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Meta-analysis of *HLA-DRB1* and *HLA-DQB1* polymorphisms in Latin American patients with systemic lupus erythematosus

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Abstract

Objective: To estimate the common effect size of *HLA-DRB1* and *-DQB1* alleles on systemic lupus erythematosus (SLE) susceptibility across Latin America populations through a meta-analysis.
Methods: Case-control studies on HLA class II association with SLE in Latin America were searched up to August 2007. The effect summary odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by means of the random effect model.
Results: Eleven studies were selected, which included 747 cases and 1180 controls. Associations with SLE susceptibility were found for HLA-DR2 (OR: 1.75; 95% CI: 1.40–2.19) and -DR3 (OR: 2.02; 95% CI: 1.44–2.83) groups. *HLA-DRB1*0301* allele disclosed the strongest association (OR: 2.14; 95% CI: 1.28–3.56). HLA-DR3-DQ2 haplotype was a risk factor (OR: 2.92; 95% CI: 1.66–5.14). A protective effect was found for the HLA-DR5 group (OR: 0.43; 95% CI: 0.27–0.67), mainly due to a negative association between *HLA-DRB1*1101* allele and disease (OR: 0.21; 95% CI: 0.06–0.72). Functional analysis of susceptibility and protective alleles revealed physicochemical differences of critical amino acids shaping the peptide-binding groove at DRβ chain allowing us to infer an approach to understand the role of HLA in SLE. No significant association was established for *HLA-DQB1* alleles.
Conclusions: HLA-DRB1 gene is a mayor factor for development of SLE in Latin Americans.

Keywords: Systemic lupus erythematosus; Latin America; HLA antigens/alleles; HLA haplotypes; Meta-analysis

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1. Introduction

Systemic lupus erythematosus (SLE) is a prototype of autoimmune diseases affecting predominantly women. It is characterized by a multisystem organ involvement because of dysregulation of self-reactive B cells leading to autoantibody production, immune complex deposition and complement activation with tissue damage [1]. The pathogenic mechanism is due to the interaction between genetic, immunologic, endocrine and environmental factors. The genetic component of SLE is established by the high concordance rates and familial aggregation of the disease. Disease concordance rate is 2–5% and 24–58% for dizygotic and monozygotic twins, respectively [2]. A recurrence risk ratio as high as 29.0 demonstrates a strong family risk [2].

1.1. Human Leukocyte Antigens (HLA) genes and SLE

The search for genes that predispose a person to develop SLE has been done through association studies of candidate genes and genome wide linkage analysis, which has had measurable success in the past few decades. Several independent genome scans in multiplex SLE families have identified a large number of genomic regions that may contain susceptibility genes [3]. Eight susceptibility loci have reached the threshold for significant linkage, with confirmation in independent cohorts: 1q23, 1q31, 1q41–42, 2q37, 4p16, 6p21, 12q24 and 16q12–13 [2,3]. Genome wide meta-analysis confirmed two suggestive regions on 6p21.1–q15 and 20p11–q13.13 [3]. The major histocompatibility complex (MHC), at chromosome 6p21.3, harbors a gene-reach and transcriptionally active segment that encodes for immunologically important genes, including the highly polymorphic HLA class I and II genes. Alterations in the nature of antigen presentation by HLA molecules to T helper cells lead to abnormal T cell response, and may be one mechanism by which these alleles contribute to pathogenic outcomes in SLE [1]. It has been suggested that genes in the HLA region represent the most important association with this autoimmune disease, specially *HLA-DRB1* and *HLA-DQB1* [2,4,5]. There are three HLA haplotypes strongly linked to development of SLE in Caucasians: 1) *HLA-DRB1*1501*(DR2)-*DQB1*0602*, 2) *HLA-DRB1*0301*(DR3)-*DQB1*0201* and 3) *HLA-DRB1*0801*(DR8)-*DQB1*0402* [2]. However, the risk alleles and haplotypes may vary depending upon ethnicity [2,6,7]. In addition, it has been suggested that HLA class II alleles are more related to autoantibody subsets than to the disease itself [8,9].

The identification of candidate genes and the understanding of genetic influences will allow us to comprehend the pathophysiology of this autoimmune entity. There are few studies about the impact of HLA class II polymorphisms on Latin American patients with SLE, and some inconsistencies exist among them due to genetic heterogeneity and small sample sizes. Meta-analysis is a useful tool that allows us to synthesize and combine data from various studies in order to improve the statistical power of outcomes in populations with important admixture as Latin America, in which individuals differ according to ancestry population component (Amerindian, European and African) [10]. The initial goal of this study was to examine the *HLA-DRB1* and *-DQB1* polymorphisms in a Colombian population with SLE. We next sought to identify the common class II HLA alleles influencing SLE in Latin Americans by carrying out a systematic revision of the literature along with a meta-analysis of all case-control

studies conducted to date, including ours, to estimate their genetic contribution to disease susceptibility.

