

## RESEARCH ARTICLE

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# Association of *acid phosphatase locus 1*\*C allele with the risk of cardiovascular events in rheumatoid arthritis patients

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## Abstract

**Introduction:** *Acid phosphatase locus 1 (ACP1)* encodes a low molecular weight phosphotyrosine phosphatase implicated in a number of different biological functions in the cell. The aim of this study was to determine the contribution of *ACP1* polymorphisms to susceptibility to rheumatoid arthritis (RA), as well as the potential contribution of these polymorphisms to the increased risk of cardiovascular disease (CV) observed in RA patients.

**Methods:** A set of 1,603 Spanish RA patients and 1,877 healthy controls were included in the study. Information related to the presence/absence of CV events was obtained from 1,284 of these participants. All individuals were genotyped for four *ACP1* single-nucleotide polymorphisms (SNPs), rs10167992, rs11553742, rs7576247, and rs3828329, using a predesigned TaqMan SNP genotyping assay. Classical *ACP1* alleles (\*A, \*B and \*C) were imputed with SNP data.

**Results:** No association between *ACP1* gene polymorphisms and susceptibility to RA was observed. However, when RA patients were stratified according to the presence or absence of CV events, an association between rs11553742\*T and CV events was found ( $P = 0.012$ , odds ratio (OR) = 2.62 (1.24 to 5.53)). Likewise, the *ACP1*\*C allele showed evidence of association with CV events in patients with RA ( $P = 0.024$ , OR = 2.43).

**Conclusions:** Our data show that the *ACP1*\*C allele influences the risk of CV events in patients with RA.

## Introduction

Rheumatoid arthritis (RA) is a complex polygenic autoimmune inflammatory disease characterized by persistent synovitis and joint damage. Several genetic polymorphisms, such as *HLA-DRB1*, *PTPN22*, *STAT4*, *TRAF1/C5* and *TNFAIP3*, have been implicated in the susceptibility to RA [1]. On the other hand, increased cardiovascular (CV) mortality is observed in patients with RA. This is the result of accelerated atherogenesis [2-4].

*Acid phosphatase locus 1 (ACP1)* is a gene located on chromosome 2p25 that encodes a low molecular weight

phosphotyrosine phosphatase (LMW-PTP), which presents two main enzymatic activities: phosphoprotein tyrosine phosphatase and flavin mononucleotide phosphatase [5]. Two different isoenzymes of LMW-PTP have been described: 'fast' (also noted as *ACP1-F* (fast), isoform 1, IF1, HCPTP-A) and 'slow' (also noted as *ACP1-S*(slow), isoform 2, IF2, HCPTP-B), that arise through alternative splicing mechanisms, in which either exon 3 or exon 4 is excised and the other retained respectively [5,6]. These two LMW-PTP isoenzymes have different molecular and catalytic properties, suggesting that they may be implicated in different biological functions in the cell [5,7]. In Caucasian populations there are three common codominant alleles of *ACP1*, *ACP1*\*A, *ACP1*\*B, *ACP1*\*C. *ACP1* alleles differ on single-nucleotide polymorphisms (SNPs), which affect both

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the total enzymatic activity and the ratio between isoforms F/S, being the ratio F/S 2:1 in ACP1\*A, 4:1 in ACP1\*B and 1:4 in ACP1\*C [5,7,8].

LMW-PTP is considered to play a key role as regulator of signaling pathways in receptor-stimulated immune cells [9]. LMW-PTP has also been involved in the regulation of many growth factors such as platelet-derived growth factor receptor (PDGFR) [10], fibroblast growth factor receptor (FGFR) [11], insulin receptor (IR) [12,13] and EphA2 receptor, a ligand that binds to the Ephrin family of signaling molecules [14]. LMW-PTP has also been implicated in the regulation of ZAP70 Kinase ( $\zeta$ -chain-associated protein kinase of 70 kDa) [15] playing a role in T-cell development and lymphocyte activation, enhancing signaling from the T cell antigen receptor [15]. Additionally, LMW-PTP has been found to be a key mediator in the integrin signaling during cellular adhesion [9].

