in type 1 autoimmune hepatitis and normal subjects

DRB1*13 status	Type 1 autoimmune hepatitis		Normal subjects	
	Total ($N = 210$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 27$)	Total ($N = 102$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 52$)
DRB1*13	38 (18)	16 (59)[a,c]	22 (22)[a]	14 (27)[c]
Heterozygous DRB1*13	35 (17)	13 (48)[b,d]	16 (16)[b]	13 (25)[d]
Homozygous DRB1*13	3 (1)	3 (11)	6 (6)	1 (2)

Significantly different from each other at the level of [a]$P = 0.0003$, [b]$P = 0.001$, [c]$P = 0.007$ and [d]$P = 0.046$

Numbers in parentheses are percentages

Table 2 Frequencies of HLA DRB1*13 in other chronic liver diseases

DRB1*13 status	Type 1 autoimmune hepatitis	Other chronic liver diseases	
	DRB1*03$^-$/DRB1*04$^-$ (N = 27)	Total (N = 396)	DRB1*03$^-$/DRB1*04$^-$ (N = 188)
DRB1*13	16 (59)[a,b]	101 (26)[a]	61 (32)[b]
Heterozygous DRB1*13	13 (48)[c]	96 (24)[c]	56 (30)
Homozygous DRB1*13	3 (11)[d]	5 (1)[d]	5 (3)

Significantly different from each other at the level of [a]P = 0.0005 and [b,c,d]P = 0.01

Numbers in parentheses are percentages

29%, P = 0.04) (Table 3), chronic hepatitis C (59% vs. 28%, P = 0.003) (Table 3), primary biliary cirrhosis (59% vs. 13%, P = 0.00005) (Table 4), chronic alcoholic liver disease (59% vs. 14%, P = 0.0006) (Table 5), nonalcoholic fatty liver disease (59% vs. 28%, P = 0.01) (Table 5), cryptogenic chronic hepatitis (59% vs. 10%, P = 0.002) (Table 6), and autoimmune cholangitis (59% vs. 26%, P = 0.02) (Table 6). In contrast, the frequency of HLA DRB1*13 in patients with type 1 autoimmune hepatitis who lacked DRB1*03 and DRB1*04 was similar to that in patients with primary sclerosing cholangitis (59% vs. 43%, P = 0.3) (Table 4).

HLA DRB1*13 as an isolated risk factor in the absence of HLA DRB1*03 and DRB1*04 occurred more commonly in type 1 autoimmune hepatitis than in patients with chronic hepatitis C (59% vs. 34%, P = 0.02) (Table 3), primary biliary cirrhosis (59% vs. 25%, P = 0.02) (Table 4), chronic alcoholic liver disease (59% vs. 23%, P = 0.04) (Table 5), and cryptogenic chronic hepatitis (59% vs. 17%, P = 0.02) (Table 6). It occurred with similar frequencies in the small number of HLA DRB1*03- and DRB1*04-restricted patients with chronic hepatitis B (59% vs. 22%, P = 0.1) (Table 3), primary sclerosing cholangitis (59% vs. 62%, P > 0.9) (Table 4), nonalcoholic fatty liver disease (59% vs. 33%, P = 0.1) (Table 5), and autoimmune cholangitis (59% vs. 43%, P = 0.7) (Table 6).

Discussion

Our study indicates that HLA DRB1*13 occurs more commonly in white North American adults with definite

Table 3 Frequency of HLA DRB1*13 in chronic viral hepatitis

DRB1*13 status	Type 1 autoimmune hepatitis		Chronic hepatitis B		Chronic hepatitis C	
	Total (N = 210)	DRB1*03$^-$/DRB1*04$^-$ (N = 27)	Total (N = 21)	DRB1*03$^-$/DRB1*04$^-$ (N = 9)	Total (N = 167)	DRB1*03$^-$/DRB1*04$^-$ (N = 83)
DRB1*13	38 (18)	16 (59)[a,b,d]	6 (29)[d]	2 (22)	47 (28)[a]	28 (34)[b]
Heterozygous DRB1*13	35 (17)	13 (48)[e]	5 (24)	1 (11)	45 (27)[e]	26 (31)
Homozygous DRB1*13	3 (1)	3 (11)[c]	1 (5)	1 (11)	2 (1)[c]	2 (2)

Significantly different from each other at the level of [a]P = 0.003, [b,c]P = 0.02, and [d,e]P = 0.04