2. Materials and methods

2.1. Colombian cohort and genotyping

This cohort consisted of 99 SLE women patients and 100 healthy controls. All patients fulfilled four or more of the ACR criteria for SLE [11] and were recruited at the Clinical Immunology and Rheumatology Unit of the "Clínica Universitaria Bolivariana-Corporación para Investigaciones Biológicas", in Medellin, Colombia. The mean age ± SD of the patients was 34.7 ± 12.9 years. The controls were selected from the geographic neighborhood of cases and matched for age, sex, ethnicity, and socioeconomic status. Additional characteristics of this cohort, and results from genetic epidemiological studies in this cohort have been described previously [12,13]. HLA typing was done by reverse dot-blot hybridization of the PCR products (Inno-LiPA assay, Innogenetics, Ghent, Belgium).

2.2. Search strategy

Electronic databases (MEDLINE, PUBMED, SCIELO, BIREME and LILACS) were searched up to August 2007 for all genetic association studies evaluating the *HLA-DRB1* and *HLA-DQB1* alleles and haplotypes and SLE in humans in all languages. The search strategy included MeSH terms and text words as follows: "Lupus Erythematosus, Systemic"[Major] AND "Major Histocompatibility Complex"[Mesh] OR "HLA-DR/DQ Antigens/genetics"[Mesh] OR "HLA-DR/DQ Antigens/Immunology"[Mesh]. No other limits were employed.

2.3. Study selection

Studies were selected if they met the following conditions: diagnosis was established by means of the American College of Rheumatology 1982 revised classification criteria for SLE [11], data was collected in Latin American surveys, the study had a case-control design, it supplied enough information to calculate the odds ratio (OR) and the manuscript was published in peer-reviewed journals as full papers, not as an abstract or similar type of summary.

2.4. Data extraction

The following information was collected from each study: author, year of publication, study population, HLA typing technique, total cases, total controls and number of individuals by each genotype from both tabular data and text. To make genotype data comparable, *HLA-DRB1* and *-DQB1* alleles were grouped according to both *HLA-DRB1* and *-DQB1* positive or negative alleles. Subsequently, serological specificities for each allele reported at the 13th International Histocompatibility Workshop and Conference were used to group data from all studies [14]. This made it possible to combine data from studies that used molecular biology for HLA genotyping with information extracted from studies that used serological techniques for this purpose.

2.5. Statistical analysis

Calculations were carried out for each *HLA-DRB1* and *-DQB1* allele as well as for each DR and DQ group according to serological specificities. For an estimate of the effect size of haplotypes involving these alleles, we grouped them as previously described and precluded alleles from *HLA-DQA1* when this information was available [15–18]. Allelic frequency was calculated as the number of cases or controls harboring at least one allele type (*HLA-DRB1* or *HLA-DQB1*) divided by the total number of chromosomes included in each of the corresponding groups. Data was analyzed using the Comprehensive Meta-Analysis version 2 program (Biostat, Englewood, NJ, 2004). The pooled OR in the meta-analysis was performed by weighting individual OR by the inverse of their variance. For each polymorphism group, the summarized effect OR as well as 95% confidence intervals (CIs) was obtained by means of both the random and fixed effect models. The random effect model was chosen because it assumes that there is a distribution of true effect sizes rather than one true effect and assigns a more balanced weight to each study. Heterogeneity was calculated by means of the Cochran's Q test. Due to the low power of this statistical test when meta-analysis includes a small number of studies, Higgins' test (I^2) was used to measure the degree of inconsistency in the results of the studies and to describe the percentage of total variation across studies that is due to heterogeneity rather than chance. Adjectives of low, moderate and high were assigned to I^2 values of 25%, 50% and 75%, respectively [19]. To assess publication bias, Funnel plots and the Egger's regression asymmetry tests were used.

The expected statistical power of each study to detect a true association between SLE and *HLA-DRB1* alleles or SLE and *HLA-DQB1* alleles, was calculated using PS Power and Sample Size Calculations Version 2.1.31