Allelic polymorphisms of the *ACPI* gene have been associated with susceptibility to several human diseases, including inflammatory and autoimmune diseases [5,16]. Interestingly, the *ACPI* gene was also associated with susceptibility to coronary atherosclerotic artery disease (CAD) [17].

Taking into account the possible influence that *ACPI* may have in the susceptibility to immune-mediated disorders and in the pathogenesis of the CV disease, in the present study we aimed to investigate the possible association of *ACPI* alleles with the susceptibility to RA as well as whether *ACPI* gene polymorphism may contribute to the increased risk of CV complications observed in patients with RA.

## Materials and methods

### Material

A set of 1,603 RA Spanish patients and 1,877 healthy individuals were included in the present study. Blood samples were obtained from RA patients recruited from the Hospital Xeral-Calde (Lugo), Hospital Universitario Marqués de Valdecilla (Santander), Hospital Universitario Bellvitge (Barcelona), and Hospital La Paz, Hospital de La Princesa and Hospital Clínico San Carlos (Madrid). All the patients fulfilled the 1987 American College of Rheumatology (ACR) criteria for the classification of RA [18].

Information related to the presence or absence of CV events was obtained in 1,284 RA patients (80.1%, 1284/1,603). Among them, 229 experienced CV events (17.8%, 229/1,284). Information on traditional CV risk factors was also collected.

Clinical features of the whole series of 1,603 RA patients are shown in Table 1.

A CV event was considered to be present if the patient had ischemic heart disease, heart failure, a

**Table 1 Demographic characteristics of the patients with rheumatoid arthritis included in the study**

Clinical feature	% (n/N)
Patients	1,603
<b>Main characteristics</b>	
Age at disease onset (years, means $\pm$ SE)	54.1 $\pm$ 14.8
Follow up (years, means $\pm$ SE)	11 $\pm$ 7.5
Female	73.5
Rheumatoid factor positive	70.3 (996/1,417)
Shared Epitope positive	63.7 (592/930)
Anti-CCP antibodies positive	58.1 (652/1,123)
<b>Cardiovascular risk factors</b>	
Hypertension	39.4 (516/1,310)
Diabetes mellitus	13.2 (171/1,300)
Dyslipidemia	41.3 (540/1,307)
Obesity	12.4 (142/1,146)
Smoking habit	24.0 (303/1,261)
<b>Patients with cardiovascular events</b>	
Ischemic heart disease	9.5 (122/1,284)
Heart failure	4.8 (62/1,284)
Cerebrovascular accidents	4.6 (59/1,284)
Peripheral arteriopathy	1.9 (25/1,284)

SE, Standard error

Anti-CCP antibodies, anti-cyclic citrullinated peptide antibodies

cerebrovascular accident or peripheral artheriopathy. Clinical definitions for CV events and classic CV risk factors were established as previously described [4,19]. The study was approved by local ethics committees from all the participating centers and all subjects provided informed consent according to the Declaration of Helsinki.

### SNPs selection and genotyping

DNA from patients and controls was obtained using standard methods. We selected four *ACPI* SNPs for the present study. rs11553742 and rs7576247 were selected because of their ability to tag classical *ACPI* alleles (that is, ACP1\*A, ACP1\*B, ACP1\*C) [5]. rs11553742 is a synonymous polymorphism located in the codon 44 (exon 3) and rs7576247 encodes an aminoacid change in the codon 105 (exon 6) from arginine, present in ACP1\*A allele, to glutamine in ACP1\*B and \*C alleles. Hence, ACP1\*A allele differs from ACP1\*C allele in two base substitutions in those positions, so the CG allele combination is responsible for the ACP1\*A allele and TA for the ACP1\*C allele. In addition, ACP1\*B allele is defined as not \*A, not \*C, that is, for the allelic combination CA. Another two polymorphisms, rs10167992 and rs3828329, were also selected because they showed association with quantitative traits related to type 2 diabetes mellitus [17]. All SNPs were genotyped with TaqMan SNP genotyping assays in a 7900 HT Real-Time

polymerase chain reaction (PCR) system, according to the conditions recommended by the manufacturer (Applied Biosystems, Foster City, CA, USA). All samples were genotyped at the same center.

