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PTPN22: Its role in SLE and autoimmunity

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Abstract

A functional variant of protein tyrosine phosphatase nonreceptor 22 (*PTPN22*) has recently been shown to be associated with multiple autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis, type 1 diabetes, and autoimmune thyroid disease. In this review, we discuss the structure and function of this gene and its disease-associated polymorphisms. In addition, we review the studies investigating the association between this gene and SLE, along with other autoimmune diseases.

Keywords

SLE; *PTPN22*; autoimmunity; genetics

Introduction

The clustering of autoimmune diseases in families has suggested to physicians and scientists that individual disease-causing genes may underlie susceptibility to multiple autoimmune diseases. Although these diseases have different manifestations, they can share similar disease mechanisms, such as reactivity to self-antigens, which may be regulated by the same genetic variants. Linkage studies have supported the hypothesis that individual genes predispose to multiple autoimmune phenotypes, since many of these diseases are linked to the same loci [1,2].

The major histocompatilibity complex, and in particular, the human leukocyte antigen (HLA) region on chromosome 6p21, has been linked to multiple autoimmune diseases. However, even within the HLA, different genes and alleles are associated with different autoimmune phenotypes. For example, HLA-DR4 is associated with rheumatoid arthritis (RA), while HLA-DR2 is associated with multiple sclerosis (MS) and systemic lupus erythematosus (SLE), and HLA-B27 is associated with ankylosing spondylitis. CTLA4 was the first gene outside of the major histocompatibility complex to be convincingly associated with 2 autoimmune diseases —autoimmune thyroid disease (AITD) and type 1 diabetes (T1D)—but the associations have been modest (odds ratio [OR] ~ 1.45 and ~ 1.15, respectively) [3].

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More recently, a functional polymorphism of the tyrosine phosphatase *PTPN22* has been associated with multiple autoimmune diseases such as SLE, RA, T1D and AITD. The wealth of evidence supporting this association, including the success of other studies replicating this finding, is quite striking and identifies this gene as a major non-HLA risk factor for many different autoimmune phenotypes. Therefore, we will discuss the structure and function of *PTPN22*, its most widely studied polymorphism R620W, and the association studies between this polymorphism and SLE along with other autoimmune diseases.

PTPN22 structure and function

The gene protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) is located on chromosome 1p 13.3–13.1 and encodes the cytoplasmic lymphoid specific phosphatase (Lyp), a powerful inhibitor of T-cell activation. The predominant isoform of this phosphatase is a 105 kDa protein. Its N-terminus, with the catalytic phosphatase site, is similar to other classical non-receptor tyrosine phosphatases. The structure of the C terminal 2/3 of the protein is largely unknown. The last 200 amino acid residues encode for 4 proline-rich sequencemotifs (P1–P4).The first of these motifs, P1, binds to the SH3 domain of the Csk tyrosine kinase, an important negative regulator of T-cell antigen receptor (TCR) signaling [4].This phosphatase is expressed solely in hematopoetic cells, with highest levels in neutrophils and natural killer cells [5].

Currently, the function of Lyp is assumed to be similar to the function of PEP, the murine ortholog of *PTPN22*. PEP is the PEST domain-enriched tyrosine phosphatase and has been designated *PTPN8*. Like Lyp, it associates with Csk, and the PEP/Csk complex acts on Lck and Fyn, 2 Src kinases that initiate TCR signaling. PEP and Csk have complementary functions: Csk phosphorylates the negative regulatory tyrosine of Lck and Fyn, and PEP dephosphorylates the positive regulatory site of Lck and Fyn. Both actions result in inhibition of TCR signaling [4]. In humans, Lyp has also been shown to act on other components of the TCR signaling pathway, including Zap70, TCRζ, Vav and CD3ε [6]. The function of PEP and Lyp have not been well studied outside of their roles in TCR signaling.

PEP knockout mice have subtle increases in their immune responses. Naïve T-cells from these mice exhibit faster growth after activation as well as increased cytokine production and proliferation after TCR restimulation. They have enhanced and sustained TCR-induced dephosphorylation of Lck. Also, PEP deficient mice have an increased number of T-cells in the effector/memory T-cell pool and increased numbers of effector and memory cells. After 6 months of age, they develop marked lymphadenopathy and splenomegaly. Large, well-formed germinal centers with increased numbers of B-cells are found in the spleen and Peyer's patches. Serologically, these mice have increased levels of IgG1, IgG2a and IgE. Even though both B- and T-cell compartments of the immune system appear to be dysregulated, these mice do not experience an increased incidence of autoantibodies or autoimmune-related organ damage [7].

