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## Identification of the *PTPN22* functional variant R620W as susceptibility genetic factor for giant cell arteritis

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## Abstract

**Objective**—To analyse the role of the *PTPN22* and *CSK* genes, previously associated with autoimmunity, in the predisposition and clinical phenotypes of giant cell arteritis (GCA).

**Methods**—Our study population was composed of 911 patients diagnosed with biopsy-proven GCA and 8,136 unaffected controls from a Spanish discovery cohort and three additional independent replication cohorts from Germany, Norway and the United Kingdom. Two functional *PTPN22* polymorphisms (rs2476601/R620W and rs33996649/R263Q) and two variants of the *CSK* gene (rs1378942 and rs34933034) were genotyped using predesigned TaqMan® assays.

**Results**—The analysis of the discovery cohort provided evidence of association of *PTPN22* rs2476601/R620W with GCA ( $P_{FDR}=1.06E-04$ , OR=1.62, CI 95% 1.29-2.04). The association did not appear to follow a specific GCA subphenotype. No statistically significant differences between allele frequencies for the other *PTPN22* and *CSK* genetic variants were evident either in the case/control or in stratified case analysis. To confirm the detected *PTPN22* association, three replication cohorts were genotyped, and a consistent association between the *PTPN22* rs2476601/R620W variant and GCA was evident in the overall meta-analysis ( $P_{MH}=2.00E-06$ , OR= 1.51, CI 95% 1.28-1.79).

**Conclusions**—Our results suggest that the *PTPN22* polymorphism rs2476601/R620W plays an important role in the genetic risk to GCA.

## Keywords

GCA; temporal arteritis; SNP; *PTPN22*; *CSK*

## INTRODUCTION

Giant cell arteritis (GCA) is a chronic vasculitis that shows a complex etiology derived from the interaction between both genetic and environmental factors.[1] Similar to most immune-related disorders, the highest susceptibility signals belong to the human leukocyte antigen (HLA) region. However, different studies have highlighted that genes involved in inflammation pathways may also be implicated in GCA susceptibility.[2] In spite of these findings, the genetic background of this condition is still poorly understood.

Although the etiology of GCA remains unclear, it is well known that innate and adaptive immune responses are involved in its pathogenesis. Several lines of evidence indicate that this vasculitis is a T cell-mediated disease with both Th17 and Th1 cells contributing to inflammation. While Th1 response is associated with chronically persistent vascular lesions, Th17 immunity appears to be more important for acute manifestations, both systemically and in the blood vessels.[3, 4]

The *PTPN22*/*CSK* pathway is a master regulator of autoimmunity, with a key role in the negative control of the signaling mediated by the T cell receptor (TCR).[5] Interestingly, several SNPs located within these two genes have been associated with autoimmunity,[6-11] suggesting that this is one of the molecular pathways shared by different autoimmune disorders.

Regarding *PTPN22*, it has been reported that two autoimmune disease-associated variants, rs2476601 (R620W) and rs33996649 (R263Q) influence the function of the protein.[12, 13] On the other hand, two *CSK* polymorphisms, rs34933034 and rs1378942, were recently identified as susceptibility factors for systemic sclerosis (SSc)[11] and systemic lupus erythematosus (SLE),[10] respectively. A functional role for the *CSK* genetic variant rs34933034\*A in SLE patients has been proposed in a recent study.[10]

Based on this, we decided to assess the role of the disease associated *PTPN22* and *CSK* polymorphisms in both predisposition to and the clinical phenotypes of GCA.

## METHODS

### Study population

A total of 911 GCA patients and 8,136 unrelated healthy controls were included in this study. First, we analyzed a discovery cohort of 623 GCA patients and 1,729 healthy controls of Spanish Caucasian ancestry. Subsequently, three independent replication cohorts were analyzed (72 GCA and 937 controls from Germany; 60 GCA and 271 controls from Norway; 156 GCA and 5,199 controls from the United Kingdom). Case and control sets were matched by geographical origin and ethnicity, but not by age (which may represent a limitation of the study). *PTPN22* rs2476601 genotype data from the control population of Germany were obtained from Hüffmeier *et al.*,[14] since this set matched geographically and ethnically our German GCA cohort. More detailed information about the UK controls can be obtained from Morgan *et al.*[15] Informed written consent from all participants and approval from the local ethical committees were obtained in accordance with the tenets of

the Declaration of Helsinki. All patients had a positive temporal artery biopsy (disruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall with or without multinucleated giant cells) and fulfilled the 1990 American College of Rheumatology classification criteria for GCA.[16] In the subphenotype analysis, the patients were stratified according to manifestations of polymyalgia rheumatica (PMR) and the presence or absence of visual ischemic manifestations (VIM; if they experienced transient visual loss including amaurosis fugax, permanent visual loss, or diplopia) and irreversible occlusive disease (IOD; if they had at least one of the following features: permanent visual loss, stroke or occlusive disease in the upper extremities or lower extremities).

