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ORIGINAL ARTICLE

Frequency of human leukocyte antigens class II-DR alleles (HLA-DRB1) in Argentinian patients with early arthritis

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Abstract

Patients with rheumatoid arthritis (RA) or undifferentiated arthritis (UA) in the CONAART database (Argentine Consortium for Early Arthritis) were assessed for genetic risk factors for RA, specifically for HLA-DRB1 alleles and the PTPN22 rs2476601 polymorphism associated with progression to RA. This is a case-control study. Blood samples were obtained to determine HLA-DRB1 genotypes by PCR-SSO Luminex and PTPN22 (rs2476601) polymorphism by allelic discrimination. A control group of individuals from the general Argentinian population were obtained from the national register of cadaveric organ donors. A total of 1859 individuals were included in this analysis: 399 patients from the CONAART database (347 patients with RA at study end and 52 patients with UA at study end, mean follow-up time 25 ± 18 months) and 1460 individuals from the general Argentinian population. Compared with the controls, the HLA-DRB1*04 and DRB1*09 alleles were more commonly detected in patients with RA diagnosis (OR (95% CI) 2.23 (1.74–2.85) and 1.89 (1.26–2.81)) respectively. Both patients with UA and the general

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population showed higher frequency of DRB1*07, DRB1*11 and DRB1*15 alleles than patients with RA. PTPN22 rs2476601 polymorphism frequency was higher in RA and UA vs the general population; however, this was significantly different only for RA vs control group (OR [95% CI] = 1.81 [1.10–3.02], $P = 0.018$. HLA-DRB1 typing and PTPN22 allelic discrimination could distinguish between patients with UA, patients with early RA, and the general population in Argentina. This is the first study of HLA-DRB1 alleles and PTPN22 polymorphism associations with progression to early RA in an Argentinian population.

Keywords Early arthritis · Genetics · Rheumatoid arthritis · Shared epitope · Undifferentiated arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint pain and swelling. Undifferentiated arthritis (UA) is usually diagnosed when signs, symptoms, and laboratory test results do not meet the American College of Rheumatology (ACR) classification for a definitive diagnosis of RA [1], although there is no current consensus on exactly how to define concepts such as early arthritis and UA [2]. Patients with UA are generally seen as having the potential for developing persistent inflammatory arthritis (including RA), but as not yet presenting with a recognized clinical pattern [3]. In early arthritis cohort studies, the proportion of patients progressing from UA to RA has been shown to vary from 6 to 55% (in studies with < 1 year of follow-up) [3] and from 13 to 54% (in studies with a follow-up period of ≥ 1 year) [4]. The proportion of patients in whom UA persists also varies, from 21 to 87% [4]. As not all patients with UA progress to RA, and about 40–50% experience self-limiting disease [5], it is important to be able to identify the patients with UA who will progress to RA and to do so as early as possible.

The risk of developing RA is known to be influenced by genetic factors including certain human leukocyte antigen (HLA) DRB1 alleles [6]. Several HLA-DRB1 alleles have been shown to be associated with RA susceptibility: *01:01, *01:02, *04:01, *04:04, *04:05, *04:08, *09:01, *10:01 and *14:02 while *01:03, *07, *13:01, and *13:02 are thought to be protective [7]. The rs2476601 polymorphism (missense 1848C → T SNP) in the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene has also been linked with RA predisposition [8]. However, the frequency of HLA alleles varies among ethnic groups, and there are relatively few studies reporting the association of HLA alleles [9–18] or PTPN22 polymorphisms [19–22] with RA in Latin American populations.

Patients for the study reported here were drawn from CONAART (CONsorcio Argentino de ARtritis Temprana—Argentine Consortium for Early Arthritis), an initiative of seven rheumatology centers across Argentina, first established in September 2008 for the purpose of the early identification and treatment of Argentinian patients with arthritis. A 2011 analysis of 413 patients in the CONAART database has previously found that 85% of the patients in this cohort had RA or UA and that patients with RA had significantly worse disease activity parameters, functional capacity, and quality of life than patients with UA [23].

In the analysis reported here, patients with RA or UA in the CONAART database were assessed for genetic risk factors for RA, specifically for HLA-DRB1 alleles and the PTPN22 rs2476601 polymorphism associated with progression to RA. This is the first study in Latin American patients with early arthritis seeking to identify such risk factors.