Table 1
Characteristics of individual studies included in meta-analysis

HLA-DRB1 and *-DQB1* polymorphisms associated with SLE						DR alleles												Haplotype				Alleles[a]	
						DR2				DR3				DR5				HLA-DR3-DQ2				DRB1	DQB1
Study date	Country	TT	Sample size	Patients	Control per case	Relative weight		Expected power $\alpha=0.05$ E (DR2)[b]=0.08		Relative weight		Expected power $\alpha=0.05$ E (DR3)[b]=0.12		Relative weight		Expected power $\alpha=0.05$ E (DR5)[b]=0.23		Relative weight		Expected power $\alpha=0.05$ E(DR3-DQ2)[b]=0.077			
						Fixed	Random	$\psi=1.3$	$\psi=2.4$	Fixed	Random	$\psi=1.7$	$\psi=2.7$	Fixed	Random	$\psi=0.2$	$\psi=0.6$	Fixed	Random	$\psi=1.4$	$\psi=3.6$		
[7]	Brasil	1[c]	197	56	2.5	13.50	13.50	0.08	0.47	12.84	12.26	0.25	0.7	21.45	16.51	0.87	0.21	NA	NA	NA	NA	NA	NA
[16]	Mexico	2[d]	128	74	0.7	4.78	4.78	0.06	0.31	6.94	8.20	0.16	0.52	10.31	12.30	0.8	0.2	17.54	17.54	0.07	0.63	NA	*0303, *0402
[15]	Mexico	2	154	58	1.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	34.23	34.23	0.09	0.76	NA	NS
[17]	Mexico	2	180	81	1.2	10.18	10.18	0.08	0.46	10.11	10.60	0.24	0.71	12.03	13.22	0.91	0.25	NA	NA	NA	NA	*0802[c], *1101[c], *0101, *0301, *1406	NA
[24]	EEUU[f]	2	175	70	1.5	7.46	7.46	0.08	0.46	9.48	10.17	0.24	0.7	11.22	12.81	0.89	0.23	NA	NA	NA	NA	*0301, *0802	*0402
[20]	Brasil[g]	2	355	47	6.6	13.95	13.95	0.1	0.52	10.68	10.97	0.28	0.73	14.35	14.27	0.88	0.19	NA	NA	NA	NA	NA	NA
Castaño et al. current	Colombia	2	199	99	1.0	17.53	17.53	0.08	0.5	14.29	13.03	0.26	0.75	11.76	13.09	0.94	0.28	48.22	48.22	0.1	0.85	*0101, *0701[c]	*0302, *0501
[22]	Mexico	2	185	107	0.7	10.44	10.44	0.07	0.43	9.03	9.85	0.22	0.69	17.83	15.51	0.91	0.27	NA	NA	NA	NA	NA	NA
[23][h]	Mexico	1	180	80	1.3	10.67	10.67	0.08	0.48	15.06	13.41	0.25	0.72	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
[18][i]	Mexico	2	180	81	1.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	*0802[c], *1101[c], *0101, *0301, *1406	*0501
[21][j]	Mexico	2	174	75	1.3	11.48	11.48	0.08	0.45	11.56	11.52	0.24	0.7	1.05	2.29	0.9	0.24	NA	NA	NA	NA	NA	NA
		Total	1927[k]	747[k]																			
Heterogeneity						*Q*	*df*	*p*-value	I^2	*Q*	*df*	*p*-value	I^2	*Q*	*df*	*p*-value	I^2	*Q*	*df*	*p*-value	I^2		
						7.3	8	0.5	0.0%	12.97	8	0.11	38.3%	15.5	7	0.03	54.9%	1.41	2	0.49	0.0%		

NA: information not available from published data, NS: statistically not significant ($p>0.05$), SLE: systemic lupus erythematosus, *Q*: Cochran's test, I^2: Higgins' test, *df*: degree of freedom, TT: typing technique.

[a] Statistically significant association.

[b] The expected probability of exposure in controls is 0.08, 0.12, 0.23 and 0.077 for HLA-DR2, -DR3, -DR5 and -DR3-DQ2 haplotype, respectively. Data estimated from the average allelic frequency across all studies included in each analysis.

[c] 1:Typing by serologic method (microlymphocytotoxicity).

[d] 2: Typing by molecular biology techniques (PCR-SSO, PCR-SSOP or PCR-SSOP reverse dot blot).

[e] Protective factor.

[f] Hispanic individuals from Texas, who are members of LUMINA group.

[g] Only Caucasian descent individuals included in the meta-analysis, seven African descent patients and one Asian were excluded from analysis.

[h] Allelic frequencies of cases were estimated adding the number of SLE patients (aCL positive and aCL negative) carrying each DR and DQ allele.

[i] Data from this study was used only in *HLA-DQB1* alleles and DQ serological specificity groups analysis, results of *HLA-DRB1* alleles are equal to [17] study.

[j] Allelic frequencies were estimated only for healthy controls and SLE patients, data on rheumatoid arthritis and rhupus patients were excluded.

[k] Individuals from [18] study were excluded from the equation because they constituted the same sample used in [17] study.

