Human Immunology 72 (2011) 581-586

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Human leukocyte antigen class II and type 1 diabetes in Latin America: A combined meta-analysis of association and family-based studies

Ricardo A. Cifuentes*, Adriana Rojas-Villarraga, Juan-Manuel Anaya

Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

ARTICLE INFO

Article history:
Received 7 January 2011
Accepted 31 March 2011
Available online 15 April 2011

Keywords:
Autoimmunity
HLA class II
Meta-analysis
Latin America
Type 1 diabetes

ABSTRACT

Conclusions from association studies could be spurious because of population stratification; therefore we combined association with family studies seeking to confirm which human leukocyte antigen (HLA) class II alleles/haplotypes were associated with type 1 diabetes (T1D) in the admixed Latin America. By calculating the effect summary odds ratios (OR) and their 95% confidence intervals (95% CI), data up to June 2010 showed that risk associations were observed with DRB1*0301-DQA1*0501-DQB1*0201 (odds ratio [OR]: 7.51; 95% confidence interval [CI]: 3.69–15.25) and DQB1*0302 in presence of DRB1*0405 (OR: 11.64; 95% CI: 3.15–43.01) or DRB1*0401 (OR: 5.85; 95% CI: 3.07–11.14). In contrast, DRB1*0404-DQB1*0302 had a nonsignificant TID risk (OR: 2.23; 95% CI: 0.91–5.43). T1D protective associations were observed with DRB1*11-DQA1*0501-DQB1*0301 (OR: 0.24; 95% CI: 0.1–0.56) and DRB1*15-DQA1*0102-DQB1*0602 (OR: 0.35; 95% CI: 0.17–0.73). These results were similar to those observed in Caucasian and other populations, thus highlighting the primary role of class II HLA in T1D regardless of ethnicity. A DRB1*04 risk hierarchy was confirmed with the DRB1*0405 being in the top. A binding prediction analysis disclosed possible receptor–ligand interactions in the HLA–antigenic peptide complex.

1. Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterized by the destruction of the pancreatic β-cells and by a multifactorial etiology with a highly important genetic component [1]. Research studies have found that the largest contribution to genetic susceptibility comes from the human leukocyte antigen (HLA) region at chromosome 6p21.3 [2,3]. This region contributes to approximately half of the T1D genetic risk [1,3], which is mostly attributable to the class II HLA DR and DQ genes [4,5]. Data from diverse populations, including a high contribution from Caucasians, have shown that specific alleles and haplotypes from these genes confer susceptibility to or protection from T1D [6] and are associated with specific antibody profiles [7].

There are different degrees of genetic susceptibility to T1D across populations [8]. Categories of consistent predisposing, neutral and protective haplotypes were found to correlate with disease incidences and the marked ethnic differences in DRB1-DQB1 frequencies [9]. In this context, it is remarkable that some association studies showed that DRB1 played a central role in susceptibility and protection in Latin Americans more intensely than in Caucasians [1].

However, the analysis of the relationship between specific alleles/haplotypes of the class II HLA and T1D in Latin America (LA) represents a research challenge. LA is characterized by low to moderate T1D incidences depending on the observed country [8] and by a universal admixture in which the relative contributions of African, European, and Amerindian gene pools vary in accordance with historical circumstances [10]. LA is a heterogeneous population in which the Spanish-Mestizo population varies from 60% to 80% in Mexico, Colombia, Venezuela, Paraguay, Chile, Peru, and Ecuador to less than 15% in Uruguay and Argentina [11]. So far, however, few populations in LA, such as Mexicans and Mexican-Americans, have participated in worldwide analyses of this topic [9,12]; despite that, there are isolated studies from other countries in which moderate genetic associations could be detected by a meta-analysis, even though some of them have low power samples [13–16].

In addition, in the association studies, spurious associations could have been caused by population stratification [17,18]. In consequence, the evidence obtained from these studies in LA must be confirmed by an alternative method, such as the family-based transmission disequilibrium test (TDT) [14], which is not influenced by stratification because it uses nontransmitted alleles as internal controls for alleles that have been transmitted from heterozygous parents to the affected offspring [14,17].