Methods

Entry into the CONAART database

Each CONAART center established a system, whereby patients with potential arthritis could be screened for inclusion either via telephone or in person at a study center. Patients were initially attended by non-medical personnel trained to carry out the first screening filter according to the pre-defined inclusion criteria (patients exhibited at least one swollen joint at screening and had symptoms lasting < 2 years). Patients were later questioned and examined by a rheumatologist. Patients were entered into the CONAART database if they exhibited at least one swollen joint at their first visit to a CONAART clinic and had symptoms lasting < 2 years [23]. Sociodemographic data, family history, clinical disease characteristics, and disease activity score in 28 joints (DAS-28) were collected at the initial visit. At each clinic visit, patients completed questionnaires on functional capacity, disease activity, and quality of life which had been translated into Spanish and culturally adapted for Argentinian patients [24]. There was no pre-defined treatment protocol for this study, with all patients receiving a treatment regimen determined by their acting physician. An additional control group of individuals from the general Argentinian population was obtained from the national register of cadaveric organ donors database (INCUCAI). All individuals gave their written consent before participating in the study, and the study was approved by the ethics committee of each participating center.

Study design

Only adult patients with a diagnosis of RA as per the 2010 ACR/EULAR criteria [25] or a diagnosis of UA as per investigator judgment were included in the case-controlled study reported here. Patients were divided into four groups based on diagnosis at study baseline and after 2 years follow-up (study end):

- Patients with a diagnosis of RA at baseline and at study end (RA → RA)
- Patients with a diagnosis of UA at baseline who progressed to RA by study end (UA → RA)
- Patients with a diagnosis of UA at baseline who had not progressed to RA by study end (UA → UA)
- Patients with a diagnosis other than RA or UA who progressed to RA by study end (Other → RA). This group was composed of only three patients, which is why no further studies were done on them.
- Blood samples were obtained and remitted to immunogenetics laboratory at *Hospital Privado de Córdoba* to determine HLA-DRB1 genotypes and PTPN22 (rs2476601) polymorphism. HLA-DR genotype frequencies were estimated for each group.
- Briefly: *DNA isolation*
- DNA was isolated from peripheral blood in a robotic workstation QIACube using a QIAmp DNA Blood Mini Kit (QIAGEN, Hilden, GE).
- HLA DRB1 typing
- Luminex-based technology has been applied to discriminate between the different HLA alleles. The typing method consists in a PCR SSO assay (LABType® SSO Typing, One Lambda Inc., CA, USA). First, target DNA was PCR-amplified using biotinylated group-specific primers. The PCR product was denatured and allowed to rehybridize to complementary DNA probes conjugated to fluorescently coded microspheres. These beads are characterized by two internal fluorescent dyes that create a unique combination of color, making them identifiable. The biotinylated PCR product bound to the microsphere was labeled with streptavidin conjugated with R-phycoerythrin. A flow analyzer (Bio-Plex 200, Bio-Rad) identified the fluorescent intensity of PE on each microsphere. Software was used to assign positive or negative reactions based on the strength of the fluorescent signal. The assignment of the HLA typing was based on positive and negative probe reactions compared with published HLA gene sequences (7).
- PTPN22 C1858T polymorphism detection
- The PTPN22 C1858T polymorphism was evaluated using an allelic discrimination assay with two allele-specific Taqman probes (Taqman SNP Genotyping Assay, ID C-16021387_20), according to the manufacturer's instructions (Applied Biosystems, CA, USA). Real-time PCR reactions were performed in a 20-μL reaction mixture using a Rotor-Gene Q detection system (QIAGEN, Hilden, GE). Sixty percent of all the samples from cases and controls were genotyped twice, and the reproducibility of genotyping in all samples was 100%.

Statistical analyses

The odds ratio (OR) and corresponding 95% confidence intervals (95% CI) of developing RA in the UA and general populations were calculated. Statistical analysis was performed with the two-tailed Pearson's chi-squared test. A P value of < 0.05 was considered statistically significant. Post hoc calculation of Bonferroni-corrected P values (Cp values) was performed for statistically significant P values only. A stepwise logistic regression model using RA vs UA diagnosis as the dependent variable was performed to identify the association of HLA-DRB1 alleles and RA development in patients with UA, adjusted by smoking, gender, and presence of rheumatoid factor (variable significance entry criteria $P < 0.15$). The statistical package STATA (Data Analysis and Statistical) (Stata Corp) version 12 was used for the analysis.

Results

Demographic and clinical characteristics at baseline

A total of 1859 individuals were included in this analysis: 399 patients from the CONAART database (347 patients with RA at study end and 52 patients with UA at study end) and 1460 individuals from the general Argentinian population. Among the CONAART patients, 333 (83.5%) were female and the mean (SD) age at symptom onset was 50 (13) years. More than two thirds tested positive for rheumatoid factor and less than a quarter smoked (Table 1).

HLA-DRB1 alleles and PTPN22 polymorphisms in RA

Compared with the GP, the HLA-DRB1*04 and DRB1*09 alleles were more commonly detected in patients with an RA diagnosis at the end of the study period (Table 2). Among patients with early arthritis, the presence of the DRB1*04 and DRB1*09 alleles did not differentiate between patients with RA and UA.