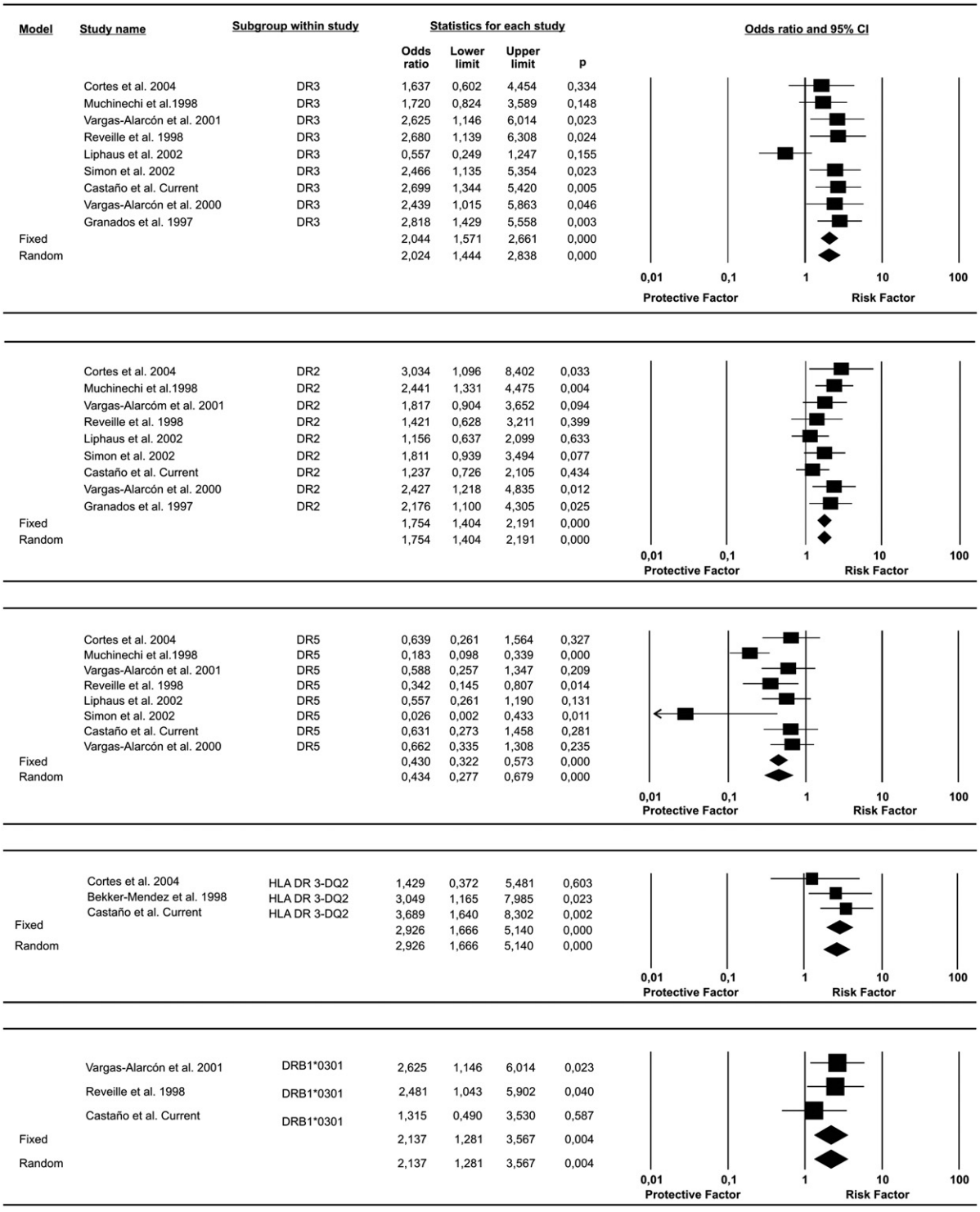

Fig. 1. Forest plots for meta-analysis of *HLA-DRB1* alleles, HLA-DR serological specificity groups and HLA-DR-DQ haplotypes. The common effect size, odds ratios, with 95% confidence intervals were calculated by the Mantel–Haenszel method. The filled squares represent the studies in relation to their weights.

(Copyright© 2004 by William D. Dupont and Walton D. Plummer, Vanderbilt Biostatistics, Nashville, TN). We use the 0.05 level of significance, expecting an OR of exposure in cases relative to controls of 1.3 and 2.4 for HLA-DR2; 1.7 and 2.7 for HLA-DR3; 0.22 and 0.63 for HLA-DR5; and 1.42 and 3.68 for HLA-DR3-DQ2. These ORs represented the 25 and 75 quartiles of the distribution of effect sizes for each allele, group or haplotype.

3. Results

3.1. Studies included

Search strategy allowed us to identify 299 studies for potential inclusion in the meta-analysis. From this large number, only 23 studies were selected and retrieved for detailed evaluation given that they were association studies in Latin American populations. Finally, eleven studies carried out on *HLA-DRB1* and *-DQB1* polymorphisms in relation to susceptibility to SLE fulfilled inclusion criteria: 1) 9 studies were included in meta-analysis of *HLA-DRB1* polymorphism, 2) 6 studies were included in *HLA-DQB1* polymorphism analysis and 3) 4 studies were included in haplotype analysis (Table 1). Two of these studies were conducted on Brazilians [7,20], 7 on Mexicans [15–18,21–23], one on Mexican Americans [24] and one on Colombians (current study) (Table 1).

3.2. Study quality

Funnel Plot and Egger's regression tests allowed us to conclude that there is no evidence of publication bias in this meta-analysis (for HLA-DR5 the t-value was 0.59, degrees of freedom (df)=6, p=0.57; for HLA-DR2 the t-value was 1.63, df=7, p=0.14; for HLA-DR3 the t-value was 0.6, df=7, p=0.56; and for HLA-DR3-DQ2 haplotype the t-value was 9.04, df=1, p=0.07).

A total of twelve studies were excluded from our analysis. Three of these were not included because they all used the LUMINA sample as did Reveille et al.'s study [25–27] and another three due to lack of sufficient data reported in the text or tables for estimating effect size [28–30]. Another two studies were excluded because they represented an isolated population in Latin America [6,31], and one of them had methodological inconsistencies [31]. Three Brazilian studies did not meet the inclusion criteria. One did not meet the requirements for the study design [32], and the other two had sample sizes that were markedly small and limited HLA genotyping, since it was carried out only on patients with specific clinical manifestations [33,34]. Finally, a study on cytokine gene polymorphisms in Colombian patients with SLE mentioned *HLA-DRB1* typing but it did not report complete and accurate data to estimate the effect size [35].

