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ORIGINAL ARTICLE

# Meta-analysis reveals an association of *PTPN22* C1858T with autoimmune diseases, which depends on the localization of the affected tissue

J Zheng[1], S Ibrahim[2], F Petersen[3] and X Yu[1,3]

Protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) is a strong susceptibility gene shared by many autoimmune diseases. The aim of this study was to explore the mechanisms underlying this relationship. We performed a comprehensive analysis of the association between *PTPN22* polymorphism C1858T and autoimmune diseases. The results showed a remarkable pattern; *PTPN22* C1858T was strongly associated with type I diabetes, rheumatoid arthritis, immune thrombocytopenia, generalized vitiligo with concomitant autoimmune diseases, idiopathic inflammatory myopathies, Graves' disease, juvenile idiopathic arthritis, myasthenia gravis, systemic lupus erythematosus, anti-neutrophil cytoplasmic antibody-associated vasculitis and Addison's disease. By contrast, *PTPN22* C1858T showed a negligible association with systemic sclerosis, celiac disease, multiple sclerosis, psoriasis, ankylosing spondylitis, pemphigus vulgaris, ulcerative colitis, primary sclerosing cholangitis, primary biliary cirrhosis, Crohn's disease and acute anterior uveitis. Further analysis revealed a clear distinction between the two groups of diseases with regard to their targeted tissues: most autoimmune diseases showing an insignificant association with *PTPN22* C1858T manifest in skin, the gastrointestinal tract or in immune privileged sites. These results showed that the association of *PTPN22* polymorphism with autoimmune diseases depends on the localization of the affected tissue, suggesting a role of targeted organ variation in the disease manifestations.

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## INTRODUCTION

Autoimmune diseases are influenced by a combination of genetic predisposition and environmental factors and are mostly polygenic disorders to which many genes contribute. Human leukocyte antigen (HLA) loci are associated with all autoimmune diseases and are the strongest genetic factors for individual predisposition.[1] Of the non-HLA susceptibility genes, variants of protein tyrosine phosphatase non-receptor type (*PTPN22*) show the strongest associations with autoimmune diseases. Initially identified as a susceptibility gene for type 1 diabetes (T1D),[2] variants of *PTPN22*, especially C1858T, have subsequently been shown to be associated with many other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Graves' disease.[3–5]

Given the important role of *PTPN22* in many autoimmune diseases, exploration of the mechanism(s) behind this association will help us to better understand the pathogenesis of disease. The human *PTPN22* gene is located on chromosome 1 and encodes a protein (called Lyp) comprising 807 amino-acid residues,[6] which contains a catalytic domain and four SH3 binding sites. The R620W mutation, resulting from the C1858T polymorphism, is located within the first SH3 binding domain of Lyp, indicating that it exerts its effects by affecting intermolecular interactions.[2] Indeed, binding of Lyp to C-terminal Src tyrosine kinase (Csk) is partially or completely disrupted, and is associated with SLE, T1D and RA.[2,3] Vang *et al.*[7] reported that R620W is a gain-of-function mutation, increasing catalytic activity and acting as a potent negative regulator of T lymphocyte activation. Further studies showed that that the R620W mutation also inhibited activation of NK cell and B cell.[8,9] Although considerable progress has been achieved in examining the function of the R620W mutation, the mechanisms underlying the association between *PTPN22* and autoimmune diseases are still largely unknown. Studies in mice provided only limited information to elucidate these regulatory processes. Murine *PTPN8*, which represents the ortholog of human *PTPN22* in mice, was successfully knocked out but the corresponding animal did not develop spontaneous autoimmune diseases.[10] There may be two reasons for this, first, R620W is a gain-of-function mutation and knockout mice (essentially a loss-of-function model) are of no help. Second, a high divergence between the human *PTPN22* and mouse *PTPN8* genes exists, which may result in functional differences of the molecule in both species.

With regard to the strong association between *PTPN22* polymorphisms and certain autoimmune diseases, extensive studies have been undertaken to evaluate the association between *PTPN22* variants and more than 20 such diseases. Although *PTPN22* is the one of the strongest non-HLA susceptibility genes for T1D, RA, SLE and Graves' disease,[2–5] no association has been observed between *PTPN22* variants and other autoimmune diseases such as systemic sclerosis (SSc), Crohn's disease, ulcerative colitis (UC) and multiple sclerosis (MS).[11–13]

[1]Laboratory of Autoimmunity, The Medical College of Xiamen University, Xiamen University, Xiamen, China; [2]Department of Dermatology, University of Lübeck, Lübeck, Germany and [3]Division of Biochemical Immunology, Department of Asthma & Allergy, Research Center Borstel, Borstel, Germany. Correspondence: Dr X Yu, Laboratory of Autoimmunity, The Medical College of Xiamen University, Xiamen University, 361005 Xiamen, China.
E-mail: xinhuayu@fz-borstel.de
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Examining the association pattern between *PTPN22* variants and autoimmune diseases will help us to understand the pathogenesis of individual diseases. It may also help us to understand the mechanism(s) underlying this association. Therefore, we for the first time performed a comprehensive meta-analysis to identify the association pattern between *PTPN22* and autoimmune diseases. We then evaluated this association pattern in detail with the aim of shedding new light on the role of *PTPN22* in autoimmune disease.

## RESULTS

### Frequency of the *PTPN22* minor allele

The frequency of the *PTPN22* C1858T minor allele varies considerably across the world (Figure 1). In brief, European populations or populations of European descent showed a higher frequency than other populations, and the frequency in northern Europe was higher than in the south. The highest T allele frequency (17.5%) was reported in northeast Russia,[14] followed by Finland (15.4%),[15] Ukraine (14.1%)[16] and Estonia (13.9%).[17] The frequency decreased toward the west, showing 11–13% in Poland,[18–20] 10–12% in Sweden,[21–23] Norway[24–26] and Germany,[24,27–29] 11.7% in Croatia, 10–11% in the Czech Republic,[30,31] 10.7% in Slovakia,[32] 9.2% in Denmark,[33] and 8–10% in the UK[34–39] and the Netherlands.[24,40–42] The decrease in the frequency toward the south was dramatic, with 7.75% in Hungary,[43] 7.23% in Belgium, 7–8% in France,[44,45] 5–7% in Spain[46–48] and 4.1% in Romania.[49] The frequency in Italy varied from 2.1 to 5.9%.[2,50–53] The lowest frequency for the *PTPN22* T allele was reported in two island populations: Sassari, Italy (2.1%)[2] and Crete, Greece (2.9%).[54] Outside Europe, the T allele frequency in populations of European descent in New Zealand ranged from 9.9 to 10.7%,[24,55] and in America it ranged from 3.8 to 10.0%.[49,56–67] Americans of non-European descent showed a very low T allele frequency, as low as 1.1% in Mexico.[68] North Africa had a similar T allele frequency to Turkey and the Middle East, which ranged from 2 to 3.5%,[69–75] however, *PTPN22* is not polymorphic in the black African population.[76] *PTPN22* is also non-polymorphic or almost non-polymorphic in some Asian populations, including Japanese, Korean, Indian and some Chinese populations.[77–81] Two Chinese populations, Uygers and Kazaks, showed relatively high T allele frequencies of 5.3% and 7.0%, respectively; both are Caucasian-related populations.[81]