Both groups with UA and individuals that form the general population showed higher frequency of DRB1*07, DRB1*11, and DRB1*15 alleles than patients with RA (Table 2), but statistical significance was only reached for RA vs GP (Table 2). Table 3 summarizes a stepwise logistic regression analysis of variables associated with development of RA vs

Table 1 Demographic and clinical characteristics of patients from the CONAART database

	Total patient population	RA → RA	UA → RA	UA → UA	Other → RA
N (%)	399 (100)	272 (68.2)	72 (18.0)	52 (13.0)	3 (0.8)
Female, *n* (%)	333 (83%)	224 (82%)	60 (83%)	46 (88%)	3 (100%)
Age at symptom onset, mean (SD) (years)	50 ± 13	50 ± 13	52 ± 13	51 ± 16	46 ± 9
Disease duration, mean (SD) (months)	9 ± 6	9 ± 6	8 ± 6	7 ± 6	6 ± 0.5
Follow-up, mean (SD) (months)	25 ± 18	26 ± 18	30 ± 17	11 ± 14	18 ± 12
Rheumatoid factor positive, *n* (%)	271 (69%)	220 (86%)	36 (58%)	13 (33%)	2 (67%)
Current smokers, *n* (%)	92 (23%)	76 (28%)	9 (13%)	7 (13%)	0

RA rheumatoid arthritis, *UA* undifferentiated arthritis, *SD* standard deviation

persistence of UA. Rheumatoid factor positivity, and the presence of HLA-DRB1*11, added significantly to the model with an inverse effect for the final diagnosis of RA. These data reflect the effect of the independent variables considering the diagnosis at the end of the observation. When we performed the regression analysis, considering the baseline diagnosis, we found minimal differences in the ORs, but without changes in the statistical significance of them.

The majority of CONAART patients and individuals of the general population were negative for the PTPN22 rs2476601 polymorphism (Table 4). PTPN22 rs2476601 polymorphism frequency was higher in RA and UA vs GP; however, this was significantly different only for RA vs GP. (OR [95% CI] = 1.81 [1.10–3.02], $P = 0.018$).

Forty-three percent of our population were current or past smokers and this was equally distributed in positive and negative DR4 (the most frequents SE allele) patients, as well as in the positive and negative PTPN22. We did not find association between smoking and DR4 or PTPN22. (for RA + UA patients, OR 0.99, 95% CI 0.67–1.15, only for RA patients, OR 0.98, 95% CI 0.63–1.54).

Discussion

This is the first study of HLA-DRB1 alleles and PTPN22 rs2476601 polymorphism associations in patients with early RA of the Argentine population. Several previous studies in Argentinian [9], Brazilian [10, 11], Chilean [12], Colombian [13], Mexican [14–16], and Peruvian [17, 18] cohorts have investigated the association of HLA-DR antigens with RA compared with the matched general population. As was seen

Table 2 HLA-DRB1 alleles frequency in RA vs the general population and vs the UA CONAART cohort

HLA-DRB1 allele	RA (*N* = 347)	GP (*N* = 1459)	UA (*N* = 52)	RA vs GP			RA vs UA		
				OR for developing RA (CI 95%)	*P* value	Cp value*	OR for developing RA (CI 95%)	*P* value	Cp value*
01*	19%	16%	12%	1.22 (0.89–1.67)	0.18		1.80 (0.72–5.37)	0.19	
03*	< 1%	< 1%	0%	1.05 (0.02–10.67)	0.96				
*04**	*50%*	*31%*	40%	*2.23 (1.74–2.85)*	*< 0.001*	*< 0.001*	1.48 (0.79–2.83)	0.19	
*07**	*13%*	*21%*	*23%*	*0.58 (0.40–0.81)*	*0.001*	*0.02*	*0.50 (0.23–1.12)*	*0.05*	*0.73*
08*	13%	17%	19%	0.71 (0.50–1.02)	0.06	0.80	0.61 (0.28–1.46)	0.20	
*09**	*12%*	*7%*	8%	*1.89 (1.26–2.81)*	*0.001*	*0.01*	1.65 (0.56–6.62)	0.35	
10*	4%	3%	2%	1.46 (0.70–2.83)	0.25		1.98 (0.29–85.97)	0.50	
*11**	*11%*	*21%*	*21%*	*0.45 (0.30–0.65)*	*< 0.001*	*< 0.001*	*0.44 (0.20–1.04)*	*0.03*	*0.42*
12*	1%	2%	2%	0.64 (0.16–1.87)	0.41		0.59 (0.06–29.85)	0.64	
13*	15%	21%	15%	0.66 (0.47–0.92)	0.01	0.112	0.95 (0.41–2.47)	0.90	
14*	14%	9%	10%	1.59 (1.09–2.29)	0.01	0.142	1.47 (0.55–4.98)	0.43	
*15**	*9%*	*15%*	*17%*	*0.55 (0.36–0.82)*	*0.002*	*0.03*	*0.47 (0.20–1.20)*	*0.06*	*0.85*
16*	10%	6%	8%	1.63 (1.05–2.48)	0.02	0.25	1.35 (0.45–5.44)	0.59	
17*	11%	14%	12%	0.80 (0.54–1.16)	0.24		0.97 (0.38–2.96)	0.95	