### Genotyping methods

Genomic DNA was extracted from peripheral white blood cells using standard procedures. Two single-nucleotide polymorphisms (SNPs) located within *PTPN22*, rs2476601/R620W and rs33996649/R263Q, and two SNPs located within *CSK*, rs1378942 and rs34933034, were genotyped using the TaqMan® allelic discrimination assay technology on a 7900HT Fast Real-Time PCR System, both from Applied Biosystems (Foster City, California, USA). For the United Kingdom samples, rs2476601/R620W was genotyped by direct sequencing.

### Statistical analysis

The overall statistical power of the analysis, according to Power Calculator for Genetic Studies 2006 software (<http://www.sph.umich.edu/csg/abecasis/CaTS/>), is shown in online supplementary table S1. Plink (v1.07) (<http://pngu.mgh.harvard.edu/purcell/plink/>) and StatsDirect v.2.6.6 (StatsDirect Ltd, Cheshire, UK) were used to perform 2×2 contingency tables and  $\chi^2$  test and/or Fisher's exact test. Odds ratios (OR) and 95% confidence intervals (CI) were obtained according to Woolf's method. The Benjamini & Hochberg (1995) step-up false discovery rate (FDR) control correction for multiple testing[17] was applied to the P-values of the discovery cohort. After correction, P-values lower than 0.05 were considered statistically significant. The allelic combinations were tested using Plink and Haploview (V. 4.2). The analysis of the combined data from all populations was performed using Plink and StatsDirect. Breslow–Day (BD) test method was used to estimate the homogeneity among populations. Pooled analyses were performed by Mantel-Haenszel test under fixed effects.

## RESULTS

After genotyping, no divergence from Hardy-Weinberg equilibrium was observed either in controls or cases ( $P > 0.01$ ), and control allelic frequencies were similar to those previously reported in equivalent European Caucasian populations.[8, 10, 11] First, we conducted an association study in a case–control set of Spanish Caucasian origin. As shown in Table 1, when allelic frequencies were compared between cases and controls, a clear association of the *PTPN22* rs2476601/R620W\*A allele with GCA was observed ( $P_{\text{FDR}} = 1.06 \times 10^{-4}$ ,  $\text{OR} = 1.62$ ,  $\text{CI}_{95\%} = 1.29\text{--}2.04$ ). Subsequently, to examine whether *PTPN22* and *CSK* polymorphisms might influence the clinical manifestations of the disease, GCA patients were stratified according to the presence of PMR, VIM and IOD (Table 1). Consistently, the subphenotype analysis also reached statistical significance for the rs2476601 polymorphism (PMR+ vs. controls:  $P_{\text{FDR}} = 9.02 \times 10^{-4}$ ,  $\text{OR} = 1.77$ ,  $\text{CI}_{95\%} = 1.30\text{--}2.40$ ; VIM+ vs. controls:

$P_{FDR}=4.10E-03$ ,  $OR=1.82$ ,  $CI\ 95\% 1.27-2.62$ ;  $IOD+$  vs. controls:  $P_{FDR}=2.19E-03$ ,  $OR=2.14$ ,  $CI\ 95\% 1.38-3.33$ ). However, no statistically significant differences between GCA patients with and without these clinical characteristics were observed (data not shown). No association with any other *PTPN22* and *CSK* genetic variants was evident either in the case/control or subphenotype analysis (Table 1).

To follow up the positive finding of an association between *PTPN22* rs2476601/R620W and GCA in the Spanish population, we attempted to confirm the detected association in a replication set of three independent cohorts of Caucasian ancestry. No heterogeneity between the ORs from the three replication cohorts was evident by BD test ( $P=0.05$ ), and therefore a combined meta-analysis was performed (Table 2 and online supplementary table S2). Statistically significant differences were observed for the *PTPN22* rs2476601\*A allele in the pooled analysis ( $P_{MH}=0.0154$ ,  $OR=1.38$ ,  $CI\ 95\% 1.07-1.77$ ) (Table 2). Subsequently, the overall meta-analysis including both the discovery and the three replication cohorts showed a consistent association between the *PTPN22* rs2476601\*A variant and GCA ( $P_{MH}=2.00E-06$ ,  $OR=1.51$ ,  $CI\ 95\% 1.28-1.79$ ; Figure 1). Again, no significant differences were found when GCA patients with and without specific clinical features were compared (data not shown).