### Diseases showing a strong association with PTPN22

Although not proven, it is believed that the *PTPN22* C1858T polymorphism is the main causal mutation for previously described associations of *PTPN22* with autoimmune diseases.[82] Therefore, we focused this meta-analysis only on the C1858T polymorphism. Due to dramatic differences in the frequency of the T allele between populations, most case–control studies have been conducted in European populations and populations of European descent. Only a few studies have been conducted in other populations such as North African, Turkish, Mexican and Indian, and then with only a small number of samples.[70–72,74,75,83,84] Therefore, to avoid any possible heterogeneity, we excluded these studies and focused on studies in European or European-descended populations.

The association between *PTPN22* C1858T and autoimmune diseases was first identified in individuals with T1D in 2004.[2] Numerous studies have been performed across the world to confirm this association. Twenty-three case–control studies were recruited for this meta-analysis with odds ratios (ORs) ranging from 1.04 to 3.15.[2,5,14,16,17,30,33,42,51,52,57,60,63,65,85–91] Only 5/23 studies failed to reach a significant threshold. As expected, the meta-analysis showed a strong association between the T allele and T1D (OR = 1.84; 95% confidence intervals (CI) = 1.72–1.96, $P < 1.0 \times 10^{-16}$) (Figure 2a).

As the most common autoimmune disease, RA is also the most extensively investigated in terms of its association with *PTPN22* C1858T. In total, 36 case–control studies were recruited for the present study with ORs ranging from 0.99 to 2.56.[3,14,15,18,22,24,26,28,32,35,39–42,54,60,67,92–103] Thirty-one out of thirty-six showed a significant association between *PTPN22* and

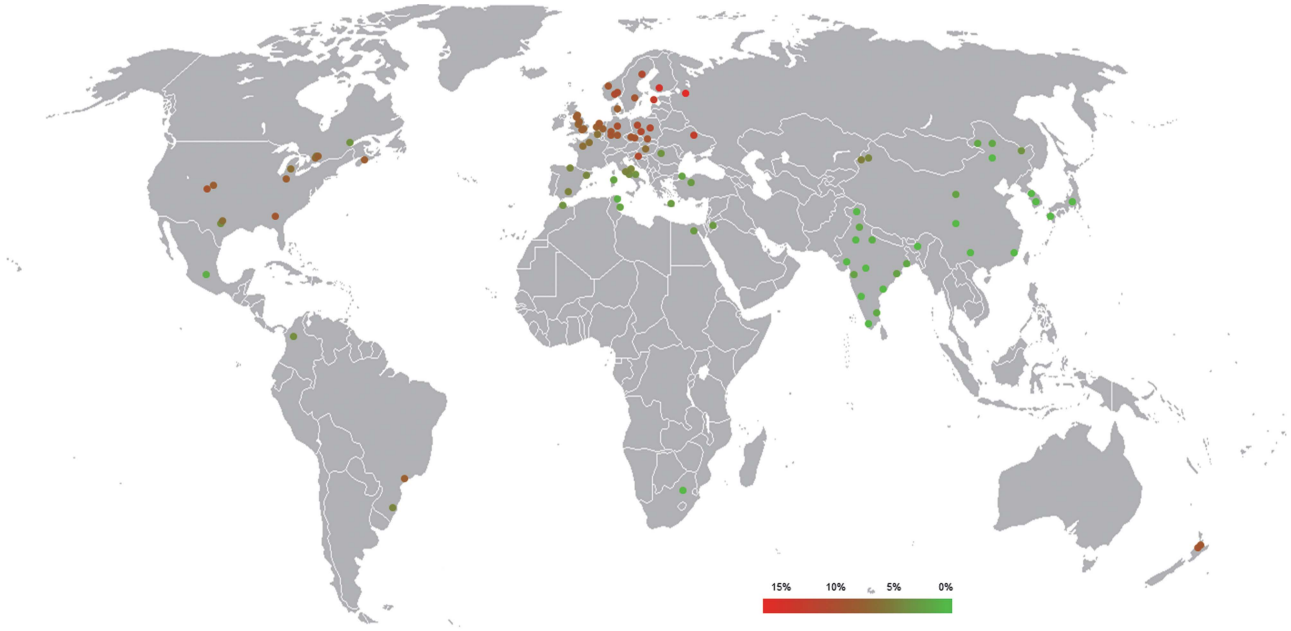


**Figure 1.** Heat map of the allele frequency of the *PTPN22* minor allele across the world. Each color-filled cycle represents a single population. Only populations with a clearly defined location are presented. All populations from USA, Canada, South America and New Zealand are of European descent.