Polymorphisms of *PTPN22*—R620W and beyond *C1858T/R620W*

Although many single nucleotide polymorphisms (SNPs) of *PTPN22* have been identified, only one non-synonymous coding SNP has been registered in public databases. In this SNP (rs2476601), cystine is changed to thymidine at nucleotide 1858 (C1858T), resulting in an amino acid change from arginine to tryptophan at codon 620 (R620W). This codon is located in the P1 proline-rich motif that binds Lyp to the SH3 domain in Csk, and the R620W substitution disrupts the binding of Lyp to Csk [8].

This mutation in Lyp is a gain of function variant and encodes for a more active phosphatase. Vang et al. showed that Lyp 620W is a more efficient inhibitor of TCR signaling compared to

Lyp 620R, after normalizing for expression levels. Lyp 620W dephosphorylates Lck and inhibits TCR mediated calcium mobilization more efficiently than Lyp 620R. In addition, the catalytic specific activity of the Lyp 620W phosphatase is ~60% higher than Lyp 620R [9]. These results show that Lyp's association with Csk is not crucial to its function, and also explain why the PEP knockout mouse may not develop an autoimmune phenotype. The PEP knockout mouse has lost Lyp function, while the Lyp 620W variant has gained function.

The R620W polymorphism has been associated with many autoimmune diseases, such as SLE, RA and T1D (see below for further discussion). How this gain of function variant leads to autoimmunity is not clear. Weaker T-cell signaling due to Lyp 620W's increased activity could result in less negative selection and a failure to delete autoreactive T-cells during thymic selection. Alternatively, increased Lyp function may inhibit regulatory T-cell activity, resulting in immune responses against autoantigens [4]. Further studies are needed to clarify how the activity of this variant leads to autoimmunity.

Allele frequency variation of R620W in different ethnic groups

One interesting aspect of the R620W (C1858T) polymorphism is the variation in allele frequency across different ethnic groups. For example, there is a noticeable decrease in minor T allele frequency in Caucasians from northern Europe to southern Europe [10]. The highest minor allele frequencies have been seen in Scandinavian countries (T allele frequency 12.3% in Sweden [11] and 15.5% in Finland [12]). Minor allele frequencies in Western Europe have ranged from 7 to 10% (Spain 7–7.4% [13], France 9.2% [14], Germany 10% [15] and UK 10.3% [16]). The lowest minor allele frequency in Europe has been observed in Italy (T allele frequency 2.1% [8]). Minor allele frequency of the T allele in US Caucasians has generally ranged from 7 to 9% [17–19], reflecting the predominantly Western European origins of this group. While the variation in allele frequency suggests that this SNP has been under selective pressure, no evidence of this effect has been found.

The C1858T SNP is substantially less polymorphic in non-Caucasian populations. In fact, this polymorphism has not been found in African or Asian populations [5,20,21]. When examining admixed populations in the US, the T allele frequency in African Americans is approximately 2% [5,20,22], while the T allele frequency in Hispanics is approximately 4–5% [5,19,22]. These allele frequency differences, even among Caucasians, emphasize the need for appropriate control populations when evaluating this SNP for disease associations to minimize the effect of population stratification.

Other *PTPN22* polymorphisms

In RA, the *PTPN22* C1858T SNP only accounts for a small part of the linkage signal seen at chromosome 1p [5]. Therefore, this SNP may be in linkage disequilibrium (LD) with the true causal variant or other genes in this region may also cause disease. To investigate whether other *PTPN22* SNPs are associated with RA, Carlton et al. sequenced this gene in 48 North American Caucasian RA cases representing all 3 C1858T genotypes. Fifteen novel SNPs were identified. Two SNPs, rs3811021 in the 3′ untranslated region and rs3789605 in a putative transcription factor binding site, were associated with RA independent of the R620W polymorphism in 2 separate samples. These 2 SNPs are in tight LD ($r^2 > 0.98$), and their minor alleles occur on the same haplotype. Interestingly, a single haplotype bearing the 620W risk allele was associated with RA, while another haplotype identical at all other SNPs but carrying the 620R non-risk allele was not associated with RA [23]. However, these findings were not replicated in a UK-based study of 951 RA patients and 228 controls [24].