3.3. Association between HLA-DRB1 and -DQB1 alleles with SLE

An association between DR2 (OR: 1.75, 95% CI: 1.40–2.19, p=0.000001), DR3 (OR: 2.02, 95% CI: 1.44–2.83, p=0.0004) and DR5 (OR: 0.43, 95% CI: 0.27–0.67, p=0.0003) serological specificity groups and SLE was demonstrated (Fig. 1). Under both, fixed and random effect models, *HLA-DRB1*0301* showed an OR of 2.14 (95% CI: 1.28–3.56, p=0.004). We found *HLA-DRB1*1101* to have a protective effect with an OR of 0.21 (95% CI: 0.06–0.72, p=0.01) [9,17]. Our analysis also suggests that *HLA-DRB1*1501* could be another risk allele for SLE susceptibility (OR: 1.80, 95% CI: 0.99–3.28, p=0.05) [9,17]. No statistically significant association was established for any of the 12 *HLA-DQB1* alleles or serological specificities at this group. Analysis of haplotypes showed that HLA-DR3-DQ2 (OR=2.92, 95% CI: 1.66–5.14, p=0.0001) is a risk factor for SLE in Latin Americans (Fig. 1). Heterogeneity was not observed in the *DRB1*0301* (Q=1.28, p-value=0.53, I^2=0%) or **1101* (Q=0.03, p-value=0.86, I^2=0%) alleles analysis. Similarly, HLA-DR2 group and -DR3-DQ2 haplotype meta-analysis did not demonstrate heterogeneity in contrast with HLA-DR3 and -DR5 serological analysis of specificity groups (Table 1).

Under a fixed model, HLA-DR7 allele (OR: 0.69, 95% CI: 0.54–0.88, p=0.003), HLA-DR2-DQ1 (OR: 2.15, 95% CI: 1.26–3.66, p=0.005) and -DR4-DQ3 (OR: 1.49, 95% CI: 1.04–2.12, p=0.03) haplotypes showed an association with SLE. Nevertheless, these analyses proved to have high heterogeneity (for HLA-DR7 there was a Q of 41.84, p=0.00001, I^2=80.88%; for HLA-DR2-DQ1 there was a Q of 7.48, p=0.02, I^2=73.28%; and for HLA-DR4-DQ3 there was a Q of 2.62, p=0.27, I^2=23.68%). Thus, these results should not be taken as conclusive outcomes. Meta-analysis for another 16 *HLA-DRB1* alleles, 6 HLA-DR serological specificity groups and 7 haplotypes were carried out but they did not show any statistical effect.

4. Discussion

Polymorphism in genes at the MHC region represents a major susceptibility factor for SLE, specially *HLA-DRB1* and *HLA-DQB1* [2,4,5]. The current meta-analysis

A

Association	Population [ref]	Allele	Pocket 1 ß86	Pocket 4 ß70	Pocket 4 ß71	Pocket 9 ß37
Risk	Asian [40]	*1501[a]	Val	Gln	Ala	Ser
	Caucasian [1,5]	*1501[a]	Val	Gln	Ala	Ser
	Afro American [2]	*1503	Val	Gln	Ala	Ser
	Caucasian [1,2]	*0301	Val	Gln	Lys	Asn
	Latin American[b]	*0301	Val	Gln	Lys	Asn
Protection	Caucasian [5]	*0701	Gly	Asp	Arg	Phe
	Latin American[b,c]	*0701	Gly	Asp	Arg	Phe
	Latin American[b]	*1101	Gly	Asp	Arg	Tyr