### Statistical analysis

Controls were tested for significant differences in their genotype distribution and Hardy-Weinberg equilibrium (HWE) theoretical distribution by means of a  $\chi^2$  test. The case-control association study was performed by  $2 \times 2$  contingency tables with  $\chi^2$  to obtain *P*-values, odds ratios (OR) and 95% confidence intervals (CI), according to Woolf's methods. The same procedure was applied in the subgroups stratified according to the presence or absence of anti-cyclic citrullinated peptide antibodies (ACPA). Association analysis for CV events in RA patients was performed via multiple logistic regression; estimates were adjusted for age at the time of disease diagnosis, gender, rheumatoid shared epitope status and traditional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, obesity and smoking habit) as potential confounders.

All *P*-values < 0.05 were considered as statistically significant. All statistical analyses were carried out with Plink [20] and haplotype analysis with Haploview [21].

The estimation of the statistical power of the study to detect an effect of a polymorphism in disease susceptibility was performed using the CaTS Power Calculator software (Center for Statistical Genetics, University of Michigan, Michigan, USA) [22]. The study had between 98 and 100% power to detect the relative risk, with an OR of 1.50 at the 5% significance level, assuming a RA Spanish prevalence of this disease of 0.5% and considering a minor allele frequency (MAF) between 0.05 and 0.25 respectively. Under the same conditions described above, our study of the risk of CV events in RA patients had a statistical power from 95% when the disease allele frequency was 0.25 to 42% for an allele frequency of 0.05.

## Results

### ACPI polymorphisms in RA patients and controls

All genetic variants analyzed did not deviate significantly from the HWE, and the genotyping success call rate was 90%. After comparing RA patients and healthy individuals, no significant differences in the *ACPI* allele and genotype frequencies were found (Additional file 1). We also assessed the possible influence of these *ACPI* polymorphisms in the presence and absence of ACPA; however, no evidence of association was observed. In addition, we performed the analysis of allelic combinations to investigate the possible association of each of these three codominant *ACPI* alleles (\*A, \*B and \*C) with RA but no significant association was found. Again, no association was observed for *ACPI* alleles when RA patients were stratified according to ACPA (Additional file 2).

### ACPI polymorphisms and CV risk in RA patients

We further investigated the possible influence of *ACPI* polymorphisms in the risk of CV events in RA patients. Of the 1,284 RA patients for whom information on presence or absence of CV disease was available, 229 had CV events (17.8%). Table 2 describes the distribution of *ACPI* polymorphisms in RA patients with and without CV events. After adjusting for classical CV risk factors, evidence of association of rs11553742\*T with the risk of CV events was observed (*P*-adj = 0.012, OR = 2.62 (1.24 to 5.53)).

The potential influence of *ACPI*\*A, \*B and \*C alleles in the CV risk of RA patients was also analyzed (Table 3). We found that the *ACPI*\*C allele was significantly associated with CV risk in RA patients after correction for classic CV risk factors (*P*-adj = 0.024, OR = 2.43). As expected, *ACPI*\*C allele (TA) included the minor rs11553742\*T allele, which was also found to be a risk factor for the CV events in RA patients (see Table 2).

In contrast, *ACPI*\*A allele (CG), which was the opposite allelic combination of *ACPI*\*C, showed a trend for

**Table 2 Differences between RA patients with and without CV events according to *ACPI* polymorphisms**

SNP	Change 1/2	Samples Set	N	Genotype, no. (frequency)			Minor allele, no. (frequency)	Allele test	
				1/1	1/2	2/2		<i>P</i> -adj*	OR (95% CI)*
rs10167992	C/T	RA with CV	215	171 (0.826)	35 (0.169)	1 (0.005)	37 (0.089)	0.321	0.72 (0.38 to 1.37)
		RA without CV	965	768 (0.799)	168 (0.175)	13 (0.014)	194 (0.102)		
rs11553742	C/T	RA with CV	221	200 (0.966)	21 (0.101)	0 (0.000)	21 (0.048)	0.012	2.62 (1.24 to 5.53)
		RA without CV	1,015	932 (0.970)	78 (0.081)	3 (0.003)	84 (0.041)		
rs7576247	A/G	RA with CV	207	112 (0.541)	76 (0.367)	18 (0.087)	112 (0.272)	0.203	0.76 (0.50 to 1.16)
		RA without CV	961	498 (0.518)	388 (0.404)	75 (0.078)	538 (0.280)		
rs3828329	C/T	RA with CV	221	88 (0.425)	103 (0.498)	28 (0.135)	641 (0.319)	0.079	1.38 (0.96 to 1.97)
		RA without CV	1,015	482 (0.502)	403 (0.419)	119 (0.124)	159 (0.363)		