PTPN22 was also sequenced in 94 European subjects with T1D who were homozygous for the 1858C allele [25]. Of the 8 novel SNPs identified, a rare non-synonymous SNP G2550C in

exon 18 (minor allele frequency 0.006) was preferentially transmitted in 15 affected sibpair families (transmitted: non-transmitted ratio 21:7, $p = 0.026$). This SNP may cause aberrant splicing of exon 18, resulting in a premature stop codon. This finding has not been replicated and the functional significance of this SNP is not known.

Since R620W is not polymorphic in Asian populations, Kawasaki et al. [26] sequenced *PTPN22* in 35 healthy Japanese subjects. Of the 5 novel SNPs identified, heterozygotes of the G-1123C SNP (rs2488457) were associated with acute onset T1D. This SNP, located in the promoter region, also had increased transmission disequilibrium compared to the R620W SNP in 89 British families multiplex for T1D. Therefore, the authors suggest that the G-1123C SNP is a more likely causal variant than the C1858T SNP. However, this observation was not replicated in a Eastern European Caucasian population [27].

While these findings confirm the association between R620W and autoimmunity, they also suggest that other, more rare, polymorphisms of *PTPN22* may also be associated with autoimmune diseases. As shown by the studies, these additional SNPs may reside in the 5′ promoter region, 3′ untranslated region, or in the same haplotype block as *PTPN22*.

PTPN22 and SLE

Case-control studies

A number of groups have investigated the association of the *PTPN22* R620W polymorphism with SLE, employing case-control and/or family-based study designs. Most published case-control studies have supported an association between this polymorphism and SLE, as summarized in Table I.

In 2004, Kyogoku et al. published the first report of an association between SLE and *PTPN22* R620W in North American Caucasian SLE subjects [17]. In this study, the overall OR for the T allele was 1.53 (95% CI 1.23–1.90). This study also showed evidence of a dose effect for the T allele, since the OR for SLE with the CT genotype was 1.37 while the OR with the TT genotype was 4.37. Subsequent studies have replicated this association not only in North American Caucasian SLE subjects [18], but also in Spanish Caucasian [13], Swedish [11] and Colombian [28] populations. ORs for the T allele range from 1.32–2.56, depending on the study population. Five studies (references [11,13,17,28,29]) were analysed together in a meta-analysis by Lee et al. [30]. Their analysis supports an association between this polymorphism and SLE risk. Although Kyogoku et al.'s finding of a dose effect for the T allele has been difficult to replicate in individual studies (likely due to the low frequency of individuals homozygous for the variant), this meta-analysis also suggests a dose-risk relationship per copy of the T allele. Notably, though, this meta-analysis only included case-control studies, and excluded family-based study designs.

Two studies in Caucasian populations have not shown an association between the R620W polymorphism and SLE. The first, published by Viken and colleagues [29], was conducted in a Norwegian population. The authors remark that their sample size was smaller than previous studies, and their study may have lacked statistical power to detect an association. However, the T allele frequency was similar between cases (10.8%) and controls (11.6%), suggesting that their negative finding may also be due to a lack of association in their study population. Kaufman et al. [19] found an association with SLE subjects derived from multiplex SLE families, but did not find an association with SLE subjects derived from sporadic SLE families (see below).

While most studies have focused on Caucasian populations (either North American or European), 3 studies have specifically investigated non-Caucasian populations with adult-

onset SLE. Both Edberg [22] and Kaufman [19] studied this polymorphism in African American and Hispanic populations, while Gomez [28] studied a Colombian population. Both Edberg and Kaufman confirmed that the minor allele frequency was quite low (approximately 2%) in African Americans. While these studies employed relatively large samples of African–American SLE cases, no association with the *PTPN22* R620W polymorphism was seen. In a Colombian population, Gomez showed that although the T allele frequency was lower (~4%) compared to Caucasians, this polymorphism was significantly associated with SLE. In North American Hispanics, both Edberg and Kaufman showed that the frequency of the T allele was also lower (4–5%) compared to Caucasians. Edberg noted that the T allele was increased in Hispanic and Puerto Rican SLE cases compared to ethnically matched controls, but the association was not significant. Kaufman noted a significant association between the variant allele and SLE in Hispanic cases but only if the cases were from families with sporadic SLE. The findings in Hispanics from both Edberg's and Kaufman's studies may be limited by their sample sizes, and larger studies are needed to answer this question conclusively.