Therefore, taking into consideration the current feasibility of carrying out a meta-analysis by combining data from independent family-based and association studies [13–16], the aim of this study was to evaluate which alleles/haplotypes of the class II HLA confer risk or protection from T1D in LA and to analyze their biologic

* Corresponding author.
E-mail address: ricardo.cifuentesgarcia@gmail.com (R.A. Cifuentes).

0198-8859/11/$32.00 - see front matter © 2011 American Society for Histocompatibility and Immunogenetics. Published by Elsevier Inc. All rights reserved.
doi:10.1016/j.humimm.2011.03.012

implications through a binding prediction approach of peptides from major T1D auto-antigens.

2. Subjects and methods

2.1. Search strategy and selection criteria

Published case-control and family studies were identified through a systematic search independently done by 2 experts that used equal search terms and databases as previously described by our group [18]. The final date for inclusion was June 2010. The search only included publications on class II HLA and T1D in LA published in three languages: Spanish, English, or Portuguese. The inclusion criteria were the following: publication of the necessary data on high-resolution alleles/haplotypes to calculate reliable odds ratios and their associated χ^2 statistic values: frequency equal to or greater than 1% in the case-control studies and five or more transmissions in the family-based studies [14]; all other selection criteria were equal to those previously described [18]. Detailed information on both the studies that were included and those that were excluded is given in Tables S1 and S2.

2.2. Data extraction

The data collected from each evaluated class II HLA allele/haplotype were the following: first author and year of study, the type of study (family-based or association), the number of alleles/haplotypes transmitted and not transmitted to affected offspring, the number of the alleles/haplotypes observed in cases and in controls, and the number of alternative alleles/haplotypes in cases and in controls.

2.3. Meta-analysis

Calculations were done by using the catmap package at R software for each allele/haplotype that had both transmission and case-control data from independent studies available [13]. Odds ratios (OR) were grouped by weighing individual OR by the inverse of their variance [14]. Thus, for each allele, the final effect OR and the 95% confidence interval were obtained by means of both random and fixed-effects models. The fixed-effects model was only used when the random-effects variance was less than or equal to zero [15] and there was no heterogeneity, defined as $p < 0.10$ by the Cochran's (Q) test; otherwise the random-effects model was chosen [16]. Publication bias was evaluated by funnel plots and sensitivity analysis.

2.4. Binding prediction of peptides to class II HLA

We evaluated the presence of peptides that could bind the class II HLA haplotypes, which had been found to be of significant T1D risk or protection, by using the Immune Epitope Database Analysis Resource (IEDB; available at http://tools.immuneepitope.org/analyze/html/mhc_II_binding.html). The peptide sources were the following major auto-antigens in T1D: islet cell protein-tyrosine-phosphatase (IA2) (GenBank ID: AAH70053), islet cell autoantigen (ICA) (GenBank ID: NP_001129492), Insulin (GenBank ID: AAA59172), islet cell cytoplasmic autoantigen (ICCA) (GenBank ID: Q16849) and glutamic acid decarboxylase (GAD) (GenBank ID: CAA01913) [11-14]. The protein sequences in a FASTA format were the input for the computational model and the peptides classified according to the consensus prediction approach were the output [19]. Peptides were good binders when the Consensus Percentile Rank was less than 1.

3. Results

From 10 countries, four studies with transmission data from 215 patients' families and 21 with data from association studies (1304 cases and 1969 controls) fit the selection criteria (Table 1). Data on 15 high-resolution alleles were available. DQB1*0302, DQB1*0201, DQA1*0501, and DQA1*0301 were T1D risk alleles in LA. DQB1*0602 and DQB1*0501 were found to be protective. DQB1*0603, DQB1*0301 and, DQB1*0402 did not pass the sensitivity analysis (Table S3, Table 2). Transmission data from the DRB1and DP alleles were not available.