Numbers in parentheses are percentages

Table 4 Frequency of HLA DRB1*13 in cholestatic liver diseases

DRB1*13 status	Type 1 autoimmune hepatitis		Primary biliary cirrhosis		Primary sclerosing cholangitis	
	Total (N = 210)	DRB1*03$^-$/DRB1*04$^-$ (N = 27)	Total (N = 52)	DRB1*03$^-$/DRB1*04$^-$ (N = 24)	Total (N = 35)	DRB1*03$^-$/DRB1*04$^-$ (N = 13)
DRB1*13	38 (18)	16 (59)[a,c]	7 (13)[a]	6 (25)[c]	15 (43)	8 (62)
Heterozygous DRB1*13	35 (17)	13 (48)[b]	7 (13)[b]	6 (25)	15 (43)	8 (62)
Homozygous DRB1*13	3 (1)	3 (11)[d]	0 (0)[d]	0 (0)	0 (0)	0 (0)

Significantly different from each other at the level of [a]P = 0.00005, [b]P = 0.002, [c]P = 0.02 and [d]P = 0.04

Numbers in parentheses are percentages

Table 5 Frequency of HLA DRB1*13 in alcoholic and non-alcoholic fatty liver disease

DRB1*13 status	Type 1 autoimmune hepatitis		Chronic alcoholic liver disease		Non-alcoholic fatty liver disease	
	Total ($N = 210$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 27$)	Total ($N = 29$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 13$)	Total ($N = 50$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 27$)
DRB1*13	38 (18)	16 (59)[a,c,d]	4 (14)[a]	3 (23)[d]	14 (28)[c]	9 (33)
Heterozygous DRB1*13	35 (17)	13 (48)[b]	3 (10)[b]	2 (15)	14 (28)	9 (33)
Homozygous DRB1*13	3 (1)	3 (11)[e]	1 (3)	1 (8)	0 (0)[e]	0 (0)

Significantly different from each other at the level of [a]$P = 0.0006$, [b]$P = 0.003$, [c]$P = 0.01$, and [d,e]$P = 0.04$

Numbers in parentheses are percentages

Table 6 Frequency of HLA DRB1*13 in non-classical syndromes

DRB1*13 status	Type 1 autoimmune hepatitis		Autoimmune cholangitis		Cryptogenic chronic hepatitis	
	Total ($N = 210$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 27$)	Total ($N = 23$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 7$)	Total ($N = 19$)	DRB1*03$^-$/DRB1*04$^-$ ($N = 12$)
DRB1*13	38 (18)	16 (59)[a,d,e]	6 (26)[d]	3 (43)	2 (10)[a]	2 (17)[e]
Heterozygous DRB1*13	35 (17)	13 (48)[b,c]	5 (22)[b]	2 (29)	2 (10)[c]	2 (17)
Homozygous DRB1*13	3 (1)	3 (11)	1 (4)	1 (14)	0 (0)	0 (0)

Significantly different from each other at the level of [a]$P = 0.002$, [b]$P = 0.004$, [c]$P = 0.01$, and [d,e]$P = 0.02$

Numbers in parentheses are percentages

type 1 autoimmune hepatitis who lack HLA DRB1*03 and DRB1*04 than in normal white adults from the same geographical region and in similarly selected patients with other chronic liver diseases. This distinction was maintained when both HLA DRB1*03 and DRB1*04 were excluded from the normal and diseased comparison groups. Our finding suggests that HLA DRB1*13 is another genetic risk factor for type 1 autoimmune hepatitis in white North American adults outside HLA DRB1*03 and DRB1*04, and in this fashion it resembles the experiences reported in Brazil and Argentina [1–4]. Whereas HLA DRB1*13 is the main susceptibility factor in South American patients, it is a minor risk factor in white North American patients. Recognition of its contribution to the autoimmune hepatitis of North America, however, expands the concepts of pathogenesis for the disease in that region.

Our findings support hypotheses that propose that diverse antigens, possibly with shared epitopes and region-specific predominance, can predispose to autoimmune hepatitis and that susceptibility to these antigenic triggers are favored by certain HLA [20–23]. Activation of the CD4+ T helper lymphocytes, which are the principal effectors of autoimmune hepatitis, occurs when the triggering antigen is optimally presented in the antigen binding groove of the class II molecule of the major histocompatibility complex (MHC). The susceptibility alleles encode the antigenic sequences within this groove and thereby optimize this presentation. The alleles of HLA DRB1*03 and DRB1*04 each encode the same six amino acid sequence between positions 67 and 72 of the β polypeptide chain of the antigen binding groove (DRβ67–72), and it is this sequence that has been associated with type 1 autoimmune hepatitis in white North American adults [20–23]. Different antigens may be presented by the same class II MHC molecules if their structural and electrostatic properties allow optimal alignment along the DRβ67–72 sequence, and they may thereby trigger the same disease [24]. This shared motif hypothesis of pathogenesis has been proposed in other autoimmune diseases, especially rheumatoid arthritis [25].