One study has also shown an association between *PTPN22* and pediatric-onset SLE. Baca et al. [31], found that the relationship between *PTPN22* R620W and pediatric SLE in a Mexican population (OR 3.09, 95% CI 1.34–7.21) may be stronger than the relationship with adult-onset SLE in Caucasian populations. Similar to Kaufman et al., this association was maintained when analysing cases with sporadic SLE (OR for T allele 3.19, 95% CI 1.35–7.52).

Family-based studies

Unlike case-control studies, family-based studies have not demonstrated an association with *PTPN22* and SLE itself (see Table II). In the initial study reporting the association with SLE [17], Kyogoku also measured the transmission of the T allele in 185 Caucasian affected sib pairs and 201 Caucasian trios. These cases were a subset of those used in their case-control analysis. The authors did not find significant evidence of association in their family-based analysis, with a transmission: non-transmission ratio (T:NT) of 70:57 ($p = 0.22$). However, the authors note that their study was underpowered to detect association of the R620W polymorphism with the transmission disequilibrium test for the OR calculated from the case-control analysis.

Subsequent family-based studies have suggested that an association exists between this SNP and particular SLE subsets, not with SLE itself. For example, Wu et al. [32] studied 902 Caucasian families derived from 4 cohorts based in the US, UK and Finland. No significant increased transmission of the T allele to affected SLE subjects was observed. Analysis of the families using affected family-based controls (utilizing homozygous parents in the statistical test) also did not reveal any significant associations. However, the T allele frequency was noted to be higher in SLE patients with AITD compared to patients with SLE alone (16.7 vs. 8.5%, OR 2.16, 95% CI 1.25– 3.72, $p = 0.008$). The authors remark that *PTPN22* R620W may be a risk factor for the development of concurrent autoimmune diseases among SLE patients.

Association patterns may also be different when considering cases with familial SLE or sporadic SLE. With familial SLE defined as having at 2 pedigree members with SLE, Kaufman [19] found an association between transmission of the T allele and SLE in their multiethnic familial SLE cohort, including their cohort of European–American pedigrees (T:NT 61:48, $p = 0.015$). In contrast, no association between transmission of the T allele and SLE was observed in the multiethnic cohort comprised of sporadic SLE pedigrees. However, the sporadic SLE cohort was smaller. Nonetheless, the association appears stronger for familial SLE subjects compared to sporadic SLE subjects. Kaufman et al. was also the first group to conduct a family-based analysis of this polymorphism and SLE in non-Caucasian populations. No significant association between SLE and transmission of the T allele was observed for the 88 African–American or 40 Hispanic pedigrees with familial SLE, but this analysis was likely

underpowered given the small number of families. Too few African–American or Hispanic trios with sporadic SLE were available for analysis.

In a family-based study investigating the role of *PTPN22* R620W with autoimmunity in general, Balada et al. [33] typed this polymorphism in 21 Spanish families, each with at least 2 members affected by an autoimmune disease. There were 64 affected and 169 unaffected family members, and SLE was the most frequently represented autoimmune disease. This polymorphism was also typed in 129 healthy blood-bank controls. The authors did not find an association between this polymorphism and the presence of an autoimmune disease when examining affected vs. unaffected family members or vs. healthy controls. Only 9 families were informative for family-based analysis, and no associations were seen. Clinical features such as ANA titres and dsDNA titres were not associated with the *PTPN22* R620W polymorphism in this group.

In a second study focusing on autoimmune diseases in families, Criswell et al. assembled 265 multiplex families, in which at least 2 of 9 “core” autoimmune diseases were present. These core diseases included RA, SLE, T1D, AITD and MS. Case-control analyses revealed associations between the *PTPN22* R620W allele and SLE, RA, T1D and AITD when compared to controls.