The comparisons of the different detected allelic combinations between cases and controls did not yield additional information (data not shown).

## DISCUSSION

Our data indicate, for the first time, an important role for *PTPN22* in the genetic susceptibility of GCA. The combined analysis of the four independent cohorts showed a strong association between the *PTPN22* rs2476601/R620W variant and this disease. The effect size detected in our study ( $OR=1.51$ ) is similar to that described for other autoimmune conditions, such as rheumatoid arthritis ( $OR=1.45$ ), SLE ( $OR=1.45$ ) or type 1 diabetes mellitus ( $OR>1.80$ ), [6, 7] and, interestingly, for other vasculitides, such as Behçet's disease ( $OR>2.0$ ) or anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis ( $OR>1.90$ ). [18, 19] Despite this, a previous study failed to show association between *PTPN22* rs2476601 and GCA; [20] however, it should be noted that the statistical power of this study was compromised because of the small sample size included in this report (96 GCA cases and 229 controls). In the subphenotype analysis, no specific association with any analyzed clinical feature was observed, indicating that this variant may represent a risk factor for the global disease. Nevertheless, this should be taken with caution, because of the low statistical power, which was a limitation of this stratified analysis.

Regarding *CSK*, our analysis had enough statistical power to detect a possible weak signal (power > 80% to detect an  $OR>1.25$  in the discovery cohort); therefore, it is unlikely that *CSK* may play an important role in GCA susceptibility. Since an association between *PTPN22* and GCA was observed, it makes sense that its interacting partner *CSK* may also play a role in this pathology, but in most of the diseases in which an involvement of *PTPN22* has been described, an association with *CSK* has not been reported. Nevertheless,

an effect of other *CSK* polymorphisms, showing low linkage disequilibrium with those analyzed in our study, in *GCA* susceptibility cannot be discarded.

Initially, the *PTPN22* allele rs2476601\*A, located within a protein–protein interaction domain, was reported as a gain-of-function allele that cause a decrease in TCR signaling. [12] However, a recent study has reported that this variant is a loss-of-function allele, leading to an accelerated degradation of lyp that results in enhanced signaling in several immune cell types.[13] Although the mechanisms underlying the role of the *PTPN22* rs2476601 genetic variant in autoimmunity remain unclear, the association of this SNP with *GCA* suggests that a deregulation of TCR signaling is involved in the pathophysiological mechanisms of this vasculitis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

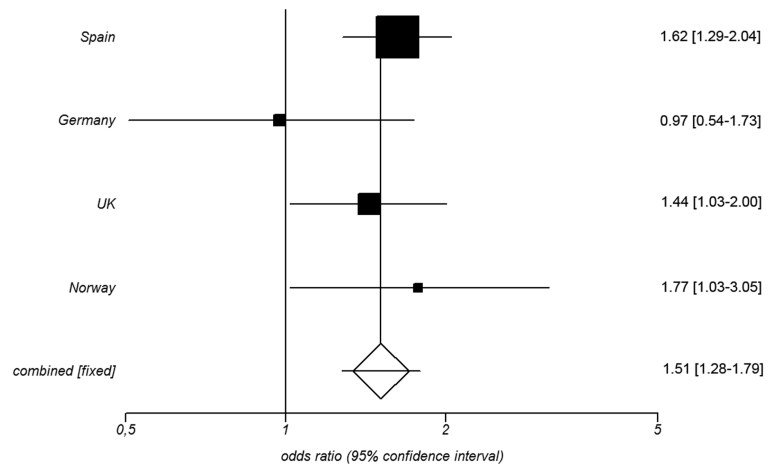
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**Figure 1.**

Forest plot showing the odds ratios (OR) and confidence intervals (CI) of the *PTPN22* rs2476601 association in the discovery and replication cohorts. OR and CI were calculated under the fixed effect model.



Table 1

Genotype and allele distribution of *PTPN22* rs2476601, rs33996649 and *CSK* rs1378942, rs34933034 in Spanish biopsy-proven GCA patients and healthy controls.

