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 8136 unaffected controls from a Spanish discovery cohort and three additional independent replication cohorts from Germany, Norway and the UK. 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(perm)=1.06E-04, OR=1.62, CI 95% 1.29 to 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(perm)=2.00E-06, OR=1.51, CI 95% 1.28 to 1.79).

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

INTRODUCTION

Giant cell arteritis (GCA) is a chronic vasculitis that shows a complex aetiology 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 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 aetiology 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 signalling mediated by the T cell receptor (TCR).3 Interestingly, several single-nucleotide polymorphisms (SNPs) located within these two genes have been associated with autoimmunity,5–11 suggesting that this is one of the molecular pathways shared by different autoimmune disorders.

Regarding PTPN22, it has been reported that two autoimmunity 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 sclerosis14 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 8136 unrelated healthy controls were included in this study. First, we analysed a discovery cohort of 623 GCA patients and 1729 healthy controls of Spanish Caucasian ancestry. Subsequently, three independent replication cohorts were analysed (72 GCA and 937 controls from Germany; 60 GCA and 271
controls from Norway; 156 GCA and 5199 controls from the UK). 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., 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. 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. In the subphenotype analysis, the patients were stratified according to manifestations of polymyalgia rheumatica (PMR) and the presence or absence of visual ischaemic 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 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 UK 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. Pooled analyses were performed by Mantel–Haenszel test and/or Fisher’s exact test. ORs and 95% CIs were obtained according to Woolf’s method. The Benjamini and Hochberg (1995) step-up false discovery rate (FDR) control correction for multiple testing 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 Haplovist (V4.2). 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.

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

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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 | Subgroup | Genotype, N (%) | 1/1   | 2/2   | MAF (%) | Allele test | p Value* | P_{FDR}† | OR (CI 95%)‡ |
|---------|-------|----------|----------------|-------|-------|---------|-------------|----------|---------|----------------|
| rs2476601 PTPN22 | A/G   | Controls (n=1729) | 13 (0.75) | 200 (11.57) | 1516 (87.68) | 6.54 | **2.66E-05** | 0.162 | 1.29 | 2.04 |
|         |       | GCA (n=623) | 4 (0.64) | 119 (19.10) | 500 (80.26) | 10.19 | 2.66E-05 | 0.162 | 1.29 | 2.04 |
|         |       | PMR+ (n=259) | 2 (0.77) | 53 (20.46) | 204 (79.54) | 11.00 | 2.26E-04 | 0.902 | 1.77 | 2.40 |
|         |       | VIM+ (n=168) | 10 (6.00) | 36 (21.43) | 131 (71.47) | 11.31 | 1.03E-04 | 4.10E-04 | 1.82 | 1.27 |
|         |       | IOD+ (n=96) | 2 (2.08) | 21 (21.88) | 73 (76.04) | 13.02 | 5.47E-04 | 2.19E-03 | 2.14 | 3.33 |
| rs33996649 PTPN22 | T/C   | Controls (n=1729) | 4 (0.23) | 110 (6.36) | 1615 (93.41) | 3.41 | 0.838 | 0.919 | 0.96 | (0.67 to 1.38) |
|         |       | GCA (n=623) | 1 (0.16) | 39 (6.26) | 583 (93.58) | 3.29 | 0.838 | 0.919 | 0.96 | (0.67 to 1.38) |
|         |       | PMR+ (n=259) | 0 (0.00) | 12 (4.63) | 247 (95.37) | 3.22 | 0.191 | 0.382 | 0.67 | (0.37 to 1.23) |
|         |       | VIM+ (n=168) | 0 (0.00) | 12 (7.14) | 156 (92.86) | 3.57 | 0.878 | 0.878 | 1.05 | (0.57 to 1.92) |
|         |       | IOD+ (n=96) | 2 (2.08) | 21 (21.88) | 73 (76.04) | 13.02 | 5.47E-04 | 2.19E-03 | 2.14 | 3.33 |
| rs1378942 CSK | C/A   | Controls (n=1729) | 281 (16.25) | 798 (46.15) | 650 (39.59) | 39.33 | 0.919 | 0.919 | 0.99 | (0.87 to 1.13) |
|         |       | GCA (n=623) | 129 (20.71) | 230 (36.92) | 264 (42.38) | 39.17 | 0.919 | 0.919 | 0.99 | (0.87 to 1.13) |
|         |       | PMR+ (n=259) | 55 (21.24) | 99 (38.22) | 105 (39.54) | 40.35 | 0.658 | 0.756 | 1.04 | (0.86 to 1.26) |
|         |       | VIM+ (n=168) | 34 (20.24) | 69 (41.07) | 65 (38.69) | 40.77 | 0.605 | 0.807 | 1.06 | (0.85 to 1.33) |
|         |       | IOD+ (n=96) | 20 (12.65) | 39 (40.63) | 37 (38.75) | 40.77 | 0.605 | 0.807 | 1.06 | (0.85 to 1.33) |
| rs34933034 CSK | A/G   | Controls (n=1729) | 72 (4.16) | 537 (31.06) | 1120 (64.78) | 39.69 | 0.091 | 0.182 | 0.86 | (0.73 to 1.02) |
|         |       | GCA (n=623) | 21 (3.37) | 176 (28.25) | 426 (68.38) | 17.50 | 0.091 | 0.182 | 0.86 | (0.73 to 1.02) |
|         |       | PMR+ (n=259) | 10 (3.86) | 79 (30.50) | 170 (65.64) | 19.11 | 0.756 | 0.756 | 0.96 | (0.76 to 1.22) |
|         |       | VIM+ (n=168) | 7 (4.17) | 47 (27.98) | 114 (67.86) | 18.15 | 0.497 | 0.807 | 0.90 | (0.68 to 1.21) |
|         |       | IOD+ (n=96) | 5 (5.21) | 24 (25.00) | 67 (69.79) | 17.71 | 0.500 | 0.822 | 0.88 | (0.60 to 1.28) |

*All p values have been calculated for the allelic model.
†Benjamini and Hochberg step-up FDR control.
‡OR for the minor allele.