Why do results from family-based studies differ from case-control studies? Case-control studies may be affected by population stratification, leading to false positive results. However, this confounder is unlikely to be playing a substantial role in this situation, given the large number of studies in different populations reporting significant findings. Family studies evaluate transmission of alleles to affected offspring, and are protected from population stratification. However, family-based study designs have less statistical power than their case-control counterparts. Therefore, some negative results may be due to type II error. Finally, as proposed by Wu and Kaufman, the actual association may be specific to a particular subset of SLE patients (e.g. SLE subjects with autoimmune thyroiditis or with familial SLE).

Disease specific phenotypes

Although most studies have focused on SLE as the phenotype of interest, some studies have also investigated whether the *PTPN22* R620W polymorphism is associated with any particular SLE-specific phenotypes. Investigations in this area are complicated by smaller sample sizes, since usually only a subset of the study population has the phenotype of interest. However, associations with a specific phenotype may be stronger than with the disease itself.

Thus far, the *PTPN22* R620W polymorphism has not conclusively been linked to any SLE-specific phenotype. While Reddy et al. [11] reported a significant association between this SNP and lupus nephritis, this finding has not been supported in other studies [13,22]. No association has been observed with the disease manifestations comprising the ACR classification criteria for SLE [13,17,22].

Gene–gene and gene–environment interactions

SLE is a genetically complex disease, and the development of lupus may require the presence of multiple genetic risk factors and/or environmental exposures. One study has investigated a potential interaction of *PTPN22* R620W polymorphism with another gene. Reddy et al. [11] studied the potential interaction of this SNP with the PDCD1 (programmed cell death 1) PD1.3A polymorphism in lupus nephritis. Their results suggest that the effects of these genes on lupus nephritis risk are independent, with the relative risk of *PTPN22* stronger than PDCD1. Studies investigating the interactions between this SNP and environmental risk factors have not been reported.

PTPN22 and other autoimmune diseases

Type 1 diabetes

The first autoimmune disease associated with the *PTPN22* R620W polymorphism was T1D, as reported by Bottini et al. [8]. This association has been replicated by other groups in both case-control and family-based analyses (for review, refer to [4]).

Rheumatoid arthritis

A large body of literature also supports association of the *PTPN22* R620W polymorphism with RA ([5,12,23,34], for review [10]). Notably, *PTPN22* appears to be associated specifically with seropositive disease (i.e. associated with the production of rheumatoid factor and/or anti-cyclic citrullinated peptide antibody) and not seronegative disease [5,35,36]. However, a weak association with seronegative RA cannot be completely discounted.

Autoimmune thyroid disease

Associations between the R620W polymorphism and AITD have also been reported. Studies support the association between this polymorphism and Graves disease in British [37,38], American [18] and Polish populations [39]. Since R620W is not polymorphic in Asian populations, it is not associated with AITD in the Japanese [21]. Although a study of German Caucasians ($n = 94$ cases) did not find an association with Hashimoto's thyroiditis [40], a larger study based in the US ($n = 194$ cases) observed an association with the T allele (OR 1.77, 95% CI 1.31–2.40) [18]. These different findings may be due to sample size and allele frequency differences or potential genetic heterogeneity.

Systemic sclerosis

Although previous studies did not find an association between *PTPN22* and systemic sclerosis (SSc) in French Caucasian ($n = 121$ SSc cases) and Spanish populations ($n = 54$ SSc cases) [14,41], a larger US-based study ($n = 850$ Caucasian SSc cases) noted an association between R620W and Caucasian SSc patients with either anti-topoisomerase or anti-centromere autoantibodies (OR 1.70 and 2.21, respectively). No association was observed for scleroderma itself. This study is also the first to investigate this polymorphism in non-Caucasian subjects with SSc. Although an increase in both CT and TT genotypes was observed in Hispanic ($n = 146$ Ssc cases) and African–American ($n = 130$ SSc cases) subjects, the association was not statistically significant. The small number of autoantibody positive non-Caucasian subjects limited the analysis of these subgroups. These findings need to be replicated in other SSc samples.

Primary Sjögren's syndrome

Conflicting evidence regarding potential association between R620W and primary Sjögren's syndrome (pSS) has also been reported. While studies in French Caucasian [42] and North American Caucasian populations [18] have not supported an association between pSS and this polymorphism, a study in Colombian subjects did find a significant association (OR 2.42, 95% CI 1.24–4.75) [28]. Associations with anti-SSA or anti-SSB antibodies have not been observed [42].