In addition, data from 15 haplotypes were available. Eight had more than one high-resolution HLA class II allele, and seven had a maximum of one high-resolution allele. Therefore, they were identified as specific and nonspecific haplotypes, respectively (Table S4).

T1D risk associations were observed with DRB1*0301-DQA1*0501-DQB1*0201 and DRB1*04-DQA1*0301-DQB1*0302 specific haplotypes. In the latter haplotype, the presence of

Table 1
Included articles in the combined meta-analysis of HLA class II alleles in Latin American (LA) type 1 diabetes (T1D) patients

Study	Country	Type of study	Families	Patients	Controls
Balducci (1994)	Venezuela	Association		42	64
Brandao (2010)	Brazil	Association		184	184
Caputo (2005)	Argentina	Association		70	79
Cruz (2004)	U.S.[a], Puerto Rico	Association		91	82
Díaz (2003)	Chile	Association		57	125
Erlich et al. (1993)	U.S.[a]	Association		44	269
Fernandes (2002)	Brazil	Association		64	181
Gorodezky (1995)	Mexico	Association		142	85
Hauache (2005)	Brazil	Association		126	75
Heward (2002)	Jamaica	Association		45	132
Krochik (2001)	Argentina	Association		79	79
Marques (1998)	Brazil	Association		41	99
Mijovic (1991)	Jamaica (Caribbean)	Association		37	82
Mimbacas (1998)	Uruguay	Association		15	15
Mimbacas (2004)	Uruguay	Family	51		
Mimbacas (2003)	Uruguay	Association		72	40
Montoya (1996)	Colombia	Association		26	56
Pérez (1996)	Chile	Association		63	74
Pérez (1998)	Chile	Association and Family	14	14	74
Rassi (2006)	Brazil	Association		6	6
Sanjeevi (1993)	U.S.[a]	Association		35	39
Santos (2001)	Chile	Family	94		
Volpini (2001)	Brazil	Family	56		
Zeidler (2001)	U.S.[a]	Association		108	72
Total			215	1304	1969

[a]Mexican-Americans.

Table 2
HLA class II alleles/haplotypes associated with type 1 diabetes (T1D) in Latin Americans (LA)

Specific alleles/haplotypes	OR	95% CI lower bound	95% CI upper bound	*p* Value	Q chi-square	Q *p* Value
Risk variants						
DRB1*0405-DQB1*0302	11.64	3.15	43.01	0.0002	4.60	0.2027
DRB1*0301-DQA1*0501-DQB1*0201	7.51	3.69	15.25	0.0000	16.16	0.0028
DRB1*0401-DQB1*0302	5.85	3.07	11.14	0.0000	32.23	0.0000
DQB1*0302	4.45	3.29	6.02	0.0000	49.8	0.0000
DRB1*04-DQA1*0301-DQB1*0302	5.79	2.43	13.79	0.0000	21.73	0.0000
DQB1*0201	2.97	2.05	4.3	0.0000	52.1	0.0000
DQA1*0501	2.43	1.34	4.38	0.0031	59.69	0.0000
DQA1*0301	2.65	1.23	5.72	0.0126	52.98	0.0000
Protective variants						
DQB1*0602[a]	0.17	0.09	0.29	0.0000	5.7	0.6807
DRB1*11-DQA1*0501-DQB1*0301[a]	0.24	0.10	0.56	0.0011	1.10	0.5768
DQB1*0402[b]	0.34	0.12	0.94	0.0386	14.92	0.0208
DRB1*15-DQA1*0102-DQB1*0602[a]	0.35	0.17	0.73	0.0054	2.98	0.3946
DQB1*0603[b]	0.39	0.18	0.87	0.0217	8.03	0.2354
DQB1*0501	0.41	0.24	0.68	0.0006	29.33	0.0005
DQB1*0301[b]	0.49	0.26	0.92	0.027	93.88	0.0000

CI, confidence interval; OR, odds ratio; Q, heterogeneity (Cochran test).
[a]Meta-analysis by the fixed-effects model.
[b]Publication bias.

