Autoimmunity Reviews 9 (2010) 407–413

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

HLA class II polymorphism in Latin American patients with multiple sclerosis

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ARTICLE INFO

Article history:
Received 2 October 2009
Accepted 3 November 2009
Available online 5 November 2009

Keywords:
Multiple sclerosis
HLA antigens
Meta-analysis
Myelin basic protein
Latin America

ABSTRACT

Objective: To identify HLA-DRB1 alleles contributing to susceptibility to multiple sclerosis (MS) in a Colombian population and to estimate the common effect size of HLA class II on MS susceptibility in Latin American populations through a meta-analysis.
Methods: A total of 65 Colombian patients with MS and 184 matched controls were included. HLA-DRB1 typing was done using the sequence-specific oligonucleotide probe method. A bivariate and a multivariate logistic regression analyses were done. Case-control studies performed in Latin America were searched up to January 2009 through a systematic review of the literature. Effect summary odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by means of the random effect model.
Results: A total of 464 cases and 2581 controls from 7 studies and the results of the present study in Colombians were analyzed. HLA-DRB1*15 (OR: 2.3; 95% CI: 1.68–3.07; $p<0.001$) and HLA-DQB1*06 (OR: 2.2; 95% CI: 1.54–3.07; $p<0.001$) groups as well as DRB1*1501 (OR: 2.6; 95% CI: 1.67–4.02; $p<0.001$), DRB1*1503 (OR: 2.2; 95% CI: 1.39–3.62; $p=0.001$) and DQB1*0602 (OR: 2.5; 95% CI: 1.66–3.71; $p<0.001$) alleles were found to be risk factors for MS. The myelin basic protein immunodominant sequence $_{221}$VHFFKNIVT$_{229}$ was predicted to strongly and simultaneously bind to HLA-DRB1*1501 and *1503.
Conclusion: The current study highlights the effect size of HLA class II in MS in Latin America and confirms similar allelic risk factors across diverse populations. Receptor-ligand interactions in the HLA-antigenic peptide complex could have potential predictive and therapeutical implications.

Contents

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1568-9972/$ – see front matter
doi:10.1016/j.autrev.2009.11.001

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system and is one of the most disabling autoimmune diseases (ADs) [1]. The precise etiology of MS is not well understood yet; however, both genetic and environmental factors are implicated. Several Human Leukocyte Antigens (HLA) have been associated with MS, but this association may vary according to the ethnic and geographical characteristics of the patients [2–4]. A primary role for HLA class I, independent of class II, has been suggested in the etiology of MS [3]. Within the class II region, the HLA-DRB1*1501 and HLA-DQB1*0602 alleles, which are in linkage disequilibrium, are the main risk alleles associated with MS in Caucasians [4]. HLA-DRB1*15 has been associated with younger age at onset and worse Expanded Disability Status Scale score [5] as well as with severe morbidity in patients with primary progressive MS [6].

Comparisons between geographical areas and ethnic groups are essential to determine the influence of environmental and genetic factors on the development of ADs. Despite the low prevalence of MS in Latin America, genetic studies in populations belonging to this geographical area offers a unique opportunity for examining the predisposition to develop MS because of the negative influence contributed by the admixture of Amerindians, Europeans and Negroids occurring 10–20 generations ago. This may resolve racial effects from genetic association with major genes [7]. The study of HLA as one of the major locus contributing to ADs will allow us to understand its common or specific influence on these diseases [2,8]. Thus, the purpose of this study was to analyze the role of HLA-DRB1 gene in susceptibility to MS in a Colombian population and to estimate the common effect size of HLA class II on the disease across Latin America populations through a meta-analysis.

2. Materials and methods

2.1. Study population

A total of 65 adult patients (10 men and 55 women) with clinically defined MS diagnosed by using McDonald's criteria [9] and evaluated in a specialized neurology center were included in this study. A total of 184 matched, unrelated, healthy individuals from the same community were included as controls. All patients and controls were born in Medellin, Antioquia, Colombia or its surroundings, a genetically well-defined population known as the "Paisa community" [7,10]. All patients gave informed consent to their inclusion in this study, which was approved by the local Ethics Committee.