Wegener's granulomatosis

One study has found an association with Wegener's granulomatosis (WG) [15]. Similar to findings in RA, the association in WG is strongest with autoantibody positive disease. A significant association was observed between the polymorphism and c-ANCA positive WG (OR 2.14, 95% CI 1.41–3.22 for T allele) but was not observed in c-ANCA negative WG. However, only 60 c-ANCA negative subjects were available for analysis. R620W was also

associated with organ involvement, so polymorphism may be associated with generalized (as opposed to limited) disease [15].

Autoimmune diseases not associated with *PTPN22* R620W

While there is a wealth of evidence that supports the association with certain autoimmune diseases, substantial literature exists supporting no association between *PTPN22* R620W and other autoimmune diseases. For example, many groups have reported a lack of association between this polymorphism and MS [18,43–45]. Also, studies have not found evidence for association between this polymorphism and inflammatory bowel disease [18,45–47].

The meta-analysis performed by Lee et al. [30] did not find evidence of association with psoriasis, celiac sprue, Addison's disease, inflammatory bowel disease, or MS. However, this meta-analysis was limited by the small number of case-control studies performed in these diseases.

Single studies have not found association with giant cell arteritis [48], primary sclerosing cholangitis [29], or ankylosing spondylitis [49] in Spanish Caucasian subjects. Investigations regarding this polymorphism with these diseases in other populations have not been reported.

Potential association with humoral immunity

These findings clearly demonstrate that *PTPN22* R620W is associated with some autoimmune diseases but not others. The polymorphism appears to be more strongly associated with autoimmune diseases characterized by autoantibody production (e.g. rheumatoid factor in RA, antibodies to dsDNA and extractable nuclear antigens in SLE, anti-thyroid stimulating antibodies in Graves' disease). However, not all autoimmune diseases associated with autoantibody production, such as pSS, have been associated with the R620W polymorphism. Further investigations are needed to elucidate why the R620W polymorphism is associated with certain autoimmune diseases but not others.

Conclusions

The extensive literature supporting the association between *PTPN22* and multiple autoimmune diseases clearly shows that this gene has a significant role in SLE and autoimmunity. However, many questions remain and many avenues of investigation need to be explored. For example, whether other genetic variants of *PTPN22* also confer disease susceptibility in non-Caucasian populations remains unanswered, especially in SLE. Also, the role of gene–gene and gene–environment interactions involving *PTPN22* has not been thoroughly investigated. As more tools are developed to conduct genetic studies, we hope these questions will be answered and a clearer understanding of autoimmune mechanisms will follow.

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Table I

Summary of case-control studies of *PTPN22* R20W and SLE.