B

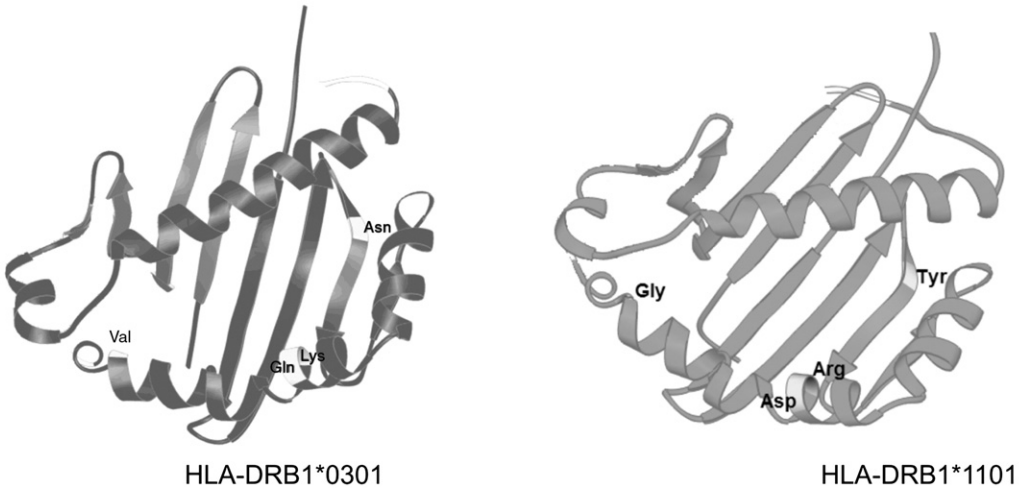

Fig. 2. *HLA-DRB1* alleles associated with SLE in different populations. A. Functional analysis of susceptibility and protective molecules reveals physicochemical differences of critical amino acids residues shaping the peptide-binding groove in the DRβ chain. Glycine is a smaller residue as compare to valine, which would restrict the size of the antigenic peptide side chain. Glutamine is a neutral amino acid residue, in contrast to the acidic and polar aspartic acid, influencing the anchor of the auto-antigen to the molecule in an opposite way. Protective alleles encode an arginine residue which is the strongest basic residue. Risk alleles determine the presence of a neutral (alanine) or less basic (lysine) residue at position β71. The polymorphic position β37 is shaped by aromatic amino acids (phenylalanine or tyrosine) encoded by the protective alleles, conferring a bigger motif than the residues associated with increased risk (serine or asparagine). [a]As part of an extended haplotype, [b]results of the current meta-analysis, [c]by the fixed model (see text for details). B. A model of peptide-binding groove at *HLA-DRB1* molecules encoded by involved alleles in Latin American individuals with SLE. Enhanced amino acids correspond to polymorphic residues at pocket 1 (position β86), pocket 4 (positions β70 and β71) and pocket 9 (position β37). The figure was generated using Ribbons v.3.0 [39].

indicates that *HLA-DRB1*0301* is associated with SLE susceptibility in Latin Americans. Analysis of serological specificities shows that not only HLA-DR3 but also HLA-DR2 groups are also risk factors. Furthermore, common effect size of HLA-DR3-DQ2 haplotype showing a positive association was statistically significant. This haplotype is one of the three that is strongly linked to the development of SLE in Caucasian individuals [2,8]. A protective effect was found for HLA-DR5 group, mainly due to a negative association between *DRB1*1101* allele and disease. The HLA-DR7 group has also been described as a protective factor [5]. In this meta-analysis, the results obtained for HLA-DR7 alleles were statistically significant under the fixed model but high heterogeneity was found by means of I^2. No *HLA-DQB1* alleles showed a significant deviation from the control group in this sample. Genotyping techniques must be taken into consideration because these methodologies have different sensitivities, which could hinder an effective comparison between the studies. However, only two studies included in this meta-analysis used microlymphocytotoxicity to determine HLA serological specificities (Table 1).

Clinical implications of HLA class II alleles have been elucidated such as that DR2 and DR3 allele carriers present an increased prevalence of lupus nephritis [4]. Latin American Mestizos SLE patients have more renal and myocardial involvement as compared to Caucasians from Latin America, as well as a higher level of disease activity [36]. Our results indicate that Latin Americans carrying the HLA-DR2 and -DR3 groups have a risk of developing SLE that is, respectively, 1.75 and 2.02 fold higher than non-carriers. Further studies in stratified samples (i.e. by lupus nephritis, by a particular antibody, etc.) might be useful in elucidating the effect of genotype on the subphenotypes.

The functional implications based on the physicochemical properties of residues encoded by susceptibility and protective alleles allow us to infer an approach to understand the mechanistic basis of the role of HLA in SLE (Fig. 2) [37–40]. Noteworthy, certain polymorphic residues at pockets 1 (β86), 4 (β70, β71) and 9 (β37) of the DRβ chain shaping the binding groove encoded by the HLA class II alleles that were significantly associated to disease in this meta-analysis can be grouped by their physical and chemical properties. Both alleles associated to increased susceptibility in the current work, *HLA-DRB1*0301* and *-DRB1*1501*, and the previously reported risk alleles in other populations (*HLA-DRB1*1501* in Asians and Caucasians; and *HLA-DRB1*1503* in Afro-American individuals) [2,6,7] encode a valine at position β86 [37]. In contrast, protective alleles such as *HLA-DRB1*0701* and *-DRB1*1101* encode a glycine at this position. The specificity of pocket 1 is modulated by this dimorphism (Val/Gly β86) [37]. At pocket 4, risk alleles mentioned above encode a glutamine at position β70, while protective alleles encode an aspartic acid at β70. Additionally, *HLA-DRB1*0701* and *-DRB1*1101* encode an arginine at position β71. This amino acid is polar and strongly basic in contrast to alanine and lysine, which are encoded by risk alleles *HLA-DRB1*1501* and *-DRB1*0301*, respectively (Fig. 2). These two positions, β70 and β71, are at pocket 4 and exert a major influence on the binding of antigenic peptides and the subsequent recognition by T cells [38]. The amino acid at the position β37 is an important residue located in pocket 9. Risk alleles, *HLA-DRB1*1501* and *-DRB1*0301*, determine the presence of polar amino acids (serine and asparagine, respectively), whereas protective alleles, *HLA-DRB1*0701* and *-DRB1*1101*, are responsible of the expression of large, aromatic and non-polar amino acids at this position (phenylalanine and tyrosine, respectively) (Fig. 2). In summary, differences in the nature of critical amino acid side chains might be related to the risk or protection conferred by *HLA-DRB1* alleles associated with SLE.