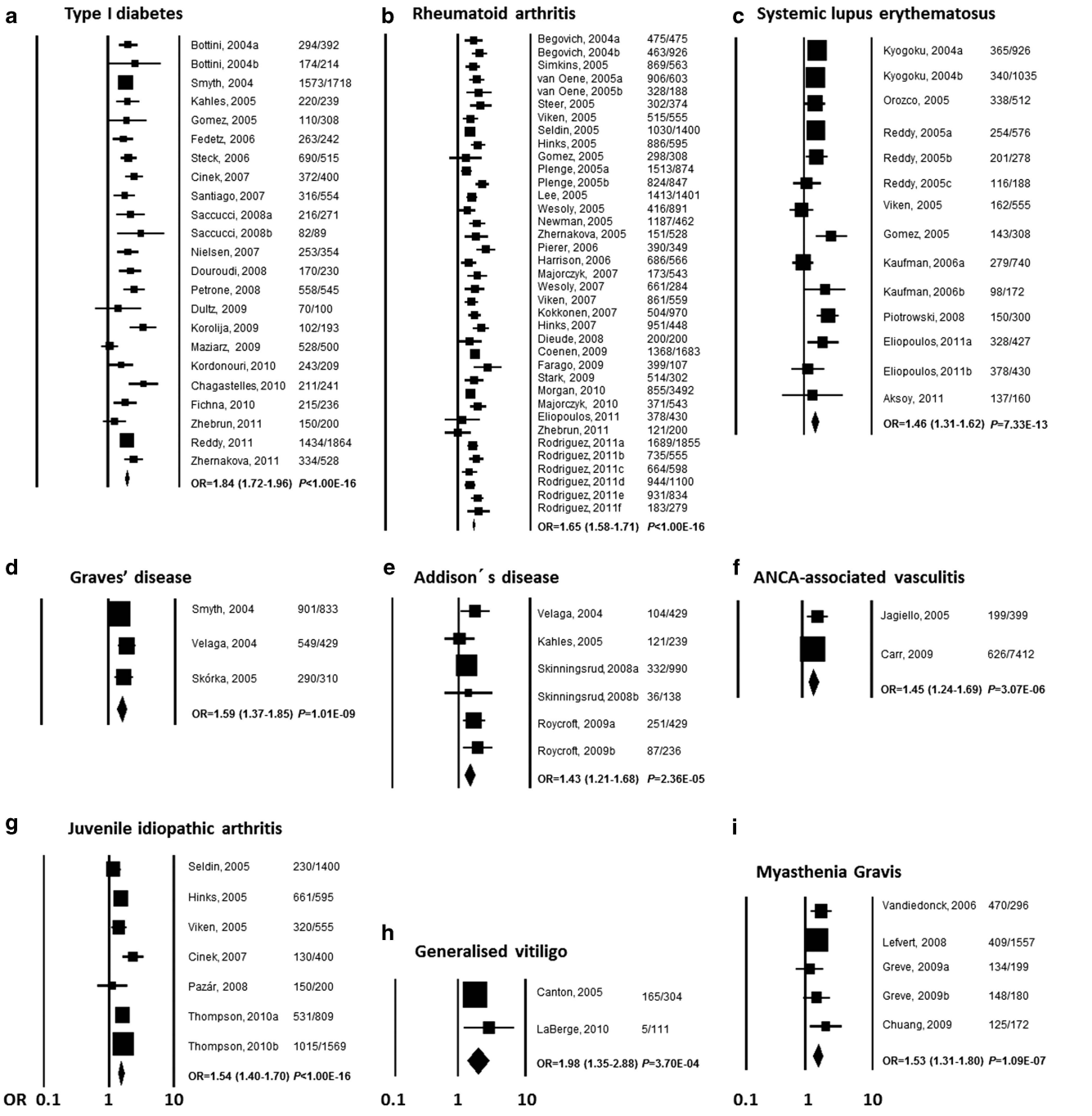


**Figure 2.** Forest plot of case–control studies of nine autoimmune diseases showing a strong association with *PTPN22*. The nine autoimmune diseases include (**a**) type 1 diabetes, (**b**) rheumatoid arthritis, (**c**) systemic lupus erythematosus, (**d**) Graves' disease, (**e**) Addison's disease, (**f**) ANCA-associated vasculitis, (**g**) juvenile idiopathic arthritis, (**h**) generalised vitiligo, and (**i**) myasthenia gravis. The information regarding individual case–control studies, including the first author name and year of publication, as well as the number of cases/number of controls, are indicated. OR and 95% CI of individual studies are represented by squares and horizontal lines, respectively. The size of the square represents the weight of the individual study in the meta-analysis. The diamonds represent the OR (center line of the diamond) and 95% CI (lateral tips of the diamond) of the fixed-effect meta-analysis. The OR, 95% CI and *P*-values for the meta-analysis are indicated by bold text.

RA. Meta-analysis showed a strong association between the T allele and RA (OR = 1.65; 95% CI = 1.58–1.71, $P < 1.00 \times 10^{-16}$) (Figure 2b).

Another common autoimmune disease, SLE has also been extensively studied. Of the 14 case–control studies recruited for this study,[4,54,60,103–108] 9 showed a significant association between *PTPN22* C1858T and SLE. Meta-analysis showed a strong association between the T allele and SLE (OR = 1.46; 95% CI = 1.31–1.62, $P = 7.33 \times 10$–13), although this was not as strong as that between T1D and *PTPN22* C1858T or RA and *PTPN22* C1858T (Figure 2c).

Even though it has not been not extensively evaluated, a strong association between Graves' disease and *PTPN22* C1858T has also been observed. All three case–control studies recruited for this meta-analysis showed a significant association between *PTPN22* C1858T and Graves' disease with ORs ranging from 1.43

to1.88.[5,20,109] Meta-analysis showed a strong association between the T allele and Graves' disease (OR = 1.59; 95% CI = 1.37–1.85, $P = 1.01 \times 10^{-9}$) (Figure 2d).

Six case–control studies evaluated the association between *PTPN22* C1858T and Addison's disease. Three showed a significant association, whereas the other three studies showed a tendency toward a positive association but failed to reach the significance threshold.[25,87,109,110] Meta-analysis showed a significant association between the T allele and Addison's disease (OR = 1.43; 95% CI = 1.21–1.68, $P = 2.36 \times 10^{-5}$) (Figure 2e).

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis includes Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome. Two case–control studies were recruited for this meta-analysis.[111,112] Meta-analysis showed a significant association between the T allele and ANCA-associated vasculitis (OR = 1.45; 95% CI = 1.24–1.69, $P = 3.07 \times 10^{-6}$) (Figure 2f).

Seven case–control studies were undertaken to investigate the association between *PTPN22* C1858T and juvenile idiopathic arthritis (JIA), five of which revealed a significant association.[15,30,43,66,103,113] Meta-analysis showed a highly significant association between the T allele and JIA (OR = 1.54; 95% CI = 1.40–1.70, $P < 1.00 \times 10^{-16}$) (Figure 2g).