DRB1*0405 or DRB1*0401 led to a significant increase in risk but a higher one in the case of DRB1*0405 (Table 2). In contrast, DRB1*0404-DQB1*0302 had a nonsignificant risk association with TID (Fig. 1, Table S4). T1D protective associations were observed with DRB1*11-DQA1*0501-DQB1*0301 and DRB1*15-DQA1*0102-DQB1*0602 specific haplotypes (Table S4, Table 2). The DQA1*0501 allele increased the risk in combination with DQB1*0201 and decreased the risk in combination with DQB1*0301.

All of the significant associated alleles belonged to the risk and protective haplotypes and the nonspecific haplotypes agreed with the specific haplotypes (Table S4) despite the fact that, in general, they included different studies. In addition, the family, association and the pooled OR showed a similar tendency for the OR both on haplotypes (Fig. 1) and alleles. This eliminated the possibility of a bias caused by one single type of study, as family data may be influenced by high-risk HLA genes.

With regard to the epitope binding prediction, no good binders from insulin were predicted. None of the auto-antigens had peptides that were good binders for the DQA1*0501-DQB1*0301 protective haplotype. Different peptides from ICCA and IA2 were predicted to be good binders for the DQ component of the risk and protective haplotypes. In contrast, peptides from GAD and ICA were only predicted to be good binders for the DQ component that is associated with risk haplotypes. Regarding the DRB1*04 component of the T1D associated haplotypes, fewer peptides from GAD, ICCA, and IA2 were predicted to be good binders for the risk alleles DRB1*0405 and DRB1*0401 than for the DRB1*0404 allele (Table 3).

4. Discussion

Despite the different degrees of admixture in LA that are associated with a nonuniform T1D incidence from one country to another, our meta-analysis that combines family and association studies confirmed that, in LA, the same alleles and haplotypes extensively described in Caucasians and other populations were found to be associated with cases of T1D or differentially transmitted to patients from their parents. In addition, the meta-analysis also gave further support to the central role of DRB1*04 in modulating the T1D susceptibility that is conferred by the DQA1*0301-DQB1*0302 haplotype.

Our results agreed not only with association studies from Mexico, Venezuela and Colombia [20], but also with family-based studies of Caucasians and Asians [6] that described DRB1*0301-DQA1*0501-DQB1*0201, DRB1*0405-DQA1-*0301-DQB1*0302, and DRB1*0401-DQA1*0301-DQB1*0302 as T1D risk haplotypes. In contrast, we did not confirm in other countries from LA the risk conferred on the Mexican population by DRB1*0404-DQA1*0301-DQB1*0302 [1,20] (Fig. 1, Tables S4 and S5). Thus, DRB1*04 alleles in LA seemed to follow a risk hierarchy that is similar to that in Caucasian and other populations [5,9]. However, we did not have data about other haplotypes involved in the above-mentioned hierarchy to evaluate, for instance, the described protection of DQA1*03:01-DQB1*03:02 when DRB1*04:03 is part of the haplotype [21,22]. At this point, in LA, as previously stated, the role that DRB1*0405 plays in conferring a higher risk compared with DRB1*0401 must be highlighted [20,22].

With regard to the protective haplotypes, we not only confirmed a protective role for DRB1*11-DQA1*05:01-DQB1*03:01 in LA as was previously described in Mexican, Colombian, and Venezuelan studies [20] but also in agreement with what was described in Caucasians, Africans, and Asians [6,9]. In this haplotype, the DQA1*05:01 allele does not seem to be involved in protection if we take into account the fact that DQA1*05011, which belongs to a risk haplotype, has an amino-acid sequence that is identical to the DQA1*05013 allele of the protective haplotype irrespective of their differences at codons 172 and 201 [23].

DRB1*15-DQA1*0102-DQB1*0602 was also a protective haplotype in LA as was universally described [6,9,20,23]. DQB1*0602 is the only class II allele found exclusively on protective DR2 haplotypes, thus suggesting that protection is mostly although not exclusively conferred by DQB1*0602. Moreover, even first-degree relatives of T1D patients with the DQB1*0602 allele and islet cell antibodies have an extremely low T1D incidence [24].

