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## HLA class II association with autoimmune hepatitis in Latin America: A meta-analysis

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### ABSTRACT

**Background:** Autoimmune hepatitis (AIH) is a chronic liver disease to which different Human Leukocyte Antigens (HLA) have been associated, according to the ethnic/geographical group affected, age of presentation, prognosis, and serologic profile.

**Objective:** To identify common HLA class II alleles contributing to susceptibility to AIH in Latin American population.

**Methods:** The present study was held through a systematic review of the literature, followed by a meta-analysis of 694 cases and 1769 controls of all case-control studies that supplied enough information for odd ratio and 95% confidence interval calculation conducted to date in Latin America.

**Results:** The serological group DQ2 was found to be risk factor for AIH, while DR5 and DQ3 were found to be protective factors in this population. At the allelic level, DQB1\*02, DQB1\*0603, DRB1\*0405, and DRB1\*1301, were found to be risk factors, while DRB1\*1302 and DQB1\*0301 alleles were protective factors. The physicochemical similarities and differences of critical amino acids encoding the peptide binding groove at pockets P1, P4, and P6 of these HLA molecules, elucidates their influence in the development of disease.

**Conclusion:** The current study strengthens the HLA component of AIH in Latin America and its relationship to other populations around the world.

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## 1. Introduction

Autoimmune hepatitis (AIH) is a chronic liver disease secondary to the loss of self tolerance of the immune system. It is characterized by changes in liver histology leading to interface hepatitis, simultaneous to the presence of multiple systemic circulating antibodies and hypergammaglobulinemia. AIH commonly affects females, in all age ranges, and it is classified in two or three groups according to its clinical behavior, age of presentation and serological characteristics [1]. AIH type 1 is described as typically presenting positive antinuclear antibodies (ANA) and/or positive anti smooth muscle antibodies (SMA), perinuclear anti-neutrophil cytoplasmic antibodies (pANCAS), associated to a better prognosis and response to treatment. On the other hand, AIH type 2 is usually diagnosed in children and young women, who have circulating liver/kidney microsome type 1 antibodies (LKM-1) in sera, and have a poorer prognosis, with frequent relapse of disease activity after treatment. A third type AIH is described in adult patients with positive soluble liver antigen/liver pancreas antibodies (SLA/LP). However it is debated whether AIH type 3 should be clinically considered an equivalent to AIH type 1, regardless of their different autoantibody profiles [2].

Genetic predisposition to autoimmune disease is indicated by the higher degree of familial aggregation, particularly among siblings, and the high concordance rate among monozygotic and dizygotic twins. Previous studies and data supporting the genetic component passed on to offspring, resulting in the onset of AIH are scarce and limited to the relationship between the presentation of AIH and other autoimmune diseases among family members [1]. However, different HLA antigens are associated to disease, according to the ethnic/geographical group affected, age of presentation, prognosis, and serologic profile. Among HLA class II alleles, both DRB1\*0301 and DRB1\*0401 were reported to be associated with AIH in North Americans, Western Asians and in North European descendents [3–5]. HLA DRB1\*0405 was reported in Japanese patients, and HLA DRB1\*13 in Indian patients with AIH [5,6]. HLA DRB1\*07 allele has been found to influence the expression of LKM-1, while HLA DRB1\*03 is considered to affect the expression of liver cytosol type 1 antibodies. HLA DQB1\*0201 allele is the common marker for AIH type 2, and is known to be in linkage disequilibrium with both HLA DRB1\*07 and HLA DRB1\*03 [7].

In the present study, the identification of common class II HLA alleles contributing to AIH susceptibility in Latin America, was examined through a systematic review of the literature followed by a meta-analysis of all case-control studies, conducted to date in this region. Meta-analyses are valued tools that allow the enhancement of the statistical power of outcomes in populations ethnically and ancestrally rich as the Latin American population. Inhabited by nearly 570 million people, the Latin American population is a composite of ancestries, ethnic groups, and races; making it one of the most diverse regions in the world.

## 2. Methods

### 2.1. Search strategy

A systematic search was held by two experts independently, in multiple electronic databases, (MEDLINE, PubMed, SciELO, BIREME, Cochrane, and LILACS) up to June of 2008 for all genetic association studies evaluating the HLA alleles in AIH in humans in Spanish, Portuguese, and English. In the search strategy the combinations of the following MeSH terms were used: “Hepatitis, Autoimmune” [Majr], “Hepatitis, Chronic” [Majr], and “HLA Antigens” [Mesh], and “South America” [Mesh], “Mexico” [Mesh], “North America” [Mesh], and “Central America” [Mesh].