Only two case–control studies evaluated the association between generalized vitiligo (GV) and *PTPN22* C1858T and both were recruited for the meta-analysis. Both studies suggested an association between GV and *PTPN22* C1858T.[34,49] Meta-analysis showed a strong association between the T allele and GV (OR = 1.98; 95% CI = 1.35–2.88, $P = 3.70 \times 10^{-04}$) (Figure 2h). This association is supported by a recent genome-wide association studies (GWAS).[114]

Case–control studies have also identified a strong association between *PTPN22* C1858T and myasthenia gravis (MG). Meta-analysis of five studies[23,45,115,116] showed a significant association between the T allele and MG (OR = 1.53; 95% CI = 1.31–1.80, $P = 1.09 \times 10^{-07}$) (Figure 2i).

### Diseases showing no or weak association with *PTPN22*

After the identification of *PTPN22* C1858T as a susceptibility gene for autoimmune disease, the association between *PTPN22* C1858T and inflammatory bowel disease was extensively investigated, including Crohn's disease and UC. Of the 11 case–control studies in Crohn's disease patients, only 2 identified an association with *PTPN22*.[12,21,29,31,37,50,55,58,67] Meta-analysis showed a very

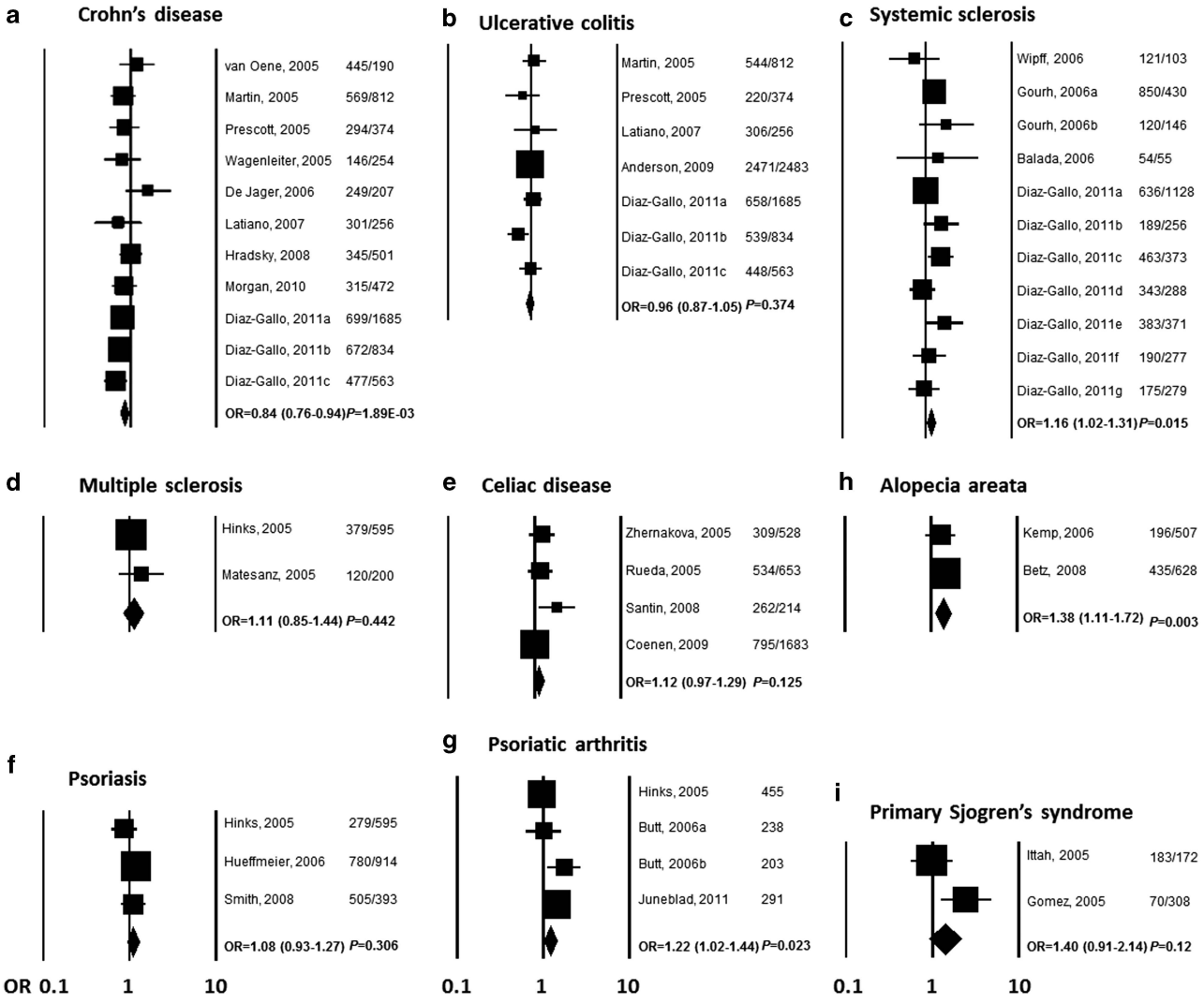


**Figure 3.** Forest plot of case–control studies of nine autoimmune diseases showing a weak or no association with *PTPN22*. The nine autoimmune diseases include (**a**) Crohn's disease, (**b**) ulerative colitis, (**c**) systemic sclerosis, (**d**) multiple sclerosis, (**e**) celiac disease, (**f**) psoriasis, (**g**) psoriatic arthritis, (**h**) alopecia areata, and (**i**) primary Sjogren's syndrome. The detailed information in the forest plot is explained in the legend to Figure 2.

weak association between the T allele and a reduced risk of Crohn's disease (OR = 0.84; 95% CI = 0.76–0.94, $P = 1.89 \times 10^{-3}$) (Figure 3a). Seven case–control studies on UC patients were recruited, six of which showed no association between *PTPN22* and UC.[12,21,29,37,50,67,117] Meta-analysis showed no association between the T allele and UC (OR = 0.96; 95% CI = 0.87–1.05, $P = 0.347$) (Figure 3b).

Another extensively studied disease is SSc, an autoimmune disease causing extensive fibrosis and vascular alterations in the skin.[13] Eleven case–control studies have been performed, but only one identified a significant association between *PTPN22* C1858T and SSc.[13,46,61,118] Meta-analysis showed a very weak association between the T allele and SSc (OR = 1.16; 95% CI = 1.02–1.31, $P = 0.015$) (Figure 3c). This is consistent with the findings of a GWAS, which failed to identify an association between PTPN22 C1858T and SSc.[119]

MS is a common autoimmune disease that targets the central nervous system. A study of family-based samples showed no association between *PTPN22* C1858T and MS.[11] This lack of association was confirmed by a GWAS.[120] Meta-analysis of two case–control studies[96,121] did not identify any association between *PTPN22* C1858T and MS (OR = 1.11; 95% CI = 0.85–1.44, $P = 0.442$) (Figure 3d).