Because of the lack of data, the influence of the haplotypes such as DRB1*0407-DQB1*0302, DRB1*0408-DQB1*0302, DRB1*0802-DQB1*0400, DRB1*1402-DQB1*0301, and DRB1*1602-DQB1*0301, which had previously been identified as indigenous in Mexican, Americans, on T1D could not be analyzed [25]. Nevertheless, taken together, data about DRB1*0802-0400 in Mexican-Americans and data from Brazil, Colombia and Venezuela about the DRB1*08-DQA1*0401-DQB1*04 haplotype (Table S4), indicates that this haplotype seems to have a tendency to be protector. However, data from association studies about different DRB1 alleles is not conclusive about their role in T1D (Table S5). Thus, these results should lead to further research on the admixed population of LA. In addi-

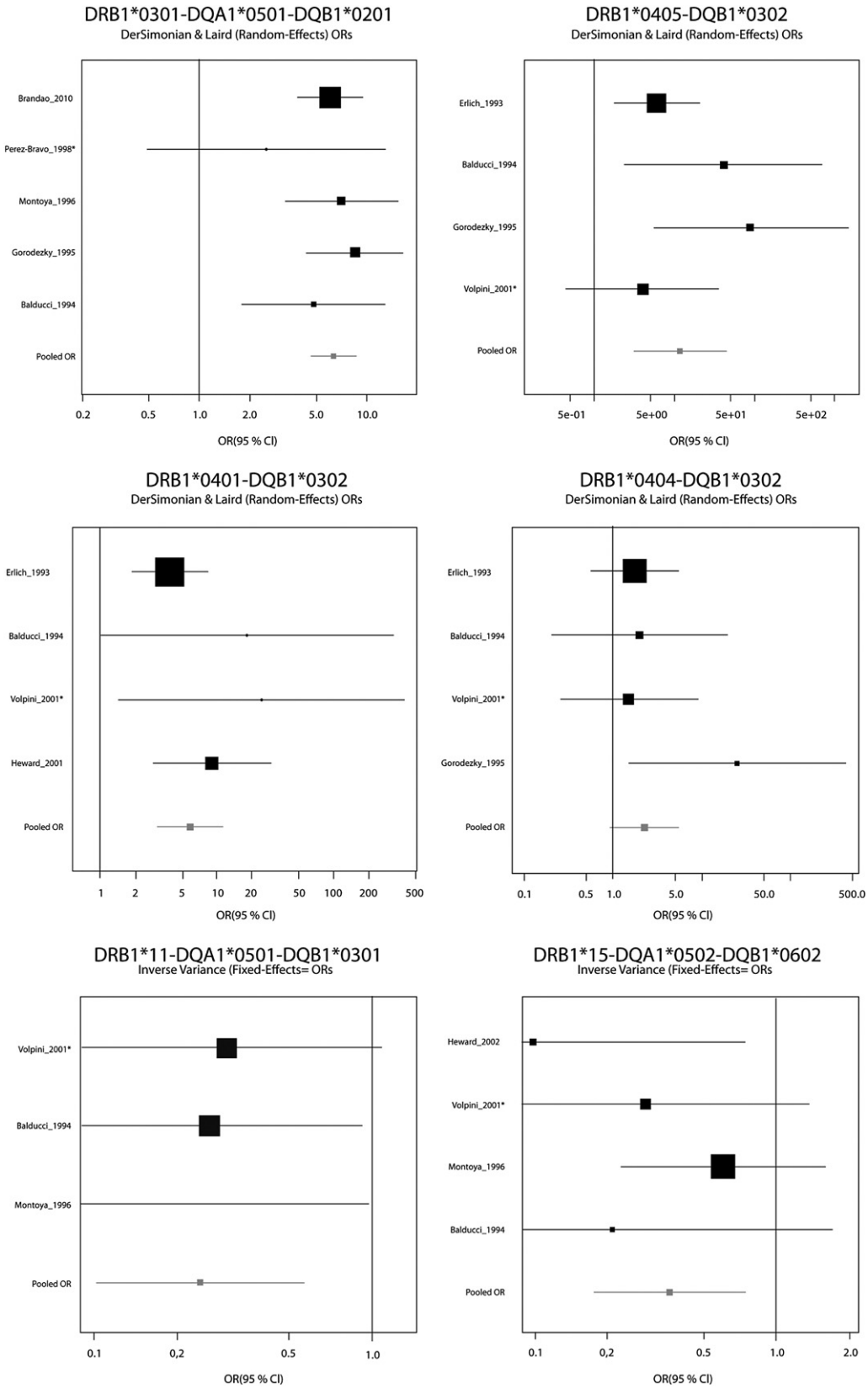

Fig. 1. Forest plots of specific HLA class II haplotypes associated with T1D. Each plot shows the effect size and precision for individual studies and for the combined effect calculated by the fixed or random model. Filled squares are proportional in size to study weights. Pooled odds ratios (OR) shows the effect summary OR for each haplotype. An asterisk after the study indicates that this of a family type.

Table 3
Peptides predicted as good binders to type 1 diabetes (T1D) risk and protective HLA class II haplotypes

AA	Haplotype component & 9-mer peptide					
	DQA1*0301-DQB1*0302 component		DQA1*0501-DQB1*0201 component		DQA1*0102-DQB1*0602 component	
GAD	SDIDFLIEE	573–591[a]	FLLEVVDIL	110–128[a]		
ICA	WFSLFADLD	449–466[a]	WFSLFADLD	450–468[a]		
	ESTDAAVQE	285–303[a]	FLSQEENEL	80–95[a]		
ICCA	FALTAVAEE	954–975[a]	FALTAVAEE	955–974[a]	QTGLQILQT	539–556[a]
	EEAAAVLPQ	554–570[a]				
IA2	FALTAVAEE	925–939[a]	FALTAVAEE	926–945[a]	VAGLLVALA	554–568[a]
