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## PTPN22 R620W polymorphism is not associated with pemphigus

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SIR, Pemphigus is a blistering autoimmune disease characterized by the production of autoantibodies against desmosomal cadherins: desmoglein (Dsg) 1 in pemphigus foliaceus (PF) and Dsg3 in pemphigus vulgaris (PV). These autoantibodies are pathogenic and cause keratinocyte detachment or acantholysis. It is widely known that pemphigus, like many other autoimmune diseases, has a genetic basis involving several different genes, mainly at the HLA locus.<sup>1</sup> PTPN22, a gene encoding a lymphoid tyrosine phosphatase, has recently been described as a candidate gene for autoimmune diseases. Indeed, a functional single nucleotide polymorphism (SNP) +1858C/T in PTPN22

(rs2476601), that leads to a change at codon 620 from arginine to tryptophan (R620W), has been reported to be associated with rheumatoid arthritis (RA) and type 1 diabetes (T1D).<sup>2</sup> Based on these data we analysed the association of this SNP with pemphigus in order to test the involvement of this gene's variability in susceptibility to pemphigus.

Blood samples were obtained from 154 unrelated patients with pemphigus (100 PF, 54 PV) with a median age of 46 years (range 20–80) and a female/male sex ratio of 4 : 1. One hundred and fifty healthy persons matched for age, sex and origin were studied as controls. Genomic DNA was purified from fresh peripheral blood leucocytes by standard methods. Genotyping of the PTPN22 rs2476601 polymorphism was carried out with a Taqman<sup>®</sup> 5' allelic discrimination assay using an ABI 7500 (Applied Biosystems, Foster City, CA, U.S.A.) real-time polymerase chain reaction system (custom assay). Ten per cent of samples randomly chosen were re-genotyped in order to evaluate genotyping accuracy; they were 100% identical. T allele and genotype frequencies were compared between cases and controls using a  $\chi^2$  test and a Fisher exact test.

The C/T genotype was detected in 3% and 1.8% of patients with PF and PV, respectively (Table 1). No patients, either with PF or with PV, had the homozygous state T/T. No significant association between PTPN22 polymorphism and the disease was observed ( $P > 0.05$ ). We also assessed our population for Hardy–Weinberg equilibrium and confirmed that there was no deviation in either patient or control groups.

To our knowledge, we are reporting the first case–control study describing PTPN22 R620W in pemphigus. Our results showed that the SNP 1858T is present in 1.3% of the Tunisian population. We found no association between the R620W phenotype and either form of the disease (PV or PF). These findings suggest that this polymorphism does not contribute to disease susceptibility.

The 1858T allele was first described in association with T1D in two different populations. This result was confirmed by others in family-based and case–control studies. PTPN22 R620W was found to be associated also with rheumatoid arthritis, Graves disease, systemic lupus erythematosus, Hashimoto thyroiditis and juvenile idiopathic arthritis.<sup>2,3</sup> Although confirmed in different populations, this association was not reported in either T1D or RA in a Colombian population.<sup>2</sup> Similar negative associations were reported with coeliac disease, Crohn disease, Sjögren syndrome and autoimmune thyroid disease in a large affected Tunisian family.<sup>2,4</sup> These

Genotype 1858	Pemphigus foliaceus		Pemphigus vulgaris	
	Patients (n = 100)	Controls (n = 100)	Patients (n = 54)	Controls (n = 50)
C/C	97 (97%)	98 (98%)	53 (98.2%)	48 (96%)
C/T and T/T	3 (3%)	2 (2%)	1 (1.8%)	2 (4%)
f (C)	98.5%	99%	99.1%	98%
f (T)	1.5%	1%	0.9%	2%

**Table 1** Genotype and allele frequencies (f) of the PTPN22 1858C/T polymorphism in patients with pemphigus foliaceus (PF) and controls and in patients with pemphigus vulgaris (PV) and controls. No statistical difference was observed between patients (PF or PV) and controls for the PTPN22 1858C/T polymorphism

data revealed ethnic variations which could explain this discrepancy and suggested also that diseases such as systemic lupus erythematosus, T1D and RA share a common mechanism that would not play a crucial role in predisposing to pemphigus. Studies that reported a positive association sought an interaction between this polymorphism and HLA, the main and common locus that implicates autoimmunity. In the present report, the small number of pemphigus patients with the T allele precludes reporting a specific interaction between the HLA locus and PTPN22.

PTPN22 is a negative regulator of T-cell receptor signalling. The +1858T allele encodes an amino acid substitution (R620W) leading to a gain of function that may act in a central or a peripheral way, leading to autoimmunity. Our report that the +1858T allele has no effect on susceptibility to pemphigus may be a reflection of the small number of patients, particularly in the PV group. It also raises the question about the influence of other candidate genes that are involved in the autoimmune response. The rarity of multiplex families presenting pemphigus has made investigation of linkage analysis difficult.<sup>1</sup> As a consequence, the candidate gene strategy is best suited to identify the genes participating in pemphigus susceptibility.

Accordingly, case-control studies have assessed polymorphisms of Dsgs, immunoglobulins, CTLA4 and genes encoding cytokines such as tumour necrosis factor, interleukin (IL)-1, IL-4, IL-6 and IL-10.<sup>5-7</sup> These data revealed a weak association with Dsg1 polymorphism 809C/T in French and Tunisian patients with PF.<sup>8</sup> Moreover, two Dsg3 haplotypes, defined by five SNPs, were also associated with British and Indian patients with PV.<sup>9</sup> Among cytokine genes, only IL6 was suspected to contribute to pemphigus pathogenesis.

This discrepancy of the associated allele reflects that common autoimmune susceptibility alleles may not be shared among all autoimmune diseases but among groups. Although a minor effect of PTPN22 could not be ruled out, there is no evidence to suggest that it could be a more modest factor requiring a large dataset to be observed. Moreover, studying other polymorphisms within PTPN22 would clarify its 'real' influence in the autoimmune process. Accordingly, two other PTPN22 polymorphisms (the -1123 G→C promoter polymorphism and the +2740C→T polymorphism within the 3' untranslated region) were described in Asian T1D.<sup>10</sup> Finally, when looking for a possible association with polymorphisms of other candidate genes, their interaction with the environment will be helpful to elucidate pemphigus aetiology.

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