Another autoimmune disease, celiac disease, affects the gastrointestinal tract. No association with *PTPN22* has been identified. Of the four studies recruited for this meta-analysis, three showed no association between *PTPN22* C1858T and celiac disease.[42,47,48,92] Meta-analysis also showed no association between *PTPN22* C1858T and celiac disease (OR = 1.12; 95% CI = 0.97–1.29, $P = 0.125$) (Figure 3e).

Psoriasis also showed no association with *PTPN22* C1858T according to our meta-analysis. Meta-analysis of three case–control studies with psoriasis[96,122,123] failed to identify any association with the T allele (OR = 1.08; 95% CI = 0.93–1.27, $P = 0.306$) (Figure 3g), which is consistent with the findings of a GWAS.[124] A psoriasis-related autoimmune disease, called psoriasis arthritis, is weakly associated with *PTPN22* C1858T. Meta-analysis of four case–control studies identified a weak association between the T allele and psoriasis arthritis (OR = 1.22; 95% CI = 1.02–1.44, $P = 0.023$) (Figure 3e).[56,96,125]

Two case–control studies have been performed for alopecia aerate (AA). One suggested a weak association with *PTPN22* C1858T, but the other did not.[27,36] Meta-analysis showed a weak association between AA and the T allele (OR = 1.38; 95% CI = 1.11–1.72, $P = 0.003$) (Figure 3f). This weak association is in line with the findings of a GWAS conducted in a Caucasian population.[126]

The association between *PTPN22* C1858T and primary Sjogren's syndrome (pSS) is not clear. One study from Columbia (70 cases and 308 controls) identified a strong association (OR = 2.42; 95% CI = 1.23–4.75, $P = 0.01$); this was similar to that for SLE, but stronger than that for RA or T1D in the same population.[60] However, another study from France (183 cases and 172 controls) failed to show any association.[44] Meta-analysis of both these studies showed a relatively high OR for the T allele (OR = 1.40; 95% CI = 0.91–2.14), but it failed to reach the significance threshold ($P = 0.12$). As no GWAS has been performed for pSS, more case–control studies are required to clarify any association between *PTPN22* C1858T and pSS.

### Stratified analyses based on autoantibodies

The first study to report an association between RA and *PTPN22* C1858T showed that it is associated with rheumatoid factor positive (RF +) RA but not with RF − RA,[3] raising the possibility that *PTPN22* C1858T affects autoantibody production. This stratified analysis, based on autoantibody status, was performed in some of the case–control studies, allowing us to conduct a stratified meta-analysis to explore the role of *PTPN22* C1858T in autoantibody production. To better evaluate the association between *PTPN22* C1858T and autoantibody status, we performed stratified meta-analysis using three comparisons: antibody-positive cases vs controls, antibody-negative cases vs controls and antibody-positive cases vs antibody-negative cases (Figure 3). Stratified analyses have been extensively evaluated in patients with RA based on the levels of RF or anti-cyclic citrullinated peptide (anti-CCP) antibodies. Meta-analysis of 11 RA case–control studies[18,22,28,40,41,95,97–99,101,102] according to RF status showed a strong association between the T allele and RF + RA (OR = 1.63; 95% CI = 1.51–1.75, $P < 1.00 \times 10^{-16}$) and a weak association between the T allele and RF − RA (OR = 1.35; 95% CI = 1.22–1.49, $P = 9.04 \times 10^{-09}$). A comparison between RF + RA and RF − RA showed that the T allele was more common in RF + RA (OR = 1.21; 95% CI = 1.09–1.35, $P = 2.79 \times 10^{-04}$) (Supplementary Figure 1a). Five RA case–control studies based on anti-CCP antibody status were recruited for the meta-analysis.[18,22,28,40,101] The results showed a strong association between the T allele and anti-CCP + RA (OR = 1.78; 95% CI = 1.59–2.01, $P < 1.00 \times 10^{-16}$) but no association between the T allele and anti-CCP − RA (OR = 1.15; 95% CI = 0.98–1.35, $P = 0.081$). Also the frequency of T allele was significantly higher in anti-CCP + RA than in anti-CCP − RA (OR = 1.45; 95% CI = 1.24–1.70, $P = 4.09 \times 10^{-06}$) (Supplementary Figure 1b).

SSc is an autoimmune disease characterized by high levels of autoantibodies against various cellular antigens including anti-topoisomerase I antibodies (ATA) and anticentromere antibodies (ACA).[118] Stratified analyses have been performed based on ATA and ACA levels in 11 case–control studies.[13,46,61,118] The present meta-analysis identified a marginal association between SSc and *PTPN22*. Stratified meta-analysis based on ATA status showed a marginal association between both ATA + SSc (OR = 1.25; 95% CI = 1.03–1.54, $P = 0.037$) and ATA − SSc (OR = 1.16; 95% CI = 1.00–1.33, $P = 0.019$) and *PTPN22* (Figure 4d). Comparison between ATA + SSc and ATA − SSc did not reveal significant differences in the T allele frequency (OR = 1.11; 95% CI = 0.90–1.37, $P = 0.323$) (Supplementary Figure 1c). Similar results were observed in the stratified meta-analysis based on ACA status, where the T allele was marginally associated with both ACA + SSc (OR = 1.28; 95% CI = 1.07–1.52, $P = 0.0058$) and ACA − SSc (OR = 1.14; 95% CI = 1.00–1.31, $P = 0.053$). There was no difference in the frequency of the T allele between ACA + SSc and ACA − SSc (OR = 1.15; 95% CI = 0.96–1.38, $P = 0.127$) (Supplementary Figure 1d).

### Association between *PTPN22* and other autoimmune diseases

Besides the autoimmune diseases mentioned above, an association between *PTPN22* and several other autoimmune diseases has been investigated, including ankylosing spondylitis (AS), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), idiopathic inflammatory myopathies (IIM), acute anterior uveitis (AAU), immune thrombocytopenia and pemphigus vulgaris (PV).[64,103,127–131] The results are summarized in Supplementary Table S1. Only one case–control study was conducted for each disease in European populations or populations of European descent, making meta-analysis impossible. However, evidence from GWAS or case–control studies conducted in other populations provides additional evidence for an association.