	EEAAAVLPQ	525–541[a]			QTGLQILQT	510–527[a]
	DRB1*0401 component		DRB1*0404 component		DRB1*0405 component	
GAD	FRMVISNPA	561–580[a]	FRMVISNPA	560–580[a]	FRMVISNPA	560–580[a]
			PGGAISNMY	248–266[a]	FVLMEQITL	216–234[a]
			LVLFTSEQS	277–294[a]		
ICA	LFADLDPLS	453–470[a]	FTTLKSLQD	259–276[a]	FTTLKSLQD	258–276[a]
ICCA			LLCLLLLSS	10–30[a]	LRLLLCLLL	14–28[a]
			LTLLQLLPK	354–374[a]		
			LLVALAVAL	585–599[a]		
			TVIVMLTPL	800–818[a]		
IA2			LRLLLCLLL	10–30[a]	LRLLLCLLL	14–28[a]
			LLTLLQLLP	354–374[a]	YGYIVTDQN	467–482[a]
			LLVALAVAL	556–570[a]		
			TVIVMLTPL	771–789[a]		

AA, autoantigen; GAD, glutamic acid decarboxylase; ICA, islet cell autoantigen; ICCA, islet cell cytoplasmic autoantigen; IA2, islet cell protein-tyrosine-phosphatase.
[a]Position in the protein.

tion to the study of the DR-DQ haplotypes, a suggested area for study could be determining other specific disease susceptibility loci by adjusting the observations for linkage disequilibrium [26] or by stratifying on the basis of DR-DQ haplotypes [27].

According to the epitope binding prediction, peptides from GAD seem to have a higher affinity for the DQA1*0301-DQB1*0302 component that confers higher risk and for the DRB1*04 component that confers lower risk to T1D. Alleles such as DRB1*0404 that confers a lower risk than DRB1*0405 and DRB1*0401 could compete with the DQA1-DQB1 component, thus lowering the peptide presentation and the generation of auto-reactive T-cells. DRB1*0404 had a predictive behavior that was similar to DRB1*0403 (Table S6), an allele, which, in the case of GAD, has led to down-modulation of DQ8 presentation of epitopes through an enhanced peptide competition as compared to weak competitors, such as DR0401 and DR0405 [28].