### 2.2. Study selection and data extraction

Inclusion criteria for the meta analysis were as follows: studies held in a Latin American country, case-control design studies that supplied enough information for odd ratio (OR) and 95% confidence interval (CI) calculation, inclusion of patients according to the International Autoimmune Hepatitis Group (IAIHG) consensus defined in 1993 and 1999, having screened patients for viral hepatitis before their inclusion, and manuscripts published in peer-review journals as full papers only [8,9]. A single study, Fainboim et al., done before 1993, was included in the meta-analysis given that the inclusion criteria of patients were similar to those consented by the IAIHG in 1993, where the previously known term, autoimmune chronic active hepatitis was used [10]. HLA DRB1 and DQB1 genotypic data were grouped according to the 13th International Histocompatibility Workshop and Conference, for adequate comparison purposes [11]. Following the same inclusion criteria mentioned before, 16 studies from around the world with relevant clinical data were chosen, six from Latin America and ten from other regions around the world (Table 1).

### 2.3. Statistical analysis

Data were analyzed using the Comprehensive Meta-Analysis version 2 program (Biostat, Englewood, NJ, 2004). The grouped OR was performed by weighing individual OR by the inverse of their variance. For each allele, the final effect OR and 95% CI were obtained by means of both random and fixed effect models. Heterogeneity was calculated by means of Cochran's ( $Q$ ) and Higgins's ( $I^2$ ) tests. Adjectives of low, moderate and high were assigned to  $I^2$  values of 25%, 50% and 75%, respectively. Publication bias was determined using funnel plots and the Egger's regression asymmetry tests, for HLA groups and alleles with more than two studies.

The expected statistical power to detect true associations between autoimmune hepatitis and HLA-DRB1 and DQB1 alleles were calculated using PS Power and Sample Size Calculations Version 2.1.31 (Copyright© 2004 by William D. DuPont and Walton D. Plummer, Vanderbilt Biostatistics,

**Table 1**  
Demographic, clinical, serological features of AIH in patients around the world<sup>1</sup>

Region	Europe				Asia				Latin America						North America				
	Germany [12]	Italy [13]	Italy [13]	UK [14]	Japan [15]	Iran [16]	China [17]	India [18]	Brazil [19]	Brazil [19]	Argentina [20]	Mexico [21]	Venezuela [22]	Colombia [23]	Colombia [24]	USA [3]	USA [13]	USA [25]	USA [26]
Type of AIH (Type 1 or Type 2)	1,2	1	2		1	1,2	1	1	1	2	1	1	1	1	1	1	1	1	1
Number of patients included	142	57	17	164	160	60	62	38	111	28	206	30	41	48	28	86	149	185	72
Age in years (mean)		45	18	53	55	8.4	46	36.3	12	4	22.5	12.5	34.9	34	38	43	47	45	50.5
Females with AIH per study	83.8	87.7	88.2	78	87.5	93.3	64.5	89.4	78.3	92.8	83.4	90	85.3	83.3	82.1	77.9	81.8	78	84.7
ANA	76	60	0	78	84	67	71	39.4			66	56.70	77	83.3	81	15	76	28	73
SMA	71	77	0	75	64	53	24	63.1			86	53.30	79	68.4	89	29	74	22	41
SMA + ANA	47				95			10.5			48	33.40	56			56		47	
Anti-mitochondrial antibodies							17	2.6						11.1	17				6
SLA								6											4
LKM-1		0	94	7		23	3					0				7	0	0	1
Liver-cytosol type 1 antibodies		0	23																0
IgG mg/dL (median)		2592	2600	2820	2610							7470	3587			3061	2460	3477	
Patients with liver biopsy		95	82					50						81	89		99		
Interface hepatitis		48	36					72.7									52	48	
Rosette formation								18.2											
Periportal hepatitis																41			
Bridging necrosis		43	43						61	54						13	10	43	
Multilobar necrosis																17	13		
Cirrhosis		9	22					10.5	53	54					40	29	24	26	56
Acute illness					6	13		39.4											
Chronic illness					94	83		60											
Acute fulminant hepatic failure						3													
Patients with associated autoimmune diseases				23	25	50		40	19	17	18	33	29	40	14	46.5			
Type 1 diabetes mellitus				5				10											
Autoimmune thyroid disease				13	12	5		8			6	10		19	11	21			
Ulcerative colitis				4	2	3										8			
Systemic lupus erythematosus					1	7					1	17		6					
Vitiligo						3		6						2					
Thrombocytopenia								6			2								
Rheumatoid arthritis				5	1			6						2		1			
Sjögren's syndrome					2			3				3				1			