Ethnic group	First author (reference)	Population source	# cases (% frequency T allele)	# controls (% frequency T allele)	OR for CT (95% CI)*	OR for TT (95% CI)*	OR for CT or TT (95% CI) *,†	Genotypic *P*-value ‡	Allelic OR (95% CI)	Alleleic *P*-value
Caucasian	Reddy [11]	Sweden	571 (16.5)	1042 (12.3)	1.42 (1.11–1.80)	1.82 (0.96–3.42)	1.46 (1.15–1.83)	0.004	1.42 (1.15–1.73)	0.0007
	Orozco [13]	Spain	338 (9.8)	1024 (7)	1.60 (1.07–2.38)	0.81 (0.07–5.71)	1.55 (1.05–2.94)	0.04	1.45 (1.01–2.09)	0.036
	Viken [29]	Norway	162 (10.8)	555 (11.6)	0. 96 (0.59–1.52)	0.68 (0.07–3.23)	0.94 (0.59–1.47)	0.98	0.92 (0.60–1.38)	0.68
	Edberg [22]	USA	647 (12.0)	637 (9.34)	1.22 (0.91–1.64)	2.69 (0.89–9.71)	1.29 (0.97–1.72)	0.065	1.32 (1.03–1.7)	0.036
	Kyogoku [17]	USA	525 (12.67)	1961 (8.64)	1.37 (1.07–1.75)	4.37 (1.98–9.65)	1.48 (1.17–1.87)	0.00009	1.53 (1.23–1.90)	0.0001
	Kaufman [19]¶	USA-familial cases	285 (11.9)	740 (8.5)	1.63 (1.15–2.30)	0.94 (0.16–3.83)	1.57 (1.12–2.21)	0.021	1.46 (1.07–1.99)	0.018
	Kaufman [19]¶	USA-sporadic cases	279 (8.2)	740 (8.5)	1.03 (0.7–1.52)	0.59 (0.06–2.88)	1.03 (0.70–1.52)	0.88	0.97 (0.68–1.37)	NS
	Criswell [18]	USA	101 (12.9)	2064 (8.5)	NA	NA	NA	NA	1.58 (1.04–2.43)	0.03
	Lee [30]	Meta-analysis of [11,13,17,28,29]			1.41 (1.22–1.63)	3.25 (1.35–7.87)	1.42 (1.23–1.64)	NA	1.49 (1.28–1.75)	<0.00001
Hispanic	Baca [31]	Mexico (childhood-onset SLE)	250 (3.4)	355 (1.1)	3.17 (1.34–7.45)	NA	3.17 (1.34–7.45)	0.007	3.09 (1.32–7.21)	0.0062
	Kaufman [19]¶	USA-sporadic cases	177 (9.6)	172 (4.9)	3.45 (1.57–7.61)	NA	2.71 (1.29–5.69)	0.002	2.06 (1.04–4.07)	0.03
	Kaufman [19]¶	USA-familial cases	72 (7.6)	172 (4.9)	2.08 (0.82–5.28)	NA	1.82 (0.77–4.31)	0.23	1.59 (0.73–3.49)	NS
	Gomez [28]	Colombia	143 (10)	308 (4)	2.15 (1.14–4.05)	NA	2.42 (1.30–4.49)	0.001	2.56 (1.49–4.39)	0.001
	Edberg [22]	USA	102 (5.9)	35 (4.2)	NA	NA	NA	NA	1.40 (0.36–7.93)	0.61
	Edberg [22]	Puerto Rico	109 (9.2)	86 (4.2)	NA	NA	NA	NA	2.38 (0.94–6.82)	0.05
African American	Edberg [22]	USA	532 (0.018)	471 (0.019)	NA	NA	NA	NA	0.93 (0.46–1.9)	0.84
	Kaufman [19]¶	USA-familial cases	169 (2.1)	494 (2.2)	1.28 (0.52–3.17)	NA	1.08 (0.45–2.62)	0.62	0.93 (0.39–2.19)	NS

Ethnic group	First author (reference)	Population source	# cases (% frequency T allele)	# controls (% frequency T allele)	OR for CT (95% CI)*	OR for TT (95% CI)*	OR for CT or TT (95% CI) *,†	Genotypic *P*-value ‡	Allelic OR (95% CI)	Alleleic *P*-value
	Kaufman [19]¶	USA-sporadic cases	255 (2.7)	494 (2.2)	1.68 (0.67–4.16)	NA	1.41 (0.58–3.43)	0.37	1.21 (0.51–2.85)	NS

*Reference group is the CC genotype;

†Chi-squared test with 1 degree of freedom (df);

‡Comparing distribution of genotypes between cases and controls using a 3 × 2 contingency table and the 2-sided Fisher's exact test with 2 df;

¶Data from the "Familial 1" cohort presented. Please consult the reference for further details about this cohort.

OR and CI are presented as listed in the reference. If not explicitly stated, OR and CI were calculated from the information provided in the reference using Fisher's exact test (Stata 9.0/SE). NA, OR/p-values could not be calculated (data either not available, or no subjects with a particular genotype); NS, not significant

Table II

Summary of family-based studies of *PTPN22* R620W and SLE. Data obtained directly from references.

Study [reference]	Population source/ethnicity	# of families	# transmissions of T allele	# non-transmissions of T allele	*P*-value
Kyogoku [17]	North American (Caucasian)	386	70	57	0.22
Wu [32]	USA, UK, Finland (Caucasian)	611 trios	105	112	0.6
Kaufman [19]	Familial cohort-multiethnic including European American, African American, Hispanic and Asian	559 (374 informative)	69	55	0.013
Kaufman [19]	Sporadic cohort- multiethnic including European American, African American, Hispanic, American Indian, Asian	552 (174 informative)	13	11	NS