A case–control study performed by Orozco *et al.*[131] in 2005 did not find an association between *PTPN22* C1858T and AS, a highly HLA B27-associated autoimmune disease. This lack of association between *PTPN22* C1858T and AS was confirmed in a GWAS.[132] In addition, no association with *PTPN22* C1858T was reported for another HLA B27-associated autoimmune disease, AAU.[129] PBC is an autoimmune disease characterized by the slow progressive destruction of the small bile ducts within the liver.[133] In 2006, Milkiewicz *et al.*[130] reported that *PTPN22* was not associated with

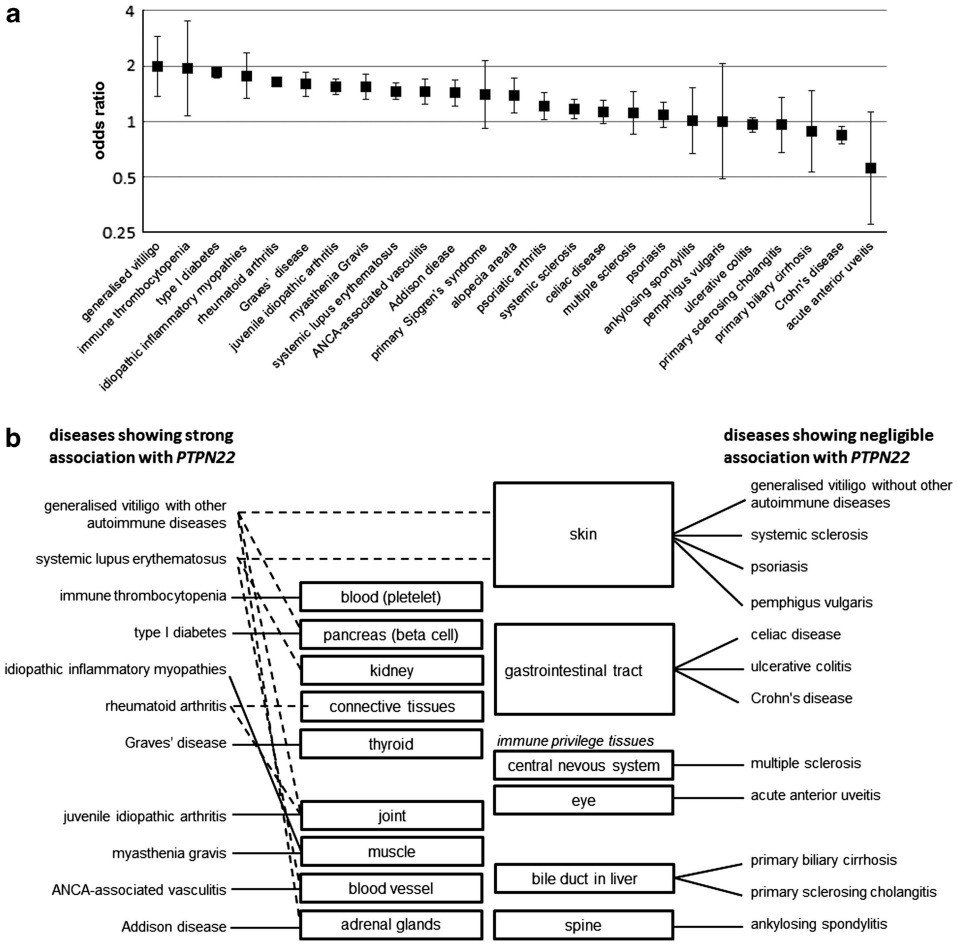


**Figure 4.** The pattern of association between *PTPN22* and autoimmune diseases. (**a**) Association between *PTPN22* and 26 autoimmune diseases. OR with 95% CI for the *PTPN22* T allele are presented. (**b**) Analysis of the target tissue specificity of 12 autoimmune diseases showing a strong association with *PTPN22* and 12 autoimmune diseases showing a negligible association with *PTPN22*. The lines connecting diseases and tissues indicate the target tissue for the associated disease, whereas the solid lines connect diseases targeting one tissue and dashed lines connect diseases targeting multiple tissues.

PBC in Canada. This result was confirmed by a GWAS in 2009 with samples from both the USA and Canada.[133] PSC is another autoimmune disease targeting the small bile ducts within the liver, and most patients with PSC also have UC.[134] As is the case for UC and PBC, *PTPN22* is not associated with PSC.[103] PV is caused by antibodies against desmoglein 1 or desmoglein 3, resulting in the loss of cohesion between keratinocytes and subsequent skin blisters.[135] In 2011, Sachdevet *et al.*[64] reported no association between *PTPN22* C1858T and PV, confirming a previous observation in a Tunisian population.[136]

A strong association between *PTPN22* C1858T and two other autoimmune diseases has been reported. Immune thrombocytopenia is characterized by antibody-mediated platelet destruction. D'silva *et al.*[128] reported a strong association between ITP and the *PTPN22* T allele in a caucasian US population. This association was confirmed in an Egyptian population.[70] Finally, a strong association between the *PTPN22* T allele and IIM was reported in a British Caucasian population.[127]

## Association pattern between PTPN22 and autoimmune diseases

So far, the association between *PTPN22* C1858T and 25 autoimmune diseases has been evaluated. Figure 4a summarizes the ORs for the T allele of the different diseases in a ranked order. The *PTPN22* T allele is strongly associated with GV, ITP, T1D, RA, GD, JIA, MG, SLE, ANCA-associated vasculitis and Addison disease. The association between pSS and *PTPN22* needs further evaluation. A weak association was observed between *PTPN22* and psoriasis arthritis and AA, and a negligible association was observed between *PTPN22* and SSc, celiac disease, MS, psoriasis, AS, PV, UC, PSC, PBC, Crohn's disease and AAU.