<sup>1</sup>Unless otherwise indicated data correspond to percentages of positive findings among the studied population with AIH in each study.

Nashville, TN). We used the 0.05 level of significance, an OR of exposure in cases relative to controls of 1.2 and 1.9 for HLA DQ2; 0.5 and 0.7 for HLA DQ3; 0.4 and 0.6 for HLA DR5; 1.8 and 2.3 for HLA DR52; 0.2 and 0.4 for HLA DQB1\*0301; 3.4 and 6.1 for HLA DQB1\*0603; 2.7 and 5.5 for HLA DRB1\*1301; 0.1 and 0.2 for HLA DRB1\*1302; 1.4 and 1.6 for HLA DQB1\*02; and 14.4 and 19.9 for HLA DRB1\*0405. These OR represented the 25 and 75 quartiles of the distribution of effect sizes for HLA groups and alleles (Table 2).

3. Results

3.1. Literature assessment

A total of 137 citations were retrieved from the initial electronic database search; 104 citations identified in MEDLINE, PubMed, and Cochrane and 33 citations in SciELO, BIREME, and LILACS databases. Out of the selected citations, 87 were eliminated given their lack of relevance, 50 were further reviewed, out of which 12 studies were eligible for meticulous revision. Seven studies were finally selected as they satisfied inclusion criteria, three from Brazil, two from Argentina, one from Mexico, and another from Venezuela [10,19–22,27,28]. The study from Czaja et al., included patients from North America and Brazil, only data of the Brazilian population was analyzed, however non significant results were obtained from the data reported [28]. Fainbom et al. [10], included only pediatric patients, all other six studies included adult and pediatric population. Goldberg et al., studied 139 patients with AIH, 28 patients of which had AIH type 2, identified by positive LKM-1 antibodies [27]. Even though serological HLA typing was performed in two studies by microcitotoxicity essays, molecular biology techniques (PCR-SSP, PCR-SSOP and PCR-RFLP) were used for the identification of specific HLA alleles in all studies [10,21]. All studies included patients with hepatic disease who were previously screened and found negative for viral hepatitis and had positive ANA and/or SMA antibodies.

3.2. HLA association

A total of 1769 Latin Americans were studied, of whom 694 were patients with AIH and the remaining healthy controls. The number of controls per case of individual studies was found in a range from 0.9 to 5.8 controls per case. The serological groups DQ2 and DR52 were found to be risk factors for AIH, while DR5 and DQ3 were found to be protective factors in this population (Fig. 1). At the allelic level, DQB1\*02, DQB1\*0603, DRB1\*0405, and DRB1\*1301, were found to be risk factors, while HLA alleles DRB1\*1302 and DQB1\*0301 were found to be protective factors (Fig. 1).

3.3. Functional analysis

Functional analysis of DQ and DR alleles revealed physicochemical similarities and differences of critical amino acids encoding the peptide binding groove at the DRβ chain (Table 3). Risk alleles, DQB1\*02 and DQB1\*0603 encode Glyβ13 and Leuβ26 at P4 pocket, while DQB1\*0301 encodes heavier amino acids; alanine and tyrosine respectively. The presence of these amino acids, changes the