CV, cardiovascular; RA, rheumatoid arthritis

\* multiple regression adjusted by age at diagnosis of the disease, gender, shared epitope status and traditional CV risk factors, that is, hypertension, diabetes mellitus, dyslipidemia, obesity and smoking habit, as potential confounders.

**Table 3 Distribution of ACP1 alleles in RA patients with and without CV events**

ACP1 allele	Haplotype	Haploype, no. (frequency)		P-adj*	OR*
		RA with CV	RA without CV		
ACP1*A	CG	110 (0.276)	525 (0.281)	0.217	0.76
ACP1*B	CA	270 (0.678)	1,263 (0.676)	0.859	1.04
ACP1*C	TA	18 (0.045)	80 (0.043)	0.024	2.43

CV, cardiovascular; RA, rheumatoid arthritis The order of the SNPs is rs11553742|rs7576247.

\* multiple regression adjusted by age at diagnosis of the disease, gender, shared epitope status, hypertension, diabetes mellitus, dyslipidemia, obesity and smoking habit.

protection against the development of CV events in RA patients, although no statistically significant association was achieved ( $P$ -adj = 0.217, OR = 0.76).

## Discussion

Since the association of *ACP1* gene with autoimmunity has previously been described [5], in the present study we sought to investigate the possible association of *ACP1* polymorphisms with RA. Furthermore, taking into account that this gene has been involved in the susceptibility to CAD [17], we also assessed whether *ACP1* variations could be involved in the risk of CV events in patients with RA. Our result revealed that *ACP1* polymorphisms do not influence the susceptibility to RA. However, these polymorphisms seem to influence the risk of CV events in these patients. In this regard, both rs11553742\*T and ACP1\*C alleles increased the risk of CV complications in patients with RA. Interestingly, rs11553742\*T has been observed to decrease the F/S ratio of the LMW-PTP isoenzymes [5]; in this regard the ACP1\*C allele, carrier of the minor allele of rs11553742, was found to produce a major amount of S isoforms and is also associated with the highest total LMW-PTP activity [8,23].

Our results are in accordance with the findings by Banci *et al.* [17], who observed that high S isoform genotypes were associated with increased risk to develop CAD. Moreover, patients with hypertrophic cardiomyopathy, an autosomal dominant disease, were found to have the highest frequencies for ACP1\*C allele and showed a linear relationship between maximum wall thickness and the amount of total LMW-PTP activity [16].

The effect of the ACP1\*C allele in the development of CV events could be explained by its possible role in the regulation of the energy metabolism and oxidative stress through its flavin mononucleotide phosphatase activity [8]. With respect to this, a negative interaction between LMW-PTP and the enzyme glutathione reductase (GSR), which affects the cellular concentration of their cofactor flavin adenosine dinucleotide (FAD), has been

described [8]. GSR is a flavoenzyme involved in the cellular antioxidant mechanism that reduces oxidized glutathione disulfide (GSSG) to the sulfhydryl form glutathione (GSH) that is an important cellular antioxidant. Low LMW-PTP activity increases the levels of cofactor flavin adenine dinucleotide (FAD) in the cytosol leading to increased activity of GSR; while higher LMW-PTP activity yields low GSR activity. Accordingly, low activity of GSR has also been found to be significantly associated with hypertension [24], and it has also been considered to be a risk factor for CV by influencing cholesterol levels [25]. Furthermore, Bottini *et al.* [26] reported that the ACP1\*A allele, the opposite allelic combination of ACP\*C, is a protective factor for hypertriglyceridemia and hypercholesterolemia in obese women.