To further examine the association pattern of *PTPN22* C1858T with autoimmune diseases, we evaluated the relationship between association status and the target tissues affected by these autoimmune diseases. We focused on diseases showing a strong association with *PTPN22* and diseases showing a negligible association with *PTPN22*. As a GWAS showed that *PTPN22* is only associated with GV in patients also suffering from other autoimmune diseases, but not associated with GV in patients with GV alone,[114] we divided GV into two subsets, including GV with concomitant autoimmune diseases and GV without concomitant autoimmune diseases. This analysis identified a fine target tissue specificity between diseases showing a strong association with *PTPN22* C1858T and diseases showing a negligible association with *PTPN22* (Figure 4b). The target tissues of diseases showing a strong association with *PTPN22* C1858T include skin (SLE and GV with other concomitant autoimmune diseases), blood (immune thrombocytopenia), pancreas (T1D and GV with other concomitant autoimmune diseases), kidney (SLE), connective tissue (RA), thyroid (GD), joint (JIA, RA, SLE and GV with other concomitant autoimmune diseases), muscle (MG and IIM), blood vessels (SLE and ANCA-associated vasculitis) and adrenal

glands (Addison's disease and GV with other concomitant autoimmune diseases). The target tissues of diseases showing a negligible association with *PTPN22* C1858T include skin (GV without any concomitant autoimmune diseases, SSc, psoriasis and PV), gastrointestinal tract (celiac disease, UC, Crohn's disease), bile duct (PSC and PBC), spine (AS) and two immune privileged tissues; the central nervous system (MS) and eye (AAU). Interestingly, although some tissues are the target for several autoimmune diseases, there is a clear distinction between those diseases showing a strong association with *PTPN22* C1858T and those diseases showing a weak or negative association with *PTPN22* C1858T. There is only one exception: skin is the target tissue for four autoimmune diseases (GV without concomitant autoimmune diseases, SSc, psoriasis and PV) that show a negligible association with *PTPN22* C1858T, and two autoimmune diseases showing a strong association with *PTPN22* C1858T (SLE and GV with concomitant autoimmune diseases). Notably, both SLE and GV with other concomitant autoimmune diseases target many tissues, indicating that skin might not be their specific target tissue. Therefore, when we exclude those autoimmune diseases that target several tissues, we see a clear distinction between autoimmune diseases showing a strong association with *PTPN22* C1858T and diseases showing a negligible association with *PTPN22* C1858T.

## DISCUSSION

The comprehensive meta-analysis carried out in the present study showed that *PTPN22* C1858T is strongly associated with nine autoimmune diseases: T1D, RA, SLE, Graves' disease, Addison's disease, ANCA-associated vasculitis, JIA, MG and GV with other concomitant autoimmune diseases. Together with 2 other *PTPN22* C1858T-associated diseases (ITP and IIM), which are not included in present meta-analysis, 11 autoimmune diseases are strongly associated with *PTPN22* C1858T, with the T allele increasing the risk of disease. The association suggests that there may be a common mechanism shared by these diseases. Exploration of these mechanisms will greatly help us to understand the pathogenesis of the diseases.

Based on two observations, a possible underlying mechanism affecting autoantibody production by *PTPN22* variants has been suggested.[82] First, some primary T-cell-mediated autoimmune diseases, for example, Crohn's disease, UC and MS, are not associated with *PTPN22* C1858T,[11,12] whereas autoantibody-associated diseases, for example, T1D, RA and SLE, are associated.[2–4] Second, several stratified analyses show that *PTPN22* C1858T is only associated with RF+ RA or anti-CCP RA+ but not with RF− RA or anti-CCP− RA.[3,40,101] However, although our analysis could indeed confirm this hypothesis for some diseases others did not fit into this model. Stratified meta-analysis for RA showed that *PTPN22* C1858T is associated with anti-CCP+ RA but not with anti-CCP− RA, and the association between *PTPN22* C1858T and RF+ RA is much stronger than that between *PTPN22* C1858T and RF− RA, suggesting that the C1858T mutation might affect the production of anti-CCP antibodies and RF. By contrast, the stratified meta-analysis for SSc did not confirm an association between *PTPN22* and ATA or ACA autoantibodies. Moreover, *PTPN22* C1858T is not associated with autoantibody status in T1D patients.[137] Finally, PV, which is an autoimmune disease mediated by autoantibodies against desmoglein 1 and desmoglein 3, is not associated with *PTPN22* C1858T; refuting the idea that *PTPN22* C1858T is associated with autoantibody status. Taken together, we have to conclude that the *PTPN22* C1858T polymorphism is in some but not all cases associated with the presence autoantibodies and that development of self-reacting antibodies is not direct consequence of this gene variation.

According to a second hypothesis, the variations C1858T could lead to enhanced generation of autoreactive T cells escaping thymic selection.[137] As this gain-of-function mutation weakens TCR signaling,[2,3,7] it is conceivable that it will result in some moderately autoreactive T cells escaping the thymic selection process. Furthermore, the C1858T variation also weakens BCR signaling in B cells[8] and, therefore, this model can be expanded to B cells as well. As a consequence, increased numbers of autoreactive T and B cells could be responsible for an enhanced risk of developing autoimmune diseases. This new model is supported by experimental evidence from a very recent breakthrough by Menard *et al.*[138] In this study, Menard *et al.*[138] showed that the R620W variation interferes with the removal of self-reacting B cells in humans by affecting both central and peripheral B-cell tolerance check points. This study clearly shows that the R620W mutation increases the generation of autoreactive B cells, which supports the above proposed model. However, because *PTPN22* as a cell signaling regulator is expressed in many immune cells, it is unlikely that *PTPN22* should affect only the generation of autoimmune T and B cells. Therefore, the mechanism behind the association could be much more complex than what this model proposed. Very recently, Zhang *et al.*[139] investigated knock-in mice and showed that the C1858T allele affects T-cell activation and positive selection, as well as the activation of dendritic- and B-cell activation. These results provide strong evidence that *PTPN22* C1858T could affect autoimmune response on several levels, including generation and activation of autoimmune cells, and in many different cell types, including T and B cells and dendritic cells. Therefore, this model need to be further revised as: *PTPN22* appears to have a role in autoimmune disease manifestations by affecting the generation and activation of immune cells.