Table 2  
HLA DRB1 and DQB1 polymorphisms associated with AIH in Latin America

Alleles	DQB1*0301			DQB1*0603			DQB1*02			DRB1*0405			DRB1*1301			DRB1*1302							
	Relative weight	Expected power <sup>a</sup> E(DQB1*0301)=0.43	ψ=0.2	Relative weight	Expected power <sup>a</sup> E(DQB1*0603)=0.08	ψ=3.4	Relative weight	Expected power <sup>a</sup> E(DQB1*02)=0.37	ψ=1.4	Relative weight	Expected power <sup>a</sup> E(DRB1*0405)=0.01	ψ=14.4	Relative weight	Expected power <sup>a</sup> E(DRB1*1301)=0.20	ψ=2.7	Relative weight	Expected power <sup>a</sup> E(DRB1*1302)=0.26	ψ=0.1					
Country of study	F	R	df	F	R	df	F	R	df	F	R	df	F	R	df	F	R	df					
Argentina <sup>b</sup> [10]	18.92	24.22	1.00	0.76	NA	NA	NA	NA	NA	NA	NA	NA	21.06	22.18	0.84	NA	NA	NA					
Argentina [20]	NA	NA	NA	0.99	1.00	NA	NA	NA	NA	1.00	1.00	45.71	25.73	1.00	1.00	27.74	27.74	1.00					
Mexico [21]	19.30	24.59	0.94	0.54	38.47	0.65	0.94	NA	NA	NA	NA	7.96	15.61	0.66	0.99	NA	NA	NA					
Brazil [19]	61.78	51.19	1.00	0.93	NA	NA	NA	70.27	70.27	0.27	0.47	NA	NA	NA	NA	NA	NA	NA					
Brazil [27]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	17.53	21.09	0.94	1.00	72.26	72.26	1.00					
Venezuela [22]	NA	NA	NA	NA	NA	NA	NA	29.73	29.73	0.15	0.25	51.20	0.72	0.72	7.74	15.40	0.99	NA					
<b>Heterogeneity:</b>	2.91	2	0.23	31.33	3.27	1	0.07	69.39	0.32	1	0.57	0	0.39	1	0.53	9.10	4	0.06	56.05	0.83	1	0.36	0

F: Fixed Model, R: Random Model, ψ: Odds Ratio, NA: Data not available, NS: Statistically not significant, Q: Cochran's Test, df: Degree of Freedom, I<sup>2</sup>: Higgins Test (%).  
<sup>a</sup> α=0.05.  
<sup>b</sup> This study only included children as patients, all other studies included adult and children as patients.