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Take-home messages

- HLA-DR2 and -DR3 groups confer susceptibility to SLE and increase the risk in Latin Americans of developing this autoimmune disease 1.75 and 2.02, respectively. HLA-DR3-DQ2 haplotype carriers have 2.93 increased fold risk to develop SLE than non-carriers.
- The *HLA-DRB1*0301* allele is involved in susceptibility to SLE in Latin Americans while the *HLA-DRB1*1101* allele is a protective factor in this population.
- Functional analysis reveals physicochemical differences of certain amino acids residues shaping the peptide-binding groove at DRβ chain according to susceptibility and protection alleles.

References

[1] Anaya JM, Shoenfeld Y, Correa PA, Garcia-Carrasco M, Cervera R. Autoinmunidad y Enfermedad Autoinmune. 1ra ed. Medellín, Colombia: Corporación para Investigaciones Biológicas; 2005.
[2] Wong M, Tsao BP. Current topics in human SLE genetics. Springer Semin Immunophatol 2006;28:97–107.
[3] Farabosco P, Gorman JD, Cleveland C, Kelly JA, Fisher SA, Ortmann WA, et al. Meta-analysis of genome-wide linkage studies of systemic lupus erythematosus. Genes Immun 2006;7:609–14.
[4] Wakeland EK, Liu K, Graham RR, Behrens TW. Delineating the genetic basis of systemic lupus erythematosus. Immunity 2001;15:397–408.
[5] Gladman DD, Urowitz MB, Darlington GA. Disease expression and class II HLA antigens in systemic lupus erythematosus. Lupus 1999;8:466–70.
[6] Smikle M, Christian N, DeCeulaer K, Barton E, Roye-Green K, Dowe G, et al. HLA-DRB alleles and systemic lupus erythematosus in Jamaicans. South Med J 2002;95:717–9.
[7] Muchinechi SR, Persoli LB, Dutra SB, Lavras LT. HLA antigens and susceptibility to systemic lupus erythematosus in Brazilian patients. Rev Bras Reumatol 1998;38:332–6.
[8] Graham RR, Ortmann W, Rodine P, Espe K, Langefeld C, Lange E, et al. Specific combinations of HLA-DR2 and DR3 class II haplotypes contribute graded risk for disease susceptibility and autoantibodies in human SLE. Eur J Hum Genet 2007;15:823–30.
[9] Reveille JD, Macleod MJ, Whittington K, Arnett FC. Specific amino acid residues in the second hypervariable region of *HLA-*