SNP	Locus	1/2	Subgroup (N)	Genotype, N (%)			Allele test				
				1/1	1/2	2/2	MAF (%)	P-value*	P <sub>FDR</sub> **	OR [CI 95%]***	
rs2476601	<i>PTPN22</i>	A/G	Controls (n=1729)	13 (0.75)	200 (11.57)	1516 (87.68)	6.54				
			GCA (n=623)	4 (0.64)	119 (19.10)	500 (80.26)	10.19	<b>2.66E-05</b>	<b>1.06E-04</b>	1.62 [1.29-2.04]	
			PMR+ (n=259)	2 (0.77)	53 (20.46)	204 (78.76)	11.00	<b>2.26E-04</b>	<b>9.02E-04</b>	1.77 [1.30-2.40]	
			VIM+ (n=168)	1 (0.60)	36 (21.43)	131 (77.98)	11.31	<b>1.03E-03</b>	<b>4.10E-03</b>	1.82 [1.27-2.62]	
rs33996649	<i>PTPN22</i>	T/C	Controls (n=1729)	4 (0.23)	110 (6.36)	1615 (93.41)	3.41				
			GCA (n=623)	1 (0.16)	39 (6.26)	583 (93.58)	3.29	0.838	0.919	0.96 [0.67-1.38]	
			PMR+ (n=259)	0 (0.00)	12 (4.63)	247 (95.37)	2.32	0.191	0.382	0.67 [0.37-1.23]	
			VIM+ (n=168)	0 (0.00)	12 (7.14)	156 (92.86)	3.57	0.878	0.878	1.05 [0.57-1.92]	
rs1378942	<i>CSK</i>	C/A	Controls (n=1729)	281 (16.25)	798 (46.15)	650 (37.59)	39.33				
			GCA (n=623)	129 (20.71)	230 (36.92)	264 (42.38)	39.17	0.919	0.919	0.99 [0.87-1.13]	
			PMR+ (n=259)	55 (21.24)	99 (38.22)	105 (40.54)	40.35	0.658	0.756	1.04 [0.86-1.26]	
			VIM+ (n=168)	34 (20.24)	69 (41.07)	65 (38.69)	40.77	0.605	0.807	1.06 [0.85-1.33]	
rs34933034	<i>CSK</i>	A/G	Controls (n=1729)	72 (4.16)	537 (31.06)	1120 (64.78)	19.69				
			GCA (n=623)	21 (3.37)	176 (28.25)	426 (68.38)	17.50	0.091	0.182	0.86 [0.73-1.02]	
			PMR+ (n=259)	10 (3.86)	79 (30.50)	170 (65.64)	19.11	0.756	0.756	0.96 [0.76-1.22]	
			VIM+ (n=168)	7 (4.17)	47 (27.98)	114 (67.86)	18.15	0.497	0.807	0.90 [0.68-1.21]	
rs34933034	<i>CSK</i>	A/G	Controls (n=1729)	5 (5.21)	24 (25.00)	67 (69.79)	17.71	0.500	0.822	0.88 [0.60-1.28]	

\* All P-values have been calculated for the allelic model.

\*\* Benjamini and Hochberg step-up false discovery rate control.

\*\*\* Odds ratio for the minor allele.

MAF, minor allele frequency; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; VIM, visual ischemic manifestations; IOD, irreversible occlusive disease

Table 2

Replication and pooled analysis of the *PTPN22* rs2476601 variant in Caucasian biopsy-proven GCA patients and controls.

Population	Subgroup (N)	Genotype, N (%)			2/2	MAF (%)	Allele test	
		1/1	1/2	2/2			P-value*	OR [CI95%]**
Germany	Controls (n=937)	9 (0.98)	164 (17.94)	741 (81.07)	9.96			
	GCA (n=72)	0 (0.00)	14 (19.44)	58 (80.56)	9.72	0.9280	0.97 [0.54-1.73]	
Norway	Controls (n=271)	1 (0.37)	56 (20.66)	214 (78.97)	10.70			
	GCA (n=60)	1 (1.67)	19 (31.67)	40 (66.67)	17.50	<b>0.0376</b>	1.77 [1.03-3.05]	
UK	Controls (n=5199)	42 (0.80)	933 (17.95)	4224 (81.25)	9.78			
	GCA (n=156)	3 (1.92)	36 (23.08)	117 (75.00)	13.46	<b>0.0319</b>	1.44 [1.03-2.00]	
Replication meta-analysis***	Controls (n=6384)	52 (0.81)	1153 (18.06)	5179 (81.12)	9.84			
	GCA (n=288)	4 (1.39)	69 (23.96)	215 (74.65)	13.37	<b>0.0154</b>	1.38 [1.07-1.77]	
Overall meta-analysis****	Controls (n=8113)	65 (0.80)	1353 (16.68)	6695 (82.52)	9.14			
	GCA (n=911)	8 (0.88)	188 (20.64)	715 (78.49)	11.20	<b>2.00E-06</b>	1.51 [1.28-1.79]	

\* All P-values have been calculated for the allelic model.

\*\* Odds ratio for the minor allele.

\*\*\* Including independent cohorts from Germany, Norway and UK

\*\*\*\* Including independent cohorts from Spain, Germany, Norway and UK