Together the data from the combined meta-analysis and from the peptide binding prediction support the existence of a universal genetic mechanism in T1D. It encourages further research on the specificity and sensitivity of the binding process and its immunologic implications. There were some peptides in our prediction approach which could help to improve our understanding about how T1D associated haplotypes work. ^{250}PGGAISNMY^{258} and ^{566}FRMVISNPA^{574} from GAD have demonstrated in vitro that they can bind some DRB1*04 molecules [28]. FALTAVAEE, a peptide from IA2 and ICCA, is also a known inducer of T-cell response in DQ8 transgenic mice [29]. It is interesting that FALTAVAEE would be able to interact with both of the DQ components of the heterozygous DRB1*0301-DQA1*0501-DQB1*0201/DRB1*0401-DQA1-0301-DQB1*0302 genotype, which is known for conferring a higher T1D risk compared with the homozygous form of those haplotypes [5]. There were also good binders for the protective haplotype DQA1*0102-DQB1*0602, such as the QTGLQILQT peptide, that warrant further research to determine not only the processing and presentation properties but also the production of regulatory T-cell clones which would explain the protective action. Some peptides from GAD have shown the property of inducing T cells that protected mice from T1D [30].

In conclusion, the finding of not only significant risk and protective alleles/haplotypes in this heterogeneous area of the world but also the fact that they are shared with other populations around the world highlights the primary role of some regions of the HLA in the genetic susceptibility to disease, regardless of ethnicity and allelic frequencies due to latitudinal gradients.

Acknowledgments

We are grateful to Cecile Dunn for reading the manuscript. This work was supported by the School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.humimm.2011.03.012.

References

[1] Gorodezky C, Alaez C, Murguia A, Rodriguez A, Balladares S, Vazquez M, et al. HLA and autoimmune diseases: Type 1 diabetes (T1D) as an example. Autoimmun Rev 2006;5:187–94.
[2] Davies JL, Kawaguchi Y, Bennett ST, Copeman JB, Cordell HJ, Pritchard LE, et al. A genome-wide search for human type 1 diabetes susceptibility genes. Nature 1994;371:130–6.
[3] Concannon P, Erlich HA, Julier C, Morahan G, Nerup J, Pociot F, et al. Type 1 diabetes: Evidence for susceptibility loci from four genome-wide linkage scans in 1,435 multiplex families. Diabetes 2005;54:2995–3001.
[4] Todd JA, Bell JI, McDevitt HO. HLA DQ beta gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. Nature 1987;329:599–604.
[5] Koeleman BP, Lie BA, Undlien DE, Dudbridge F, Thorsby E, de Vries RR, et al. Genotype effects and epistasis in type 1 diabetes and HLA-DQ trans dimer associations with disease. Genes Immun 2004;5:381–8.
[6] Erlich H, Valdes AM, Noble J, Carlson JA, Varney M, Concannon P, et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: Analysis of the type 1 diabetes genetics consortium families. Diabetes 2008;57:1084–92.
[7] Mehers KL, Gillespie KM. The genetic basis for type 1 diabetes. Br Med Bull 2008;88:115–29.
[8] DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. Diabet Med 2006;23:857–66.
[9] Thomson G, Valdes AM, Noble JA, Kockum I, Grote MN, Najman J, et al. Relative predispositional effects of HLA class II DRB1-DQB1 haplotypes and genotypes on type 1 diabetes: A meta-analysis. Tissue Antigens 2007;70:110–27.
[10] Salzano FM. Interethnic variability and admixture in Latin America—social implications. Rev Biol Trop 2004;52:405–15.
[11] Serrano-Rios M, Goday A, Martinez Larrad T. Migrant populations and the incidence of type 1 diabetes mellitus: An overview of the literature with a focus on the Spanish-heritage countries in Latin America. Diabetes Metab Res Rev 1999;15:113–32.
[12] Valdes AM, McWeeney S, Thomson G. HLA class II DR-DQ amino acids and insulin-dependent diabetes mellitus: Application of the haplotype method. Am J Hum Genet 1997;60:717–28.

