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

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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

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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.