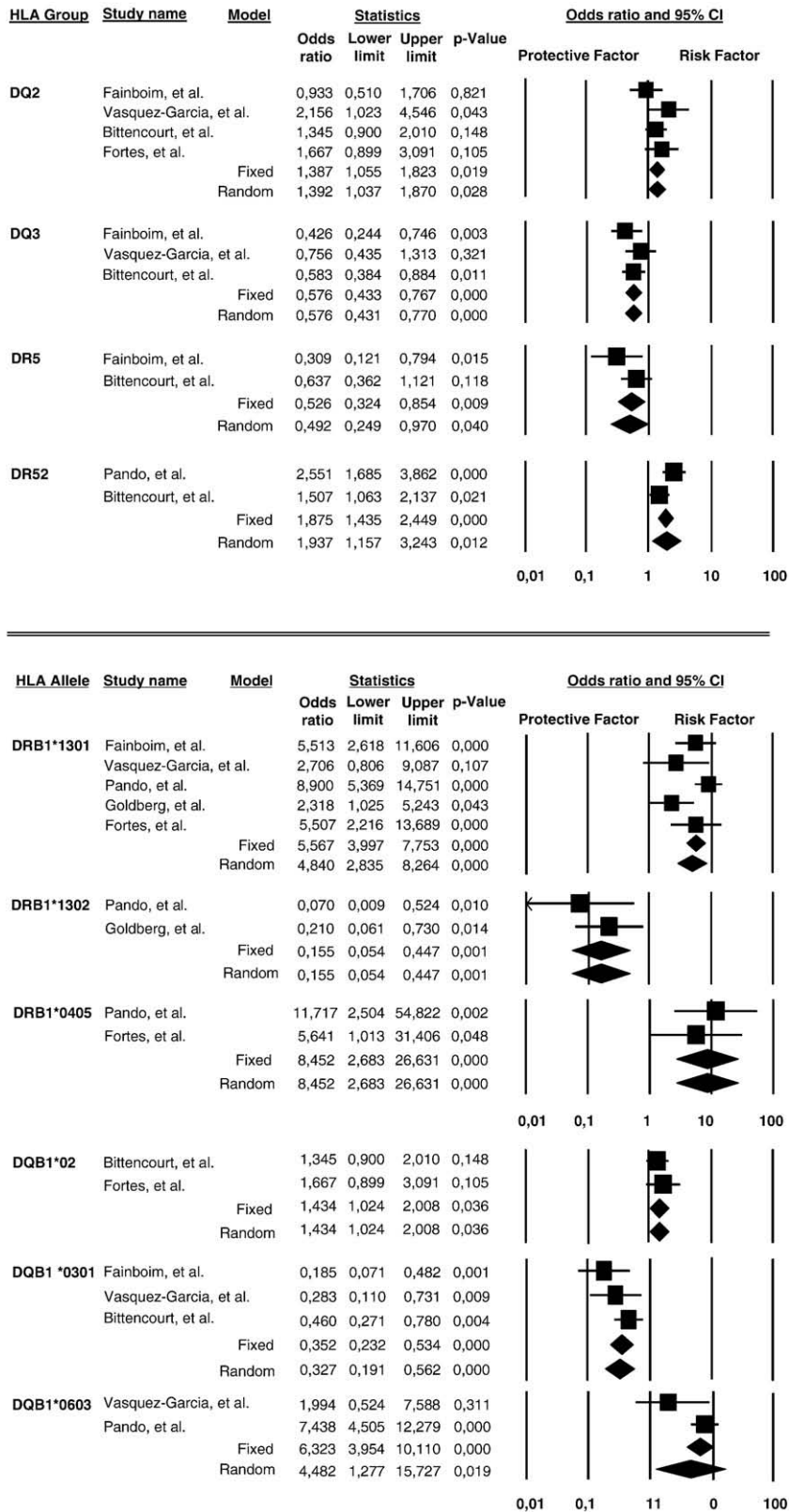


Fig. 1. Meta-analysis forest plot for AIH in Latin America. Meta-analysis forest plot for HLA Serologic Specificity DR and DQ groups and for HLA DRB1 and DQB1 alleles found in AIH in Latin America. Each plot shows the effect size and precision for individual studies and for the combined effect. Filled squares are proportional in size to study weights.

**Table 3**  
HLA DRB1 and DQB1 amino acid residue configuration at HLA pockets

Association	Allele	Studied population	HLA pocket and positions of amino acid residues								
			P6 $\beta$ 13	P4 $\beta$ 69	P4 $\beta$ 70	P4 $\beta$ 71	P4 $\beta$ 72	P4 $\beta$ 73	P4 $\beta$ 74	P1 $\beta$ 86	
Risk	*0301	North America, Northern Europe [3,4]	S	E	Q	K	R	G	R	V	
	*0401	North America, India, Northern Europe [3–5,29]	H	E	Q	K	R	A	A	G	
	*0405	Latin American, Japan [6,20,22]	H	E	Q	R	R	A	A	G	
	*1301	Latin American, India, North America [10,20–22,27,33]	S	E	D	E	R	A	A	V	
	*1302	Latin America, India, North America [20,27]	S	E	D	E	R	A	A	G	
Protection	*1501	North America, Northern European [3,4]	R	E	Q	A	R	A	A	V	
	DQB1		P4 $\beta$ 13	P4 $\beta$ 26	P6 $\beta$ 30	P6 $\beta$ 37	P9 $\beta$ 38	P9 $\beta$ 57			
Risk	*02	Latin America, Europe, North America [4,12,13,19,22]	G	L	S	I	V	A			
	*0603	Latin American [20,21]	G	L	H	Y	A	D			
Protection	*0301	Latin American [10,19,21]	A	Y	Y	Y	A	D			

Letters correspond to amino acid configurations: S—serine, E—glutamate, Q—glutamine, K—lysine, R—arginine, G—glutamine, V—valine, H—histidine, A—alanine, L—leucine, Y—tyrosine, I—isoleucine, D—aspartic acid.

structural accommodations of the P4 pocket, which seems to offer protection against autoimmune disease [30].

At position 30, DQB1 risk factor alleles share polar and hydrophilic amino acids, histidine and serine, in the P6 pocket. Whereas DQB1\*0301 encodes the aromatic amino acid tyrosine.

In the DR $\beta$  chain, position  $\beta$ 86 is known to be a critical peptide binding factor for T cell recognition [31]. The functional susceptibility for AIH given by HLA DRB1\*1301 and DRB1\*0301, is possibly associated with the peptide binding groove conformation at pocket P1, Val  $\beta$ 86. Contrastingly, DRB1\*1302, a protective factor, only differs from DRB1\*1301 as it has a smaller amino acid residue, glycine, at this position.