Given a role of *PTPN22* in generation and activation of immune cells, the question arises why several autoimmune diseases lack any association to *PTPN22*. Our analysis indicates that the C1858T mutation has a negligible effect on 12 autoimmune diseases: Crohn's disease, UC, celiac disease, SSc, MS, psoriasis, PSC, PBC, AS, PV, AAU and GV without other concomitant autoimmune diseases. Together with the 11 autoimmune diseases that show a strong association with *PTPN22* C1858T, a remarkable distribution pattern becomes visible that suggests a novel mechanism how some diseases could be related to *PTPN22* variations. If associations are considered with regard to the targeted tissues, a clear distinction between diseases showing a strong association with *PTPN22* C1858T and those showing a negligible association was found. Interestingly, the target tissues for most diseases showing a negligible association with *PTPN22* are skin (in GV without concomitant other autoimmune diseases, SSc, psoriasis and PV), the gastrointestinal tract (in celiac disease, UC and Crohn's disease) and some immune privileged sites such as the central nervous system (in MS) and the eye (in AAU). Compared with other tissues, both skin and the gastrointestinal tract have exposed surfaces and therefore may be more affected by environmental factors. This raises the possibility that autoimmune diseases associated with these tissues might be triggered by some environmental factor(s), for example, bacterial infection. One typical example is Crohn's disease. Nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*), a receptor of bacterial peptidoglycan, has been identified as the strongest non-HLA susceptibility gene for Crohn's disease,[140,141] indicating a role for bacteria in the development of this disease. Regarding immune privileged tissues, some proteins responsible for triggering the deletion of autoreactive T and B cells are not expressed in the central immune system, allowing autoreactive lymphocytes to escape from central selection.[142,143] Under normal physiological conditions, these autoreactive T and B cells are inactive because they are unable to enter immune privileged tissues; however, when immune privilege is disturbed, these autoreactive T and B cells may gain access to these tissues and cause an autoimmune response.

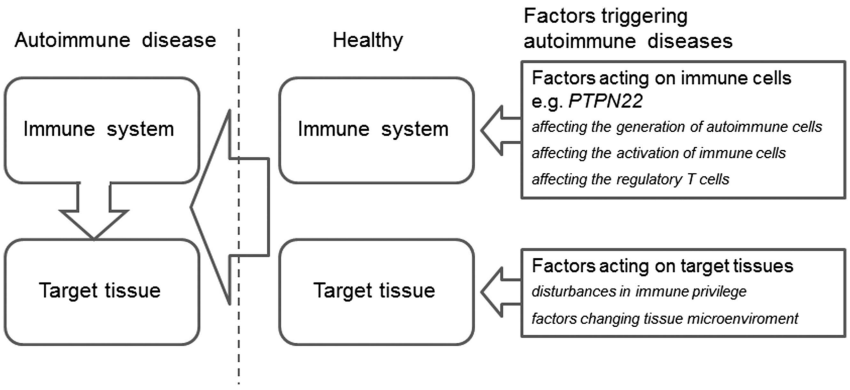


**Figure 5.** A model of the mechanism underlying the association between *PTPN22* and autoimmune diseases. In healthy individuals, autoimmune response is a tolerant state and does not attack target tissue. However, the break of such tolerance can be triggered by at least two group of factors. The first group consists of factors acting on immune cells, and the other group consists of factors acting on target tissues. *PTPN22* belongs to the first group.

Based on previous knowledge that *PTPN22* affects the generation and activation of immune cells and our own findings regarding the association pattern and target tissue specificity, we propose a new model explaining the association between *PTPN22* C1858T and autoimmune diseases (Figure 5). In a healthy state, some autoreactive immune cells may escape from the central immune system. However, they are not active because they show low autoreactivity, lack access to the target antigens or are suppressed by regulatory T cells. Therefore, the autoimmune response will not manifest in the organ. Autoimmune disease (as the result of a misdirected autoimmune response) may be triggered in two ways. First, autoimmune diseases can be triggered by factors acting on immune cells, resulting in the generation of autoimmune cells or activation of immune cells. This may cause unwanted autoimmune responses and a consequent development of autoimmune diseases. The second way involves factors acting on the target tissues. For example, bacterial infection or environmental noxa may lead to a proinflammatory microenvironment in the target tissue resulting in an activation of self-reactive T and B cells with principal low autoreactivity. Such factors could also be involved in the disturbance of immune privilege, for example, by changing the permeability of the brain–blood barrier, enabling the entrance of autoreactive lymphocytes into these tissues and initiating autoimmune disease. Within this view, the main effect of *PTPN22* in autoimmunity maybe its capacity to affect immune cells. This could explain our observation that *PTPN22* C1858T appears to be strongly associated with those autoimmune diseases, which are primarily triggered by factors dysregulating immune cells, whereas no or only low association is observed in autoimmune diseases primarily triggered by factors acting on target tissues.

In summary, our comprehensive analysis reveals an extraordinary association between *PTPN22* polymorphism and a defined set of autoimmune diseases, which correlates with specific target tissues, where the corresponding disease manifests. Thus, we propose a new model for the mechanism underlying the association between *PTPN22* and autoimmune disease.

## MATERIALS AND METHODS

### Identification of eligible studies

An exhaustive search of the Medline database was performed to identify eligible studies (the last search update was August 2011). First, the key word 'PTPN22' was used for the search without any limitations, and retrieved abstracts for 498 articles. Second, we reviewed these 498 abstracts and identified relevant articles that studied the association between the *PTPN22* C1858T polymorphism and autoimmune disease. Finally, we reviewed the full text of all the relevant articles and identified eligible studies based on following criteria: (a) the study population was European or of European-descent, (b) the study was original and (c) the patients were sporadic cases. We excluded the following: (a) studies containing overlapping data, (b) studies in which the allele frequency could not be ascertained, (c) studies in which family members had been studied and (d) GWAS. Supplementary Table S2 lists all studies used for meta-analysis.

### Data extraction

Data extraction was conducted independently by two authors and consensus was achieved regarding the data. The following information was collected from each study: the first author's name, the year of publication, the population of origin, the type of autoimmune disease, the number of cases and controls, the different genotypes of the cases and controls, and the number of T and C alleles in both cases and controls. For studies including subjects from different ethnic groups, only samples from Europeans or those of European descent were extracted. For studies including several independent case–control populations, each case–control population was extracted separately.

### Data evaluation and statistical analysis

For the control group in each study, we assessed departures from the Hardy–Weinberg equilibrium using the $\chi^2$-test. The allele frequencies for the *PTPN22* C1858T polymorphism were determined in each study using the allele-counting method. We then examined the allelic effect of T (minor allele) vs C (major allele). The C allele was considered as the reference allele and the T allele was considered the variant allele. The OR, 95% CI and *P*-values were estimated for each study. Meta-analysis was performed to calculate the pooled OR, 95% CI and *P*-values using the fixed-effects model.[144] Statistical analysis was performed using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Genes and Immunity website (http://www.nature.com/gene).