DQA1 and *DQB1* chain genes promote the Ro (SS-A)/La (SS-B) autoantibody responses. J Immunol 1991;146:3871–6.
[10] Sans M. Admixture studies in Latin America: from the 20th to the 21st century. Hum Biol 2000;72:155–77.
[11] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
[12] Correa PA, Molina JF, Pinto LF, Arcos-Burgos M, Herrera M, Anaya JM. TAP1 and TAP2 polymorphisms analysis in Northwestern Colombian patients with systemic lupus erythematosus. Ann Rheum Dis 2003;62:363–5.
[13] Gomez D, Correa PA, Gomez LM, Cadena J, Molina JF, Anaya JM. Th1/Th2 cytokines in patients with systemic lupus erythematosus: is tumor necrosis factor alpha protective? Semin Arthritis Rheum 2004;33:404–13.
[14] Marsh SGE, Albert ED, Bodmer WF, Bontrop RE, Dupont B, Erlich HA, et al. Nomenclature for factors of HLA system, 2002. Tissue Antigens 2002;60:407–64.
[15] Bekker-Mendez C, Yamamoto-Furusho JK, Vargas-Alarcón G, Ize-Ludlow D, Alcocer-Varela J, Granados J. Haplotype distribution of class II MHC genes in Mexican patients with systemic lupus erythematosus. Scand J Rheumatol 1998;27:373–6.
[16] Cortes LM, Baltazar LM, Lopez-Cardona MG, Olivares N, Ramos C, Salazar M, et al. HLA class II haplotypes in Mexican systemic lupus erythematosus patients. Hum Immunol 2004;65:1469–76.
[17] Vargas-Alarcón G, Salgado N, Granados J, Gómez-Casado E, Martinez-Laso J, Alcocer-Varela J, et al. Class II allele and haplotype frequencies in Mexican systemic lupus erythematosus patients: the relevance of considering homologous chromosomes in determining susceptibility. Hum Immunol 2001;62:814–20.
[18] Granados J, Zúñiga J, Acuña-Alonzo V, Rosetti F, Vargas-Alarcón G. Influence of alleles and haplotypes of the main histocompatibility complex on the susceptibility to systemic lupus erythematosus in the Mexican population. Gac Med Mex 2006;142:195–9.
[19] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[20] Liphaus B, Goldberg AC, Kiss MH, Silva C. Analysis of human leukocyte antigens of class II-DR in Brazilian children and adolescents with systemic lupus erythematosus. Rev Hosp Clin Fac Med Sao Paulo 2002;57:277–82.
[21] Simón JA, Granados J, Cabiedes J, Morales JR, Varela JA. Clinical and immunogenetic characterization of Mexican patients with 'rhupus'. Lupus 2002;11:287–92.
[22] Vargas-Alarcón G, Granados J, Martínez-Laso J, Gómez-Casado E, Zuñiga J, Salgado N, et al. Lack of association between the polymorphism at the heat-shock protein (HSP70-2) gene and systemic lupus erythematosus (SLE) in the Mexican mestizo population. Genes Immun 2000;1:367–70.
[23] Granados J, Vargas-Alarcón G, Drenkard C, Andrade F, Melín-Aldana H, Alcocer-Varela J, et al. Relationship of anticardiolipin antibodies and antiphospholipid syndrome to HLA-DR7 in Mexican patients with systemic lupus erythematosus (SLE). Lupus 1997;6:57–62.
[24] Reveille JD, Moulds JM, Ahn C, Friedman AW, Baethge B, Roseman J, et al. Systemic lupus erythematosus in three ethnic groups: I. the effects of HLA class II, C4, and CR1 alleles, socioeconomic factors, and ethnicity at disease onset. Arthritis Rheum 1998;41:1161–72.
[25] Uribe AG, McGwin Jr G, Reveille JD, Alarcón GS. What have we learned from a 10-year experience with the LUMINA (lupus in minorities; nature vs nurture) cohort? Where are we heading? Autoimmun Rev 2004;3:321–9.
[26] Calvo-Alen J, Reveille JD, Rodríguez-Valverde V, McGwin Jr G, Baethge BA, Friedman AW, et al. Clinical, immunogenetic and outcome features of Hispanic systemic lupus erythematosus patients of different ethnic ancestry. Lupus 2003;12:377–85.
[27] Fernández M, Alarcón GS, Calvo-Alén J, Andrade R, McGwin Jr G, Vilá LM, et al. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. Arthritis Rheum 2007;57:576–84.
[28] Acosta G, Díaz A, Granados J, Gaytán M, Parrao C, Torres C. Association between Sm antibodies and HLA haplotypes in a group of patients with SLE. Rev Hosp Jua Mex 1999;66:3–7 [Spanish].
[29] Graham RR, Ortmann WA, Langefeld CD, Jawaheer D, Selby SA, Rodine PR, et al. Visualizing human leukocyte antigen class II risk haplotypes in human systemic lupus erythematosus. Am J Hum Genet 2002;71:543–53.
[30] Arnett F, Thiagarajan P, Ahn C, Reveille JD. Associations of anti-beta2-glycoprotein I autoantibodies with HLA class II alleles in three ethnic groups. Arthritis Rheum 1999;42:268–74.
[31] Smickle MF, Barton EN, DeCeulaer K, Williams WN, James OB. Systemic lupus erythematosus, rheumatoid arthritis and HLA phenotypes in Jamaicans. West Indian Med J 1995;44:11–3.
[32] Liphaus BL, Kiss MH, Goldberg AC. *HLA-DRB1* alleles in juvenile-onset systemic lupus erythematosus: renal histologic class correlations. Braz J Med Biol Res 2007;40:591–7.
[33] Araújo MN, Silva NP, Andrade LE, Sato EI, Gerbase-DeLima M, Leser PG. C2 deficiency in blood donors and lupus patients: prevalence, clinical characteristics and HLA-associations in the Brazilian population. Lupus 1997;6:462–6.
[34] Balthazar PA, Gabriel Júnior A, de Oliveira DP, de Oliveira MA, Rosales T, Iglesias SS, et al. HLA-DR in patients with systemic lupus erythematosus with anti-ribonucleoprotein antibodies and in mixed connective tissue disease. Rev Hosp Clin Fac Med Sao Paulo 1985;40:249–53 [Portuguese].
[35] Guarnizo-Zuccardi P, Lopez Y, Giraldo M, Garcia N, Rodriguez L, Ramirez L, et al. Cytokine gene polymorphisms in Colombian patients with systemic lupus erythematosus. Tissue Antigens 2007;70:376–82.
[36] Pons-Estel BA, Catoggio LJ, Cardiel MH, Soriano ER, Gentiletti S, Villa AR, et al. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". Medicine 2004;83:1–17.
[37] Stern L, Brown J, Jardetzky T, Gorga J, Urban R, Strominger J, et al. Crystal structure of the human class II MHC protein HLA-DR1 complexed with an influenza virus peptide. Nature 1994;368:215–21.
[38] Ou D, Mitchell LA, Tingle AJ. A new categorization of HLA DR alleles on a functional basis. Hum Immunol 1998;59:665–76.
[39] Carson M. Ribbon models of macromolecules. J Mol Graph 1987;5:103–6.
[40] Hong GH, Kim HY, Takeuchi F, Nakano K, Yamada H, Matsuta K, et al. Association of complement C4 and HLA-DR alleles with systemic lupus erythematosus in Koreans. J Rheumatol 1994;21:442–7.