HLA human leukocyte antigen, *RA* rheumatoid arthritis, *GP* general population, *UA* undifferentiated arthritis, *OR* odds ratio, *CI* confidence interval, *Cp value* Bonferroni-corrected *P* value

Table 3 Stepwise logistic regression model using RA vs UA diagnosis as dependent variable

Variables	OR	95% CI	*P*
Rheumatoid factor positive	11.34	5.54–23.19	< 0.001
Smoking (past or present)	1.18	0.59–2.39	0.640
HLA-DRB1*04	0.92	0.47–1.80	0.805
HLA-DRB1*11	0.31	0.14–0.73	0.007

OR odds ratio, *CI* confidence interval, *HLA* human leukocyte antigen

in our study, the majority of these previous studies also reported the association of HLA-DR4 with susceptibility to RA [9, 10, 12–15, 18] as has a meta-analysis of HLA-DRB1 polymorphisms in Latin American patients with RA [26]. However, only one study of patients in Brazil also reported the association of HLA-DR9 with susceptibility to RA [10], and three studies reported the association of HLA-DR14 with susceptibility to RA [10, 16, 17], which this study did not find.

The study reported here found that the HLA-DRB1*11 allele (corrected *P* value < 0.001), and to a lesser extent the HLA-DRB1*07 and DRB1*15 alleles (corrected *P* value < 0.05), was associated with protection against the development of RA compared with GP. Similarly, four other studies also identified HLA-DRB1*11 as protective against RA [9, 10, 15, 17] but only one additionally identified HLA-DRB1*07 and *15 as protective [15].

Our study also compared the association of HLA-DRB1 alleles in patients with RA with those found in patients with UA; no comparison of HLA-DRB1 alleles in RA vs UA has been reported in Latin American populations before. No alleles associated with RA susceptibility were seen more frequently in RA than UA, but the protective alleles HLA-DRB1*11, DRB1*07, and DRB1*15 which were identified when comparing RA patients with the general population were also identified with the RA vs UA comparison (although corrected *P* values were non-significant). HLA-DRB1*07 and DRB1*15 have both been previously associated with less severe forms of RA [27].

In this study, we also identified that the PTPN22 rs2476601 polymorphism was associated with susceptibility to RA in this population of Argentine patients with early RA. Four studies in Mexican [19, 20] and Colombian [21, 22] patients with RA have also previously shown that this polymorphism is associated with an increased risk for RA in Latin American patients. Our study additionally shows this polymorphism to be present in patients with UA at a rate similar to that found in RA in Argentinian patients, but the differences with the general population were not significant.

Table 4 Presence of PTPN22 rs2476601 polymorphism in RA, UA, and GP

PTPN22 rs2476601	RA	UA	GP
Positive	50 (14%)	8 (16%)	31 (9%)
Negative	293 (85%)	42 (84%)	329 (91%)

PTPN22 protein tyrosine phosphatase non-receptor type 22, *RA* rheumatoid arthritis, *UA* undifferentiated arthritis, *GP* general population

Gene-environment interaction between smoking and HLA-DRB1 SE and PTPN22 was seen for seropositive RA in three major case control studies of Caucasian populations: the Swedish EIRA study, the North American NARAC study, and the Dutch Leiden EAC [28, 29]. We did not find association between smoking and HLA-DR4 (the most frequent SE allele) or PTPN22. However, we cannot rule out a type 2 error, based on the limited number of patients.

This study did have some limitations. The major limitation was the lack of data describing the presence of anti-cyclic citrullinated peptide (anti-CCP) antibody, which was not available for approximately half of the patients described in this study. Previous studies have found significant associations between the presence of anti-CCP and certain HLA-DRB1* alleles [10] or the PTPN22 rs2476601 polymorphism [20], but such analysis was not possible in this study.

The sample size of UA patients who remained with this diagnosis is small and the chances of error may be high when compared with other groups.

Other candidate genes, possibly associated with the development of RA, were not tested in our study and would remain pending for future analysis.

Conclusions

HLA-DRB1 typing and PTPN22 allelic discrimination could distinguish between patients with UA, patients with early RA, and the GP general population in Argentina.

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Compliance with ethical standards

Disclosures None.

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