2.2. DNA extraction and HLA typing

Genomic DNA was extracted from 10 mL of EDTA-anticoagulated peripheral blood or from 4 mL of saliva from each individual. To isolate the DNA from the blood, the standard salting out method [11] or the PROBE protocol was used. DNA purification from saliva was done by using Oragene DNA Self-Collection Kit (DNA Genotek Inc, Ottawa, Canada) according to the manufacturer's specifications.

Class II HLA-DRB1 typing was done by using the DRB1 Kit (INNO-LiPA Kits from Innogenetics NV, Belgium) as previously described [10].

2.3. Search strategy and selection criteria

A systematic review of Electronic Databases (MEDLINE, PubMed, SciELO, BIREME, EMBASE, Cochrane and LILACS) was done independently by two experts. The final date for inclusion was January 2009. The search only included publications on HLA-Class II alleles and susceptibility to MS in Latin America published in any of these three languages: Spanish, English or Portuguese. The search strategy used MeSH terms and the text words: "Multiple Sclerosis" [Major] and HLA DR/DQ antigens in combination with all Latin American countries, including Caribbean islands [MeSH]. For the search in the Spanish and Portuguese databases, the DeCS terms (Descriptores en Ciencia de la Salud): "Esclerosis Múltiple", "Antígenos HLA" and "Complejo Mayor Histocompatibilidad" were used. No other criteria were taken into account.

The inclusion criteria were the following: 1) MS diagnosis established using Poser's or Macdonald's criteria [9,12]; 2) case-control design of the study; 3) use of molecular techniques to determine HLA polymorphisms; 4) publication of sufficient information to calculate odds ratios (ORs); 5) being focused on a well defined Latin American population, and; 6) manuscript's publication in a peer-reviewed journal as full paper. Summaries or abstracts were not accepted.

2.4. Data extraction

The following information was collected from each study: author, year of publication, a detailed description of ethnicity in the studied population, HLA typing technique used, MS type, diagnosis criteria for MS, Hardy-Weinberg (HW) test information (if available), and total number of cases, controls, individuals and/or alleles per genotype reported in tables as well as in the manuscript's text. Serological specificities for each allele reported at the 13th International Histocompatibility Workshop and Conference were used to group data from all studies (expert assigned nomenclature) [13].

2.5. Statistical analysis

2.5.1. Colombian "Paisa population"

First, the association between genetic data results at the allelic level in the "Paisa population" and MS were assessed by bivariate analyses. χ^2 tests or Fisher's exact tests were applied to dichotomous factors. Next, for each specific allele that was significantly associated with MS in bivariate analyses, a gender-adjusted multivariate logistic regression model was estimated. This model considered MS as the dependent variable and all the alleles that were significantly associated with MS in the bivariate analyses as independent variables. Nagelkerke *R*-square was calculated to determine the proportion of variability in the logistic regression model. Adjusted OR (AORs) that measured the effect size of specific alleles on MS were computed together with their 95% confidence intervals (CI). The adequacy of logistic models was assessed using the Hosmer–Lemeshow goodness-of-fit test with the null hypothesis that the data were generated by the fitted model. All of the statistical analyses were done by using the Statistical Package for the Social Sciences (SPSS, v.15, Chicago, IL).

2.5.2. Meta-analysis

Data were analyzed using the Comprehensive Meta-Analysis version 2 program (Biostat, Englewood, NJ, 2004). Calculations were carried out for each HLA-DRB1 and HLA-DQ allele using low or high resolution based on information available in each article. ORs were grouped 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. The selection of the computational model was done based on the expectation that the studies shared a common effect size. The random effect model was preferred because it assumes that there is a distribution of true effect sizes