FDR, false discovery rate; GCA, giant cell arteritis; IOD, irreversible occlusive disease; MAF, minor allele frequency; PMR, polymyalgia rheumatica; SNP, single-nucleotide polymorphism; VIM, visual ischaemic manifestations.
association of the PTPN22 rs2476601/R620W*A allele with GCA was observed (PFDR=1.06E-04, OR=1.62, CI 95% 1.29 to 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: PFDR=9.02E-04, OR=1.77, CI 95% 1.30 to 2.40; VIM+ vs controls: PFDR=4.10E-03, OR=1.82, CI 95% 1.27 to 2.62; IOD+ vs controls: PFDR=2.19E-03, OR=2.14, CI 95% 1.38 to 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 (PMH=0.0154, OR=1.38, CI 95% 1.07 to 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 (PMH=2.00E-06, OR=1.51, CI 95% 1.28 to 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).

Table 2 Replication and pooled analysis of the PTPN22 rs2476601 variant in Caucasian biopsy-proven GCA patients and controls

| Population | Subgroup (N) | Genotype, N (%) | Allele test | p Value* | OR (CI 95%)† |
|------------|--------------|----------------|-------------|----------|--------------|
| Germany    | Controls (n=937) | 1/1  9 (0.98) 164 (17.94) 741 (81.07) 9.96 | 0.9280 | 0.97 (0.54 to 1.73) |
|            | GCA (n=72) | 0 (0.00) 14 (19.44) 58 (80.56) 9.72 | 0.0376 | 1.77 (1.03 to 3.05) |
| Norway     | Controls (n=271) | 1 (0.37) 56 (20.66) 214 (78.97) 10.70 | 0.0154 | 1.38 (1.03 to 1.77) |
|            | GCA (n=60) | 1 (1.67) 19 (31.67) 40 (66.67) 17.50 | 0.0319 | 1.44 (1.03 to 2.00) |
| UK         | Controls (n=5199) | 42 (0.80) 933 (17.95) 4224 (81.25) 9.78 | 0.0376 | 1.77 (1.03 to 3.05) |
|            | GCA (n=156) | 3 (1.92) 36 (23.08) 117 (74.65) 13.46 | 0.0154 | 1.38 (1.07 to 1.77) |
| Replication meta-analysis‡ | Controls (n=6384) | 52 (0.81) 1115 (17.06) 5719 (81.12) 9.84 | 0.0319 | 1.44 (1.03 to 2.00) |
|            | GCA (n=288) | 4 (1.39) 69 (23.67) 215 (74.65) 13.37 | 0.0154 | 1.38 (1.07 to 1.77) |
| Overall meta-analysis§ | Controls (n=8113) | 65 (0.80) 1353 (16.68) 6695 (82.52) 9.14 | 0.0154 | 1.38 (1.07 to 1.77) |
| GCA (n=911) | 8 (0.88) 188 (20.64) 715 (78.49) 11.20 | 2.00E-06 | 1.51 (1.28 to 1.79) |

*All p values have been calculated for the allelic model.
†OR for the minor allele.
‡Including independent cohorts from Germany, Norway and UK.
§Including independent cohorts from Spain, Germany, Norway and UK.
GCA, giant cell arteritis.

Figure 1 Forest plot showing the ORs and CIs of the PTPN22 rs2476601 association in the discovery and replication cohorts. OR and CI were calculated under the fixed effect model.
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) and, interestingly, for other vasculitides, such as Behçet’s disease (OR > 2.0) or antineutrophil cytoplasmic antibodies-associated vasculitides (OR > 1.90). Despite this, a previous study failed to show association between PTPN22 rs2476601 and GCA; 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 analysed 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 analysed 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 causes a decrease in TCR signalling. 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 signalling in several immune cell types. 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 signalling is involved in the pathophysiological mechanisms of this vasculitis.

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Contributors FDC, AWM, MAG-G and JM were involved in the conception and design of the study. AS, AM, SLM and FDC contributed in the analysis and interpretation of data. AM and AS drafted the manuscript. RS, IAM-F, JH-R, MCC, SC, ICM, IN, RB, BS, MIG-V, JM, NDC-C, AU, BM-A, ISM, EBM, CM, ER, NB, JL, OM, BAL, FM, TW, AW and MAG-G collected samples and participated in analysis and interpretation of data. FDC, SLM, JM, MAG-G, RS, IAM-F, JH-R, MCC, SC, ICM, IN, RB, BS, MIG-V, JM, NO-C, AU, BM-A, ISM, EBM, CM, ER, NB, JL, OM, BAL, FM, TW and AWM revised critically the manuscript draft. All authors approved the final version of the manuscript.

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