[13] Nicodemus KK, Catmap: Case-control and TDT meta-analysis package. BMC Bioinformatics 2008;9:130.
[14] Kazeem GR, Farrall M. Integrating case-control and TDT studies. Ann Hum Genet 2005;69:329–35.
[15] Koskinen LL, Einarsdottir E, Dukes E, Heap GA, Dubois P, Korponay-Szabo IR, et al. Association study of the IL18RAP locus in three European populations with coeliac disease. Hum Mol Genet 2009;18:1148–55.
[16] Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006; 11:193–206.
[17] Spielman RS, McGinnis RE, Ewens WJ. Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus (IDDM). Am J Hum Genet 1993;52:506–16.
[18] Rojas-Villarraga A, Botello-Corzo D, Anaya JM. HLA-Class II in Latin American patients with type 1 diabetes. Autoimmun Rev 2010;9:666–73.
[19] Wang P, Sidney J, Dow C, Mothe B, Sette A, Peters B, et al. A systematic assessment of MHC class II peptide binding predictions and evaluation of a consensus approach. PLoS Comput Biol 2008;4;e1000048.
[20] Gorodezky C, Olivo A, Alaez C, Vazquez MN, de la Rosa G, Debaz H, et al. High- and low-risk molecular sequences in autoimmune diseases. An analysis of type I diabetes in Latin America. Gac Med Mex 1997;133(Suppl 1):125–32.
[21] Pugliese A. Genetics of type 1 diabetes. Endocrinol Metab Clin North Am 2004;33:1–16.
[22] Rewers A, Babu S, Wang TB, Bugawan TL, Barriga K, Eisenbarth GS, et al. Ethnic differences in the associations between the HLA-DRB1*04 subtypes and type 1 diabetes. Ann N Y Acad Sci 2003;1005:301–9.
[23] Yasunaga S, Kimura A, Hamaguchi K, Ronningen KS, Sasazuki T. Different contribution of HLA-DR and -DQ genes in susceptibility and resistance to insulin-dependent diabetes mellitus (IDDM). Tissue Antigens 1996;47: 37–48.
[24] Pugliese A, Kawasaki E, Zeller M, Yu L, Babu S, Solimena M, et al. Sequence analysis of the diabetes-protective human leukocyte antigen-DQB1*0602 allele in unaffected, islet cell antibody-positive first degree relatives and in rare patients with type 1 diabetes. J Clin Endocrinol Metab 1999;84: 1722–8.
[25] Erlich HA, Zeidler A, Chang J, Shaw S, Raffel LJ, Klitz W, et al. HLA class II alleles and susceptibility and resistance to insulin dependent diabetes mellitus in Mexican-American families. Nat Genet 1993;3:358–64.
[26] Qu HQ, Marchand L, Szymborski A, Grabs R, Polychronakos C. The association between type 1 diabetes and the ITPR3 gene polymorphism due to linkage disequilibrium with HLA class II. Genes Immun 2008;9:264–6.
[27] Cheung YH, Watkinson J, Anastassiou D. Conditional meta-analysis stratifying on detailed HLA genotypes identifies a novel type 1 diabetes locus around TCF19 in the MHC. Hum Genet 2011;129:161–76.
[28] Ge X, James EA, Reijonen H, Kwok WW. Differences in self-peptide binding between T1D-related susceptible and protective DR4 subtypes. J Autoimmun 2011;36:155–60.
[29] Chang KY, Unanue ER. Prediction of HLA-DQ8beta cell peptidome using a computational program and its relationship to autoreactive T cells. Int Immunol 2009;21:705–13.
[30] Di Lorenzo TP, Peakman M, Roep BO. Translational mini-review series on type 1 diabetes: Systematic analysis of T-cell epitopes in autoimmune diabetes. Clin Exp Immunol 2007;148:1–16.