RA is a complex polygenic disease and, besides the association of *HLA-DRB1\*04* shared epitope alleles with CV disease [4,27], recent reports have also emphasized the potential implication of other gene polymorphisms in the increased risk of CV events observed in patients with RA. In this regard, interactions between *NOS* gene polymorphisms and *HLA-DRB1\*04* shared epitope alleles seem to confer an increased risk of developing CV events in these patients [28]. Also, the A1298C polymorphism in the *MTHFR* gene was found to predispose to CV risk in RA [29]. More recently, an association of the *TNFA* rs1800629 gene polymorphism with predisposition to CV complications in RA patients carrying the rheumatoid shared epitope was also described [30].

## Conclusions

Our data show for first time the association of the ACP1\*C allele with increased susceptibility to CV events in patients with RA. This effect may be based on the major production of the S isoform of LMW-PTP by this allele, which may influence the regulation of energy metabolism and the response to oxidative stress.

## Additional material

### Additional file 1: Genotype and allele distribution of ACP1 polymorphisms in Spanish RA patients and healthy subjects.

Supplementary table S1 shows the genotype and allele frequencies of *ACP1* polymorphisms in Spanish RA patients and healthy controls. That table also shows the lack of association among cases and controls.

### Additional file 2: Distribution of ACP1 alleles in Spanish RA patients and healthy controls.

Supplementary table S2 shows the frequencies of *ACP1* alleles in Spanish RA patients and individuals controls. No association was observed.

## Abbreviations

ACP1: acid phosphatase locus 1; ACPA: anti-cyclic citrullinated peptide antibodies; ACR: American College of Rheumatology; CAD: coronary atherosclerotic artery disease; CI: confidence intervals; CV: cardiovascular;

FAD: flavin adenine dinucleotide; FGFR: fibroblast growth factor receptor; GSH: glutathione; GSR: glutathione reductase; GSSR: glutathione disulfide; HWE: Hardy-Weinberg equilibrium; IR: insulin receptor; LMW-PTP: low molecular weight phosphotyrosine phosphatase; MAF: minor allele frequency; OR: Odds ratio; PCR: polymerase chain reaction; PDGFR: platelet-derived growth factor receptor; RA: rheumatoid arthritis; SNP: single-nucleotide polymorphism.

#### Acknowledgements

We thank Sofia Vargas, Sonia Rodríguez and Rodrigo Ochoa for their excellent technical assistance, and Mercedes García Bermudez for her comments in the analysis of CV events. We thank Banco Nacional de ADN (University of Salamanca, Spain), which supplied part of the control DNA samples, and we thank all patients and donors for their collaboration.

This work was supported by two grants from Fondo de Investigaciones Sanitarias PI06-0024 and PS09/00748 (Spain) and by the RETICS Program, RD08/0075 (RIER) from the Instituto de Salud Carlos III (ISCIII), within the VI PN de I+D+i 2008-2011 (FEDER). MT was supported by the Spanish Ministry of Science through the program Juan de la Cierva (JCI-2010-08227).

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#### Authors' contributions

MT, JEM, NB and JM made substantial contributions to the conception and design of the study, and the interpretation of data. MT carried out genotyping, analysis of data and drafted the manuscript. JEM carried out genotyping. CGJ, RLM, JAMF, RB, AB, DPS, LRR, BFG, AMO, IGA and CGV were involved in the acquisition of cardiovascular data in the different Spanish hospitals included in this study. JL carried out the analysis and interpretation of the data. JM and MAGG were involved in revising the manuscript and gave final approval of the version to be published.

#### Competing interests

The authors declare that they have no competing interests.

Received: 19 April 2011 Revised: 9 June 2011 Accepted: 18 July 2011

Published: 18 July 2011

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doi:10.1186/ar3401

**Cite this article as:** Teruel *et al.*: Association of *acid phosphatase locus 1\*<sup>C</sup>* allele with the risk of cardiovascular events in rheumatoid arthritis patients. *Arthritis Research & Therapy* 2011 **13**:R116.

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