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Lack of association between ankylosing spondylitis and a functional polymorphism of *PTPN22* proposed as a general susceptibility marker for autoimmunity

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Ankylosing spondylitis (AS) is a common chronic rheumatic disease whose aetiology arises as a result of the contribution of environmental factors and a strong genetic component.[1] One crucial point in the pathogenesis of the disease is the regulation of T cell response.[2] Recently, it has been shown that the functional 1858 C/T polymorphism of *PTPN22*, the gene that encodes a lymphoid-specific protein tyrosine phosphatase (LYP), is associated with several autoimmune diseases (ADs), supporting the hypothesis that common aetiopathological pathways are shared by different ADs.[3] LYP has a key role as a negative regulator of T cell activation.[4] It seems that the single nucleotide polymorphism (SNP) 1858 C/T disrupts the interaction between LYP and Csk, probably leading to an overactivated T cell response.[5]

Taking into account the functional relevance of the *PTPN22* 1858 C/T polymorphism, and its association with a wide range of ADs, this study aimed at investigating for the first time the possible implication of the SNP for susceptibility to AS.

A total of 197 patients with AS meeting the modified New York criteria for AS[6] were recruited from Hospital Virgen de las Nieves (Granada, Spain) and Hospital Xeral-Calde (Lugo, Spain). A total of 551 blood bank donors and bone marrow donors were included as healthy controls. All the subjects were of white Spanish origin. Samples were genotyped for *PTPN22* 1858C→T variants as previously described.[7] Statistical analysis to compare allelic and genotypic distributions was performed by χ^2 test using Statcalc program (Epi Info 2002; Centers for Disease Control and Prevention, Atlanta, GA, USA).

We found no statistically significant differences after comparing allele and genotypic frequencies of *PTPN22* 1858C→T between patients with AS and controls (table 1).

In addition, comparison of genotypes carrying the T allele (CT+TT *v* CC) between patients with AS and controls did not reach statistically significant skewing.

Similarly, no statistically significant differences were found when we stratified patients with AS according to HLA-B27 status (data not shown).

The lack of association that we show here might be due to a false negative, given our underpowered sample size. Because of this, we cannot completely exclude a weak effect of this polymorphism in AS and further investigations in different populations are required.

Recent studies of the *PTPN22* 1858C/T polymorphism have reported a lack of association with some ADs.[8] The lack of association with these ADs may indicate a common aetiological mechanism that is different from the associated ADs. It has been proposed that the susceptibility of the polymorphism may predispose individual subjects to autoimmunity by promoting the generation of autoantibodies that contribute to disease onset and progression.[9] The existence of humoral abnormalities in PTPN22 knockout mice strengthens the hypothesis that autoantibody production is a prominent feature of the ADs that are associated with *PTPN22*.[10] Based on that, the lack of autoantibody production in AS might explain the negative association between *PTPN22* 1858C/T polymorphism and this condition.

In conclusion, the lack of association of *PTPN22* with some ADs emphasises that susceptibility factors for AD are not shared among all ADs.

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Table 1 Allele and genotype frequencies of the *PTPN22* 1858C→T polymorphism in 197 patients with AS and 551 healthy controls

	Patients with AS (%)	Healthy controls (%)	p Value*	OR (95% CI)
C/C	166 (84.3)	462 (83.8)	0.89	1.03 (0.65 to 1.65)
C/T	28 (14.2)	84 (15.2)	0.72	0.92 (0.56 to 1.5)
T/T	3 (1.5)	5 (0.9)	0.47	1.69 (0.32 to 8.17)
C	360 (91.4)	1008 (91.5)	0.95	0.99 (0.64 to 1.52)
T	34 (8.6)	94 (8.5)	0.95	1.01 (0.66 to 1.55)

*3×2 contingency table, overall p value = 0.73.

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Treatment of ankylosing spondylitis with pamidronate: an open label study

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Non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy constitute the standard treatment for patients with ankylosing spondylitis (AS). Currently, there are no good disease modifying agents. Tumour necrosis factor antagonists, though effective, are very expensive and associated with an increased risk of infections. Pamidronate, an amino bisphosphonate is believed to have anti-inflammatory properties. We evaluated the role of pamidronate infusions in patients with AS refractory to NSAIDs.

Twenty one patients fulfilling modified New York criteria[1] for AS with active disease despite use of the maximal dose of two NSAIDs were recruited. Active peripheral arthritis and use of disease modifying antirheumatic drugs were reasons for exclusion. The mean (SD) age of the patients (male: female 20:1) was 31.6 (8.7) years and the mean (SD) disease duration 9.2 (5.5) years. The treatment regimen comprised monthly pamidronate infusions (60 mg over 4 hours) for 6 months. Patients were allowed to continue taking NSAIDs. Patients were assessed for response in the four Assessment in Ankylosing Spondylitis (ASAS) domains: Bath AS Functional Index (BASFI), pain on a visual analogue scale (VAS), patient global assessment VAS, and inflammation (morning stiffness—mean of items 5 and 6 of the Bath AS Disease Activity Index (BASDAI)).[2]

Fifteen patients completed all six infusions. Four were withdrawn owing to serious adverse effects. Two patients were excluded for protocol violation and loss to follow up, respectively. Figure 1 shows the effects of pamidronate on ASAS outcome domains among the patients completing all six infusions. None of the outcome measures improved significantly, although pain and global assessment showed a trend towards improvement (table 1).

The ASAS responses were analysed on an intention to treat basis. Only 4/21 (19%) patients achieved an ASAS 20 response and no one achieved an ASAS 40 response. In two patients the disease activity increased by more than 20% in all the four domains.

Maksymowych *et al* documented significant efficacy of pamidronate infusions in AS.[3–5] Improvement in disease activity (BASDAI 25% reduction in 63% patients), function, global assessment, and metrology were seen at 6 months among patients receiving 60 mg pamidronate infusions.[5] This corresponded to an ASAS 20 response of 60.2% in a post hoc analysis.[6] Our patients had moderately active disease and we expected similar response rates. However, the 19% ASAS 20 response rate achieved was no different from the 25% expected in controls.[7] None of the patients achieved an ASAS 40 response, considered to be a more robust tool. The results are more like those observed by Haibel *et al*, who

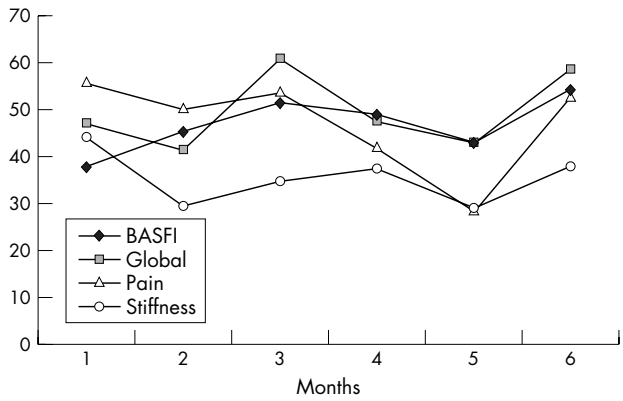

Figure 1 Effect of pamidronate infusions on ASAS domains for disease activity.