The alleles of HLA DRB1*13 encode a different DRβ67–72 sequence in the antigen binding groove of the class II MHC molecule, and this difference will not accommodate the same triggering antigens associated with the alleles of HLA DRB1*03 and DRB1*04 [21–23]. The predominant association of HLA DRB1*13 with type 1 autoimmune hepatitis in Brazil and Argentina suggests that HLA DRB1*13 favors the presentation of triggering antigens that are common to this region, and the hepatitis A virus may be one of several such agents [8]. Hepatitis A virus infection is common in South America [26], and it has been implicated as a cause of autoimmune hepatitis

[27–29]. Our finding suggests that HLA DRB1*13 in North American patients may favor the presentation of antigens that are less common or that are presented less optimally than the antigens presented by HLA DRB1*03 and DRB1*04.

*DRB1*1301*, which is one of the 63 alleles associated with HLA DRB1*13 [30], has been associated with protracted hepatitis A virus infection in South America [8], and it is the allele that has been associated with the autoimmune hepatitis among children of this region [1, 2, 4]. Other HLA DRB1*13 alleles may protect against infection, such as *DRB1*1302* [2, 8, 31], or promote the presentation of diverse antigens with epitopes that are homologous with self-antigens and capable of overcoming self-tolerance [20–23]. By understanding the allelic risk factors for the disease in different geographical regions and ethnic groups, it may be possible to identify the triggering agent or antigens for the disease in that region [22, 23]. Our study is too small to determine the allelic associations of HLA DRB1*13 with the type 1 autoimmune hepatitis of our North American patients. Future studies utilizing a collaborative network of medical centers with a large number of patients will be necessary to establish these associations, determine the responsible alleles, track etiologic agents, and determine differences in clinical features and outcome.

HLA DRB1*13 occurred as frequently in patients with PSC with and without DRB1*03 and DRB1*04 as in patients with type 1 autoimmune hepatitis who lacked HLA DRB1*03 and DRB1*04. In this regard, PSC differed from the other diseases included in our comparison population. Our statistical analyses were limited by the small number of patients in the individual disease groups, especially when populations were restricted by HLA DRB1*03 and DRB1*04. PSC, however, was the only disease category in which the frequency of HLA DRB1*13 was the same as in type 1 autoimmune hepatitis with and without restriction for HLA DRB1*03 and DRB1*04. These similarities between PSC and type 1 autoimmune hepatitis may have reflected the small size of our PSC group (35 patients), but this size was no less representative of an alternative disease state than that of chronic hepatitis B (21 patients), chronic alcoholic liver disease (29 patients), autoimmune cholangitis (23 patients), and cryptogenic chronic hepatitis (19 patients), in which significant differences with type 1 autoimmune hepatitis had been demonstrated. Unlike the other disease comparisons, PSC has a known association with HLA DRB1*03 [19, 32, 33], and our findings support other observations that have included HLA DRB1*13 among its susceptibility factors [34, 35].

The key HLA haplotypes that have been associated with susceptibility to PSC have included *DRB3*0101-DRB1*0301* and *DRB3*0101-DRB1*1301* [34, 35]. Furthermore, HLA DRB1*04 has been associated with protection from PSC [19], and the haplotype containing *DRB1*04-DQB1*0501* has been proposed in this regard [34, 35]. The similar occurrence of HLA DRB1*13 in our restricted patients with type 1 autoimmune hepatitis and in similarly restricted patients with PSC does not negate the relevance of HLA DRB1*13 as a risk factor for type 1 autoimmune hepatitis. In contrast, it supports the potential importance of HLA DRB1*13 in both conditions, further emphasizes the genetic similarities between these diseases, and expands the hypotheses of etiology and pathogenesis for each.

In summary, HLA DRB1*13 occurs more commonly in white adults with definite type 1 autoimmune hepatitis who lack HLA DRB1*03 and DRB1*04 than in similarly restricted normal adults and patients with other chronic liver diseases from the same geographical region. HLA DRB1*13 may be another risk factor for type 1 autoimmune hepatitis in this population outside HLA DRB1*03 and DRB1*04, and in this small group there may be an opportunity to track different etiologic factors. The frequency of HLA DRB1*13 in patients with type 1 autoimmune hepatitis who are restricted for HLA DRB1*03 and DRB1*04 is similar to that in PSC, and these diseases with shared genetic predispositions may differentiate because of their triggering antigens or other autoimmune modifiers that are in synergy (epistasis) with the principal genetic drivers [17].

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