The valine→glycine phenomenon at  $\beta$ 86, has also been described in the DR $\beta$  chain of other DRB1 alleles, associated to systemic lupus erythematosus (SLE) [32]. In SLE DRB1\*1501, DRB1\*1503, DRB1\*0301, also share the presence of valine at  $\beta$ 86, while their protective counterparts DRB1\*0701, DRB1\*1101 have a glycine at this position. However, the amino acid configuration of other risk and protective alleles does not fully support this association in AIH. According to their amino acid sequences, no direct relationship that favors susceptibility was seen between DRB1\*0405 and DRB1\*1301 in AIH. DRB1\*0401 and DRB1\*0405 alleles share amino acid glycine at position  $\beta$ 86, whereas DRB1\*1501 encodes a valine at  $\beta$ 86.

Position  $\beta$ 71 in the D $\beta$  chain is highly polymorphic among the susceptibility and risk alleles. However, DRB1\*1501, a protective allele among North Americans and Northern Europeans, contains alanine at  $\beta$ 71 [3,4]. The hydrophobic nature of alanine, might not facilitate a specific union to this residue, therefore behaving as a protective factor.

#### 4. Discussion

The present meta-analyses shows particular HLA specificities associated with AIH in Latin Americans. HLA DQ2 and DR52 groups were found as risk factors, while the previously described HLA DR3 group, which confers susceptibility for AIH in other continents, was not found significant in Latin American patients. HLA DQ2 has also been found in a relative high frequency in European and North American patients with AIH [12,13].

HLA allele DRB1\*1301, formerly described in individual studies as a risk factor for developing AIH among Latin

Americans, was confirmed in this study. This allele has been found in a high frequency among North Americans who do not carry HLA DRB1\*03 and DRB1\*04 alleles. A relationship between DRB1\*1301 and viral triggers, such as Hepatitis A virus, has been hypothesized [33].

Although most of the studies included focused on specific risk alleles according to the different AIH types, this meta-analysis searched for risk alleles joining the two main types of AIH as a single group. AIH in children and young patients, including those classified as AIH type 2, is commonly described as a more aggressive disease with higher probability of treatment failure; a clinical behavior that is shared with other autoimmune disease with onset at a young age. This clinical behavior is worth of further study as it might be related of a phenomenon similar to that which occurs in “genetic anticipation” described in Mendelian diseases and in some complex autoimmune diseases such as rheumatoid arthritis (RA) [34]. According to the results, HLA polymorphisms might affect the predisposition to AIH regardless of the clinical phenotype of disease.

Clinical and serological features of AIH do not differ greatly within the different populations around the world. AIH seems to be diagnosed in advanced clinical stages in Latin America and Western United States, where cirrhosis is a more frequent outcome, compared to Europe and India [13,18,19,24–26] (Table 1). Geographical and racial differences associated to a prompt access to a competitive health system, interact with the apparent clinical behavior of disease. However, an association between the DRB1\*04 alleles, found to be a risk factor for the Latin American population, and AIH developing in elderly patients, who develop cirrhosis, has already been described [35].

Polyautoimmunity (i.e. autoimmune diseases co-occurring within individuals) has been noticed in patients with AIH, especially with autoimmune thyroid disease (AITD); a shared characteristic with other autoimmune diseases [36]. In addition HLA DRB1\*0401 and DRB1\*0405, risk factors for AIH, encompass a sequence motif called a “shared epitope” (SE), which spans amino acid positions 69 to 74 in the third diversity region of the outermost domain of the HLA DRB1 molecule [37,38]. This SE is associated with RA in several ethnic groups including Latin Americans [39]. AIH shares the genetic complexity with RA, type1 diabetes mellitus and other autoimmune diseases [39,40].

In conclusion, this meta-analysis provides insights into the genetic factors that influence susceptibility of AIH in Latin America and emphasize that autoimmune diseases are likely to share common susceptibility variants.

### Take-home messages

- There are particular HLA specificities associated with AIH in Latin Americans. HLA DQ2 and DR52 groups were found as risk factors while DR5 and DQ3 were found to be protective factors in this population.
- The genetic component of autoimmune hepatitis in Latin America has a relationship with other populations around the world.
- Autoimmune diseases are likely to share common susceptibility variants.

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